HARWOOD-NUSS'

CLINICAL PRACTICE OF EMERGENCY MEDICINE

Sixth Edition

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Allan B. Wolfson

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Design Coordinator: Holly McLaughlin
Manufacturing Coordinator: Beth Welsh
Marketing Manager: Stephanie Kindlick
Prepress Vendor: Aptara, Inc.

6th edition

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9 8 7 6 5 4 3 2 1

Printed in the United States of America

ISBN 13: 978-1-4511-8881-3
ISBN 10: 1-4511-8881-1
Library of Congress Cataloging-in-Publication Data available upon request

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To my family, friends, mentors, and colleagues, and to the many residents and students who continue to teach me so much.
Allan B. Wolfson, MD

To my wife Nicola and my children, Jared and Joanna, for their patience and support of my time-consuming endeavors; and to my parents, Rene and Charlotte, for their earliest support of my career aspirations.
Robert L. Cloutier, MD, MCR

To Lisa, Eric, and Adam for the love and support they continue to give me. And to the residents and faculty at UCSF Fresno for making my job so much fun for so many years.
Gregory W. Hendey, MD

Thanks to the authors for sharing their valuable insight and wisdom; to Beth, Eric, Ali and Amanda for their never-ending understanding and love; and to the faculty and residents at Hennepin County Medical Center who have taught me so much. Special thanks to Ann for picking me for her program, not so many years ago.
Louis J. Ling, MD

To Cathy, Sofia, and Sam for being so supportive. And to the memory of my father, John F. Rosen, MD. And to the residents and faculty at Beth Israel Deaconess Medical Center with whom I am proud to work.
Carlo L. Rosen, MD

This book is dedicated to my wife Anna and my children, Jacob and Isaac. Without their support and love, nothing would be possible.
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Preface

This sixth edition of *Harwood-Nuss' Clinical Practice of Emergency Medicine* continues in the tradition of its predecessors as an up-to-date, authoritative, and concise single-volume source that covers essentially all areas of emergency medicine. It serves as a ready reference for the clinician at the bedside, and also as an educational resource for trainees and more experienced emergency medicine practitioners.

Our goal has been to produce an eminently readable book that emphasizes critical thinking in everyday emergency practice. The contributing authors are practicing emergency physicians with years of practical bedside experience, impressive academic qualifications, and wide-ranging expertise in their subjects. As in previous editions, the chapters are clinically focused and practical, not only highlighting traditional teaching and accepted evidence-based practice but also examining what remains controversial or under investigation.

As emergency medicine has changed, so has this book. The table of contents has been revised and many chapters have been completely rewritten to take into account new approaches to many emergency conditions. The most popular and distinctive features of the book, including the **Common Pitfalls** section and the **Critical Interventions** summary, have been expanded to include a **Key Testing** section in almost every chapter.

The entire text is available in an online edition which includes additional text, tables, and figures, as well as a large set of accompanying review questions and answers, now numbering more than 1,200 expertly edited items, which provides an unmatched additional resource for study or review.

Finally, this preface would be incomplete if it did not acknowledge our debt to Dr. Ann Harwood-Nuss, who served as editor-in-chief for the first three editions of this book. Her vision and dedication continue to inspire our efforts.

Allan B. Wolfson, MD
Editor-in-Chief

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Medical Foramen

INTRODUCTION

The Approach to the Patient in the Emergency Department

Robert L. Wears

> … in the physician or surgeon, no quality takes rank with imperturbability … Imperturbability means coolness and presence of mind under all circumstances, calmness amid storm, clearness of judgment in moments of grave peril, immobility, impassiveness, or, to use an old and expressive word, *phlegm.* It is the quality which is most appreciated by the laity though often misunderstood by them; and the physician who has the misfortune to be without it, who betrays indecision and worry, and who shows that he is flustered and hurried in ordinary emergencies, loses rapidly the confidence of his patients.
>
> —Sir William Osler, *Æquanimitas*

It is one thing to practice medicine in an emergency department (ED); it is quite another to practice emergency medicine. The effective practice of emergency medicine requires an approach, a way of thinking that differs from other medical specialties.

Its physical limitation to the ED is perhaps the least important of emergency medicine's characteristics. Five factors have led emergency physicians to develop a unique approach to the patient: the pressure of time and volume, the variety of conditions faced, the paucity of information, the limitation of therapeutic options, and the constraint of disposition.

TIME AND VOLUME PRESSURE

More than any other specialists, emergency physicians experience clinical work as turbulent flow in a constricted channel. In a true emergency, seconds to minutes may make the difference between life and death or serious disability. In these situations, emergency physicians, contrary to much of their previous training, must be prepared to "treat first and ask questions later."

Also, the time available for an emergency physician to evaluate and think about any given patient is severely limited by the demands of other patients being managed concurrently. In most practices, during the busiest part of the day an emergency physician has on average only 10 to 15 minutes per patient for evaluation, testing, treatment, disposition, and documentation. Whether this is adequate or not is immaterial; the reality is that no more time is available.

The combination of time and volume pressures forces emergency physicians to be much more aware of priorities among patients. Although trauma surgeons occasionally face triage conditions, emergency physicians are the only practitioners who routinely make (at least mental) triage decisions every day.

VARIETY OF CONDITIONS

As a specialty in breadth rather than depth, emergency physicians must manage a wider variety of conditions than any other specialists, save perhaps family practitioners in remote settings. In addition, unlike other specialists, emergency physicians must shift cognitive frames rapidly. Practicing emergency medicine is like carefully lining up a putt, then dropping the putter, picking up a tennis racket to return a volley or two, quickly sidestepping an onrushing tackler, and then returning to sink the putt.

PAUCITY OF INFORMATION

Emergency physicians frequently deal with episodes of real or perceived crises in patients of whose past course they are unaware. Old records are often unavailable, electronic records may be

available but of doubtful provenance (1), and patients' memories are limited in scope and reliability. The information-gathering options available in the ED are similarly limited. Only a small subset of the vast diagnostic armamentarium is available to the emergency physician within a reasonable time.

LIMITED THERAPEUTIC OPTIONS

Options for treatment are limited as well. Often, emergency physicians can provide only temporizing or symptomatic treatment, whereas definitive management must be deferred to another specialist. In addition, in emergency situations, the tolerance for therapeutic failures or misadventures is more limited than in nonemergencies.

Although one may not realize it when viewing the chaotic, turbulent activity of a busy ED, emergency medicine possesses a certain elegance enforced by these constraints. There is an attractive intellectual simplicity in meeting the challenge of providing timely, accurate care using primarily one's own hands and brain, supplemented by a few, limited laboratory and imaging tests.

CONSTRAINT OF DISPOSITION

Every patient interaction an emergency physician has must soon be ended. This forces emergency physicians to focus on the "bottom line." No matter how uncertain the diagnosis or how much extended observation or testing might help, every patient encounter in the ED ultimately reduces to three binary decisions: Is the patient sick or not sick? If sick, should I treat or not treat? Should I admit or discharge? These questions must be answered despite the lack of definitive information, the lack of time to collect or consider additional information, or the lack of availability of advice from colleagues and consultants.

A FRAMEWORK FOR APPROACHING THE ED PATIENT

There are many sources that outline the mechanics of history taking and physical examination, and this section does not discuss these

areas in detail. Instead, it concentrates on how they are different in emergency medicine.

The first question to be asked on initial approach to a patient in the ED is, “Do I need to resuscitate this patient?” Corollaries to this question are, “How great is the threat?” and “How soon must I act?” The first question is usually answered in the first few seconds at the bedside and is as often based on an overall *gestalt* of the chief complaint and the patient’s general appearance as on specific complaints or vital sign abnormalities.

In true emergencies, the usual sequence of history, physical examination, laboratory testing, and treatment is altered by the need to take rapid action. In the most extreme cases, the sequence becomes treatment, physical examination, laboratory testing, and history.

When action is urgently required, the emergency physician must commit to it unhesitatingly. This requires mental preparedness; there is no time to ponder the benefits and risks of the various options for managing acute upper airway obstruction. The thinking required must be invested ahead of time, and a plan of action internalized by the physician before the situation requiring it arises.

If action is to be effective, it often must be initiated before all the information bearing on the decision is available. This requires a “bias toward action” in the emergency physician’s mind. While this is occasionally a source of criticism from other specialists who fail to understand emergency medicine, in the proper circumstances it can save lives. A simplistic example of bias toward action is putting a patient with chest pain on a cardiac monitor on arrival to the ED; clearly the diagnosis of heart disease has not yet been made, so it is not certain that the monitor is truly “needed,” but we anticipate a potential need and act without waiting for confirmation. A more dramatic example is sudden upper airway obstruction, where the decision to perform a cricothyroidotomy must be made promptly; to wait until the need is clear may be to wait too long.

Part of the art of emergency medicine is the ability to reliably discriminate between cases requiring urgent action and those allowing a more measured approach. Maintaining a bias toward

action should not be used as an excuse for an indiscriminate, “shoot-from-the-hip” approach to the patient; it is a tool that the emergency physician must learn to use effectively.

BEDSIDE EVALUATION

If resuscitation or other urgent interventions are not required, the usual framework for patient evaluation (history, physical, laboratory, treatment, disposition) can be used. However, in the ED, certain factors require more or less emphasis or alteration (Table INT.1).

Table INT.1

Rules to Guide the Bedside Evaluation of the Emergency Department Patient

Introduce yourself to everyone
Shake hands
Sit down
Relieve pain early
Do not interrupt
Provide information
Explain what will happen
Provide updates
Be helpful

Patients and physicians in EDs are generally complete strangers, and thus patients have legitimate questions about the emergency physicians they have just met: Are they capable? Can they be trusted? Consequently, the first task faced by the emergency physician, even before information gathering begins, is to build a working relationship with the patient right away (2).

The initial contact the physician makes should be social—an introduction. This should include everyone in the room, and should be accompanied by physical contact—a handshake or touch. This establishes a tone of personal respect for the patient and helps enlist

the family, if present, in an alliance with the physician. As early as possible the physician should show empathy with the patient by acknowledging recognition of an apparent need. This can be done by an offer to relieve apparent pain, if appropriate.

The body language of the physician–patient encounter is important. Often in the ED, the standing physician presides over the supine, frequently disrobed patient, presenting an authoritarian image that can be threatening to patients. As often as possible, therefore, the physician should sit while conducting the initial interview, ideally bringing his or her head to the same level as the patient's (3). This is especially important in dealing with children, but should not be neglected in adult patients.

The information-gathering phase of the encounter should begin with a general, open-ended approach, such as, "How can I help you?" or "Tell me your story." More direct approaches, such as "What is your problem?" risk being misinterpreted. It is important to remember that both parties, not just the physician, are interested in gathering information at this time. Patients' desires for information, explanation, and reassurance are great, but are seldom met by physicians (4,5). One way emergency physicians can meet this almost insatiable need for information early in the encounter is by commenting about findings during the physical examination: "Your heart sounds normal," or "Your throat looks red" (2).

Given the time pressures of emergency medicine, physicians typically fear losing control of the interview and attempt to keep the patient focused and on target. Observations of physician–patient interactions show that patients are interrupted by the physician on average about 18 seconds after they begin to relate their history, but that if uninterrupted, 80% can get their story out within 1 minute (6). Physicians' time concerns are real, but if the physician dominates the interview, the patient will become passive and volunteer little (6); the physician will then have to spend additional time extracting information later. In addition, the chief complaint may not always be mentioned first; failure to wait for the true chief complaint to emerge can lead to false trails and lost time (2). Considering the gain in rapport with the patient and the potential

for mischief with early interruption, it seems wise for emergency physicians to discipline themselves to be quiet for the first 60 seconds of the interview.

The introduction of electronic records is a potentially intrusive factor in patient–physician communication. Initially there were concerns that physicians might be perceived as paying more attention to the computer than to the patient, although as this technology becomes more ubiquitous, patients will likely come to treat the physician–computer interaction as routine.

However, it is important that the bullet point, checkbox nature of electronic charting not be allowed to prevent the physician and patient from codeveloping the narrative of illness (or injury). Understanding about that nature of a patient's problem is acquired iteratively; early information leads to the development of a tentative structuring and categorization which guides further investigation, but which is itself modified according to newer information; the structure and categories change as understanding improves. But if the full narrative never comes into existence, this cycle of increasing understanding is broken, and the physician is left with a model of the patient's problem that has been prematurely frozen in an unfinished and perhaps even erroneous state (7,8). Thus, it is good practice to take a history and perform a physical examination before interacting with a charting template.

DISPOSITION

Once the initial assessment is complete, the physician should outline the plan to the patient, and should give an honest estimate of about how long it will take. It is also useful to provide some anticipatory guidance about the probable outcome, particularly in complex, chronic problems that are unlikely to be resolved in an ED evaluation. During the wait for laboratory results, consultations, or observation, the patient and family should be updated periodically on progress and asked if there is anything they need.

Finally, once a disposition is reached, the plan should be carefully and clearly communicated to the patient and family. Particularly if

the patient is to be discharged, specific instructions about follow-up and reasons to return to the ED should be covered. Because patients are likely to have difficulty remembering a series of detailed explanations or instructions (9), it is most helpful if they are given instructions in writing. Having a printed instruction sheet does not relieve the physician of the obligation to instruct the patient, but it does help to reinforce those instructions once the patient has left the ED.

A FRAMEWORK FOR DECISION MAKING IN EMERGENCY MEDICINE

Medicine is essentially about resolving ambiguity through action; in emergency medicine, this process is intensified. However, a great deal of medical decision making occurs at a subconscious level where it is inaccessible to the physician. Although formal decision-making models do not describe physicians' mental processes well, they can provide some useful insights into the nature of decision making in the ED.

MANAGEMENT, NOT DIAGNOSIS

Traditionally, medicine has focused on diagnosis as the clinician's central important task. Emergency medicine makes it clear that this is erroneous: In medicine in general, and especially in emergency medicine, the central task is not diagnosis, but management; not so much "what is going on?" as opposed to "what should we do now?" Often a diagnosis cannot be made under the constraints of an ED evaluation; the great insight that emergency physicians have contributed to their colleagues in other specialties is the notion that there need not always be a diagnosis. If one can be made, it is extremely helpful, but if not, decisions must still be made and actions must still be taken.

In addition, patients want more than simply a diagnosis. They want explanation and reassurance. For example, parents will not be satisfied to know that their child's abdominal pain is caused by gastroenteritis; they want to know that it is not appendicitis. Simply

providing the diagnosis, however correct, dismisses the parents' concerns and leaves them unsatisfied. By empathizing with their fears, the physician can strengthen rapport with the family and take a position as their friend and ally, rather than as a remote authority. Thus the intellectual task is to devise a reasonable plan of management, which may include, but not be limited to, making a diagnosis.

DECISION THRESHOLDS

The concept of "decision threshold" (10) clarifies some of the processes at work when emergency physicians make decisions and adds specificity to the often used but somewhat vague concept of "index of suspicion." Consider the following hypothetical scenario of the simplest possible situation in emergency medicine: There is only one disease under consideration and there are only two possible actions—to treat or not treat—based on the emergency physician's assessment of the patient. In this scenario, there are four possible outcomes: The patient either has the disease and may be treated or not treated, or does not have the disease and is treated or not treated. The optimal management decision depends on the values of these outcomes and on the probability that a particular patient (or group of patients) actually has the disease in question.

If the patient is almost certainly nondiseased (i.e., the probability of disease is near zero), then the correct decision is to not treat, because treatment entails costs and risks of its own. Conversely, if the patient surely has the disease (probability near 1), then the correct decision is to treat, because the costs and risks of treatment are outweighed by the negative consequences of failing to treat. Therefore, there must be some *threshold* probability between 0 and 1 at which the decision is a toss-up; that is, either choice will produce about the same outcome. This treatment threshold need not (and often does not) coincide with the diagnostic thresholds that clinicians traditionally have been taught. Consequently, the clinician's task is not necessarily to make a diagnosis, but to judge

whether the probability of disease is clearly over or clearly under the treatment threshold, and to act accordingly.

The threshold approach can be extended to more complex problems. For example, a more realistic scenario allows use of a diagnostic test to improve the physician's initial assessment. Now there are two decision thresholds. At very low probabilities of disease, it is better not to test and not to treat, because the outcome of large numbers of false positives erroneously treated outweighs that of the occasional diseased patient detected. Similarly, at very high probabilities, it is better not to test, but to treat everyone, because the consequences of large numbers of false negatives erroneously denied treatment outweigh the occasional nondiseased patient spared unnecessary treatment. At intermediate probabilities, testing and treating only those patients with a positive test will produce the best overall outcome. Thus, the clinician's task is to decide whether a given patient's probability of disease lies either below the no treat–test threshold, or above the test–treat threshold. Testing is useful only in changing the management decision in the area between the two thresholds. While there may be other benefits to testing besides producing a change in management (e.g., reducing uncertainty or clarifying prognosis) (11), the threshold approach provides a rationale for understanding physicians' differing choices when faced with seemingly similar clinical scenarios.

In framing decision making in this way, it is important to note that a very broad idea of "test" is used. Anything that helps physicians revise their assessments is considered a test in this sense, so therapeutic trials, periods of observation, clinical scoring systems, or practice guidelines could all be considered "tests" because they help physicians sort out the probabilities of diseases. There is interesting evidence that physicians' diagnostic and management performance improves when they can take advantage of the nonverbal cues that accompany face-to-face communication, even though this "test" occurs largely at a subconscious level (12).

One drawback of the threshold concept is that it can taken to the extreme and result in a very narrow, overrational approach to problem solving (13). However, the way in which emergency

physicians resolve the question of whether or not to act (or what actions to take) seems to be by the use of naturalistic or "event-driven" decision making (14). This contrasts strongly with the algorithmic or analytical decision-making process taught in medical school. Naturalistic decision making is effective in settings characterized by ill-defined problems; dynamic, uncertain environments; shifting, unclear, or competing goals; tight but nonlinear or hidden coupling between actions and their effects; time pressure; high stakes; and scant opportunity for learning by trial and error.

The decision-making process can be divided into several phases. First, the physician classifies the current situation as typical or atypical, based on the matching of critical cues to stored patterns or schemata. If the situation is typical, the stored patterns will evoke a customary set of responses. If it is not typical, variations of customary responses are considered first, and then novel, "one-of-a-kind" responses are considered. Clearly, experience is critical in developing a sufficiently rich set of stored schemata such that the vast majority of clinical problems can be recognized and dealt with by such a preplanned response.

Next, the physician engages in serial evaluation of the available courses of action, beginning with the most typical response, and evaluating each by mentally simulating the expected outcomes. Once a sufficiently satisfying action is discovered, it is implemented. In other words, there is generally not a search for the best of all possible responses, but for a sufficiently good response. The payoff for accepting a good, but not necessarily best, response is that decisions can be quick and almost effortless. In fact, a great deal of physicians' expertise seems to lie in their ability to constructively perceive the problem, which seems to lead automatically to a solution without much conscious effort. This contrasts sharply with the slow and laborious analytic approach of exhaustively considering all the possibilities and eliminating them one by one until the best option is identified.

Learning this method of decision making is not easy. It can be gained with experience supplemented by feedback and reflection,

and is generally communicated by narratives of meaningful cases (15). It does not appear to be attainable through application of formal analytical methods. Such methods have their place, but they have not proven useful in helping medical students or residents to become physicians.

Common Pitfalls

There are three common pitfalls in the approach to the patient in the ED.

- The first is tunnel vision. Here the physician, in single-minded pursuit of the disposition, fastens onto a single complaint (typically the first offered) without waiting to be sure that the patient's *chief* complaint has been elicited. A related error is the premature closure of hypothesis generation (e.g., assuming that chest pain is caused by myocardial ischemia without first mentally ruling out the possibilities of aortic dissection, pulmonary embolism, esophageal rupture, or pericarditis). This problem often afflicts the less experienced, who, once having reached a characterization of the problem, are reluctant to reopen consideration of it (16).
- The second pitfall is just the opposite: an inability to see the forest for the trees. Here the physician is unable to rank findings in any order of importance, is reluctant to close off hypothesis generation, or is unable to integrate the findings into a small number of possible explanations. This is frequently manifested by procrastination in decision making, perhaps hidden behind a cascade of laboratory testing. The ability to simultaneously entertain a modest number of possible explanations for the patient's problem without prematurely settling on one, or letting the number in contention grow too large, is the "golden mean" between these two problems.
- The final pitfall is failure to attend to the patient. Time "gained" by failing to attend to the social interaction with patient and family is likely to be lost later, as missing information may not be extracted except by persistent questioning, leaving the

physician at risk of pursuing many false leads before happening across the true trail. More important, perhaps, is to remember that the doctor–patient interaction remains at its most fundamental level a meaningful *social* encounter, on which all healing and care, in the broadest sense, are based.

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SECTION I
Resuscitation

Section Editor: JEFFREY J. SCHAIDER

Medical Foramen

CHAPTER 1

Airway Management

Tarlan Hedayati and Michael F. Murphy

Airway evaluation and management to ensure continuing and adequate gas exchange remain the first priority of resuscitation, taking precedence over other interventions. Further, it is widely recognized that a conceptual framework focused on rapid airway evaluation, critical action analysis and performance, and facility with an array of airway management techniques minimizes the risk of failure and improves outcome (1).

The failure to maintain a patent airway and the failure to affect adequate gas exchange are the cornerstones of emergency airway management. Decisions regarding how and when the airway will be managed depend on the integration of numerous factors including the skills and knowledge of the physician, the equipment available, the condition of the patient, and the anatomy of the airway.

There are only four ways to provide gas exchange for the patient who is not breathing:

1. Bag–mask ventilation (BMV)
2. Extraglottic device (EGD)
3. Endotracheal intubation (ETI)
4. Surgical airway (usually cricothyrotomy in emergency medicine)

Emergency ETI performed by emergency physicians has been the most discussed, researched, and published over the years (2).

By the early 1970s, ETI had become a skill integral to the practice of emergency medicine. It was generally accomplished either nasally or orally employing varying degrees of brute force. By the mid to late 1990s, most emergency practitioners employed neuromuscular

blockade in some form most of the time to facilitate oral ETI. It had become evident that neuromuscular blockade not only made the technical task of intubation easier and faster but that the complication rates were lower and the success rates higher. However, for many practitioners, the need to evaluate the airway for difficulty and the development of a systematic method of doing so lagged behind the clinical introduction of rapid sequence intubation (RSI). There was also the need to expand the rescue options beyond cricothyrotomy.

BMV, long considered to be the cornerstone of airway management (Chapter 2), is a critically important skill in emergency medicine. However, it has become apparent that BMV is a difficult skill to teach and maintain (3). In recent years, EGDs (e.g., laryngeal mask airways [LMA], King LT Airway), which are easily inserted and highly successful at achieving adequate gas exchange, have increasingly emerged as potential first-line gas exchange techniques.

The current challenges facing emergency airway managers include the following:

- Should EGDs supplant BMV as the first-line airway management technique?
- Which patients *should not* receive paralytics?
- Is cricoid pressure still recommended to prevent passive regurgitation and aspiration of gastric contents?
- How is the airway best rescued in the event intubation and/or ventilation is impossible or has failed?

THE DECISION TO INTUBATE

The following are the five generally accepted indications to secure an airway by ETI in emergency medicine practice:

1. Failure of the patient to maintain a patent airway
2. Failure of the patient to adequately protect the airway from aspiration
3. Failure of the patient to maintain adequate gas exchange (oxygen and carbon dioxide)

4. Need for the initiation of paralytic agents or therapeutic hyperventilation
5. Inability of the patient to adequately clear secretions

A sixth indication that is frequently invoked is intubation prior to transport, when it is reasonably anticipated that although an indication to intubate does not exist now, one may develop during the transport. This risk-to-benefit analysis recognizes the practicalities and challenges of intubating in a transport vehicle.

There are probably few other situations in emergency practice when judgment and knowledge of the anticipated clinical course of a disorder are as crucial to the emergency physician as the decision to intubate a patient (4).

EVALUATION OF THE PATIENT

Human beings protect their airway at all costs, triggering an extreme autonomic response when threatened. ETI stimulates a similar autonomic response. As such, potent medications are generally employed to attenuate the adverse responses to laryngoscopy and intubation such as hypertension, tachycardia, increased intracranial pressure (ICP), and bronchospasm. The emergency physician must attempt to balance the anticipated aggression of the response to intubation by selecting appropriate classes and dosages of medication to mitigate them. Underdosing may fail to mitigate an aggressive response; overdosing may produce hypotension or premature apnea.

The evaluation of the *patient* to be intubated is focused on the three crucial organ systems: The central nervous system (CNS), the cardiovascular system, and the respiratory system. The patient's hemodynamic stability, physiologic reserve of vital organ systems, and the anticipated response to laryngoscopy and intubation dictate which medications and what doses are required to maintain stability and mitigate adverse effects during the procedure.

EVALUATION OF THE AIRWAY

Airways that are difficult to manage are fairly common in emergency medicine with some estimates being as great as 20% of all emergency intubations. However, the incidence of intubation failure is quite uncommon (0.5% to 2.5%). Moreover, the disastrous situation of being able to neither intubate nor ventilate rarely occurs (0.1% to 0.5%) (2).

The most important way to avoid airway management failure is to predict when difficulty is likely to be encountered with BMV, ETI, EGD, or cricothyrotomy, particularly if one is relying on the latter two techniques to rescue the airway in the event of ETI or BMV failure.

The distinction among the terms difficult laryngoscopy, difficult ETI, difficult BMV, difficult EGD, difficult cricothyrotomy, and difficult airway is important. For instance, difficulty with BMV or an EGD when ETI is easily performed would not be described as a difficult airway. Rather, the narrative would describe each independently.

The failed airway is clearly defined as three failed attempts at intubation and/or failure to maintain oxygen saturations. The difficult airway is not so easily defined. Rather than a strict definition, the concept of the difficult airway has the following five "dimensions."

1. Difficult BMV
2. Difficult laryngoscopy
3. Difficult intubation
4. Difficult EGD
5. Difficult cricothyrotomy

These five dimensions can be reduced to the following four technical operations:

1. Difficult BMV
2. Difficult EGD
3. Difficult laryngoscopy and intubation
4. Difficult cricothyrotomy

The evaluation of the airway for difficulty in an emergency must be done quickly, with care taken not to omit anything important. Mnemonics are efficient memory aid strategies, so one for each

technical operation has been crafted to permit a rapid and complete evaluation (Table 1.1).

TABLE 1.1
Mnemonics Useful in Evaluating the Airway for Difficulty

Difficult Bag–Mask Ventilation: MOANS
- M: Mask seal, male sex, Mallampati
- O: Obese or upper airway obstruction
- A: Aged
- N: No teeth
- S: Snores, "stiff"

Difficult Extraglottic Device: RODS
- R: Reduced mouth opening
- O: Upper airway obstruction
- D: Distorted airway
- S: "Stiff"

Difficult Laryngoscopy and Intubation: LEMON
- L: Look externally
- E: Evaluate 3–3–2
- M: Mallampati
- O: Upper airway obstruction
- N: Neck mobility

Difficult Cricothyrotomy: SMART
- S: Surgery recent or remote
- M: Mass
- A: Access or anatomy
- R: Radiation
- T: Tumor

Difficult Bag–Mask Ventilation

If the emergency physician is uncertain that neuromuscular blockade-facilitated orotracheal intubation (RSI) will be successful, he or she must be confident that BMV or EGD-facilitated ventilation is possible or at the very least that a cricothyrotomy can be performed rapidly.

The five indicators of difficult BMV (5,6) can be easily recalled for rapid use in the emergency setting by using the mnemonic MOANS (Table 1.1) (7).

- *Mask seal, Male sex, Mallampati.* Bushy beards, crusted blood on the face, or a disruption of lower facial continuity are the most common examples of conditions that may make an adequate mask seal difficult. Male sex and Mallampati scores of 3 or 4 have also been associated with difficult mask ventilation.
- *Obese or obstructed.* Patients who are obese (body mass index [BMI] >26 to 28 kg/m^2) are often difficult to ventilate adequately by bag and mask. Parturients at term; patients with angioedema, Ludwig angina, upper airway abscesses (e.g., peritonsillar), or epiglottitis; and others ought to be considered at this juncture.
- *Advanced age.* Patient age older than 55 to 57 years is associated with a higher risk of difficult BMV, perhaps because of a loss of muscle and tissue tone in the upper airway with age.
- *No teeth.* An adequate mask seal may be difficult in the edentulous patient, perioral tissues tend to cave into the structurally unsupported mouth.
- *Stiff or snores.* Patients with high airway resistance or diminished pulmonary compliance are exceedingly difficult to adequately manage with a bag and mask, as are patients who snore.

Difficult Extraglottic Devices

Four factors may indicate that EGDs may be unsuccessful at rescuing the airway and may be remembered using the RODS mnemonic (Table 1.1) (8):

- *Restricted mouth opening.* Depending on the EGD to be employed, a certain amount of oral access is critical to employ the device.
- *Obstruction.* Upper airway obstruction at the level of the larynx or lower will not be bypassed through the use of an EGD.
- *Disrupted or distorted anatomy.* The “seat and seal” of the EGD may be compromised by a disrupted or distorted airway. In

addition, a seal may be exceedingly difficult or impossible to achieve in the face of a fixed flexion deformity of the neck (9).

- *Stiff lungs or cervical spine.* Ventilation with an EGD may be difficult or impossible in the face of substantial increases in airway resistance (e.g., severe asthma) or decreases in pulmonary compliance (e.g., pulmonary edema). In addition, patients unable to fully extend the neck may prove to be difficult to ventilate with EGDs due to improper positioning of the EGD.

Difficult Laryngoscopy and Intubation

Difficult laryngoscopy and intubation ordinarily implies that the operator had a poor view of the glottis. Cormack and Lehane (10) provided some clarity to the way physicians think of the "difficult airway" by parsing the act of intubation into its two subcomponents: Laryngoscopy and intubation. They also introduced the most widely used system of categorizing the degree of visualization of the larynx during laryngoscopy (Fig. 1.1) (7). Cormack–Lehane view grades 3 (epiglottis only visible) and 4 (no glottic structures at all visible) are often used as surrogates to represent difficult laryngoscopy and to predict difficult intubation. View grades 1 (visualization of the entire laryngeal aperture) and 2 (visualization of the posterior cords and arytenoids) are not typically associated with difficult intubation, although some grade 2's may be very anterior and difficult or impossible to intubate.

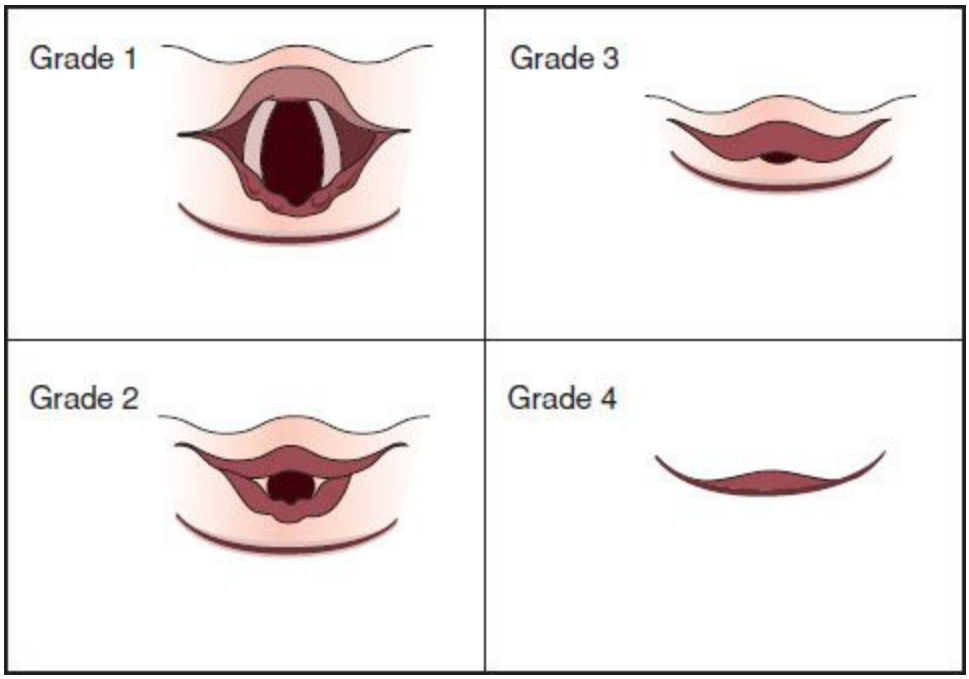

FIGURE 1.1 Cormack and Lehane system of categorizing the degree of visualization of the larynx during laryngoscopy.

The mnemonic LEMON (Table 1.1) is a useful guide to identifying as many of the risks as quickly as possible to meet the demands of an emergency situation.

- *Look externally.* If the airway looks difficult, it probably is! A litany of physical features is associated with difficult laryngoscopy and intubation, making the glottic aperture difficult to visualize. A small mandible may indicate that the tongue is "retrofitted" over the larynx; a large mandible elongates the pharyngeal axis, serving to extend the distance to the larynx beyond the visible horizon. Buck teeth block access to the oral cavity and also elongate the length of the oral axis. A high, arched palate is often associated with a long narrow oral cavity, making access a problem. A short neck may mean the larynx is positioned higher in the neck relative to the base of the tongue, making it more difficult to bring the glottis into view. Lower facial disruption interferes with adequate mask seal and may make the glottis impossible to find.

- *Evaluate 3–3–2.* This step recognizes the importance of the geometric relationships of various parts of the airway to successful intubation (11). One ought to be able to open one's mouth with the width of three of their own fingers, accommodate three of their own fingers between the tip of the mentum and the hyoid bone, and fit two fingers between the hyoid bone and the thyroid notch. The first "three" assesses the adequacy of oral access. The second "three" addresses the capacity of the mandibular space to accommodate the tongue on laryngoscopy. More than or less than three fingers are both associated with greater degrees of difficulty in visualizing the larynx at laryngoscopy. The former because the length of the oral axis is elongated; the latter because the mandibular space may be too small to accommodate the tongue, leaving it to obscure the view of the glottis. The final "two" identifies the location of the larynx in relation to the base of the tongue. If more than two fingers are accommodated, the larynx is further below the base of the tongue beyond the visible horizon. Fewer than two fingers may mean that the larynx is tucked up under the base of the tongue and may be difficult to expose. This condition is often called *anterior larynx*.
- *Mallampati score.* Mallampati determined that the degree to which the posterior oropharyngeal structures are visible is loosely associated with intubation success (12). He had patients sit on the side of the bed, open their mouths as widely as possible, and protrude their tongues as far as possible, without phonating. Figure 1.2 depicts how the scale is constructed. Although classes I and II patients are associated with low intubation failure rates, the importance with respect to the wisdom of using neuromuscular blockade rests with those patients in classes III and IV, particularly those in class IV where intubation failure rates may exceed 10%. By itself, the scale is neither sensitive nor specific; however, it is easily performed in an emergency and may reveal important information about access to the oral cavity and the potential for difficult glottic visualization.

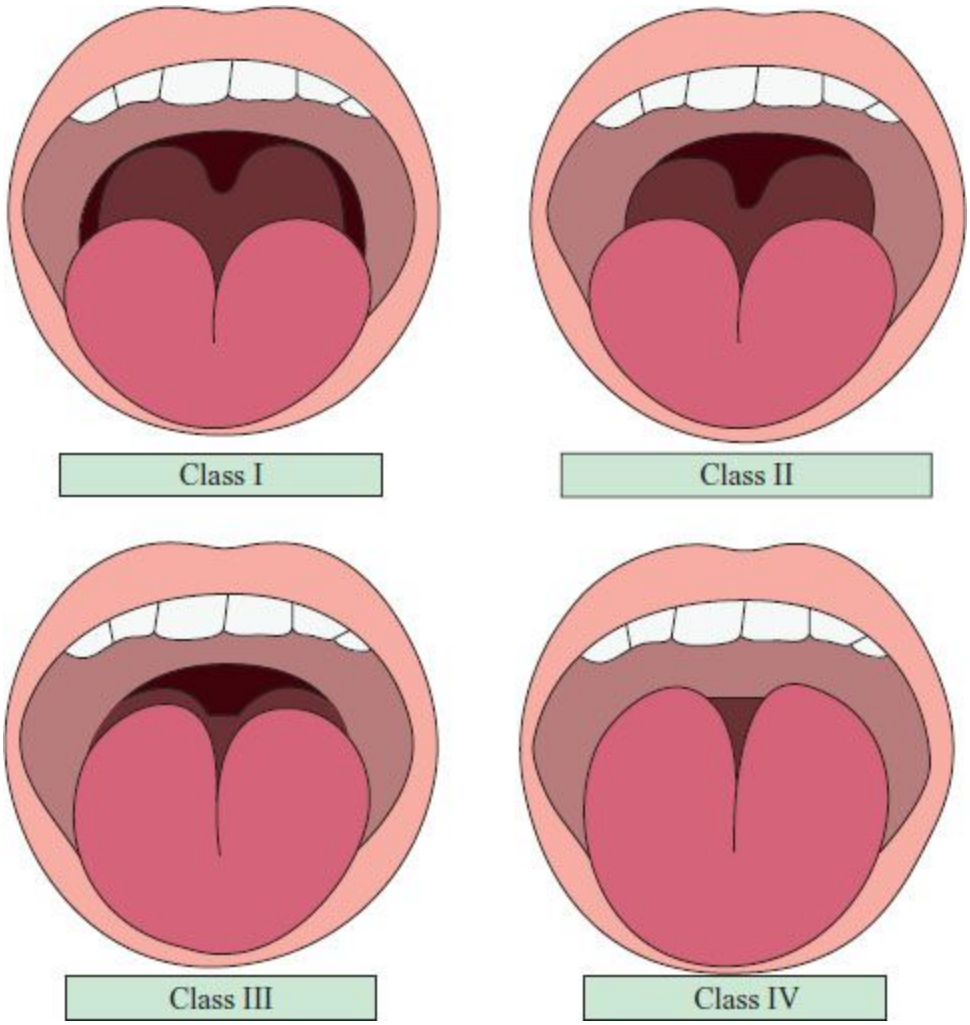

FIGURE 1.2 Mallampati score.

- *Obstruction.* Upper airway obstruction is always a difficult airway. The four cardinal signs of upper airway obstruction are muffled voice ("hot potato voice"), difficulty swallowing secretions (either because of pain or obstruction), dyspnea, and stridor. The first two signs do not ordinarily herald imminent total upper airway obstruction; dyspnea and stridor are much more sinister. The presence of stridor generally indicates that the airway has been reduced to 4.5 mm or less (13). Upper airway obstruction should always be managed with extreme care. The administration of small doses of opioids and benzodiazepines to manage anxiety may induce total obstruction due to diminished upper airway musculature tone.

- *Neck mobility.* The ability to position the head and neck is one of the factors employed to achieve an optimal view of the larynx. Although cervical spine immobilization, of and by itself, does not automatically lead to one, it should be considered in addition to other features indicating difficulty.

Difficult Cricothyrotomy

There are no absolute contraindications to performing an emergency cricothyrotomy. However, some conditions may make it difficult or impossible to perform the procedure. It is imperative to identify those conditions up front, particularly if one is relying on a rapidly performed cricothyrotomy as a rescue technique. The mnemonic SMART (Table 1.1) is used to quickly assess the patient for features that may indicate a difficult cricothyrotomy.

- *Surgery—Recent or remote:* The anatomy may be distorted making the airway difficult to find or access.
- *Mass:* A hematoma or infective process in the direct path of the cricothyrotomy produces a mass effect that may make the procedure technically difficult, but should never be considered a contraindication in a life-threatening situation.
- *Access or anatomy:* Obesity should be considered a surrogate for any problem that makes percutaneous access to the anterior neck problematic. A fixed flexion deformity of the cervical spine and halo traction make cricothyrotomy more difficult.
- *Radiation:* Past radiation therapy may distort tissues, making the procedure difficult.
- *Tumor:* Tumor in or around the airway may present difficulty from an access perspective as well as from bleeding.

No single indicator, combination of indicators, or weighted scoring system of indicators can be relied on to assure success or predict failure when it comes to oral intubation. Thus, emergency physicians must evaluate the airway for difficulty, identify those factors known to increase the degree of difficulty, match them to the skill, experience, and judgment of the individual performing the intubation, and make the following decision: Does this airway meet

the threshold of being sufficiently difficult to warrant using the difficult airway algorithm or is it safe to proceed directly to RSI?

RAPID SEQUENCE INTUBATION

"RSI is the administration, after preoxygenation, of a potent induction agent followed immediately by a rapidly acting neuromuscular blocking agent (NMBA) to induce unconsciousness and motor paralysis for tracheal intubation" (14). Attenuating the adverse responses to intubation, maintaining adequate oxygen saturations, and protecting the airway from aspiration are integral to the procedure.

The adage in anesthesia with respect to neuromuscular blockade to facilitate the orotracheal intubation of a patient who has some effective spontaneous ventilation has always been "don't take anything away from the patient that you cannot replace." Although such a rigid principle is not always consistent with the realities of emergency airway management, it is useful to remember.

The use of NMBAs assumes that the operator is entirely versed in BMV, the use of extraglottic rescue devices, airway evaluation for difficulty, and the performance of a surgical airway.

Walls and Murphy (14) have referred to the steps of RSI as the "Seven P's of RSI." It is a useful framework for discussing the procedure.

- *Preparation.* Establish IV access, place the patient on a cardiac monitor and pulse oximetry, and prepare intubation equipment.
- *Preoxygenation.* This is a crucial step, permitting oxygen saturations to remain acceptable during the period of apnea as the NMBA becomes fully effective. The goal is to replace the nitrogen in the patient's functional residual capacity (FRC, normally 30 mL/kg) with oxygen. The ability to do so varies with the time available, the ability of the oxygen delivery apparatus to deliver the high concentrations of oxygen used, and the patient's condition.
- *Pretreatment.* The goal of pretreatment is to attenuate the adverse responses to intubation, particularly the surges in heart

rate, blood pressure, ICP, and airway resistance. Ideally, the pretreatment medications ought to precede the induction agent by 3 minutes to be optimally effective. Not all patients are equally at risk from these responses. Based on the best available evidence and expert recommendations at least the following patients should be pretreated (15).

- Those suspected of having elevated ICP and imperfect autoregulation may benefit from lidocaine 1.5 mg/kg and fentanyl 3 to 13 μ/kg (ordinarily 3 to 5 μ/kg). In addition, a defasciculating dose of a nondepolarizing paralytic decreases fasciculations and reduces ICP. It has been taught that typically 1/10 of the intubating dose of any available paralytic agent will achieve this.
- Those with significant ischemic heart disease or major vessel dissection or rupture may benefit from fentanyl 3 to 13 &b.mu;/kg (ordinarily 3 to 5 &b.mu;/kg). Caution ought to be exercised in administering fentanyl to patients with compensated or uncompensated shock.
- Adults with significant existing reactive airway disease may benefit from lidocaine 1.5 mg/kg.
- Children up to the age of 10 years, or any patient with hemodynamically significant bradycardia and receiving succinylcholine may receive atropine 0.01 to 0.02 mg/kg (minimum 0.1 mg; maximum 0.5 mg). This recommendation is currently considered to be controversial and the administration of atropine is optional.

- *Paralysis with induction.* Induction and paralytic agents are rapidly administered intravenously. Induction agents have profound effects on all three vital organ systems: The CNS, cardiovascular system, and ventilation. These effects depend on the particular drug, the patient's underlying physiologic condition, and the dose and speed of injection of the drug. Because RSI requires rapid administration of the sedative induction agent, the choice of drug and the dose must be tailored to capitalize on desired effects, while minimizing adverse side effects (Table 1.2). In some cases, an amnestic dose

may be selected, rather than an induction dose. While the sedative induction dose might be tailored, the dose of the NMBA is not (e.g., succinylcholine 1 to 2 mg/kg; rocuronium 1 to 1.5 mg/kg).

- *Protection and positioning.* Though controversial, the use of cricoid pressure, or the Sellick maneuver, to prevent regurgitation and aspiration is maintained until proper placement of the endotracheal tube (ETT) is confirmed. Premature release of cricoid pressure is a common error and may place the patient at risk of aspiration, particularly if an inadvertent esophageal intubation has occurred. Cricoid pressure must be released immediately should active vomiting occur; otherwise, there is danger of esophageal rupture. Most experts on airway management agree that positioning the head and neck is an important step in gaining the best view of the larynx with conventional laryngoscopy. It has long been taught that the "sniffing the morning air" or "sipping English tea" positioning of the head and neck, when possible, is best. Although there is some dissension as to whether this positioning does indeed deliver the best view of the larynx, most agree that it is a reasonable place to start (16).
- *Placement and proof.* The tube is passed through the laryngeal cords. Proper ETT placement is confirmed and proven using physical examination as well as devices such as the end-tidal CO_2 detector.
- *Postintubation management* (PIM). The tube should be secured using commercially available devices or basic tape to prevent accidental extubation. If tape is used, then a "bite block" or oral airway should also be placed to avoid accidental cutting of the tube should the patient bite down. A postintubation chest radiograph is the standard practice to confirm placement of the tube and assess the depth of intubation. Finally, postintubation sedation with or without paralytics should be provided.

TABLE 1.2
Induction Agents and Dosage Selection

Induction Agent (mg/kg)	Stable Patient	Unstable Patient	Very Unstable Patient[a]
Etomidate	0.3	0.15–0.2	0.1
Propofol	1	0.5	0
Midazolam	0.3	0.1	0.01–0.02
Pentothal	3	1.5	0
Ketamine	1.5	1	0.5

[a]The recommended doses are empiric and intended to produce amnesia in patients who are severely ill. Some practitioners may elect to administer none of these agents in this situation.

APPROACH TO THE AIRWAY: HOW TO PROCEED

Once one has decided that intubation is indicated, one progresses rapidly to identifying exactly what kind of airway the patient has and how the practitioner will proceed:

- Is this a "crash" airway where the patient is unconscious, unresponsive, and near death (17)?
- Is this a difficult airway where one anticipates difficulty with BMV, laryngoscopy and intubation, EGD rescue, or cricothyrotomy?
- If neither of these exists, RSI is reasonable.
- Has a failed airway supervened?

This systematic approach to airway management in the emergency department encompasses all possible presentations. Identifying the type of airway to be managed permits the practitioner to select an appropriate course of action. Algorithms are presented below for each of these clinical presentations. Figure 1.3 depicts this conceptual framework (17).

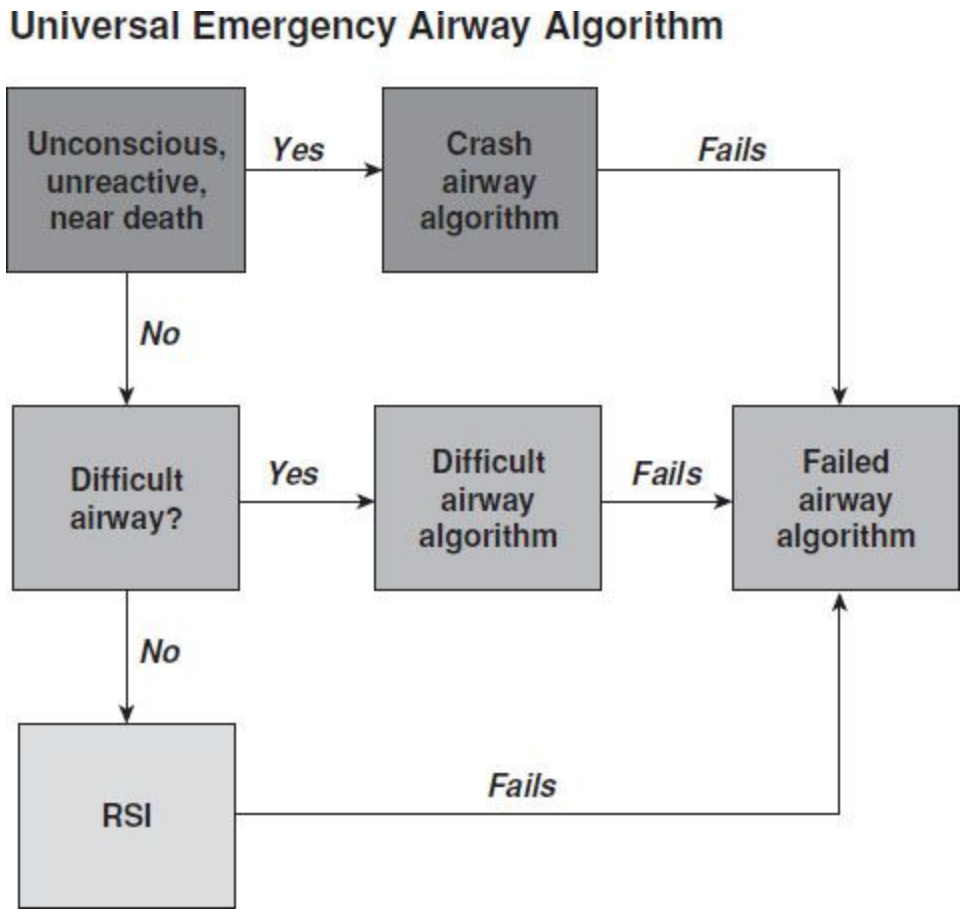

FIGURE 1.3 Universal emergency airway algorithm.

Crash Airway Algorithm

The patient who presents in an unresponsive state or is deemed unlikely to respond in any way to direct laryngoscopy is said to have a crash airway, and the crash airway algorithm (Fig. 1.4) is employed (17). Noteworthy points in the crash airway algorithm include the following.

- BMV is occurring as preparations are made to intubate.
- The initial action is to attempt oral intubation immediately via direct laryngoscopy without pharmacologic assist.
- If the first attempt at orotracheal intubation is unsuccessful, it is assumed that the patient is not optimally relaxed, and succinylcholine is administered in an increased dose.
- If BMV is unsuccessful at any time and if intubation has failed, a failed airway is present, and one proceeds to the failed airway

algorithm (Fig. 1.5).

- Once three attempts have failed, one proceeds to the failed airway algorithm (Fig. 1.5).

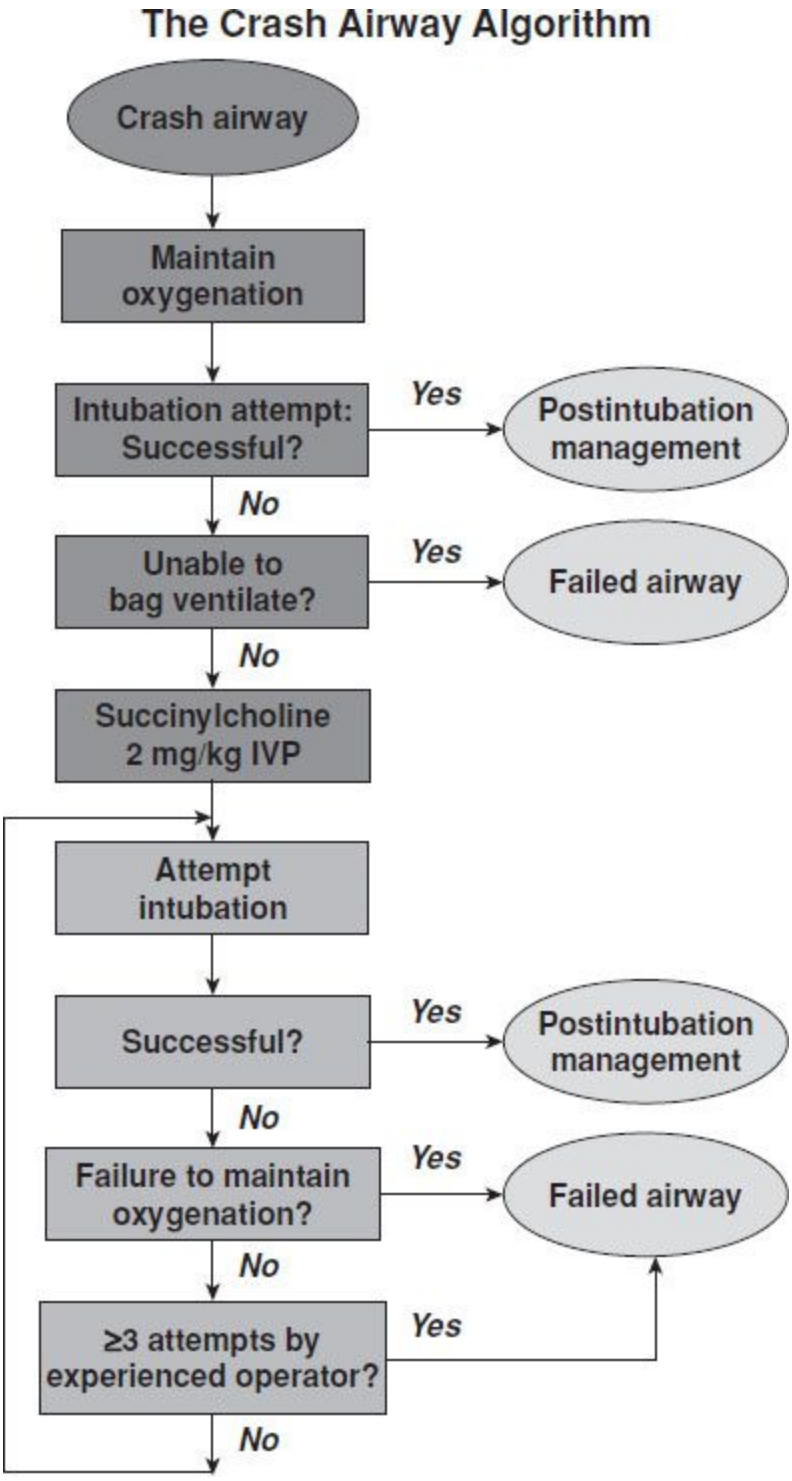

FIGURE 1.4 The crash airway algorithm.

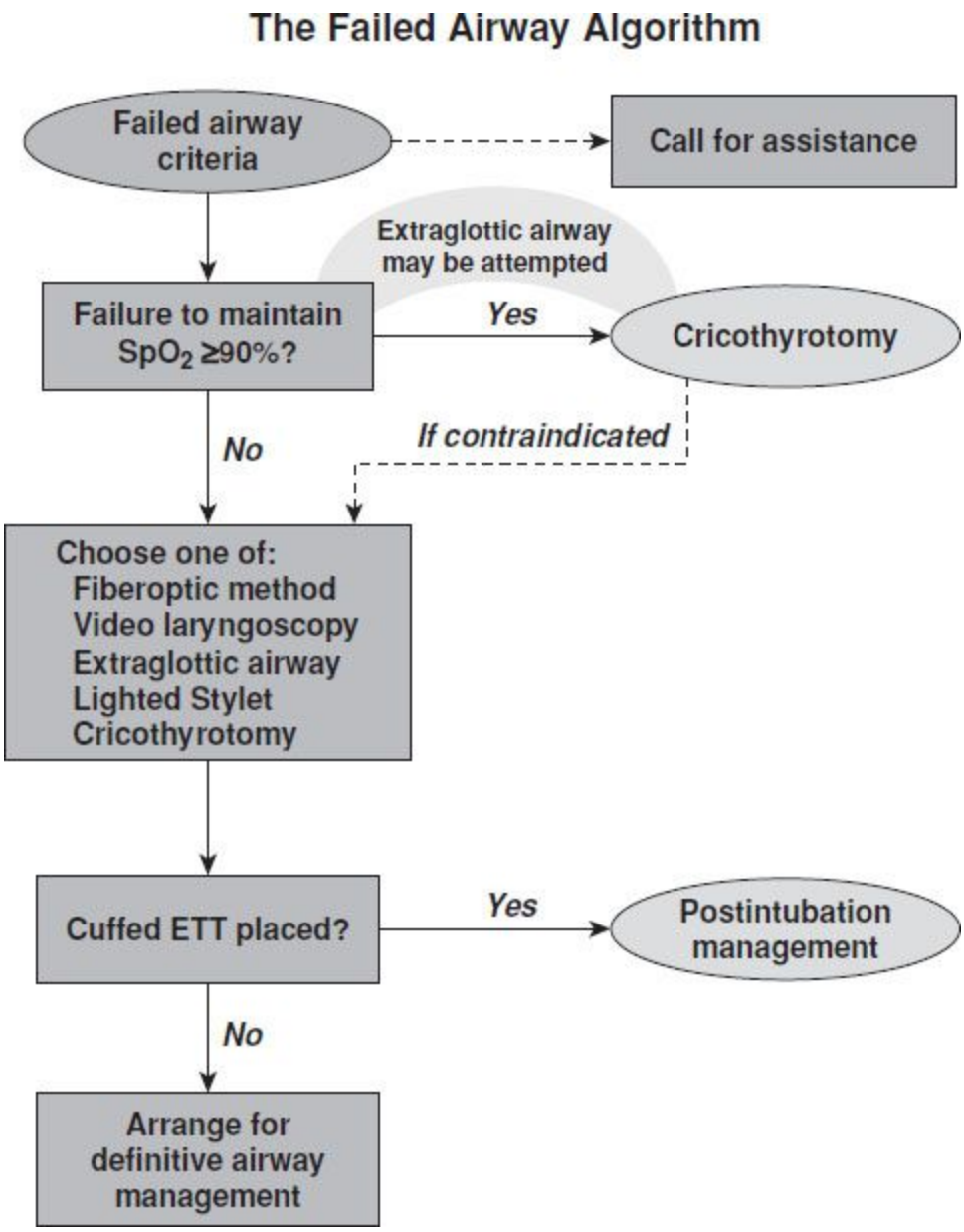

FIGURE 1.5 The failed airway algorithm.

Difficult Airway Algorithm

Should the situation not be a crash airway, one must determine whether it is a difficult airway. Although all emergency intubations are difficult to some degree, the evaluation of the airway for those features that reliably predict difficult BMV, difficult laryngoscopy, difficult EGD rescue, or difficult cricothyrotomy is extremely important. In the event the airway is judged to be difficult, the

difficult airway algorithm (Fig. 1.6) is used (17). The evaluation for difficulty is presented in the next section.

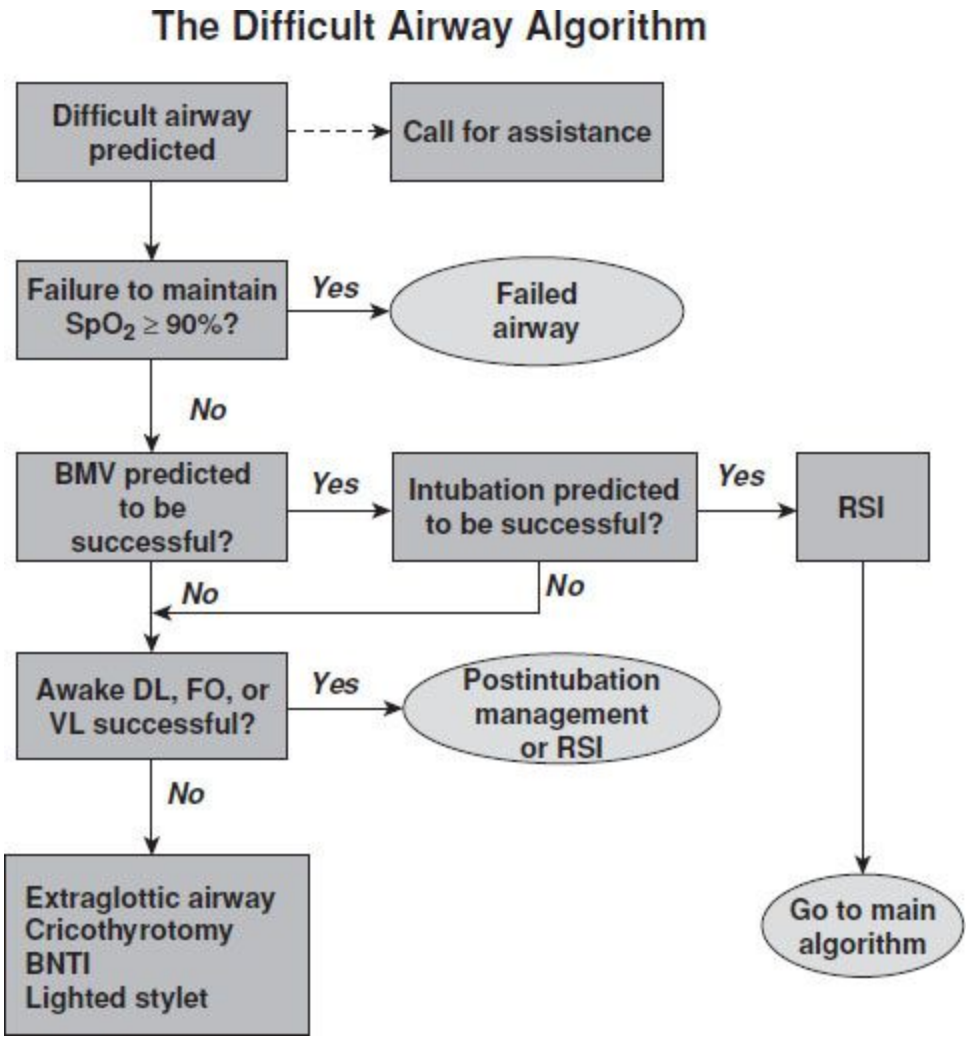

FIGURE 1.6 The difficult airway algorithm.

Noteworthy points in the difficult airway algorithm include the following:

- This iteration of the difficult airway algorithm recognizes that the emergency physician may be forced to act before a detailed evaluation of the airway can be performed. RSI is recommended, though this action must be accompanied by preparations to perform a surgical airway ("double set up") and to ensure the immediate availability of an EGD in the event of failure (18).

- Determine how much time is available. If ventilation and oxygenation are adequate, then a careful assessment and a planned approach can be undertaken. If not, does BMV provide adequate ventilation and oxygenation? If not, the situation is equivalent to a "can't intubate; can't oxygenate" failed airway, and one proceeds to the failed airway algorithm (Fig. 1.5) (17).
- If the patient can be adequately oxygenated, the next step is to consider RSI. If BMV or gas exchange rescue with EGD are deemed unlikely to succeed or if success at laryngoscopy and intubation is felt to be questionable, RSI is not recommended.
- Awake laryngoscopy is the cornerstone of difficult airway management. An "awake look" is intended to either intubate the nonparalyzed patient orally or identify whether the patient can be safely paralyzed and intubated using an RSI technique. An awake look in an emergency airway situation relies virtually entirely on the intravenous titration of systemically active sedation and topical anesthesia.
- If at any time oxygenation and ventilation become inadequate, the situation has become a failed airway. If oxygenation remains adequate, several options remain, all of which place a cuffed (in adults) ETT in the trachea.

In the absence of an identified crash or difficult airway, RSI is the method of choice for airway management in the emergency department.

Failed Airway Algorithm

The failed airway is easily defined as follows:

1. Three failed attempts at orotracheal intubation by a skilled intubator, or
2. Failure to maintain acceptable oxygen saturations.

The practical problem in day-to-day practice is recognizing failure when it occurs and changing gears rapidly to deal with it appropriately. Clinically, the failed airway presents itself in two ways.

1. Time is available: "Can't intubate; *can* oxygenate."

2. Immediate action is required: "Can't intubate; *can't* oxygenate."

Noteworthy points in the failed airway algorithm (Fig. 1.5) include the following (17):

- Unlike the difficult airway, when the placement of a cuffed tube in the trachea is the goal, the failed airway calls for immediate action to provide emergency oxygenation by whatever appropriate maneuvers are available, regardless of whether this action results in a secure, protected airway. The devices considered for the failed airway are somewhat different from, but inclusive of, the devices used for the difficult airway.
- When a failed airway has been determined to be present, the response is dictated by whether BMV is possible and adequate.
- A "can't intubate; *can't* oxygenate" situation mandates immediate cricothyrotomy. The airway manager may elect to attempt to rapidly place an alternative device, usually an EGD (17,19), simultaneously with the preparation for a cricothyrotomy, in the hope that a "can't intubate; *can't* oxygenate" situation can be converted into a "can't intubate; *can* oxygenate" situation.
- If at any time during the management of the failed airway adequate oxygenation and ventilation cannot be assured, immediate performance of a cricothyrotomy is mandated.

RESCUE DEVICES

Airway rescue devices can be divided into the following two groups, depending on the situation.

- "Can't intubate; *can't* oxygenate." Cricothyrotomy is the standard method of airway management in this situation. However, devices that can be inserted rapidly and are associated with high success rates include the Combitube and the intubating laryngeal mask airway (Fastrack). The advantage of the Fastrack compared to the Combitube is the ability to intubate through the Fastrack.
- "Can't intubate; *can* oxygenate." Videolaryngoscopes, flexible and rigid endoscopic devices, and nasotracheal intubation

require time to perform and are inappropriate in an emergency situation where ventilation and oxygenation must not be delayed.

SELLICK MANEUVER

Brian Sellick introduced cricoid pressure in 1961 as a protective measure, reasoning that backward pressure on the cricoid cartilage would occlude the upper esophagus and further reduce the incidence of aspiration. With widespread use of the technique in all arenas of airway management by the late 1980s, it assumed the status of “Standard of Care” in emergency patients and others at risk of aspiration.

However, scientific evidence that the maneuver actually reduces the incidence of aspiration remains lacking due to the rarity of clinically evident or significant aspiration, and it will likely remain that way. In the meantime, investigators have shown that the esophagus is not entirely obstructed by the Sellick maneuver. In addition, the maneuver is often not performed correctly, it attenuates lower esophageal sphincter tone, and it hinders placement of and ventilation through an LMA. It has also been found to produce partial or total airway obstruction that may hinder mask ventilation and ETI. Furthermore, cricoid pressure may lend a false sense of security if done incorrectly and some anesthetists have seen regurgitation in spite of its application. Three reviews on rapid sequence induction and cricoid pressure have pointed out that there have been no randomized controlled trials comparing the incidence of regurgitation on induction with and without cricoid pressure in patients at high risk of regurgitation (20).

On the positive side, there is evidence that the position of the esophagus during cricoid pressure is irrelevant, as the maneuver leads to compression of the upper esophagus and hypopharynx, providing some degree of protection from the passage of alimentary tract contents into the hypopharynx (21).

CONFIRMATION TECHNIQUES

Endoscopic bronchoscopy remains the gold standard of verifying correct ETT placement by permitting direct visualization of tracheal rings. Visualization of the ETT entering the larynx also provides a highly reliable method of verifying intratracheal placement. Detection of expired carbon dioxide provides reliable evidence of tracheal rather than esophageal intubation and is the standard of care in emergency medicine. In nonarrested patients, carbon dioxide detection is highly reliable, indicating correct placement 99% to 100% of the time (22). Soft drinks in the stomach that contain carbon dioxide may mimic the exhaled carbon dioxide from the lungs for a couple of breaths, the so-called “cola complication,” although this confounding result ought not to persist beyond six breaths.

The migration of an ETT from the trachea to the esophagus during the tosses and turns of transport is an ever present hazard. It has been demonstrated that the continuous monitoring of exhaled carbon dioxide during the prehospital phase of care minimizes the risk of such displacement going unrecognized (23).

As might be expected, carbon dioxide detection techniques tend to be less accurate in identifying correct placement of the ETT in patients with circulatory arrest, with reported false-negative rates (carbon dioxide not detected, tube in the trachea) as high as 30% to 35% (24). In this circumstance, the endotracheal placement of the tube can be evaluated by an esophageal detector device (EDD) that consists of a self-inflating suction bulb or syringe armed with an adapter to fit a standard ETT connector. The collapsed bulb or syringe rapidly fills with air if the ETT is in the trachea; it does not inflate if the tube is in the esophagus, with a specificity of approximately 99%. Use of this device instead of carbon dioxide detection is not recommended because of its failure to detect esophageal intubation in as many as 20% of cases (24).

Physical examination techniques used to confirm intratracheal placement of an ETT, although neither sensitive nor specific, remain important adjuncts to more elaborate techniques, particularly in the cardiopulmonary arrested patient. Auscultation of the chest for breath sounds and of the epigastrium for absence of air entry into

the stomach, observation of chest motion during ventilation, and condensation inside the ETT during exhalation are common, but notoriously unreliable, methods of ascertaining proper ETT placement.

In summary, although carbon dioxide detection remains the most reliable method of verifying tracheal placement of the ETT in prehospital care, the incorporation of multiple methods of confirmation is superior to any single method.

SUMMARY

RSI by emergency practitioners is associated with high success rates and low complication rates. The challenge is to recognize those patients who should not be paralyzed and to develop alternative skills to successfully manage those airways. There is no "recipe" of RSI pretreatment and induction medications that can be applied in every case. A careful assessment of risk and benefit is required in each patient to select the appropriate medication and its dose. An array of airway management skills is required to appropriately manage difficult airways and rescue failed airways.

CRITICAL INTERVENTIONS

- Evaluate the airway prior to airway intervention
- Preoxygenate patients prior to RSI
- Perform cricothyrotomy or insert ILMA in patients who cannot be ventilated or intubated
- Know when not to paralyze a patient
- Recognize airway management failure immediately

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CHAPTER 2 Airway Procedures

Eric F. Reichman

Airway management is one of the most basic, crucial, and important aspects of emergency medicine. Without oxygen, the brain begins to die within minutes. The mission for airway management is to ensure airway patency, to protect the airway from contamination (blood, fluids, and/or food), to provide supplemental oxygen, and to institute positive pressure ventilation when spontaneous respirations are inadequate or absent. Airway management can be as simple as lifting a snoring patient's chin or as involved as awake fiberoptic-guided endotracheal intubation.

A thorough understanding of anatomy is essential for the performance of any medical procedure. Untoward events related to a procedure are often the result of inexperience and/or an inadequate understanding of the regional anatomy, and the airway procedures are no exception. From the evaluation of external anatomic landmarks to the performance of nerve blocks for fiberoptic intubation, understanding the anatomy of the airway will result in fewer attempts at intubation and improved success with fewer iatrogenic misadventures.

CLINICAL PRESENTATION

Airway intervention is required if there is uncertainty about whether the patient's airway patency, respiratory drive, or oxygenation can be maintained without intervention. Inadequate ventilation may occur for a variety of reasons. Spontaneously breathing patients may develop an airway obstruction caused by food, blood, secretions, or tissue obstruction as a result of the loss of the normal pharyngeal

tone. Unconscious patients should have their airway secured and receive mechanical ventilation. Despite spontaneous respiration, the unconscious patient is at risk for aspiration of gastric contents. The conscious patient with airway obstruction is in obvious distress and is more likely to have an obstruction caused by a foreign body, tissue swelling from an infection, laryngeal edema, cancer, or laryngospasm.

Endotracheal intubation can be performed to administer resuscitation medications, ensure a patent airway, deliver oxygen, isolate the airway, reduce the risk of aspiration of gastric or oral contents, suction the trachea, ventilate the patient, or apply positive pressure ventilation. Other indications include altered mental status, head injury requiring hyperventilation, hypoxemia, hypoventilation, apnea, lack of a gag reflex, and unconsciousness.

ED EVALUATION

Evaluation of the airway includes an internal and external examination. The internal examination should evaluate the patient's dentition, palate, and tongue. Note any protuberant incisors, loose teeth, broken teeth, dental work, and dental devices. Determine if the palate is normal, high and arched, or cleft. Determine if the tongue is elevated, larger, or wider than normal in comparison to the oral cavity. A common classification used by anesthesiologists to grade the difficulty of laryngoscopy and intubation involves the identification of the size the tongue in relation to the faucial pillars, the soft palate, and the uvula (1). External evaluation of the airway is a critical step to a successful intubation. External inspection should include mouth opening, atlantooccipital extension, and thyromental distance. External inspection should also identify obvious problems (e.g., cervical collars, face and/or neck trauma, severe micrognathia, massive obesity, etc.). Please refer to Chapter 1 for a more detailed discussion of this topic.

There are numerous differences between the adult's and the child's airway (2). The head-to-body ratio is larger in the child, which results in neck flexion when the child is supine. Placing a rolled towel under the child's shoulders will correct the flexion. Children

have a small mouth with a relatively large tongue when compared to an adult, making orotracheal intubation difficult. The presence of adenoidal tissue in the child makes nasotracheal intubation difficult and orotracheal intubation the preferred method. The most important difference is that the narrowest portion of the infant and child's airway is below the vocal cords at the cricoid cartilage. In an adult, the narrowest point is at the level of the vocal cords. An endotracheal tube (ETT) may pass through the vocal cords of a young child but might not advance past the cricoid cartilage because of normal anatomy. Forcing an ETT past the vocal cords might result in trauma to the airway and subsequent tracheal stenosis. The child's laryngeal inlet is narrow and more susceptible to obstruction. The U-shaped epiglottis and a more acute angle between the epiglottis and glottis cause the aryepiglottic folds to be more midline. Children have a relatively shorter trachea, making both right main bronchial intubation and accidental extubation much easier. The narrower diameter of the trachea with smaller spaces between the cartilaginous rings makes a tracheostomy more difficult to perform.

Traditional teaching holds that cuffed ETTs increase the risk of ischemic damage to the tracheal mucosa due to compression between the cuff and the cartilaginous rings. This resulted in the old mandate to use uncuffed ETTs in children younger than 8 years of age. There have been numerous advances in modern ETTs that are changing this orthodoxy (3). Current American Heart Association guidelines now recommend, but do not require, a cuffed ETT for children older than 28 days of age. In the first 28 days of life, the cricoid narrowing functions as a cuff. For children over 28 days of age, the cuffed ETT is just as safe as an uncuffed ETT. The high volume, low pressure cuffs found on currently available ETTs allow the cuff to produce a seal at much lower pressures. The use of cuffed ETTs is becoming more common in pediatric ICUs and emergency departments. Several studies have shown no increase in postintubation stridor or reintubation when cuffed ETTs are used in controlled settings with regular cuff pressure monitoring.

ED MANAGEMENT

Basic Airway Management

Basic airway management is a fundamental skill that must be mastered by all caregivers. With an oxygen source, a means to deliver positive pressure ventilation, attention to detail in positioning, and the use of airway adjuncts, it is usually possible to prevent hypoxia and hypercarbia in the apneic patient.

Patient Positioning

The first goal of airway management is the establishment of a patent airway. The importance of proper positioning cannot be overemphasized. The success of airway management is predicated on this very basic, but often overlooked, issue. Placing the patient in the "sniffing" position may correct many upper airway obstructions because of soft tissue impingement. The "sniffing" position is achieved by flexing the cervical spine approximately 15 degrees and extending the atlantooccipital joint maximally. This position can also be achieved with the chin-lift or jaw-thrust maneuvers. If the patient is obese or has large breasts, the normal sniffing position is often insufficient for relieving an airway obstruction. A ramp or shoulder roll placed under the upper back will result in the "sniffing" position.

Jaw-Thrust Maneuver

The jaw thrust is one of the most basic maneuvers and an initial method of establishing a patent airway. The jaw-thrust maneuver is a two-handed technique. The operator is positioned at the head of the patient and places his or her fingers on the angles of the mandible bilaterally, displacing it anteriorly (Fig. 2.1). A face mask may be simultaneously held in place with the operator's thumbs and index fingers.

FIGURE 2.1 The jaw-thrust maneuver. (From Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013, with permission.)

Chin-Lift Maneuver

The chin lift is also one of the most basic maneuvers to establish a patent airway. The chin lift is performed by placing the fingers under the tip of the mandible and lifting the chin in an anterior and cephalic direction (Fig. 2.2). Do not place the fingers on the soft tissue of the submandibular space, because this will elevate the tongue and cause further obstruction. The patient's head may be tilted slightly posterior to aid in opening the airway.

FIGURE 2.2 The chin-lift maneuver. (From Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013, with permission.)

Nasopharyngeal Airways

In addition to proper positioning, one can use various aids to overcome pharyngeal obstruction and facilitate effective ventilation (4). The most commonly used devices are oropharyngeal (oral) and nasopharyngeal (nasal) airways. Regardless of which device is chosen, it is important to place a large-enough airway to bridge the area of soft tissue impingement on the pharynx. Nasopharyngeal airways are soft-rubber or plastic tubes that are inserted through the nostril and into the oropharynx, just above the epiglottis. They are available in numerous sizes; the larger inner diameter is associated with the longer tubes. A size 30- to 32-French tube is appropriate for most adults. Nasopharyngeal airways can be safely placed in the conscious, semiconscious, and unconscious patients. They can also be used when an oropharyngeal airway cannot be placed (e.g., in cases of oral trauma, braces, seizures, trismus, etc.).

Insertion of a nasopharyngeal airway is a quick and rapid procedure. Choose the proper size nasopharyngeal airway. The

correct size is estimated by placing the airway next to the patient's face. Place the flared end of the airway near the tip of the patient's nose. The airway's tip should be at the external auditory canal. Liberally apply water-soluble lubricant or anesthetic jelly to the nasopharyngeal airway. If not contraindicated, apply a vasoconstrictor to the patient's nasal mucosa. Gently insert the nasopharyngeal airway with the beveled tip against the nasal septum to prevent it from getting caught on the turbinates laterally. Insert the airway completely until the flared tip is against the nostril, and rotate it 90 degrees so that it is concave upward. Slight rotation often facilitates the passage of the airway if resistance is encountered during insertion. Supplementary oxygen or positive pressure ventilation with a bag-valve-mask device can be started after the insertion of the airway.

Insertion of a nasopharyngeal airway is associated with complications. If too long, the airway may cause laryngospasm and vomiting. The airway may also be placed with its tip in the esophagus, resulting in gastric distention and subsequent aspiration. Nasal mucosal injury upon insertion can result in epistaxis and aspiration of blood.

Oropharyngeal Airways

The oropharyngeal airway is a semicircular plastic device that holds the tongue up and away from the posterior pharyngeal wall. The oropharyngeal airway is less traumatic and more easily placed than a nasopharyngeal airway. An oropharyngeal airway must only be used in an unconscious patient, or it may cause laryngospasm and vomiting. An 8-, 9-, or 10-cm oral airway is appropriate for most adults.

Insertion of the oropharyngeal airway is a quick and simple procedure. Choose the proper size of oropharyngeal airway. The correct size is estimated by placing the airway next to the patient's mouth. The distal tip should lie just above the angle of the mandible. Clear the mouth and oropharynx of any blood, secretions, or vomit. Open the patient's jaw, and separate the teeth. Insert the oropharyngeal airway curved side down. The tip will slide along the

palate. After insertion, rotate the airway 180 degrees so that the curve of the oropharyngeal airway follows the curvature of the tongue. An alternative method is to use a tongue blade to depress the tongue and then insert the oropharyngeal airway as above. If the tongue blade is used, the oropharyngeal airway may also be inserted with the curve side upward. Supplementary oxygen or positive pressure ventilation with a bag-valve-mask device can be started after the insertion of the airway.

Insertion of an oropharyngeal airway is not a benign procedure. The airway can push the tongue posteriorly and further obstruct the oropharynx if not inserted properly. Significant lacerations can occur if the lips or tongue are caught between the teeth and the oral airway. The airway can force the epiglottis closed against the vocal cords if it is too long, resulting in complete airway obstruction. Too small an airway will force the tongue against the pharynx, producing an obstruction.

Mask Ventilation

Once mastered, expertise with bag-mask ventilation (BMV) allays the urgency to intubate and permits one to rescue a failed intubation. BMV is a prerequisite to the use of neuromuscular blocking agents to facilitate intubation. Provided one takes steps to minimize the risks of gastric aspiration, BMV for prolonged periods is not unreasonable if intubation is not possible.

Face masks are made of clear plastic, have a soft seal, and have an anatomic shape that conforms to the contours of the patient's face. Typical adult sizes are 3, 4, or 5. The size must be large enough to completely cover the nose and mouth but not be so large as to allow a leak. The key to effective mask ventilation is ensuring a continually patent airway. A patent airway is initially achieved by placing the patient in the "sniffing" position coupled with a combination of chin lift, jaw thrust, oral airway, or nasal airway. Neglecting this key maneuver results in using excessive positive pressure ventilation in an attempt to compensate for an obstructed upper airway. A bag-mask device can deliver 50 to 100 cm of water pressure to the upper airway with an adequate mask seal, which is more than sufficient

pressure to insufflate the stomach if the airway is not optimally opened.

There are two ways to properly hold a face mask (4). The one-handed technique is performed with the nondominant hand (Fig. 2.3). Place the little, ring, and middle fingers under the side of the patient's mandible. Place the index finger and thumb on the bottom and top portion of the mask. This technique allows the operator to simultaneously lift the mandible and extend the atlantooccipital joint while applying enough downward pressure to create an airtight seal. The dominant hand is used to ventilate the patient with the bag-valve device. The bag-valve device is used to provide positive pressure ventilation. The device consists of a self-inflating bag connected to oxygen on one end and a one-way (nonrebreathing) valve on the other. The valve is connected to the mask or other airway device to allow one-way flow of oxygen.

FIGURE 2.3 The one-handed, one-person, mask-ventilation technique. (From Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013, with permission.)

A two-handed, two-person technique may be necessary in patients with facial hair, are obese, are elderly, or are edentulous. Both of the operator's hands are applied to the face mask to aid in the creation of a tight seal and proper airway alignment (Fig. 2.4). Place the index, middle, ring, and small fingers of the left hand on the body of the left half of the mandible. Position the right hand similarly on the right half of the mandible. Place the face mask on the patient's face. Apply both thumbs to the mask, and apply pressure to create a seal. Anteriorly elevate the mandible to perform the jaw-thrust maneuver. The second person applies positive pressure through the bag-valve device.

FIGURE 2.4 The two-handed, two-person, mask-ventilation technique. (From Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013, with permission.)

A standard adult resuscitation bag is 1,500 mL. The goal is to deliver 500 to 600 mL of tidal volume at a rate of 24 breaths/min. Smaller devices are available for children, infants, and neonates. Typical ventilation volumes are 5 to 8 mL/kg per breath. Provided the airway is patent, significant insufflation of the stomach is unlikely. The cadence should be similar to the "squeeze …release … release" cadence recommended by advanced cardiac life support (ACLS) but at a slightly faster pace.

The specific type of bag employed in BMV is also important (4). Recent studies demonstrate that bags that minimize dead space, incorporate unidirectional air flow valves (e.g., “duck bill” inspiratory valves), and use one-way expiratory valves to prevent the entrainment of room air during inspiration will deliver 90% to 97% oxygen to spontaneously breathing or ventilated patients. This delivery is in sharp distinction to improperly configured bags that will provide high oxygen concentration during active bagging but deliver only 30% oxygen during spontaneous patient breathing as a result of the entrainment of room air.

Complications of Basic Airway Management

The most serious complication of basic airway management is aspiration of gastric contents, resulting in an acute chemical pneumonitis. It is a significant risk when airway management is needed emergently or routinely in the pregnant, trauma, diabetic, or obese patient. Less-serious complications include soft tissue trauma to the lips, tongue, oral cavity, and eyelids. Tooth fractures or avulsions are uncommon but possible. Facial nerve dysfunction caused by pressure effects of the mask is transient. Corneal abrasions, conjunctival chemosis, and increased intraocular pressure are common with masks that are too large.

Intubation

Orotracheal Intubation

Orotracheal intubation is both common and life-saving. Orotracheal intubation is the primary and preferred method of airway management that every emergency physician must master (3). With proper preparation, definitive control of the airway can be obtained. Airway control assures that the patient can be oxygenated and ventilated when the patient cannot do this on his or her own.

Orotracheal intubation is relatively contraindicated in patients who do not need it, who are likely to be injured by the procedure, whose injuries make success unlikely, or in whom less-invasive techniques may suffice. Intubation may be difficult in patients with likely cervical spine injuries, severe arthritis, severe orofacial

injuries, deep airway obstruction, gross deformities of the head and neck, or a quickly changing obstruction (edema or an expanding hematoma). Choose a surgical airway if the manipulation or time required for oral endotracheal intubation puts the patient at risk for spinal injury or hypoxia.

The evaluation, preparation, and technique for orotracheal intubation are complex and essential. Firmly grasp the laryngoscope in the left hand. Insert the tip of the laryngoscope blade into the right side of the patient's mouth. Smoothly advance the blade inward while keeping pressure against the tongue. Move the blade toward the midline to trap and push the tongue to the left, "clearing a path" for your gaze.

Lift the patient's airway up and forward exactly along the long axis of the laryngoscope handle (Fig. 2.5). Do not "cock" or "crank back" on the laryngoscope handle with the wrist, or the back of the laryngoscope blade may break the maxillary incisors. If intubating with the curved Macintosh blade, advance the tip into the vallecula, lift the laryngoscope handle to raise the tongue–jaw–epiglottis unit (Fig. 2.5), visualize the vocal cords, and insert the ETT. If intubating with the straight Miller blade, insert the blade completely, lift the laryngoscope handle to raise the tongue–jaw–epiglottis unit (Fig. 2.6), visualize the vocal cords and airway, and insert the ETT. Advance the ETT until the cuff passes through the vocal cords and 2 to 3 cm into the trachea. Inflate the cuff, assess for proper placement, and secure the ETT in place.

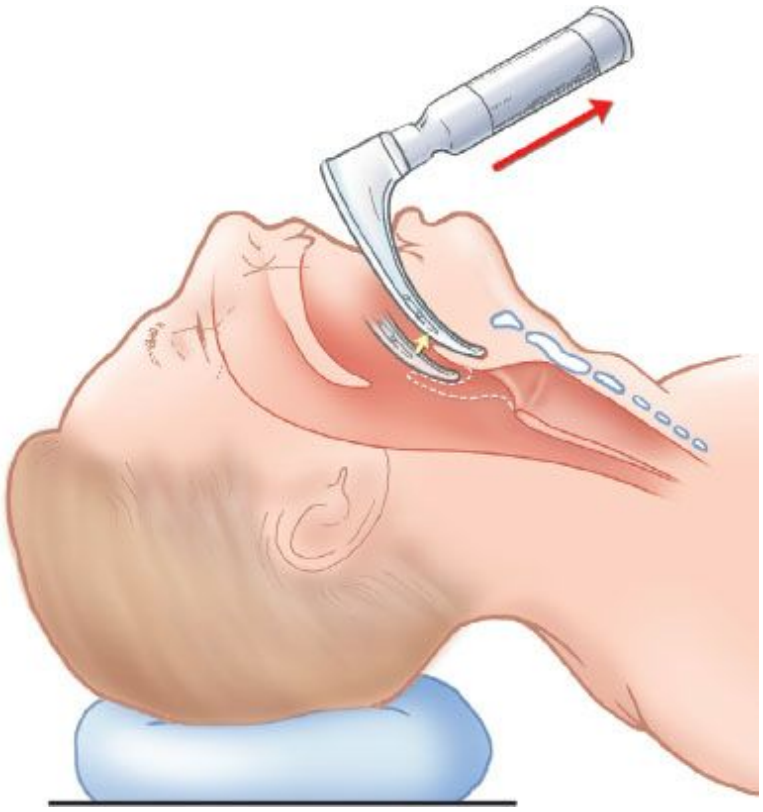

FIGURE 2.5 Intubation with the Macintosh blade. The blade is inserted into the vallecula to elevate the mandible, tongue, and epiglottis as a unit. (From Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013, with permission.)

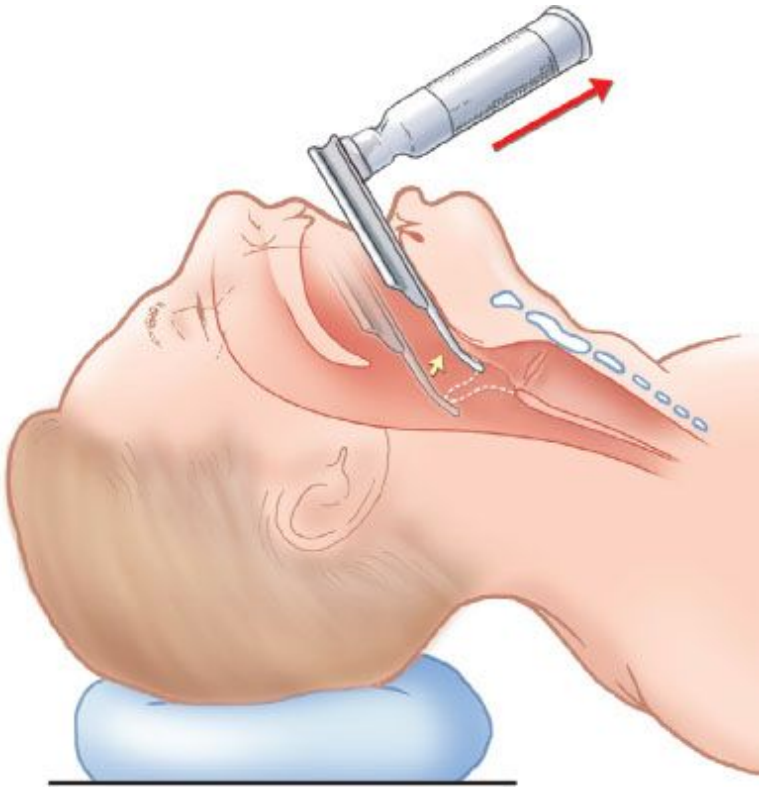

FIGURE 2.6 Intubation with the Miller blade. The blade is inserted into the vallecula to elevate the mandible, tongue, and epiglottis as a unit. (From Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013, with permission.)

Numerous complications are associated with orotracheal intubation (3). Hypoxia often results from prolonged intubation attempts and misplaced ETTs. Bradycardia can be produced by pharyngeal manipulation. Bradycardia may be especially pronounced in children because of their higher vagal tone. Pretreatment with atropine (0.02 mg/kg, with a minimum dose of 0.15 mg) in children younger than 6 years of age can prevent bradycardia. Increased intracranial pressure that is transient can occur as a result of the direct laryngoscopy. Direct mechanical complications from the laryngoscope include lacerations of the lips, trauma to the pharyngeal wall, broken teeth, or dentures that may be aspirated. Vomiting and aspiration can cause subsequent chemical and bacterial pneumonitis. Prolonged stimulation of the pharynx may cause apnea, bronchospasm, or laryngospasm.

Nasotracheal Intubation

Nasotracheal intubation is an alternative to orotracheal intubation to secure an airway in the spontaneously breathing patient (5). Nasotracheal intubation allows awake intubations while the patient maintains protective airway reflexes and avoids the risks of paralytic agents. It is a fairly simple procedure that should be considered in patients with spontaneous respirations in whom an oral airway is considered difficult and in those with an anticipated short intubation period. Nasotracheal intubation is well tolerated by most patients and produces less reflex salivation than orotracheal intubation, thus leading to fewer attempts of self-extubating.

Nasotracheal intubation is contraindicated in patients with apnea, with severe facial or maxillofacial fractures, with basilar skull fractures, with head injury and an elevated intracranial pressure, with nasal or nasopharyngeal obstruction, receiving thrombolytics, with a coagulopathy, or receiving parenteral anticoagulants. Nasotracheal intubation is also contraindicated in patients with neck injuries, as the procedure may increase morbidity and mortality. Nasotracheal intubation should not be performed in neonates, infants, and young children.

Prepare for the procedure. Apply a topical vasoconstrictor to shrink the nasal mucosa. Apply a topical anesthetic to the nasal mucosa. Dilate the nasal passage with your little finger or a series of increasingly larger size nasopharyngeal airways. Choose an ETT. The proper size tube should be at least 0.5 to 1 mm smaller than the size chosen for orotracheal intubation of the same patient.

Insert the ETT into the nostril with the bevel facing the septum (Fig. 2.7A). Advance the ETT with gentle pressure along the nasal floor to pass it through the nasal cavity (Fig. 2.7B). Continue advancing the ETT as resistance is met while it makes a 90-degree change of direction into the oropharynx. Advance the ETT through the oropharynx and into the laryngopharynx (Fig. 2.7C). Listen for breath sounds through the proximal end of the ETT while advancing it. As soon as an exhalation is heard, the patient will take a breath. Advance the ETT during inhalation. The vocal cords are opened their widest during inspiration, which facilitates passage of the ETT.

Inflate the cuff (Fig. 2.7D), begin ventilation, confirm proper positioning, and secure the ETT.

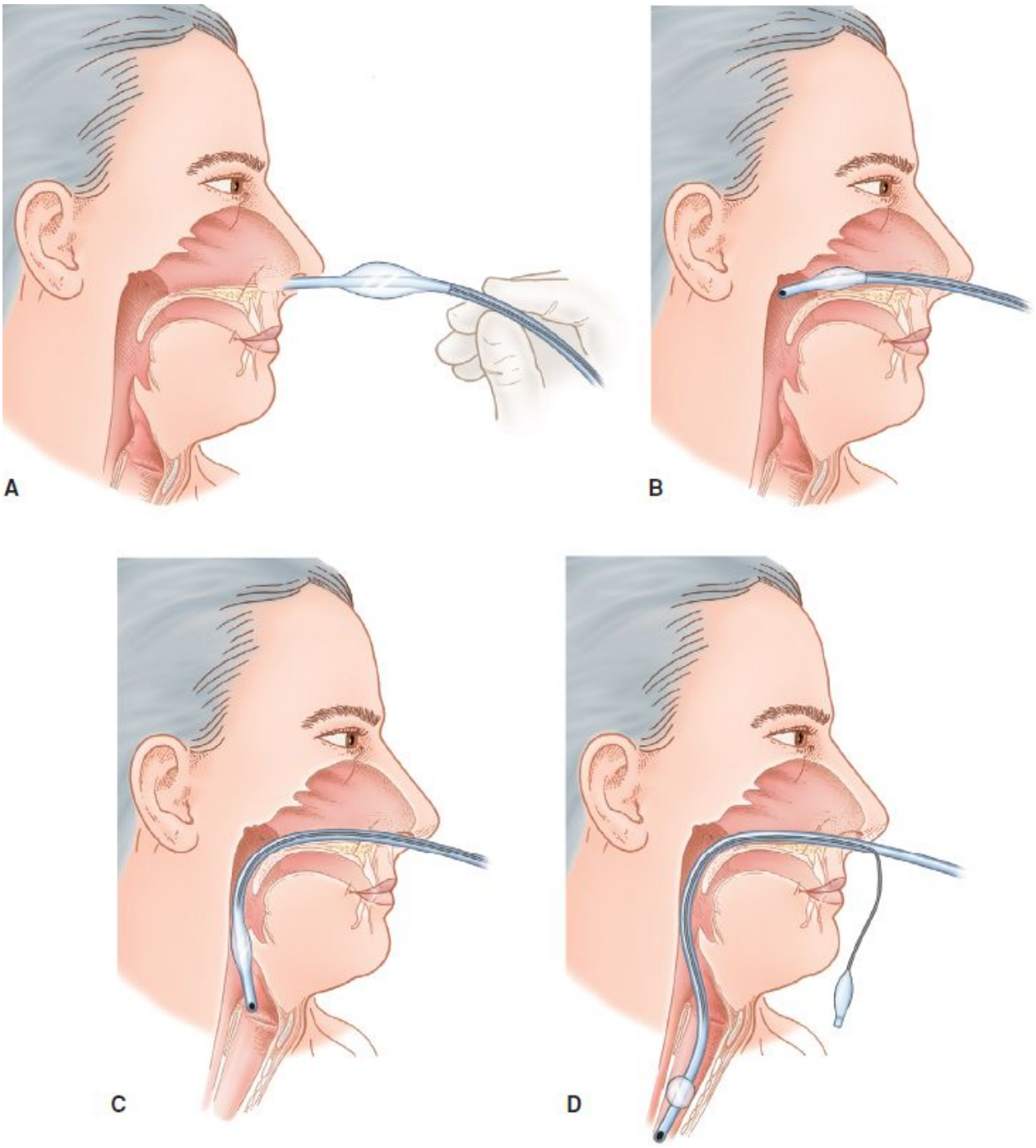

FIGURE 2.7 Nasotracheal intubation. (From Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013, with permission.)

The immediate complications of nasotracheal intubation include epistaxis, laryngeal and tracheal trauma, mucosal avulsion, retropharyngeal laceration, turbinate avulsion, intracranial placement, bacteremia, esophageal intubation, and prolonged attempts to place the ETT. Many of these complications can be prevented by choosing the appropriate-size ETT, facilitating nasal mucosal vasoconstriction, and applying lubricant to the ETT. Long-term complications include maxillary sinusitis, retropharyngeal abscess, mediastinitis, nasal mucosal necrosis, and cellulitis.

Digital (Tactile) Orotracheal Intubation

Digital (tactile) intubation is a viable alternative airway management technique with which every practitioner of emergency medicine should be familiar (6). Digital intubation is a rapid and safe method to intubate a patient. It is an ideal method for intubating a comatose or paralyzed patient if the patient's upper airway cannot be visualized because of secretions or blood. Digital intubation also should be considered when intubating the patient with a known or suspected cervical spine fracture as this technique requires minimal head and neck movement. Digital intubation is also a variable method for out-of-hospital intubation. The main danger of this procedure involves the healthcare worker performing the intubation being at risk for having his or her fingers bitten. This technique should only be performed on patients who are paralyzed or unconscious.

Stand to the patient's right side, and face the patient. Insert the right index and middle fingers into the right side of the patient's mouth. Elevate the epiglottis with the index finger (Fig. 2.8). Insert the ETT into the patient's mouth between the two fingers, and advance the tip into the trachea. Advance the ETT an additional 3 to 4 cm. Inflate the cuff, begin ventilation, confirm proper tube placement, and secure the tube.

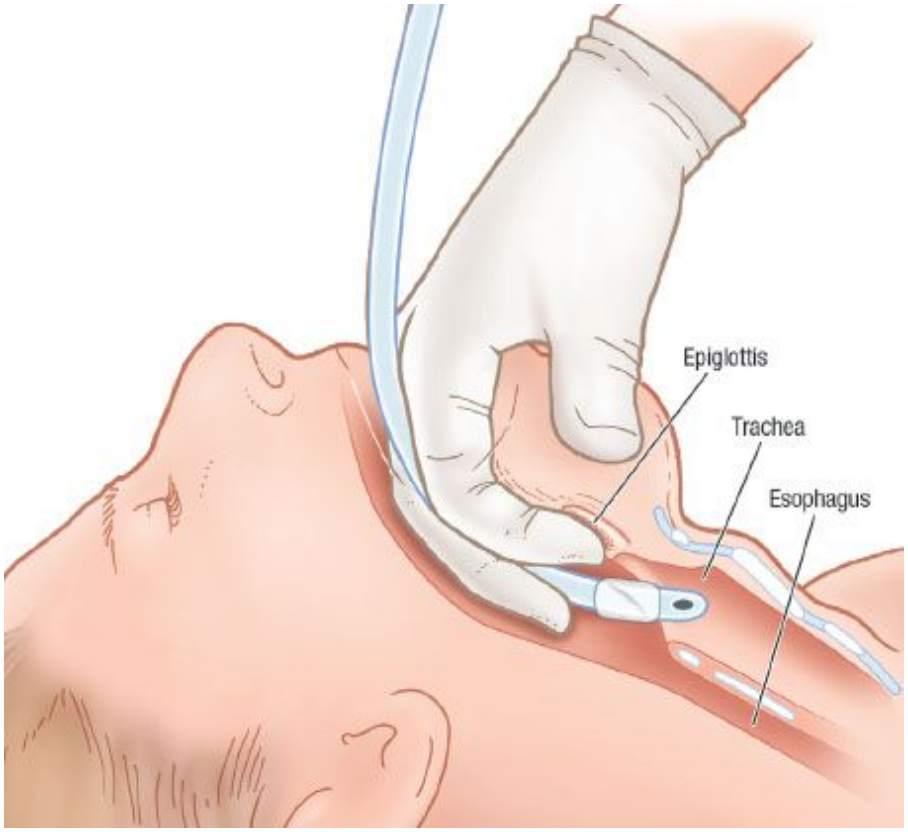

FIGURE 2.8 Digital orotracheal intubation. (From Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013, with permission.)

Supraglottic Airway Devices

Supraglottic devices all allow positive pressure ventilation with placement of the device above the glottis, and thus they are classified as supraglottic devices. The most commonly used of these devices are the esophageal–tracheal Combitube (ETC) or the laryngeal mask airway (LMA) described later in this chapter. The advantage of a supraglottic device is that it allows ventilation without tracheal placement. The majority of these devices can be inserted blindly and quickly by minimally trained personnel, which makes them ideal for prehospital providers, in hospital arrests where no airway providers are available, or as a rescue device in the setting of a failed intubation. In general, supraglottic devices have a cuff that inflates in the posterior pharynx and obstructs the proximal airway above the distal port, allowing positive pressure ventilation of the lungs.

Laryngeal Mask Airway and Intubating Laryngeal Mask Airway

The LMA is a novel device that fills the gap in airway management between endotracheal intubation and the use of a face mask (7). The LMA was designed primarily as a means of providing ventilatory support while avoiding the fundamental disadvantage of the need to visualize and penetrate the vocal cords with an ETT. The LMA is blindly introduced into the hypopharynx to form a low-pressure seal around the laryngeal inlet and to permit positive pressure ventilation.

Many disadvantages of the standard LMA became apparent with widespread use of the device. The intubating laryngeal mask airway (ILMA) was then developed through the aid of analysis of magnetic resonance images of the human pharynx and laboratory testing of ETTs.

The LMA and ILMA are proprietary devices of a single company (LMA North America, San Diego, CA). Numerous other companies produce similar laryngeal mask devices with a variety of modifications as to not interfere with the LMA and ILMA patents. These other devices are used and inserted similarly to the LMA and ILMA with some minor differences specific to each device.

The indications for the use of the LMA and the ILMA parallel the general indications for active airway management. Either the LMA or the ILMA may be used in the event of a failed endotracheal intubation. These devices have a role in securing the airway preemptively in patients with an “anteriorly” situated larynx. However, there is a conspicuous absence of airway protection from aspiration.

There are no absolute contraindications to the use of either the LMA or the ILMA. However, there are several relative contraindications, including patients at an increased risk of regurgitation or aspiration; with airway obstruction at or below the larynx; with low pulmonary compliance or high airway resistance (e.g., morbidly obese, bronchospasm, pulmonary edema, pulmonary fibrosis or thoracic trauma); and who cannot open their mouth at least 1.5 cm. The LMA and ILMA are relatively contraindicated in

cases of pharyngeal pathology. Pathology includes, but is not limited to, abscesses, hematomas, or tissue disruptions.

The LMA is a disposable unit that conforms to the contours of the hypopharynx with its lumen facing the glottic opening (Fig. 2.9). The unit consists of an airway tube, inflation line, and mask. The technique for inserting the LMA is rather simple (7). Position the patient's head as for endotracheal intubation in the "sniffing" position. Insert and advance the LMA into the oral cavity in one smooth movement following the curvature of the pharynx until it enters the hypopharynx and resistance is felt. Inflate the cuff with the recommended volume of air. When correctly positioned, the tip of the LMA cuff lies at the base of the hypopharynx against the upper esophageal sphincter, the sides lie in the pyriform fossae, and the upper border of the mask lies at the base of the tongue, pushing it forward (Fig. 2.9). Secure the LMA in a fashion similar to that used to secure an ETT.

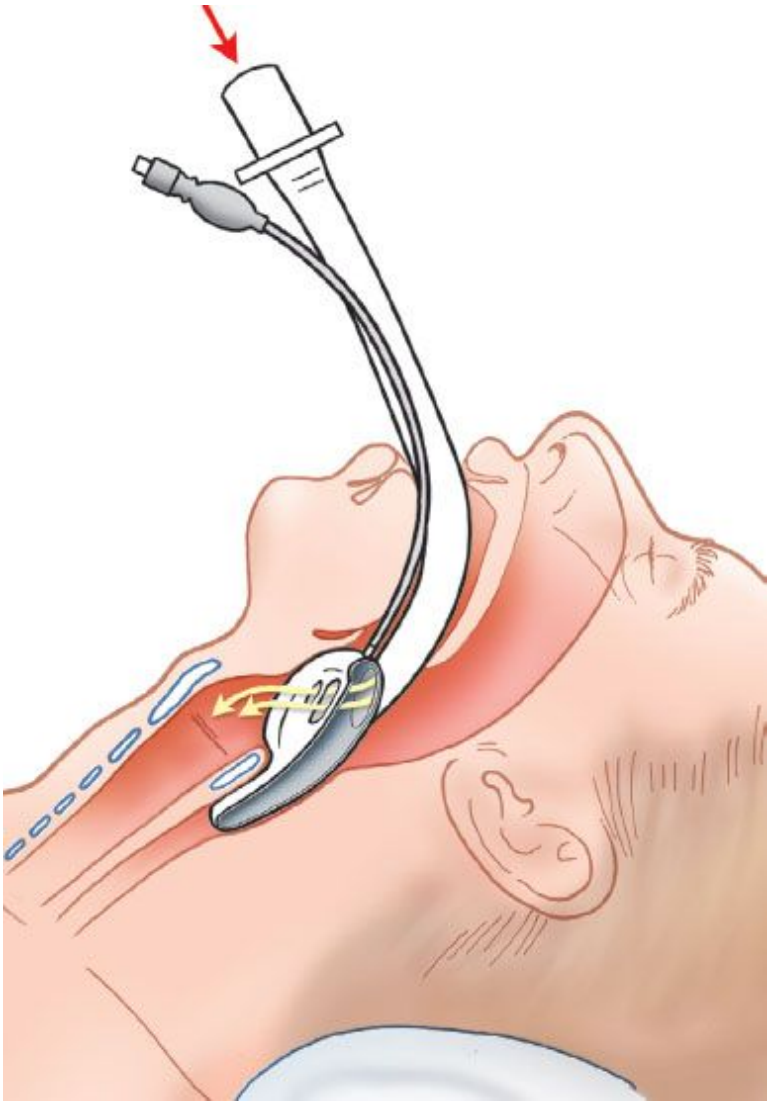

FIGURE 2.9 Sagittal view of the airway demonstrating correct placement of the laryngeal mask airway. (From Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013, with permission.)

The form of the ILMA was derived from head and neck sagittal magnetic resonance imaging studies. The ILMA consists of an anatomically curved steel tube connected to the standard LMA cuff. The ILMA has several significant modifications that make it different from the LMA. These modifications include a stainless steel airway tube covered with silicone rubber, a handle fused to the airway tube, and a larger inner diameter (13 mm vs. 9 mm) than the LMA. The

mask of the ILMA is similar to that of the LMA with two major modifications. A ramp inside the distal airway tube directs an ETT into the center of the aperture and into the patient's airway. The ILMA has a large, single, and stiff epiglottic-elevating bar designed to lift the epiglottis away from the path of the advancing ETT.

The insertion of the ILMA is not too dissimilar from the standard LMA (7). Confirm proper placement of the ILMA with a bag-valve device attached to the proximal end of the airway tube, and ventilate the patient. The ILMA may be left in this placement (Fig. 2.10A). Alternatively, an ETT can be inserted through the ILMA and into the trachea (Fig. 2.10B).

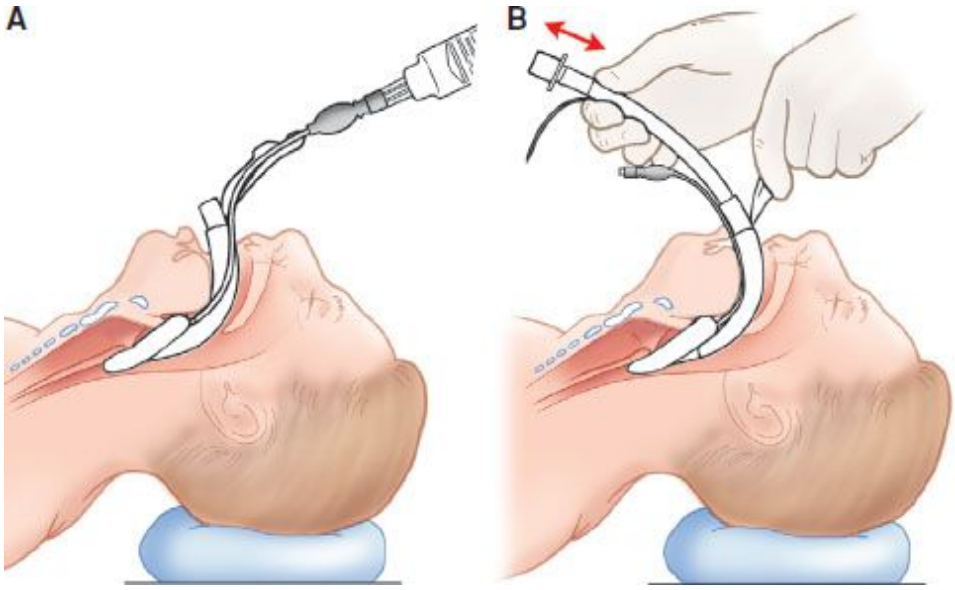

FIGURE 2.10 Insertion of the intubating laryngeal mask airway. (From Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013, with permission.)

There are numerous documented complications associated with the use of the LMA and ILMA. An obvious complication, and potentially the most devastating, is the failure to successfully place the device or to attain a satisfactory laryngeal seal. The incidence of failure to attain satisfactory ventilation is quite low. Other complications include aspiration, cuff herniation, contusions, lingual nerve injury, tongue numbness, parotid gland swelling, hypoglossal nerve palsy,

unilateral vocal cord paralysis, dental trauma, laryngospasm, bronchospasm, and cardiac arrhythmias.

Double Lumen Airway Tube Intubation

The ETC (Kendall Sheridan, Mansfield, MA) and the EasyTube (EzT; Teleflex Medical, Kernen, Germany) are double-lumen, double-tubed, and double-cuffed airway devices that can be blindly inserted into the unconscious and unresponsive patient (8). The ETC and EzT are most often used in the prehospital setting by emergency medical technicians not trained in standard orotracheal intubation and by paramedic-level rescuers as an alternative when standard orotracheal intubation fails.

These devices are inserted blindly into a patient's airway. If the distal tip enters the trachea, the patient is ventilated through the shorter tube, and the distal cuff prevents aspiration of gastric contents into the trachea. If the distal tip enters the esophagus, the patient is ventilated through the longer tube whose proximal ports lie in the hypopharynx while the distal cuff will occlude the esophagus.

Certain contraindications should be mentioned. The ETC and EzT should not be used on patients with an intact gag reflex. The size limits of the standard ETC prevent its use in patients shorter than 5 ft in height. The smaller SA model can be used in shorter adults and adolescent patients from 4 to 5.5 ft in height. Neither model can be used in people shorter than 4 ft in height. The ETC and EzT are contraindicated if the patient has known esophageal disease or an airway obstruction.

Insert the ETC or EzT into the midline of the patient's open mouth (Fig. 2.11A). Advance the device in a downward curved motion until the patient's teeth or alveolar ridge lie between the two printed bands (Fig. 2.11B). Inflate the pharyngeal cuff with air. The device will slightly withdraw from the patient's mouth. Inflate the distal cuff with air.

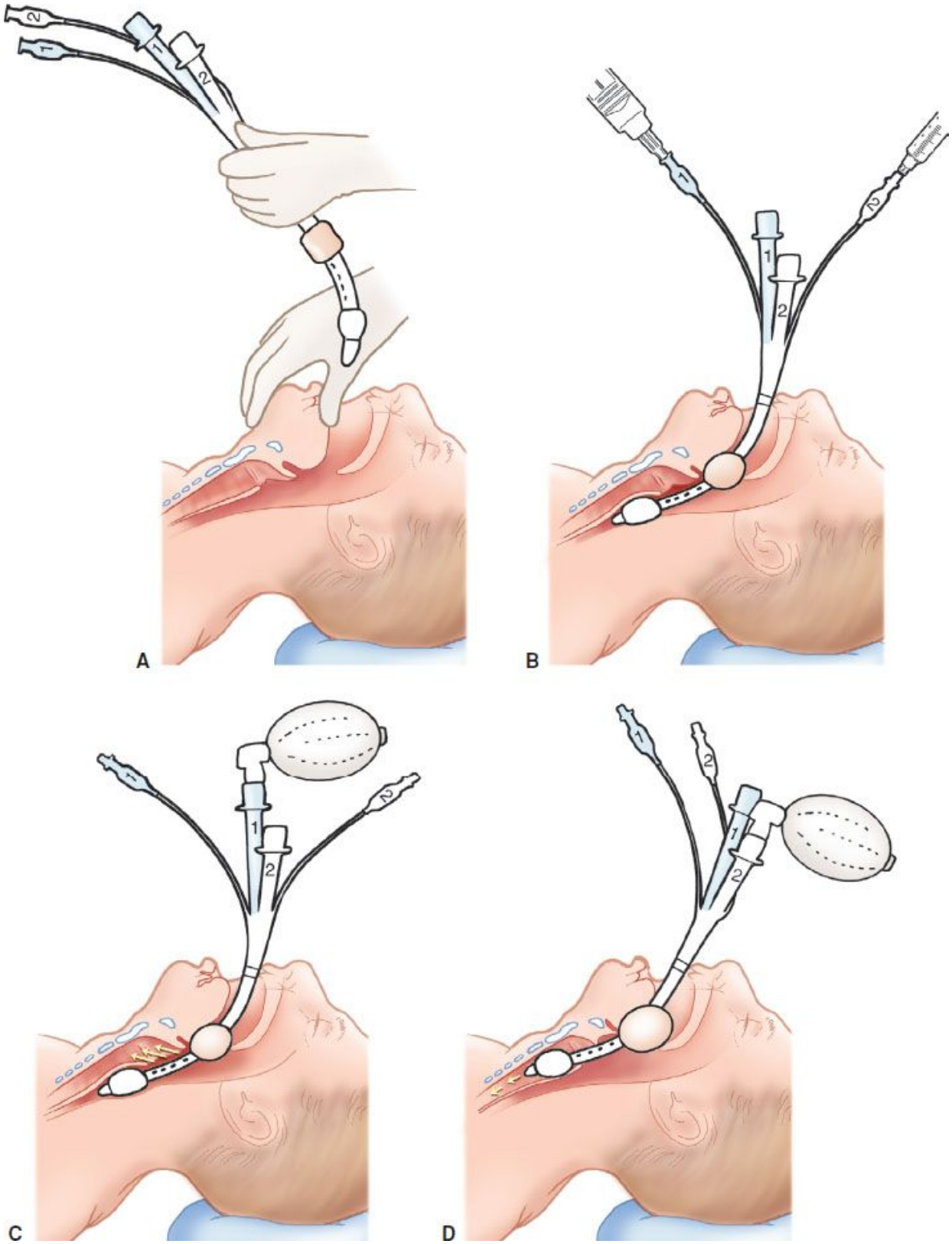

FIGURE 2.11 Intubation with the esophageal–tracheal Combitube. (From Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New

York, NY: McGraw-Hill; 2013, with permission.)

Because most intubations are esophageal, begin ventilation through the longer blue tube labeled No. 1 (Fig. 2.11C). Auscultation of breath sounds, symmetric rise of the chest, fogging in the tube for more than six breaths, and lack of gastric insufflation confirm placement within the esophagus and ventilation through the proximal ports (Fig. 2.11C). If no breath sounds are auscultated and gastric insufflation occurs, the trachea is intubated (Fig. 2.11D). Begin ventilation through the shorter clear tube and verify by auscultation the presence of breath sounds. Secure the device using the standard method of taping or a commercially available ETT holder.

Despite the potential utility of the ETC or EzT in acute situations, several disadvantages must be kept in mind (8), including its high cost and bulky packaging. A rigid cervical collar might cause great difficulties in the proper placement of this device. There is a risk of esophageal injury. There is no way to suction the trachea with the open distal port in the esophagus. It is important to note that resuscitation drugs that can be routinely given through an ETT cannot be given through the device positioned with the tip in the esophagus. Significant soft tissue injury can occur as a consequence of the tip of the device or the balloons containing too much air.

Laryngeal Tube

The laryngeal tube (LT; King Systems, Noblesville, IN) is available in a variety of styles and is a device similar to the ETC and EzT. The LT has a single port placed between an oropharyngeal cuff and an esophageal cuff. The LT lacks a distal port. The device is designed to be placed in the same way as the ETC and EzT. Insert the LT blindly in the midline until significant resistance is felt. Inflate both cuffs, and begin ventilation through the port in the glottis. Adequate ventilation is confirmed by auscultation, chest rise, and end-tidal CO_2 measurements. The most significant difference as compared to the ETC and EzT is the single port opening in the hypopharynx. The distal tip is designed to be placed in the esophagus. The LTD models

have no distal port to allow for esophageal and gastric suctioning. The LTS-D models have a distal port to allow for esophageal and gastric suctioning.

Advanced Airway Devices

Intubating Introducers

Intubating introducers were first described by Dr. Robert Macintosh when a gum rubber urologic stylet was used as a device to aid in intubation (9). The device was inserted into the trachea, and an ETT advanced over the stylet. This "Seldinger-type" intubation did not gain widespread use until much later. Intubating introducers are now often considered standard equipment in the management of difficult airways.

Multiple intubating introducers are currently available (10). Two of the most common are the Eschmann (Eschmann Tracheal Tube Introducer, SIMS Portex, Inc., Keene, NH) and the Frova (Cook Medical Inc., Bloomington, IN). Both of these devices have a 30-degree bend at the tip and are rigid enough to hold an additional bend placed in the shaft of the introducer by the physician. There are differences between the two devices. The Frova is a single-use item, and the Eschmann is designed for multiple uses. The Frova has a central port that can provide limited ventilation, and the Eschmann is a solid introducer. The Eschmann is more flexible and may potentially decrease the forces transmitted to the airway and decrease airway trauma.

Although there are slight differences between the two devices, they are used in a similar manner (Fig. 2.12). Perform direct laryngoscopy in the standard fashion. An intubation introducer can be used if a limited view is obtained or a difficult airway is predicted. The vocal cords or epiglottis should be visualized to use the introducer effectively. Insert the introducer with the 30-degree bend at the tip and the introducer distance markings aimed anteriorly (Fig. 2.12A). Advance the stylet under the epiglottis (Fig. 2.12B). If the vocal cords are visualized, continue to advance the stylet through the cords. If only the epiglottis is visualized, gently

advance the stylet “blindly” while relying on the 30-degree bend to direct it into the trachea (Fig. 2.12C). Continue to advance the stylet until the 25-cm mark is positioned at the patient’s lips. This motion should place the tip of the stylet in the midtrachea and should avoid entering either the left or right mainstem bronchus (Fig. 2.12D).

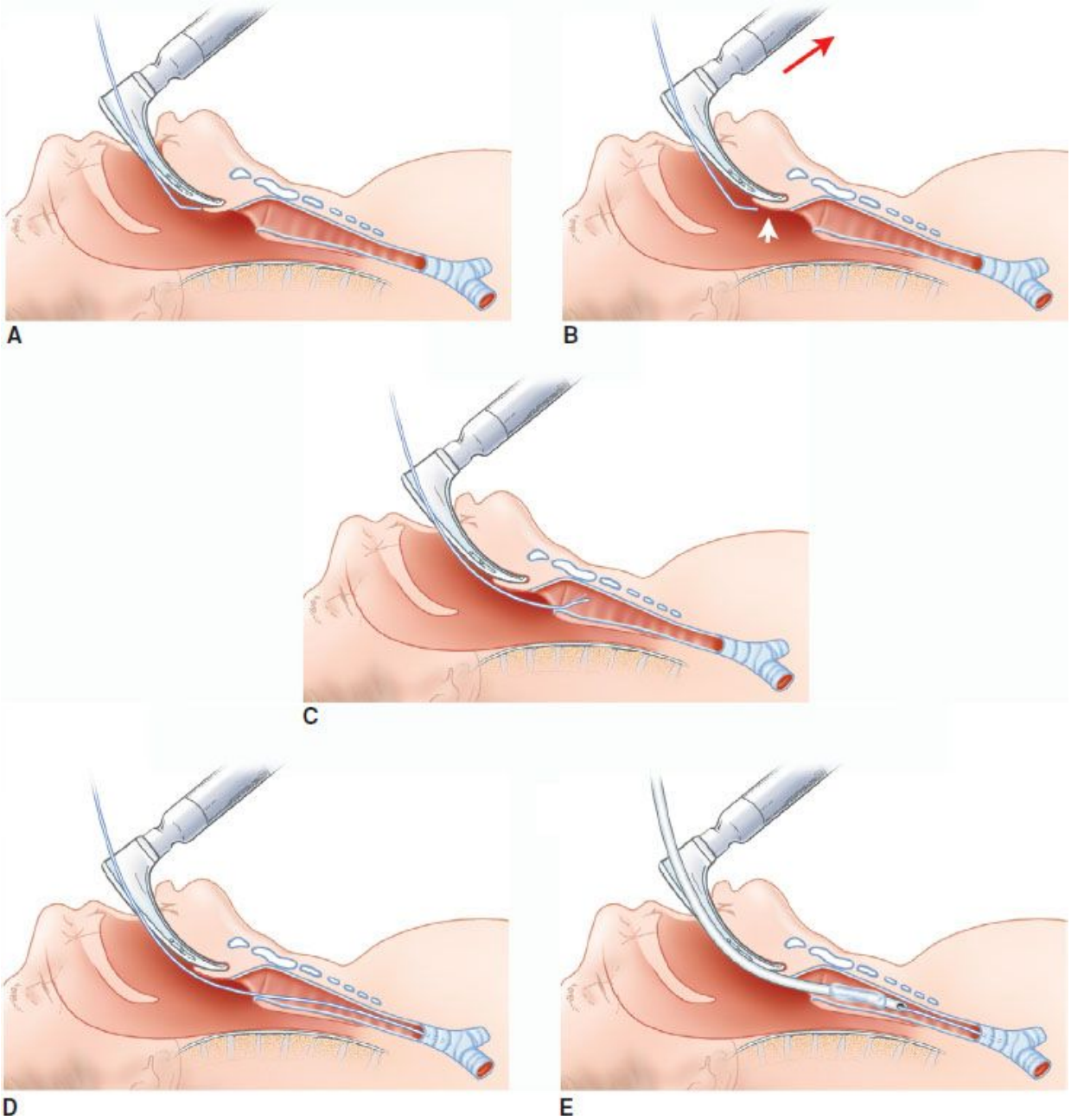

FIGURE 2.12 Intubation using a bougie or intubating introducer. (From Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013, with permission.)

Tracheal placement of the stylet is identified by one of four methods. The most reliable method is direct visualization of the stylet passing through the vocal cords. The second method is feeling the transmission of vibratory clicks as the advancing stylet tip contacts the tracheal rings. Absence of this sensation does not confirm esophageal placement. The third method is noting the presence of a cough in a patient who is sedated but not paralyzed. The final method is advancement of the introducer until there is distal holdup or blockage of advancement as the introducer enters the distal airways. This advancement is potentially the most dangerous of the methods and should not be used if any other method can confirm placement.

Advance the ETT over the introducer while maintaining direct laryngoscopy (Fig. 2.12E). This method allows easier placement of the ETT by minimizing curvature of the airway. Advance the ETT to the appropriate depth. If there is difficulty in advancing the ETT, it can be gently rotated 90 degrees to the right and left to promote passage through the vocal cords. Remove the introducer while firmly holding the ETT so it does not change position. Confirm proper ETT placement, and secure it in position.

The complications for this procedure are similar to direct laryngoscopy with the additional risk of airway trauma from the intubating introducer. The use of intubating introducers and bougies is an easily learned technique to improve endotracheal intubation when an anticipated or actual difficult airway is encountered.

Video Laryngoscopy

Video laryngoscopy is a relatively new method of indirect laryngoscopy. Video laryngoscopy involves a laryngoscope blade with a camera or another optical device attached to the end of the blade. The laryngoscope is then attached to a view screen. These devices are different from fiberoptic devices in that they require viewing on a screen, as there is no optical port on the device. Two more commonly available devices are multiple versions of the GlideScope (Verathon Inc., Bothell, WA) and the C-MAC Video Laryngoscope (Karl Storz Endoscopy Ltd., Tuttlingen, Germany).

Video laryngoscopy allows for indirect viewing of the epiglottis and vocal cords, and hence indirect orotracheal intubation (11). The indirect view can be obtained with minimal force and less manipulation of the airway. This may lead to decreased movement of the cervical spine as compared to other techniques. Video laryngoscopy can also provide for a better view of the epiglottis and vocal cords when compared to direct laryngoscopy. Video laryngoscopy may be easier to learn than either direct laryngoscopy or other methods of indirect laryngoscopy. Viewing images on a screen can be used as a teaching adjunct either during the intubation or can be recorded and reviewed at a later time.

Video laryngoscopy can be used for both routine and difficult intubations. This technique may be of additional benefit in patients with predicted difficult airways, limited laryngoscopic views during direct laryngoscopy, or restricted cervical spine movement. Video laryngoscopy is contraindicated when there is a proximal obstruction preventing passage of an ETT. The camera placement midway on the blade decreases the risk of occlusion of the camera with secretions, but occlusion is still a possibility.

The GlideScope consists of a 60-degree curved laryngoscope blade and handle combination with a camera embedded in the blade midway on the device. There are light emitting diode (LED) lights mounted adjacent to the camera. The device is attached to a color liquid crystal display (LCD) screen for image viewing. The GlideScope is available in three sizes (small, medium, and large). The small size is similar to a Macintosh size 0 blade, the medium is similar to a Macintosh size 2 blade, and the large is similar to a Macintosh size 3 blade. The benefit of this design is the camera mounted at the midpoint of the blade that allows for a wider view and less obstruction of the view with debris and secretions in the airway. The similarity to a standard Macintosh blade helps facilitate the GlideScope use with providers skilled in direct laryngoscopy.

To orotracheal intubate with a GlideScope, the first step is preparation. Turn on the device, and position the screen for the intubator to view. Prepare an ETT containing a stylet curved to a 60-degree or 90-degree angle. Open the patient’s mouth with the right

hand while the GlideScope is advanced with the left hand in the midline and posteriorly. When the blade enters the oropharynx, the physician views the screen. Continue to advance the blade in the midline until the epiglottis is seen. The blade is either in the vallecula or underneath the uvula. Apply slight upward pressure in a tilting motion to visualize the vocal cords. Once the vocal cords are visualized, advance the ETT until it is viewed on the screen. Continue to advance the ETT through the vocal cords. The ETT can be used without the stylet to decrease the angle of the posterior portion of the tube if there is difficulty in passing the ETT. The GlideScope can be manipulated while viewing on the screen to decrease the laryngeal angle and help in ETT placement.

The C-MAC Video Laryngoscope is a similar device to the GlideScope. This device consists of a Macintosh blade with a camera at the distal aspect of the blade. The C-MAC is used in a similar method to the GlideScope and standard Macintosh blade. The C-MAC improves laryngoscopic views of the epiglottis and vocal cords.

The complications associated with the different video laryngoscopes are not yet well studied. It can be anticipated that the complications are similar to those of direct laryngoscopy and fiberoptic devices.

Overall, video laryngoscopy is a useful device for the management of both uncomplicated and complicated airways. Video laryngoscopy improves views of the epiglottis and vocal cords. It requires less force than direct laryngoscopy, which may cause less airway trauma, less cervical spine movement, and decreased hemodynamic response to intubation. Lastly, video laryngoscopy is a strong educational tool for teaching airway management.

Rigid and Semirigid Fiberoptic Devices

This category of devices is one of the most rapidly growing areas of difficult airway management. Fiberoptic devices allow for indirect visualization of the larynx, similar to the flexible fiberoptic scopes and rigid fiberoptic scope blade combinations. This device allows for airway management without the force and movement of the airway inherent to direct laryngoscopy. The benefit is decreased cervical

spine motion during laryngoscopy (12,13). These devices demonstrate improved views of the larynx, allowing for increased endotracheal intubation rates in difficult airways.

There are numerous advantages to the rigid and semirigid devices when compared to flexible fiberoptic scopes. These devices are often easier to learn and master when compared to flexible fiberoptic scopes. The rigid and semirigid devices are designed to function similar to or in conjunction with direct laryngoscopy. Their rigidity and shape conforms to the airway. This allows easier passage through the pharynx and past the tongue. These devices are often less expensive and more durable than flexible fiberoptic scopes.

The indications for the use of rigid and semirigid devices are the same as for direct laryngoscopy. They can be used as a primary device in uncomplicated airways, in potentially difficult airways, or as a secondary device after a failed intubation attempt. Rigid and semirigid devices are contraindicated, as are other fiberoptic devices, if there is a proximal airway obstruction and relatively contraindicated when the airway contains vomitus, blood, or copious secretions that may obstruct the optical port.

These devices can be used either as an adjunct to direct laryngoscopy or as a single instrument for endotracheal intubation. Most rigid and semirigid devices have a site for attachment of a viewer or can be connected to a monitor for viewing. These devices represent a useful adjunct in the management of the difficult airway. Rigid and semirigid devices often require less training to master than flexible fiberoptic scopes. Although there is still limited evidence of their use in the emergency department, it is likely these devices will become commonly used in airway management.

There are multiple rigid and semirigid devices on the market including the Bonfils Retromolar Intubation Fiberscope (Karl Storz Endoscopy Ltd., Tuttlingen, Germany), the Levitan FPS (Clarus Medical, Minneapolis, MN), the Video Optical Intubating Stylet (VOIS, VOLPI AG, Schlieren, Switzerland), and the TrachView Intubating Videoscope (Parker Medical, Englewood, CO). Although there is evidence that the use of these devices improves laryngeal views in the difficult airway, there is little evidence comparing these

devices to each other. Preference for a device is often user and institution specific.

Fiberoptic Endoscopic Intubation

The flexible fiberoptic bronchoscope has become a popular and useful instrument for placing ETTs in awake and nonparalyzed patients. This bronchoscope is unique because its flexible cord allows it to conform to the patient's anatomy, making intubation possible in a variety of clinical situations when direct laryngoscopy is likely to be difficult or impossible. When performed properly, awake fiberoptic tracheal intubation is more accepted by patients and is associated with fewer hemodynamic changes than awake laryngoscopy. Fiberoptic intubation may be used to orally or nasally intubate a patient (14). It provides excellent visualization of the airway.

A fiberoptic intubation is indicated when it is anticipated that a direct laryngoscopy might be difficult to perform such as in morbidly obese patients; in patients with a limited mandibular opening, an unstable or immobile cervical spine, macroglossia, or micrognathia; in patients who appear to have pathologic airway anatomy (e.g., tracheal deviation, stenosis, tumors, trauma); and in patients who appear to be at increased risk for dental damage.

Proficiency in the skills required for fiberoptic intubation requires both instruction and practice. In most instances, it is a lack of expertise with the fiberoptic bronchoscope that results in technical problems, inadequate patient preparation, and prevents the successful completion of fiberoptic intubation. Successful intubation is also prevented by blood or secretions obstructing the fiberoptic port. Patients who are hypoxic or require assisted ventilation by mask are poor candidates. Contraindications specific to nasal fiberoptic intubation include coagulopathy, significant midface trauma, severe intranasal pathology, cribriform plate fracture, and cerebrospinal fluid leak.

Prepare the fiberoptic bronchoscope. Apply antifog solution to the insertion cord tip, or place the tip in warm water. Apply a thin film

of silicone spray or water-soluble lubricant onto the flexible insertion cord. Insert the flexible insertion cord completely through the ETT.

Insert and navigate the insertion cord tip through the nose or mouth until the glottic opening comes into view. Advance the insertion cord tip toward and past the vocal cords. Advance the insertion cord tip further to bring the bifurcation of the trachea at the carina into view. Advance the ETT over the insertion cord and into the trachea. Securely hold the ETT, and remove the insertion cord. Inflate the ETT cuff, begin ventilation, confirm proper tube placement, and secure the tube.

Although the fiberscope is passed through the glottis and into the trachea with direct vision, the ETT is passed blindly over the fiberoptic bronchoscope. It is possible to cause injury to the arytenoids. The ETT may also be blocked in the nasal cavity or larynx, resulting in epistaxis, nasal turbinate fracture, and tearing of the tracheal tube cuff.

Rigid Fiberoptic Scopes and Blades

The Bullard laryngoscope is the most well-known of the rigid fiberoptic scopes. Other commonly used devices include the Airtraq (King Systems Corp., Noblesville, IA), the Upsherscope (Mercury Medical, Clearwater, FL), and the WuScope (Achi Corporation, Fremont, CA). These devices are all rigid devices with a built-in optical and light system, a rigid blade, and a channel for the ETT. The most significant difference among these devices is the Airtraq, is a single-use disposable device and the others are reusable.

These devices have waned in popularity as flexible and semirigid fiberoptic scopes have become more prevalent and simpler to use. The major limitation of these devices is their complex design and difficulty in ETT advancement after visualization of the vocal cords. Two of them require multiple pieces to be assembled before use—not a desirable characteristic when a device is required in an emergency or as a rescue technique after a failed airway by direct laryngoscopy. The Airtraq, a single-piece disposable device, may overcome some of these limitations, but the evidence to support its use in the emergency department is limited.

Surgical Airways

Cricothyroidotomy

Cricothyroidotomy is a technique that has been in use since the early 1900s. This technique has evolved into the surgical airway of choice for emergent situations in which other less-invasive intubation methods have failed or are contraindicated (15). There are numerous advantages to performing a cricothyroidotomy instead of a tracheostomy. A cricothyroidotomy is easier, faster, and safer to perform. It can be performed in less than 2 minutes. A cricothyroidotomy can be performed by those with little to no surgical training. It does not require the support of an operating room and a large amount of equipment. The anatomic landmarks are superficial, easily seen, and easy to palpate. Cricothyroidotomy does not require a deep dissection. The cricothyroid membrane is not covered by any structures that would interfere with the procedure. A cricothyroidotomy can be performed with the neck in a neutral position. The procedure has fewer associated complications than a tracheostomy.

There are a few absolute contraindications to performing a cricothyroidotomy. The most important contraindication is when the patient can be endotracheally intubated by less-invasive methods. Partial or complete transection of the airway is a contraindication to a cricothyroidotomy. In these cases, a tracheostomy is the preferred method to secure the airway. Finally, a cricothyroidotomy should not be performed in cases of significant injury or fracture of the cricoid cartilage, larynx, and/or thyroid cartilage. Relative contraindications to performing a cricothyroidotomy are the presence of a coagulopathy, massive neck swelling, or a hematoma in the neck; all of which increase the risk of bleeding and distortion of the anatomy.

Stabilize the large thyroid cartilage. The immobilization of the larynx cannot be overemphasized. If the larynx is not secure and the landmarks are lost, the procedure will fail. Identify the anatomic landmarks necessary to perform this procedure. This identification is critical to the performance of a cricothyroidotomy.

There are numerous techniques to perform a cricothyroidotomy (15). The surgical techniques require a skin incision carried down through the cricothyroid membrane (Fig. 2.13A). This is followed by grasping the thyroid cartilage with a tracheal hook to control the airway (Fig. 2.13B). The tract is dilated (Fig. 2.13C), and a tracheostomy tube or ETT is inserted into the trachea (Fig. 2.13D). A percutaneous kit is available and uses a modified Seldinger technique to perform a cricothyroidotomy. A needle cricothyroidotomy is performed in children, instead of the surgical approach.

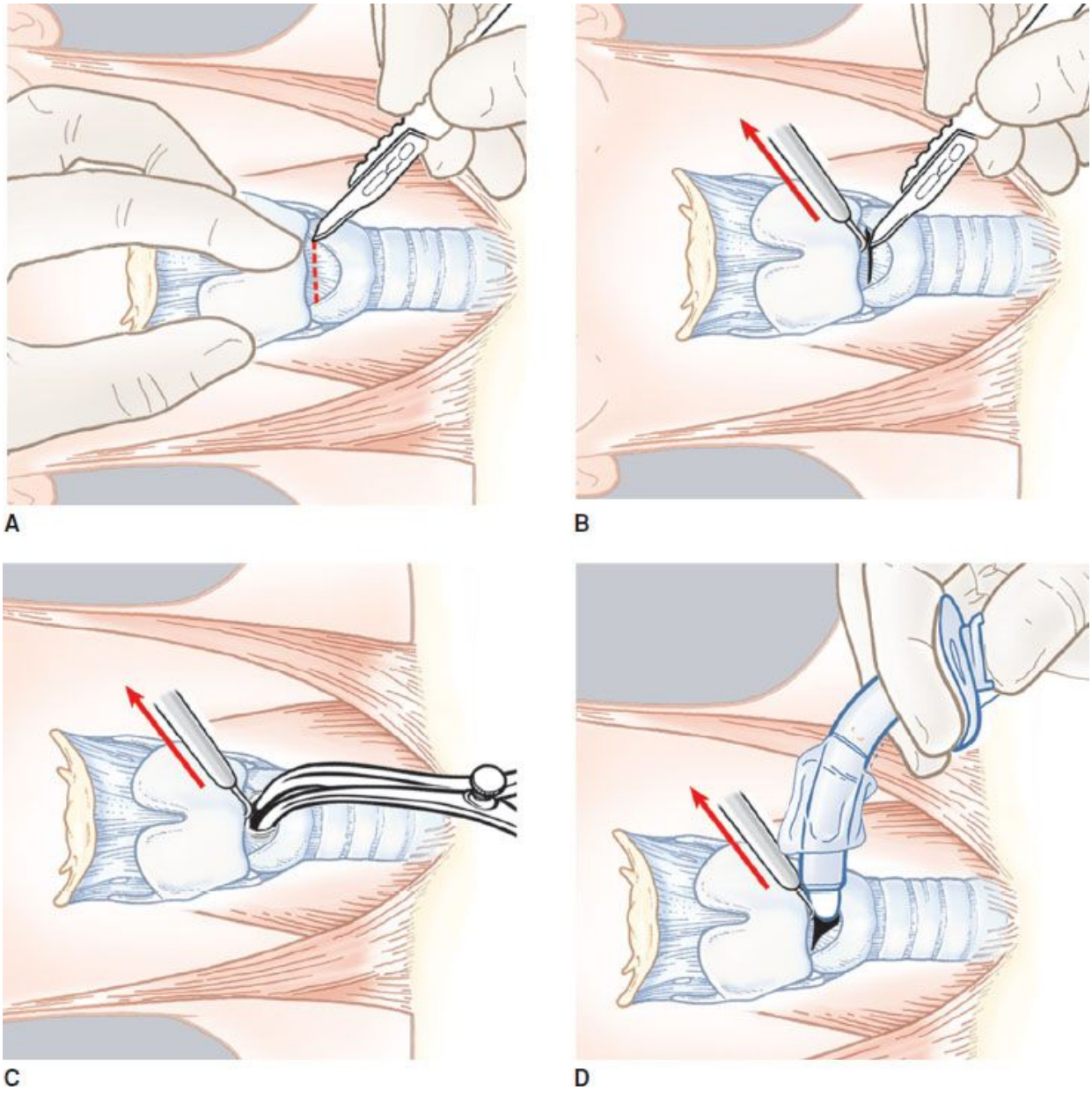

FIGURE 2.13 Cricothyroidotomy. (From Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013, with permission.)

Complications following a cricothyroidotomy can be classified as early or late based on when they occur. Early complications will be recognized either immediately after insertion of the tracheostomy tube or within a few hours. These complications include tube malposition, laryngeal injury, bleeding, and infection. Late complications may not be apparent for weeks to months following the procedure. These complications include progressive airway obstruction and chronic voice changes.

A cricothyroidotomy is a potentially life-saving technique. It is an important procedure for the emergency physician to be skilled in as it may represent the only access to the patient's airway. Cricothyroidotomy can be used to provide oxygenation and ventilation to a patient when other less-invasive airway control methods have failed or are contraindicated. It is a relatively safe, simple, and reliable procedure that can be performed within a few minutes. Knowledge of the anatomy of the anterior neck is essential to minimize early complications.

Tracheostomy

A tracheostomy is an ancient and time-honored technique for securing and maintaining an artificial airway. Modern emergency physicians have many options for airway management. They are skilled in a variety of invasive, noninvasive, and surgical procedures to optimize the management of a patient's airway. The role of tracheostomy for emergent airway access has diminished as newer, safer, and equally effective techniques have evolved. Familiarity with the methods for tracheostomy is still valuable (16). Knowledge of proper techniques, possible indications, limitations, and likely complications will guide one's judgment in critical moments when it most counts. Understanding the procedure for a tracheostomy allows emergency physicians to properly care for a problem or complication

when a patient with a tracheostomy tube presents to the emergency department.

When performed under emergency circumstances, a tracheostomy is fraught with danger. There are only three clinical settings in which an emergency tracheostomy should be considered (16). The first is laryngotracheal injuries with airway disruption. The second is the need for a surgical airway in an infant or a small child where a cricothyroidotomy is contraindicated. The third is the need for an airway when all other methods have failed.

A cricothyroidotomy is the procedure of choice when an invasive approach to the airway is needed. Compared with a tracheostomy, the cricothyroidotomy is faster, is more direct, relies predominantly on external landmarks, requires only a single operator, can be done with ambient lighting, and requires a limited amount of equipment. In contrast, a tracheostomy is a procedure requiring multiple steps. The procedure involves direct visualization to dissect through vascular structures and requires better light than is commonly present at the bedside. It is easier, and thus faster, if one has an assistant, proper suctioning equipment, and electrocautery. Without these advantages, the technique is difficult and likely to be complicated. The average time to establish an airway by tracheostomy is too long for the true emergency in a patient who lacks an airway.

Tracheal Confirmation Devices

Confirmation of ETT placement within the trachea is one of the most important steps of endotracheal intubation. If the ETT is placed within the esophagus or pharynx, it must be quickly recognized, and tracheal intubation or effective ventilation promptly performed. This necessity has led to a vast array of techniques to confirm correct ETT position.

One of the most sensitive and specific tests for correct ETT placement is direct visualization of the ETT passing through the vocal cords and into the trachea. This can be done by direct laryngoscopy or a fiberoptic device. When the ETT is visualized passing through the vocal cords, tracheal placement is confirmed;

however, this cannot be done in all cases. Because of the life-threatening complications of a misplaced ETT, correct placement must be confirmed by multiple methods.

Methods of tracheal confirmation can be separated into three categories: Clinical examination, tests based on anatomic differences between the trachea and esophagus, and tests based on physiologic differences (17). The clinical examination findings of tracheal intubation are symmetric chest rise, absence of sounds over the epigastrium, bilateral breath sounds in the axilla, condensation in the ETT with ventilation, and direct visualization of the ETT passing through the cords. Although all of these findings can have false positives and negatives, in combination, these findings are sensitive and specific indicators of tracheal intubation.

Tests for tracheal intubation that rely on anatomic differences include esophageal detector devices (EDDs), transtracheal illumination, and transtracheal ultrasound. These tests rely on the structural difference of the esophagus and trachea, as well as their relative position in the neck. EDDs rely on the flexible esophagus collapsing when negative pressure is applied while the cartilaginous trachea is unaffected by negative pressure. The negative pressure is applied by either a syringe-like device or self-inflating bulb attached to the ETT. When the syringe-like device is used, an ETT in the trachea results in no resistance or rebound of the plunger during aspiration of 40 to 60 mL of air into the syringe. If the ETT is placed within the esophagus, the esophagus will collapse around the ETT, preventing large-volume aspiration and causing rebound of the plunger.

Self-inflating bulbs work in a similar method to the syringe-like devices. Deflate the bulb, and attach it to the end of an ETT. The bulb is then allowed to inflate passively. Inflation should take less than 4 seconds if the ETT is within the trachea. Reinflation of the bulb may be prolonged or not occur if the ETT is within the esophagus.

In the transtracheal illumination technique, alighted stylet is placed through the ETT and illuminated. If the ETT and stylet are within the trachea there should be a discreet glow seen on the

anterior neck. If the ETT is placed within the esophagus, the posterior position of this structure, as well as its muscular wall and soft tissue will cause a diffuse dull light in the neck. This method is best used when the physician is comfortable with lighted stylet intubation.

Transtracheal ultrasound relies on ultrasonographic images to confirm correct ETT position. This can be done by either the dynamic or the static method. In the dynamic method, the trachea is visualized with a high-frequency linear transducer. The ETT is then visualized entering the trachea, and position is confirmed. The static method uses ultrasound to confirm tracheal placement after the ETT has been placed. Although there is limited evidence to support its use at this time, ultrasound may become a commonly used method for ETT confirmation in the emergency department (18,19).

The tests for tracheal intubation that rely on physiologic differences include capnometry, the Beck Airway Airflow Monitor (BAAM, Great Plains Ballistics, Lubbock, TX), and pulse oximetry. Capnometry relies on detection of CO_2 in exhalation. In a healthy preoperative patient, capnometry is a highly sensitive and specific test for tracheal intubation. In the emergency setting, capnometry can be limited by CO_2 in the gastrointestinal tract and in situations where respiration is limited or absent, such as cardiac arrest and severe pulmonary edema. There are two commonly used methods of capnometry in the emergency department: colorimetric and quantitative capnometry or capnography. Colorimetric capnometry uses a device that contains purple-colored pH paper that releases hydrogen ions when in contact with CO_2, turning the paper yellow. The device is attached to the end of the ETT between the bag-valve-mask device and the respiratory adapter. Ventilate the patient, and check the colored indicator paper after five to six breaths to allow for washout of residual carbon dioxide.

Capnography samples the exhaled gasses and calculates end tidal CO_2, which is displayed as a number or a graph on a physiologic monitor. The advantage of capnography instead of colorimetric capnometry is a continuous reading of end tidal CO_2. This reading

allows for both continuous monitoring of ETT position and continuous monitoring of respiration. In the noncardiac arrest patient, capnography is a very useful tool in confirming ETT placement (19).

The BAAM is a novel device that contains a whistle that attaches to the respiratory connector of an ETT. Air exiting the proximal end of an ETT results in a whistle. In a spontaneously breathing patient this device works well to confirm tracheal placement. This device is best used in a nasotracheal intubation of an awake (sedated) intubation. In an apneic patient, the chest can be compressed, and the forced exhalation of air can cause the whistle. If the tube is placed in the esophagus, there should be no air movement with respiration or chest compression. There is very limited evidence to support the use of the BAAM.

Pulse oximetry is a commonly used device that is a poor predictor of esophageal intubation. In a preoxygenated patient, it can take several minutes for hypoxia to present, regardless of esophageal or tracheal intubation. If the ETT is misplaced, confirmation is desired before hypoxia ensues. Although pulse oximetry is a useful adjunct for monitoring for intubation, it is not an ideal agent for confirmation of tracheal intubation.

The last method for confirming ETT position is the chest radiograph. Although chest radiographs are taken after almost every endotracheal intubation, it is difficult to determine endotracheal or esophageal position in a single anteroposterior (AP) view. Indications of esophageal placement include ETT visualized outside the tracheal shadow or an ETT in the midline below the carina. A chest radiograph is best utilized to determine tracheal position of a confirmed tracheal intubation.

The clinical examination, in addition to capnometry or EDDs, are the best methods for determination of tracheal intubation. In the nonarrest patient, either colorimetric or continuous capnography is very sensitive and specific. In the postarrest patient, capnometry can be difficult to interpret, and the clinical examination and EDDs are the best methods to confirm the tracheal tube position (20).

CRITICAL INTERVENTIONS

- Properly position the patient's head to optimize the view of the vocal cords during orotracheal intubation.
- Prepare sequential airway securing techniques when faced with a potentially difficult airway.
- Video-assisted intubation devices should be considered as a primary intubation device as well as for failed direct laryngoscopy.
- Confirm proper position of ETT after intubation.

DISPOSITION

Almost all patients who require the airway management techniques as described in this chapter will be admitted to an intensive care setting. The patient who is intoxicated, has taken too much medication, or used illicit substances may be the exception to admission.

Common Pitfalls

- Proper patient positioning is very basic but often overlooked.
- Simple maneuvers using the jaw thrust, chin lift, nasopharyngeal airway, or oral airway can prevent hypoxia and hypercarbia in the apneic patient.
- Orotracheal intubation is the airway of choice.
- The emergency physician must know several alternative techniques for airway management when orotracheal intubation fails or is contraindicated.
- The cricothyroidotomy is the preferred surgical airway in an emergency.

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CHAPTER 3 Cardiopulmonary Arrest

Christopher Ross and Theresa M. Schwab

Sudden cardiopulmonary arrest (SCA) and sudden cardiac death (SCD) typically result due to ventricular dysrhythmias resulting in hemodynamic collapse due to the sudden cessation of cardiac activity. The triad of unconsciousness, apnea, and pulselessness defines cardiopulmonary arrest. Cardiovascular disease causes about a third of all worldwide mortality with half of this caused by SCD (1). SCD is defined as an unexpected natural death from a cardiac cause that occurs instantaneously or within 1 hour from the onset of an abrupt change in clinical status in a person without a prior condition that would appear to be fatal. The term SCD is used to describe cardiac arrest whether or not resuscitation occurs. The term can be misleading because not all affected individuals die. Patients who do not die after cardiac arrest have “aborted SCD.” By convention, the term describes both fatal and nonfatal cardiac arrest (2).

Resuscitation was described more than 100 years ago. It was only in the late 1950s that closed-chest cardiac massage, mouth-to-mouth ventilation, and electrical defibrillation were incorporated into practice guidelines in an attempt to improve survival. Although advances in emergency medical services (EMSs) and in the field of resuscitation have occurred, the rate of survival of cardiac arrest victims who are neurologically intact remains dismally poor (3). Although survival assessments have reached widely disparate conclusions based on study populations in the out-of-hospital setting, survival rates range from 4% to 15% (4). Survival to hospital discharge has been reported to increase in those treated with

bystander cardiopulmonary resuscitation (CPR), EMS, and when the underlying rhythm was ventricular fibrillation (VF) (2). In-hospital survival of SCD has been reported to be 22% survival to hospital discharge (5). The concept of extending treatment into the community is a fairly new phenomenon. In the 1970s, it was demonstrated that advanced cardiac life support (ACLS) by trained paramedics could significantly improve resuscitation and survival in patients suffering cardiac arrest. Training laypersons in the community to deliver CPR has been shown to increase survival of SCD. The availability of automatic external defibrillators to trained persons such as police and flight attendants and their use by these people prior to EMS intervention also increases survival (2).

The epidemiology of SCD parallels that of ischemic heart disease with up to 70% of patients with known coronary artery disease (CAD) succumbing to SCD. The incidence increases with age and cardiac risk factors such as smoking, diabetes, left ventricular hypertrophy, and hypercholesterolemia. The biggest risk factor for SCD is previous CAD, especially if there is associated left ventricular dysfunction (6). The more cardiac risk factors and electrocardiogram (ECG) abnormalities present, the higher the risk of SCD.

The effect of race on SCD is controversial as it is difficult to separate socioeconomic influences from a true genetic predisposition. That being said, black patients appear more likely than whites to experience SCD at a younger age and with lower survivability. Black patients are also more likely to have an unwitnessed arrest and have their initial rhythm being a less favorable one for resuscitation (7). Men are three to four times more likely than women to experience SCD. This difference can be explained by the difference in the incidence of CAD and the hormonal protection women have before menopause. Recent major life changes, women who are not married or who have no children or few children, high-stress lifestyle, and type A personality are all factors that increase the risk for SCD, although the validity of some of these claims remains controversial. There may be both seasonal and circadian patterns for risk assessment in SCD because SCD is more likely to occur in the winter months. SCD, like acute myocardial infarction (AMI), is most likely

to occur in the first few hours after awakening from sleep as a consequence of increased sympathetic stimulation (7). Modifiable risk factors play a role in risk of SCD. There was a 92% reduction in SCD in female patients who did not smoke, had an appropriate weight, exercised, and ate an appropriate diet (8).

The ECG can identify patients at an increased risk for SCD. ECG findings consistent with previous or current ischemic disease such as old myocardial infarction (MI), left ventricular hypertrophy, interventricular conduction delay, repolarization abnormality, or any current of injury pattern are significant predictors of SCD. Some studies report that a powerful predictor of SCD is three or more premature ventricular contractions (PVCs). Other studies state that high-risk forms of PVCs such as multifocal, bigeminy, short coupling with R-on-T phenomenon, and three or more consecutive ectopic beats are more predictive. There are also specific ECG findings such as interventricular conduction delays, QT prolongation, delta waves, and an increase in resting heart rate of more than 90 beats per minute that place patients at a higher risk.

Multiple factors trigger SCD in a susceptible myocardium, but the final mechanisms for triggering the fatal ventricular dysrhythmias is unclear. Significant coronary stenosis is the most common abnormality found in SCD patients, although more than half of SCD patients have no previous history of CAD. Fewer than half of all SCDs occur during an AMI. In fact, cardiac arrest during AMI is associated with an improved outcome when compared to cases not occurring in this setting. Other factors involved include other structural abnormalities and transient electrophysiologic disturbances (Table 3.1). In the majority of cases, the terminal rhythm of VF has occurred from the initiating event of a ventricular tachydyrhythmia (7).

TABLE 3.1
Risks Associated with Sudden Cardiac Death

Structural Abnormalities

- Coronary artery disease and acute myocardial infarction
- Hypertrophic cardiomyopathy
- Valvular heart disease
- Dilated cardiomyopathy
- Inflammatory and infiltrative disorders

Primary Electrophysiologic Abnormalities

- Congenital long QT syndrome
  - Jervell and Lange-Nielsen
  - Romano-Ward
- Acquired long QT syndrome
  - Antidysrhythmics (class IA, class III)
  - Antihistamines (terfenadine, astemizole)
  - Antimicrobials (erythromycin, clarithromycin, azithromycin, ketoconazole, chloroquine)
  - Antipsychotics (phenothiazine, haloperidol, risperidone)
  - Antidepressants (tricyclic antidepressants, ketanserin, zindeline)
  - Antimotility (cisapride)
  - Electrolytes (hypokalemia, hyponatremia, hypocalcemia, hypomagnesemia)
  - Organophosphates
  - Intracranial hemorrhage and trauma
  - Bradydysrhythmias
  - Dietary (anorexia nervosa, liquid protein diets)
- Wolff–Parkinson–White syndrome
- Brugada syndrome
- Idiopathic ventricular tachycardia
- Specialized conduction system abnormalities
  - Lenègre disease
  - Lev disease

Prolongation of the QT interval on the ECG increases the risk of SCD as a consequence of the increased risk of polymorphic ventricular tachycardia (VT). This prolongation predisposes myocardium to re-entry phenomenon. Re-entry is the major mechanism by which a dysrhythmia is created and maintained, although triggered activity and increased automaticity are also important. A minority of cases of SCD begins with a bradydysrhythmia or an organized rhythm without a pulse (pulseless

electrical activity [PEA]). VF usually begins with a run of sustained or nonsustained VT that degenerates to VF.

The net result of the dysrhythmia is global cessation of blood flow and corresponding ischemic injury to various organs. Resultant hypoxia and hypotension cause cessation of aerobic metabolism within seconds. Anaerobic metabolism occurs that cannot meet the metabolic demands of the tissues, and subsequent cell death ensues if spontaneous circulation is not resumed. The time before irreversible cell death is dependent on the metabolic rate of the organ system. Both the heart and brain have high metabolic rate and are very sensitive to ischemic insults. Thus the probability of achieving successful resuscitation from cardiac arrest is related to the interval from onset to institution of resuscitative efforts, the setting in which the event occurs, the mechanism (VF, VT, PEA, or asystole), and the clinical status of the patient prior to the cardiac arrest.

Although estimates vary widely, VF and pulseless VT are responsible for 25% to 35% of all out-of-hospital episodes of SCD. PEA accounts for as much as 25%. The acute management of patients with SCD is based upon the underlying electrocardiographic rhythm. During the course of resuscitation, patients may manifest many different rhythms, and therapy is modified based on these changes.

CLINICAL PRESENTATION

Patients suffering from SCD do not have any more specific complaints than those suffering any major cardiac or pulmonary event. Often, symptoms such as increasing angina, dyspnea, palpitations, easy fatigability, and other nonspecific complaints are experienced by these patients in the preceding days to months of the event. However, the onset of the terminal event of SCD, if instantaneous or abrupt, is cardiac in origin in more than 95% of patients. Dysrhythmic events, characterized by a high likelihood of patients being awake and active immediately prior to the event, are dominated by VF as the electrical mechanism, and have a short duration of terminal illness. Patients who have circulatory failure deaths tend to have more systemic medical problems and present with a higher incidence of asystole and PEA. A cardiac arrest may be

characterized by symptoms such as prolonged angina or the pain of an MI, acute shortness of breath, palpitations, and lightheadedness. The complete loss of consciousness in this setting is the *sine qua non* in cardiac arrest. The natural history of cardiac arrest is to progress to death within minutes unless expedient interventions are undertaken.

Phases of Resuscitation

Many researchers now consider there to be three distinct time-sensitive phases of cardiac arrest: electrical, circulatory or hemodynamic, and metabolic. Treatment emphasis varies according to the phase (9).

The electrical phase occurs during the first 4 minutes of arrest caused by VF. This is the period when immediate defibrillation is likely to be successful. As ischemia progresses, the success of attempted defibrillation diminishes without CPR. The hemodynamic or circulatory phase occurs during the period of 4 to 10 minutes after sudden cardiac arrest. This phase is characterized by transition to slow VF wavelets as ischemic metabolites accumulate in the myocardium. The patient may remain in VF. Although early defibrillation has traditionally been advocated for all patients found in VF, there is evidence that patients with time-sensitive phases caused by prolonged pulselessness may benefit from well-performed CPR to generate adequate cerebral and coronary perfusion prior to the initial attempts at defibrillation. There is insufficient evidence to determine if the 1½ to 3 minutes of CPR should be provided prior to defibrillation (10). CPR should be performed while a defibrillator is being readied for use. Treatment of the metabolic phase, which is defined as occurring after >10 minutes of pulselessness, stresses postresuscitation measures including hypothermia therapy. In the absence of conversion into a perfusing rhythm, patients who have reached this phase generally do not survive.

ED EVALUATION AND MANAGEMENT

Many of the recommendations stated in this chapter are taken from the guidelines for CPR introduced in 2010 by the American Heart Association. The new CPR guidelines evolved from emerging evidence-based resuscitation studies (Table 3.2). Based on their extensive review, the AHA and European Resuscitation Council (ERC), in collaboration with the International Liaison Committee on Resuscitation (ILCOR), published updated guidelines for BLS and ACLS.

TABLE 3.2
Levels of Evidence for Interventions

Class I	Definitely helpful
Class IIA	Acceptable, probably helpful
Class IIB	Acceptable, possibly helpful
Class III	Not indicated, may be harmful
Class indeterminate	No recommendation until further evidence available

Return of spontaneous circulations (ROSCs) is dependent on restoration of adequate cardiac function. Restoration of normal brain function is the defining factor of a successful resuscitation. The likelihood of attainment of both of these goals decreases with each passing minute of the cardiac arrest. Healthcare providers need to orchestrate simultaneous assessment and management of a cardiac arrest victim.

Patients require airway and ventilatory support, control of cardiac dysrhythmias, and cardiac output stabilized to restore organ perfusion. Emphasis is on immediate, uninterrupted, high-quality CPR and early defibrillation. These procedures along with advanced life support measures such as endotracheal intubation, pacing, pressor agents, and insertion of an intravenous (IV) line carry out these goals in resuscitation. The final goal is to restore ROSC before irreversible neurologic damage occurs. If the patient is resuscitated, rapid diagnosis and proper management of the pathologic condition that precipitated and resulted from the arrest are essential for optimal outcome. Treatment with mild hypothermia also improves cerebral resuscitation in these patients.

Basic Cardiopulmonary Resuscitation

Americans spend about a billion dollars a year on some form of CPR training or retraining. Yet the utility of this training is limited in the field because of the poor outcome of community cardiac arrests. CPR alone is of little value for restoring effective circulation and preventing brain death. The survival from SCD is dependent on a series of actions represented by the AHA Chain of Survival: early access to 911, early CPR, early defibrillation, and early advanced care.

An algorithmic approach to the unresponsive victim is used. Once a victim is found unresponsive, activation of the EMS system should occur. The activation of the EMS system to allow rapid initiation of ACLS protocols is the first step in the graduated response to care. If the lay rescuer finds an unresponsive victim who is breathing abnormally or not at all, CPR should be initiated. Trained healthcare providers should take no longer than 10 seconds to check a pulse before CPR is initiated. For lay person/untrained personnel, chest compression only CPR (no intervening breaths) is recommended (11). For trained personnel, compressions should be performed prior to rescue breaths in a ratio of 30:2 with a rate of 100 compressions per minute. The patient's airway can then be opened, followed by two breaths that should make the chest rise. Healthcare providers can then check for a pulse and, if it is absent, can initiate CPR in cycles of 30 compressions to two breaths. The function of basic CPR is to provide some blood flow to vital organs until more definitive treatment, such as defibrillation, can be initiated. Once a defibrillator arrives, the electrical rhythm of the heart can be ascertained, and, if a shockable rhythm is present, defibrillation can occur.

Most studies show a benefit of layperson CPR in the resuscitation of victims of cardiac arrest, especially when initiated early. "Hands only" CPR is a potentially lifesaving technique involving no mouth-to-mouth contact and has been the focus of the American Heart Association media blitz to educate the public that patients who get immediate CPR have twice the survival of those who do not. The earlier the CPR is applied the better the outcome becomes. Cardiac

output generated by standard chest compressions is <10% to 30% of baseline and decreases precipitously with both time to initiation and duration of chest compressions. Endogenous mechanisms direct blood flow preferentially to the heart and brain during the early minutes of resuscitation. This distribution of blood flow is ideal during CPR because the goal is to generate myocardial perfusion adequate to restore organized electrical activity and effective mechanical function of the heart while minimizing ischemic brain injury. This response becomes ineffective within minutes of circulatory arrest; so early intervention is the key to survival.

The mechanism of blood flow during closed-chest compressions has been continuously debated. The major theories include (a) the direct cardiac compression model in which CPR squeezes the heart between the sternum and the thoracic spine, creating a pressure gradient between the ventricles and the great arteries and (b) the thoracic pump mechanism in which the thorax acts as a pump when the chest is compressed, generating pressure gradients between intrathoracic and extrathoracic structures. In either method, the valve system in the heart allows forward, rather than retrograde, blood flow (12) (See Figure 3.1. The boxes bordered with dotted lines indicate actions or steps performed by the healthcare provider but not the lay rescuer.)

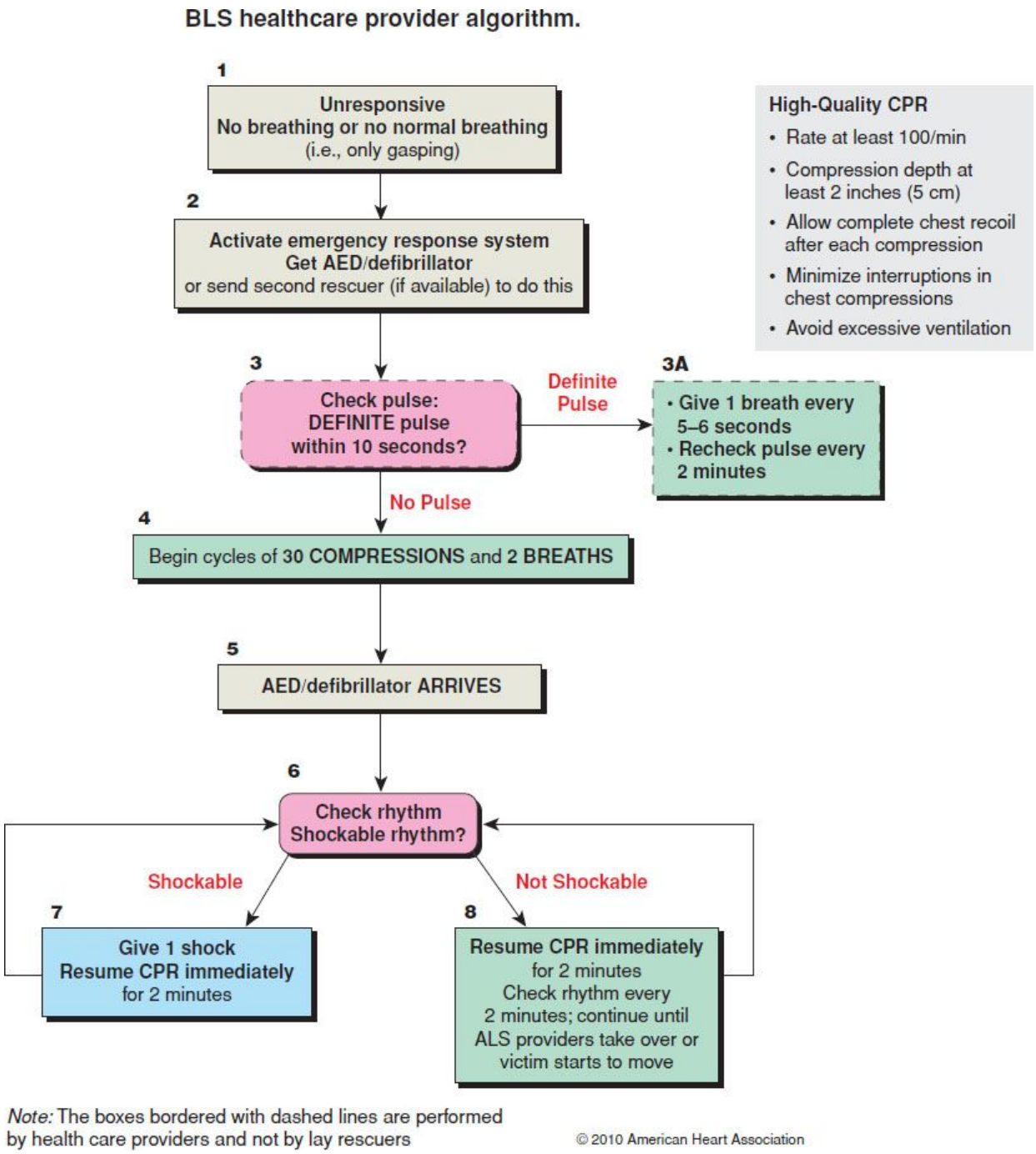

FIGURE 3.1 Adult basic life support healthcare provider algorithm. (From Berg RA, Hemphill R, Abella BS, et al. Part 5: Adult basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122: S685–S705.)

The mechanism used to stimulate blood flow back to the heart is controversial. It was recently recognized that a small vacuum occurs in the thorax after each chest compression. New devices have been developed to increase this vacuum effect, such as the vest approach, active compression–decompression, and an impedance threshold valve. Using these adjuncts for resuscitation in this manner has been tried, but clinical results have proven disappointing for many reasons, including an inability to implement the mechanism and an inability to overcome the standard CPR mindset. Thus, CPR has changed very little in the past 20 years.

CPR has now taken a more central role in the provision of BLS. The current focus is on high-quality CPR. Poor performance of CPR is one factor contributing to poor outcomes. Multiple studies assessing both in-hospital and prehospital CPR performance have shown that trained healthcare providers consistently fail to meet BLS guidelines. Outcomes from sudden death are dependent on the effectiveness of chest compression, and chest compressions are thought to be the most important element of CPR. When performed at a rate of 100 compressions per minute, with a downstroke of at least 38 mm and allowing the chest to recoil fully between each downstroke, coronary perfusion pressures are optimized, and ROSC is maximized. Most importantly, interruptions in compressions, regardless of how brief, result in a decline in coronary perfusion pressure and result in worse outcomes (13). Clinicians must strive to minimize interruptions of compressions, because interruptions that exceed 15 seconds appear to significantly reduce the success of resuscitation, increase myocardial dysfunction, and significantly reduce survival. The new guidelines mandate that for routine resuscitation, only a single shock, rather than a sequence of three shocks, be delivered so that there is minimal interruption of compressions. Another mandate is to immediately resume chest compressions after defibrillation, decreasing the delay that occurs for a visual confirmation of rhythm. If there is a delay in recognizing that a perfusing rhythm has occurred, continuing chest compressions is not likely to be damaging. The 2010 ACLS protocols stress initiating advanced

procedures (advance airway, medication, and reassessments) in a way that does not interrupt CPR (14).

The precordial thump was originally advocated for use in a witnessed cardiac arrest scenario. A forceful precordial thump can convert patients from VF or pulseless VT into a perfusing rhythm. However, patients can also be converted from coordinated cardiac activity to VF, pulseless VT, or asystole. There is little recent literature in the form of peer-reviewed studies, but there are numerous case reports of both benefit and risk (15). The precordial thump should not be used for unwitnessed out-of-hospital cardiac arrest. The precordial thumb may be considered for patients with witnessed, monitored, unstable VT including pulseless VT if a defibrillator is not immediately available, but this should never delay CPR and shock delivery (13).

Airway

After assessing a cardiac arrest victim's unresponsiveness and activating the response system (in the community, the EMS system and the code team in a hospital are activated), the next step is airway management if there is no immediate access to a defibrillator. In a cardiac arrest victim, the most common reason for airway obstruction is from the tongue falling back in the oropharynx. The airway can be opened by performing either a jaw-thrust or head-tilt–chin-lift maneuver (see Chapter 2). The jaw thrust is the better maneuver if any trauma is suspected or if cervical spine immobilization is required (16).

If the airway is still obstructed after these maneuvers, one must be concerned about an obstructed airway from another cause. The Heimlich maneuver, or subdiaphragmatic abdominal thrust, is the recommended procedure for clearing the obstructed airway of a foreign body. The rescuer's hand is positioned between the patient's xiphoid and navel, and several quick thrusts are administered in an attempt to relieve the foreign body obstruction. If the victim is unconscious, like a victim of SCD, the abdominal thrust maneuver may be accompanied by attempts to visualize the foreign body in the pharynx and by finger sweeps to remove the foreign body.

Breathing

The 2010 AHA Guidelines for CPR and Emergency Cardiovascular Care (ECC) recommend the initiation of compressions before ventilations. Blood flow depends on chest compression and delays in, and interruptions of, chest compressions reduce chance of survival. Beginning CPR with 30 compressions rather than two ventilations leads to a shorter delay to first compression. Once chest compressions have been initiated, a trained rescuer should deliver rescue breaths by mouth-to-mouth or bag mask to provide oxygenation and ventilation. The compression to ventilation ratio of 30 chest compressions to 2 ventilations should be followed. During the initial phase of cardiac arrest, the pulmonary vessels and the heart are likely to contain sufficient oxygenated blood to meet markedly reduced demands, and here the importance of compressions supersedes that of ventilations (16). As pulselessness persists, properly performed ventilations become more important, but clinicians must continue to ensure that ventilations do not interfere with the continuity of chest compressions. In the patient with an advanced airway, one asynchronous ventilation (not necessarily coordinated with chest compression) should be given 8 to 10 times per minute and should be delivered in as short a period as possible, while avoiding excessive ventilatory force. Only enough tidal volume should be given to obtain a chest rise. Multiple studies have shown that hyperventilation during resuscitation is routine either through higher rates or increased volumes. Hyperventilation raises intrathoracic pressure, which decreases venous return, pulmonary perfusion, cardiac output, and cerebral and coronary perfusion pressures. This hyperventilation reduces the success of defibrillation and decreases overall survival (16).

Bag mask ventilation is the first choice for BLS ventilation but should give way to alternative airway ventilation methods once ACLS providers are available. Tracheal intubation remains the procedure of choice for the unconscious, apneic patient, although there is no study directly addressing the timing of advanced airway placement during ACLS. This skill is not without significant challenges, and ACLS guidelines recommend intubation be

performed by those experienced in the procedure. Physical examination, an end-tidal carbon dioxide detector, or an esophageal detection device can confirm correct tube placement in the trachea. Continuous quantitative waveform capnography is recommended for confirmation and monitoring of endotracheal tube placement, CPR quality, and to aid in the detection of ROSC.

Other airway maneuvers recommended instead of bag valve masking are the laryngeal mask airway or the esophageal–tracheal Combitube (see Chapter 2). Once definitive airway management has occurred, the ventilations are administered independent of the chest compressions at a rate of 8 to 10 per minute.

Circulation

Lay rescuers and healthcare providers have difficulty detecting a pulse in unresponsive patients. Healthcare providers also often take too long trying to feel for a pulse. Lay rescuers should not check for a pulse and healthcare providers should spend no longer than 10 seconds feeling for a pulse. If a pulse check is undertaken, the carotid pulse should be checked because it is the most reliable pulse to check in low-flow states. If no pulse is detected, chest compressions should be instituted. The victim needs to be placed on a firm surface or backboard to assist mechanically with the compressions. The heel of the hand is placed on the lower half of the sternum and depressed 1.5 to 2 in in the adult. In children, the compression depth should be 1 to 1.5 in, and in neonates, it should be 0.5 to 1 in. The recommended compression rate is 100 times per minute in adults (ratio of 30:2 until an advanced airway is placed). Rescuers should push hard and push fast, allow complete chest recoil between compressions, and minimize interruptions in compressions for all victims (13).

Advanced Life Support

Defibrillation

The passage of current through the heart causes defibrillation with the goal of restoring a perfusing cardiac rhythm. If energy and current are too low, the delivered shock will not terminate the

dysrhythmia; if energy and current are too high, myocardial damage may result. Because of ischemia, acidosis, and electrophysiologic deterioration, a longer duration of VF correlates with a higher defibrillation threshold (17).

Modern day defibrillators deliver electrical shocks in one of two ways. Monophasic waveforms deliver current in one direction through the heart. Biphasic waveforms are used to deliver current through the heart, reverse polarity, and return through the myocardium. As a result, the energy needed for successful conversion of tachydysrhythmias with biphasic technology is often significantly less than that required with monophasic waveforms. The latest defibrillators and automated external defibrillators (AEDs) use biphasic waveform technology. If a biphasic defibrillator is available, providers should use the manufacturer's recommended energy dose for terminating VF (usually 120 to 200 J). If the provider is unaware of the effective dose range, the provider may use the maximal dose. Second and subsequent energy levels should be at least equivalent, and higher energy levels may be considered if available (14).

Current is directly related to the energy set on the defibrillator and inversely related to the transthoracic impedance. The transthoracic impedance can be minimized by attention to several factors, including position of the defibrillation paddles, the amount of energy selected on the defibrillator, firm pressure on the paddles, the use of conductive material between the skin and paddles, employment of sets of shocks, and the coordination of the shock with the end-expiratory phase of ventilation.

Defibrillation should be used quickly because delay will reduce the effectiveness of the resuscitation. If VF is corrected within 1 minute, there is a survival rate of $>90\%$; however, the survival rate falls by 10% per minute following the initiating event. In this fashion, public access defibrillation (PAD) has the potential to be one of the greatest advances in the treatment of SCD since the development of CPR. The mechanism for PAD is in the form of an AED. AEDs are computerized devices that are simple and reliable to operate; they allow lay rescuers with minimal training to administer this life-saving intervention. Self-adhesive electrode pads are provided with

application diagrams; voice and text prompts guide the rescuer through a few simple steps. A dysrhythmia analysis algorithm automatically interprets the rhythm and either recommends countershock, to be given by the push of a button, or no countershock. After the shock, the device immediately re-evaluates the rhythm and determines whether to recommend an additional shock. Flight attendants, security personnel, sports trainers, police officers, firefighters, lifeguards, family members, and many other trained laypersons have used AEDs successfully in the field.

In the past several years there have been significant changes in our understanding of the physiology of cardiac arrest and the technology used for defibrillation. Biphasic defibrillators, which measure impedance between the electrodes placed on the patient and adjust the energy delivered accordingly, successfully defibrillate approximately 85% of patients with the first shock. The 2010 guidelines restrict the recommended energy delivery to 360 J when using a monophasic defibrillator. With a biphasic defibrillator the suggested energy level is 200 J. The single major change regarding shock delivery in the most recent guidelines is to no longer recommend three-stacked shocks. The single shock should be followed by 2 minutes of CPR with no pulse check. Although there are no randomized controlled trials comparing the one-shock strategy to the three-shock strategy, the evidence for a reduction of coronary perfusion pressure with the interruption of chest compressions was felt to be compelling enough to recommend the one-shock strategy. Early after cardiac arrest, immediate defibrillation is likely successful. The question of intentionally delaying defibrillation to perform CPR is controversial with differing results in out-of-hospital studies. If a defibrillator is immediately available and VF or pulseless VT is evident, a 120-J biphasic shock should be delivered preceding airway management and IV line placement. If VF or pulseless VT is sustained after the initial 120-J shock, higher energies of 200 J are tried later in the resuscitation.

There is a wide variation in the ability of rescuers to determine pulselessness. The AHA 2010 BLS guidelines recommend that CPR performed by the lay rescuer be initiated immediately without a

pulse check upon determining unconsciousness in a patient without signs of respiratory effort. Healthcare providers must not spend >10 seconds checking for a pulse and should start CPR immediately if no pulse is felt. Agonal or gasping breaths should not be taken as evidence that organized respiratory effort is present. Further, the guidelines recommend that CPR be resumed for 2 minutes without a pulse check after defibrillation, regardless of the resulting rhythm. Data suggest that after defibrillation the myocardium does not provide effective cardiac output and that CPR may improve postdefibrillation perfusion (14).

Pharmacologic Therapy

Pressor Agents

Historically, catecholamine-induced adrenergic receptor stimulation is the therapy most commonly used in cardiac arrest, with epinephrine being the drug used most often. Epinephrine stimulates α_1 and α_2 receptors almost equally, and β_1 and β_2 receptors in a ratio of 1:4. We now realize that trials validating the use of epinephrine in cardiac arrest are not well defined because there are no prospective clinical trials. Although some study results have raised doubts about the benefit of epinephrine, including a large prospective study published in 2012, pending more conclusive data or a formal change in ACLS protocols, epinephrine is still recommended in accordance with ACLS guidelines (18). “High-dose” epinephrine was endorsed in cardiac arrest if regular-dose epinephrine was unsuccessful in resuscitation, only to have the endorsement rescinded by the AHA when larger numbers revealed no benefit and potential harm with such administration. Some studies found that patients may have a higher incidence of ROSC with high-dose epinephrine but no improvement in neurologic outcome. Patients with irreparable central nervous system (CNS) injury may result in significant burden on families and healthcare resources. At present, meta-analyses have not determined if high-dose epinephrine is better, worse, or the same as standard dose. The current recommended dose is epinephrine 1 mg initially

intravenously/intraosseously, with repeated doses every 3 to 5 minutes, but the optimal dose has not been established (19).

Vasopressin, also termed antidiuretic hormone, is also part of the treatment armamentarium for the cardiac arrest victim who has VF or pulseless VT. Vasopressin produces the same positive effects as epinephrine in terms of vasoconstriction and increasing the blood flow to the brain and heart during CPR. Vasopressin may not have the adverse effects on the heart that epinephrine does, such as increased ischemia and irritability and, paradoxically, the propensity for VF. Circulating endogenous vasopressin concentrations were high in patients undergoing CPR, and levels in successfully resuscitated patients are significantly higher than in patients who died. Meta-analysis of trials comparing vasopressin with epinephrine for cardiac arrest found no evidence of improved overall outcome or in any subgroup associated with vasopressin therapy (19). Vasopressin is given as a single one-time dose (40 U IV/IO) because of the much longer half-life of 10 to 20 minutes. Vasopressin can be administered as an alternative to the first or second dose of epinephrine.

There is limited experience with vasopressin in PEA or asystole, so epinephrine remains the pressor of choice empirically.

Antidysrhythmic Agents

The role of antidysrhythmic drugs is to suppress premature ectopic complexes and improve symptoms related to palpitations. Most of the antidysrhythmic agents raise the fibrillation threshold and are thus useful for preventing recurrent VF in patients who have been successfully defibrillated.

Amiodarone is categorized as a class III antidysrhythmic but contains characteristics of all four Vaughan Williams classes. Amiodarone can be considered for VF/pulseless VT that is refractory to CPR and vasopressor therapy. In blinded randomized controlled trials in adults with refractory VT/VF in the out-of-hospital setting, paramedic administration of amiodarone (300 mg or 5 mg/kg) improved survival to hospital admission rates when compared with administration of placebo or 1.5 mg/kg or lidocaine (20). This study demonstrated no difference between the amiodarone and placebo

groups in hospital discharge of patients with good neurologic functioning, although the study was underpowered for these observations. Additional studies documented consistent improvement in defibrillation response when amiodarone was given to humans or animals with VF or hemodynamically unstable VT. In the ALIVE trial of patients with persistent or recurrent VF despite defibrillation and epinephrine, the number of patients surviving to hospital admission was higher with amiodarone. The ARREST trial in patients with resistant VF/VT again showed increased survival to hospital admission in the amiodarone group. Time to therapy with amiodarone was an independent predictor of survival (21). No study has shown or been powered to show differences in survival to hospital discharge when comparing amiodarone to lidocaine. Amiodarone has been associated with more treatment requiring adverse effects including hypotension and bradycardia when compared to lidocaine but this has been attributed to the vasoactive solvents, as when these products were removed, there was no more hypotension that associated with lidocaine administration (22). The dosage of amiodarone in VF/pulseless VT arrests is 300 mg IV push.

Lidocaine has been used to treat VF/pulseless VT but with little evidence to support its use. The only evidence for lidocaine's use is from a large historical trial in which receipt of the drug was associated with improved resuscitation and admission alive to hospital. This study had nursing staff present only for the lidocaine cohort, which could explain the difference in survival alone (23). Lidocaine has thus taken an indeterminate role in ACLS and is primarily used if amiodarone is unavailable. The initial recommended dosage of lidocaine is 1 to 1.5 mg/kg IV/IO push. This dose can be followed with 0.5 to 0.75 mg/kg every 5 to 10 minutes for refractory VF to a maximum of 3 mg/kg.

Procainamide is no longer considered an antiarrhythmic option if amiodarone or lidocaine is unsuccessful in breaking VT/VF, given the time required for infusion of an effective dose of procainamide. Procainamide is an effective agent for suppressing ectopic ventricular complexes and VT, as well as other perfusing ventricular dysrhythmias. Procainamide has a limited use in cardiac arrest

because of the slow loading to therapeutic doses. Procainamide is administered in an infusion of up to 50 mg/min to a total maximum of 17 mg/kg. The previous use of procainamide in cardiac arrest was supported by only one retrospective comparison study of 20 patients (24).

Magnesium has an unclear mechanism of action in treatment of dysrhythmias. Magnesium's primary use is in the management of *torsades de pointes,* although this indication has not had formalized trials. There have been studies that show a correlation between normal magnesium levels and successful resuscitation, but the administration of supplemental magnesium to patients in arrest has not been studied. Three randomized controlled trials have not shown a benefit of magnesium administration in VF arrest in out-of-hospital and in-hospital settings. Its routine use is not recommended in cardiac arrest. The dosage of magnesium is 1 to 2 g IV push in this specific subset of torsades patients.

Guidelines for Cardiac Arrest

The AHA developed guidelines for treatment of patients in cardiac arrest. Every few years the protocols are updated to include the latest in cardiovascular literature, so clinicians should be aware of the most recent version. Although the ACLS treatment for patients in cardiac arrest is based on the ECG monitor rhythm, the clinician must always consider the etiology of the arrest in developing a treatment plan. Cardiac arrest is an endpoint of a physiologic process that results in the loss of circulation and ventilation. Treatable causes of cardiac arrest should always be thought of during resuscitation (Table 3.3).

TABLE 3.3
Most Frequent Causes of Asystole and Pulseless Electrical Activity

Hypovolemia	Tension pneumothorax
Hypoxia	Tamponade (cardiac)
Hydrogen ion (acidosis)	Thrombosis (cardiac)
Hyperkalemia/hypokalemia	Thrombosis (pulmonary)
Hypothermia	Toxins (β blockers, Ca^{++} channel blockers, digoxin)

Ventricular Fibrillation and Pulseless Ventricular Tachycardia

The key to the treatment of patient with VF or pulseless VT (Fig. 3.2) is to remember that successful resuscitation depends on electrical defibrillation. All other treatments, including CPR, intubation, and drugs, are merely attempts to prepare the patient for successful defibrillation. Defibrillation should be attempted as soon as the diagnosis is made.

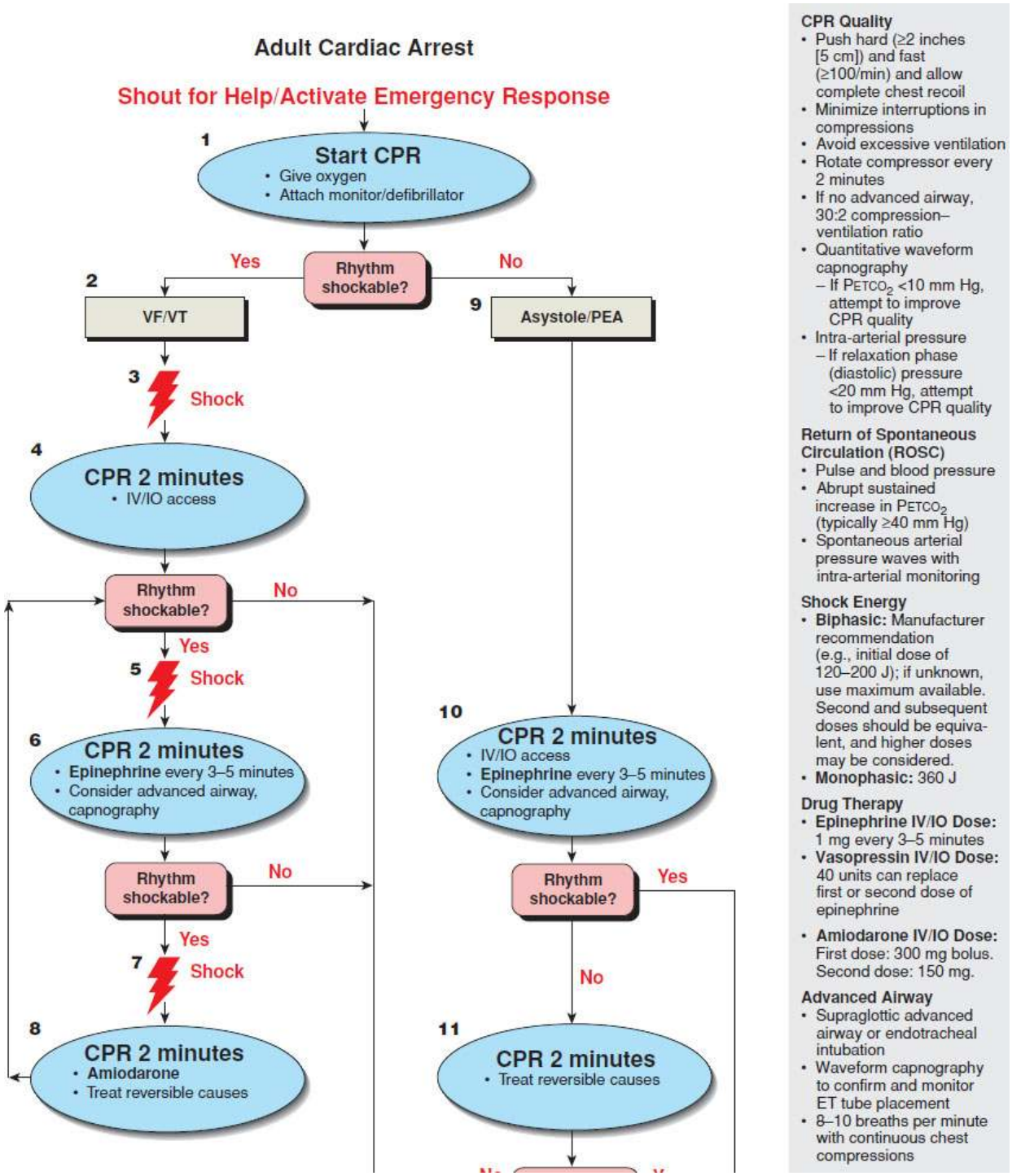

FIGURE 3.2 Advanced cardiac life support pulseless algorithm. (Neumar RW, Otto CW, Link MS, et al. Part 8: Adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency

Cardiovascular Care. *Circulation*. 2010;122: S729–S767.)

If defibrillation is unsuccessful, CPR is initiated, the trachea is intubated, and an IV line is placed as soon as possible. Epinephrine or the more recently endorsed vasopressin is the first recommended pharmacologic agent. After administration of the drug, attempts at defibrillation should occur. Antidysrhythmic drugs may be useful in preventing refibrillation once the patient has been electrically defibrillated. Amiodarone is recommended as the first antiarrhythmic agent. Subsequent treatment with magnesium, procainamide, or lidocaine may be used if first-line medications are ineffective. Treatment with sodium bicarbonate should be initiated if there is clinical suspicion of hyperkalemia, tricyclic antidepressants, or pre-existing acidosis. Shock-resistant VF develops in only 10% to 25% of all cardiac arrests, yet 87% to 98% of these patients die.

Asystole

Asystole (Fig. 3.2) is a cardiac arrest rhythm associated with no discernible electrical activity on the ECG. The patient with primary asystole has a poor prognosis for resuscitation. The single most important therapy for asystole is to search for, identify, and reverse any treatable cause. Asystole is often a secondary event, resulting from VF that has been present for several minutes or longer that then has led to the loss of all electrical activity as a result of hypoxia, acidosis, and death of myocardial tissue. The asystolic patient may actually be in fine VF when using confirmation in another lead on the monitor. The diagnosis of asystole should thus be confirmed by checking a straight-line rhythm on three leads. If there is any suspicion of fine VF masking as asystole, the clinician should proceed to immediate defibrillation. As in VF, the clinician must consider the underlying process that precipitated asystole and focus treatment in this specific area while following ACLS protocols (Table 3.3). These conditions cause only the clinical deterioration of these conditions; they do not cause the rhythm.

An important minority of SCD events begins with a bradydysrhythmia that degenerates to asystole. Bradyasystole occurs when there is an intrinsic failure of the heart's electrical system. This failure can be in the form of failure to generate or propagate an adequate number of ventricular depolarizations per minute to sustain consciousness and other vital functions. It is unclear why bradyasystole, which uses very little myocardial oxygen and should have enough high-energy phosphate stores to initiate an ROSC, has such a dismal outcome in the majority of cases. Certainly, the underlying myocardial and valvular dysfunctions in conjunction with systemic insults are entwined in this process. Several studies that used cardiac pacing in this setting showed poor outcomes. To be effective, pacing must be initiated in the first few minutes after arrest. Pharmacologic treatment of asystole involves the use of epinephrine to improve myocardial and cerebral blood flow during CPR. There is conflicting evidence of the benefit of atropine in cardiac arrest. The latest guidelines suggest that routine use of atropine during PEA or asystole is unlikely to have a therapeutic benefit. For this reason atropine has been removed from the cardiac arrest algorithm (14).

Pulseless Electric Activity

PEA (Fig. 3.2) is coordinated electrical activity of the heart (other than VT or VF) without a palpable pulse. In this scenario, either the heart cannot pump at all (true electrical–mechanical dissociation [EMD]) or myocardial contractions do occur but without a palpable pulse (pseudo-EMD). PEA is the term used to describe both true and pseudo-EMD. Primary PEA, like asystole, has a very poor prognosis. The differential of causes of PEA is the same as for asystole.

PEA is the result of a primary disorder of electromechanical coupling in myocardial cells. PEA is most often associated with global myocardial-energy depletion and acidosis resulting from ischemia or hypoxia. Pseudo-EMD is a transient state in the progression to EMD and has the same etiology. In these cases of severely decreased flow, patients must be evaluated for cardiac and extracardiac causes of severe shock.

Intubation and ventilation with 100% oxygen plus an IV fluid bolus can begin the resuscitation. Careful consideration of the common causes of PEA should dictate subsequent interventions. Bedside ultrasonography might allow the treating physician to determine whether or not the heart is beating and whether or not pericardial fluid is present. Alternatively, the placement of an arterial line can be used to differentiate severe shock states from true EMD. In cases where these modalities are unavailable, the clinician must consider the differential and decide whether or not needle thoracostomy and pericardiocentesis are indicated. Once extracardiac causes of EMD are excluded, treatment recommendations include epinephrine to improve myocardial and cerebral blood flow during cardiac arrest and atropine if the ECG shows bradycardia.

As per the above section, atropine is no longer recommended for PEA arrests.

The absence of proven efficacy of sodium bicarbonate and the numerous adverse effects associated with its use have led to the recommendation that it not be routinely used during CPR. It can create extracellular alkalosis that will shift the oxyhemoglobin saturation curve and inhibit oxygen release. It can produce hypernatremia and therefore hyperosmolarity. It produces excess CO_2, which freely diffuses into myocardial and cerebral cells and may paradoxically contribute to intracellular acidosis (14). Sodium bicarbonate may have a role in the treatment of PEA when there is a specific cause such as known hyperkalemia, pre-existing bicarbonate-responsive acidosis, or a tricyclic antidepressant overdose or when alkalinization of the urine is indicated (as in aspirin or other drug overdoses). The classic dose of sodium bicarbonate is 1 mEq/kg.

Therapeutic Mild Hypothermia

Therapeutic hypothermia following hypoxic–ischemic insults has long been thought to offer nonspecific cellular protection. Neurologic injury is the most common cause of death in patients with out-of-hospital cardiac arrest and contributes to the mortality of in-patients with cardiac areas. By lowering the core temperature even a few

degrees reduces the risk of neurologic injury. A large body of evidence now suggests that the protective effects of cooling are much greater than can be explained by the reduction in oxygen and glucose. In animal models, hypothermia has been shown to foster neuroprotection, reduction of free radicals and excitatory neurotransmitters, and stabilization of membranes. Several reports of accidental hypothermia with good neurologic outcome after prolonged ischemic periods led to research in the use of hypothermia in the setting of injury and after surgery. Recent data show positive effects of mild therapeutic hypothermia after cardiac arrest. Some studies have demonstrated a decrease in mortality and a better neurologic outcome in patients who are cooled to 32°C to 34°C for 12 to 24 hours (25). Based on the published evidence, it has been recommended that mild therapeutic hypothermia be provided for the treatment of unconscious patients after prehospital cardiac arrest. Specifically, unconscious adult patients with ROSC after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C within 6 hours and maintained in this range for 12 to 24 hours after cardiac arrest.

Initiating and Discontinuing Resuscitation Efforts

It was classically taught that CPR should be instituted for all patients in cardiac arrest, except in two circumstances: (a) The patient made it clear, while competent and informed, that he or she did not want resuscitation efforts to be instituted; or (b) successful resuscitation would be futile because the patient has clear signs of irreversible death, such as *rigor mortis,* dependent lividity, or decapitation.

In the last 15 years, several studies challenged the usefulness of initiating ACLS protocols in all patients. In most geographic areas, all cardiac arrest patients are transported to the nearest emergency department (ED) for definitive care despite the futility of the resuscitation efforts and the attendant hazards to motorists, pedestrians, and EMS personnel. Transportation of all patients to the nearest ED can limit the availability of EMS personnel to care for other patients; increase patient waiting time; decrease ED, hospital bed, and equipment availability; and increase the costs.

Termination of resuscitation (TOR) guidelines can identify nonsalvageable patients. There is ample evidence that patients that fail out-of-hospital ACLS interventions do not survive to hospital discharge and that ED interventions in this patient population result in survival with good neurologic outcome in $<1\%$ of patients (26). No survivors of asystolic patients have been documented in normothermic patients with a call to arrival time by EMS personnel >8 minutes. Once undertaken, resuscitation efforts are generally continued until it is clear that the patient is not responding to them. The longer the patient remains in cardiac arrest without response, the worse the prognosis is for survival. After 30 minutes of resuscitation attempts, the prognosis is very poor. Consequently, the clinician must exercise his or her judgment as regards TOR.

Emergency physicians and paramedics are obligated to respect patients' wishes regarding resuscitation. In most cases, these wishes may be known through documentation on advance directives. The patient and patient's healthcare provider should update these forms and have them ready for paramedics or ED personnel, so that they can be used in an emergency situation. Many communities have developed a standardized "do not resuscitate" form that patients and their physicians can fill out. These forms document the patients' wishes and provide guidance for both EMS and hospital personnel.

There are three cardiac arrest characteristics that are associated with survival to hospital discharge: ROSC prior to transport, a shock given prior to transport, and cardiac arrest witnessed by EMS personnel (26). In any case of cardiac arrest, the decision to either not initiate or terminate advanced care is determined by the clinician using the best clinical judgment and knowledge of futility situations.

Invasive Cardiopulmonary Resuscitation

Studies in animal models show that techniques of invasive CPR, such as open-chest CPR and cardiopulmonary bypass, and the use of direct mechanical-assist devices improve hemodynamics, resuscitation, and the chances of surviving cardiac arrest. It has also been demonstrated that when invasive CPR is applied late in the treatment protocol (after more than 15 minutes of total arrest time), there is no

improvement in resuscitation. The resources required to provide many of the interventions, principally invasive perfusion technologies, cannot be justified unless there is clear benefit. The allocation of such resources to provide intensive resuscitation and postresuscitation support needs to be addressed from both medical and societal viewpoints.

Quality of Resuscitation Efforts

The use of capnometry to monitor end-tidal CO_2 levels during CPR provides a noninvasive assessment of the cardiac output generated by CPR. Other measures, such as invasive hemodynamic parameters, although useful, cannot realistically be used in an acute resuscitation setting. The quality of resuscitation efforts should also be assessed retrospectively by systemically tracking key variables and the outcome of resuscitation efforts in both the in-hospital and out-of-hospital settings.

Postresuscitation

The goals of postcardiac arrest care are to optimize cardiopulmonary function and vital organ perfusion. The resuscitation of a cardiac arrest victim does not end with an ROSC. The underlying medical conditions leading to the arrest as well as the complications of prolonged global ischemia must be carefully managed to result in an optimal outcome. Although the neurologically intact victim of a cardiac arrest is rare, there is no reliable way to determine the prognosis of an individual patient immediately after resuscitation.

Because the majority of patients have a cardiac etiology for their arrest, immediate focus in the early postresuscitation period should involve looking for an acute coronary syndrome. An ECG should be performed to look for evidence of MI. Administration of all cardiac therapies can be initiated if ischemic heart disease is the presumptive diagnosis. Heparin, aspirin, thrombolytics, and angioplasty can all be considered. Antidysrhythmic therapy for all patients who presented with VF/pulseless VT should also be initiated. Patients with high-risk conduction abnormalities, such as right bundle branch blocks

associated with a hemiblock, second-degree type II blocks, third-degree heart blocks, or new left bundle branch block, should have transthoracic pacing pads placed and used if necessary.

Mild hypothermia seems to be a sufficient compromise between the beneficial effects of mitigation of ischemic membrane damage and reperfusion injury and the adverse risks of dysrhythmic, inflammatory, hemodynamic, and coagulation disorders. Mild hypothermia is potentially the first direct therapy for the brain after cardiac arrest.

DISPOSITION

Patients who survive initial resuscitation should be admitted to the intensive care unit where therapeutic hypothermia care may be continued and further intensive monitoring accomplished. Postresuscitation patients who have evidence of an acute coronary syndrome may be moved to the catheterization laboratory.

Common Pitfalls

- Failure to stay calm and approaching the patient in an organized fashion. It is important to remember that resuscitation efforts require a well-disciplined team in which each member plays a role. Optimal patient care depends on management in a well-controlled, calm environment that is focused on each individual task. The emergency physician should take control of the situation and lead all players in the resuscitation.
- Failure to provide consistent ongoing CPR during SCD.
- Administration of amiodarone, bicarbonate, magnesium, or procainamide endotracheally. The only medications that can be administered via the endotracheal tube are epinephrine, atropine, lidocaine, and naloxone.
- Erroneously giving intracardiac medications. There are no current indications to give intracardiac medications.
- Failure to suspect hyperkalemia in renal failure patients for patients in cardiac arrest. Resuscitation of these patients should include calcium gluconate, bicarbonate, and insulin with glucose. Be sure to look for monitor and ECG manifestations of

hyperkalemia such as hyperacute T waves, prolongation of the QRS complex, or a sine wave pattern.

- Failure to defibrillate in the appropriate manner. The majority of patients in VF can be defibrillated. If unsuccessful, review your technique. One paddle should be placed to the right of the sternum below the right clavicle, and the other should be placed in the midaxillary line at the level of the nipple. If the paddles are too close together, the skin, rather than the heart, may be getting the current. Alternatively, the AP position may be used over the left precordium. Firm pressure of approximately 25 lb should be applied to each paddle, and the appropriate contact gel must be used. The shocks should be given in pairs or triplets to decrease the transthoracic impedance and improve the chances of successful defibrillation.
- Mistaking *torsade de pointes* for VT or fibrillation. Although antidysrhythmic drugs are commonly ineffective in terminating torsades, electrical cardioversion is usually successful. Further treatment with magnesium sulfate, isoproterenol, or overdrive pacing decreases the QT interval and prevents recurrence.
- Failure to induce postresuscitation hypothermia.

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CHAPTER 4
Shock

Emanuel P. Rivers, David Amponsah, John Gallien, and Anja K. Jaehne

More than 1.5 million cases of shock present to United States (US) emergency departments (EDs) each year, and the number is increasing, particularly in patients older than 65 years. The incidence of septic shock, for example, has increased markedly for the past 10 years, with an annualized increase of 8.7% and more than 600,000 cases presenting to EDs each year in US (1). The annual economic burden for the care of patients in US with septic shock alone is more than $60 billion. Mortality from shock remains high despite better understanding of the underlying pathophysiology and aggressive treatment. Approximately 30% to 45% of patients in septic shock and 60% to 90% of those with cardiogenic shock die within 1 month of presentation. Over the last decade, the illness severity and duration for shock patients has significantly increased in EDs in US (2,3). Because of this, ED management is a central role in improving outcomes for these fragile patients.

Shock is defined as an impairment of circulatory function leading to global tissue hypoxia. The presentation may be as subtle as mild decompensated heart failure (4,5) or as obvious as the ultimate shock state of cardiac arrest. It is estimated that 12% of patients with undetected severe sepsis and septic shock are admitted to general medical floors, which is frequently associated with morbid and lethal consequences after hospital admission (6,7). Irrespective of the type of ED presentation, timely diagnosis and aggressive intervention prevents complications and significantly improves survival (7), especially in the ED setting (7).

PHYSIOLOGY

The principles of oxygen delivery (Do_2) and utilization are paramount to the understanding of shock. A maximum of four molecules of oxygen are loaded onto each molecule of hemoglobin as it passes through the lungs. If all available oxygen sites are occupied (four per molecule of hemoglobin), then the arterial oxygen saturation (Sao_2) is 100% (Fig. 4.1). Arterial oxygen concentration (Cao_2) is the amount of oxygen bound to hemoglobin plus the amount dissolved in plasma. Oxygen delivery (Do_2) is the product of the Cao_2 and cardiac output (CO). Oxygen consumption ($\dot{V}o_2$) reflects a sensitive balance between supply and demand. Normally, the tissues consume about 25% of the oxygen carried on hemoglobin, and venous blood returning to the right heart is about 65% to 75% saturated venous oxygen saturation (Svo_2). When oxygen supply is insufficient to meet demand, the first compensatory mechanism is an increase in CO. If the increase in CO is inadequate, the amount of oxygen extracted from hemoglobin by the tissues increases (systemic oxygen extraction or OER), reflected in a decrease in Svo_2.

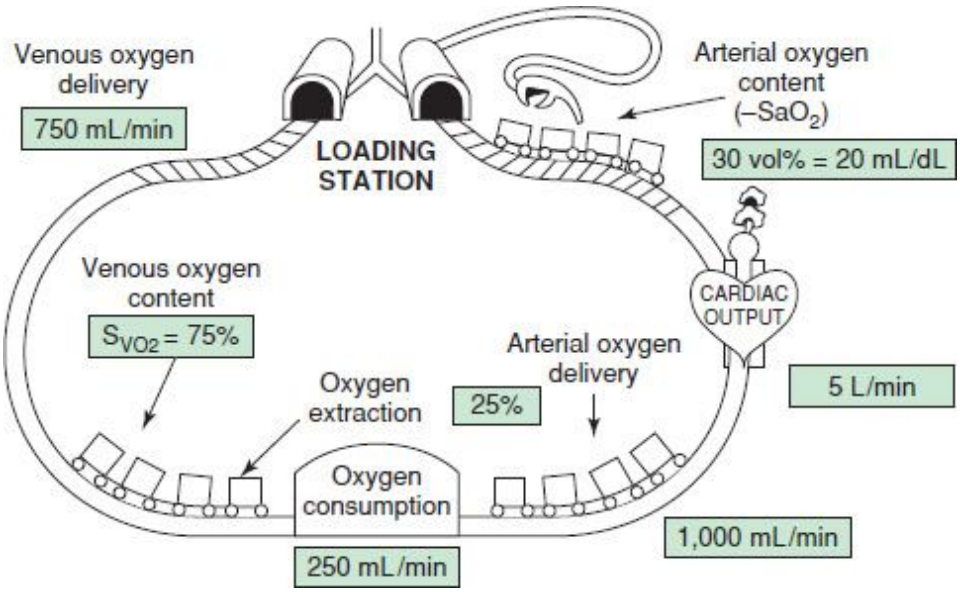

FIGURE 4.1 Oxygen saturation, content, and delivery.

When compensatory mechanisms (increased OER or decrease in SvO_2 less than 50%) fail to correct the imbalance between tissue supply and demand, anaerobic metabolism occurs, resulting in the formation of lactic acid (normally between 0.5 and 1.9 mmol/L). Most cases of lactic acidosis are caused by inadequate Do_2, but lactic acidosis occasionally can develop from an excessively high oxygen demand, as in status epilepticus or other nonhypoxic causes of lactic acidosis. In other cases, lactic acidosis occurs because of impairment in tissue oxygen utilization, as in septic shock, cyanide poisoning, and immediately after resuscitation from cardiac arrest. A normal Svo_2 and adequate Do_2 with an elevated lactate indicate such an impairment. An elevated lactate is a marker of impaired Do_2 or utilization and correlates with short-term prognosis of critically ill patients in the ED (8,9). However, a normal lactate is not infrequent in patients with shock (10,11). Svo_2 can also be used as a measure of the balance between tissue oxygen supply and demand. Svo_2 is measured through a pulmonary artery catheter, but similar information can be obtained from the central venous oxygen saturation ($Scvo_2$), which correlates well with Svo_2 and is more easily obtained in the ED setting (12).

Thus, shock is circulatory insufficiency caused by tissue Do_2 that is insufficient to meet oxygen demands. The result of shock is global hypoperfusion or tissue hypoxia and is manifested by a decreased venous oxygen content and metabolic acidosis (lactic acidosis). Global tissue hypoxia alone can independently activate the inflammatory response and serve as a comorbid variable in the pathogenesis of all forms of shock (13). The failure to diagnose and treat global tissue hypoxia in a timely manner leads to an accumulation of an oxygen debt, inflammation (14), organ dysfunction, and increased mortality.

CLINICAL PRESENTATION

The clinical presentation of shock can range from dramatic to subtle. Shock can be instantly apparent, as with acute myocardial infarction, anaphylaxis, or hemorrhage, whereas some patients may have few

symptoms other than generalized weakness, lethargy, or altered mental status. Symptoms that suggest volume depletion include bleeding, vomiting, diarrhea, excessive urination, insensible losses as a result of fever, or orthostatic light-headedness. A history of cardiovascular disease is important, particularly episodes of chest pain or symptoms of congestive heart failure (particularly systolic dysfunction). Prior neurologic diseases (e.g., Parkinson) can render patients more susceptible to complications from hypovolemia because of autonomic dysfunction. Use of medications, both prescribed and nonprescribed, is important. Some medications cause volume depletion (e.g., diuretics), whereas others depress myocardial contractility (e.g., β-blockers and calcium channel blockers) and others are vasodilators (e.g., niacin, erectile dysfunction, or prostatic hypertrophy drugs). The previous use of corticosteroids may predispose the patient to adrenal insufficiency. The possibility of an anaphylactic reaction to a new medication should also be considered.

The clinical presentation of shock varies depending on the precipitating cause such as cardiogenic, hypovolemic, obstructive, or distributive. Although not specific, physical findings taken as a composite may be useful in the assessment of patients in shock (Table 4.1). No single vital sign or physical finding is diagnostic of shock, as vital signs are frequently insensitive in detecting and assessing the severity of tissue hypoperfusion. Measurement of blood pressure can be particularly difficult because of peripheral vascular disease, tachycardia with a small pulse pressure, arteriovenous dialysis fistulas and dysrhythmias such as atrial fibrillation. Shock is usually, but not always, associated with systemic arterial hypotension, which is systolic blood pressure <90 mm Hg. Nonsustained hypotension, or a single episode, carries a significantly increased risk of death during hospitalization, which makes it a clinically significant and meaningful event (15).

TABLE 4.1
Clinical Findings in Shock

Temperature

- Hyperthermia, hypothermia, or afebrile, especially in the elderly

Skin

- Pale, dusky, clammy, cyanosis, mottling over the knees
- Sweaty
- Altered temperature
- Decreased capillary refill

Central Nervous System

- Acute delirium or brain failure
- Restlessness, disorientation, confusion, psychosis
- Coma

Neck

- Neck-vein distention or flattening

Respiratory

- Tachypnea
- Increased minute ventilation
- Increased dead space
- Bronchospasm
- Hypocapnia, respiratory failure, adult respiratory distress syndrome
- Respiratory alkalosis

Cardiovascular

- Tachycardia; S3 may result from high-output states
- Dysrhythmias
- Hypotension
- Increased then decreased pulse pressure
- *Pulsus paradoxus*
- Elevated shock index (heart rate: systolic blood pressure >1)
- β-Blockers may blunt response

Gastrointestinal

- Ileus
- Gastrointestinal bleeding
- Pancreatitis
- Acalculous cholecystitis
- Mesenteric ischemia from low-flow states

Renal

- Oliguria, anuria, and unexplained metabolic acidosis; paradoxical polyuria

Heme

- Hemoconcentration
- Decreased platelets
- Decreased fibrinogen
- Increased fibrin split products
- Increased D-dimers

Because blood pressure is the product of flow and resistance (mean arterial pressure [MAP] = CO × systemic vascular resistance [SVR]), the blood pressure may not fall in the presence of decreased CO if there is an increase in peripheral vascular resistance (Fig. 4.2). The insensitivity of blood pressure in detecting inadequate flow to tissues and global tissue hypoxia has been repeatedly confirmed. Thus, shock may occur with a normal blood pressure, and hypotension may occur without shock.

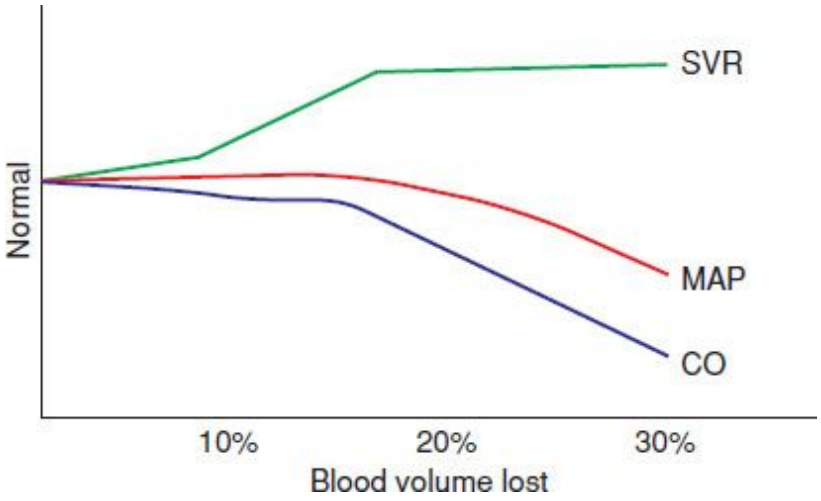

FIGURE 4.2 Relationship of SVR (systemic vascular resistance), MAP (mean arterial pressure), and CO (cardiac output) with volume loss.

The onset of shock provokes a myriad of autonomic responses, many of which serve to maintain perfusion pressure to vital organs. Stimulation of the carotid baroreceptor stretch reflex activates the sympathetic nervous system leading to (a) arteriolar vasoconstriction, resulting in redistribution of blood volume from the skin, skeletal muscle, kidneys, and splanchnic viscera; (b) an increase in heart rate and contractility that increases CO; (c) constriction of venous capacitance vessels, which augments venous return; (d) release of the vasoactive hormones epinephrine, norepinephrine, dopamine, and cortisol to maintain arteriolar and venous tone; and (e) release of antidiuretic hormone and activation of the renin–angiotensin axis to enhance water and sodium conservation to maintain intravascular volume. These compensatory mechanisms

attempt to maintain DO_2 to the most critical organs: the coronary and cerebral circulation. During this process, blood flow to other organs, such as to the kidneys and gastrointestinal tract, may be compromised, leading to organ failure.

The cellular response to decreased DO_2 is adenosine triphosphate (ATP) depletion, leading to ion pump dysfunction, influx of sodium, efflux of potassium, and reduction in membrane resting potential. Cellular edema occurs secondary to increased intracellular sodium while cellular membrane receptors become poorly responsive to the stress hormones insulin, glucagon, cortisol, and catecholamines. As shock progresses, lysosomal enzymes are released into the cells with subsequent hydrolysis of membranes, deoxyribonucleic acid, ribonucleic acid, and phosphate esters. As the cascade of shock continues, the loss of cellular integrity and the breakdown in cellular homeostasis result in cellular death (Fig. 4.3). The failure of the cell to utilize oxygen or perform cellular respiration is impaired, and thus endogenous heat generation is impaired. This process gives rise to hypothermia, a common clinical feature of shock. These pathologic events give rise to the metabolic features of hemoconcentration, hyperkalemia, hyponatremia, prerenal azotemia, metabolic acidosis, hyper- or hypoglycemia, and lactic acidosis.

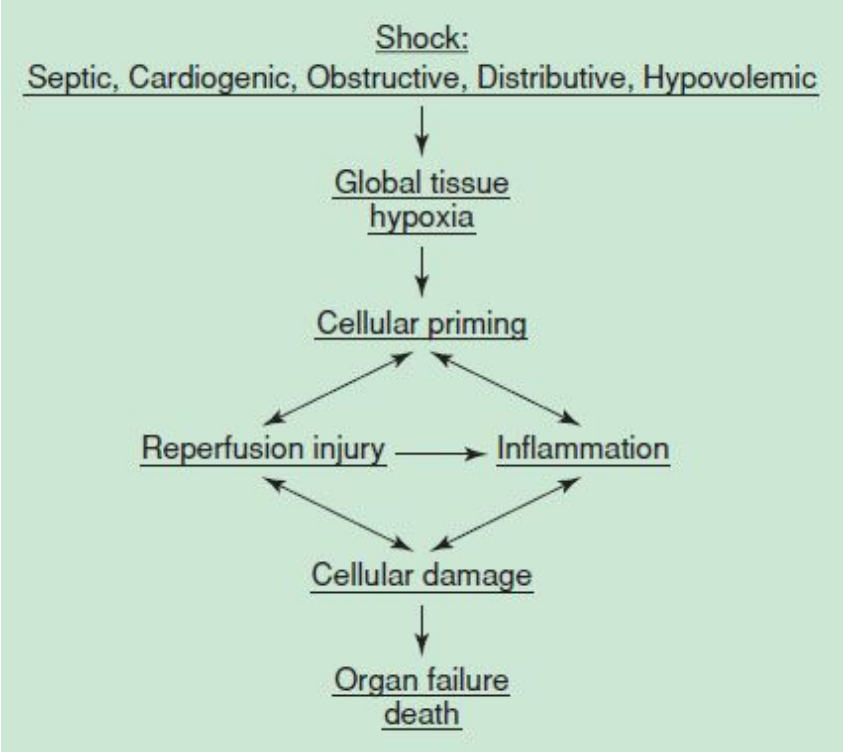

FIGURE 4.3 Mechanism of cell death.

The clinical presentation of early shock is often characterized as a syndrome called the systemic inflammatory response syndrome (SIRS). SIRS is defined as the presence of two or more of the following features: (a) temperature >38°C (100.4°F) or <36°C (96.8°F); (b) heart rate >90 beats/min; (c) respiratory rate >20 breaths/min; and (d) white blood cell count >12 × 10^9/L, <4 × 10^9/L, or with >10% immature forms or bands. SIRS may occur in any shock state. The stimulus for SIRS is a complex elaboration of humoral and cellular pro- and anti-inflammatory products, which induces a panendothelial cell disruption or generalized inflammation within the vast capillary network in each organ. The hemodynamic consequence of SIRS is the generation of global tissue hypoxia from hypovolemia, vasodilation, and myocardial suppression. There is an increase in oxygen demands secondary to fever or an increased work of breathing. Cytopathic tissue hypoxia develops when there is a defect in the peripheral utilization of oxygen in the tissues.

As SIRS progresses, organ dysfunction and the multiorgan dysfunction syndrome (MODS) ensue. This syndrome is characterized

by organ failures such as acute lung injury, adult respiratory distress syndrome, disseminated intravascular coagulation, hepatic failure, adrenal and renal failure, among others. Early detection and interruption of these hemodynamic perturbations are key for improving survival. Table 4.2 compares shock states.

TABLE 4.2
Comparison of Shock States

	Focused Ultrasound Assessment (16)	MAP	CVP	$Scvo_2$	Lactate	CI	SVR	Comment
Cardiogenic	Depressed left ventricular (LV) contractility Global hypokinesis Plethoric IVC, JVD Pulmonary edema/effusion	↓	↑	↓	↑	↓	↑	Myocardial infarction or decompensated heart failure
Obstructive	Large pericardial effusion or tamponade RV chamber dilatation and/or strain Right heart thrombus Paradoxic septal wall motion	↓	↑	↓	↑	↓	↑	Pulmonary embolus or pericardial tamponade, tension pneumothorax
Hypovolemic	Hypercontractile LV with small chamber size Decreased IVC diameter Ruptured aortic aneurysm Hemoperitoneum	↓	↓	↓	↑	↓	↑	Hemorrhagic or hypovolemic
Septic	LV contractility normal/abnormal IVC normal/abnormal Decreased CO/CI							
Stage 1	LV contractility normal/abnormal Decreased IVC diameter Decreased CO/CI	↓ or Normal	↓	↓	↑	↓	↑	Early sepsis, hypovolemia
Stage 2	IVC diameter normal	↓	Normal	↑	↑	↑	↓	Compensated
Stage 3	Depressed LV contractility	Normal	↑	↓	↑	Normal	Normal	Myocardial suppression
Stage 4	LV contractility normal/abnormal Decreased or normal CO/CI	↓	Normal	↑↑	↑	↑	↓	Impaired tissue oxygen utilization or cytopathic tissue hypoxia
Distributive	LV contractility normal/abnormal IVC normal or abnormal	↓	↓	↓	↑	↓	↓	Anaphylaxis, spinal shock

MAP, mean arterial pressure; CVP, central venous pressure; $Scvo_2$, central venous blood saturation; CI, cardiac index; SVR, systemic vascular resistance.

DIFFERENTIAL DIAGNOSIS

The four classifications of shock are based on etiology:

- Hypovolemic (caused by inadequate circulating volume), as in hemorrhagic shock
- Cardiogenic (caused by inadequate cardiac pump function), as in anterior wall acute myocardial infarction
- Distributive (caused by peripheral vasodilatation and maldistribution of blood flow), as in sepsis, anaphylaxis, or spinal cord injury
- Obstructive (caused by extracardiac obstruction to blood flow), as in a pulmonary embolus, cardiac tamponade, or tension

pneumothorax.

Although there may be an initial predominant cause of shock, as the shock state persists or progresses to irreversible end-organ damage, other pathophysiologic mechanisms become operative and can create a mixed picture.

ED EVALUATION

The clinical presentation and the presumptive etiology of shock dictate the use of ancillary studies. A battery of standard arterial blood gas, hematologic, coagulation, and biochemical tests usually provides an assessment of each organ function and may detect an abnormality that requires specific treatment. A wide range of laboratory abnormalities may be encountered in shock, but most abnormal values merely point to the particular organ system that is either contributing to or being affected by the shock state. No single laboratory value is sensitive or specific for shock. Additional studies, including an electrocardiogram (ECG), a chest radiograph (CXR), and source-specific plain radiographs or computerized tomography (CT), should also be done.

Most EDs in US have portable ultrasound systems available. These ultrasound systems used by appropriately trained ED physicians can be used in the evaluation of shock patients and may help to characterize the etiology of the shock state in a timely fashion. Bedside ultrasound assessment in the early evaluation of patients in shock should focus on volume status and anatomic function, with the assessment of the heart, IVC, jugular veins, and aorta (17).

Hemodynamic monitoring is important in the assessment of patients in shock and evaluation of response to treatment. Monitoring capabilities vary from institution to institution but should include pulse oximetry; ECG monitoring; continuous, noninvasive, preferably intra-arterial blood pressure monitoring if there is vasopressor-dependent or persistent hypotension; end-tidal CO_2 monitoring; central venous pressure (CVP) monitoring; and continuous central venous oximetry. Because hemodynamic measurements are physiologic values, they should be used to answer specific physiologic questions rather than to serve as therapeutic end

points. Table 4.3 outlines adjuncts to aid in the evaluation of patients in shock.

TABLE 4.3
Adjuncts that Guide Therapeutic Interventions

Base deficit	Base deficit is an indicator of metabolic acidosis and is an index of hemodynamic and tissue perfusion changes in shock. Base deficit predicts illness severity in intra-abdominal hemorrhage and blunt trauma.
Lactate and lactate clearance	Initial lactate levels have been shown to be predictive of outcome. Normalization of lactate levels or lactate clearance also is predictive of severity of the inflammatory response, morbidity, and mortality.
Invasive blood pressure monitoring	Intense vasoconstriction caused by sympathetic activity or vasopressors given will cause the cuff pressure to underestimate true blood pressure. A Doppler used in conjunction with a sphygmomanometer may provide a more accurate measure of systolic blood pressure once Korotkoff sounds are no longer audible. Intra-arterial pressure measurement is preferable because vasoactive drugs can cause rapid swings in blood pressure, and multiple blood samplings typically are required.
CVP	CVP aids in assessing volume status. CVP is preferred for the long-term administration of vasopressor therapy and provides rapid access to the heart if pacemaker placement is required. CVP may not reliably reflect the left ventricular filling pressure in clinical states such as pulmonary embolus, obstructive airway disease, right ventricular infarction, and pericardial effusion. Common iliac venous pressure can approximate CVP.
$Scvo_2$	$Scvo_2$ closely approximates $Smvo_2$ and can be monitored continuously using infrared oximetry. This technology enables the clinician to detect clinically unrecognized global tissue hypoperfusion in the treatment of myocardial infarction, general medical shock, trauma, hemorrhage, septic, hypovolemic, end-stage heart failure, cardiogenic shock during and after cardiopulmonary arrest.
Arterial–central venous Pco_2 difference	Increased $(a\text{-}v)Pco_2$ are seen in acute circulatory failure and inversely correlate with the CI. Central venous and mixed venous carbon dioxide values can be interchanged to determine cardiac index (5).
Pulmonary artery catheterization	The standard of care for assessing cardiac status. Catheterization is valuable in determining left-sided heart filling and pulmonary artery pressure and for assessing the cause of pulmonary edema. The physician can obtain cardiac output and mixed venous oxygen saturation. The physician will be able to calculate hemodynamic (i.e., SVR) and oxygen transport variables (Vo_2 and Do_2). The effectiveness of this monitoring technique on improving outcome is questionable.
Bedside ultrasound assessment (RUSH EXAM)	Three-step goal-directed ultrasound assessment of the pump (heart), the tank (inferior vena cava and jugular veins), and the pipes (aorta). This early ultrasound assessment may help to differentiate shock etiologies and guide treatment by focusing on anatomy and physiology (16).
Noninvasive CO	CO can be measured by transesophageal Doppler, cutaneous bioimpedance, and lithium dilution, transthoracic echocardiography (AV CSA × VTI).
Gastric tonometry and sublingual capnography	Serial measurements of gastric and sublingual mucosal blood flow are based on hydrogen ion diffusion and carbon dioxide elimination. Inadequate visceral perfusion, as evidenced by persistently low intramucosal pH or increased sublingual carbon dioxide concentration after resuscitation, is associated with subsequent organ dysfunction and death.
$Srao_2$	$Srao_2$ correlates with blood volume, central venous O_2 saturation, and arterial O_2 saturation
Metabolic cart	Metabolic cart is directly measured $\dot{V}o_2$ without a pulmonary artery catheter. A reduction in $\dot{V}o_2$ after acute myocardial infarction predicts cardiogenic shock and mortality after human cardiac arrest

CVP, central venous pressure; $Scvo_2$, central venous blood saturation; $Smvo_2$, mixed venous O_2 saturation; Pco_2, partial pressure of carbon dioxide; $(a\text{-}v)Pco_2$, arterial–mixed-venous carbon dioxide gradients; CI, cardiac index; SVR, systemic vascular resistance; Vo_2, oxygen consumption; Do_2, oxygen delivery; CO, cardiac output; $Srao_2$, retinal venous O_2 saturation.

ED MANAGEMENT

The *ABCDE* tenets of shock resuscitation are fundamental to deliver enough oxygen to the tissues to meet the metabolic demands of the tissues (Fig. 4.4). These tenets include establishing an Airway, controlling the work of Breathing, optimizing the Circulation, assuring adequate oxygen Delivery, and achieving End points of resuscitation.

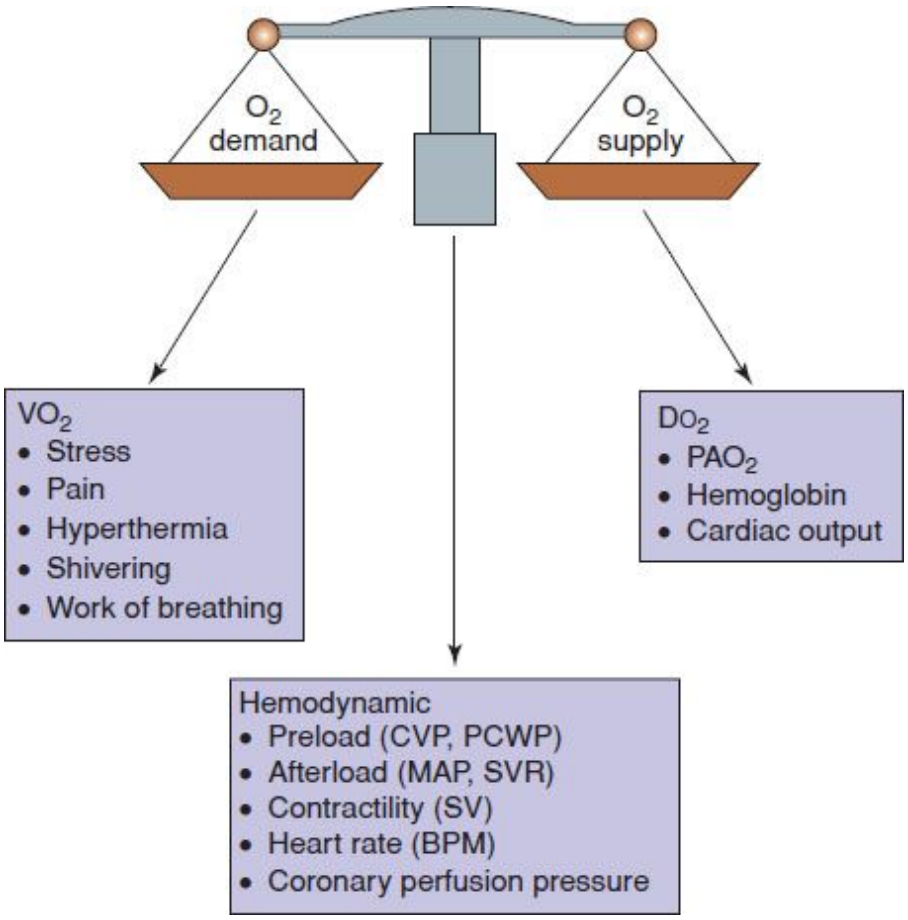

FIGURE 4.4 Balance between oxygen supply and demand. BPM, beats per minute; CVP, central venous pressure; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; SV, stroke volume; SVR, systemic vascular resistance.

Establishing an Airway

Airway control is best obtained through endotracheal intubation. This provides airway protection, positive pressure ventilation (oxygenation), patency, and pulmonary toilet. Sedatives, which are frequently used to facilitate intubation, can exacerbate hypotension through arterial vasodilatation, venodilation, and myocardial suppression. Etomidate, often used during the induction of intubation, has also been implicated in causing transient adrenal dysfunction; however, its impact on mortality is controversial (18–20). Furthermore, positive pressure ventilation reduces preload, increases pulmonary vascular resistance, and decreases CO. The

combination of these interventions can lead to acute hemodynamic compromise. Volume resuscitation or application of vasoactive agents may be required prior to intubation and positive pressure ventilation.

Controlling the Work of Breathing

Control of breathing is required when tachypnea accompanies shock. Respiratory muscles are significant consumers of oxygen during shock and contribute to lactate production. Mechanical ventilation, muscle relaxation, and sedation decrease the work of breathing and preserve the DO_2 used for more vital organs and have been shown to improve survival (21). Sao_2 should be restored to $>93\%$, and ventilation controlled to maintain an arterial carbon dioxide pressure ($Paco_2$) of 35 to 40 mm Hg. Attempts to normalize pH >7.3 by hyperventilation are not beneficial. Mechanical ventilation not only provides oxygenation and corrects hypercapnia, but it assists, controls, and synchronizes ventilation, which ultimately decreases the work of breathing. Ventilatory airway pressure (plateau) should be maintained less than 30 mm Hg to minimize barotrauma and hemodynamic embarrassment.

Optimizing the Circulation

In restoring the balance between systemic Do_2 and demands, optimization of circulatory dysfunction begins with a thoughtful manipulation of preload, afterload, contractility, and coronary perfusion pressure, while maintaining an optimal heart rate.

Circulatory or hemodynamic stabilization begins with intravascular access through large-bore peripheral venous lines. Trendelenburg positioning, historically considered necessary for maintaining perfusion in the hypotensive patient, does not improve cardiopulmonary performance in comparison with the supine position. Trendelenburg positioning may worsen pulmonary gas exchange and predispose to aspiration. If a volume challenge is urgently required, an alternative to the Trendelenburg position is to raise the patient's legs above the level of the heart with the patient

supine. Central venous access aids in assessing volume status (preload) and monitoring S_{CVO_2}. Central venous access is the preferred route for the long-term administration of vasopressor therapy and provides rapid access to the heart if pacemaker placement is required. Early central venous access has been associated with improved mortality in septic shock (22).

Fluid resuscitation begins with isotonic crystalloid; the amount and rate are determined by an estimate of the hemodynamic abnormality. Except for the patient in cardiogenic shock with pulmonary edema, most patients in shock have either an absolute or relative volume deficit. Fluid is given rapidly in set quantities (e.g., 500 or 1,000 mL) every 20 to 30 minutes, with reassessment of the patient after each bolus. Patients with a modest degree of hypovolemia usually require an initial 20 to 40 mL/kg of isotonic crystalloid. More fluids may be necessary with profound volume deficits (23).

The colloid-versus-crystalloid (24) resuscitation controversy remains despite evidence that there is a slight increase in mortality when colloids are used for volume replacement in critically ill patients (25). Some studies have found a lower incidence of pulmonary edema and possibly greater benefit in elderly patients with colloid resuscitation, although survival is not statistically improved. Recent data has associated albumin therapy with worse outcomes in head trauma patients, but with improved or equal outcomes in severe sepsis and septic shock. In addition, the use of starches has been associated with worse outcomes in severe sepsis and septic shock, leading to higher rates of renal failure and need for renal replacement therapy in a randomized clinical trial (26). In the acute situation with severe shock, colloids may be considered to achieve rapid plasma expansion using less volume than crystalloids. Without invasive hemodynamic monitoring, noncardiogenic pulmonary edema may be difficult to differentiate from cardiogenic pulmonary edema in the ED. Even though the former may respond to fluids, fluids should be minimized in a patient with clinical or radiographic evidence of pulmonary edema until appropriate monitoring is established.

Vasopressor agents (Table 4.4) are used when there has been an inadequate response to volume resuscitation or when a patient has contraindications to volume infusion. Vasopressor agents are most effective when the vascular space is “full” and least effective when the vascular space is depleted. However, vasopressors may be necessary early in the treatment of shock, before volume resuscitation is complete, to prevent potentially lethal consequences of prolonged systemic arterial hypotension. This is especially important in elderly patients with significant coronary and cerebrovascular disease. Rapidly restoring the MAP to 60 mm Hg or systolic pressure to 90 mm Hg might avoid the coronary and cerebral complications of decreased blood flow. Vasopressor agents have variable effects on the α- and β-adrenergic receptors (27).

TABLE 4.4
Commonly Used Vasoactive Agents

Drug	Dose/Mixture	Action	Effects				
			Cardiac Stimulation	Vasoconstriction	Vasodilation	Cardiac Output	Side Effects/Comments
Dopamine	0.5–25 µg/kg/min 200–400 mg/250 mL	α, β, and dopaminergic	++ at 2–10 µg/kg/min	++ at 7 µg/kg/min	+ at 0.5–5 µg/kg/min	Usually increases	Tachydysrhythmias; increases myocardial O_2 consumption; a cerebral, mesenteric, coronary, and renal vasodilator
Norepinephrine	0.01–0.5 µg/kg/min 4 mg/250 mL	Primarily α_1, some β_1	++	++++	0	Slight decrease	Dose-related, reflex bradycardia; useful when loss of venous tone predominates; spares the coronary circulation
Phenylephrine	0.15–0.75 µg/kg/min 10 mg/250 mL	Pure α	0	++++	0	Decrease	Reflex bradycardia, headache, restlessness, excitability, rarely dysrhythmias; ideal for patients in shock with tachycardia or supraventricular dysrhythmias
Ephedrine	5–25 mg	α and β	+++	++	+	Increase	Causes palpitations, hypertension, cardiac arrhythmias; an indirect-acting central nervous system stimulant; limited long-term value as therapy for shock
Vasopressin	0.01 to 0.04 U/min	α	++++				Primarily α; outcome data of its use is lacking. Infusions of >0.04 U/min may lead to adverse, likely vasoconstriction-mediated events; reserved for refractory hypotension
Epinephrine	0.01–0.75 µg/kg/min 1 mg/250 mL	α and β	++++ at 0.03–0.15 µg/kg/min	++++ at 0.15–0.30 µg/kg/min	+++	Increase	Causes tachydysrhythmia and leukocytosis; increases myocardial oxygen consumption
Dobutamine	2–20 µg/kg/min 250 mg/250 mL	β_1, some β_2, and α_1 in large dosages	++++	+	++	Increase	Causes tachydysrhythmia, occasional gastrointestinal distress, an increase in myocardial oxygen consumption, and hypotension in volume-depleted patient; has less peripheral vasoconstriction than dopamine; can cause fewer arrhythmias than isoproterenol
Isoproterenol	0.01–0.02 µg/kg/min 1 mg/250 mL	β_1 and some β_2	++++	0	++++	Increase	Causes tachydysrhythmia, facial flushing, and hypotension in hypovolemic patients; increases myocardial oxygen consumption; never use

Using vasopressors has potential pitfalls. While improving perfusion pressure in the large vessels, vasopressors may decrease capillary or microcirculatory blood flow and have been implicated with increased mortality in septic shock. Vasopressors also may alter the relationship between volume and pressure measurements through their effect on the pulmonary and peripheral vascular beds. In other words, vasopressors will falsely elevate intracardiac filling pressures (i.e., CVP). Vasopressors should be used judiciously, generally only after volume resuscitation. Volume assessment should

be a dynamic process. When multiple vasopressors are used, they should be simplified as soon as the most therapeutic agent is identified.

Assuring Adequate Oxygen Delivery

Once blood pressure is stabilized through optimization of preload and afterload, Do_2 can be assessed and further manipulated. Arterial saturation should be returned to physiologic levels (93% to 95%), and hemoglobin maintained at a level >10 g/dL. This hemoglobin threshold has been debated in steady-state critically ill patients but remains recommended in the shock phase of disease (28) more specifically when the $ScvO_2$ is less than 69.5% (29). If CO and stroke volume (SV) can be assessed, both of these parameters should be optimized using afterload-reducing agents, volume infusion, and inotropic agents in incremental amounts until Svo_2 or $Scvo_2$ and lactate are normalized.

The control of $\dot{V}o_2$ is important in restoring the balance of oxygen supply and demand to tissues. A hyperadrenergic state results from the compensatory response to shock, physiologic stress, pain, and anxiety. Shivering frequently results when a patient is unclothed for examination and then left inadequately covered in a cold resuscitation room. The combination of these variables increases systemic oxygen consumption. Pain further suppresses myocardial function, thus impairing Do_2 and $\dot{V}o_2$. Providing analgesia, muscle relaxation, warm covering, anxiolytics, and even paralytic agents, when appropriate, decreases this inappropriate $\dot{V}o_2$.

Tissue oxygen extraction assesses adequacy of the resuscitation in meeting the oxygen needs of the tissues. Sequential examination of lactate and Svo_2 or $Scvo_2$ is a method to assess adequacy of tissue oxygen extraction. Continuous measurement of Svo_2 or $Scvo_2$ through fiberoptic technology can be performed in the ED (12). Other technologies also have the potential to assess tissue perfusion during resuscitation.

Achieving End Points of Resuscitation

Normalization of blood pressure, heart rate, and urine output are traditional end points. Global tissue hypoxia can still persist in patients resuscitated from shock even with normalization of vital signs (30) and urine output (31,32). Because these parameters may underestimate the degree of remaining hypoperfusion and oxygen debt, more physiologic end points have been investigated (5,33). No therapeutic end point is universally effective; however, they are used to provide metabolic confirmation that adequate tissue oxygenation has been achieved (Table 4.3). The goals of resuscitation are to maximize survival and to minimize morbidity by using objective hemodynamic and physiologic values to guide therapy. A goal-directed approach at achieving urine output $\geq$0.5 mL/kg/h, CVP 8 to 12 mm Hg, MAP 65 to 90 mm Hg, and $Scvo_2$ $\geq$70% during ED resuscitation of septic shock significantly decreases mortality (7).

Bicarbonate Use in Shock

The primary treatment for acidosis in shock is to reverse the underlying cause. Because this goal is not rapidly attainable, intravenous bicarbonate is often administered. The rationale for giving bicarbonate is that it diminishes myocardial depression and counteracts the insensitivity to endogenous catecholamines attributed to acidosis. However, experimental data indicate that exogenous bicarbonate can actually worsen intracellular acidosis, and prospective studies do not show any benefit from its use. Bicarbonate (34) also shifts the oxygen–hemoglobin dissociation curve to the left and impairs tissue unloading of hemoglobin-bound oxygen. However, many clinicians are reluctant to withhold bicarbonate. A compromise is to partially correct the metabolic acidosis through the course of time. The bicarbonate deficit is determined, which is equal to

$$(\text{normal } HCO_3^- - \text{the patient's } HCO_3^-) \times 0.4 \times \text{body weight in kilograms}$$

Half of this amount is infused slowly, with the remainder infused throughout 6 to 8 hours to achieve a pH $\leq$7.25.

Resuscitative Adjuncts

Adjuncts that can guide therapeutic interventions are evolving. A variety of invasive and noninvasive adjuncts (Table 4.3) are available to monitor the response to shock resuscitation.

DISPOSITION AND PROGNOSIS

Pathogenic mechanisms such as cytopathic tissue hypoxia (a form of irreversible shock) can occur within the first few hours of an ED stay, rendering therapy in the intensive care unit less effective. Current national increases in ED patient acuity and overcrowding have resulted in extending the golden hour into hours and even days, consequently requiring the provision of critical care in the ED. The benefit of timely ED intervention in traumatic and nontraumatic critical illness is significant; standard ED care can significantly decrease morbidity and predicted mortality in as little as 6 hours of treatment (35). In addition, application of an algorithmic approach to optimize hemodynamic end points with early goal-directed therapy in the ED reduces mortality by an absolute 16% in patients with severe sepsis or septic shock (7).

Documentation and communication are important. Resuscitation in the ED is commonly performed in "ordered chaos." Even though resuscitation is systematic and thoughtful, miscommunication with the critical care specialist accepting the patient can undo the benefits of initial treatment. A system-oriented problem list with an assessment and plan, including all procedures and complications, should be verbally communicated and written or dictated prior to transfer. For prolonged ED stays, notations regarding patient status, diagnostic and therapeutic intervention, and sentinel events should be provided frequently.

Prediction of outcomes has not been fully studied; however, some clinical variables, for example, severity of shock, temporal duration, underlying cause, pre-existing vital organ dysfunction, and

reversibility, are associated with poor outcome. Persistently elevated lactate level, base deficits, and decreased $Scvo_2$ are prognostic for morbidity and mortality in trauma, septic shock, and after cardiac arrest. Outcome predictions using physiologic scoring systems in the ED are also being studied.

Common Pitfalls

- Failure to monitor appropriately. Be aware of malfunction of arterial blood pressure monitoring equipment, such as dampening of the arterial line or disconnection from the transducer.
- Failure to adequately volume resuscitate. Global tissue hypoxia may persist even after resuscitation to normal vital signs (30) and urine output (32). The hospital mortality in this subset of patients can be >50% (7). The early use of vasopressors may "falsely" elevate CVP and disguise hypovolemia.
- Failure to recognize a pneumothorax after placement of central venous access.
- Failure to recognize the underlying cause of shock when using only bedside ultrasound in patient assessment.
- Failure to recognize an occult penetrating injury (a bullet hole or stab wound) or occult bleeding (from a ruptured spleen or ectopic pregnancy).
- Failure to recognize anaphylactic shock caused by an administered medication (e.g., penicillin) or by medication taken before arrival.
- Failure to diagnose cardiac tamponade, e.g., in the dialysis patient or in the cancer patient.
- Failure to recognize adrenal insufficiency. The incidence of adrenal dysfunction can be as high as 20% in this subset of patients (18).

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CHAPTER 5 Vascular Access

Eric F. Reichman

The practice of emergency medicine frequently requires access to the venous and sometimes the arterial circulation of a patient (1). Vascular access allows for blood sampling, medication administration, blood product administration, hydration, patient monitoring (i.e., arterial lines and pulmonary artery catheters), and insertion of cardiac pacing wires. Peripheral venous puncture is the most common invasive procedure performed in the emergency department (ED). Peripheral vein cannulation is performed on a daily basis and is the cornerstone of circulatory resuscitation.

There are many techniques with which to access a patient's venous or arterial circulation. Venous puncture (venipuncture) or arterial puncture with a needle is only indicated for the sampling of blood. Medications may be administered as a one-time dose via this technique, but the risk of extravasation is high. Venous cannulation (intravenous [IV] placement) is indicated for repeated sampling of venous blood. Venous cannulation is also performed for the administration of medications, fluid solutions, blood products, and nutritional support.

There are some general contraindications to peripheral vascular access. Arteries and veins should not be accessed through infected skin. Do not withdraw venous blood from a vein proximal to a running IV infusion. The blood sample will be tainted or diluted by the infused solution. A hole in the vein may allow blood, infused solutions, and medications to extravasate into the surrounding tissues. Venipuncture and venous cannulation of veins in an extremity with an arteriovenous fistula should be avoided. Veins in

the upper extremity that may be needed for arteriovenous fistula construction for hemodialysis in the future should not be punctured unless absolutely necessary.

Complications specific to each technique and site are discussed more fully in this chapter. Venous and arterial catheters should be assessed immediately after their placement and be reassessed frequently. The assessment must include the skin puncture site, catheter function, the neurovascular status of the distal extremity, and the patient's overall condition.

GENERAL PRINCIPLES FOR INTRAVENOUS ACCESS

Although veins can dilate and constrict somewhat on their own, they do so mostly in response to the pressure within them. The use of venous tourniquets, dependent positioning, "pumping" via muscle contraction, and the local application of heat or nitroglycerin ointment all contribute to venous engorgement. These maneuvers can be used to aid in the performance of a venipuncture or peripheral venous access.

The vascular anatomy can affect access (2). Deficient perivascular connective tissue permits the vein to "roll" from side to side and evade the needle. Tough connective tissue can impede the entry of a flexible catheter while serving to stabilize the vein and prevent its collapse. Venous valves allow unidirectional flow and prevent blood from pooling in the dependent portions of the extremities. Valves can block the passage of a catheter through and into a vein. Valves are more numerous at the points where tributaries join larger veins and in the lower extremities. Valves are almost absent within the large central veins, the veins of the head, and the veins of the neck.

Peripheral veins are easiest to access at the apex of the "Y," formed when two tributaries merge into a larger vein or where the vein is straight and free of branches and valves for two or so proximal to the site of puncture. These sites tend to be anchored and "roll" less than other sites.

The angle of insertion of the needle varies depending on the depth of the vein being punctured. A shallow angle (30 to 45 degrees) should be used for small and superficial veins. A more obtuse angle

(60 degrees) should be used to access deeper veins. Very small and superficial veins should be entered at a very acute angle (15 to 30 degrees).

Fluid Flow Considerations

Both the diameter and the length of the infusion device affect the flow rate through the catheter. Viscous fluids (e.g., blood products and albumin) infuse more slowly than less viscous fluids (e.g., saline). These relationships can be seen in the solution of Poiseuille equation for ideal fluid flow through a cylindrical tube. The pressure gradient and resistance to flow is inversely proportional to the length of the catheter tubing. Flow rates decrease as catheter length increases. Using the shortest possible catheter permits the highest fluid infusion rates. Catheter diameter changes will have the most effect on flow rates. The flow rate increases to the fourth power as the catheter internal radius increases. Maximal flow rates result from using the largest bore or largest internal diameter (i.e., smallest gauge) catheter that will fit inside the vein. Large-bore venous catheters are preferred for high-volume infusions.

Venous Cannulation

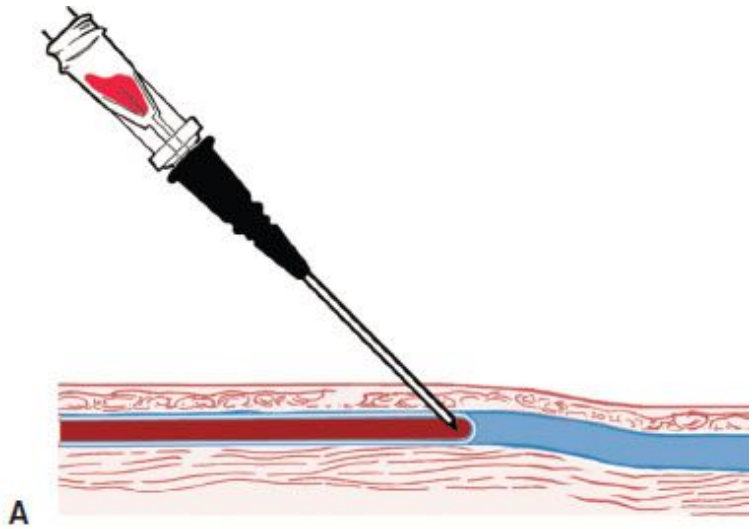
There are four main techniques of venous cannulation (2). The first is the needle-only technique using a butterfly-type needle. This method is seldom used today. The catheter-over-the-needle is the most commonly used technique for peripheral venous cannulation. The catheter-through-the-needle technique is occasionally used but not very popular. The Seldinger wire-guided technique is most commonly used for central venous access.

Identify the vein to be cannulated and the site of the skin puncture. Clean the area of any dirt and debris. Cleanse the skin with isopropyl alcohol, chlorhexidine, or povidone iodine. Apply a tourniquet to the extremity, proximal to the venous cannulation site, to engorge the vein. Additional engorgement of the vein can be accomplished by placing the extremity in a dependent position, “pumping” via muscle contractions of the extremity, and the

application of heat or nitroglycerin ointment over the vein. Optionally, a small subcutaneous wheal of local anesthetic solution may be placed at the skin puncture site to provide comfort to the patient.

The needle-only technique is used occasionally for short-term venous access in young children and elderly patients with fragile veins. This system is prone to malposition and infiltration. The tip of the needle can easily lacerate the vein if the needle is not secure and allowed to move. This technique is, therefore, recommended only for venous blood draws and not venous cannulation.

The catheter-over-the-needle systems are most commonly used for venous access (Fig. 5.1). The infusion catheter fits closely over a hypodermic needle. Placement of these catheters is usually quick and simple. Several considerations should always be kept in mind when using a catheter-over-the-needle. Intravascular placement is indicated by a flash of blood in the hub of the needle. If the patient's venous pressure is very low or if the needle is long and narrow, both sides of the vessel may be traversed (through and through) before the practitioner realizes that the needle was within the vein. If the tip of the needle is withdrawn from the vein, the catheter will not advance. If the catheter is advanced when the tip of the needle but not the catheter is within the vein, the catheter will not advance. The catheter will push the vein off the needle. Depressing the skin just distal to the puncture site and pulling it distally can prevent the vein from "rolling."



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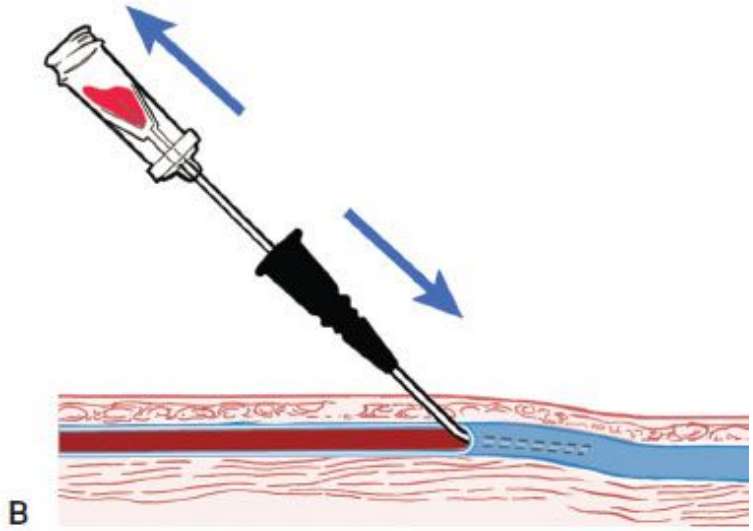

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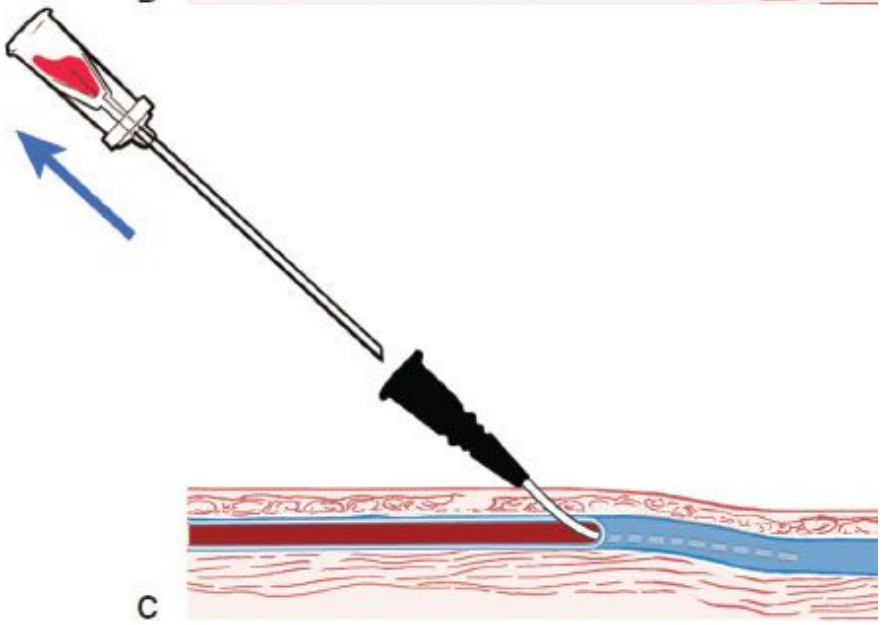

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FIGURE 5.1 The catheter-over-the-needle technique. (Reprinted with permission from Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013.)

As opposed to the over-the-needle approach, the catheter-through-the-needle technique eliminates the need for a needle that is as long as the catheter and eliminates the possibility of pushing the vein off the end of the needle when the catheter is advanced (2). The main disadvantage of this technique is the possibility of the needle tip shearing off the catheter, resulting in a catheter embolism. This complication is prevented by using proper technique. Another disadvantage is an increased risk of hematoma formation because the needle used for venipuncture must be larger in diameter than the catheter.

The Seldinger technique allows for the placement of a catheter over a wire rather than directly over a needle. The wire used must be longer than the catheter. The needle used to insert the wire can be short and of a smaller gauge than the catheter. The Seldinger technique is most commonly used for central venous catheter insertion.

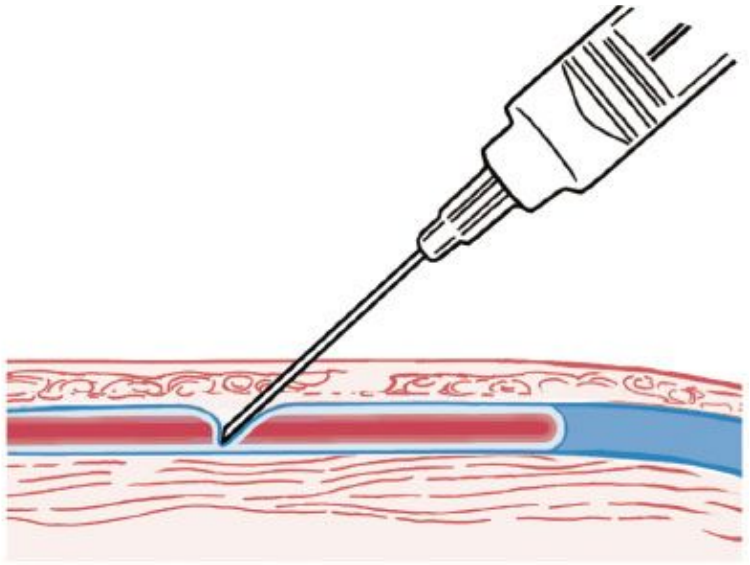
VENIPUNCTURE AND PERIPHERAL INTRAVENOUS ACCESS

The upper extremity is preferred to the lower extremity for vein cannulation (3). Distal placement should be attempted before moving more proximal (3). Avoid veins overlying a joint. These simple principles allow the patient maximum mobility and increase the chance of successfully cannulating a vein. It is easiest to insert a venous cannula where two tributaries merge and form a "Y." Choose a straight portion of vein without branches to minimize the chance of hitting valves within the vein and to make threading the catheter easier.

Peripheral Venipuncture

Stabilize the vein with the nondominant hand. Insert the needle attached to a syringe or vacuum tube adapter, with the bevel upward, into the vein at a 45- to 60-degree angle. Lower angles, at times nearly parallel to the skin, are often required to enter very narrow or superficial veins. Apply negative pressure to the syringe. A flashback of blood in the hub of the needle indicates that the tip of the needle is within the vein. Pulsatile blood indicates an arterial puncture. Unless venous blood is specifically needed for a test, collect the necessary samples before removing the needle. No additional harm will be done by withdrawing a blood sample from an artery that has already been punctured.

If no blood is obtained, slowly advance the needle until it is deeper than the judged depth of the vein. The tip of the needle can collapse the vein and prevent the flashback of blood (Fig. 5.2A). Slowly withdraw the needle to just beneath the skin. The vein will often have been punctured through-and-through (Fig. 5.2B). If this is the case, blood will flash back into the syringe as the needle is withdrawn (Fig. 5.2C). If no blood is obtained by the time the needle is withdrawn to just beneath the skin, redirect the needle, and make another attempt at puncturing the vein. Never sweep the point of the needle around without withdrawing it as the sharp bevel can lacerate nearby structures.



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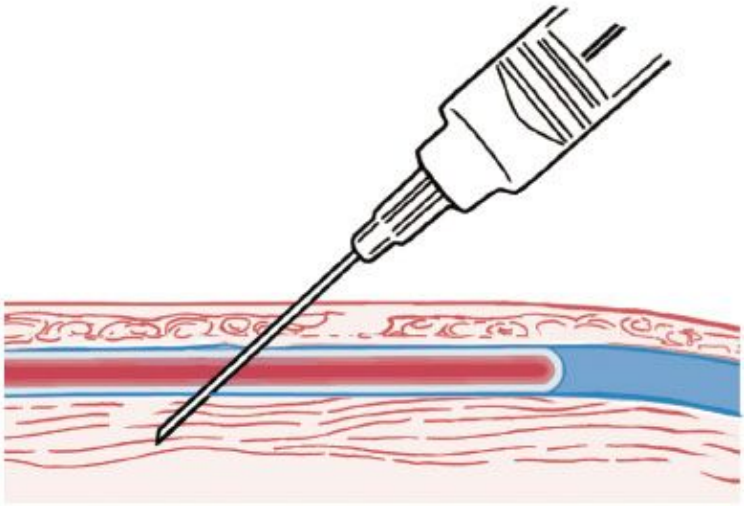

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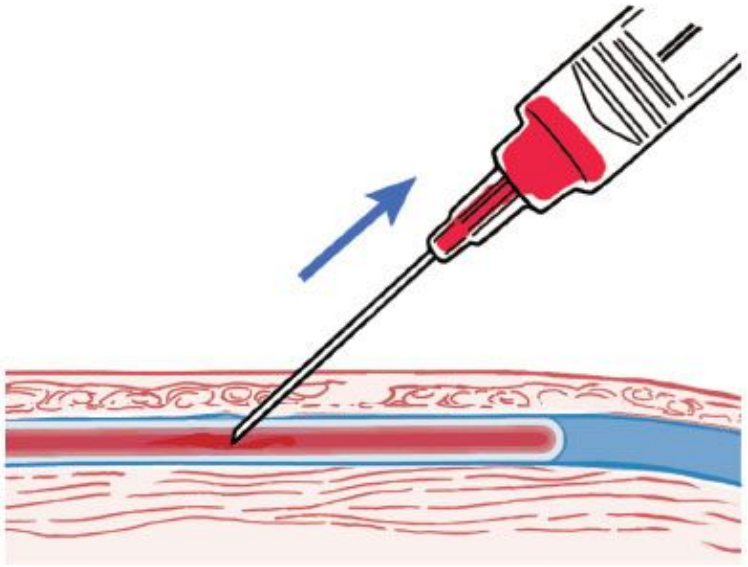

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FIGURE 5.2 Through-and-through puncture of a vein. (Reprinted with permission from Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013.)

Peripheral Intravenous Cannulation

Vein cannulation begins with a successful venipuncture (2). Insert the catheter-over-the-needle through the skin and into the vein (Fig. 5.1A). A flash of blood in the hub of the needle confirms that the tip of the needle is within the vein. Advance the catheter-over-the-needle an additional 2 to 3 mm to ensure that the catheter is within the vein. Securely hold the hub of the needle. Advance the catheter until its hub is against the skin (Fig. 5.1B). Withdraw the needle leaving the catheter in place (Fig. 5.1C). Apply pressure with the nondominant index finger over the catheter to prevent blood from exiting the catheter. Attach IV tubing to the catheter hub, and begin the infusion. Secure the catheter with tape.

A modified Seldinger technique (described later in this chapter) with a radial artery catheterization kit is very useful for deep brachial and external jugular venous catheterization (3). The depth of the deep brachial vein combined with overlying skin (which is often scarred from previous venous punctures) makes catheterization with the usual 1.25-in catheter difficult. The external jugular vein is quite mobile, and the overlying tissues are fairly tough. This combination can make threading an over-the-needle catheter into the vein, without pushing the vein off the end of the needle, quite difficult.

Pediatric Considerations

Venipuncture and peripheral venous access can be quite a challenge in the infant and small child (3). Proper restraint of the extremity will greatly aid the process. Aside from the techniques discussed above, there are a few techniques that can aid pediatric vascular access. The scalp veins can be used for venous access in newborns. Scalp veins are most easily cannulated with a small (23- to 25-gauge) butterfly needle or catheter. A rubber band can be placed about the

baby's head as a tourniquet. Other veins commonly used include those of the antecubital fossa, dorsal hand, dorsal foot, the external jugular vein, and the saphenous vein at the knee or groin. For small and superficial veins, place a small bend at the hub of the catheter-over-the-needle assembly. This bend provides a less-acute angle and easier entry into the vein. The best guide to the gauge (diameter) of catheter to use is to compare the catheter to the vein. The catheter should be at least slightly smaller than the vein. In practice, the smallest readily available catheters are 24 gauge. Keeping a peripheral IV line from being pulled out by an active toddler is quite a challenge. Each institution has its own "recipe" for securing pediatric IVs including taping securely, covering the catheter with a cut plastic medicine cup, and covering the whole assembly with a gauze roll or stockinette.

Assessment

The IV line should flush easily. Any infusions should flow by gravity alone. Progressive swelling at the catheterization site indicates a hematoma formation or extravasation of infused fluids. Peripheral infusions of vasopressors, IV contrast, and caustic solutions require the skin puncture site to be assessed frequently and carefully as extravasation may lead to extensive local soft tissue necrosis. Pain at the IV access site must be taken seriously and should prompt a search for the cause.

Complications

The main complications of venipuncture are pain and hematoma formation. Other complications include nerve injury and usually reversible paresthesias. Infection is uncommon from simple venous sampling. In addition to these complications, venous catheters have additional risks. IV catheters increase the risk of superficial venous thrombosis and thrombophlebitis. It is possible to injure a number of structures in the neck or cause a pneumothorax during external jugular vein cannulation with inadvertent deep penetration. Extravasation of some IV solutions can cause local skin necrosis.

Extravasation of large volumes into a muscle compartment can lead to a compartment syndrome, although this is rare with superficial peripheral venous lines. Infections can often be prevented by using aseptic technique, using sterile dressings, and changing peripheral catheters every 48 to 72 hours. The rare complications of peripheral nerve palsies, pressure necrosis, and compromised peripheral circulation do occasionally occur. Complications can be prevented by making frequent neurovascular checks to any restrained extremity, padding all pressure points, and avoiding the placement of circumferential tape on an extremity.

CENTRAL VENOUS ACCESS

Percutaneous cannulation of the central veins is an essential technique for both long-term and emergent medical care (4). Access to the major veins of the torso allows rapid high-volume fluid resuscitation, administration of concentrated ionic and nutritional solutions, and hemodynamic measurements. The right internal jugular vein is generally preferred to the left internal jugular vein as the site of central venous cannulation. The right internal jugular vein provides a nearly straight and direct route to the superior vena cava. The dome of the right lung is somewhat lower than that of the left lung and thus decreases the chance of a pneumothorax during catheter placement. The thoracic duct is relatively large and lies high in the left chest. These anatomic considerations favor the right internal jugular approach to central venous cannulation to minimize complications.

The internal jugular route is acceptable for central venous access in most cases. This route allows ready access to the superior vena cava for long-term central venous access, caustic or concentrated infusions, and central venous pressure monitoring. Pulmonary artery catheters and transvenous pacing wires can be introduced through the right internal jugular vein. The internal jugular vein is accessible without terminating cardiopulmonary resuscitation (CPR) efforts, although chest compressions and the lack of carotid pulsations make accessing it difficult. The risk of a pneumothorax is probably less with the internal jugular vein cannulation as opposed to the

subclavian vein route, although patient mobility is less and discomfort is greater. In a coagulopathic patient, the internal jugular vein puncture site is compressible, but hematoma formation may lead to compromise of the airway.

The subclavian vein is the preferred route for longer-term central venous access. This site allows for ambulation (unlike a femoral line) and neck movement without discomfort (unlike a jugular line). The catheter is concealable under clothing, making outpatient use more acceptable.

The femoral vein is often the preferred route for emergency central venous cannulation in many patients. The femoral vein is not a suitable route for ambulatory patients beyond the initial resuscitation and stabilization period. Femoral venous access is relatively easy during CPR and often does not require the cessation of chest compressions. The femoral vein is easily compressible. This makes it preferable to the subclavian vein in coagulopathic patients or those undergoing thrombolysis, although peripheral access would be preferred in these cases. A femoral vein central line should be changed as soon as possible to another site because of the increased rates of infection compared to other locations.

Internal Jugular Vein

Central Approach

Place the patient in the Trendelenburg position with their head down 15 to 30 degrees. Rotate the patient's head away from the side that will be cannulated. Excessive rotation will distort the anatomic landmarks and may bring the internal jugular vein closer to the carotid artery.

Insert the needle at a 30- to 60-degree angle at the apex of the triangle formed by the sternal and clavicular heads of the sternocleidomastoid muscle and the clavicle (Fig. 5.3). Direct the needle toward the ipsilateral nipple. Shallower angles cause a greater amount of subcutaneous tissues and structures to be traversed before entering the vessel but are generally necessary in children whose

vessels are smaller. Steeper angles make insertion of the catheter over the guidewire difficult as the guidewire tends to kink.

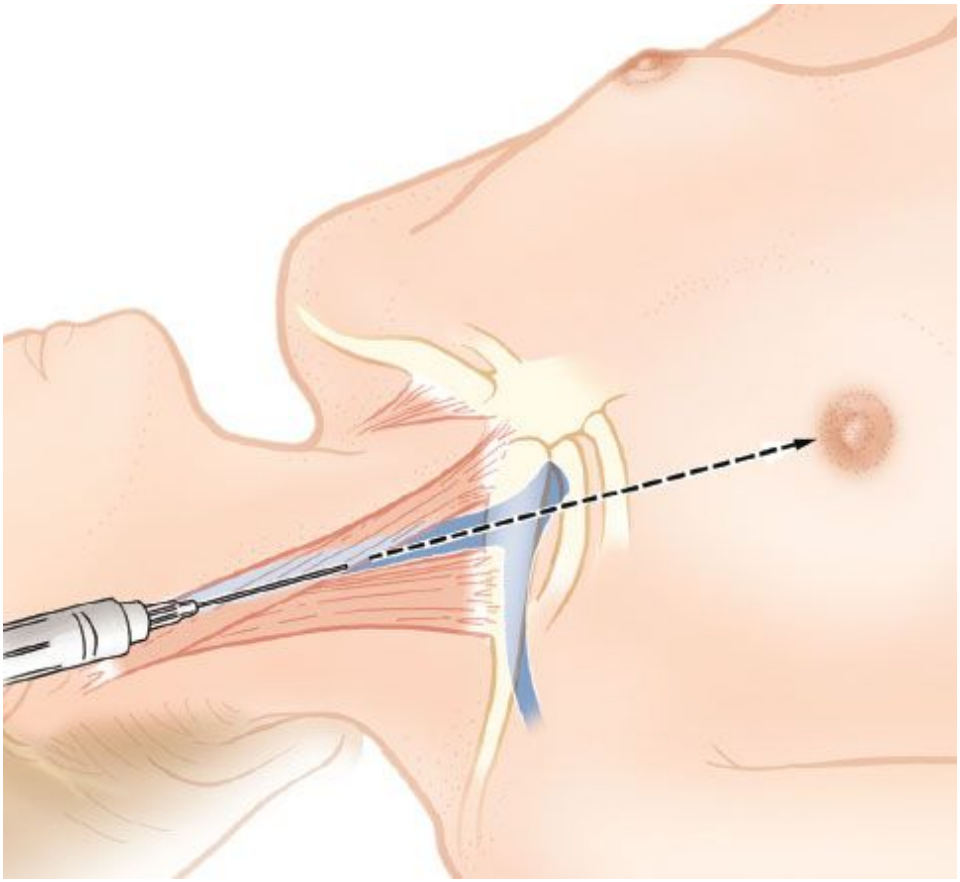

FIGURE 5.3 Central approach to the right internal jugular vein. (Reprinted with permission from Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013.)

Anterior Approach

The skin puncture site is at the anterior border of the sternal head of the sternocleidomastoid muscle, just lateral to the carotid artery (Fig. 5.4). Enter the skin at a 45- to 60-degree angle. Direct the needle toward the ipsilateral nipple. The internal jugular vein should be encountered within 3 to 5 cm in an adult. If the vein is not encountered by 5 cm, withdraw the tip of the needle to the subcutaneous space, and redirect it slightly medially.

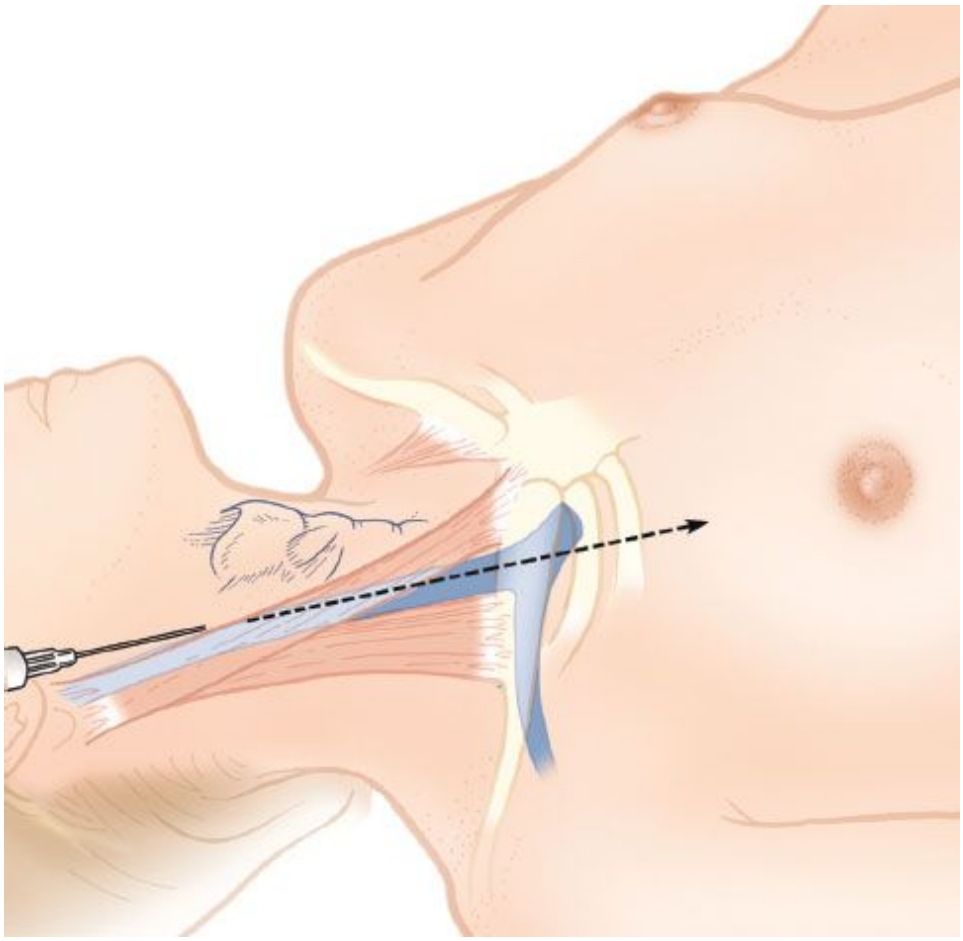

FIGURE 5.4 Anterior approach to the right internal jugular vein. (Reprinted with permission from Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013.)

Posterior Approach

Enter the skin at the posterior edge of the sternocleidomastoid muscle, one-third of the way from the clavicle to the mastoid process (Fig. 5.5). Alternatively, the point where the external jugular vein crosses the lateral border of the sternocleidomastoid muscle can be used. Direct the needle under the muscle at a 30- to 45-degree angle to the skin toward the sternal notch. Place the index finger of the nondominant hand in the sternal notch to provide a landmark with the patient draped. The internal jugular vein should be encountered within 5 cm in an adult. This approach is not recommended in children.

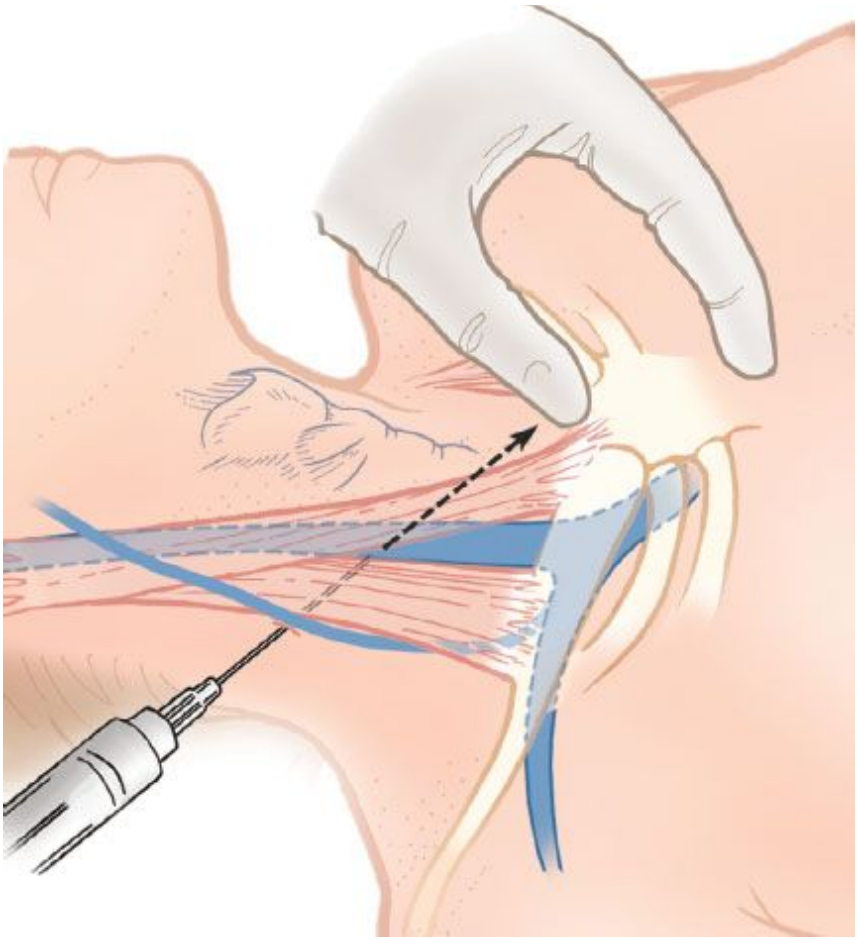

FIGURE 5.5 Posterior approach to the right internal jugular vein. (Reprinted with permission from Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013.)

Subclavian Vein

Infraclavicular Approach

The infraclavicular approach to the subclavian vein is most commonly used. This technique is easier to perform and less likely to result in a pneumothorax than the supraclavicular approach. Several different skin entry sites have been described (4). Some clinicians feel that the preferred entry site is 1 cm caudal to the junction of the medial third and middle third of the clavicle. The subclavian vein lies just posterior to the clavicle at this site. Direct the needle just superior and posterior to the suprasternal notch while staying as close to the frontal (coronal) plane as possible. The needle and

syringe should be parallel to the bed (Fig. 5.6A,B). Placing the nondominant index finger in the sternal notch will help to guide placement (Fig. 5.6A).

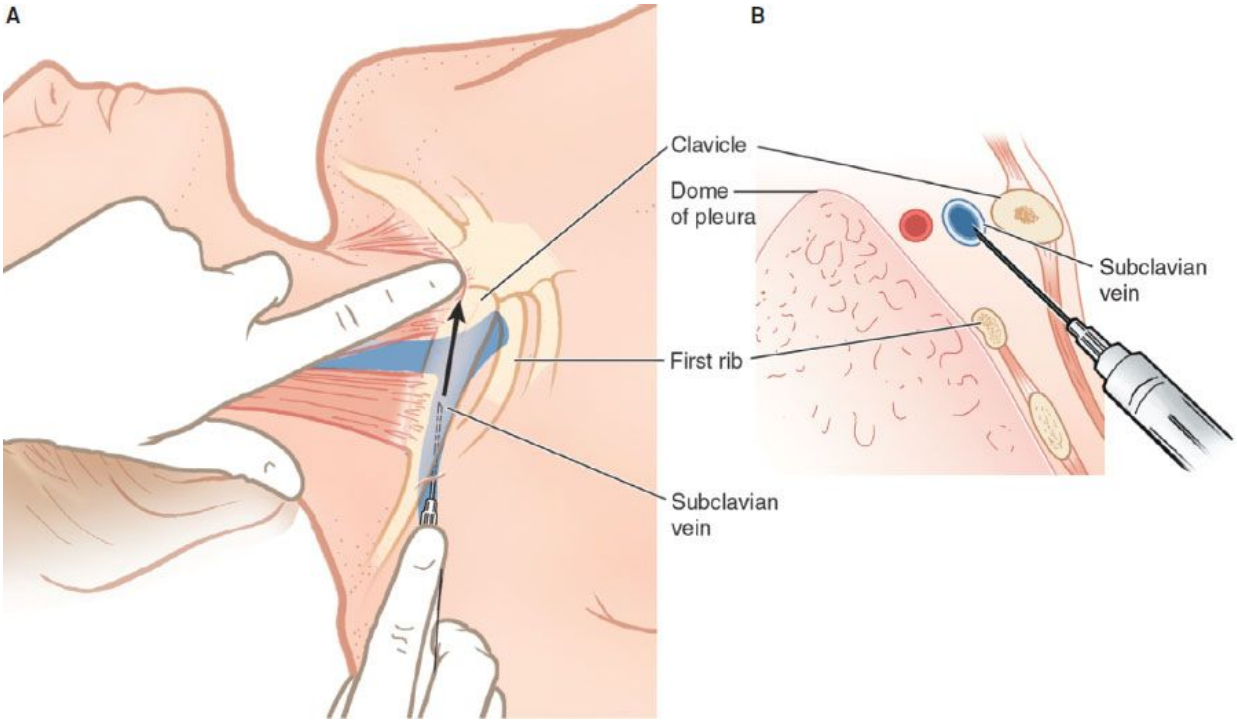

FIGURE 5.6 Infraclavicular approach to subclavian vein cannulation. (Reprinted with permission from Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013.)

Some practitioners prefer to enter the skin inferior to the clavicle at the deltopectoral groove, or the point just lateral to the midclavicular line along the inferior surface of the clavicle. This is the point where the skin may be maximally depressed. Direct the needle parallel to the bed and toward the sternal notch. This entry site may make it easier to keep the needle in the coronal plane. The distance before entering the subclavian vein is longer than in the preceding approach, and the protection offered by the first rib is lost.

An additional alternative landmark exists. Palpate the bony tubercle, or protrusion, on the inferior surface of the clavicle and approximately one-third to one-half the length of the clavicle from the sternoclavicular joint. The advantage of this site is that it is a definitive landmark and avoids approximating distances as described

for the other sites previously described. The needle is inserted parallel to the bed and aimed just posterior to the sternal notch.

Supraclavicular Approach

Although most practitioners are more comfortable with the infraclavicular approach to the subclavian vein, the supraclavicular approach offers some advantages (4). These advantages include the subclavian vein being closer to the skin, the route from a right-sided skin puncture site to the superior vena cava being more direct, the procedure avoiding the hazards of a left-sided puncture (i.e., the thoracic duct), and the skin entry site being more accessible during CPR. The complication rate for the supraclavicular approach is probably lower than that for the infraclavicular approach with an experienced clinician.

The skin is entered at a point 1 cm lateral to the lateral border of the clavicular head of the sternocleidomastoid muscle and 1 cm superior to the clavicle (Fig. 5.7A,B). The needle should bisect the angle formed by the clavicle and the lateral border of the sternocleidomastoid muscle (Fig. 5.7A). Direct the needle toward the contralateral nipple or a point just superior and posterior to the sternal notch. Orient the needle bevel medially. The subclavian vein should be entered within 2 to 3 cm in an adult. The length of catheter inserted will be a few centimeters less than that for the infraclavicular approach.

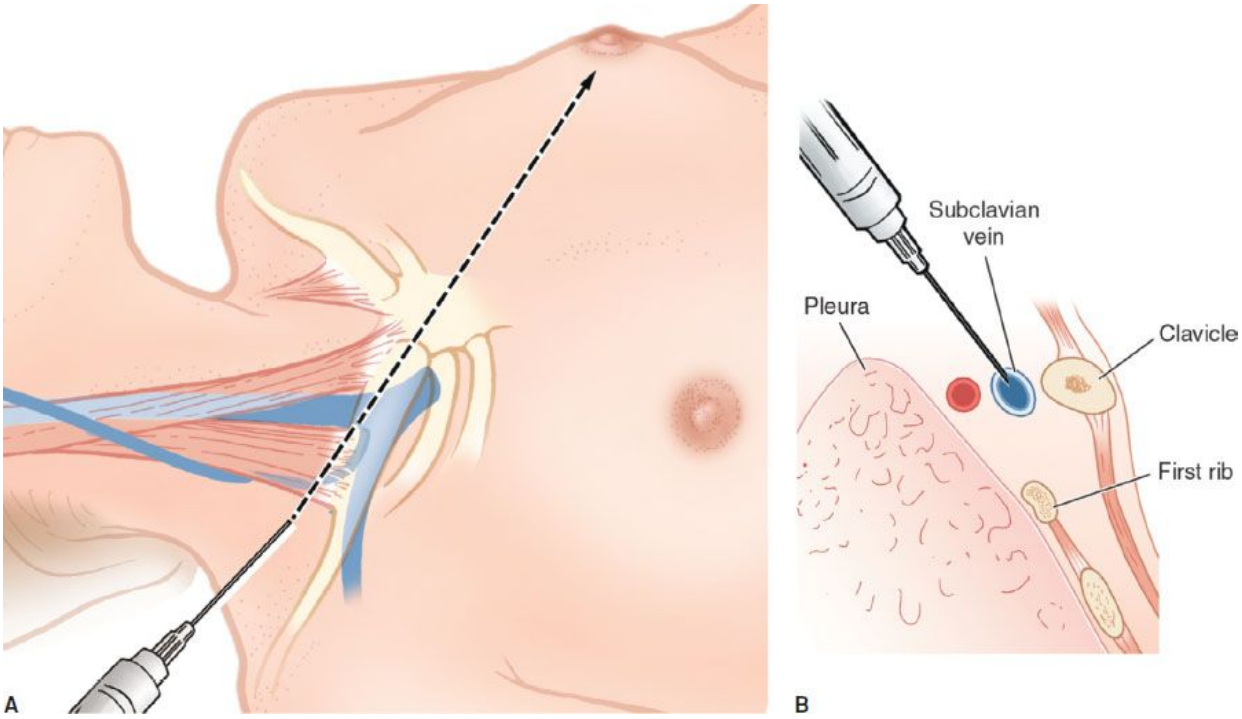

FIGURE 5.7 Supraclavicular approach to subclavian vein cannulation. (Reprinted with permission from Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013.)

Alternative skin entry sites and approaches have been described. Enter the skin 1 cm medially and 1 cm superiorly to the midpoint of the clavicle with the needle directed toward the ipsilateral sternoclavicular joint. The skin can be entered just posterior to the clavicle, at the junction of the medial third and middle third of the clavicle, with the needle directed toward the ipsilateral sternoclavicular joint and parallel to the coronal plane. This last approach is probably the simplest, although the study cited was performed on cadavers rather than live patients.

Femoral Vein Catheterization

Premeasuring from the insertion site to the xiphoid process will give the maximum catheter insertion depth. The needle should enter the skin 2 to 4 cm inferior to the midpoint of the inguinal ligament and 1 cm medial to the femoral artery pulse (Fig. 5.8). The needle should

enter the skin 1 to 2 cm inferior to the inguinal ligament and 0.5 cm medial to the femoral artery pulse in an infant or young child.

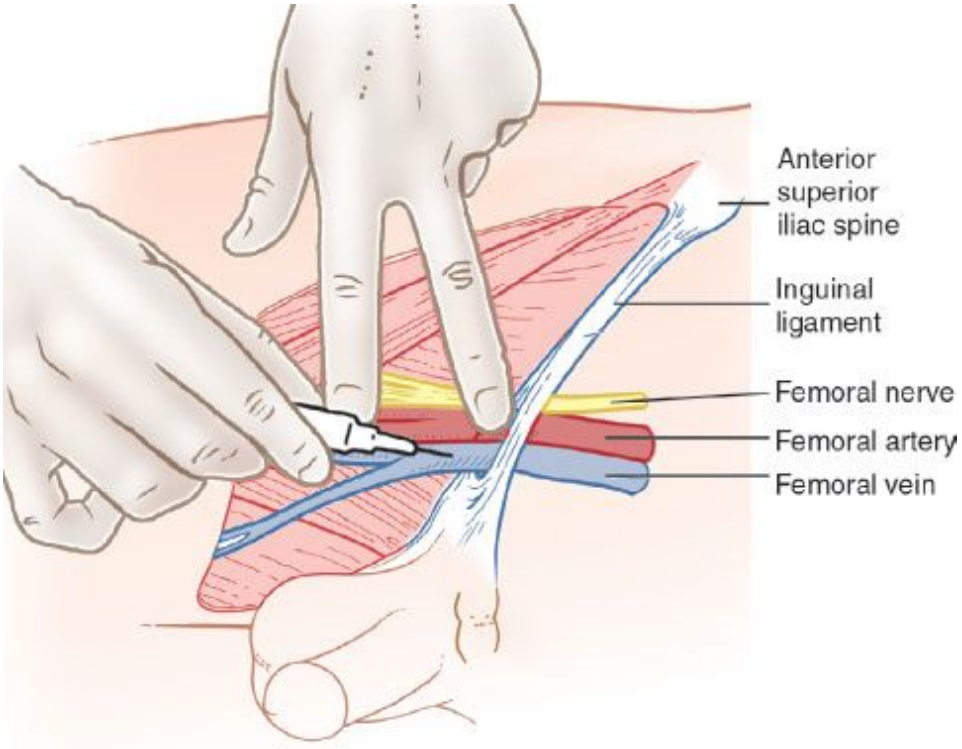

FIGURE 5.8 Femoral vein cannulation. (Reprinted with permission from Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013.)

Two site-specific considerations deserve mention. The use of a "finder" needle is unnecessary because there are no vital structures in the area other than the femoral artery that is compressible if it is punctured. The introducer needle is directed at a 45- to 60-degree angle to the skin and parallel to the long axis of the thigh. Shallower angles may be necessary in very small and thin patients. Use caution to avoid puncturing the posterior wall of the vein above the inguinal ligament because this can result in a retroperitoneal hemorrhage.

Seldinger Technique

There are numerous anatomic approaches to obtain central venous access (4). This includes three approaches to the internal jugular vein, two approaches to the subclavian vein, and one approach to the

femoral vein. A more detailed discussion of the anatomy and approaches can be found elsewhere (1,4). Regardless of the approach, the Seldinger technique is the preferred method.

Clean, prep, and drape the area. Position the patient based on which central vein is to be accessed. Several cardinal rules for the insertion of the catheter should be observed. Always occlude the open hub of a needle or catheter in a central vein to prevent an air embolism. Never let go of the guidewire to prevent its embolization into the central venous circulation. Never apply excessive force to the guidewire on insertion or removal if resistance is met. Doing so may injure the vessel, break the guidewire, or embolize a piece of the guidewire.

Attach the thin-walled needle to a 5-mL syringe containing 1 mL of sterile saline. Insert the needle while applying negative pressure to the syringe by withdrawing the plunger. Advance the needle into the vein (Fig. 5.9A). If the vein is not located within 3 to 5 cm, stop advancing the needle. Withdraw the needle slowly while continuing to aspirate. Often, the vessel will have been completely traversed upon insertion, and blood will flash back into the syringe as the needle is withdrawn. Stabilize and hold the needle perfectly still with the nondominant hand once blood returns in the syringe. Remove the syringe. Occlude the open hub of the needle with the thumb of the nondominant hand while keeping the small finger of the hand in contact with the patient’s skin.

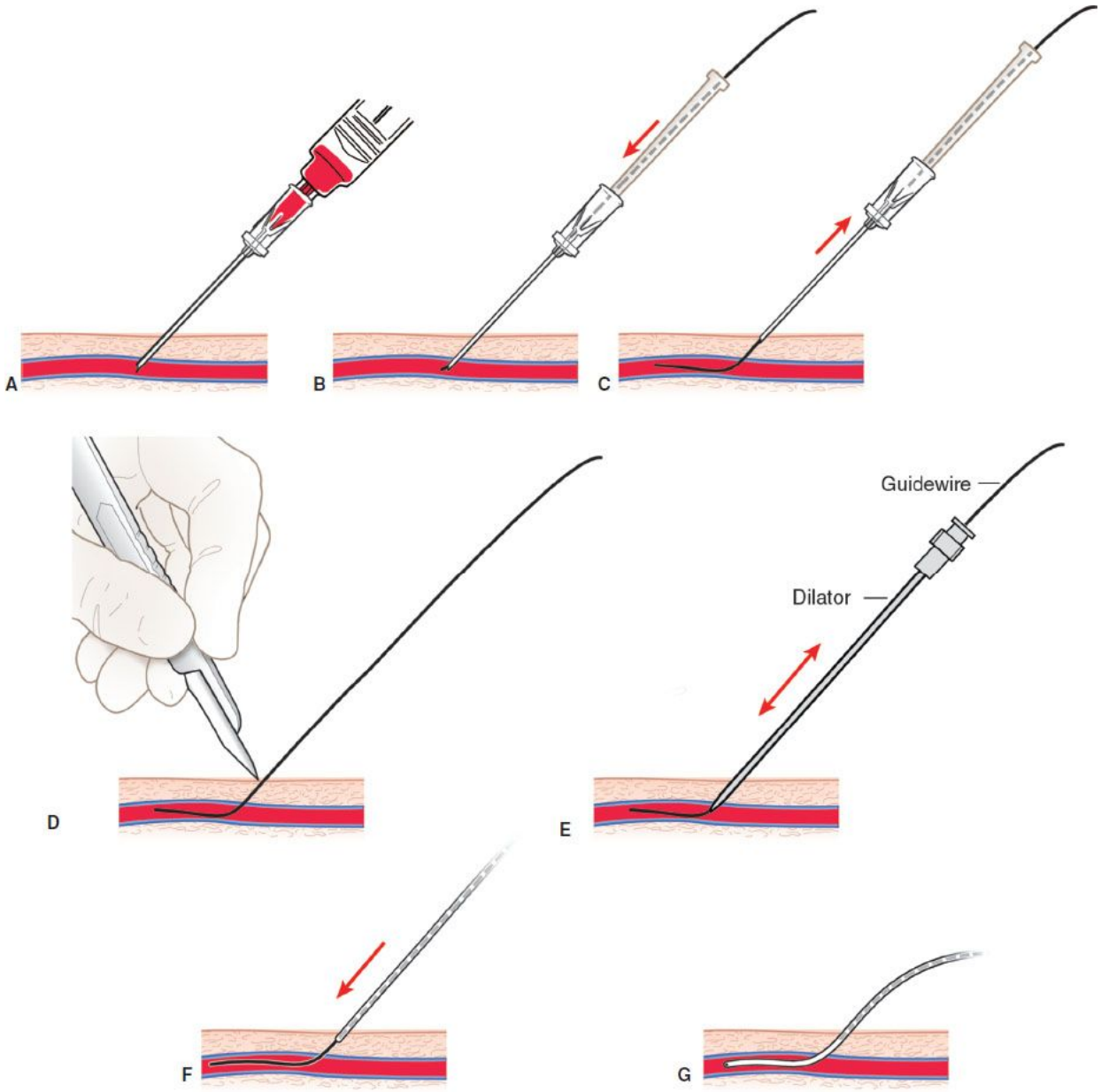

FIGURE 5.9 The Seldinger technique for central venous access. (Reprinted with permission from Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013.)

Grasp the guidewire and its sleeve with the dominant hand. Slide the sleeve forward to straighten out the "J" of the guidewire. Insert the wire sleeve into the hub of the needle (Fig. 5.9B). Advance the guidewire through the needle and into the vein (Fig. 5.9B). The guidewire should advance easily into the vein. Withdraw the needle and guidewire sleeve over the guidewire while securely holding the

guidewire (Fig. 5.9C). Grasp the guidewire with the nondominant hand as soon as the guidewire is visible between the tip of the needle and the skin.

Make a small incision in the skin adjacent to the guidewire using a no.11 scalpel blade (Fig. 5.9D). Place the dilator over the guidewire, and advance it into the vein (Fig. 5.9E). Continue to advance the dilator until its hub is against the skin. Do not release hold of the guidewire at any time. Remove the dilator over the guidewire. Place the catheter tip over the guidewire. Advance the catheter over the guidewire and into the vein to the desired depth (Fig. 5.9F). The depth is typically 10 to 15 cm for the internal jugular or subclavian approaches, or completely to the hub for femoral central venous lines. Securely hold the catheter in place, and remove the guidewire (Fig. 5.9G). Occlude the open catheter lumen with a sterile-gloved finger to prevent air embolization and excessive blood loss.

Attach a syringe to the catheter hub, and aspirate blood to confirm that the catheter is within the vein. Withdraw any necessary blood samples. Attach infusion tubing or a cap to the port, and flush the catheter to prevent a blood clot from obstructing the lumen. Securely attach the catheter to the skin with nylon or silk sutures. Cover the skin puncture site with a sterile dressing. Obtain a chest radiograph to evaluate for central line placement complications such as a pneumothorax, hemothorax, hematoma, and/or line malpositioning.

Pediatric Considerations

The anterior or central approach to the internal jugular vein is preferred for children. Appropriate catheter sizes and lengths are shown elsewhere (4). The child must be sedated and immobilized prior to attempts at cannulation of the internal jugular or subclavian vein.

The femoral vein is the vein of choice if central venous access is needed in a combative child who cannot be completely restrained. The patient need not be in Trendelenburg position, the consequences of a misdirected needle are less severe, and the procedure is less threatening as the face is not draped. A shallower angle of skin entry is necessary to access the femoral vein compared to an adult. Enter

the skin 1 to 2 cm inferior to the inguinal ligament and 0.5 mm medial to the femoral artery.

Assessment

Examine the patient after central line placement. Examine the lung fields carefully to exclude a significant pneumothorax. Vital signs should be rechecked. Obtain a portable anteroposterior chest radiograph to verify line tip placement in the superior vena cava and to rule out a procedural-related pneumothorax. Check the catheter site for hematoma formation or hemorrhage along the dilated catheter track. Control any hemorrhage with direct pressure. Check the function of the catheter by aspiration and infusion through all ports.

Most femoral vein catheters can be fully inserted. Premeasurement is recommended to make sure that the catheter tip will not reach the right atrium. If there is any doubt about the catheter position, postinsertion abdominal and chest radiographs should be obtained. The tip of the catheter must be at or below the xiphoid process of the sternum. Reassess the lower extremity distal to the catheter to determine any change in the neurovascular status after line placement.

Removal of the Central Venous Catheter

Place the patient in the Trendelenburg position when removing a central venous catheter from the internal jugular or subclavian vein. Place the patient supine to remove a femoral vein catheter. Remove the dressing overlying the skin puncture site. Cut the suture securing the catheter to the skin. Ask the patient to exhale and hold their breath. Briskly remove the catheter, and cover the puncture site with a gauze dressing. Apply an occlusive dressing to the site for the first 1 to 2 days after the catheter has been removed if the catheter had a large diameter or had been in place for more than 2 to 3 days. The skin puncture site should be observed for signs of infection twice a day for 48 hours.

Complications

Complications associated with central venous access are numerous. The internal jugular and subclavian access has a myriad of potential complications (1,4). These complications include infection, vessel laceration, catheter malposition, pneumothorax, hemothorax, chylothorax, carotid artery puncture, stroke, airway compromise, air embolism, cardiac dysrhythmias, cardiac puncture, pericardial tamponade, and death. The guidewire can become entrapped, necessitating surgical or interventional radiology removal. Thrombosis of the catheter or vein may lead to pulmonary embolism. Infection may result in septic emboli or endocarditis. Complications during catheterization occur in proportion to the operator's inexperience (6). If the patient is unlikely to survive complications, the most experienced person available should perform the procedure.

Deep venous thrombosis of the femoral and more distal veins is a recognized complication of femoral venous lines. Inadvertent cannulation of the femoral artery may occur. This is particularly true during an episode of severe hypotension or cardiac arrest during central venous line placement. If intra-arterial placement is unrecognized, infusion of vasopressors into the artery may result in ischemic injury to the distal limb.

ULTRASOUND GUIDANCE FOR VASCULAR ACCESS

Ultrasound is a very useful tool to assist with peripheral or central vascular access, whether arterial or venous (8). Ultrasound can provide direct visualization of vessel cannulation, which can reduce the number of attempts and minimize complications. Although somewhat controversial because most community-based EDs do not yet have ultrasound capabilities, it is likely to emerge as the standard of care in the near future.

There are both static and dynamic ultrasonographic methods to assist in vascular access. The static method uses ultrasound to identify the vessel to be cannulated, but ultrasound is not used during the actual puncture. Rather, ultrasound is used to identify the vessel's location. A mark is made on the skin above the vessel. The

ultrasound probe is then slid 0.5 to 1 cm along the course of the vessel, and a second mark on the skin is made. This mark provides the direction of needle entry. An estimation of the angle required to reach the vessel can be determined by evaluating its depth. This technique allows the operator to remove the probe from the field and have both hands free to perform the procedure. The dynamic method uses ultrasound to visualize the puncture of the vessel in real time.

A high-frequency (5 to 10 MHz) linear probe should be used when attempting vascular access. High-frequency probes sacrifice tissue penetration for increased resolution. High-frequency probes provide better resolution at shallow depths and thus a better picture of superficial tissue. This resolution is important when visualizing vascular structures that are generally small and superficial.

The operator can place the vessel in the center of the screen and maximize its size by adjusting the depth (Fig. 5.10). Using the centimeter scale that is usually at the side of the screen, the operator can gauge the degree to which a needle should be inserted to enter the vessel based on the distance of the insertion site to the probe and the distance from the probe to the vessel (Fig. 5.11).

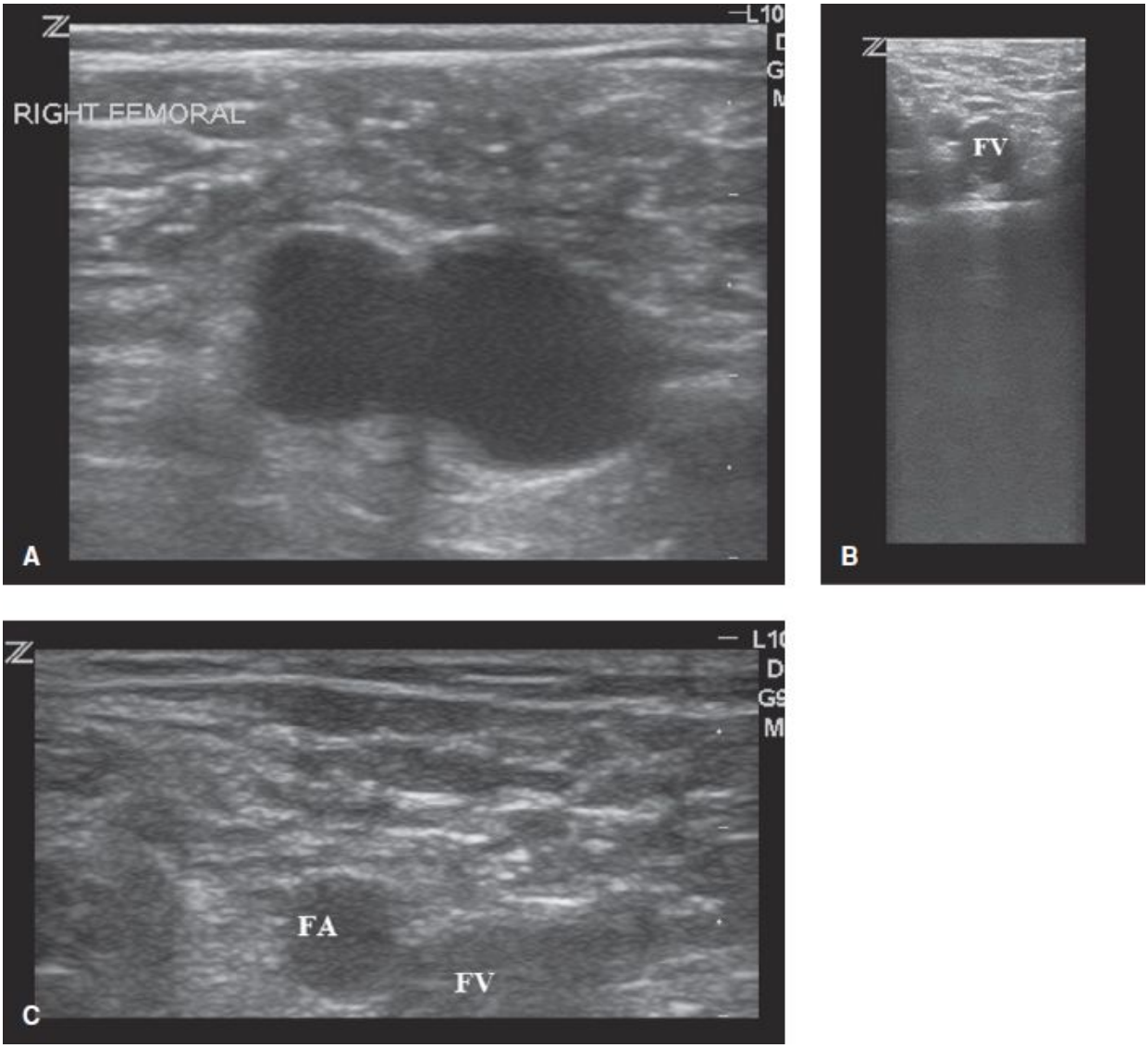

FIGURE 5.10 Ultrasound field of depth. **A:** Appropriate depth. **B:** Inappropriate settings of depth. Deep depth is not required and results in a small image on the ultrasound machine screen. **C:** Inappropriate depth setting as vascular structures should be completely visible and in the center of the screen. FA, femoral artery; FV, femoral vein.

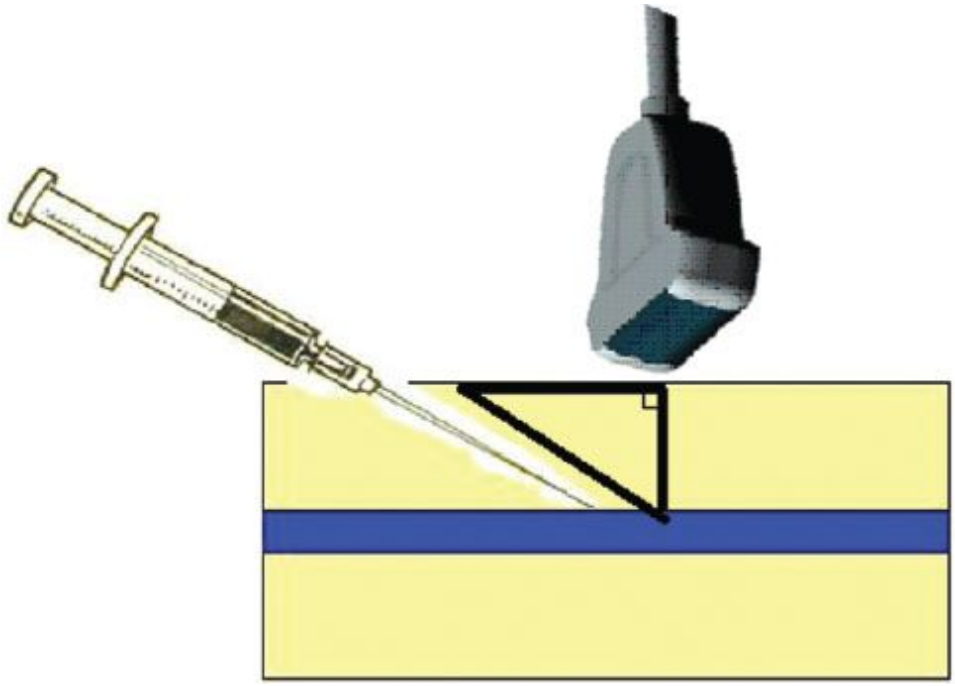

FIGURE 5.11 Estimation of needle insertion angle and depth.

Before beginning the procedure, one must always ensure that the catheter chosen is of sufficient length to penetrate the soft tissues and enter the target vessel.

Basic Principles

Ultrasound requires a gel between the probe and the skin surface to transmit the acoustic signals. Most commercially available gels are good transmitters but are not sterile. When using ultrasound for vascular access, the probe should be placed inside a commercially available probe cover or sterile glove with transducer gel inside the cover or glove and with sterile gel between the probe cover and the skin to maintain a sterile environment and protect the probe from contamination.

Long-Axis Approach

This approach allows the operator to see the length of the needle enter the vessel as well as to appreciate the angle of insertion and length of catheter required to adequately cannulate the vessel. Place the probe on the site determined by anatomic landmarks with the

probe marker toward the patient's head and perpendicular to the patient's skin (Fig. 5.12A). Locate the long-axis view of a fluid-filled (black) vessel (Fig. 5.12B). Adjust the depth to maximize the size of the vessel, and position the vessel in the center of the ultrasound machine screen. Adjust the gain as previously described.

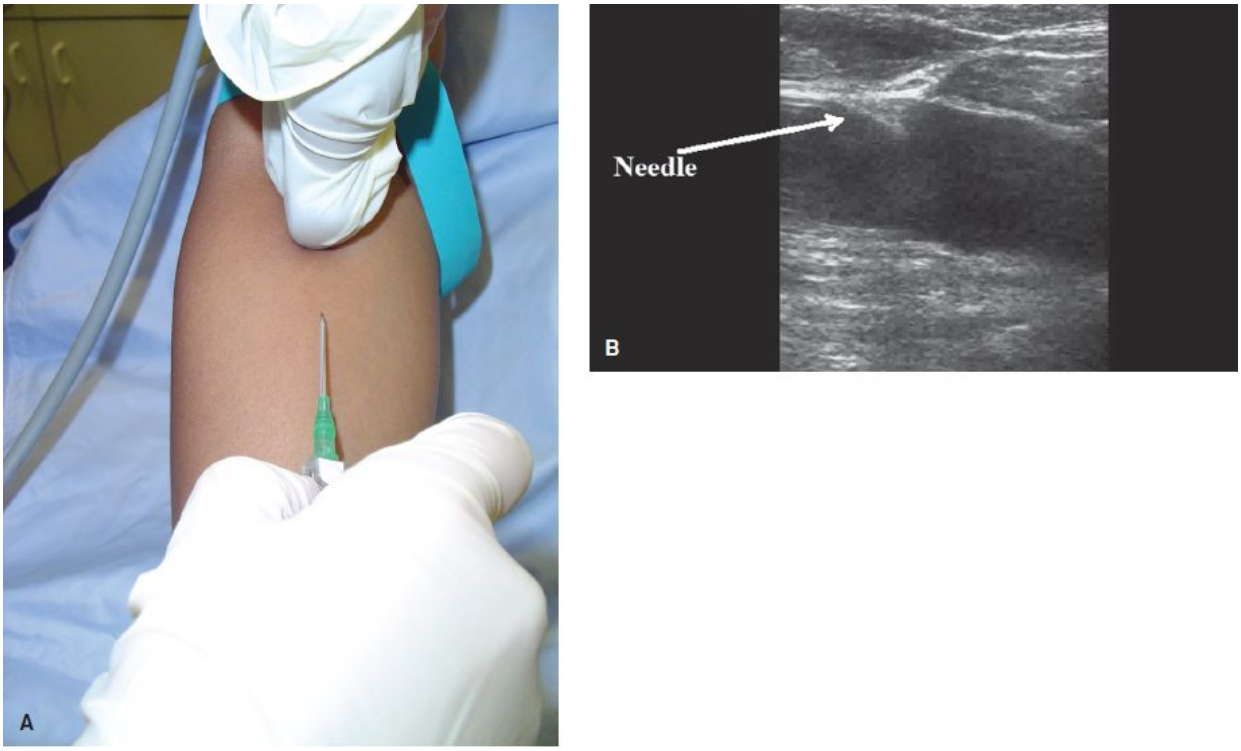

FIGURE 5.12 Long-axis approach. **A:** Probe marker toward patient's head. **B:** Needle entry into the vessel.

To determine if the vessel is arterial or venous, apply downward pressure on the area. Venous structures should be fully compressible, except in the setting of a thrombus. Arterial structures will not be fully compressible and should be pulsatile. Slide the probe several millimeters medially and laterally to locate the paired vessels (artery and vein), and determine which is the artery and which is the vein. Once the operator is certain of the vessel to be cannulated, enter the skin with the needle aligned directly with the long axis of the probe (Fig. 5.12A), and observe as the needle enters the vessel. The needle will appear as a bright white linear object as it travels through the

tissue below the probe. There may be a degree of tenting of the vessel as the needle enters (Fig. 5.12B).

Short-Axis Approach

This approach allows visualization of both the artery and the vein on the ultrasound machine screen. Place the probe on the site determined by anatomic landmarks with the probe marker toward the operator's left, perpendicular to the patient's skin (Fig. 5.13A). Locate the short-axis view of the fluid-filled (black) vessels. Adjust the depth to maximize the size of the vessels, and position them in the center of the ultrasound machine screen. Identify the artery and vein by applying vertical pressure to the area as described previously. The operator may see the needle tip on the screen as a bright white dot that casts a shadow (Fig. 5.13B). Distortion of the soft tissues as the needle passes or tenting of the vessel wall just before the vessel is entered may sometimes be the only signs seen.

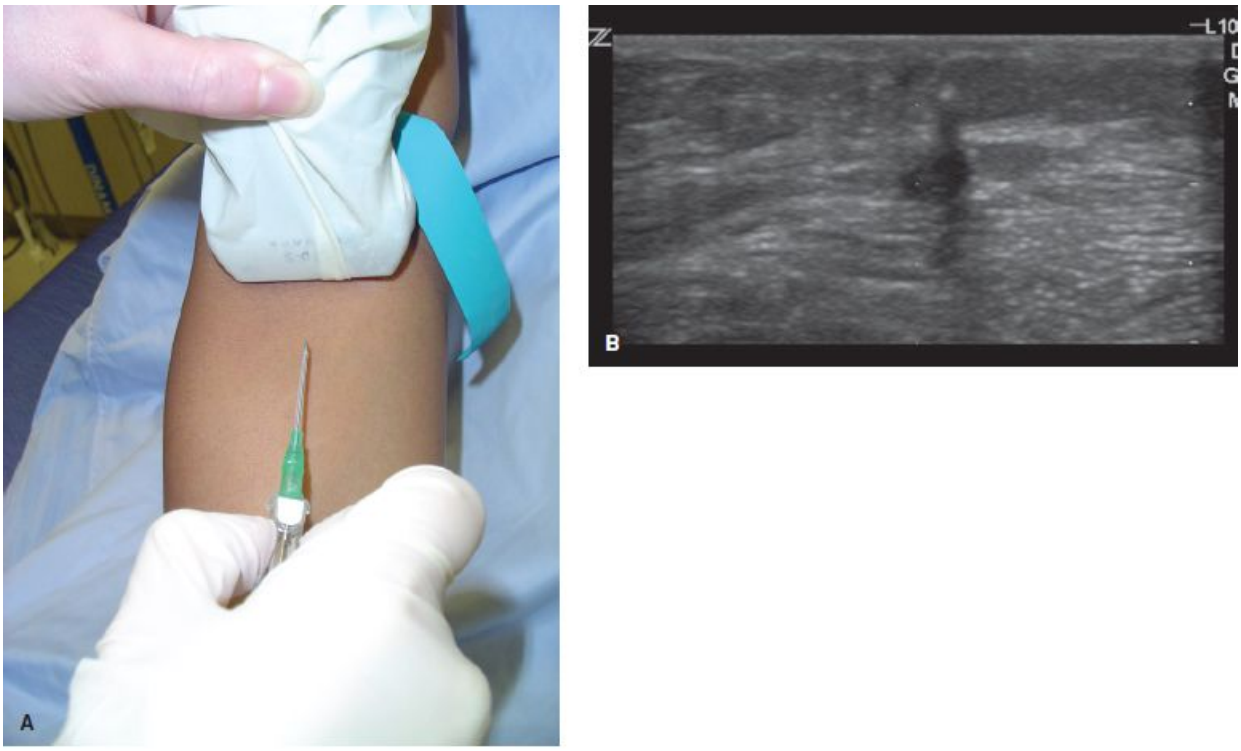

FIGURE 5.13 Short-axis approach. **A:** Probe marker toward operator's left. **B:** Needle entry into the vessel with shadowing and tenting of the vessel wall visible.

It is important to remember that the probe should be in a position to visualize the point of entry of the needle into the vessel and not so close to the skin insertion site that the operator only sees a point of passage of the needle through soft tissue, which means the needle tip is actually passing out of the view on the ultrasound machine screen. If the first attempt is unsuccessful and the needle needs to be repositioned, withdraw it to just below the surface of the skin before redirecting it toward the vessel. If the probe marker is to the operator's left and the ultrasound machine screen marker is also to the left, by directing the needle to the left it will move appropriately on the screen.

The use of color Doppler to help distinguish an artery from a vein may be beneficial when using the short-axis approach (Fig. 5.14). Doppler signals depend on direction of flow. Convention dictates that red represents flow toward the probe and blue represents flow away from the probe. Alter the tilt of the probe so that arterial flow is directed toward the probe and causes arteries to appear red on the ultrasound machine screen.

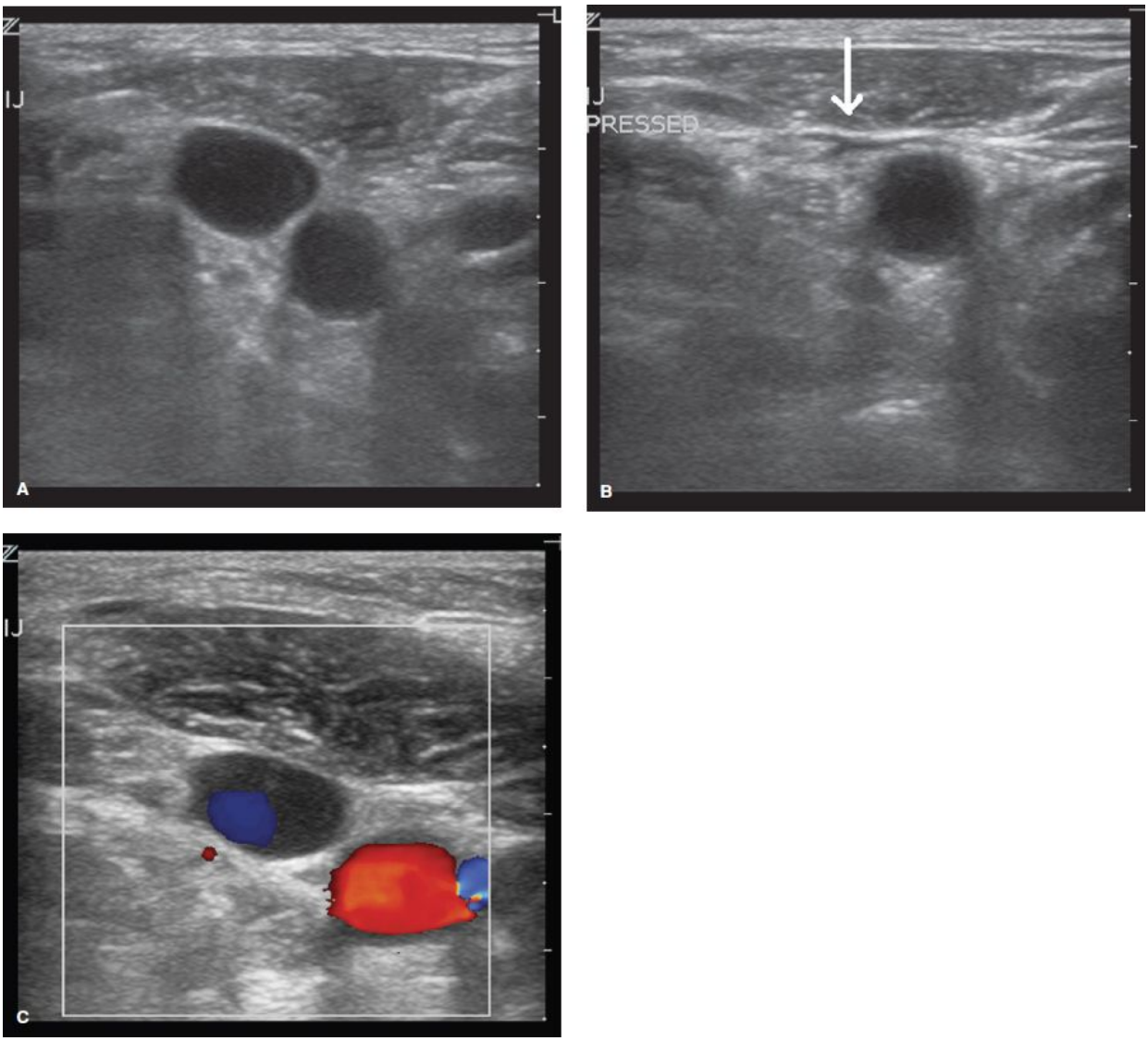

FIGURE 5.14 Distinguishing an artery from a vein. **A:** The left internal jugular vein and adjacent carotid artery. **B:** Compression of the skin with the ultrasound probe results in compression of the vein (arrow) and not the artery. **C:** Doppler reveals more intense flow in the carotid artery than in the internal jugular vein.

The short-axis approach is the preferred, though slightly less intuitive, method for vascular access in most cases. Because it gives the operator direct visualization of the artery and the vein, the operator can see which vessel (i.e., artery or vein) has been entered and can easily guide lateral movement's if the first attempt is unsuccessful.

SPECIAL CONSIDERATIONS FOR PERIPHERAL VENIPUNCTURE

Emergency physicians are often faced with patients who have difficult vascular access. Prior IV drug abuse, peripheral vascular disease, hypotension, and debilitation increase the likelihood of difficulty in obtaining peripheral vascular access (9). Ultrasound can provide direct visualization of deep peripheral veins and confirmation of catheter placement.

External Jugular Vein Cannulation

Place the patient in the Trendelenburg position to distend the external jugular vein. Turn the patient's head toward the opposite side. Clean and prep the skin of the neck. Place the nondominant thumb or index finger above the midportion of the clavicle to obstruct outflow and distend the external jugular vein. Align the catheter-over-the-needle parallel to the vein with the bevel of the needle upward. Enter the vein midway between the angle of the mandible and the midclavicle. Insert the catheter-over-the-needle during inspiration, when the valves of the external jugular vein are open. Be sure to cover the hub of the needle or catheter with a finger at all times to prevent an air embolism. The remainder of the technique is similar to that described previously.

Deep Brachial Vein Cannulation

Extend the patient's arm. Identify by palpation the brachial artery pulse in the antecubital fossa. Clean and prep the skin of the antecubital fossa. Place a tourniquet on the upper arm. Reidentify the brachial artery pulse. Place a catheter-over-the-needle onto a 5-mL syringe. Insert the catheter-over-the-needle just medial or lateral to the brachial artery pulse and at a 30- to 45-degree angle to the skin with the tip of the needle pointing cephalad. Advance the catheter-over-the-needle while applying negative pressure to the syringe. A flash of blood in the syringe indicates that the vein has been entered. The remainder of the technique is similar to that described previously.

Ultrasound can be used to facilitate brachial vein cannulation. First, cleanse and prepare the site, apply a tourniquet, and prepare the probe as described previously. Using the short-axis approach, identify the vessel to be cannulated. Scan proximally and distally to isolate the portion of vessel that is at the shallowest depth and of the greatest diameter to increase the likelihood of successful cannulation.

It is extremely important to estimate the distance the needle will need to be inserted to enter the vessel (the hypotenuse to the triangle; Fig. 5.11). The risk of failure or subsequent infiltration is increased if the catheter used is not longer than this estimate. The cannulation site should be reconsidered or a longer catheter obtained.

Although ultrasound does allow direct visualization of the vessels, it does not change the chance of vessels "rolling." Use the minimal pressure required to maintain probe contact with the skin and to prevent venous compression of peripheral veins, which are shallow and pliable.

ACCESSING INDWELLING CENTRAL VENOUS LINES

A variety of indwelling central venous access devices have been developed to avoid repeated venipunctures and permit direct access to the central circulation (5). These devices may be partially or completely implanted under the patient's skin and include tunneled catheters, Perm-a-Caths, Hickman catheters, Groshong catheters, and Mahurkar catheters. The emergency physician must be able to access these devices to administer medications and withdraw blood samples without damaging the device or causing it to thrombose. The most important elements after accessing indwelling lines are to prevent the central venous line from clotting off and to avoid contaminating the line.

There are several contraindications to accessing indwelling central venous lines. Fully implanted devices should not be accessed through infected skin. Phenytoin and diazepam cannot be given via silicone indwelling central venous lines as they can crystallize and permanently obstruct the catheter lumen. Devices used for hemodialysis should only be accessed in a true emergency and if no

other method of venous access can be readily obtained. This guideline is intended to prevent loss of the patient's dialysis access.

Accessing a partially implanted central venous catheter is simple and similar to accessing a capped peripheral IV catheter. The Luer cap can be removed entirely and the catheter lumen accessed directly with a syringe if an infusion is to be subsequently started.

A noncoring Huber-type needle must be used to access subcutaneous injection ports. A small-gauge standard hypodermic needle can be used in a dire emergency if a noncoring needle is not available. The diaphragm covering the injection reservoir can be damaged by a standard hypodermic needle, leading to subcutaneous hemorrhage and requiring surgical replacement of the implanted device.

It is extremely important to prevent the indwelling central venous catheter from becoming thrombosed after it is used. Flush the Hickman and Broviac catheters with 3 to 5 mL of heparinized saline (100 U/mL). Flush the Groshong catheter with 5 mL of normal saline. Flush dialysis catheters with the volume printed on the catheter (usually $\leq$2 mL) with heparinized saline (1,000 U/mL). Flush fully implanted catheters with 3 to 5 mL of heparinized saline (100 to 200 U/mL). Heparin may be contraindicated in some patients because of bleeding or thrombocytopenia. Sterile saline is an alternative but may result in catheter thrombosis.

PERIPHERAL VENOUS CUTDOWN

Venous access in the critically ill patient is of utmost importance. Peripheral venous access can be extremely difficult because of vascular collapse from shock, previous injury to the vessel, obesity, or scars. Direct visualization of the vein to be cannulated will often be quicker and more successful than indirect visualization with central venous lines (10). To perform peripheral venous cutdowns, one must understand the anatomy and details of venous cannulation (10). Practicing the cutdown technique before its critical need will help with placement in the emergent setting. Emergency physicians should be knowledgeable of the anatomy of the saphenous vein at

the ankle, the saphenous vein at the groin, and the basilic vein at the elbow.

The primary indication for a peripheral venous cutdown is the need for venous access in a patient with no peripheral access and in whom central access is not obtainable or contraindicated (10). This is the ideal procedure for the IV drug user with no peripheral veins, burn patients, the patient in cardiorespiratory arrest, or the hypovolemic trauma patient. This is also an excellent technique for emergent pediatric vascular access after other access attempts (i.e., intraosseous access, central venous access, peripheral venous access —including scalp veins) have failed.

Greater Saphenous Vein Isolation at the Ankle

The saphenous vein is easily found and isolated at the ankle (Fig. 5.15). Extend and externally rotate the lower extremity. Identify the medial malleolus of the tibia. Find the spot 2.5 cm anterior and 2.5 cm superior to the medial malleolus. The greater saphenous vein will be found at this site. Alternatively, the vein will be found two fingerbreadths above and two fingerbreadths in front of the medial malleolus (Fig. 5.15A).

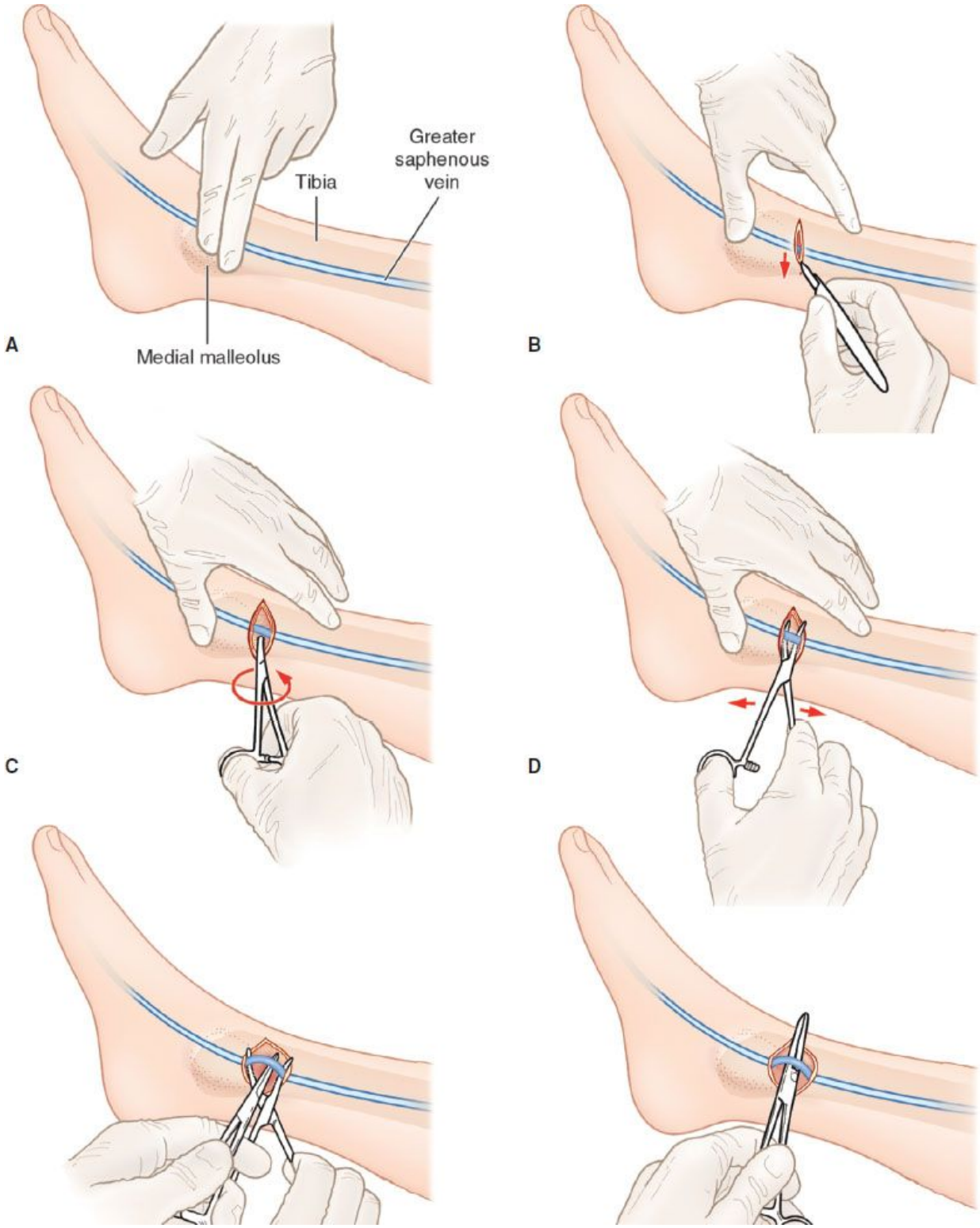

FIGURE 5.15 Isolation of the greater saphenous vein at the ankle. (Reprinted with permission from Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013.)

Stretch the skin taught over the distal tibia with the nondominant hand (Fig. 5.15B). Transversely incise the skin overlying the greater saphenous vein using a no. 10 scalpel blade, from the anterior tibial border to the posterior tibial border (Fig. 5.15B). This incision should be superficial to expose only the subcutaneous tissue. An incision into the subcutaneous tissue may transect the vein causing significant bleeding, difficulty visualizing the surgical field, and difficulty finding the ends of the vein, which may retract proximally and distally.

Isolate the greater saphenous vein. Insert a curved hemostat along the posterior border of the tibia, and scrape the tip along the tibia. Advance the hemostat along the tibia while scraping the periosteum until the tip reaches the anterior border of the tibia (Fig. 5.15C). Widely open the arms of the hemostat (Fig. 5.15D). This motion will open the jaws of the hemostat and separate the saphenous vein from the saphenous nerve and fibrous strands of connective tissue. Insert a straight hemostat (Kelly clamp) between the jaws of the curved hemostat and below the greater saphenous vein (Fig. 5.15E). Remove the curved hemostat to leave the straight hemostat elevating the greater saphenous vein (Fig. 5.15F).

Greater Saphenous Vein Isolation at the Groin

The groin vasculature offers the potential for massive infusion of blood or fluids in a matter of minutes. These vessels are closer to the central circulation and large enough to easily accommodate IV tubing, cut off at a 45-degree angle, as a catheter. The greater saphenous vein is superficial at the groin and lies in a meshwork of subcutaneous tissue superficial to the femoral artery and vein.

Identify the location where the scrotal or labial fold meets the thigh (Fig. 5.16). Identify the lateral edge of the mons pubis. Identify the point where a vertical line from the lateral edge of the mons pubis meets a horizontal line from the scrotal/labial fold. Make a 6-cm, transverse, medial-to-lateral incision with a no.10 scalpel blade on the patient's thigh starting where the scrotal or labial fold meets the thigh. Extend the incision laterally until it meets the vertical line

from the lateral edge of the mons pubis. Dissect the subcutaneous tissue to locate the greater saphenous vein.

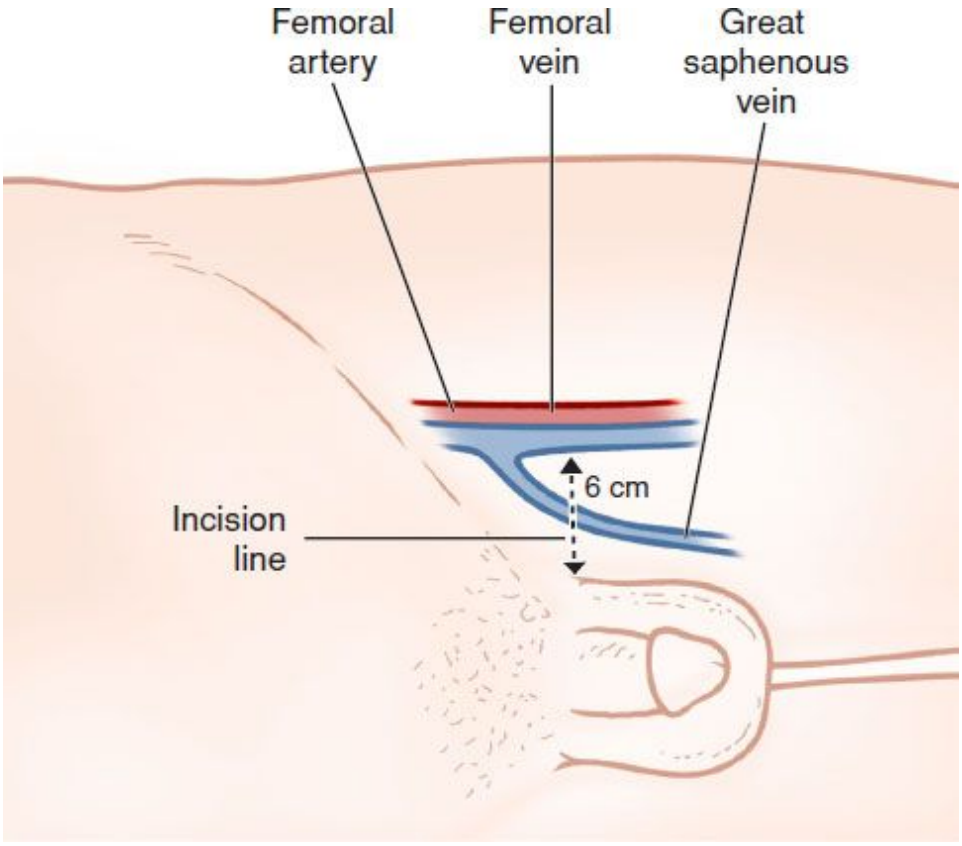

FIGURE 5.16 Isolation of the greater saphenous vein at the groin. (Reprinted with permission from Reichman EF. *Emergency Medicine Procedures*. 2nd ed. New York, NY: McGraw-Hill; 2013.)

Basilic Vein Isolation at the Elbow

The basilic vein may be used for a peripheral venous cutdown. This procedure is often performed when the greater saphenous vein cannot be accessed because of lower-extremity amputation, deformity, injury, or trauma. This site is not ideal as accessing it may interfere with resuscitative efforts. The vein is deep, small, and often hard to find.

Techniques for Cannulation of the Vein

There are a number of techniques to cannulate a vein after it has been isolated (10). Either of the following techniques can be used to cannulate the greater saphenous vein or basilic vein. The techniques include a surgical technique using IV tubing, a Seldinger technique, a modified Seldinger technique, and an IV catheter technique. It is important to realize that this may be a lifesaving procedure in an emergent setting, and the rapid and definitive cannulation of the vessel is the primary goal and not the technique chosen.

The complications of a peripheral venous cutdown include arterial injury, nerve injury, phlebitis, thromboembolism, wound dehiscence, and wound infection. The incidence of complications ranges from 2% to 15% (10). The difficulty in reporting complications is that there is a high mortality rate in patients undergoing this procedure because of the underlying problem requiring emergent vascular access (i.e., hypovolemia, sepsis, shock, trauma, etc.).

INTRAOSSEOUS INFUSION

Obtaining peripheral vascular access in the critically ill pediatric or adult patient may be difficult and time consuming. An alternative route to IV infusion for blood, drug, and fluid administration is to insert an intraosseous line (11). Intraosseous infusion is quick, safe, and effective in compromised neonates and adults when other vascular access techniques fail or are contraindicated (11). The procedure is technically straightforward.

The intraosseous needle is inserted through the cortex and into the bone marrow (medullary) cavity of a long bone. Numerous anatomic sites can be used to access the medullary cavity. The most traditional site, which is favored in pediatric patients, is the flat anteromedial surface of the proximal tibia. The distal tibia just above the medial malleolus and the greater tuberosity of the humerus are the preferred sites in adults. It is easier to penetrate the cortex of the medial malleolus and the greater tuberosity of the humerus in the adult than the thicker cortex of the proximal tibia. A third site for intraosseous access is the flat anterior surface of the distal femur. The sternum can be used, but this route is difficult and associated with numerous complications.

Intraosseous line placement is contraindicated in diseased or osteoporotic bone. Avoid placement of an intraosseous line through areas of cellulitis, abscess, or burns. Fractures in the ipsilateral bone increase the risk of extravasation-induced compartment syndrome and nonunion of the fractures. Failed placement of an intraosseous line in the same bone is a relative contraindication.

Use only specifically designed intraosseous needles for this procedure. Spinal needles bend, do not penetrate the cortex, and have increased resistance to fluid flow. Standard hypodermic needles often bend and do not penetrate the cortex of the bone. Both of these types of needles may break while being inserted and may injure the healthcare provider.

The most common complication of intraosseous infusion is extravasation of fluid. Localized infections may occur after intraosseous needle placement. Injury to the growth plate and bone marrow embolism are possible. The flow rate of fluid through an intraosseous line is slower than that through a peripheral IV line.

UMBILICAL VESSEL CATHETERIZATION

Umbilical vessel catheterization can be used as a reliable method for vascular access, fluid resuscitation, blood transfusion, medication administration, frequent blood sampling, and cardiovascular monitoring. Either the umbilical artery or vein may be used for vascular access (12). It is possible to access the umbilical artery up to 7 days after birth. The umbilical vein can be accessed for up to 2 weeks of age.

Umbilical artery catheterization is more desirable than umbilical vein catheterization because it allows frequent arterial blood gas sampling and continuous blood pressure monitoring in addition to fluid, blood, and medication administration. Unfortunately, umbilical artery catheterization is more difficult and time consuming to perform, especially in unskilled hands. Therefore, umbilical vein catheterization is the preferred procedure for the infant in shock in need of rapid resuscitation. Arterial access can be obtained later in a more controlled environment, such as in the neonatal intensive care unit.

The umbilical vein and arteries can easily be differentiated by examination of a cross section of the umbilical cord. The umbilical vein is a single vessel with thin walls and a large lumen. It is usually flattened in one direction. There are two thick-walled umbilical arteries that are significantly smaller in diameter than the umbilical vein. Occasionally, only a single umbilical artery is present.

Umbilical vessel catheterization in the ED should only be performed on severely ill neonates in whom peripheral vascular access attempts have failed. Never insert an umbilical catheter if there are any signs of infection on or around the remnant of the umbilical cord. Umbilical vessel catheterization is contraindicated if a neonate is older than the previously stated ages or an abdominal abnormality exists.

ARTERIAL PUNCTURE AND CANNULATION

Arterial blood gas sampling is an essential component of the care of many ED patients (13). Arterial blood gas sampling provides key information regarding a patient's oxygenation and acid–base status. Arterial cannulation allows for continuous and accurate blood pressure monitoring and frequent blood gas sampling in the care of the critically ill patient. A modified Allen test should be performed to assess the adequacy of the collateral circulation to the hand prior to radial artery puncture or cannulation. An alternative method of evaluating the collateral circulation involves the use of a pulse oximeter with a visual pulse waveform display.

The preferred site for the initial attempt at arterial puncture or cannulation is the radial artery. Other acceptable second-attempt sites of access include the femoral, dorsalis pedis, brachial, posterior tibial, and superficial temporal arteries. Arterial puncture may be performed to obtain a single blood sample.

Arterial cannulation can be accomplished by numerous techniques (1,13). The catheter-over-the-needle technique is the most basic method, yet possibly the one associated with the lowest rate of successful cannulation. It is the direct introduction of the catheter-over-the-needle in a manner similar to that of inserting an IV catheter. The second technique for arterial cannulation is a

Seldinger-type technique (i.e., catheter-over-the-wire) utilizing one of a number of prepackaged commercially available kits. A double arterial wall puncture technique may offer an advantage in passing the guidewire and catheter into the true arterial lumen. This technique for cannulation theoretically may be associated with greater vascular damage. Finally, a cutdown technique may be performed to cannulate an artery. This technique is primarily used for the brachial or radial arteries but may be used to access other peripheral arteries.

Arterial puncture and catheterization are generally safe procedures with an incidence of clinically significant complications under 5% (14). The primary complications of arterial catheterization are infection, bleeding, arterial injury, and intra-arterial thrombosis. Infection is usually limited to the site of catheterization. Nerve injury can occur from direct puncture or neuropathy as a result of a hematoma formation and subsequent nerve compression. Small hematomas are common after arterial puncture. Major bleeding is unusual. Rare complications include the formation of a pseudoaneurysm or arteriovenous fistula.

Common Pitfalls

- Know the anatomy and common variations of the major veins used for vascular access.
- Be familiar with the equipment and techniques for venous access before performing the procedure.
- Have a backup plan for an alternative vascular access site if the attempts at the primary site are unsuccessful.
- Anticipate difficult central venous line placement or complications because of a particular patient's anatomic variation from normal.
- Be sure to align the ultrasound probe marker and the screen marker.
- Always optimize the ultrasound machine screen depth and gain.
- Always differentiate artery from vein if ultrasound is available.
- Always maintain sterile technique.
- Involve a second operator to make both hands available when using ultrasound.

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SECTION II
High-Risk Chief Complaints

Section Editor: CARLO L. ROSEN

CHAPTER 6 Chest Pain

Judd E. Hollander

Chest pain is the second most common chief complaint in patients presenting to the emergency department (ED). However, when combined with other symptoms that potentially represent myocardial ischemia, pulmonary embolism (PE), or aortic dissection (such as back pain, neck pain, shortness of breath, etc.), the evaluation of patients with "chest pain equivalents" is the most commonly evaluated diagnostic entity.

The evaluation of chest pain is complicated by the fact that the differential diagnosis includes several life-threatening entities that must be rapidly diagnosed (acute myocardial infarction [AMI], aortic dissection, PE) while recognizing that the majority of patients with chest pain have less urgent conditions. The emergency medicine approach to determining the etiology of chest pain cannot focus solely on what is more likely and what is less likely. It must focus on reducing the likelihood of the serious causes of chest pain to an acceptable threshold. This is usually considered to be less than a 1% to 2% likelihood of missing the diagnosis or having 30-day adverse events (1–3).

CLINICAL PRESENTATION

Chest pain, shortness of breath, and other symptoms of potential acute coronary syndrome present an initial diagnostic challenge. The cardiac, pulmonary, gastrointestinal, abdominal, and musculoskeletal systems all share somatic or visceral nerve roots, making it difficult to accurately distinguish the etiology of chest

pain based upon history and physical examination. Demographic characteristics, traditional risk factors, chest pain characteristics, and physical examination are insufficiently accurate to exclude life-threatening diagnoses by themselves (4,5), but they can help direct appropriate diagnostic testing. Unfortunately, there is no sufficient availability of diagnostic tests for acute coronary syndrome with enough sensitivity to confidently rule out the condition rapidly in the ED. Therefore, after a thorough evaluation, the clinician is often left admitting or observing many patients to rule out acute coronary syndrome. Patients with AMI can have a wide variety of symptoms, making diagnosis difficult—in fact, atypical symptoms are so common that up to 40% of non–ST-segment elevation AMIs go unrecognized by the patient (6).

Classically, the pain of an AMI or acute coronary syndrome is substernal or left chest pressure or aching and may have radiation to the arm or neck. High-risk features of AMI, such as left arm radiation, substernal location, and past history of AMI are reliable with good interrater reliability and can be used to predict increased risk of AMI. On the other hand, low-risk features such as pleuritic, positional, and sharp chest pain have poor reliability making it difficult to rule out ACS (4). Traditional cardiac risk factors, such as hypertension, family history of heart disease at a young age, diabetes, and increased cholesterol help predict development of coronary disease over decades, but the absence of them is not useful to risk stratify patients in the ED (5).

Aortic dissection classically presents with a severe anterior tearing pain that may radiate to the back between the shoulders. The pain can be perceived as migratory, as the dissection extends. Patients often appear sick and may be writhing in pain. A pulse differential is actually very uncommon and lack of one should not be considered to exclude the condition.

A prominently pleuritic pain with or without shortness of breath can be caused by pleural inflammation from PE, pneumonia, pleurisy, and pericardial inflammation (from pericarditis or myocarditis). Pericarditis may be positional and is classically worse with lying down but the pericardial rub is easier to hear when

patients are sitting up. Pneumothorax is usually sudden onset and worse with breathing. Fever and purulent cough suggest pneumonia.

Esophageal spasm, gastroesophageal reflux disease, and other GI causes of chest pain can be difficult to diagnose in the ED. They can have pain similar to ACS in terms of quality, location, radiation, and intensity and can also be associated with ill appearance and diaphoresis, although shortness of breath is less common. Cholecystitis and biliary colic are likely to have right upper quadrant or midepigastric tenderness and as long as complete physical examination is performed, they should be able to be diagnosed.

The ability to reproduce pain by pushing on the chest wall is likely to be misleading. Although musculoskeletal causes of chest pain are common, approximately 6% of patients diagnosed with costochondritis are actually having an AMI (7). Undressing the patient and examining their skin should identify most cases of herpes zoster, although patients can have burning dermatomal pain for a couple of days before the rash becomes evident.

Patients may improve with either a “GI cocktail” or with nitroglycerin whether or not their symptoms were from a GI or cardiac etiology. Clinicians should not rely on response to treatment in determining the etiology of pain (8,9).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of chest pain is large. Although often broken down into the organ system involved (cardiac, pulmonary, gastrointestinal, abdominal, or musculoskeletal), it is better broken down into diagnostic categories in terms of levels of urgency. The treatment of each of these conditions is not covered in this chapter, but can be found in the chapters on each specific disease.

Critically time-sensitive conditions are those that can worsen rapidly if left untreated or can benefit from time-sensitive surgical or medical interventions. These include Type A and B aortic dissection, ST-segment elevation myocardial infarction (STEMI), hemodynamically significant PE, tension pneumothorax, pericardial

tamponade, esophageal perforation, and mediastinitis. All these conditions have interventions that can improve outcome, if the diagnosis is made in a timely manner.

Urgent or emergent diagnoses to consider before ED disposition include acute coronary syndromes (non–ST-segment elevation myocardial infarction [NSTEMI] or unstable angina), submassive (nonhemodynamically significant) PE, pneumonia, pneumothorax, pericardial effusion, pericarditis, cholecystitis, pancreatitis, and Fitz-Hugh–Curtis. Significant delays in treatment of patients with these conditions can result in adverse outcomes.

Chest pain can result from cardiac conditions where myocardial demand outstrips myocardial supply, or myocardial injury occurs even without coronary artery disease. Such conditions include cocaine- or amphetamine-induced ischemia, hypertropic cardiomyopathy, myocarditis or valvular heart disease (aortic stenosis in particular).

Less urgent conditions that may still cause significant discomfort to patients include intercostal strain, costochondritis, rib pain, radicular pain from cervical or thoracic spine disease, and herpes zoster or postherpetic neuralgia all of which may be radicular in nature. Gastrointestinal conditions such as gastroesophageal reflux disease or peptic ulcer disease may be suggested by symptoms. Pleurisy or epidemic pleurodynia can mimic more severe conditions. Mitral valve prolapse is associated with chest pain, the etiology of which is unclear. Fibromyalgia and psychiatric causes of chest pain should also be considered and they can be difficult to distinguish from more serious causes of chest pain.

DIAGNOSTIC APPROACH

Since the differential diagnosis of chest pain is broad and the history and physical examination often lack sufficient accuracy to exclude the most serious conditions, the diagnostic approach must take into account the pretest probability of these serious conditions while performing diagnostic testing to reduce the posttest probability of missing one of the serious causes to less than 1% to 2%. Clinical

features particularly concerning for high-risk conditions are noted in Table 6.1. The absence of any of these features should not be used to exclude the possibility of these conditions. More detailed descriptions of the classic presentations of each condition can be found in the chapter specific to that disease.

TABLE 6.1
Selected Clinical Features that Raise Particular Concern for Serious Conditions in Patients with Chest Pain[a]

Feature	Raises Particular Concern About
Severe tearing pain	Aortic dissection
Sudden onset of pain	Aortic dissection, PE, pneumothorax
Pain radiation to back, shoulders	Aortic dissection, AMI
Migratory/extending pain	Aortic dissection
Pain similar to but worse than prior AMI	AMI
Symptoms only on exertion	Unstable angina/AMI, aortic stenosis
Pain worse supine, better sitting	Pericarditis
Pleuritic chest pain	PE, pericarditis, myocarditis, AMI, pneumothorax, pneumonia
Chest pain following severe vomiting	Esophageal rupture, mediastinitis
Shortness of breath	PE, pneumothorax, AMI, pericardial tamponade, pneumonia
Cough	Pneumonia, PE
Syncope	Aortic dissection, AMI, PE, pericardial tamponade, valvular heart disease
Hypotension	Aortic dissection, AMI, tension pneumothorax, pericardial tamponade, severe sepsis (pneumonia, mediastinitis, abdominal conditions)
Fever	Pneumonia, AMI, PE/infarction, mediastinitis, abdominal infections
Crepitance in chest wall or neck	Esophageal rupture, mediastinitis, pneumothorax
Distant heart sounds	Pericardial tamponade
Hypoxia	Pneumonia, pulmonary embolism, heart failure

[a]The absence of these symptoms should never be used in isolation to exclude any serious condition.

AMI, acute myocardial infarction; PE, pulmonary embolism.

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12-Lead Electrocardiogram

The diagnostic approach should begin with a 12-lead electrocardiogram (ECG). Ideally the ECG should be accomplished within 10 minutes of arrival and is often done in conjunction with triage and before or concurrent with the history and physical examination. The 12-lead ECG will identify STEMI and allow STEMI

protocols to be activated in a timely manner (see chapter on AMI). ST-segment depressions or T-wave inversions may identify patients with non–ST-segment elevation acute coronary syndromes. PR depression or diffuse ST-segment elevations can suggest pericarditis or myocarditis. P pulmonale, right axis deviation, right ventricular strain pattern, right bundle branch block, or an S1Q3T3 suggest PE. Electrical alternans suggests pericardial tamponade. Unfortunately, a normal ECG cannot exclude any of these conditions—it is normal in 5% and nondiagnostic in as many as 50% of patients with AMI. Similarly, it is normal or nondiagnostic in up to 85% of patients with aortic dissection.

If the ECG does not show STEMI, further diagnostic testing is usually dictated by the history, physical examination, and results of chest radiography.

Chest Radiography

Most but not all chest pain patients will receive chest radiography. The diagnosis of pneumonia, pneumothorax, esophageal perforation, mediastinal emphysema, free air under the diaphragm, and pleural effusion are easily made.

Most patients with ACS will have nondiagnostic chest radiography. A widened mediastinum raises concerns regarding aortic dissection (10). A widened aortic knob or widened mediastinum increases the odds of aortic dissection 11-fold. It can be found in up to 76% of such patients. Aortic displacement and pleural effusions are other findings that can be associated with aortic dissection.

Although most patients with PE will not have pathognomonic findings on chest radiography, a Hampton hump (wedge-shaped pleural defect), Westermark sign (decreased vascularity distal to the occlusion) can suggest its diagnosis. More commonly seen are nonspecific findings such as atelectasis, pleural effusion, or elevated hemidiaphragm.

After consideration of the history, physical examination, ECG, and chest radiograph further diagnostic testing is usually dictated based upon likelihood of each item remaining in the differential diagnosis.

Cardiac Troponins

Most patients with chest pain will receive laboratory testing for cardiac troponin. Cardiac troponin elevation is the gold standard for the diagnosis of AMI, although it can also be elevated in conditions of myocardial injury unrelated to thrombotic occlusion. Current ACC/AHA guidelines still advise serial troponin values for 8 to 12 hours or at least one cardiac troponin 8 to 9 hours after chest pain onset (11).

High-sensitivity cardiac troponin, which is expected to be on the market in the US in late 2013, has approximately 90% sensitivity and 80% to 85% specificity for the diagnosis of AMI at the time of ED arrival and the sensitivity rises to nearly 100% within 3 hours of arrival (12–14). This will allow more rapid "rule outs" than contemporary assays (15).

Regardless of the etiology of the troponin elevation, more troponin is always worse than less troponin. By definition, high-sensitivity troponins will result in measurable troponin values in 50% of the health population. Measurable amounts of troponin, even though below the upper limit of normal conventional assays (for example, still below 0.04) portend a worse prognosis than when below the level of detection. Troponin is associated with a worse prognosis in AMI, heart failure, renal failure, sepsis, GI bleeds, cocaine use, and asymptomatic volunteers.

High troponin elevations are most likely from AMI, but other etiologies of chest pain such as PE can have low-grade troponin elevations. The use of delta troponins (two troponins 2 hours apart) can determine whether the troponin is rising, in which case it is most likely due to myocardial ischemia, or is stable, in which case it is usually due to some other etiology. The precise delta value is assay and patient population dependent, so the EP should know the test performance characteristics at his or her own institution.

D-Dimer

D-dimer is a relatively nonspecific test that can be useful to assist in the diagnosis of PE and aortic dissection. In patients with a low pretest probability for PE, a negative D-dimer can obviate the need

for further diagnostic testing. D-dimer is a nonspecific test, and is often elevated in the absence of PE in patients who are elderly, have recent surgery, malignancy, trauma, or infections. Therefore, it should not be ordered indiscriminately and when ordered routinely at triage, should not mandate further testing for PE. Pretest probability assessment and pulmonary embolism "rule out" criteria testing should be used to determine whether patients need further noninvasive testing for PE (3) (see Pulmonary Embolism chapter). A negative D-dimer reduces the likelihood of aortic dissection dramatically, as the LR is 0.07 (16). It may be used to rule out the diagnosis in low-risk patients.

Computed Tomography

CT scans can help identify pneumothorax, pericardial effusion, mediastinitis, esophageal perforation, pneumonia, and abdominal causes of chest pain. CT angiography can be used to diagnose aortic dissection, coronary artery disease and myocardial ischemia, and PE. The timing of contrast injection, amount of contrast, and imaging protocol differ depending upon whether the CT is being done for evaluation of PE, aortic dissection, or coronary anatomy. There are three randomized controlled trials demonstrating that coronary CTA is safe, effective, more efficient, and cost-effective for the evaluation of low- to intermediate-risk patients with potential acute coronary syndromes and nondiagnostic ECGs. There was a less than 1% event rate in patients with normal coronary CTA over the ensuing 30 days, 6 months, and 1 year, and coronary CTA resulted in a shorter length of stay and higher ED discharge rate (17–19).

Some advocate "triple rule-out" scans where the contrast bolus is timed to provide diagnostic information about all three of those serious conditions. There are comparisons of triple rule-out scans with dedicated coronary CTA but there have not been comparative studies evaluating diagnostic utility of triple rule-out scans with dedicated PE and aortic dissection scans (20).

Bedside Ultrasound

Bedside ultrasound can be used to identify intra-abdominal catastrophes (abdominal aortic aneurysm/rupture), cholecystitis,

biliary colic, pneumothorax, pleural effusion, pericardial tamponade and pericardial effusions, cardiac wall motion abnormalities suggestive of myocardial ischemia, ventricular dysfunction, and valvular heart disease. It cannot, however, distinguish old from new wall motion abnormalities and cannot be used to "rule out" an acute coronary syndrome, since it misses approximately 6% of NSTEMI.

Myocardial Perfusion Imaging

Resting sestamibi imaging can identify myocardial ischemia at the time of presentation. Technetium sestamibi is distributed within the myocardium in proportion to myocardial blood flow and it has prolonged retention with minimal redistribution. A normal scan identifies patients with a very low likelihood of AMI or cardiac death (none of 338 patients) over the ensuing year (21). The ERASE trial found that, when compared to the typical ED evaluation (cardiac markers and ECG), the use of rest sestamibi scans resulted in similar diagnostic ability but a higher rate of ED discharges (22).

Stress myocardial perfusion imaging or stress echocardiography is common postacute care and often used in observation units to exclude exercise-induced ischemia. Patients with an uneventful observation period, negative cardiac markers, and a normal stress test can be safely discharged with a referral for follow-up. There is evidence supporting the use of immediate exercise testing in low-risk ED chest pain patients without known ventricular dysfunction and with normal or nonspecific ECGs, even without serial cardiac marker determination (23,24).

CRITICAL INTERVENTIONS

- Obtain an ECG within 10 minutes of arrival.
- Obtain cardiac troponin results within an hour of arrival.
- Obtain chest radiography to help identify many possible causes of chest pain.
- Treat tension pneumothorax clinically without waiting for radiographic imaging.
- Do not forget to assess skin, chest wall, and abdominal causes of chest pain.

- Treat vital signs depending upon differential diagnosis. Some conditions (aortic dissection) require more aggressive treatment of blood pressure and heart rate.
- Safely reduce pain, regardless of etiology. Since response to nitrates and GI cocktail do not help you discern pain etiology, some patients can be given analgesics, nitrates, and a GI cocktail to help make them comfortable, regardless of the cause of the pain.

DISPOSITION

The disposition of the patient with chest pain depends upon which conditions remain in the differential diagnosis after the initial evaluation. Most STEMI patients will go from the ED to the cardiac catheterization laboratory for primary percutaneous intervention. NSTEMI and type B aortic dissection should be admitted to the intensive care unit. Type A dissection requires surgical intervention and will either go directly to the operating room or to an intensive care unit for management while awaiting operative intervention. Massive PE (PE with hemodynamic instability), pericardial tamponade, esophageal perforation, and mediastinitis are other conditions that might require immediate surgical intervention.

Pneumothorax, cholecystitis, biliary colic, and pancreatitis are usually admitted to the hospital. Submasssive PE can be treated either as an inpatient or an outpatient as long as anticoagulation can be assured. In some practices, patients with a pneumothorax can be discharged home following tube thoracostomy. Likewise, some patients who improve rapidly with biliary colic or mild pancreatitis and can take fluids by mouth may be referred for outpatient management. Most gastrointestinal etiologies of chest pain and most chest wall causes can be treated as an outpatient.

Unfortunately, the majority of patients who present to the ED with chest pain or the equivalent are not found to have a specific cause for their symptoms and therefore are placed in a pathway to “rule out” an acute coronary syndrome. Most commonly, these patients are placed in observation where they receive serial cardiac

troponin measurements over 8 to 24 hours followed by some form of stress testing either prior to departure or within 72 hours. These protocols are compliant with ACC/AHA and European Society of Cardiology guidelines. Low-risk patients with potential ACS or PE do not require telemetry monitoring (25).

Patients less than 40 years old without cardiac risk factors or an abnormal ECG are safe for discharge without a "rule-out" protocol (26–28). Recent data strongly suggests that it may be appropriate to discharge patients with a Thrombolysis In Myocardial Infarction (TIMI) score of 0 or 1, a nonischemic ECG and two negative high-sensitivity troponin values within 2 hours (15).

Three randomized controlled trials have now shown the coronary CTA enables discharge of a greater percentage of patients in a shorter time frame (17–19). Patients with a maximal stenosis of less than 50% can be safely discharged with an exceedingly low likelihood of an adverse event in the near term. Angiographic presence of a stenosis or lack thereof is more useful than the coronary calcium score, which is best thought of as analogous to a cholesterol—a test to suggest patients who might benefit from primary preventive measures.

Appropriate referral for outpatient management should be made for those patients discharged home in whom a diagnosis was not made. Although they may not have life-threatening causes for their pain, the symptoms will require further investigation and treatment.

Common Pitfalls

- Relying too heavily on clinical judgment or classic clinical characteristics to determine the diagnostic approach.
- Using lack of traditional cardiac risk factors or a normal ECG to exclude acute coronary syndrome for the differential diagnosis.
- Relying on the response or lack of response to a GI cocktail or sublingual nitroglycerin to help diagnose a patient with chest pain.
- Assuming a troponin elevation is "false positive." More troponin is always worse than less troponin in every condition that has

been studied.
- Being too focused on ACS and not considering other serious causes of chest pain, such as aortic dissection or esophageal rupture.
- Overzealous pain management (e.g., with nitroglycerine or narcotics) resulting in adverse events in patients who otherwise did not have a serious condition.
- Believing "close follow-up" will identify at-risk patients with serious causes of chest pain.

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department patients with chest pain and possible acute coronary syndrome. *Ann Emerg Med.* 2012;59:115–125.

CHAPTER 7

Abdominal Pain

Diane M. Birnbaumer and Daniel P. Runde

Abdominal pain is simultaneously one of the most common and challenging chief complaints in emergency medicine. Abdominal pain accounts for 8% of the >120 million annual emergency department (ED) visits and is among the top 10 most common reasons people come to the ED (1). Its causes range from benign processes that present with severe pain to fatal processes that present with subtle findings. Despite improving imaging modalities, patients with abdominal pain continue to be diagnostically challenging. Even in patients who have undergone an appropriate workup, approximately 30% of patients will be discharged with the diagnosis of undifferentiated abdominal pain.

CLINICAL PRESENTATION

The importance of a thorough history and physical examination is absolutely paramount, as it helps narrow the vast differential diagnosis and focuses diagnostic testing. Failure to actually gather the relevant information (history and physical examination) is a more frequent cause of misdiagnosis than is misinterpretation of the data gathered.

When obtaining the history and performing a physical examination, it is important to understand that there are three major types of abdominal pain: *visceral, somatic,* and *referred* pain. They differ based on the anatomic pathway relaying the pain signal.

Visceral pain is relayed by afferent visceral fibers that are located in the walls of hollow organs and capsules of solid organs. These

fibers are stimulated by stretching, distension, and excessive contraction. The visceral pain fibers originate from both sides of the spinal column, and enter the spinal column at multiple levels. This results in the perception of a poorly localized, midline pain that is described as dull or aching.

Somatic pain results from irritation of the parietal peritoneum. Pain is relayed by myelinated, unilateral afferent fibers that travel to a specific level in the spinal cord, making this pain more localized. It is usually described as sharp, intense, and well localized. Somatic pain is responsible for the physical findings of tenderness to palpation, guarding, and rebound.

Abdominal pain often begins as visceral pain and then progresses to somatic pain as the inflammation spreads to involve the parietal peritoneum. As an example, the early epigastric pain of gallbladder distension is characteristic of visceral pain whereas the right upper quadrant (RUQ) pain caused by local peritoneal inflammation with cholecystitis is deep somatic pain.

Referred pain is discomfort perceived at a site distant from the diseased organ. The diseased organ and the body area to which the pain is referred have overlapping transmission pathways at the level of the spinal cord. A common example of referred pain is shoulder pain caused by irritation of the diaphragm from free air or blood. In the same manner, extra-abdominal organs may cause referred pain to the abdomen, such as myocardial ischemia or pneumonia causing epigastric pain.

History

When evaluating the patient with abdominal pain, a thorough history of the abdominal pain is crucial. Specifically, the physician should determine the onset, time course, character, location, aggravating and alleviating factors, associated symptoms, and whether there are previous episodes of abdominal pain. The general medical and social history should also be obtained, including past medical and surgical history, medications, allergies, tobacco, alcohol and illicit drug exposure, recent travel, and toxic exposures.

Onset

Sudden onset of severe pain is very concerning and is assumed to be due to a surgical condition, until proven otherwise. Vascular emergencies such as mesenteric ischemia or a ruptured abdominal aortic aneurysm, aortic dissection and intestinal perforation, or torsion of a viscus may all present this way. Sudden onset of severe pain with an unimpressive physical examination is typical for a vascular catastrophe or torsed organ. Nonsurgical causes of abrupt onset of abdominal pain include renal colic and myocardial infarction. The physician should determine what the patient was doing when the pain began. Pain related to eating may be secondary to peptic ulcer disease, gallbladder disease, or mesenteric ischemia (intestinal angina). Pain that began during physical activity may be caused by a rectus abdominal muscle tear and hematoma, or myocardial ischemia.

Progression of Pain

The physician should question the patient about whether the pain is constant or intermittent and, if constant, whether it has been increasing or decreasing in severity. Pain that begins slowly and gradually progresses is typical of an inflammatory or infectious process such as appendicitis, diverticulitis, or salpingitis. Pain that is improving over time is less likely to be surgical in nature.

Location

In addition to onset, location may be one of the most useful pieces of information in determining the etiology of pain. Visceral pain is perceived either as epigastric, periumbilical, or infraumbilical, depending on the embryologic origin of the involved organ. Visceral pain tends to be poorly localized and midline whereas parietal (somatic) pain tends to be well localized and unilateral. It is important to determine whether the location has changed over time or radiates to a distant site.

Character

The severity and character of the pain are important historical factors. Dull aching pain is more likely to be visceral, and sharp

pain is more likely to be somatic. Crampy intermittent pain is often because of bowel obstruction. Colicky pain often indicates nephrolithiasis or gallstone disease. Severe tearing back pain is classic for aortic dissection.

Aggravating and Alleviating Factors

The patient should be asked about how the pain changes with food, movement, position, or medications. Pain that is intensified by the car ride to the hospital or other movement is indicative of peritoneal irritation. The pain of pancreatitis is often exacerbated by lying in the supine position. The pain of myocardial ischemia may be relieved with rest.

Associated Symptoms

The physician should determine the presence or absence of fever, nausea, vomiting, diarrhea, constipation, hematemesis, hematochezia, melena, dysuria, or hematuria. It is important to ask women about abnormal or increased vaginal discharge or vaginal bleeding and to ask men about testicular or penile complaints (swelling or pain). When patients complain of vomiting and abdominal pain, it is useful to determine which came first. Typically, in surgical diseases, the abdominal pain almost always precedes the vomiting, whereas the converse is true in most cases of gastroenteritis and nonspecific causes. As both cardiac and pulmonary processes can present with abdominal pain, an appropriate history should include questions about the presence of chest pain, shortness of breath, or cough. Also, the patient should be asked about the presence of flank or back pain. Patients with abdominal aortic aneurysm, aortic dissection, or renal colic may have pain that radiates to these areas.

Previous Episodes

Previous episodes of the pain should be investigated. Chronic recurrent abdominal pain involves a wide differential diagnosis; when obtaining the history, it is important to try to identify triggers of the abdominal pain. If the patient has undergone diagnostic studies in the past, there may be no point in repeating the workup

unless there is a significant change in symptomatology or an emergent concern. If pain is recurrent, it may be related to the menstrual cycle. Pain that begins 2 weeks after the start of the menstrual cycle is suggestive of mittelschmerz, but this remains more or less a diagnosis of exclusion.

Past Medical History

Cardiovascular diseases including hypertension, atrial fibrillation, and valvular disease place patients at higher risk for vascular diseases such as mesenteric ischemia, abdominal aortic aneurysm, aortic dissection, and myocardial infarction. A gynecologic history should be obtained, including menstrual history, history of sexually transmitted diseases, and previous ectopic pregnancy.

Past Surgical History

Previous abdominal surgeries place patients at greater risk for conditions such as bowel obstruction resulting from adhesions (2).

Medications

A medication history should be obtained, including prescription medications, over-the-counter preparations, herbal supplements, and steroid use. It is essential to investigate any recent use of antibiotics which increases the risk of developing a *Clostridium difficile* infection. Certain drugs place patients at higher risk for hepatitis and pancreatitis.

Social History

Alcohol abuse increases the risk of gastroinestinal (GI) bleeds, pancreatitis, hepatitis, and cirrhosis. Heroin withdrawal may present with abdominal pain, nausea, and vomiting. Cocaine and amphetamine use may increase the risk of mesenteric ischemia.

Other

Recent traumatic events such as motor vehicle collisions or blows to the abdominal wall or back can result in rectus sheath hematoma, intraperitoneal bleeding, duodenal hematoma, or traumatic pancreatitis. A history of recent food intake, sick contacts, and travel is important for patients with suspected gastroenteritis.

Finally, a history of any toxic exposures (e.g., lead) may also reveal the cause of the abdominal pain.

Physical Examination

The physical examination should always begin with an evaluation of the vital signs. When interpreting the vital signs, the emergency physician should take into account any medications that may affect heart rate or blood pressure (i.e., β-blockers). Tachycardia and hypotension should alert the physician to possible sepsis, dehydration from volume loss or third spacing, or hemorrhage from gastrointestinal bleeding, abdominal aortic aneurysm, or ruptured ectopic pregnancy. Fever makes an infectious etiology more likely, although absence of a fever should not be used to rule out an infectious cause of the pain. This is especially true in the elderly or immunocompromised patient who may present with infectious etiologies, but no fever. Because an oral temperature may be falsely low owing to factors such as mouth breathing or consumption of cold liquids, the more reliable rectal temperature should be obtained if infection is suspected. Tachypnea may be secondary to pain, hypoxia, sepsis, anemia, or metabolic acidosis. Pulse oximetry should be obtained to assess for hypoxia.

The general appearance of the patient may reveal clues to the diagnosis. A patient with peritonitis will lie still whereas a patient with renal colic may present writhing in the bed. The patient's level of alertness, mental status, and orientation are also important. Lethargy and confusion are concerning for toxic ingestions, sepsis, or other causes of hypoperfusion.

The patient's skin should be carefully examined. Pale, cool, diaphoretic skin suggests shock or a low-volume state (dehydration or bleeding). Jaundice may be present in patients with biliary or hepatic disease. The skin should be examined for rashes. Skin findings such as petechiae and spider hemangiomas are suggestive of liver disease. Whether the mucous membranes are moist or dry should be noted; dry membranes suggest dehydration. Oral thrush or hairy leukoplakia may indicate undiagnosed immunocompromise.

When examining the heart and lungs, the physician should listen for rales, rhonchi, wheezing, or other abnormal breath sounds that indicate a pulmonary etiology of abdominal pain. The patient's rhythm and the presence of murmurs should be noted, as atrial fibrillation and valvular disease put patients at risk for mesenteric ischemia caused by emboli.

The abdominal examination should start with inspection. The physician should look for distention, hernias, and the presence of surgical scars and auscultate for bowel sounds noting their frequency, quality, and pitch. Obstruction and processes that cause inflammation within the GI tract result in increased bowel sounds whereas processes that cause inflammation outside of the GI tract such as peritonitis result in diminished bowel sounds. With obstruction, high-pitched tinkling bowel sounds may be present; in patients with an ileus, bowel sounds may be absent. Percussion may aid in the diagnosis of ascites, obstruction, organomegaly, or perforation, and tenderness to percussion may indicate peritonitis.

When palpating the abdomen, the physician should assess for location of tenderness, the presence of voluntary and involuntary guarding, and peritoneal signs. It is recommended to begin with gentle palpation, starting farthest away from the suspected location of tenderness. If the patient is able to tolerate gentle palpation, then deeper palpation should be used to localize the area of tenderness. Palpation at one location may cause pain at a different location. An example of this is seen in patients with appendicitis and is referred to as *Rovsing sign* (pain experienced at *McBurney point* during deep palpation of the left lower quadrant). The physician should examine for masses or organomegaly. In assessing for RUQ pathology, the physician should note the presence of a *Murphy sign*. During deep palpation of the RUQ, the patient is asked to take a deep breath. If inspiration is arrested in midcycle, this is suggestive of cholecystitis (positive *Murphy sign*). In elderly patients, the physician should assess for an abdominal aortic aneurysm by listening for bruits and assessing for the presence of an infraepigastric pulsating mass.

Voluntary guarding may be due to anxiety, fear, or discomfort. Maneuvers that aid in relieving voluntary guarding include warming

of the hands, examination with the patient's thighs flexed, deep inspiration by the patient, and reassurance from the physician. Involuntary guarding or rigidity will not resolve with these maneuvers and is more indicative of surgical disease. *Peritoneal signs* are markers of surgical disease. Classically, peritonitis was assessed by examining for the presence of *rebound tenderness,* increased tenderness when the examiner let go after deep palpation of the abdomen. Rebound tenderness may be present even in the absence of peritonitis, and some advocate using other methods to look for peritonitis. These include the *cough test* (the abdominal pain will worsen abruptly when the patient coughs), jostling the gurney, or striking the patient's heels to precipitate the pain. Rigidity and peritoneal signs may be absent in the elderly even in the presence of peritoneal irritation and surgical disease. This may be attributed to the relatively thin musculature of the abdominal wall in older patients.

Carnett's test can be used to help determine whether abdominal pain arises from the abdominal wall. While in the supine position, the patient is asked to lift the head off the stretcher, and the abdomen is palpated. If the source of the pain is intra-abdominal, the contracted musculature of the abdominal wall will provide shielding and diminish tenderness. If the source of pain is the abdominal wall, the tenderness will be the same or even increased.

It is important to examine for umbilical, inguinal, femoral, and surgical incision hernias, especially in the elderly. In this age group, approximately 10% of cases of obstruction are due to hernias, and they are often undiagnosed.

Examination of the back is necessary to check for costovertebral angle tenderness that may indicate either pyelonephritis or ureteral obstruction.

Women of childbearing age with lower quadrant or suprapubic pain should undergo a pelvic examination to aid in differentiating salpingitis or ovarian pathology from appendicitis or diverticulitis. The results of the pelvic examination should be interpreted carefully, as women with appendicitis may also have cervical motion tenderness and adnexal tenderness. Adnexal or cervical

motion tenderness suggests pelvic inflammatory disease; if present, mucopurulent discharge from the cervical os increases the likelihood. In women with RUQ pain, particularly if evaluation for gallbladder disease is negative, the pelvic examination may also be helpful. *Fitz-Hugh–Curtis* syndrome, a perihepatitis caused by pelvic inflammatory disease, may present with complaints of right upper abdominal pain, and the patient may have no pelvic complaints. The diagnosis can be missed if the pelvic examination is not performed, especially as transaminases and other liver function tests are generally not elevated in this condition.

The digital rectal examination is helpful in assessing for a positive stool guaiac, melena, or hematochezia, and it may also aid in the diagnosis of prostate disease, perirectal disease, and rectal foreign bodies. A testicular examination should be performed to assess for torsion, epididymitis, or masses.

Patients with abdominal pain may remain in the ED for hours during their evaluation and workup. Repeat abdominal examination is very useful in these patients as changes over time may clarify the cause of their illness.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of abdominal pain is extensive and includes both intra-abdominal and extra-abdominal sources of pain (Tables 7.1 and 7.2). A thorough history and physical examination are crucial in determining the etiology of the pain and narrowing down this vast list of possible causes.

TABLE 7.1
Surgical Causes of Abdominal Pain

Abdominal aortic aneurysm[a]	Diverticulitis[b]
Mesenteric ischemia[a]	Ovarian torsion[b]
Ectopic pregnancy[a]	Cholecystitis
Perforated viscus[a]	Cholelithiasis
Aortic dissection[a]	Ascending cholangitis[b]
Appendicitis[b]	Ovarian cysts

[a]Immediate life threat.
[b]Surgical urgency.

TABLE 7.2
Nonsurgical Causes of Abdominal Pain

Myocardial infarction	Acute intermittent porphyria
Diabetic ketoacidosis	Heavy metal poisoning
Pneumonia	Abdominal tabes (Dietl crisis)
Inflammatory bowel disease	Abdominal epilepsy
Irritable bowel syndrome	Abdominal migraine
Esophagitis	Black widow spider bite
Prostatitis	Vasculitis
Intra-abdominal malignancy	Abdominal angina
Mesenteric lymphadenitis	Intestinal pseudo-obstruction
Gastroenteritis	Sickle cell crisis
Peptic ulcer disease	Right-sided colonic diverticulitis
Gastritis	Meckel diverticulitis
Hepatitis	Familial Mediterranean fever
Pelvic inflammatory disease	Massive intravascular hemolysis
Tubo-ovarian abscess	Narcotic withdrawal
Mittelschmerz	Factitious or drug-seeking behavior
Endometriosis	Psychogenic abdominal pain
Herpes zoster	Addisonian crisis
Abdominal wall contusion	Spastic colon
Acute glaucoma	

It is of utmost importance to rule out the immediately life-threatening causes of abdominal pain. These include immediate life threats such as ruptured or leaking abdominal aortic aneurysm, splenic rupture, ruptured ectopic pregnancy, and myocardial infarction and potential life threats, including perforated viscus, intestinal obstruction, mesenteric ischemia, and pancreatitis. Once

the life threat is ruled out, focus should be placed on diagnosing emergent surgical entities such as testicular and ovarian torsion, incarcerated hernia, ascending cholangitis, appendicitis, cholecystitis, gallstone pancreatitis, and diverticulitis.

Although many causes of abdominal pain originate from the abdominal organs, extra-abdominal causes of abdominal pain also occur. Upper abdominal pain may have a pulmonary etiology such as pneumonia, pneumothorax, or pulmonary embolism or a cardiac etiology such as myocardial infarction. Lower abdominal pain may be of genitourinary or pelvic origin.

Certain groups of patients presenting with abdominal pain deserve special attention because of their higher rates of misdiagnosis and increased morbidity and mortality. These groups include the elderly patients with human immunodeficiency virus (HIV) infection, women of childbearing age, and the very young. The pediatric patient with abdominal pain is discussed in Chapter 228, Abdominal Pain."

Abdominal Pain in the Elderly

The conditions causing abdominal pain in elderly patients are usually more serious and urgent, but despite this they may present with a relatively benign history and physical examination. Of patients older than age 60 who present to the ED with abdominal pain, nearly 60% are admitted, 18% go directly to the operating room or have an invasive procedure, and 5% die within 2 weeks of presentation (3). The elderly often have comorbid illnesses confusing the clinical situation and may have hearing loss or underlying dementia or aphasia, making obtaining an adequate history more difficult. Elderly patients may be unable to physiologically mount the typical response to pain and infection. They may lack fevers despite surgical disease, and laboratory values may be normal. As the risk of mortality in patients presenting with abdominal pain increases with each decade of life, the clinician's suspicion for a serious disease must be higher in elderly patients. The spectrum of disease is also different in elderly patients, with

surgical causes accounting for more than half of the cases in patients presenting to the ED and nonspecific abdominal pain accounting for only 15% of cases (3). Elderly patients are also at increased risk for abdominal catastrophes such as mesenteric ischemia, ruptured abdominal aortic aneurysm, and intestinal volvulus. Further adding to the diagnostic difficulty, elderly patients presenting with acute coronary syndrome are much more likely to present with atypical symptoms such as shortness of breath, generalized fatigue, and abdominal pain.

Abdominal Pain in Patients with HIV

HIV-positive patients with abdominal pain are at risk for unusual conditions related to their immunocompromised state, the associated disease processes, and the side effects caused by the antiretroviral medications. In the HIV-positive patient with abdominal pain, the pain is attributable to the immunocompromised state or medications in 65% of cases (4); the three most common disorders are GI non-Hodgkin lymphoma, pancreatitis, and cytomegalovirus (CMV) enterocolitis. The latter may be life threatening, as it can cause a toxic megacolon and colonic perforation. Drug-induced pancreatitis may be fulminant and has a mortality rate of approximately 10% (4). This is most often associated with didanosine but is also reported with the use of lamivudine (especially in children), zalcitabine, or stavudine. In the immunocompromised patient it is essential to rule out infectious and surgical causes of abdominal pain before attributing it to a medication side effect (see Chapter 191).

Women of Childbearing Age

Women of childbearing age presenting with abdominal pain are often among the most challenging patients. A pregnancy test is of utmost importance for women early in their pregnancy or for any sexually active woman of childbearing age presenting with abdominal pain, as a positive result raises the possibility of ruptured ectopic pregnancy. The differential diagnosis of abdominal pain in

this group is broadened by a number of possible genitourinary and pelvic pathology (ovarian torsion, ovarian cysts, ruptured ovarian cyst, mittelschmerz, pelvic inflammatory disease, and ectopic pregnancy), complicating the diagnostic workup and potentially leading to misdiagnosis. The difficulty in accurately diagnosing these patients is underscored by the fact that up to one-third of nonpregnant women of childbearing age with appendicitis are initially misdiagnosed (5).

In pregnant women, the gravid uterus becomes an intra-abdominal organ later in pregnancy and may shift the anatomic location of other organs, resulting in confusing presentations. By the second half of pregnancy, in some patients the appendix has moved out of the right lower quadrant, so appendicitis may present with tenderness ranging anywhere from the right lower quadrant, the midabdomen, the right flank, or even under the ribs. For more information on abdominal pain and pelvic pain in women of childbearing age, see Chapter 129, “Pelvic Pain.”

Many of the more common causes of abdominal pain are covered in separate chapters in this book. In addition, several other causes of abdominal pain deserve special mention.

Porphyria

The porphyrias affect the biosynthesis of heme and result in the accumulation of excessive porphyrins and their precursors. They are inherited enzyme disorders, almost always autosomal dominant with poor penetrance. They are characterized by abdominal pain with or without manifestations of autonomic dysfunction or neuropsychiatric symptoms. Other presenting conditions in patients with porphyria include demyelinating syndromes, syndrome of inappropriate antidiuretic hormone secretion, hypertensive crisis, and acute psychosis. There are many variants depending on the particular enzyme deficiency and the heme precursor that accumulates. The most common porphyria that causes abdominal pain is acute intermittent porphyria. Many drugs can precipitate attacks; a partial list is in Table 7.3.

TABLE 7.3
Drugs that May Precipitate Attacks of Acute Porphyria

Alcohol	Imatinib mesylate
Barbiturates	Mephenytoin
Carbamazepine	Meprobamate
Chloroquine	Methyprylon
Chlorpropamide	Metoclopramide
Clonazepam	Phenytoin
Danazol	Progestins
Diclofenac	Pyrazolones
Ergots	Rifampin
Estrogens	Succinimides
Ethchlorvynol	Sulfonamide
Glutethimide	Valproic acid
Griseofulvin	

The diagnosis is difficult, given the low prevalence. The pain of porphyria is usually out of proportion to physical signs, and fever is usually absent. A family history is helpful but not always present. Although not totally sensitive or specific, a Watson–Schwartz urine test should be ordered to look for porphobilinogen. The urine dipstick for urobilinogen yields a strong false-positive result. The diagnosis is made by a finding of elevated 24-hour levels of urine and stool porphyrins.

Abdominal Vasculitis

Abdominal vasculitis occurs in several disease processes, but polyarteritis nodosa, systemic lupus erythematosus, and Henoch–Schönlein purpura are among the most common. The spectrum of presentation varies from acute severe ischemia to mild pain, malabsorption, and abdominal angina.

Patients with abdominal vasculitis may have peripheral manifestations as well. The abdominal pain may be epigastric or periumbilical, reflecting ischemia of the foregut or midgut, respectively. Fever is prominent in some cases. The key issue in these cases is to consider the diagnosis in the first place, and then to

obtain the appropriate tests, such as angiography. Abdominal vasculitis should always be considered in patients with abdominal pain who also have a history of rheumatologic disease.

Angioedema

Hereditary angioneurotic edema is transmitted as an autosomal dominant trait. Symptomatic patients have low levels of C1′ esterase inhibitor (type 1), or they have a dysfunctional inhibitor (type 2); either condition allows activation of the complement system. Initial symptoms usually arise in adolescence but can have their onset in later life.

Classically, patients with angioedema do not have urticaria. Angioneurotic edema of the skin involves the deeper portions of the dermis and the subcutaneous layers as well and does not cause pruritus, whereas urticaria results from edema in the superficial layers of the skin and is pruritic.

Attacks of hereditary angioneurotic edema may begin with abdominal pain due to angioedema of the bowel wall. The pain is often colicky and is associated with nausea and vomiting, but there are scant physical findings in the abdomen. Fever is usually absent, and white blood cell counts are normal. During an attack, serum levels of C2 and C4 are low. Between attacks, the diagnosis can be established by assaying for the presence of the C1′ esterase inhibitor. Attacks of angioedema are self-limited but generally last 24 to 72 hours.

Use of angiotensin-converting enzyme inhibitors (ACE inhibitors) has also been associated with angioedema of the small bowel. Strong consideration should be given to withholding ACE inhibitors in patients with persistent, unexplained abdominal pain. See Chapter 176, “Angioedema.”

Sickle Cell Disease

Patients with sickle cell disease and vasoocclusive painful crisis can present with pain almost anywhere in the body, including the abdomen. What is not commonly appreciated is that a few patients

with homozygous sickle cell disease have their first painful crisis in their late teens or early 20s, frequently presenting with cryptogenic abdominal pain. Patients with established sickle cell disease can also pose a diagnostic challenge because their abdominal pain can be caused by a vasoocclusive event involving any of the abdominal viscera or the abdominal wall.

In addition, almost all patients with sickle cell disease have gallstones; acute cholecystitis, common duct obstruction, and ascending cholangitis are ever-present dangers in these immunocompromised patients. Abdominal pain also can develop for reasons unrelated to sickle cell disease, but the primary process may be misdiagnosed as crisis pain.

The laboratory evaluation of sickle cell patients with abdominal pain is often misleading. Many vasoocclusive crises are not associated with fever, and the white blood cell count is typically chronically elevated in these patients, commonly with a left shift. In addition, many sickle cell disease patients may be icteric because of chronic hemolysis. Many have intrinsic liver disease as well, but liver function test abnormalities are not helpful unless there is a significant deviation from baseline values. For patients presenting with RUQ pain, diagnosis can be assisted by the use of abdominal ultrasonography, nuclear scans of the biliary system, or abdominal computed tomography (CT) scanning. See Chapter 199, “Sickle Cell Disease.”

Chronic Lead Intoxication

Chronic lead intoxication can present as a painful abdominal crisis (lead colic). Abdominal pain can be slowly progressive or subacute in onset. There is abdominal tenderness with voluntary guarding, but true peritoneal findings are rare. Patients commonly complain of fatigue, weakness, musculoskeletal pains, irritability, and constipation. Anemia is usually evident, and the red blood cells show basophilic stippling. An occasional patient may have the triad of lead nephropathy, “saturnine” gout, and hypertension. The

diagnosis is made by determining blood lead and erythrocyte protoporphyrin levels.

Addison Disease

Although rare, Addison disease can present as a dramatic acute syndrome with vasomotor collapse, altered mental status, and characteristic electrolyte abnormalities. A subacute-to-chronic form of the disease, however, can present with recurrent abdominal pain, often associated with nausea and vomiting and usually with a negative abdominal examination. Other presenting complaints include salt craving, anorexia, weight loss, and generalized weakness. Characteristic physical findings include orthostatic hypotension, freckling and hyperpigmentation of the skin, and surgical scars. Classic laboratory findings include hyperkalemia, hyponatremia, mild azotemia, mild metabolic acidosis, and hypoglycemia.

The most common cause of primary adrenal insufficiency is idiopathic or autoimmune destruction of the gland. Patients with AIDS have a high incidence of adrenal gland involvement from a number of mechanisms. See Chapter 209, “Adrenal and Pituitary Disorders.”

Opioid Withdrawal

Opioid withdrawal frequently produces crampy abdominal pain, often associated with nausea, vomiting, and diarrhea. Diagnosis of this syndrome is frequently difficult unless the patient admits to narcotic addiction. Other signs and symptoms of opioid withdrawal (e.g., mydriasis, rhinorrhea, and piloerection) may be present, but these features are rarely prominent.

Psychogenic Abdominal Pain

Psychogenic abdominal pain involves a diverse group of psychiatric disturbances, including somatoform disorders, eating disorders, conversion reactions, depression, Munchausen disorder, and

hypochondriacal neurosis. Abdominal pain can also occur as a somatic delusion or as a hallucinatory phenomenon, but it generally is found in association with bizarre symptoms and evidence of underlying thought disorder. Women represent a disproportionately large percentage of patients with psychogenic abdominal pain. Early psychiatric consultation is important, but it must be kept in mind that psychogenic abdominal pain must always remain, to some degree, a diagnosis of exclusion.

DIAGNOSTIC APPROACH

Appropriate laboratory and imaging tests should be ordered in the context of the history and physical examination.

Laboratory Testing

Women of childbearing age should have a pregnancy test; sensitive and rapid bedside urine pregnancy tests can be used. A positive pregnancy test in a patient with abdominal pain should raise the concern for an ectopic pregnancy.

A complete blood count, although frequently ordered, should be interpreted with caution. A normal white blood cell count should not be used to rule out appendicitis, an elevated white blood cell count is not specific to the diagnosis, and even serial white blood cell counts may not aid in making the diagnosis. Although low hemoglobin suggests occult blood loss, it may be normal initially in rapid, acute blood loss.

Like the complete blood count, the urinalysis, although often indicated in the workup, should also be interpreted with caution. Any inflammatory process adjacent to the ureters (such as appendicitis) can cause a positive urinalysis in the absence of a urinary tract infection. Hematuria may be due to a urinary tract infection, nephrolithiasis, trauma, tumor, or an abdominal aortic aneurysm. Hematuria in patients with an abdominal aortic aneurysm may be misleading and can delay the diagnosis while a urinary workup is performed. Therefore, a patient with risk factors for abdominal aortic aneurysm who presents with flank or

abdominal pain and hematuria should be evaluated for an aneurysm as well as for urinary tract disease. If there is concern that the patient may become hemodynamically unstable, a rapid bedside ultrasound should be performed to assess for the aneurysm. If there is little concern that the patient may become unstable, then the abdominal CT can assess for both conditions.

The measurement of serum electrolytes (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, and creatinine) is helpful in determining hydration status, in guiding volume replacement, and in diagnosing metabolic disturbances. The creatinine is necessary to assess renal function and to determine whether a patient can receive IV contrast for imaging. Assessing the blood glucose may help diagnose new onset or poorly controlled diabetes. Diabetic ketoacidosis can present with abdominal pain and nausea and vomiting.

A lipase should be ordered when pancreatitis is suspected. Lipase is a more sensitive and specific indicator of pancreatitis than amylase, and an elevation of three times the normal value of the lipase is suggestive of pancreatic inflammation. Less sensitive and specific than lipase, amylase levels may be elevated in many disease processes including peptic ulcer disease, small-bowel obstruction or ischemia, common duct stone, ectopic pregnancy, renal failure, alcohol intoxication, or facial trauma (salivary amylase).

Serum transaminases, bilirubin, alkaline phosphatase, and coagulation studies are often ordered in certain patients with a tender RUQ or symptoms suggestive of biliary or liver disease. However, these studies are of little to no clinical utility for making the diagnosis of biliary colic or cholecystitis. Thus, if biliary colic or cholecystitis is suspected, an ultrasound should be performed to make the diagnosis (6).

Other studies may be useful when specific diagnoses are considered. For instance, the serum lactate may be elevated in patients with mesenteric ischemia, although this is generally a late finding, and a normal lactate should not be used to exclude the diagnosis in a patient with a concerning history or examination.

Radiographic Studies

Plain films are primarily useful when certain disease processes are suspected: obstruction, perforation, and foreign body. The acute abdominal series includes supine and upright views of the abdomen and a single upright chest view. Of these three views, the upright chest x-ray is the single most useful view to assess for free air, although free air may be absent on plain films in as many as one-half of patients with visceral perforation. If the patient is unable to stand upright, a left lateral decubitus film can be obtained to look for air–fluid levels and free air. When perforation is suspected and plain films are negative, abdominal CT scanning is a more accurate way to make the diagnosis. The chest x-ray can also help to diagnose pneumonia, pleural effusions, or other pulmonary causes of abdominal pain. The kidney, ureter, and bladder film in combination with ultrasound may be helpful in evaluating urinary stone disease, but this approach is less sensitive than helical CT.

Ultrasound can be used to image intra-abdominal organs such as the liver, spleen, pancreas, gallbladder, kidneys, uterus, and ovaries. It is the imaging modality of choice in the patient with RUQ pain or presumed pelvic pathology. Other conditions that ultrasound can detect include aortic aneurysm, pancreatic pseudocyst, and ureteral obstruction. Transvaginal ultrasound can help determine intrauterine versus ectopic pregnancy and other pelvic pathology. Appendicitis can be diagnosed with good accuracy in the hands of an experienced ultrasonographer, though its utility decreases in patients with a large body habitus and CT remains the modality of choice in making this diagnosis unless radiation is a concern (e.g., children and pregnant women). In many hospitals, emergency physicians perform goal-oriented ultrasonography in an attempt to reduce time to diagnosis and improve patient care for patients with abdominal pain. Emergency physicians can accurately diagnose cholelithiasis (7), as well as ectopic pregnancy, abdominal aortic aneurysm, and hydronephrosis as an indicator of ureteral colic.

CT has become a mainstay in diagnosing many diseases presenting with abdominal pain. Helical CT can identify kidney

stones, abdominal aortic aneurysm, appendicitis, diverticulitis, splenic or liver lacerations or infarctions, intra-abdominal abscesses, bowel obstruction, and free air. Although many of these diagnoses can be made without using contrast, IV contrast is helpful for detecting mesenteric ischemia and oral contrast for diagnosing intra-abdominal abscesses. In patients with adequate body fat stores, the stranding associated with appendicits is usually easily seen without oral contrast. However, in patients with little body fat, oral contrast may be necessary to increase the accuracy of CT in making this diagnosis. In stable patients with suspected abdominal aortic aneurysm, CT without oral or IV contrast should be performed, as it is a fast, accurate method of identifying the pathology. Such patients can be transported to the radiology suite without waiting for the creatinine to return or oral contrast to be administered. In addition, CT to diagnose ureteral stone does not require contrast administration. CT is now considered the imaging procedure of choice for patients with suspected mesenteric ischemia (8). Although angiography remains the gold standard for diagnosing thromboembolism, it is an invasive, time-consuming, potentially nephrotoxic, and costly procedure and should be performed only when acute mesenteric ischemia cannot be established by noninvasive modalities (8). It should be emphasized that although modern CT scans are increasingly sensitive, they may still be falsely negative in a significant minority of patients, and their results should not be used to trump physician judgment in cases where there is a high degree of suspicion for infectious or surgical pathology.

Patients presenting with epigastric pain and a nontender abdomen who are older than the age of 50 or have cardiac risk factors should have an electrocardiogram. In addition, unstable patients and the elderly should have an electrocardiogram as part of their workup for abdominal pain. Relief of pain after “GI cocktail” does not preclude myocardial ischemia and should not be used to rule out cardiac disease.

CRITICAL INTERVENTIONS

In patients presenting with acute abdominal pain the major goals are as follows:

- Stabilize the patient, replenish volume loss, and transfuse if necessary
- Treat the pain and control emesis
- Treat the pain
- Administer antibiotics when indicated
- Obtain surgical or obstetric consultation if necessary

If ruptured ectopic pregnancy is suspected:

- Emergent gynecology consultation should be obtained.
- If available, a bedside FAST ultrasound should be performed to look for free fluid in the abdomen.
- A blood type should be drawn and at least two large-bore IVs should be started.

In the hemodynamically unstable patient, life-threatening conditions should be rapidly ruled out.

- These include ruptured abdominal aortic aneurysm, myocardial infarction, ruptured ectopic pregnancy, adrenal insufficiency, perforated viscus, mesenteric ischemia, and sepsis.

Immediate resuscitation should start with the airway, breathing, and circulation first.

- This includes supplemental oxygen, IV access with two large-bore IVs and continuous cardiac monitoring.
- Volume resuscitation should begin with crystalloid infusion and then packed red blood cell transfusion if bleeding is suspected.
- If the patient remains hypotensive, vasopressors may be necessary.

In the hypotensive patient who does not respond to volume replacement, acute adrenal crisis may be the cause. If adrenal insufficiency is suspected:

- A stress dose of IV steroids (hydrocortisone 100 mg or dexamethasone 10 mg) should be administered; dexamethasone may be preferable, as using it will not interfere with diagnostic testing for adrenal insufficiency.

Medications are indicated to treat pain and nausea and vomiting.

- Multiple studies have shown that treating undifferentiated abdominal pain with judicious amounts of narcotic analgesia does not affect diagnostic accuracy.
- Morphine in 2- to 5-mg increments or fentanyl in 50- to 100-μg increments can be titrated to the desired effect.

When infections are a consideration, appropriate antibiotics should be initiated early.

- If sepsis from an undifferentiated abdominal source is a concern, then broad-spectrum antibiotics should be started, covering gram-positive, gram-negative, and anaerobic bacteria.

Management of porphyria is largely supportive.

- IV glucose infusion may abort attacks.
- IV hematin also may be helpful, although its efficacy has not been proven (2).

In patients with angioedema, because the upper airway can be involved acutely, a major clinical concern is sudden upper airway obstruction:

- Management may call for epinephrine administration, intubation, or cricothyrotomy.
- Treatment is otherwise supportive.

DISPOSITION

Patients with surgical or gynecologic disease should be evaluated by a surgeon or gynecologist and may require admission for treatment and operative intervention. The more challenging dispositions arise in patients with abdominal pain of unclear etiology. If possible, it is prudent to observe these patients for 6 to 12 hours before discharge, particularly if they are elderly. Observation may be helpful in differentiating surgical from nonsurgical disease. Patients with abdominal pain of uncertain cause that improves while in the ED can be discharged to home with close follow-up. In these patients, the most accurate and appropriate discharge diagnosis is abdominal pain of unclear etiology; it is important to resist labeling these patients with a more specific and sometimes speculative diagnosis.

Common Pitfalls

- Failure to obtain a thorough and accurate history and physical examination.
- Failure to diagnose an abdominal aortic aneurysm in patients who present with flank pain and hematuria.
- Failure to order a pregnancy test in all women of childbearing age to rule out the possibility of ectopic pregnancy.
- Relying on a normal white blood cell count to rule out the diagnosis of appendicitis or other infectious causes of abdominal pain, particularly in the elderly.
- Failure to recognize that the urinalysis may be abnormal in patients with processes that inflame the ureters, such as appendicitis or salpingitis.

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CHAPTER 8
Shortness of Breath

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Shortness of breath refers to difficult, labored, or uncomfortable breathing. Shortness of breath results when ventilatory demand exceeds respiratory function. A mismatch between supply and demand of oxygen and failure of CO_2 elimination is the mechanism that produces the sensation of shortness of breath. Table 8.1 details the most frequently encountered causes and the most common etiologies of acute shortness of breath seen in the emergency department (ED).

TABLE 8.1
Causes of Acute Shortness of Breath

Alcohol	Imatinib mesylate
Barbiturates	Mephenytoin
Carbamazepine	Meprobamate
Chloroquine	Methyprylon
Chlorpropamide	Metoclopramide
Clonazepam	Phenytoin
Danazol	Progestins
Diclofenac	Pyrazolones
Ergots	Rifampin
Estrogens	Succinimides
Ethchlorvynol	Sulfonamide
Glutethimide	Valproic acid
Griseofulvin	

CLINICAL PRESENTATION

Patients commonly present to the ED complaining of shortness of breath. The clinical evaluation is guided by the history—is the shortness of breath new onset without any previous determination of the underlying cause or is the patient experiencing an acute exacerbation of a chronic respiratory, cardiovascular, or neuromuscular condition (1)? Once the initial assessment ensures that the airway is patent and oxygenation is adequate, a thorough history should be obtained. The duration and onset of the sensation of shortness of breath; associated chest pain or palpitations; precipitating factors such as exertion, exercise, or anxiety; associated paresthesias of the mouth and fingers; the number of pillows the patient uses to sleep; concomitant coughing or sputum production; exercise tolerance; tobacco use; recreational drug use; and occupational history are several important factors that can help narrow the differential diagnosis. Past medical history of asthma, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), coronary artery disease, and valvular heart problems should be sought. Paroxysmal nocturnal dyspnea (PND), breathlessness that occurs while sleeping, is usually associated with left ventricular failure. Orthopnea, the presence of shortness of breath in the recumbent position, is also associated with left ventricular failure but can be associated with COPD.

On physical examination, the patient's vital signs, mental status, body position, use of accessory muscles, conjunctival and mucous membrane color, skin and nail bed color, upper airway examination, neurologic examination, cardiovascular and pulmonary examinations may give valuable clues to the etiology.

DIFFERENTIAL DIAGNOSIS

Anaphylaxis

Anaphylaxis is a severe allergic reaction involving one or more body systems that produces signs and symptoms such as hives, flushing, pruritus, angioedema, stridor, shortness of breath, bronchospasm, tachycardia, and hypotension. Death from anaphylaxis usually results from respiratory obstruction or cardiovascular collapse.

Symptoms typically occur within 2 minutes of exposure to the triggering antigen but occasionally may occur as late as 2 hours (2). See Chapter 175 for further discussion.

Upper Airway Obstruction

Obstruction of the upper airway may be the consequence of foreign body aspiration, epiglottitis, croup, angioedema, peritonsillar or retropharyngeal abscess, or neuromuscular dysfunction. The nature of the presenting picture depends on the site and degree of the obstruction as well as the underlying cause. Cough, stridor, shortness of breath, aphonia, or hoarseness may be present. These conditions may not cause complete airway obstruction, but rapid deterioration is possible in these patients, and the emergency physician must be ready to provide immediate airway intervention. Alternative techniques to conventional direct laryngoscopy may be necessary; these include fiberoptic-guided intubation/video-assisted devices, bougie-assisted endotracheal intubation, blind nasotracheal intubation, lighted or optical stylets, flexible or rigid fiberoptic scopes, supraglottic airway devices (LMA, intubating LMA, PLMA), retrograde intubation, percutaneous transtracheal jet ventilation, and surgical airways (3). See Chapter 1 for further discussion.

Pulmonary Embolism

Pulmonary embolism (PE) is an obstruction of the pulmonary artery or one of its branches by an embolus, usually a blood clot derived from the deep venous system of the leg or pelvic veins. The diagnosis of PE is often subtle and may be difficult to make. The actual incidence of PE in the United States is unknown, but it is estimated to be greater than 650,000 cases annually and estimates are that the diagnosis is missed more than 400,000 times each year (4).

The classic findings of chest pain, shortness of breath, and hemoptysis are found in fewer than 20% of patients with a PE (4). Common complaints in addition to the classic symptoms include malaise, weakness, extremity discomfort, dizziness, or syncope (4).

Clinical suspicion plays a key role in the decision to pursue an evaluation for acute PE. Patients at high risk include those who have had a previous PE or deep vein thrombosis (DVT), surgery within the last 3 months, travel more than 4 hours in the past month, trauma to lower extremity and pelvis during the past 3 months, malignancy, cardiopulmonary disease, and women during pregnancy or in the postpartum period (4).

A ventilation–perfusion scan, spiral computed tomography scan, and pulmonary angiogram, used in conjunction with the clinical pretest probability, D-dimer assay, and duplex Doppler evaluation of the lower extremities, will help the physician determine the likelihood of PE and the necessity of anticoagulation and admission. See Chapter 79 for further discussion.

Myocardial Ischemia

Patients with myocardial ischemia classically present with chest pain. However, a significant number of patients present with symptoms other than chest pain, termed *anginal equivalents.*

Shortness of breath either new onset or associated with exertion, is the most common anginal equivalent symptom, particularly in the geriatric patient (5). Patients with known coronary artery disease or those with significant risk factors for coronary artery disease who present to the ED with shortness of breath in the absence of chest pain should be evaluated for myocardial ischemia. See Chapter 82 for further discussion on the evaluation of coronary syndromes.

Congestive Heart Failure

CHF is a complex clinical syndrome resulting from either a structural or functional disorder of the heart that restricts the ventricular filling or the ejection of blood (6). Acute precipitating factors of CHF include increased sodium intake, noncompliance with medications, acute myocardial infarction, dysrhythmia, or anemia. The most common causes of CHF are coronary artery disease and hypertension, valvular heart disease, and cardiomyopathy.

Pertinent information obtained on history includes the presence of dyspnea, orthopnea or PND, peripheral edema, exercise intolerance, and fatigue. The physical examination may reveal jugular venous distention, rales, cardiac S3 gallop, hepatojugular reflux, ascites, and peripheral edema (6). Pulmonary edema may also lead to bronchospasm and wheezing, often termed *cardiac asthma*. Chest radiography may reveal cardiomegaly, pulmonary vascular redistribution, Kerley B lines, pleural effusion, and peribronchial cuffing. The measurement of B-type natriuretic peptide (BNP) has become a useful tool for the diagnosis of CHF in patients presenting to the ED with acute shortness of breath. BNP is synthesized as preproBNP in the cardiac ventricles and is released as a result of left ventricular wall stress (7). See Chapter 83 for further discussion.

Chronic Obstructive Pulmonary Disease

Although COPD is a chronic disorder, acute exacerbations of diminished respiratory function often bring patients to the ED. Exacerbations are usually caused by a worsening of airflow obstruction due to increased bronchospasm, increased sputum production from superimposed respiratory infection, environmental irritants (such as tobacco smoke), or cardiovascular deterioration. The patient may present with progressive shortness of breath, increased sputum production, and audible wheezing. Hypoxemia, tachypnea, cyanosis, and agitation may be seen. Signs of hypercarbia such as confusion, stupor, inadequate respiratory effort, or apnea may be seen and indicate severe compromise with impaired gas exchange. Findings on physical examination may include a barrel chest, pursed lips breathing, cyanosis, tripoding, and use of accessory muscles (8). Auscultation may reveal a combination of diminished breath sounds, a prolonged expiratory phase, wheezes, or rales (8). The chest radiograph may reveal an increased anterior–posterior diameter, flattened diaphragms, hyperinflated lungs, attenuation of the peripheral lung markings, and, in cases of superimposed infection, an infiltrate. See Chapter 77 for further discussion.

Asthma

Asthma is a chronic inflammatory condition resulting from bronchial hyperresponsiveness and airway obstruction leading to the clinical manifestations of recurrent episodes of wheezing, chest tightness, shortness of breath, and cough (9). The physical examination may reveal an increased AP diameter of the chest due to air trapping, tachypnea, wheezing, and mild-to-severe respiratory distress. Auscultation may be misleading in the case of severe obstruction; wheezing may be absent, as bronchial airflow is diminished to such an extent that no sound is audible. Chest radiographs may be normal, demonstrate a pneumothorax (PTX) or pneumomediastinum or, in the case of a precipitating infection, reveal an infiltrate. See Chapter 76 for further discussion.

Pneumonia

Pneumonia classically presents as an acute febrile illness with cough and purulent sputum production. Pneumonia should be suspected in patients with newly acquired lower respiratory symptoms (cough, sputum production, or shortness of breath), especially if these symptoms are accompanied by fever, altered breath sounds to include bronchial breath sounds, egophony, or rales.

Classification of pneumonia is based on the environmental contact where the infection was acquired. This classification can then be used to guide the clinician to the likely offending agent and choose the appropriate treatment (10). For ED patients, pneumonia is classified as either community-acquired or healthcare-associated pneumonia (HCAP). *Streptococcus pneumoniae* remains the most common etiology of community-acquired pneumonia (10). HCAP is typically caused by *Pseudomonas aeruginosa, Klebsiella pneumoniae, Legionella,* and methicillin-resistant *Staphylococcus aureus* (10). Immunosuppressed patients may present with staphylococcal pneumonia or pneumonia caused by opportunistic organisms such as *Pneumocystis carinii,* mycobacteria, or fungal organisms.

A chest radiograph may demonstrate lobar consolidation, as in bacterial pneumonia; patchy infiltrates, suggesting staphylococcal

pneumonia, *Haemophilus influenzae,* or gram-negative pneumonia; interstitial infiltrates, suggesting *Mycoplasma, Legionella,* or *Pneumocystis;* or cavitary lesions, as in tuberculosis. However, there is considerable clinical overlap among these entities. Early recognition is important, so that appropriate empiric antibiotic treatment can be administered promptly. See Chapter 74 for further discussion.

Pneumothorax

PTX, or air in the pleural cavity, can occur spontaneously or as the result of trauma (see Chapter 31). Spontaneous PTX typically occurs in tall, thin, young males, and smoking greatly increases the likelihood (11). The cause of the spontaneous PTX is the rupture of a subpleural bleb or bullae, which is usually apical in location in 90% of cases (11). Spontaneous PTX also may be seen in patients with asthma, COPD, and tuberculosis and in AIDS patients with *P. carinii* pneumonia. Traumatic PTX results from blunt or penetrating trauma to the chest. Concomitant hemothorax, pulmonary contusion, and bronchial rupture may be present.

Patients may present to the ED in obvious respiratory distress or may complain of shortness of breath and pleuritic chest pain. Auscultation may reveal unilateral diminution of the breath sounds associated with increased tympany on percussion. Subcutaneous emphysema also may be present. Signs of imminent cardiovascular collapse such as hypotension, mediastinal shift, and the aforementioned findings may herald a tension PTX, prompting swift needle chest decompression prior to any further examination or diagnostic studies. Chest radiography may reveal an obvious PTX or may only show subtle findings. In the supine patient, the only sign of a PTX may be an abnormally prominent costophrenic angle on the AP or PA view. Ultrasonography at the bedside is a sensitive and specific imaging modality for the diagnosis of PTX. The anterior, lateral, and posterior lung should be scanned from the apex to the base with the patient in either supine or sitting position. If the scan

reveals the lung sliding effectively, there is no PTX with a negative predictive value of 100% (11).

Observation is indicated in a patient with a small PTX if there is no significant dyspnea. Patients, who meet this criterion, may be observed in ED for 3 to 6 hours on oxygen. If the PTX does not progress on chest radiograph at the end of the observation period, they may be discharged home with close follow-up within 24 hours (11). Patients with a large PTX, a small PTX but with significant dyspnea, or those that fail observation should undergo invasive management with either aspiration of the pleural space or small bore chest tube placement.

DIAGNOSTIC APPROACH

The most important initial step in the management of shortness of breath is to secure the airway and ensure oxygenation and circulation. The physician should then perform a rapid, complete history and physical examination to elucidate the cause of the shortness of breath and formulate a diagnostic plan if the etiology is not readily identified (12).

Pulse oximetry is an easy, noninvasive monitoring technique that allows low-cost, continuous, reliable measurements of oxygen saturation (12). Every person who presents to the ED complaining of shortness of breath should have his or her oxygen saturation measured. Pulse oximetry may be inaccurate in reflecting oxygen saturation in the presence of high carboxyhemoglobin levels, methemoglobinemia, and low-perfusion states (12), and it does not relay any information about PCO_2.

Arterial blood gas measurement may be necessary in evaluating patients who present with shortness of breath. Blood gases demonstrate the severity of gas exchange impairment and are useful as diagnostic tools as well as for establishing a baseline for monitoring therapy. The physician should use discretion, however, when obtaining blood gases. In cases of mild shortness of breath with a normal oxygen saturation on room air, blood gases are not needed.

The chest radiograph is a valuable diagnostic tool in elucidating the cause of shortness of breath and should be obtained in most all cases. Diagnostic radiographic findings can be expected in certain entities, such as pneumonia, PE, and PTX. However, the chest radiograph may be entirely normal, even when significant illness is manifested by shortness of breath. Special views of the chest may be helpful in certain circumstances. The lateral decubitus view may confirm the presence of a pleural effusion. Inspiratory–expiratory or positional films may indicate a bronchial foreign body.

The measurement of BNP can play an important role in the diagnosis of undifferentiated dyspnea. A BNP of 100 pg/dL or greater is consistent with the diagnosis of CHF with a sensitivity of 90%, specificity of 76%, and an accuracy of 81% for differentiating CHF from other causes of dyspnea (7). In addition, BNP has been shown to be useful to predict outcomes for CHF patients to include hospital readmission, and mortality (7). Other diagnostic studies may be helpful when evaluating a patient with shortness of breath. An electrocardiogram (ECG) can show abnormalities of heart rate and rhythm or evidence of ischemia, injury, or infarction. An ECG may also be helpful in evaluating patients with a suspected pulmonary embolus, although suggestive changes are present in only a minority of patients. Anemia is an important cause of shortness of breath, and a check of the patient's hemoglobin or hematocrit may be useful as part of the workup. Rarely, bedside laryngoscopy or bronchoscopy may provide a definitive diagnosis, especially in the case of upper airway obstruction or suspected foreign body.

CRITICAL INTERVENTIONS

- If the clinical condition warrants consideration of mechanical ventilation, the physician should determine whether the patient is a candidate for noninvasive positive pressure ventilation (NIV) (13). Evidence-based guidelines recommend the use of NIV in patients with severe COPD exacerbations with a pH <7.35 and relative hypercarbia, respiratory failure caused by cardiogenic

pulmonary edema with no evidence of shock, and acute coronary syndrome requiring urgent coronary revascularization (13). Contraindications include acute lung injury, cardiorespiratory arrest, severe encephalopathy, severe upper gastrointestinal bleeding, hemodynamic instability, unstable cardiac rhythms, facial or neurologic surgery, facial trauma or deformity, upper airway obstruction, the inability to cooperate or protect the airway, the inability to clear secretions, and patients who are at high risk for aspiration (13). Endotracheal intubation should be performed if any of these contraindications are present.

- In patients with anaphylaxis, a patent airway must be established and maintained. Immediate treatment with epinephrine (1:1,000 dilution in a dose of 0.3–0.5 mL intramuscularly) repeated every 5 to 15 min as needed (2). Intravenous epinephrine is reserved for patients in shock. The typical dose is 5- to 15-μg/min continuous infusion titrated to effect (14). Additional treatment includes antihistamines, to block both H1 and H2 receptors, and steroids. Observation after treatment is needed owing to a delayed, second phase of reactivity that may occur; a period of 24 h of observation in a monitored setting is prudent.
- Once a preliminary diagnosis is made, treatment should be appropriately tailored to alleviate the patient's shortness of breath. Specific therapies can be found in the chapters devoted to each of the differential diagnoses.

DISPOSITION

The disposition of the dyspneic patient depends on the cause of the respiratory difficulty, the severity of the respiratory compromise, and the success of the ED treatment. Any patient with continuing shortness of breath despite treatment should be admitted for further evaluation and treatment. Depending on the clinical condition and diagnosis, the patient may need observation on the general ward, on telemetry, or in the intensive care unit. The patient may be safely discharged home if he or she has improvement in or resolution of shortness of breath and an appropriate diagnosis, such as an asthma

exacerbation, has been made. When considering discharge in dyspneic patients, it is important to ensure that they are back to their baseline respiratory status, will be able to obtain the medications prescribed, are capable of caring for themselves at home, and will have adequate, prompt follow-up care.

Common Pitfalls

- Relying on pulse oximetry alone to gauge a patient's respiratory status (gives no information about PCO_2)
- In patients with clinical signs of a tension PTX, waiting for radiographic confirmation before decompressing the pleural space
- Withholding oxygen for fear of blunting the hypoxic respiratory drive in a patient with COPD; correcting hypoxia takes precedence
- Failing to realize that the absence of wheezing in a patient with asthma or COPD in respiratory distress indicates severe airway obstruction

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CHAPTER 9
Syncope

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Syncope is a sudden and transient loss of consciousness that is associated with a loss of postural tone and that resolves spontaneously and completely without intervention. In the United States, syncope accounts for an estimated 740,000 emergency department (ED) visits annually. This represents approximately 0.8% of all ED visits nationally. Nationally, approximately one-third of all ED patients with syncope are admitted, representing approximately 2% of all admissions from the ED (1). Although the pathophysiology of syncope is related to a transient decrease in cerebral blood flow, the etiologies of syncope are myriad and range from the benign to the life threatening. This range of severity contributes to the problematic nature of the ED evaluation of the patient with syncope. In addition, the lack of accurate historical information and the fact that patients are usually asymptomatic when evaluated combine to fuel diagnostic uncertainty and often leads to extensive testing in the ED. Annual healthcare costs associated with syncope in the United States exceed $3.8 billion, an amount comparable to the total annual hospital costs of asthma, chronic obstructive pulmonary disease, and HIV (2). The emergency physician is faced with the challenge of identifying those patients with potentially life-threatening processes (e.g., dysrhythmias, pulmonary embolism, subarachnoid hemorrhage, acute coronary syndromes), other patients who may require hospitalization and intervention (e.g., patients with bradycardia or medication-induced orthostatic hypotension), and those patients who have a more benign cause of syncope. When the initial ED evaluation of a patient

presenting with syncope does not reveal a clear etiology, the emergency physician must determine which patients require further diagnostic evaluation and monitoring and which patients can be safely discharged home.

CLINICAL PRESENTATION

A detailed history and thorough physical examination remain the cornerstone of accurate diagnosis of syncope in the ED. However, even with a thorough initial evaluation, a definitive etiology of syncope is often difficult to establish. Historical information should focus on the events and symptoms before, during, and after the episode, as well as on the past medical and medication histories. Certain elements of the history of the episode may direct the emergency physician toward possible causes of syncope. Tongue biting, the presence of a postictal period, or urinary incontinence may suggest that seizure rather than syncope caused the patient's symptoms (3). Syncope occurring while the patient is seated or reclining is more likely to have a cardiac etiology (4), whereas syncope that occurs after standing may suggest orthostatic hypotension (5). Exertional syncope, especially in younger patients, raises concerns about structural defects producing fixed cardiac output, such as hypertensive cardiomyopathy. Absent or brief preceding symptoms, including palpitations and dizziness, may be associated with dysrhythmias, whereas longer prodromes, often including nausea or vomiting, more commonly accompany neurally mediated syncope, also known as *vasovagal syncope* or *neurocardiogenic syncope.* Obvious precipitating events or stresses may lead one to consider the diagnosis of neurally mediated syncope, but caution should be exercised, because these prodromal symptoms are often subjective and agreement on the presence of "vagal" symptoms and the eventual diagnosis is inconsistent among physicians (6).

Corroborating history from witnesses and prehospital care providers is a vital source of information and should be obtained whenever possible. These individuals are often able to provide

information that the patient is unable to provide, including estimation of duration of loss of consciousness, evidence of seizure activity, and duration of confusion or lethargy after the episode.

A detailed medication history should also be obtained. Vasoactive medications, including antihypertensive agents, antianginal medications, and medications used to treat erectile dysfunction, may lead to syncope because of their vasodilatory effects. Medication interactions may prolong the QT interval and lead to potentially life-threatening dysrhythmias. Elderly patients in particular are more susceptible to medication effects that may cause syncope, and close attention should be directed to potential medication interactions in these individuals.

The role of patient age in the diagnostic evaluation of syncope is not clearly defined. Some studies have demonstrated the importance of age as a predictor of poorer outcome in patients with syncope of any cause, but other studies suggest that age is not an independent predictor of adverse outcome in syncope (7,8). Clearly, there is no single age that places a patient at higher risk for serious outcomes. It should be recognized that while syncope in younger patients is often caused by a single pathologic process, in older patients it is often multifactorial. Older patients are especially prone to syncope as a consequence of a combination of age-related alterations in the cardiovascular system, multiple comorbidities, and the use of numerous medications (9).

The medical history should focus on predisposing conditions that place patients with syncope at a higher risk for serious outcomes. Of particular note, attention should be paid to any history of cardiovascular disease. A history of coronary artery disease places patients at greater risk (10), and a history of poor left ventricular function or heart failure is consistently predictive of a greater risk of sudden death (6,11). Syncope in the patient with heart failure is a poor prognostic sign, and patients with impaired left ventricular function may be at higher risk for sudden death, even when they are diagnosed with a noncardiac etiology for their syncope (12).

Physical examination should focus on vital signs, a careful cardiovascular examination, and a detailed neurologic evaluation.

Vital sign abnormalities, including persistent tachycardia or hypotension, are of concern and must prompt a search for an underlying cause. Orthostatic hypotension (usually defined as a decrease in systolic blood pressure with standing of 20 mm Hg or greater) may identify some patients with syncope related to volume depletion, autonomic insufficiency, or medications. However, it is a common finding in up to 40% of asymptomatic patients older than 70 years and 23% of patients younger than 60 (13). The diagnosis of orthostatic hypotension as a cause of syncope should be approached with caution and should probably represent a diagnosis of exclusion in low-risk patients, because many high-risk patients also have orthostasis.

Physical examination findings of congestive heart failure, including elevated jugular venous pressure, dependent edema, and rales are concerning predictors of sudden death after syncope. Murmurs that may be indicative of valvular heart disease or outflow obstruction should prompt further evaluation for structural heart disease, usually with echocardiography.

Abdominal pain or tenderness associated with syncope must be investigated, with close attention to possible intra-abdominal pathology or hemorrhage. Rectal examination, with testing of the stool for blood, is recommended if gastrointestinal hemorrhage is suspected.

A detailed neurologic examination should be performed. Because syncope is associated with complete and spontaneous return to normal neurologic function, focal neurologic deficits should raise concerns for other diagnoses including stroke and transient ischemic attack (TIA), and prompt further investigation, including brain imaging, Although objective evidence of seizure activity is difficult to ascertain, lateral tongue biting and signs of urinary incontinence suggest seizure, although the absence of either of these does not exclude the diagnosis. Some studies have suggested that anterior tongue biting is more commonly associated with syncope, whereas lateral tongue biting is more suggestive of seizure (14). Seizures classically present with a prodromal aura or “warning” symptoms and are typically followed by a postictal period in which the patient

is often lethargic, agitated, or confused, with a gradual return to full consciousness. More than 5 minutes of loss of consciousness and rhythmic movements can be seen in both seizures and syncope but are far more common in patients who have had a seizure.

DIFFERENTIAL DIAGNOSIS

The transient reduction in cerebral blood flow that is responsible for most causes of syncope results in temporary underperfusion of both cerebral hemispheres simultaneously or sections of the brainstem thought to be responsible for the conscious state (the reticular activating system). Transient reversible underperfusion in the brain may also be caused by a sudden increase in intracranial pressure from trauma or other brain injuries that limit cerebral blood flow (Table 9.1).

TABLE 9.1
Differential Diagnosis of Syncope (From Higher to Lower Risk)

Cardiac Causes

Arrhythmias

Bradyarrhythmias: Second- and third-degree heart block, sinus node dysfunction, pacemaker malfunction

Tachyarrhythmias: Ventricular tachycardia, ventricular fibrillation, supraventricular tachycardia, torsades pointes

Pump failure

Myocardial infarction or ischemia

Valvular disease

Aortic or mitral stenosis, acute aortic, mitral, or tricuspid insufficiency

Outflow obstruction

Hypertrophic cardiomyopathy, pulmonary hypertension, pulmonary embolism, atrial myxoma, prosthetic valve dysfunction

Impairment of venous return

Pericardial tamponade

Other cardiovascular causes

Aortic dissection, Brugada syndrome

Neurologic

Subarachnoid hemorrhage, vertebrobasilar disease, peripheral and autonomic neuropathies, seizure

Systemic Hypotension

Hypovolemia, acute blood loss, dehydration, medications

Endocrine

Hypoglycemia

Medications

Vasodilators, calcium channel blockers, β-blockers, nitrates, diuretics, antiarrhythmics, angiotensin-converting enzyme inhibitors

Reflex Mediated

Neurally mediated syncope

Carotid sinus hypersensitivity, situational syncope (micturition, defecation), vasovagal syncope

Psychiatric Disease

Major depression, somatization disorder, panic disorder, substance abuse

Dysrhythmias produce syncope by decreasing ventricular filling and stroke volume, resulting in hypotension and diminished cerebral blood flow. Loss of consciousness may also occur as a result of transient bradyarrhythmias. In pacemaker-dependent patients,

pacemaker malfunction may produce syncope as a result of bradyarrhythmias or pacemaker-induced tachycardia.

Syncope can also be a manifestation of an obstruction to blood flow in the heart. Exertional syncope may be because of aortic stenosis or hypertrophic cardiomyopathy, both of which are also associated with tachyarrhythmias. Other valvular diseases, such as severe mitral stenosis, may also cause syncope. Mitral stenosis is most commonly associated with syncope during periods of atrial fibrillation.

Acute pulmonary hypertension can cause a functional obstruction to pulmonary flow, abruptly decreasing left ventricular preload and thus cardiac output. This is most likely the mechanism of syncope associated with massive pulmonary embolism. In patients with chronic pulmonary hypertension, activities that acutely raise intrathoracic pressure, such as coughing or Valsalva during defecation, can produce the same phenomenon.

Other causes of cardiac-related syncope include sudden left ventricular dysfunction or ventricular dysrhythmia associated with myocardial ischemia or infarction. Patients with pericardial tamponade, constrictive pericarditis, and constrictive myocardial disease may develop impairment of venous return, leading to decreased left ventricular output and resulting in syncope.

Reflex-mediated syncope is a common cause of syncope in all populations. Neurally mediated syncope (including vasovagal syncope) can be precipitated by painful or emotional situations. Other types of neurally mediated syncope include carotid sinus hypersensitivity and situational syncope (with micturition or defecation), which may share components of a common pathophysiologic mechanism. Most patients with vasovagal syncope have normal baseline vital signs and hemodynamics, and have immediate return to normal vital signs after their syncopal episode (15).

Syncope may be a manifestation of psychiatric illness. Studies have documented a high prevalence of psychiatric illness among patients with syncope, particularly patients with syncope of unknown origin (16). Psychiatric disorders include somatoform

disorders, mood disorders (including major depression), anxiety disorders (including panic attacks), and substance abuse (17).

Seizures also can cause a transient loss of consciousness. Although syncope may be associated with generalized shaking movements ("convulsive syncope"), seizure is usually associated with postictal disorientation, may be preceded by sensory auras, and may be accompanied by lateral tongue biting and urinary incontinence.

TIAs and stroke rarely cause syncope. For cerebrovascular disease to cause a loss of consciousness, either both cerebral hemispheres or the brainstem must be deprived of blood flow. In a patient with a prior hemispheric infarction, marked ischemia or infarction on the contralateral side may cause a loss of consciousness, but it is unlikely that this alteration in consciousness would be transient and resolve spontaneously. Similarly, vertebrobasilar ischemia may cause syncope, but it is usually associated with other manifestations of brainstem dysfunction such as diplopia, vertigo, or nausea.

Subarachnoid hemorrhage can produce syncope, presumably as a result of a sudden increase in intracranial pressure. The complaint of headache or the appearance of focal neurologic findings in a patient with syncope should raise this possibility.

Medications can produce syncope by several mechanisms. Certain medications result in volume depletion, orthostasis, gastrointestinal hemorrhage, or depressed left ventricular function. Other medications have a proarrhythmic effect that may result in syncope.

Endocrine causes of syncope include hypoglycemia, which is easily recognized by blood glucose testing and is easily treated by administration of supplemental glucose.

Other causes of syncope include hypotension secondary to acute blood loss, dehydration, and disorders of autonomic function, including peripheral neuropathies and central nervous system disease.

DIAGNOSTIC APPROACH

The history and the physical examination may identify an underlying cause of syncope in nearly half of the patients (18).

Although the electrocardiogram (ECG) provides diagnostic or clinically useful information in only approximately 5% of patients with syncope, a 12-lead ECG should be obtained to help identify myocardial infarction or life-threatening dysrhythmias. An ECG may also aid in the identification of a prolonged QT interval or other potentially life-threatening conditions, including Brugada syndrome and pre-excitation syndromes, as the cause of syncope. Although the definition of *abnormal* ECG varies among the many studies examining their role in the diagnosis of syncope, particular attention should be paid to any nonsinus rhythm, signs of ischemia, or conduction abnormalities.

If a significant dysrhythmia is suspected, cardiac monitoring for up to 72 hours may be warranted. However, many dysrhythmias discovered in the 24- to 72-hour window are asymptomatic. The diagnostic yield of longer-term monitoring is higher, and thus its utilization is justified if there is clinical suspicion of dysrhythmia. This is also true for patients with recurrent syncope of unknown etiology (19).

Brain imaging with noncontrast head computed tomography (CT) may be useful and appropriate in a patient population with syncope and concomitant signs of trauma above the clavicles, a history consistent with a seizure, symptoms of neurologic disease such as headache, or focal neurologic findings. Head CT should be routine in patients taking warfarin (20). However, the yield of head CT in other patient populations is low, and this test should be employed judiciously (21).

The utility of routine blood tests is limited. Blood tests are commonly ordered but often do not yield diagnostically useful information (22). Measurement of blood glucose is a simple test that may be of benefit, especially in patients with diabetes or in whom seizure, rather than syncope, is suspected. If blood loss is suspected, hemoglobin or hematocrit may be useful, although it should be recognized that they may be normal in the early stages of blood loss. Women of childbearing age who experience syncope should be evaluated with a pregnancy test. However, a physician should not automatically interpret pregnancy as the sole cause of a syncopal

episode. Rather, a complete evaluation should be performed to search more closely for an etiology. Growing evidence suggests that cardiac enzymes may be of little value if drawn routinely on patients with syncope unless they have other signs or symptoms suggestive of myocardial ischemia (23,24). Psychiatric evaluation should be considered in patients with known psychiatric illness, no organic heart disease, and recurrent syncope.

The most recent clinical policy from the American College of Emergency Physicians recommends that patients with syncope should receive a 12-lead ECG (Level A recommendation—generally accepted principles for patient management that reflect a high degree of clinical certainty). The policy also recommends that laboratory testing and advanced investigative testing such as echocardiography or cranial CT scanning not be routinely performed unless guided by specific findings in the history or physical examination (Level C recommendation—based on preliminary, inconclusive, or conflicting evidence, or in the absence of any published literature, based on panel consensus) (25).

CRITICAL INTERVENTIONS

- Goal of initial evaluation is identification and treatment of cause of syncope, if possible.
- As with all patients, assessment of the adequacy of the patient's airway, breathing, and oxygenation must be assessed immediately.
- Pulse oximetry and cardiac monitoring should be instituted in all ill-appearing patients and in patients in whom a cardiac etiology of syncope is considered.
- Bedside determination of the patient's blood glucose level should be performed at presentation.
- Intravenous (IV) access should be established in patients with hypotension, tachycardia, evidence of hypovolemia, or significant blood loss.
- Immediate resuscitation with crystalloid solutions and packed red blood cells, as clinically indicated, in patients with hypotension,

or evidence of hypovolemia.
- Emergent consultation with the appropriate services should be obtained when the clinical picture is consistent with a life-threatening emergency such as a ruptured abdominal aortic aneurysm, ruptured ectopic pregnancy, or pericardial tamponade.

DISPOSITION

It is often the case that despite a thorough history and physical examination, no obvious cause of syncope is identified. In these cases, the emergency physician must determine which patients require further diagnostic evaluation and monitoring and in what setting. As with the evaluation of chest pain, the role of the emergency physician in evaluating syncope has moved from the goal of determining a specific etiology of syncope to one of risk stratification, identifying those patients at highest risk of serious short-term outcomes.

A number of recent studies have attempted to identify predictors of short-term adverse outcomes in ED patients whose initial workup did not reveal an obvious cause of syncope (Tables 9.2 and 9.3) (6,10,26,27). However, there is no set of objective criteria that is 100% sensitive for determining which patients are at risk for serious outcomes and would benefit from admission to the hospital for further diagnostic evaluation. Moreover, the value of hospital admission in preventing a subsequent adverse outcome has not been demonstrated.

TABLE 9.2
The San Francisco Syncope Rule

CHESS Mnemonic
C: History of congestive heart failure
H: Hematocrit <30%
E: Abnormal ECG
S: A patient complaint of shortness of breath
S: A triage systolic blood pressure <90 mm Hg

From Quinn JV, Stiell IG, McDermott DA, et al. Derivation of the San Francisco Syncope Rule to predict patients with short-term serious outcomes. *Ann Emerg Med.* 2004;43(2):224–232.

TABLE 9.3
The Boston Syncope Criteria

The modified Boston Syncope Criteria state that if syncope is clearly dehydration or vasovagal in etiology and the ED workup at physician discretion is otherwise normal, then these patients may be discharged even with risk factors.

Syncope Risk Factors for Adverse Outcome:

I. Signs and symptoms of acute coronary syndrome

1. Complaint of chest pain
2. Ischemic ECG changes (ST elevation or deep ST depression)
3. Other ECG changes (any abnormal atrial heart rhythm) or new STT wave change
4. Complaint of shortness of breath

II. Worrisome cardiac history

5. History of CAD, hypertrophic or dilated cardiomyopathy
6. History of congestive heart failure or LV dysfunction
7. History of or current ventricular tachycardia, ventricular fibrillation
8. Pacemaker
9. ICD
10. Antiarrhythmic medication not including digoxin, b blockers, or cc blockers

III. Family history of sudden death

11. Family history (first-degree relative) with sudden death, HOCM, Brugada syndrome, or long QT syndrome

IV. Valvular heart disease

12. Significant heart murmur by history or heard in the ED

V. Signs of conduction disease

13. Multiple syncopal episodes within the last 6 months
14. Rapid palpitations
15. Syncope *during exercise*
16. QT interval >500 ms
17. High grade or complete heart block

VII. Volume depletion

18. Gastrointestinal bleeding
19. Hematocrit <30
20. Dehydration not corrected in the ED

VI. Persistent abnormal vital signs in the ED

21. Respiratory rate >24
22. O_2 saturation <90
23. Sinus rate <50 or sinus rate >100
24. Blood pressure <90

VIII. CNS

25. Primary CNS event (i.e., SAH, stroke)

From Grossman SA, Fischer C, Lipsitz LA, et al. Predicting adverse outcomes in syncope. *J Emerg Med*. 2007;33(3):233–239.

Patients who are judged to be at risk for dysrhythmia or sudden death should be admitted to an inpatient unit, observation unit, or other monitored area. Although the definition of high-risk patient is not consistent across the studies to date, certain clinical and diagnostic features appear to indicate a high risk of dysrhythmia; these include older age with associated comorbidities, an abnormal ECG, hematocrit $<30\%$ (if obtained), and history or presence of heart failure, coronary artery disease, or structural heart disease. Patients with near syncope (patients who feel like they are going to pass out but do not) have similar risks for adverse outcome when compared to patients who actually do have transient loss of consciousness and should be treated similarly (28,29). Patients presenting to the ED with syncope determined to be of benign etiology (clearly vasovagal or dehydration related) with a negative ED workup should be considered for discharge regardless of the presence of other risk factors (30).

Common Pitfalls

- Discharging a patient without performing a complete history and physical examination
- Failure to obtain an ECG and measure the blood sugar
- Failure to utilize outside resources such as family, ambulance crews, and bystanders in obtaining a complete history of events surrounding the syncopal episode

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Thomas P. Martin to the content of this chapter.

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CHAPTER 10

Fever

Sarah A. Sterling and Alan E. Jones

Fever is one of the oldest and most widely recognized signs of disease and accounts for numerous adult and pediatric visits to the emergency department (ED). Although the exact temperature that constitutes a fever is debatable, most consider a rectal temperature of 38°C in children and a temperature of 38.3°C in adults to represent a fever.

Body temperature is regulated by the preoptic area of the anterior hypothalamus. This area acts like a thermostat, continuously balancing heat production versus heat loss. Heat production is controlled by altering the basal metabolic rate by varying the level of circulating thyroxin, which in turn increases cellular metabolism. In addition, body heat is produced by increasing muscle activity (shivering when cold or the shaking chill of a fever), the fastest and most sensitive means of heat production. The principal method of adjusting body heat loss is to vary the volume of blood flowing to the skin's surface through vasoconstriction and vasodilation, decreasing and increasing heat loss, respectively. The exocrine sweat glands also contribute to heat loss, cooling the body by vaporization.

The hypothalamic thermostat has an inherent set point of about 37°C but ranges from 36° to 37.8°C. This set point is affected by the normal daily circadian rhythm, with temperatures lowest around 4 AM and gradually increasing throughout the day to peak between 6 and 10 PM. This diurnal pattern is often apparent in clinical practice with most fevers lower in the morning and higher in the evening.

The phenomenon of night sweats, most commonly related to tuberculosis or lymphoma, represents a nocturnal fluctuation in the hypothalamic set point, causing a slight rise in body temperature that leads to reactive perspiration.

Not all elevations of body temperature necessarily constitute a fever. A true fever is an elevation in body temperature caused by a change in the hypothalamic set point. This new higher set point causes the body to engage its normal heat-generating mechanisms, like shivering or shaking, to raise the body temperature until the new set point is reached. In hyperthermia, however, the body attempts to maintain a normal temperature but its homeostatic mechanisms (i.e., vasodilation, increasing sweat production) are insufficient to reduce body temperature and eventually become overwhelmed. Temperatures $>41^{\circ}C$ ($106^{\circ}F$) almost always represent hyperthermia and not a true fever (1,2).

Elevation of the hypothalamic set point appears to be mediated by cytokines, which are released from lymphocytes, monocytes, and macrophages in response to exogenous and endogenous pyrogens. Exogenous pyrogens include microorganisms and their metabolic by-products, drugs, and other toxins, and endogenous ones include neoplasms and metabolic processes. Cytokines travel via the bloodstream to the hypothalamus, where they act to increase prostaglandin synthesis, primarily prostaglandin E2 (PGE2). This causes an elevated cyclic adenosine monophosphate (cAMP) level, which raises the hypothalamic set point by affecting peripheral vasoconstriction and internal heat production. Fever is maintained until pyrogen levels fall or until prostaglandin production is inhibited. Aspirin, ibuprofen, and acetaminophen exert their antipyretic effects by blocking central hypothalamic prostaglandin synthesis, but have no effect on circulating pyrogens. Corticosteroids can block the release of endogenous pyrogens as well as inhibit prostaglandins but are relatively weak antipyretics, nevertheless.

Other cytokines produced in response to pyrogens include interleukins (ILs), tumor necrosis factor (TNF), and interferons (IFNs). It is generally believed that bacteria and their products of metabolism typically provoke release of IL-1. In contrast, viral

proteins appear to stimulate IFN. IL-1 induces the liver to produce acute phase reactants, including C-reactive protein (CRP), which are responsible for the elevated erythrocyte sedimentation rate (ESR) associated with some fevers. Although IFN is a potent pyrogen, it does not enhance production of acute phase reactants. Though not yet clearly supported by data, this is the rationale behind the expectation of an elevated ESR and CRP level with a bacterial fever but not with one of viral etiology. Procalcitonin, the precursor to calcitonin produced in the thyroid, rises from undetectable in well individuals to measurable levels within 2 to 3 hours (peaking in 24 hours) in patients with sepsis. Some studies have suggested this marker, rather than the later rising CRP, may be more specific for infection. Several studies have examined the use of CRP and procalcitonin as potential biomarkers of sepsis, which could be used in clinical practice to differentiate patients with bacterial versus nonbacterial infections; however meta-analyses suggest that procalcitonin is not yet ready to be deployed into routine clinical practice (3). While the use of these biomarkers appears promising, research is ongoing to determine their clinical utilization.

Many metabolic abnormalities are associated with the febrile state. Fever increases both the oxygen tension (PO_2) and the carbon dioxide tension (PCO_2) and shifts the oxyhemoglobin dissociation curve to the right, resulting in lower oxygen saturation. Fever also seems to lower the seizure threshold, which can result in seizures in children who do not have a predisposition to epilepsy (febrile seizures). Fever can also cause reactivation of latent herpes simplex infections and other chronic viral conditions.

Although higher metabolic demands are placed on the febrile patient, evidence suggests that fever has some physiologic benefits and protective effects as well. Neutrophils, macrophages, and lymphocytes are most active at elevated temperatures. In addition, higher temperatures decrease the level of serum iron, a substrate needed by many bacteria to replicate. Fever also seems to inhibit certain viruses, such as Coxsackievirus and poliovirus (1,4).

Despite this, many patients and parents, as well as practitioners, believe that fever is harmful or likely to cause harm. Many studies have shown that "fever phobia," initially described in the 1980s, persists. A recent study in a pediatric ED showed that more than 50% of caregivers would define fever at $<37.8^{\circ}C$ ($100^{\circ}F$) and a large majority would treat a fever $<37.8^{\circ}C$ (5). Despite these beliefs, no studies have shown true fevers to be harmful. In addition, research has shown that the response to antipyretics does not allow the differentiation between serious (e.g., bacterial) and nonserious (e.g., viral) infections (2). Fever anxiety can be greatly reduced when patients and caregivers are educated on the risks and benefits of fever and its proper management.

CLINICAL PRESENTATION

Though most febrile patients present to the ED with a chief complaint of fever, many present with more generalized complaints. Elderly patients, or their caregivers, may complain of generalized weakness, malaise, or a change in mental status. Parents may bring in infants who are eating poorly or appear lethargic. In these patients, fever may be an incidental finding, discovered only on review of systems or review of vital signs.

In children, a fever documented at home should be treated as real, even in the absence of a documented fever in the ED. One study found that while children referred to an ED by a general practitioner were more severely ill, approximately one in four children who self-reported with parents required extensive diagnostic testing, intravenous (IV) or aerosolized medications, or hospital admission (6). Studies have also found parents can correctly detect fever by palpation alone with sensitivities and specificities as high as 91% and 79%, respectively, reported in one study (7). Further, although bundling of infants can affect skin temperature, research has shown it has no effect on the rectal temperature of a healthy infant; so elevated rectal temperatures should not be attributed to bundling (8).

In the elderly, fever may be more difficult to detect and define. Previous studies have shown that while mean rectal temperature was similar to younger patients (37˚C), elderly patients had less diurnal variation (9). Another study found that lowering the definition of fever to 37.8˚C (100˚F) increased the sensitivity of predicting an infection to 70% (vs. 40% if 38.3˚C is used), while the specificity remained at 90% (10). Elderly patients may also have an impaired ability to mount a fever response altogether, with 20% to 30% of elderly patients who had a serious bacterial or viral infection having a decreased or absent fever response in some studies. To complicate the evaluation of this patient population more, the elderly may have a delayed fever response as well, which can be delayed more than 12 hours in 12% of patients despite known infection (9).

Similarly, immunocompromised patients with a low-grade fever may suffer from an acute, life-threatening condition, but may be unable to mount a febrile response. These findings highlight the importance of a high index of suspicion for infection in the setting of functional decline in the elderly or immunocompromised patient, and the need for reassessment after initial physical examination and evaluation.

History

Important points to address in the history include the following:

- Duration and magnitude of fever
- Associated symptoms
- Close contacts with similar illness
- Past medical history associated with immunocompromise
  - For example, HIV, diabetes, chronic renal failure, blood dyscrasia, alcohol or drug abuse
- Recent hospitalizations
- Presence of medical hardware
  - For example, prosthetic valves, ventriculoperitoneal shunts
- Current medications
  - Recent antibiotics or chronic steroid use

    - Serotonergic or neuroleptic drug
    - Last time and dose of antipyretics
- Recent travel
    - Areas with endemic malaria, parasitic, or fungal infections
    - Prolonged immobility or symptoms concerning for venous thromboembolism
- Occupational exposures
    - For example, medical personnel or postal worker/governmental official with possible biologic weapon exposure

Physical Examination

The most important observation during the physical examination is the patient's overall appearance and mental status. Specifically, does the patient look well or toxic? Does the patient have an altered mental status, which might indicate infection or sepsis, especially in the elderly? The overall impression of the patient and their general well-being is vital in determining pretest probabilities which will guide and direct the patient's workup.

The importance of reviewing vital signs cannot be overstated. Tachycardia and hypotension should not be ignored or attributed solely to a febrile response or faulty reading. One study found that hypotension, even if it is transient, significantly increases mortality in patients admitted to the hospital with sepsis (11). In the presence of a fever, the pulse can be expected to increase by approximately 18 beats/min for each 1°C increase in temperature. However, some diseases are associated with relative bradycardia for the degree of fever (pulse–temperature dissociation). This dissociation is classically seen with typhoid fever, but may also be seen in Legionnaires' disease, mycoplasmal infections, drug fever, factitious fever, and some viral syndromes. In addition, patients taking β-blockers may be unable to increase their pulse in response to a fever.

Tachypnea may also be an important indicator of significant infection or acid–base disturbance. Tachypnea and dyspnea are

often suggestive of pulmonary disease, whereas tachypnea without dyspnea may indicate sepsis or metabolic acidosis of any cause. In a study of nursing home patients, tachypnea >25 was the highest predictor of disease, with a sensitivity of 90% and a specificity of 95% for pneumonia (12).

The history will usually direct the physician to the most likely source of infection, though this may be challenging in patients with an altered mental status. In the absence of localizing symptoms, a thorough examination should be undertaken. The entire body should be examined for rashes, decubitus ulcers, cellulitis, track marks (needle marks), or lymphadenopathy. Rashes may suggest a viral exanthem, vasculitis, meningococcemia, tick-borne infection (e.g., Rocky Mountain spotted fever or Lyme disease), or toxic shock syndrome (staphylococcal or streptococcal). Lymphadenopathy associated with fever may suggest malignancy, autoimmune disorders, or infection. Tender, localized adenopathy is usually associated with an infection in the region drained by the involved nodes, whereas malignant nodes are usually painless, rubbery, and firm. The most common cause of acute generalized adenopathy is infectious mononucleosis.

The head and neck examination may also offer important clues to the source of infection. Nuchal rigidity or meningismus may indicate meningitis; however, these signs are often absent, particularly in the elderly or children. The eyes should be examined for scleral icterus, which could indicate hepatitis, cholecystitis, or ascending cholangitis. Examination in and around the ears may reveal otitis externa or media or may suggest mastoiditis. The oropharynx may show evidence of pharyngitis, peritonsillar or retropharyngeal abscess, or periodontal infection. Purulent rhinorrhea may suggest sinusitis or, in children, a nasal foreign body. Sore throat, drooling, and fever may suggest epiglottitis. It is important to remember that patients may not present classically, so airway edema, stridor, or hoarseness should be taken seriously as they could indicate significant infection and a potential airway emergency.

The chest should be examined for indications of a pulmonary or cardiac cause of fever. Localized rales or rhonchi suggest pneumonia. As x-ray findings can lag behind physical findings, an early pneumonia may not be visible on x-ray. A pericardial rub is indicative of pericarditis, and a new heart murmur suggests endocarditis, especially in IV drug users. However, functional murmurs may increase because of fever-induced tachycardia.

The abdomen should be examined for signs of peritoneal irritation or ascites. Localized pain may suggest cholecystitis, appendicitis, pancreatitis, or diverticulitis. Suprapubic pain suggests a urinary tract infection (UTI), and should prompt an evaluation for costovertebral angle (CVA) tenderness, which could indicate pyelonephritis. A rectal examination may demonstrate evidence of a perirectal abscess or prostatitis. In male patients with a urethral discharge, a sexually transmitted infection is likely and a swollen or painful testicle suggests epididymoorchitis. In females, a pelvic examination can be performed to evaluate for vaginal and cervical discharges and/or cervical motion tenderness suggestive of pelvic inflammatory disease, tuboovarian abscesses, or a retained vaginal foreign body. In neonates, examination of the periumbilical area is necessary to evaluate for omphalitis.

Examination of the musculoskeletal system is often overlooked in febrile patients, but examination of the spine may reveal tenderness suggestive of osteomyelitis, discitis, or epidural abscess (especially in IV drug users). A detailed examination of the extremities may demonstrate a septic or inflamed joint, or it may suggest osteomyelitis, myositis, or deep vein thrombosis (DVT). In addition, any retained catheters, such as peripherally inserted central catheter (PICC) lines or hemodialysis (HD) ports, should be evaluated for erythema, rubor, or discharge surrounding the catheter and regarded as a potential source of infection.

DIFFERENTIAL DIAGNOSIS

Infection

Infection is the most common cause of fever. Infection may originate in any portion of the body and lead to a febrile response, whether from bacterial or viral etiology. Fever may indicate localized infection, or may indicate a more significant systemic process, like sepsis. One of the more challenging aspects of practicing emergency medicine is determining the significance of infection and identifying patients early in the spectrum of sepsis.

Systemic Inflammatory Response Syndrome and Sepsis

Systemic inflammatory response syndrome (SIRS) indicates that the body has initiated a global inflammatory/immune response. SIRS is associated with a higher likelihood for organ dysfunction and organ failure. Although SIRS can result from noninfectious etiologies, in the setting of suspected or confirmed infection, if a patient has two or more SIRS criteria (Table 10.1), they meet the definition of sepsis (13,14).

TABLE 10.1
SIRS Criteria

Temperature	≤36°C or ≥38°C
Heart rate	≥90 beats/min
Respiratory rate	≥20 breaths/min or $PaCO_2$ <32 mm Hg
White blood cell count	≥12,000 or ≤4,000 cells/mm^3 or >10% bands

Severe Sepsis and Septic Shock

According to consensus definition, severe sepsis is sepsis, or suspected infection with systemic manifestations, and evidence of organ dysfunction. Septic shock is sepsis-induced hypotension (systolic blood pressure [SBP] <90 mm Hg or mean arterial pressure [MAP] <70 mm Hg, or an SBP 40 mm Hg below the patient's baseline) that does not respond to IV fluids. In addition, patients may have evidence of tissue hypoperfusion as indicated by an elevated blood lactate level, oliguria, renal failure, coagulopathy, or acute lung injury (15). Despite much attention to this area and aggressive treatment strategies, once septic shock occurs, the mortality rate remains high.

Drug-Induced Hyperthermia Syndromes

Drug-induced hyperthermia syndromes include neuroleptic malignant syndrome (NMS), malignant hyperthermia (MH), and serotonin syndrome (SS). Because all three syndromes have similar presentations, with severe muscle contraction and hyperpyrexia, they share common complications of rhabdomyolysis, myoglobinemia, and intravascular hemolysis. Temperatures $>42^{\circ}C$ cause central nervous system (CNS) damage, initially to the more sensitive cerebellum and eventually to the cerebral cortex, brainstem, and spinal cord. Patients may also develop pulmonary embolism, cardiovascular collapse, myocardial infarction, and acute respiratory failure.

NMS is a rare idiosyncratic reaction to neuroleptic medications. It has also been reported in patients taking lithium. NMS is thought to result from dopamine depletion in the brain, possibly in combination with increased anticholinergic activity. NMS presents with fever (temperature in excess of 41°C has been reported), muscle rigidity, and elevated creatine phosphokinase (CPK). Other findings may include altered mental status and autonomic instability. Symptoms develop rapidly over 1 to 3 days. Muscular rigidity of the thorax may impair breathing. Autonomic dysfunction may cause severe variations of both blood pressure and pulse, and some patients may develop seizures (eTable 10.1).

eTABLE 10.1
Diagnostic Criteria for NMS

History of neuroleptic medication use PLUS:

- Fever
- Muscle rigidity
- Elevated CPK

OR two of the above, PLUS four of the following:

- Tachycardia
- Abnormal blood pressure
- Tachypnea
- Altered mental status
- Diaphoresis
- Leukocytosis

MH is a rare, genetically determined reaction to inhaled anesthetic gases, depolarizing muscle relaxants (e.g., succinylcholine) and other agents. Succinylcholine is more likely to cause MH than inhaled anesthetic gases. The offending agent triggers the release of calcium by the sarcoplasmic reticulum resulting in increased muscle contraction and oxygen consumption. Masseter muscle spasm is generally noted initially, and then generalized muscle rigidity leads rapidly to hyperpyrexia. Symptoms typically develop as soon as 30 minutes following administration, though initial or recurrent symptoms may be delayed up to 48 hours later.

SS is a reaction to serotonin-active agents and most commonly occurs after a dosage increase of a serotonergic drug or with the addition of a potentiating drug to a serotonin-active agent. Common drugs that may cause SS are listed in eTable 10.2. Of particular note, the combination of triptans and serotonergic drugs has recently been shown to be a major cause of SS. SS involves an alteration in mental status, autonomic dysfunction, and increased neuromuscular activity, the latter causing a rise in temperature. Diagnostic criteria for SS are presented in eTable 10.3. Symptoms can be seen within 15 minutes of ingestion and can last for up to several hours. The duration of symptoms in other cases is dependent

on drug half-life, but, in severe cases, symptoms can persist for weeks.

TABLE 10.2
Surviving Sepsis Campaign Guidelines

To be completed within 3 hrs:

- Measure lactate level
- Obtain blood cultures prior to administration of antibiotics
- Administer broad-spectrum antibiotics
- Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L

To be completed within 6 hrs:

- Start vasopressors to maintain an MAP ≥65 mm Hg if hypotension does not respond to initial fluid bolus
- With persistent hypotension despite volume resuscitation or initial lactate ≥4 mmol/L:
  - Measure central venous pressure (CVP)[a]
  - Measure central venous oxygen saturation (ScvO2)[a]
- Repeat lactate if initial lactate was elevated[a]

[a]Targets for resuscitation: CVP of ≥8 mm Hg, ScvO2 of ≥70%, normalization of lactate.

eTABLE 10.2
Drugs Associated with Serotonin Syndrome

Selective inhibitors of serotonin uptake:
- Fluoxetine
- Paroxetine
- Fluoxetine/Olanzapine
- Sertraline
- Trazodone
- Meperidine
- Dextromethorphan
- Citalopram
- Escitalopram
- Fluvoxamine

Specific serotonin agonists:
- Buspirone
- LSD, Mescaline
- Triptans

Nonspecific serotonin agonists:
- Bromocriptine
- Bupropion
- Phenytoin
- Tryptophan
- Levodopa
- Lithium

Nonspecific inhibitors of serotonin reuptake:
- Clomipramine
- Venlafaxine
- Duloxetine
- Sibutramine
- Nefazodone

Agents that increase serotonin release:
- Amphetamine
- MDMA (Ecstasy)
- Cocaine
- Codeine
- Reserpine

Monoamine oxidase inhibitors:
- Pargyline
- Phenelzine
- Isocarboxazid
- Procarbazine
- Tranylcypromine
- Isoniazid
- Moclobemide
- Selegiline

Other drugs:
- Chlorpheniramine
- Brompheniramine
- Ginseng
- St. John's wort
- Tramadol

eTABLE 10.3
Diagnostic Criteria for Serotonin Syndrome

TABLE 10.3
Treatment of Malignant Hyperthermia

- Discontinue precipitating agent
- Administer dantrolene 2.5 mg/kg IV, up to 10 mg/kg/day
- Infuse D5W with sodium bicarbonate to maintain urinary output
- Monitor systemic pH to prevent alkalosis
- Cool patient with cooling blanket, ice packs, or evaporation
- Monitor for electrolyte imbalance and cardiac dysrhythmias
- Avoid the use of calcium antagonists or digoxin
- Agents safe for use in patients with MH: Vecuronium, pancuronium, etomidate, propofol, opiates, barbiturates, and benzodiazepines

The addition OR increase in dosage of serotonergic agent, PLUS three of the following:

- Fever
- Mental status changes (drowsiness, agitation, confusion, seizure, coma)
- Diaphoresis
- Diarrhea
- Myoclonus (lower more than upper extremities)
- Mydriasis
- Tremor
- Incoordination
- Hyperreflexia
- Autonomic dysfunction (hypertension, tachycardia, tachypnea)

Other Drug-Related Causes

Although any drug can cause a febrile reaction, penicillin and penicillin analogs are the most frequent causative agents. Many of the herbal and naturopathic supplements used by patients may interact with other medications causing fever as well. Drugs that are commonly associated with a drug fever are listed in eTable 10.4; however, drug fever should always be a diagnosis of exclusion.

eTABLE 10.4
Drugs Commonly Associated with Fever

Antibiotics
- Amphotericin
- β-Lactams
- Cephalosporins
- Isoniazid
- Nitrofurantoin
- Penicillins
- Rifampin
- Sulfonamides
- Vancomycin

Anticancer Drugs
- Bleomycin
- Streptozocin

Anticonvulsants
- Carbamazepine
- Phenytoin
- Barbiturates

Cardiac Drugs
- Hydralazine
- Methyldopa
- Nifedipine
- Procainamide
- Quinidine

Nonsteroidal Anti-Inflammatory Drugs
- Ibuprofen
- Salicylates

Others
- Cimetidine
- Iodides
- Interleukin

Some drugs used recreationally or as toxic ingestions (overdoses) are associated with elevated temperature, including cocaine, amphetamines, belladonna alkaloids, tricyclic antidepressants, and monoamine oxidase inhibitors. Salicylates as acute overdoses or in chronic poisoning may also cause fever. Chronic salicylate

intoxication may present similarly to sepsis, particularly in the elderly.

Venous Thromboembolism

Research using patient data from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study found, after eliminating other sources of fever, 24% of patients with a pulmonary embolus were febrile. Although the fever in the majority of these patients was low grade, 6% had a temperature of at least 38.3˚C and 2% had a temperature of at least 38.9˚C (16).

A recent study of more than 14,000 patients found that almost 5% of patients who had a DVT presented with a fever. They also found that in patients with a DVT, those who were febrile on presentation had a twofold higher mortality rate than those who were afebrile (17).

Central Nervous System Lesions

Structural lesions, head trauma, and strokes can cause elevated temperature either by direct destruction of the hypothalamic thermoregulatory center (hypothermia is more likely) or, more commonly, by blood irritating the central receptors in the preoptic area. Acute subdural hematomas may elevate body temperature, and therefore nonaccidental trauma should be considered in the differential diagnosis of an irritable infant with unexplained fever.

Rheumatologic and Connective Tissue Disorders

Fever may be the initial manifestation of many connective tissue and rheumatologic disorders. In systemic lupus erythematosus (SLE), fever is the initial symptom in 5% of cases. In older patients, temporal arteritis may present as recurrent fevers with no identifiable source.

Neoplastic Diseases

Although many different malignancies and tumors may produce fever, the most common are leukemia, Hodgkin disease and nonHodgkin lymphoma, hepatoma, and atrial myxoma. However, since the underlying disease and/or its treatment often leaves the patient immunosuppressed, it is important to eliminate occult infection as the etiology of the fever.

Inherited Diseases

Patients with familial Mediterranean fever have recurrent fevers of variable intervals, symptoms of polyarthralgias, and chest (pleural) and abdominal pain; however, this is a diagnosis of exclusion.

Endocrine Disorders

Thyroid disorders, including hyperthyroidism and subacute thyroiditis, and adrenal disorders, especially adrenal insufficiency (Addison disease), often include findings of fever.

DIAGNOSTIC APPROACH

An accurate temperature measurement is of utmost importance when approaching a patient with a report of fever. This is particularly true in the case of the very young, very old, or immunosuppressed patient, yet is often omitted for the sake of convenience. Recorded temperatures may vary widely depending on the method used to obtain them. Rectal temperatures have long been the gold standard, but because of the invasiveness and relative difficulty in obtaining them, easier methods are often employed. Newer generation urinary catheters allow for bladder temperature measurement, which is also an accurate method of core temperature measurement. Multiple studies have shown that none of these alternative methods consistently provides a reliable measurement of core temperature that is comparable to the rectal temperature. In addition, there appears to be no standard correction factor that may be used to improve their accuracy.

The rectal temperature tends to be 0.7°C higher than a simultaneously obtained oral temperature, although oral

temperatures can vary more than 1.6°C, depending on where the probe is positioned in the mouth, the respiratory rate (an increase in respiratory rate results in decreased oral temperature), and the recent consumption of cold or warm foods or liquids.

Many studies have shown axillary, tympanic, and temporal artery temperatures are poorly sensitive for detecting fevers and that no reliable conversion factor to determine rectal temperature exists. While study results for pacifier thermometers have shown good correlation with rectal temperatures, poor sensitivity remains an issue. In addition, due to the need for patient cooperation (sucking the pacifier) and relatively long time periods for readings to results (several minutes), they have little practical use in the ED (7).

Laboratory Evaluation

While no test exists that easily identifies patients with serious infections, a thorough understanding of certain basic laboratory tests can greatly enhance patient evaluation. Although the WBC count is the oldest and best known screening test used to differentiate serious bacterial infections from other disorders, it is not specific or sensitive in either adults or children. Though still commonly used in clinical practice, a recent large systematic review found leukocytosis had a sensitivity and specificity of only 58% and 73%, respectively, for predicting serious bacterial infection in children (18). In a study of adults with unexplained fever after careful physical examination, only 15% had a WBC count $\geq$15,000/μL, and only 56% of those patients were subsequently shown to have a bacterial source (19). Several noninfectious processes including burns, fractures, steroids, diabetic ketoacidosis, and Addison disease can increase the WBC count. Patients with low WBC counts ($<$1,000/μL), however, are at significant risk for occult bacterial infections.

A “left shift” is only slightly more useful. Neutrophilia may occur secondary to emotional or physical stress, acute or chronic inflammation, benign or malignant tumors, myeloproliferative disorders, asthma, seizures, or medications such as steroids, lithium,

or epinephrine. Neutrophil counts >30,000/μL have been reported secondary to strenuous exercise, seizures, and lithium use. In addition, a total neutrophil band count >1,500/μL was found in approximately one-third of adult patients with unexplained fever, of which only half proved to have bacterial infections (19).

The occurrence of thrombocytopenia in septic patients has been recognized for many years. Studies have shown longer stays in the intensive care unit and a higher mortality rate in patients with thrombocytopenia. Acute phase reactants, ESR and CRP, are often used to help recognize patients with serious occult infections, though both of these tests lack sensitivity and specificity. The ESR is often used as a screening test for temporal arteritis, bacterial endocarditis, tuberculosis, osteomyelitis, septic joints, and occult bacteremia in children.

CRP is more sensitive and specific and rises faster than the ESR, but is not particularly useful in the ED currently. Procalcitonin is another biomarker of interest for differentiating those patients with significant infections. A large systematic review looking at the diagnostic value of laboratory tests in identifying serious bacterial infections in children found that both CRP and procalcitonin had potential diagnostic value; however, there was no consensus on what cutoff values should be used for ruling in or out serious infections (18). Though both CRP and procalcitonin appear promising, further studies are needed to improve sensitivity and specificity before they can be used consistently in the ED.

Elevated lactate levels reflect tissue hypoxia and decreased global perfusion in the seriously ill patient and are associated with mortality in sepsis that is independent of organ dysfunction (20). In the most recent update to the Surviving Sepsis Guidelines, sepsis-induced hypoperfusion was defined as hypotension after fluid bolus or a lactate ≥4 mmol/L (15). In addition, research has shown that even moderate elevations in lactate (2 to 4 mmol/L) are associated with worse clinical outcomes (21). Further, a previous study has also shown that septic patients with an elevated lactate (≥4 mmol/L) who were normotensive, had a mortality rate similar to septic patients who were hypotensive (20% and 19%,

respectively) (22). A point-of-care lactate can easily and quickly be obtained from a venous or arterial blood gas sample and rapidly help to risk stratify the patient and direct their care and disposition.

A urinalysis may also identify an infectious source of fever and indicate a UTI or pyelonephritis. In uncomplicated UTIs, urine cultures are probably not necessary at the time of initial diagnosis, though in elderly women, men, children, or patients who are pregnant or have comorbid diseases, and in cases resistant to therapy, urine cultures are recommended. In adults in whom there is a high clinical suspicion but a negative urinalysis, urine cultures should be obtained and treatment initiated. The formation of significant levels of nitrites or leukocytes in the urine occurs over time (up to 6 hours), and therefore, patients with urinary frequency may have a falsely negative urinalysis. Conversely, 10% to 50% of nursing home patients have chronic asymptomatic bacteriuria (essentially 100% in those with indwelling catheters), so the diagnosis of UTI as a cause of fever or mental status changes should be made with some caution (12).

Like many laboratory tests, there is no consensus on the value of routine blood cultures in febrile patients. The incidence of bacteremia in the ED has been reported to vary from 2.6% to as high as 10.7% of febrile patients. Mortality from bacteremia ranges from 20% to 40%; there are no data, however, on mortality for clinically unsuspected bacteremia.

Sklar and Rusnak (23) examined the value of outpatient blood cultures in febrile adults discharged from the ED. In this study, 5 of 86 patients subsequently proved to have positive blood cultures; 4 were subsequently admitted. No long-term morbidity was noted. Of these patients, 3 were diagnosed with endocarditis and 1 with pyelonephritis. The fifth patient, who refused to return for admission, had presumed pneumococcal endocarditis. Each of the patients with endocarditis had identifiable risk factors (2 with murmur and a history of rheumatic fever, 1 on dialysis and with a murmur, and 1 IV drug abuser). Other studies have shown that patients with underlying illnesses, most commonly diabetes, are at greater risk for bacteremia, and this study seems to support those

findings. Therefore, it is prudent to limit outpatient blood cultures to febrile patients who have underlying diseases or risk factors (e.g., murmurs, IV drug use, immunosuppression, diabetes).

For inpatients, the current recommendations are to obtain cultures in patients who are septic, have an altered mental status, are ill appearing with unexplained leukocytosis, or are immunocompromised. In addition, some recommend blood cultures to identify the causative organism in pneumonia, osteomyelitis, meningitis, or septic arthritis, but in general it is preferable to obtain cultures directly from the infected site. Blood cultures are rarely helpful adjuncts in the management of immunocompetent patients with simple infections.

Laboratory studies, such as liver function tests or thyroid function tests, may identify a potential etiology for fever (such as hepatitis or thyroid storm) and should be directed based on historical clues and physical examination findings. Serologic testing may confirm the presence of other entities causing fever, such as amebiasis, mononucleosis, toxoplasmosis, chlamydial infections, cytomegalovirus (CMV), brucellosis, and HIV/AIDS. Specific studies on stool or cultures of the oropharynx could also be ordered when the history supports their consideration.

Cerebrospinal fluid (CSF) analysis can be obtained in patients with fever, headache, photophobia, and signs of meningeal irritation such as nuchal rigidity, Kernig sign (with the thigh flexed at the hip, there is pain or resistance with knee extension), or Brudzinski sign (passive flexion of the head onto the chest induces flexion of the lower limbs). The CSF should be routinely analyzed for protein, glucose, Gram stain, and cell count with differential. In selected cases, a venereal disease research laboratory (VDRL)/rapid plasma reagin (RPR) for syphilis, viral cultures, or tests for bacterial antigens should be added. Indwelling ventriculoperitoneal (VP) shunts may be accessed for obtaining CSF in the patient with symptoms of fever and meningitis with or without hydrocephalus.

Various antigenic tests are available; they have the advantage of identifying a specific organism when positive. Latex agglutination is rapid, economical, and noninvasive. Better results are obtained with

urine than with serum or CSF, presumably because the antigens are more concentrated in urine. Unfortunately, these tests historically have had a high specificity (>99%) but a low sensitivity. Enzyme-linked immunosorbent assay (ELISA), an immunologic test, is much more sensitive in detecting pneumococci than latex agglutination. An ELISA assay is also used to detect West Nile virus IgM, but this test may be falsely negative if tested too early because IgM takes time to develop.

Quicker means of identifying organisms grown in blood cultures are also available. DNA probes have been developed that, when mixed with the growth from positive blood culture bottles, directly and rapidly identify *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae, Enterococcus* sp., and *Streptococcus agalactiae.* Polymerase chain reaction (PCR) is useful in diagnosing viral meningitis and has a high sensitivity and specificity for herpes simplex type I, Epstein–Barr virus, *Enterovirus,* and *Cytomegalovirus* (considered the gold standard for CMV). PCR can also detect tuberculosis and acute neurosyphilis.

For discussion on the workup and management of fever in infants and children, see Chapter 222.

Neutropenic Cancer Patients

The management of neutropenic cancer patients (absolute neutrophil count <500 cells/mm^3 or a count <1,000 cells/mm^3 with a predicted decrease to <500 cells/mm^3) presenting with a fever is evolving. Whereas previous guidelines recommended admission and IV antibiotics for all of these patients, recent strategies focus on early oral therapy, outpatient management, and discontinuation of antibiotics in low-risk patients. Recommended evaluation of febrile neutropenic patients includes a thorough history and physical examination to localize a source of fever; CBC with differential, liver, and renal function tests (necessary for antibiotic choices); and blood cultures for bacteria and fungi (one set from any central venous access device and one peripheral set). Urinalysis should be performed, but urethral catheterization is discouraged in this patient population. Urine culture should be

obtained if the urinalysis is abnormal, if there are signs or symptoms of a UTI, or if there is an indwelling catheter. Chest radiography should be obtained only if indicated by respiratory signs or symptoms or if there is consideration of outpatient therapy. Site-directed studies based on history and physical examination (e.g., lumbar puncture [LP], aspiration, and culture of abscesses) are also recommended. In addition, caution should be used in obtaining rectal temperatures in neutropenic patients due to the risk of causing occult bacteremia from rectal probe insertion.

Because neutropenic patients with bacterial infections cannot reliably be distinguished from noninfected patients at presentation, empiric IV antibiotics should be administered promptly. After evaluation, patients who look well, have no focus of bacterial infection (including vomiting or diarrhea), and are felt to be at low risk for severe infection may be considered for outpatient antibiotic therapy if they can be carefully observed at home and have prompt access to health care 24 hours a day. Factors favoring a low risk of infection in adults are listed in eTable 10.5.

eTABLE 10.5
Factors Favoring Low Risk of Infection in Adults with Febrile Neutropenia

- Age <60 yrs
- Absolute neutrophil and monocyte counts ≥100 cells/mm^3
- Normal chest radiograph
- Normal/near normal hepatic and renal function tests
- Outpatient status at time of fever onset
- Duration of neutropenia <7 days or expected resolution in <10 days
- No evidence of IV catheter site infection
- Early evidence of bone marrow recovery
- Malignancy in remission
- Peak temperature <39°C
- No prior history or treatment of fungal infection
- Asymptomatic or does not appear ill
- Absence of neurologic or mental status changes
- Absence of abdominal pain
- No comorbid conditions or complications (e.g., diabetes, hypotension)

From Mellors JW, Horwitz RI, Harvey MR, et al. A simple index to identify occult bacterial infection in adults with acute unexplained fever. *Arch Intern Med.* 1987;147(4):666–671.

For discussion of the workup and management of infants and children, see Chapter 222.

Imaging Studies

A chest radiograph should be obtained in patients with lower respiratory complaints and examination abnormalities, or any patient who is at high risk for aspiration, such as an elderly patient with altered mental status or a patient with a history of alcohol abuse. Routine chest radiographs are commonly obtained in patients who present with fever without an obvious source as well. This practice is probably based on studies that show a lack of auscultatory findings in patients with infiltrates on chest radiographs. In one study, physical examinations performed by an experienced internist, pulmonologist, and infectious disease subspecialist were only 47% to 69% sensitive in detecting radiographically proven pneumonia. However, all of these patients

had symptoms suggestive of pneumonia and did not represent patients with a fever and no source (24).

Signs or symptoms should guide the need for other imaging studies. Plain films may reveal osteomyelitis in patients with fever and bone pain, but bone scans and magnetic resonance imaging (MRI) are more sensitive. Abdominal radiographs may identify free air (bowel perforation), appendicoliths (appendicitis), or "thumbprinting" or gas in the bowel wall (mesenteric ischemia). Patients with fever and abdominal pain may benefit from an ultrasound to evaluate for the presence of cholecystitis or tuboovarian abscess. Ultrasound may also be of use in localizing soft tissue abscesses as fever source, especially in the IV drug user. Computed tomography (CT) scans should be used in selected patients to evaluate for appendicitis, abdominal abscess, or diverticulitis. MRI is the study of choice to rule out epidural abscess. Echocardiography (particularly transesophageal echocardiography [TEE]) should be used to evaluate suspected endocarditis patients for valvular disease. It may also be used in the patient with suspected pericardial effusion from inflammatory, malignant, or infectious processes.

CRITICAL INTERVENTIONS

- Initiation of antibiotics as appropriate
  - Should be based on the type and site of infection if possible
  - Send appropriate cultures prior to antibiotics if possible
- Do not delay antibiotics for LP in suspected meningitis
- Check lactate in patients with suspicion of infection and SIRS criteria
- A protocolized, quantitative resuscitation in severe sepsis and septic shock
  - See Table 10.2 for treatment recommendations
- Antipyretics for patient discomfort or tachycardia
  - Acetaminophen: 15 mg/kg in children, 650 to 1,000 mg in adults
    - May repeat every 4 to 6 hours depending on dose

- Maximum dose: 90 mg/kg/day or 4 g/day
- Ibuprofen: 10 mg/kg in children, 400 to 600 mg in adults
  - May repeat every 6 to 8 hours depending on dose
  - Maximum dose: 40 mg/kg/day or 2.4 g/day
    - Should not be used for more than a few days at max dose
  - Not approved for infants <6 months old
- Repeat vital signs and reassess patient frequently
- Drug-related fever
  - Stop offending agent
  - MH: See Table 10.3 for treatment recommendations
  - SS: Supportive care is the mainstay of treatment
    - Benzodiazepines may help with hyperactivity
  - NMS: Specific treatment not well established
    - Dantrolene: Most useful in patients with prominent muscle contraction
    - Bromocriptine mesylate: Use alone or in combination with dantrolene
      - Most useful when dramatic muscle rigidity is not present
    - Levodopa and carbidopa–levodopa: Useful in many patients
      - Particularly useful in cases associated with medication withdrawal
- Aggressive cooling measures in hyperthermia
  - If temperature >41°C, cool to 39°C within 30 minutes
  - Use cool water spray with fans or cooling blankets
  - Control shivering with benzodiazepines or chlorpromazine
    - Avoid phenothiazines in NMS
  - Monitor for rhabdomyolysis, electrolyte abnormalities, and disseminated intravascular coagulopathy (DIC)
  - Remember: This is not a true fever, so antipyretics are typically ineffective

DISPOSITION

When considering the disposition of the febrile patient, the most important considerations are age and general health. Infants who are younger than 90 days old or incompletely immunized require a

more extensive evaluation and may require admission or discharge with close follow-up.

For a discussion of the management of infants and children with a fever, see Chapter 222.

Patients who appear nontoxic and have no medical problems have a very slight chance of developing a serious infection (with the exception of IV drug abusers). As the age and presence of underlying medical problems increase, the chance of serious occult infection increases and makes admission advisable. Keating et al. (25) found that 95% of patients who were older than 60 years and had a temperature >38.3°C (101°F) on admission to the ED had a serious infection, and 92.5% required admission.

Most patients with unexplained fever and neutropenia or malignancy should be admitted for further workup. Patients with diabetes are at special risk, as are patients who are taking corticosteroids. Alcoholics are also considered to be immunosuppressed and at increased risk for complications. Also, pregnancy-related immunosuppression increases morbidity and mortality in pregnant females and may necessitate admission for infections that would otherwise be handled on an outpatient basis.

The postsplenectomy patient is at special risk for developing clinically unapparent bacteremia, usually from *S. pneumoniae.* These patients often have fever and a flu-like syndrome as their only complaints. Even when promptly diagnosed and started on antibiotics, the mortality rate remains high (50% to 75%). Although most postsplenectomy patients should be immunized against *S. pneumonia,* it is important to approach these patients cautiously and keep a high level of suspicion.

If good follow-up can be arranged, specimens for cultures can be obtained in the ED, and the nontoxic, low-risk patient can be discharged and rechecked in 24 hours when initial culture results become available. Continued follow-up or contact is necessary until cultures are confirmed to be negative.

Common Pitfalls

- Failure to obtain a rectal temperature, especially in the elderly or immunosuppressed
- Discounting parental reports of fever in infants who are afebrile in the ED
- Attributing fever in infants to overbundling
- Failure to check a lactate when clinically appropriate
- Relying on the WBC count or the response to antipyretics to determine the presence or seriousness of an infection
- Disregarding (even transient) hypotension
- Failure to perform a protocolized, quantitative resuscitation in septic patients
- Failing to reassess patient's response to treatment and repeat vital signs
- Failure to immediately and aggressively cool patients with severe hyperthermia (>41°C)

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CHAPTER 11

Altered Mental Status and Coma

J. Stephen Huff and Marcus L. Martin

Viewed from a physiologic perspective, consciousness is the sum of the activities and interactions of the reticular activating system and the cerebral cortex. A useful model is to think of the general state of alertness and wakefulness as arising in the reticular activating system, a group of neurons in the brainstem. Cognition, language, personality, and higher awareness of the environment are functions of the cerebral cortex. Coma results from the dysfunction of either the reticular activating system, the bilateral cerebral cortices, or both the reticular activating system and the cerebral cortices.

CLINICAL PRESENTATION

A patient with an altered mental status presents along a spectrum of consciousness. In the drowsy or lethargic state, there is slightly decreased wakefulness and interaction with the environment, but the patient may be aroused by verbal stimuli or light touch. Coma is the state in which the patient cannot be fully aroused to normal alertness by any environmental stimuli. The deeply comatose patient has failure of the arousal system and is unable to be awakened by vigorous sensory stimulation. Obtundation and stupor are intermediate states where the patient may be awakened only briefly by energetic stimulation. Rather than using clinical terms that are sometimes inexact, a simple description of the patient's

response to the examiner's stimulus is preferred for clarity in communication.

Some other disorders of consciousness include the recently described "minimally conscious state" in patients with inconsistent but discernible evidence of partial consciousness; these patients may demonstrate sustained visual fixation and limited motor function including localizing stimuli and automatic movements such as scratching. The *persistent vegetative state* is characterized by complete absence of self or environmental awareness but with preserved capacity for stimulus-induced or spontaneous arousal. Sleep–wake cycles are preserved. The *locked-in syndrome* is a mimic of altered consciousness. Because of damage to efferent motor tracts, patients appear to lack responsiveness but have preserved consciousness, cognition, and emotion; they are tetraplegic and are unable to speak. Sometimes vertical eye movements are the only remnant of voluntary motor activity. This syndrome is often due to pontine infarction, but high cervical spinal cord injuries and severe drug-related dystonias may simulate the syndrome. Clinicians may underestimate the degree of awareness in patients with altered mental status and it is best to assume that some element of comprehension is preserved.

Pathophysiologic causes of coma may range from dysfunction at the cellular level to grossly visible pathologic changes of the brain. Impairment at the larger structural level includes focal injury to central nervous system (CNS) structures, which may result from increased intracranial pressure, reduction in cerebral perfusion pressure, or from direct destruction due to tumors, trauma, stroke, or hemorrhage. Dysfunction of many of the body's organ systems may impair CNS function at a cellular level. This may occur with hypothyroidism or adrenal insufficiency, with disturbances of electrolyte regulation such as hypo- or hypernatremia, hypercalcemia, or other metabolic disturbances, such as hypoglycemia or hyperosmolar states. Illnesses resulting in renal or hepatic damage may cause encephalopathies with impairment of neurotransmitters likely being the mechanism. Hypoxia from pulmonary or cardiac etiologies may also affect CNS function.

Hypotension with decreased cerebral perfusion may result from a primary cardiac etiology, sepsis, or volume loss from gastrointestinal (GI) bleeding or trauma. External environmental or toxic insults may also cause CNS depression through a direct effect at the cellular level or secondarily through damage to specific organ systems.

In general, when the CNS function is impaired at the cellular level, global CNS dysfunction follows and focal clinical findings such as hemiparesis or abnormal extraocular movements are not present on examination. Some notable clinical exceptions are hypoglycemia, hyperglycemia, and hepatic failure where focal findings may be seen. Pupillary light reflexes generally remain intact with toxic and metabolic causes of altered mental status, except when the CNS depression is caused by certain toxins that affect pupillary size, such as anticholinergics or opiates.

There are often focal findings on examination when a destructive process causes structural damage to a specific area of the CNS. Localized lesions of the CNS may also induce an additional injury process such as cerebral edema secondary to a tumor or hemorrhage, or vasospasm following aneurysmal subarachnoid hemorrhage.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of coma is extensive (Table 11.1). In the emergency department (ED), history and physical examination will help narrow the possibilities. History will often suggest a likely cause and all sources—family, witnesses, emergency medical service (EMS) providers, and medical records—should be considered. The emergency physician must identify reversible causes and remediate injury when possible while simultaneously pursuing a strategy to sort the patient with altered mental status into structural, metabolic, infectious, toxic, environmental, or other etiologies. An organized approach is necessary to detect easily remedial cause, prevent ongoing neurologic injury, and determine a diagnostic strategy.

TABLE 11.1
Differential Diagnosis of Altered Mental Status and Coma

Metabolic Causes
Electrolyte disorders
Hypernatremia
Hyponatremia
Hypercalcemia
Hypoglycemia
Hypermagnesemia
Diabetic ketoacidosis
Hyperglycemic hyperosmolar states
Hypothyroidism
Thyrotoxicosis
Adrenal insufficiency
Hepatic encephalopathy
Uremia
Thiamine deficiency (Wernicke encephalopathy)

Infectious Etiologies
Meningitis
Encephalitis
Intracranial abscess
Sepsis

Vascular Causes
Hypertension
Hypotension
Vasculitis
Cerebrovascular accident (thrombotic or hemorrhagic)
Subarachnoid hemorrhage (aneurysm or AVM)

Neurologic Structural Etiologies
Tumor
Hydrocephalus
Intracerebral hemorrhage

Seizures
Status epilepticus

Trauma
Subdural hematoma
Epidural hematoma
Cerebral contusion
Diffuse cerebral edema

Toxicologic Etiologies
Carbon monoxide
Ethanol, methanol, isopropyl alcohol, ethylene glycol
Drug abuse and overdose

Environmental Etiologies
Heatstroke
Hypothermia
High-altitude cerebral edema (HACE)
Near drowning
Dysbarism

Hypoxia and Hypoglycemia

In the evaluation of any patient with mental status changes or coma, failure of substrate supply necessary for neuronal function (oxygen, glucose) must always be considered. After briefly evaluating for hypoxia and initiating oxygen supplementation, hypoglycemia, another common cause of altered mental status that is readily

detectable and reversible, must be considered. Hypoglycemia is most common in patients on insulin therapy. It may be due to dosage errors, missed meals, a change in exercise pattern, or erratic absorption from injection sites. Interaction with other drugs, such as β-blockers or salicylates, may potentiate hypoglycemia. The oral hypoglycemic agents may also produce hypoglycemia. Many of these agents have a long duration of action, and pharmokinetics may change with overdosage, so the patient should be carefully observed for recurrent hypoglycemia or admitted. Hypoglycemia may also occur with alcohol intoxication and some other toxins. Renal or hepatic disease and other processes such as sepsis also increase the risk that a patient will develop hypoglycemia.

When blood glucose levels fall to a level of 50 to 70 mg/dL, symptoms of CNS excitation may appear; these may include anxiety, tremor, sweating, and occasionally hallucinations. As the glucose level falls further, progressive CNS depression and coma occur. Brainstem reflexes are preserved until late. Loss of consciousness is usually preceded by a period of confusion but may happen suddenly. Hypoglycemia may also cause focal neurologic signs including hemiparesis and should be considered early in the differential diagnosis of stroke. Other described signs of hypoglycemia include hyperreflexia, pupillary dilation, tachycardia, and primitive movements such as sucking movements of the lips, forced grasping, and extensor plantar responses.

Hyperglycemia

At the other end of the glycemic spectrum are the hyperglycemic conditions that may also cause altered mental status. Diabetic ketoacidosis (DKA) may be seen as the initial presentation of new-onset juvenile diabetes, in a known diabetic with poor compliance, or in a diabetic with a precipitating stressful event such as infection. A history of polyuria, polydipsia, nausea, vomiting, or abdominal pain may be obtained. Acetone-tinged breath or Kussmaul breathing may be present. Hyperosmolar hyperglycemic nonketotic coma typically occurs in an older patient with undiagnosed diabetes or

type II diabetes experiencing another intercurrent illness. Gram-negative pneumonia, uremia with vomiting, or acute viral illnesses are the most commonly reported predisposing conditions. In contrast to DKA, the patient often has a longer period of symptoms before presentation.

Adrenal and Thyroid Emergencies

Though unusual in clinical practice, adrenal and thyroid emergencies are important to consider in the differential diagnosis of coma since treatment may be lifesaving. In a patient with suspected myxedema coma, history may reveal symptoms or prior treatment of hypothyroidism. Radioactive iodine treatment is associated with a relatively high incidence of delayed hypothyroidism. A history of noncompliance with thyroid medications may be obtained. Clinically, mild hypothermia, hypotension, and bradycardia may be present as well as periorbital and pretibial nonpitting edema. On neurologic examination, the muscle relaxation phase of the deep tendon reflexes is often described as delayed. Laboratory studies may reveal hyponatremia, hypo-osmolarity, and an elevated creatine phosphokinase as well as abnormalities in the thyroid laboratory panel.

Thyroid storm rarely presents as coma. Confusion, agitation, or occasionally hallucinations are more common. Temperature above 38°C (hyperthermia), tachycardia, and cardiac failure may be present. Often there is a precipitating event such as trauma or infection.

Acute adrenal crisis may occur because of an acute exacerbation of chronic adrenal insufficiency, rapid cessation of chronic steroid medications, or adrenal hemorrhage. Physiologic stressors such as infection, trauma, or surgery may all precipitate an adrenal crisis. Nausea, vomiting, abdominal pain, and fever may be present. Hypovolemic shock may develop and the mental status may deteriorate into lethargy or coma. A patient with known adrenal insufficiency or who is taking glucocorticoid replacement

medication may not develop dehydration and hypotension until late in the course of adrenal crisis.

Hypertension

There is no distinct level of hypertension that correlates with mental status changes. In a patient with altered mental status and severe hypertension, possible causes include intracerebral hemorrhage or hypertensive encephalopathy. Hypertension is often present in subarachnoid or intracerebral hemorrhages. Hypertension, headache, altered mental status, and focal findings such as hemiparesis or aphasia are consistent with intracerebral hemorrhage. Subarachnoid hemorrhages may present with diffuse neurologic findings on examination and mental status changes range from confusion to coma. The classic history is the sudden onset of a severe headache associated with nausea and vomiting. A patient may give a history of prodromal headaches in the preceding weeks. In a small number of patients with subarachnoid hemorrhage, the computed tomography (CT) scan is normal. If a subarachnoid hemorrhage is suspected and the CT scan is negative, a lumbar puncture must be performed. Hypertensive encephalopathy is a diagnosis of exclusion. Funduscopic changes such as papilledema or hemorrhages will be present. Posterior reversible encephalopathy syndrome (PRES) is associated with uncontrolled hypertension and visual changes. MRI is the confirmatory procedure showing changes suggesting white-gray matter edema involving the posterior cerebral regions.

Toxic Causes

There are a wide variety of medications and illicit substances that may produce mental status changes. Correct diagnosis requires obtaining an adequate history and recognizing the toxidromes that appear in some specific toxic exposures.

High doses of benzodiazepines may produce sedative–hypnotic effects. Cardiac depression is usually minor, as is respiratory depression. However, respiratory depression may become severe if

benzodiazepines are combined with other CNS depressants, in the elderly, or in patients with underlying respiratory disease.

Opiates and barbiturates may produce severe respiratory depression and hypotension. Miosis is usually present with opiates (exceptions are meperidine, propoxyphene, and tramadol, with which pupils may be of normal size). Pulmonary edema is most commonly seen with intravenous (IV) heroin overdose but may occur in other opiate or barbiturate intoxications. Cutaneous bullae and hypothermia may occur with sedative–hypnotic overdoses and are associated with prolonged unresponsiveness.

Ethanol intoxication may produce a somnolent, difficult-to-arouse patient with varying degrees of respiratory depression. Ingestion of ethanol substitutes such as methanol, ethylene glycol, or isopropyl alcohol also occurs in the alcoholic or with intentional overdoses. Isopropyl alcohol can present as stupor in a known alcoholic or as an encephalopathy of unknown cause in persons with hidden addictions. In addition to CNS depression, GI effects (abdominal pain, gastritis, nausea, or vomiting) and cardiac toxicity can occur. The major metabolite of isopropyl alcohol is acetone; as such, the severe anion-gap metabolic acidosis seen in methanol and ethylene glycol poisoning is not seen with isopropyl poisoning. In methanol intoxication, the patient may present with visual changes ranging from blurred vision to blindness. Calcium oxalate crystals may be present in the urine of patients who have ingested ethylene glycol. The osmolal gap should be calculated and any discrepancy that cannot be attributed to ethanol ingestion alone should prompt consideration of ingestion of other osmotically active substances.

Ingestion of tricyclic antidepressants may produce rapid mental status changes, coma, seizures, and cardiovascular effects. Sinus tachycardia is most commonly noted. The QRS complex may become widened and atrial or ventricular dysrhythmias may occur. Anticholinergic effects such as delayed gastric emptying, decreased bowel sounds, and mydriasis may be present.

A history of tinnitus and vomiting may lead the clinician to suspect salicylate intoxication. Chronic salicylism in the elderly is often subtle. Respiratory alkalosis in adults or metabolic acidosis in

children may be seen. Acetaminophen and salicylate levels should be obtained in the patient suspected of an intentional ingestion. Carbon monoxide or cyanide toxicity should be suspected if the patient has been in a fire. Carbon monoxide poisoning should also be suspected in colder weather, particularly if the patient or others in the household have experienced flulike symptoms. Arterial blood gas levels may show a normal PO_2, but the measured hemoglobin saturation may be low. Arterial blood co-oximetry should be performed to quantitate carboxyhemoglobin and to look for other abnormal hemoglobin complexes.

Seizures

Convulsive seizures are easily recognized. The clinician must remember that the seizures may be a symptom of a disease process, injury, ingestion, or withdrawal, and that epilepsy (unprovoked recurrent seizures) is largely a diagnosis of exclusion. Following generalized convulsions, patients often have altered mental status. Patients are frequently described as *postictal,* yet there is no definition or test for this condition or any consensus as to the duration. However, the clinician must always consider a broad differential diagnosis of altered mental status or complications of the seizures, particularly if the patient does not have improvement of level of consciousness over 20 to 30 minutes following cessation of the convulsive activity. Should the patient's mental status not improve following cessations of generalized convulsions, the possibility of subtle status epilepticus must be considered. Subtle status epilepticus, also known as *epileptic encephalopathy* and by other terms, is present when the abnormal electrical seizure activity is continuing in the absence of motor movements. Nonconvulsive status epilepticus, sometimes used as a synonym, may also present with prolonged confusion or altered mental status. These uncommon nonconvulsive seizures with clouded consciousness or confusion require a high level of suspicion for recognition. Typically there is a history of seizures. Neurology consultation with electroencephalographic evaluation may be required for recognition.

DIAGNOSTIC APPROACH

The initial assessment of a patient presenting with coma or transient loss of consciousness should be performed in a relatively short time and combined with stabilization procedures. The state of consciousness is determined by assessing functions of both cerebral cortical and the ascending reticular activating system. Key observations will often help determine whether the disease is of the brainstem or cerebral hemispheres.

Before the unresponsive patient arrives in the ED, field personnel should assist with airway support and administer oxygen. The spine is immobilized and stabilized if there is the possibility of trauma. IV access is obtained, and cardiac monitoring is initiated. Point-of-care glucose testing should be performed if possible, and the patient should receive glucose if hypoglycemic or if there is suspicion of hypoglycemia. Support procedures not performed by field personnel should be quickly initiated in the ED.

The history, physical examination, and serial neurologic examinations are all of importance. However, life-threatening and reversible processes causing coma or altered level of consciousness should be considered before detailed history and physical examinations are performed; these include hypoxia, hypoglycemia, poisoning, infections, and increased intracranial pressure. Evaluation of the cardiorespiratory status and blood glucose takes precedence over investigation of other potential etiologies. Glucose administration to a patient with stroke or other brain injury may theoretically worsen the injury process and should be avoided when possible by using reliable point-of-care testing.

Obtaining historical information proceeds with patient stabilization. Information should include the abruptness of change in mental status, preceding events, medical history, current medications, and use of toxic agents. The clothing should be checked for suicide notes and drug bottles, and any medical alert tags should be noted. After the ABCs have been addressed, the patient is evaluated for signs of injury, including pupillary asymmetry and reactivity, hemotympanum, and other signs of head

trauma. Assess vital signs including a core body temperature. The level of consciousness is documented, and the Glasgow Coma Scale is usually used to roughly quantify the patient's condition though limitations of the scale have been noted (see Chapter 22). Recently the FOUR score has been validated for use in comatose patients. The FOUR score includes some assessment of brainstem reflexes and may find use in the ED (Table 11.2).

TABLE 11.2
The Four Score

Eye Response
4 = eyelids open or opened, tracking, or blinking to command
3 = eyelids open but not tracking
2 = eyelids closed but open to loud voice
1 = eyelids closed but open to pain
0 = eyelids remain closed with pain

Motor Response
4 = thumbs-up, fist, or peace sign
3 = localizing to pain
2 = flexion response to pain
1 = extensor response to pain
0 = no response to pain or generalized myoclonus status

Brainstem Reflexes
4 = pupil and corneal reflex present
3 = one pupil wide and fixed
2 = pupil or corneal reflex absent
1 = pupil and corneal reflex absent
0 = absent pupil, corneal, and cough reflex

Respiration
4 = not intubated, regular breathing pattern
3 = not intubated, Cheyne–Stokes breathing pattern
2 = not intubated, irregular breathing
1 = breaths faster than ventilator rate
0 = breathes at ventilator rate or apnea

Adapted from Wijdicks EF, Bamlet WR, Maramattom BV, et al. Validation of a new coma scale: The FOUR score. *Ann Neurol.* 2005;58:585–593.

Respirations should be briefly observed before deciding if ventilatory support is necessary. Apneustic breathing, characterized by deep inspiration followed by a long apneic phase and only a few breaths per minute, suggests brainstem failure. Irregular ataxic breathing is an ominous sign of brainstem failure. Cheyne–Stokes respirations may be due to bilateral dysfunction of structures deep in the cerebral hemispheres, bilateral cerebral infarctions, congestive heart failure, hypertensive encephalopathy, or other systemic causes.

Examination of the patient's eyes may be the single most important assessment in the evaluation of coma. Coma by definition is an eyes-closed unresponsive state. An unresponsive patient who has open eyes may actually be in a persistent vegetative state or have the locked-in syndrome. The fundi are examined for evidence of papilledema or lack of venous pulsations, which might suggest increased intracranial pressure.

The shape and size of pupils and their reactions are recorded. Reactive asymmetric pupils differing in size by 1 to 2 mm (physiologic anisocoria) may be seen in 10% of normal people. In cases of toxic or metabolic coma, pupils are likely to remain small, equal, and reactive. A fixed, unilaterally dilated pupil in an unresponsive patient suggests a structural cause of coma and uncal herniation. Local trauma or topical mydriatics can also cause unilateral pupillary dilation. Stimulation of the cornea tests another brainstem reflex arc and will cause an eye to blink if the fifth and seventh cranial nerves are intact.

The patient with a possible head or neck injury presents a problem in testing doll's eye maneuvers (oculocephalic reflex) because the neck should not be manipulated. Cold water caloric testing (oculovestibular reflex) may be performed without moving the neck if additional testing for unresponsiveness or testing for additional brainstem reflexes is needed. The slow phase of caloric eye movements tests brainstem functions, and the fast phase tests cerebral functions. The rapid eye movements of nystagmus are present only in an awake patient with functioning cerebral cortices. The presence of nystagmus in an apparently unresponsive patient

indicates cortical functioning and in fact suggests psychogenic or pseudocoma. Caloric testing, performed correctly in a comatose patient, may help differentiate a brain stem lesion from a hemispheric lesion. If the brainstem is functioning normally in a comatose patient, the eyes will deviate conjugately toward the side where ice water is flushed into the ear and nystagmus will be absent. Cold calorics involve the vestibular system, the afferent functions of cranial nerve VIII, brainstem interneurons, and efferent functions of cranial nerves III (abduction of eyes) and VI (abduction).

The neck is flexed to check for nuchal rigidity if there is no contraindication or possible injury. Rigidity of the neck or resistance to flexion suggests meningeal inflammation due to meningitis or subarachnoid hemorrhage. However, the absence of nuchal rigidity cannot reliably exclude meningitis or other processes of meningeal irritation.

The patient's posture is observed, and the response to stimulation is noted. Decorticate and decerebrate posturings are abnormal postures that may be present in the deeply comatose patient. *Decorticate* or *flexor* posturing is characterized by flexion of the upper extremities with extension in the lower extremities and suggests injury to the brain above the level of the midbrain. *Decerebrate* or *extensor* posturing is characterized by arms that are extended, adducted, and hyperpronated, and legs that are extended with feet plantar flexed. Decerebrate posturing occurs in patients with infarcts of the brainstem above the level of the midpons and also in patients with large cerebral hemorrhages that destroy or compress the lower thalamus and midbrain. This motor pattern typically emerges with lesions of the internal capsule or cerebral hemisphere that interrupt the corticospinal pathways. Clinical disease patterns often cloud the demarcation between flexor and extensor posturing, and motor responses may shift back and forth depending on the location of the lesion and pressure effects on the upper brain stem.

The diagnostic approach to patients with coma or alterations in consciousness must be systematic. Orderly evaluation, with

simultaneous stabilization, is of the utmost importance. Early recognition and correction of reversible causes and prevention of further brain damage by definitive intervention are the basic principles of treatment in patients with altered consciousness. There are three primary pathologic processes that produce coma: expanding mass lesions that secondarily destroy the reticular activating system; brain stem lesions that directly damage the reticular activating system; and diffuse toxic, metabolic, or infectious processes that disrupt brain function globally. CT scanning will aid in identifying lesions that need neurosurgical treatment. In carbon monoxide poisoning, patients immediately receive high-flow oxygen. Patients suspected of meningitis receive IV antibiotics promptly when the diagnosis is considered. Patients intoxicated with ethanol receive supportive care and careful observation, and clinical determination that head injury or methanol, ethylene glycol, or isopropyl alcohol is not responsible for their presentation. In addition to general supportive care, metabolic causes, such as hypothyroidism, adrenal insufficiency, and electrolyte abnormalities receive specific treatment.

CRITICAL INTERVENTIONS

- Suggested steps in the management of the comatose patient are as follows:
- Assess the ABCs, establish and maintain the airway, and protect the patient from aspiration.
- Administer oxygen and provide ventilation as needed.
- Establish IV access and support circulation.
- Draw blood for rapid glucose determination. Other laboratory evaluation may include electrolytes, calcium, and renal and liver function; drug screen; arterial blood gas determination; complete blood count; thyroid function studies; or platelet count, depending upon the clinical situation.
- Interventions are tailored to the individual patient. If indicated by the rapid glucose determination, glucose should be administered as 25–50 mL of 50% dextrose solution to adults

and 2 mL/kg of 25% dextrose solution to children. In patients with possible thiamine depletion (alcoholics and those with other causes of chronic malnutrition), 100 mg thiamine should be administered intravenously. If a narcotic toxidrome is present or if a narcotic overdose is suspected, 2–4 mg of naloxone should be given intravenously in adults (0.01–0.1 mg/kg in children). In cases of suspected elevated intracranial pressure, measures to transiently decrease intracranial pressure including hyperventilation to reduce pCO_2 to about 35 mm Hg and administration of IV mannitol (0.5–1 g/kg) should be performed. Fluid restriction may be necessary; cerebrospinal fluid may need to be drained by intraventricular catheter by consultants. Empiric antibiotic coverage should be promptly administered in cases highly suspicious of meningitis. Antibiotic coverage should not be delayed by the diagnostic workup (i.e., inability to perform lumbar puncture due to delay in obtaining a head CT). If generalized seizures are present, a benzodiazepine (lorazepam or diazepam) is considered the initial drug of choice (see Chapter 156). The Glasgow Coma Scale, FOUR score, or other assessments are recorded.

- An electrocardiogram should be obtained, pulse oximeter applied, and a Foley catheter placed. If extreme hypothermia or hyperthermia is present, the cause of this should be sought and appropriate environmental issues initiated bring the temperature toward normal. An exception to this is the patient with return of spontaneous circulation after cardiac arrest: Institution of therapeutic hypothermia may be indicated. After the initial treatment of reversible causes and stabilization, definitive workup and therapy are instituted to prevent further CNS damage. In addition to diagnostic laboratory studies, plain radiographs (cervical spine series, chest x-ray), and head CT scan may prove helpful. CT scanning has assumed a prominent role in the evaluation of the comatose patient because of its accessibility and the ability to detect hemorrhage, edema, and masses. Lumbar puncture should be performed in suspected cases of

meningitis, encephalitis, or subarachnoid hemorrhage; this typically follows a cranial CT. MRI may be useful in some cases but is typically not available on an urgent basis.

DISPOSITION

All patients with significantly altered mental status require admission for continued evaluation and treatment after diagnostic evaluation. Consultation is required on any potentially operable focal lesions, and immediate contact with a neurosurgeon or transfer to an appropriate facility is essential. When transferring comatose patients, it is important to provide advanced life support care. Such patients generally require definitive airway control before transfer. In patients in whom there is no surgically treatable disease, consultation with either a neurologist or internist for intensive care unit admission is indicated if a rapidly reversible cause of the coma is not identified.

Common Pitfalls

- Failure to check a bedside glucose level in all patients with altered mental status.
- Delaying neurosurgical or neurologic consultation in patients with a focal abnormality requiring immediate intervention.
- Delaying the establishment of an airway, cardiovascular support, and provision of adequate oxygen and glucose to the patient with severely altered mental status.
- Failure to reexamine the patient.
- Ascribing alteration in mental status to postictal state.

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CHAPTER 12 Headache

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CLINICAL PRESENTATION

Headache is the reason for approximately 2% of all emergency department (ED) visits (1). This large number of patients can be divided into two groups—those with benign causes (≥95%) and those with treatable illnesses that are life, limb, vision, or brain threatening (≤5%) (1,2). These two groups are not always easily distinguished, and delay in the diagnosis of meningitis and subarachnoid hemorrhage (SAH) is an important reason for malpractice payments in emergency medicine (3).

The brain parenchyma is insensate (4). Head pain results from tension, traction, distention, dilation, or inflammation of the pain-sensitive structures external to the skull, portions of the dura, and the blood vessels. Because all of these mechanisms are likely mediated by a final common biochemical pathway resulting in pain, a favorable response to analgesics, or even the more specific antimigraine agents, should not be used to judge the cause of an individual headache (5).

These basic facts highlight two points: Headache is common, and the potential for serious diagnostic error exists. Given that emergency physicians work under both time and resource utilization pressures, physicians must develop a logical, practical, and accurate approach to distinguish between the two groups of patients (6,7).

Physicians have three tools to make this critical distinction: The history, the physical examination, and diagnostic tests.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of headache can be organized in several ways. The International Headache Society method (Table 12.1), although comprehensive, is cumbersome for use in the ED. Another method of sorting the differential diagnosis is by temporal pattern. For example, is the current headache a chronic recurring one or is it a new-onset unusual event? Still a third method, and one that is consistent with the way emergency physicians work, is the division of headaches into the two groups listed previously. The problems that are life, limb, brain, or vision threatening are referred to as cannot-miss diagnoses (6,8). These disorders result in serious morbidity or mortality if untreated (Table 12.2).

TABLE 12.1
International Headache Society Classification

Diagnostic Group: Headache Associated with	Comments
Migraine	Requires five or more attacks of a specific nature. For migraines with neurologic deficits (e.g., ophthalmoplegic), other etiologies should be excluded
Tension type	Requires 10 or more attacks of specific nature. Absence of nausea, vomiting, and photophobia
Cluster and chronic paroxysmal hemicrania	Always unilateral. Periorbital location lasting minutes to hours. Associated with eye, nose, or face symptoms (e.g., rhinorrhea)
Miscellaneous headaches unassociated with structural lesions	This group includes a variety of brief (idiopathic stabbing headache), situational (cough, exertional, coital) headache syndromes
Head trauma	This group includes the minor postinjury headaches
Vascular disorders	A very important group for emergency physicians, which includes brain ischemia and infarction and all forms of intracranial hemorrhage, venous sinus thromboses, giant cell arteritis, arterial dissections, and hypertensive encephalopathy
Nonvascular intracranial disorders	Includes idiopathic intracranial hypertension, post-LP headache, and headaches from meningitis, encephalitis, and brain abscess and tumor
Substances or their withdrawal	Includes drugs and food additives (e.g., monosodium glutamate headache, or Chinese restaurant syndrome); also includes headache from carbon monoxide poisoning
Noncephalic infection	Includes pain due to febrile illnesses (e.g., pyelonephritis, pneumonia, and acute viral syndromes)
Metabolic disorder	Includes headaches from hypercarbia or high altitude illness
Disorders of HEENT-associated (includes dental)	Includes narrow angle closure glaucoma. Note that for sinus headache to be confidently diagnosed, specific criteria must be followed. Chronic sinusitis should not cause headache
Cranial neuralgias, nerve trunk and deafferentation pain	Most of these are cranial neuropathies and herpes zoster
Not classifiable	Others

From Goldstein JN, Camargo CA Jr, Pelletier AJ, et al. Headache in United States emergency departments: Demographics, work-up and frequency of pathological diagnoses. *Cephalalgia.* 2006;26(6):684–690.

TABLE 12.2
“Cannot Miss” Causes of Headache (see Text for Definition)

Diagnosis	Suggestive History and Physical Findings	Diagnostic Testing
Meningitis and encephalitis	Fever, stiff neck, jolt accentuation, altered mental status, seizure	LP (if preceded by a CT because of concern for raised intracranial pressure, give antibiotics before CT)
Subarachnoid hemorrhage	Abrupt onset of severe headache, stiff neck, third nerve palsy	CT scan LP if CT is nondiagnostic
Stroke (ischemic or hemorrhagic)	Abrupt onset and focal neurologic deficit conforming to an arterial territory	CT scan; MRI if available will give more information (should not delay thrombolytic therapy)
Dissection of craniocervical arteries	Neck pain, abrupt onset, variable presence of neurologic deficit	MRA (or conventional angiography)
Hypertensive encephalopathy	Severe (usually chronic) hypertension Often papilledema and other signs of end-organ damage	Careful, titratable lowering of BP to ~25% off the peak BP will decrease the headache
Idiopathic intracranial hypertension	Obese, female patient Papilledema, often sixth nerve palsy	LP (following an imaging study, that by definition will be normal)
Giant cell arteritis	Nearly always age >50 years Symptoms of polymyalgia rheumatica Abnormal scalp vessels on examination	ESR Temporal artery biopsy
Acute angle closure glaucoma	Painful red eye with midposition pupil and corneal edema	Tonometry
Intracranial mass (tumor, abscess, hematoma)	Any neurologic finding, focal or generalized	CT scan; if available, MR will give more information
Cerebral venous sinus thrombosis	Hypercoagulable state of any type	MRI and MRA with venous phase
Carbon monoxide poisoning	Cluster of cases, winter season	COHb level
Pituitary apoplexy	Visual acuity or field abnormalities Known pituitary tumor	MRI

Overall, primary headache disorders such as migraine, cluster, and tension headaches are by far the most common causes of headache (9). Detailed discussions of the primary headache syndromes and the other individual disease entities are discussed in other chapters (Chapters 156 and 157). This chapter focuses on strategies to avoid missing these cannot-miss diagnoses.

DIAGNOSTIC APPROACH

The physician has two parallel and related goals: Correct diagnosis and effective treatment, with the first goal facilitating the second. Not only is it perfectly acceptable to begin treating the pain before the diagnosis is made, but it is preferable. Faster pain control results in greater patient satisfaction and more rapid disposition, and if a subsequent lumbar puncture (LP) is needed, a more relaxed patient.

Because most patients have benign causes of their headaches, and because of the limiting issues of both time and cost, most patients do not require further evaluation beyond history and physical examination. Physicians must decide who requires further evaluation and who can be safely treated and discharged with appropriate follow-up.

All patients with acute headache associated with new neurologic deficits must be evaluated sufficiently to explain the cause of those deficits. The same is true for those with significant abnormalities in the head, eyes, ears, nose, and throat (HEENT) examinations and the vital signs. However, the more common and more difficult situation is the patient whose physical examination is normal. In this group of patients, physicians must use the history, past medical and family history, and other epidemiologic factors to decide upon further evaluation. As with any painful symptom, the standard attributes of the pain—location, severity, quality, onset, timing and duration, associated symptoms, alleviating and exacerbating factors—are used to try to make the distinction between benign and cannot-miss diagnoses. Each of these factors must be factored into the equation. There is no single response to any single question that automatically triggers a workup.

The *location* of pain is less helpful in making this distinction than it is with other types of pain; there is significant overlap between benign and serious causes (8). Some recommend working up patients whose headaches are consistently on the same side (10). *Severity* of pain also has limitations. Although the "worst-of-life" headache suggests a more serious problem, most severe headaches in the ED have benign causes (11,12). This is partly because of the variability of patients' pain thresholds and partly because overall, most headaches have benign causes. That said, increasing severity should lower one's threshold for further diagnostic testing, and most patients with the abrupt onset of a worst-of-life headache should be evaluated for SAH (8). Defining the *quality* of pain is crucial (8). It is important to ask in detail about the patient's prior headaches. A new headache that is qualitatively unique and unusual for the patient may be more significant than the "worst-ever" headache in another patient whose current headache is similar in quality to prior episodes, only more severe. *Onset* is another important feature that drives decision-making. Abrupt or "thunderclap" onset suggests intracranial hemorrhage or cerebral venous sinus thrombosis, although once again, there is a broad differential diagnosis, and most abrupt-onset headaches are benign (13). For abrupt-onset headaches, the activity at onset sometimes suggests the etiology, for example, in coital headache or benign exertional headache (14,15). However, although these activities are sensitive for the corresponding diagnoses, they are not specific; SAH must be ruled out. Importantly, many SAH patients develop their headache during quiet activity or even sleep (16).

Defining the *timing* and *duration* of the pain is useful. Worrisome features include new acute headache, or a subacute headache that is increasing in severity. Long-standing duration (years) of a headache or a similarly long history of intermittent headaches is less likely to be a cannot-miss cause, assuming that sufficient history is taken to ensure that there is nothing new or different to the prior headache pattern. Very fleeting headaches, termed *jabs and jolts,* that last seconds are generally benign (17).

Similarly, *associated symptoms* can be important. Nausea and vomiting occur with migraine but also suggest intracranial mass, blood, or infection. Again, comparison with prior headaches is important. The significance in a patient with migraines who always vomits with them is different from the migraineur who is now vomiting for the first time. The same is true of photophobia. Visual abnormalities suggest migraine, idiopathic intracranial hypertension, temporal arteritis, and pituitary apoplexy. Diplopia from a pupil-involving third nerve palsy suggests a cerebral aneurysm or other mass (18). Diplopia from a sixth nerve palsy is seen with elevated or abnormally low intracranial pressure of any cause, presumably due to stretching of the sixth cranial nerve. Associated syncope, seizure, or any focal neurologic symptoms associated with a new headache should generally prompt an evaluation.

Exacerbating and *alleviating* factors are less helpful with headache. For example, the classic history that a headache from brain tumor increases on awakening is neither specific nor sensitive (19). It is also seen in patients with chronic lung disease and hypercarbia (which worsens during sleep). Headache from intracranial hypotension, either spontaneous or post-LP tends to worsen on standing upright, and headache due to acute sinusitis often worsens on bending forward with the head dependent (20). In terms of alleviating factors, diagnostic significance should not be ascribed to pain relief, even with over-the-counter medications. New medications or the discontinuation of a medication may also be diagnostically relevant in some patients (21).

Patients frequently use the word *migraine* loosely to refer to any bad headache or *sinusitis* to refer to any frontal headache. Unless these diagnoses have been substantiated by a prior medical evaluation, it is preferable to simply use the less specific but more accurate word *headache* (6). Sinusitis is a relatively uncommon cause of headaches; many of these patients actually have migraines (22,23). Tension headaches and migraines are very common. The lifetime incidence of migraine is about 11% (24); therefore, even patients with true histories of tension headaches or migraines will occasionally develop new headaches of another cause. This fact

underscores the importance of carefully exploring the difference between a patient's prior headache and the one that led to the current ED visit.

The epidemiologic context is important. A family or past history of cerebral aneurysm increases the likelihood of an aneurysmal cause. Poorly treated hypertension may lead to hypertensive encephalopathy. Vascular risk factors can result in stroke. Hypercoagulability or a past or family history of thromboembolic events should raise the possibility of cerebral venous sinus thrombosis. Obesity increases the possibility of idiopathic intracranial hypertension (pseudotumor cerebri), especially in women. New-onset headache at older ages also suggests a secondary cause (1,2). Most migraine headaches begin before age 30, and very few begin after age 50. Therefore, physicians must have a lower threshold to work up older patients with new headaches. Specifically, giant cell arteritis, tumors, subdural hematoma, and medication-related headaches should be considered in this group. Patients who are HIV positive or have a history of cancer represent other groups in whom a lower threshold to pursue evaluation seems justified. Winter season and common source clusters are associated with carbon monoxide poisoning. Although migraine is the most common cause of headache in pregnancy, other disorders such as stroke, SAH, cerebral venous sinus thrombosis, and of course eclampsia must also be considered (25).

The International Headache Society definition of tension and migraine headaches requires multiple episodes to definitively diagnose migraine or tension headache (26). Migraine is defined by 5 or more episodes of a throbbing headache that has certain characteristics (7), and tension headache is defined as 10 or more episodes. Although all of these patients must have their first headache at some point in time, most do not present to the ED. Therefore, diagnosing a patient with a new, different headache with a primary headache disorder opens the door to misdiagnosis.

The physical examination starts with the general appearance and vital signs. General appearance can be deceiving and is, at least in part, a function of a given patient's pain threshold. Nevertheless, the

patient who is shielding the eyes from the light, while consistent with migraine, also suggests meningeal irritation. Fever is not a symptom of migraine and suggests infection or a several-day-old SAH.

Isolated hypertension is an uncommon cause of headache; however, it is a common result of headache. Patients with headache may have a high blood pressure reading due to the pain, stress, or the presence of underlying intracranial pathology. Reducing the blood pressure and treating the pain pharmacologically may make the patient look and feel better without identifying the underlying etiology. In some specific causes of headache, such as stroke, overzealous blood pressure reduction can be detrimental (27). On the other hand, in hypertensive encephalopathy (elevated blood pressure with signs of end-organ damage), the headache is directly related to the elevated pressure. In these cases, reduction of the blood pressure by about 25% of its peak value is usually followed by rapid improvement of the patient's symptoms. The emergency physician should have a low threshold for brain imaging (and possibly LP) in patients with hypertension and a headache that is otherwise worrisome based on onset, severity, quality, and associated symptoms.

The emergency physician should also look for signs of meningeal irritation. Meningismus, stiffness on passive flexion of the neck (to be distinguished from just pain without stiffness on neck flexion) results from infections (meningitis) or irritation (SAH). However, this finding is not reliably present, and its absence does not exclude either condition. The same is true of Kernig and Brudzinski signs (see Chapter 185). One physical finding that has been found to be more reliable in meningitis is jolt accentuation. This sign is positive if, when the patient is asked to turn their head horizontally (as if shaking their head "no") two to three rotations per second, the baseline headache increases (28).

The HEENT examination may reveal the headache's cause (Table 12.3). Vesicles on the scalp, tip of the nose, or external ear canal suggest herpes zoster. Scalp lesions suggest a first or second cervical root involvement; tip of the nose lesions suggest that the first

division of the trigeminal nerve is involved and should prompt a careful slit-lamp examination to detect corneal involvement. Vesicles in the ear canal are associated with the Ramsay Hunt syndrome (herpes zoster infection causing seventh nerve palsy). Temporal artery tenderness, nodularity, or thickening is seen with giant cell arteritis. A red eye with an edematous cornea and midposition pupil suggests narrow angle closure glaucoma. Proptosis or chemosis suggests a cavernous sinus thrombosis.

TABLE 12.3
Common HEENT Findings that Suggest Particular Diagnoses

Finding	Diagnosis	Comments
Vesicles on scalp	Herpes zoster of upper two cervical roots or V-1 root of trigeminal nerve	Usually unilateral pain Must examine scalp carefully
Vesicles on tip of nose	Herpes zoster of V-1 root of trigeminal nerve	Carefully examine the cornea with slit lamp
Vesicles in external ear canal	Ramsay Hunt syndrome	Carefully examine the seventh and eighth cranial nerves
Temporal artery nodules, tenderness or thickening	Giant cell arteritis	Ask patients about visual symptoms; consider empiric steroid use and arranging temporal artery biopsy
Red eye and corneal edema	Acute narrow angle closure glaucoma	Pupil is usually midposition Consult ophthalmology
Proptosis of eye Chemosis of conjunctiva	Cavernous sinus thrombosis	Neurosurgical consultation and MRA with venous phase

The physician should perform a complete neurologic examination on patients with headache. New neurologic abnormities should trigger a workup beyond the history and physical examination, although some migraine patients, specifically those with aura, will have neurologic deficits. An abnormal mental status with a new

headache always must be explained and suggests increased intracranial pressure or a diffuse process such as meningitis, encephalitis, or severe carbon monoxide poisoning. Several cranial nerve findings suggest particular causes of a headache (Table 12.4).

TABLE 12.4
Common Cranial Nerve Findings of Diagnostic Significance in Patients with Headache

Finding	Diagnosis	Comments
Decreased visual acuity	Giant cell arteritis Acute narrow angle closure glaucoma	Carefully examine the eye and the temporal arteries Send ESR in patients >50 years old
Visual field cut	Mass lesion Pituitary apoplexy	Location depends on the specific field cut (this may be a parenchymal problem rather than a cranial neuropathy)
Third nerve palsy	SAH Cavernous sinus thrombosis	Check the pupil (usually involved in SAH; usually spared in "diabetic" third nerve palsy)
Sixth nerve palsy	Any condition associated with increased or decreased ICP Basilar meningitis (e.g., Lyme, tuberculous, cryptococcal, etc.) Cavernous sinus thrombosis	Look for papilledema Consider pseudotumor or cerebral venous sinus thrombosis Consider LP if brain imaging is negative
Direction changing nystagmus	Cerebellar or brainstem stroke	This can occur with any central lesion causing vertigo
Lower motor neuron seventh nerve palsy	Bell palsy Ramsay Hunt syndrome	This may present with severe ear or retroauricular pain
Eighth nerve palsy (diminished hearing or vertigo)	Ramsay Hunt syndrome	See above; also look for vesicles in the external auditory canal

The remainder of the neurologic examination (power, sensation, cerebellar function, gait, and reflexes) should be performed. Abnormalities in these areas suggest a mass lesion or focal brain ischemia or infarction; the specific findings are a function of the location of the pathology. The ocular fundi should be inspected for signs of raised intracranial pressure, but the appearance of papilledema can be delayed and is not always present. Physicians should also look for venous pulsations in the retina. Their presence is strongly indicative of normal intracranial pressure, while the converse is not true. Two aspects of the neurologic examination that are frequently omitted are visual fields and gait testing. Both are important in that they cover a large amount of neuroanatomic territory. Field cuts are seen in patients with pituitary apoplexy (29). A new headache, especially occipital, associated with ataxia, nystagmus, or other cerebellar findings suggests a cerebellar stroke (30,31). Gait abnormalities may also have an impact on safe disposition from the ED.

Based on the history and physical examination, patients will fall into one of the three categories. The first is patients who have abnormal physical examinations in whom the need for further diagnostic testing is unambiguous. The second is patients whose examinations are normal and whose histories do not suggest the presence of a cannot-miss diagnosis. The last category is patients with normal physical examinations and worrisome histories that trigger further diagnostic testing (Table 12.5). Separating out these last two categories is largely a matter of experience, judgment, and meticulous attention to detail in the history and physical examination.

TABLE 12.5
Factors Suggesting Further Evaluation Should Be Pursued Beyond History and Physical Examination

Headache-Related or Patient-Related Factors	Diseases to be Considered	Evaluation
First or worst headache (HA)	All diseases in Table 12.2	Varies (Table 12.2)
Increasing frequency or severity	Mass lesion	Consider brain imaging
Associated with altered mental status	Elevated ICP	Brain imaging, LP if negative results of imaging, COHb level
	Encephalitis and meningitis	
	Carbon monoxide poisoning	
Associated with new neurologic deficits	Any of the intracerebral diagnoses	Varies, but includes brain imaging
Visual symptoms	Idiopathic intracranial hypertension, pituitary apoplexy, migraine with aura	Brain imaging
		LP for idiopathic intracranial hypertension
		(Note: If visual symptoms classic of migraine aura, other testing may not be necessary)
With fever and meningismus	Meningitis, SAH	LP (CT first in many cases—see text)
New onset after 50 years of age	Tumor, SDH, giant cell arteritis	Brain imaging
		ESR
New onset in HIV-positive patients	Meningitis, lymphoma, opportunistic infections	Varies, but usually includes both brain imaging and LP
New onset in patients with cancer	Tumor or cerebral venous sinus thrombosis	Brain imaging, ideally MRI but CT may suffice

Once the decision has been made to pursue other diagnoses, there are a limited number of tests to be performed. The choice of which tests, and what sequence, is partly a function of the specific differential diagnosis and the intrinsic limitations of the tests. This latter point cannot be overemphasized. Every test, including magnetic resonance imaging (MRI) in acute stroke (32), has some limitations that the physician must factor into the decision making. Again, the response to analgesics of any class must not be assigned any diagnostic significance.

Brain imaging has revolutionized the diagnosis of patients with headache. Computed tomography (CT) scanning and MRI allow diagnoses of conditions much earlier and with far greater precision. CT scanning is widely available and extremely rapid, and there is a great deal of experience with its interpretation among radiologists and emergency physicians. A noncontrast CT scan is extremely sensitive for acute intraparenchymal blood and very sensitive for subarachnoid blood, but small or older subarachnoid bleeds may not be visible. Physicians may miss subtle findings (33). Some tumors and abscesses will not show on a scan performed without IV contrast, although most masses large enough to cause a significant headache will be associated with some abnormality on a noncontrast head CT.

In general, MRI is superior to CT, especially in evaluating vascular and neoplastic lesions, infections, and pathology at the cervicomedullary junction and in the posterior fossa (10). MRI and CT have equivalent accuracy for imaging acute blood (34), but

specific imaging sequences are needed and communication with the radiologist is important. When MRI is required but unavailable, the emergency physician should consider transferring the patient, performing CT with IV contrast, or obtaining neurologic consultation to discuss other options.

MRI permits much greater detail of the brain anatomy and physiology than CT scanning. Blood vessels, both arterial and venous, can now be evaluated by magnetic resonance angiography (MRA). Brain tumor, abscesses, and pituitary apoplexy are easily visible. Carotid and vertebral artery dissections, cerebral aneurysms, and cerebral venous sinus thromboses are best diagnosed with MRA or MR venography. Although MRA is the preferred test, CT angiography (CTA) or venography are rapidly improving and are increasingly useful for diagnosing aneurysms, cervical artery dissections, and cerebral venous sinus thrombosis (35–37). However, no test is perfect. Cases have been described in which a cerebral aneurysm was missed by MRA, despite the fact that both patients presented with third nerve palsies, and the clinician expressed concern for a posterior communicating artery aneurysm to an experienced neuroradiologist, who carefully reviewed the films (38). This underscores the fact that even in the face of negative imaging studies, it is important to pursue hard physical findings. In some cases, the traditional gold standard for vascular pathology—catheter angiography—may be indicated, along with neurologic consultation.

Despite these sophisticated imaging tests, there is still a role for the LP. For cases of suspected SAH in which the CT scan is nondiagnostic, and for suspected meningitis, an LP will establish those diagnoses with nearly 100% sensitivity. However, like all tests in medicine, even the LP has limitations. Rare cases of meningitis can be associated with no white blood cells (39), and late-presenting cases of SAH may have no red blood cells (6,8). After 2 weeks, even xanthochromia may disappear. Measuring the opening pressure may help to distinguish traumatic LP from true SAH, as well as help with the diagnosis of idiopathic intracranial hypertension and cerebral venous sinus thrombosis (6,8).

Guidelines recommend that all patients with a thunderclap headache being evaluated for SAH with a negative CT have an LP (40). Recent studies suggest that sensitivity of CT done within 6 hours of headache onset approaches 100% sensitivity and that in this group of patients, LP may not be necessary (33,41). The best study was a prospective ED study of over 3,000 patients, 8% of whom had SAH (a typical ED population) (41). However, another retrospective article argues for caution; however, it is not clear that many of the patients labeled as having SAH actually had a true SAH (as opposed to an incidental unruptured aneurysm) (42,43). As of 2013, guidelines have not yet been changed. If physicians choose not to perform an LP in rule-out SAH patients who have a negative CT done within 6 hours, they must carefully understand the limitations in this group (classic thunderclap headache presentation, normal neurologic examination, CT interpretation by a competent attending level radiologist) (33,41,44).

On specific occasions, other tests may be diagnostic (e.g., the erythrocyte sedimentation rate [ESR] in giant cell arteritis, tonometry for acute narrow angle closure glaucoma, and carboxyhemoglobin levels in carbon monoxide poisoning, in whom standard pulse oximetry may be falsely normal).

Given the limitations of individual tests, it should be clear that sometimes a series of tests is necessary. For example, if a CT scan is negative in a possible SAH patient, an LP should be performed (see above). If an ESR is normal in an elderly patient with a new headache, the physician should consider performing brain imaging because giant cell arteritis is much less likely. If a CT scan is negative in a patient with a clear-cut focal neurologic finding, an MRI should be considered.

One other test to be considered is a neurologic consultation. Although the emergency physician should be able to diagnose the vast majority of patients with headache who seek care in the ED, there may be times when a neurologist can supply a useful perspective, either in real time or in follow-up. The timing of consultation is a function of the specific differential diagnosis, the pace of the patient's illness, and the availability of that service. In

patients with a new, definite neurologic finding on physical examination and normal results of brain imaging, the physician should strongly consider urgent or emergent consultation to sort out the possibilities.

CRITICAL INTERVENTIONS

- Although rarely required, patients with headache whose level of consciousness is declining should be intubated.
- Patients should be treated aggressively but the response to analgesics should not be used to conclude that the etiology is benign.
- In ill patients with possible bacterial meningitis, CT is not always indicated. However when the clinician decides to do a CT prior to LP, dexamethasone and antimicrobials should be administered and blood cultures obtained BEFORE the CT.
- When lowering the blood pressure in patients with hypertensive encephalopathy, the emergency physician should try to target a blood pressure of about 25% lower than the peak pressure on presentation.
- In pregnant or postpartum women with severe headache, although preeclampsia and eclampsia are the likeliest diagnoses, other possible causes such as posterior reversible encephalopathy, reversible cerebral vasoconstriction syndrome, and venous sinus thrombosis should be considered.
- In elderly patients with new headaches, an ESR should be sent when the diagnosis of giant cell arteritis is considered as it can lead to blindness if untreated.

DISPOSITION

Most patients with headache will be discharged after successful treatment of their acute pain. This includes patients with the diagnoses of primary headache disorders and those who have had a negative evaluation. For patients with suspected SAH, for example, many studies looking at outcomes after negative CT scans and normal spinal fluid examination have all found that these patients do

not develop SAH after this workup. However, because occasional patients are outliers and because abnormal tests are occasionally incorrectly interpreted as normal, follow-up is important.

Because time can sometimes be an effective diagnostic tool, arranging follow-up for patients with headache is important. This may be with their primary care physician or a neurologist. This does not pertain to patients with abnormal physical examinations, whose further evaluation should take place urgently, often in the hospital, and in consultation with the physician who will be doing the follow-up.

Common Pitfalls

- Failure to inquire about prior headache details and how they compare to the current one.
- Failure to understand that some patients with serious pathology will not appear very ill.
- Failure to critically consider patient-initiated words such as *migraine* and *sinusitis,* in the absence of a substantiated diagnosis.
- Failure to perform (and document) complete neurologic and HEENT examinations.
- Failure to realize that there is no diagnostic significance to successful treatment of headache pain with any kind of analgesic or antimigraine drug.
- Failure to perform an LP after a nondiagnostic head CT in patients being evaluated for possible SAH (see the text above regarding ultra–early-presenting patients).
- Failure to know that hypertension is not usually the cause of a new headache.
- Failure to explain new focal neurologic findings. If the first test (e.g., a CT scan) is negative, consider a second test (e.g., MRI or neurologic consultation), because the physical finding is still present and requires explanation.

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CHAPTER 13 Weakness

Andy Jagoda

Patients presenting to the emergency department (ED) with a complaint of weakness pose a challenge because the complaint is often nonspecific and the differential diagnosis is large. Successful ED management depends on a systematic evaluation. Specific attention to potentially life-threatening etiologies is the principal focus, and diligence in data gathering is essential to the establishment of a diagnosis. A detailed history and physical examination guide the selection of appropriate diagnostic studies. Though rarely encountered, when approaching the patient with a complaint of weakness, consideration is given to disorders such as toxic exposures, metabolic abnormalities, botulism, myasthenia gravis, and Guillain–Barré syndrome because of their associated high morbidity and mortality. The emergency physician should consider these and all other disorders that can precipitously compromise the respiratory and functional status of the patient when approaching a patient with the chief complaint of weakness.

The complaint of "dizziness" may accompany that of "weakness," and, at times, patients use these terms interchangeably. There is considerable overlap in their etiologies. In the ambulatory care setting, dizziness is the most common presenting complaint in patients older than 75 years (1). *Weakness* is defined as a decrease in muscle strength or power. It may be a focal symptom, involving a single muscle group, or it may be generalized. Dizziness is imprecisely interpreted by patients and may be used to describe lightheadedness, disequilibrium, disorientation, confusion, or vertigo (see Chapters 14 and 70). The emergency physician must appreciate

the distinction between these symptoms and attempt to understand the patient's intended meaning. This chapter specifically addresses those patients who present with a complaint of "weakness."

CLINICAL PRESENTATION

The historical features that are important when assessing the patient with weakness are the acuity of onset and duration of symptoms, exacerbating and mitigating factors, presence of associated symptoms, and location is the weakness, focal or generalized (2). Sudden onset of weakness may suggest a metabolic derangement or infection: A slower progression of symptoms from days to weeks may suggest Guillain–Barré syndrome or myasthenia gravis, although these illnesses may also have accelerated courses. A history of symmetric ascending weakness in a patient with a recent respiratory illness or influenza vaccine will aid in the diagnosis of Guillain–Barré syndrome. The weakness of myasthenia gravis may fluctuate, and a careful history is needed to elicit a progression of symptoms throughout the day or an association with exercise or repeated activity, such as chewing or combing one's hair. Recent illness, other medical problems, recent vaccination, occupational history, travel history, history of tick bites, use of medications, and use of recreational drugs are important factors in assessing the patient complaining of weakness. A thorough review of systems includes inquiry about recent weight loss, fever or sweats, visual changes (including diplopia), difficulty swallowing, joint or muscle pain, palpitations, change in bowel habits, and skin rashes. Occupational or recreational exposures may indicate drug toxicity.

The patient's age is an important consideration in developing the differential diagnosis in a patient with weakness. The elderly have a higher incidence of comorbid medical conditions than their younger counterparts. The elderly are also at higher risk of acute central nervous system (CNS) and cardiovascular events. They are more likely to present with occult infections and metabolic disorders that are symptomatically manifested as weakness (1). In the pediatric age group, infantile botulism and intussusception are two rare but important considerations. Infantile botulism may be seen in children

days old to more than 1 year of age. This variant of botulism is much more common than food-borne or wound botulism; it presents with weakness, poor tone, poor suck, or constipation.

The physical examination in a patient complaining of weakness includes a full set of vital signs, orthostatic monitoring, oxygen saturation, and a finger blood glucose. Supplemental oxygen is indicated if hypoxemia is present; the airway must be secured if there is a potential for imminent compromise. Tachycardia, with or without hypotension, suggests volume depletion or toxic drug ingestion. Rectal temperature measurement is particularly important, because infection frequently presents with nonspecific complaints, such as weakness. A blood glucose level should be obtained early during the evaluation, as hypoglycemia may present with an array of symptoms, including weakness. The ears, sinuses, thyroid, and cardiac status should be assessed, as well as a careful evaluation for signs of trauma, which may suggest physical abuse. A rectal examination, including a guaiac test for occult blood, is recommended in select cases.

The neurologic examination begins early in the course of the patient's evaluation with an assessment of the mental status, for example, assessment of orientation and attention. Altered mental status, including confusion, slowness, or agitation, may represent underlying disease or toxic exposure such as in carbon monoxide poisoning and organophosphate exposure. Suspicion of cognitive defects may prompt a formal mental status evaluation depending on the clinical setting (3). Abnormal neuropsychiatric testing in a patient with carbon monoxide poisoning may indicate the need for hyperbaric oxygen therapy. Cranial nerve testing in the patient with a complaint of weakness focuses on the motor examination. Ptosis can be an early sign of myasthenia gravis, in which case it is usually symmetric (4). When myasthenia is a consideration, having the patient hold an upward gaze for several minutes is helpful in assessing for fatigue. Difficulty with accommodation can be the earliest sign of weakness due to botulism and does not occur with myasthenia. Diplopia due to weak oculomotor muscles should be assessed, with an emphasis on the evaluation of the sixth cranial nerve. The abducens is the longest intracranial cranial nerve and the

most sensitive to toxins such as botulism or to increased pressure from intracranial mass lesions.

The remainder of the neurologic examination in the patient complaining of weakness concentrates on motor strength, deep tendon reflexes, and assessment for muscle atrophy and fasciculations. Table 13.1 lists the motor strength grading system (from 0 to 5), which permits standardization of documentation of the motor examination among examiners. Deep tendon reflexes are graded on a scale from 0, indicating areflexia, to 4, signifying hyperreflexia, with 2 being normal. *Upper motor neuron* diseases, such as multiple sclerosis, will typically present with hyperactive reflexes in comparison to the diminished or absent reflexes seen in diseases of the *lower motor neuron,* as in Guillain–Barré syndrome. Acute spinal cord lesions, such as in a conus medullaris lesion or transverse myelitis, can often initially present with areflexia early in its course. Cauda equina syndrome is due to impingement of the lumbar and sacral nerve roots, commonly from a ruptured vertebral disk. These patients will present with distal motor weakness, areflexia, urinary retention, and anesthesia in the saddle distribution.

TABLE 13.1
Motor Strength Grading System (Medical Research Council Scale)

Grade	Definition
5	Normal strength
4	Active movement against gravity and resistance
3	Active movement against gravity (no resistance from physician)
2	Active movement with gravity eliminated (no resistance from physician)
1	Flicker or trace contraction
0	No visible or palpable contraction

Both upper and lower motor neuron diseases can initially present with the complaint of weakness. The important distinguishing characteristics are listed in Table 13.2. *Upper motor neurons* arise in the cerebral cortex, and their axons extend through the subcortical white matter, internal capsule, brainstem, and spinal cord, where

they synapse directly with lower motor neurons or interneurons, fine-tuning motor activity. *Lower motor neuron* cell bodies lie in the brainstem motor nuclei and anterior horn of the spinal cord. Their axons extend to the skeletal muscles they innervate.

TABLE 13.2
Upper Versus Lower Motor Neuron Weakness

Clinical	Upper Motor Neuron	Lower Motor Neuron
Weakness	Weakness greater in the arm extensors and leg flexors; weakness often unilateral	Weakness often in one muscle group; extensor same as flexor
Deep tendon reflexes	Increased	Decreased
Muscle tone	Increased	Decreased
Fasciculation	None	Present
Muscle atrophy	None	Severe
Babinski sign	Present	Absent

The weakness of *upper motor neuron* disease is generally unilateral, the Babinski sign is present, muscle tone is increased, deep tendon reflexes are increased, and no fasciculations are visible or palpable. In general, distal muscle groups are more severely affected than are proximal groups. *Lower motor neuron* disease affects single muscle groups. Flexors and extensors are equally compromised in an extremity. Deep tendon reflexes and muscle tone are decreased with lower motor neuron disease. Muscle atrophy and fasciculation are long-term results of lower motor neuron lesions.

Amyotrophic lateral sclerosis (ALS) is a combined upper and lower motor neuron disease that can clinically present as a mixed picture. The etiology of ALS is unclear but it is a disease involving the destruction of the anterior horn cells in the spinal column and the Betz cells in the motor cortex of the CNS. The clinical presentation is of asymmetric weakness in the distal motor groups with sensory sparing. Patients often have muscle fasciculations of lower motor neuron disease but associated positive Babinski signs and hyperreflexia as seen in upper motor neuron disorders.

Lower motor neuron diseases can arise from a muscle-based disorder, a neuropathic-based disorder, or a myoneural junction source. Table 13.3 illustrates several symptoms, physical signs, and

laboratory findings that distinguish the etiologies of lower motor neuron weakness. Weakness due to a myopathy tends to involve proximal muscle groups, whereas neuropathic disease (Guillain–Barré syndrome) affects distal muscle groups. Myoneural junction diseases have a more distal distribution and are particularly inclined to affect respiratory and bulbar muscle groups (myasthenia gravis and botulism).

TABLE 13.3
Myopathy Versus Neuropathy Versus Myoneural Junction Disease

Clinical	Myopathy	Neuropathy	Myoneural Junction
Distribution	Proximal > distal	Distal > proximal	Diffuse, especially bulbar and respiratory muscles
Reflexes	Decreased	Decreased	Normal
Sensory involvement	–	+	–
Atrophy	±	±	–
Fatigue	±	±	+
Serum CPK	Normal to elevated	Normal	Normal
Example	Polymyositis	Guillain–Barré syndrome	Myasthenia gravis

CPK, creatine phosphokinase.

Spinal cord disorders from compressive or traumatic injury can also present with weakness involving motor function distal to the defect, as well as sensory and autonomic nerve dysfunction. In comparison to atraumatic cord disorders, such as in multiple sclerosis, traumatic cord lesions generally present acutely with distinct sensory and motor findings, as seen with the saddle anesthesia in patients with cauda equina syndrome. Autonomic dysfunction is also seen more commonly in spinal cord injuries manifesting with hypotension or priapism. Detailed history (including anticoagulation, recent fall or trauma, immune status, fever, intravenous drug abuse, spinal procedure, or surgery) is often necessary to make the diagnosis. An uncommon and occasionally overlooked diagnosis of spinal epidural abscess can be made in the setting of a patient with a history of intravenous drug abuse presenting with severe back pain, fever, and progressive lower extremity weakness.

When psychogenic weakness is considered in the differential diagnosis, several maneuvers may be helpful. Weak muscles give way to pressure in a smooth fashion, but psychogenic weakness usually results in a jerking or sudden release. In a patient with upper extremity weakness from organic disease, making a fist should not result in wrist extension (unless there is an isolated lesion of the flexor tendons); in functional states, the wrist extends as the patient tries to make a fist. In patients with psychogenic bilateral lower extremity weakness, attempts to lift one leg against resistance result in the other leg firmly thrusting downward, whereas in patients with organic disease, the downward thrust is diminished or absent.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the weak patient is extensive. Division of the etiologies into broad categories, such as metabolic, toxic, infectious, structural, endocrinologic, cardiac, and rheumatologic, permits a more organized approach to this extensive list. In this section, the diagnoses are also presented in order from high risk to low risk. Detailed history taking and careful examination should direct the physician to one of these categories. Diagnostic testing may then be used to narrow the differential diagnosis and determine the management plan for the patient's condition.

Metabolic

Metabolic derangements that can present with weakness include hypoxia, hyperthermia, and alterations in serum glucose, potassium, sodium, phosphate, magnesium, and calcium (5). Severe hypokalemia presents with generalized weakness and paralysis due to a dysfunction of potassium regulation (6). This state may be induced by medications such as diuretics as well as gastrointestinal losses; it also rarely occurs in association with genetic disorders such as familial periodic paralysis. Hyperkalemia, though typically known for its effects on the myocardium, is a lesser known cause of weakness presenting with ascending paralysis, ultimately leading to respiratory failure (6). One of the most frequently seen causes of weakness in the ED is hypoglycemia, which accounts for an average of 380,000 ED

visits per year in the United States (7). During the summer, elderly patients with heat exhaustion will frequently present to the ED with weakness due to dehydration and inability to regulate their temperature.

Cardiovascular

Weakness may be the only complaint in the elderly patient with acute myocardial infarction (MI); this must be in the differential diagnosis for all geriatric patients presenting with nonspecific complaints. In one study of symptoms of MI in the elderly with autopsy-proven MI, 20% of the patients initially presented with weakness (8). As the population ages, more patients will present with atypical complaints of MI such as weakness or shortness of breath.

Myocarditis is another serious but often missed cause of weakness in a patient with a recent viral infection. Patients complain of weakness as part of a constellation of symptoms that includes cough, dyspnea, myalgias, fever, vomiting, or diarrhea. In one study, up to 60% of patients with myocarditis did not have chest pain (9).

Other cardiovascular causes of weakness associated with lightheadedness or presyncope are due to transient decreased cerebral perfusion. These disorders include postural hypotension, carotid and vertebral artery insufficiency, cardiac dysrhythmias, vasovagal events, and states of decreased cardiac output.

Central Nervous System Lesions

Structural lesions in the CNS generally present with focal weakness. Weakness, in association with changes in speech, visual loss, diplopia, paresthesias, and dizziness, are frequently associated with the diagnosis of stroke (10). Patients with brainstem infarcts can present with difficulty swallowing, talking, or breathing, in addition to weakness. Lesions in the frontal lobes, basal ganglia, and cerebellum can cause disequilibrium.

Lesions in the spinal canal such as epidural hematoma and abscess and metastatic cancer can result in weakness that is symmetric and distal to the site of compromise. Transverse myelitis is an infrequent

yet debilitating demyelinating disease of the spinal cord presenting with an acute onset of back pain, lower extremity weakness or paralysis, and sensory deficit below the level of involvement. The etiology is unknown but thought to be related to a recent viral infection or autoimmune disorder. The clinician should suspect this disease in a patient with a recent viral illness presenting with both weakness and sensory deficit below a cord level. This disease should not be confused with Guillain–Barré syndrome. Though also preceded by a viral syndrome, the physical examination findings of Guillain–Barré syndrome will typically demonstrate sparing of the anal sphincter and hyporeflexia with progressive weakness in an ascending pattern over days to a week. Clinical findings of transverse myelitis generally progress over 24 hours and include diminished or absence of strength and sensation below the level of involvement, sphincter dysfunction, hyperreflexia, and urinary incontinence or retention.

Specific Neuromuscular Diseases

The patient with myasthenia gravis will present with weakness of a specific muscle group associated with blurred vision, diplopia, and ptosis. Patients with Guillain–Barré present with generalized ascending paralysis with variable sensory deficits. ALS is a disease that affects both upper and lower motor neurons and can present with a mixed picture. Myopathies caused by metabolic derangements, medications, and inflammatory states may present with symmetric proximal muscle weakness with preservation of sensory function.

Infections

All infections can potentially cause weakness, either through nonspecific mechanisms, such as those seen with mononucleosis or hepatitis, or from specific toxins affecting neuromuscular function, such as poliomyelitis, botulism, Guillain–Barré, or tick paralysis. Sinus and ear infections can affect the labyrinthine system and produce lightheadedness or vertigo. The human immunodeficiency virus (HIV) can directly or indirectly cause the full spectrum of weakness, from nonspecific fatigue to neuropathies and myelopathies.

Chronic fatigue syndrome, thought to be viral in origin, requires an extensive workup to exclude all other processes before the diagnosis can be established. This diagnosis should not be made in the ED.

Medications and Toxins

Prescription mediations can produce generalized weakness (Table 13.4). There are usually no focal findings on examination. In one study of 106 patients with a chief complaint of weakness and dizziness, 9% of all patients and 20% of those older than age 60 had symptoms attributed to prescription medications (1). Drugs associated with vasodilatation, bradycardia, or diuresis can produce orthostatic blood pressure changes, often giving the patient the feeling of weakness.

TABLE 13.4
Commonly Used Drugs and Other Substances Associated with Weakness

Myopathies
Steroids
Alcohol
Heroin
Clofibrate
Epsilon-aminocaproic acid
Diuretics
Laxatives
Amphotericin
D-Penicillamine
Cimetidine
Procainamide

Neuropathies
Carbon monoxide
Heavy metals
Polychlorinated biphenyls
Isoniazid
Nitrofurantoin
Gold

Neuromuscular Junction Disease
Organophosphates
Carbamates

Certain toxins can present with the sudden onset of weakness, leading to acute respiratory compromise. Other toxins present with a slowly progressive course and subtle complaints. Organophosphates and carbamates act at the neuromuscular junction by inhibiting acetylcholinesterase. Patients present with a constellation of symptoms including lacrimation, defecation, salivation, and weakness, which can progress rapidly to paralysis and respiratory failure. The ability to recognize this toxidrome is critical to early medical treatment and public health intervention. In contrast, poisonings from heavy metals can be subtle and present with a slowly progressive course. In these cases, a thorough history is necessary to elucidate the cause of the patient's symptoms. Carbon monoxide exposure still remains the leading cause of death from poisoning in the United States. Patients may present with weakness and headache as their only complaints. The emergency physician should consider

this diagnosis in patients presenting with weakness especially during the winter months.

Endocrine

Hypothyroidism is the most common endocrine cause of weakness and is often initially misdiagnosed (see Chapter 206). Thyrotoxic periodic paralysis can present with weakness as a primary complaint, probably mediated through hypokalemia (5,11). Adrenal insufficiency, perhaps the most life-threatening endocrine etiology of weakness, may present with hypotension, hyperkalemia, and hyponatremia (see Chapter 207). It is a diagnosis that must be considered in weak patients on chronic steroid therapy. The diabetic patient with hyperglycemia can present with generalized weakness from diabetic ketoacidosis or nonspecific neurologic deficits secondary to hypoglycemia (Chapters 201 to 204). Cobalamin deficiency (vitamin B12), which is most commonly seen with pernicious anemia, is an important cause of lower extremity weakness and is infrequently considered in the emergency setting. In addition to lower extremity weakness, the patient often complains of paresthesias and tongue discomfort and has a macrocytic anemia on laboratory analysis.

Rheumatologic

Weakness is a prominent complaint of most rheumatologic diseases and occasionally is the primary presenting symptom. Systemic lupus erythematosus, polymyositis, dermatomyositis, polymyalgia rheumatica, and particularly myasthenia gravis must all be considered in patients presenting with symmetric weakness.

Psychogenic Weakness

This diagnosis should be made after an exhaustive search for the cause of weakness has excluded both metabolic and systemic diseases. Patients with conversion disorder may present with paralysis of a specific muscle group that is not anatomically consistent. The symptoms of these patients are subconscious, which is

in contrast to the malingering patient, whose actions are purposeful and often have secondary gain. Although the evaluation of this group of patients can often be difficult and resource consuming, the diagnosis of psychogenic weakness should be one of exclusion after other diagnoses have been considered (12).

DIAGNOSTIC APPROACH

An exhaustive history and physical examination should be performed to uncover the subtle details essential in establishing the cause of a patient's complaint of weakness. The patient's definition of *weakness* must first be clarified. Whether the weakness is focal muscle weakness or generalized fatigue must be determined early in the evaluation. If the patient complains of muscular weakness, then the clinician must determine whether it is focal or generalized, proximal or distal. The information gathered from the history and physical examination guides further testing. In general, a complete blood count, serum chemistry, and urinalysis should be obtained. A sedimentation rate may be helpful if rheumatologic disease is suspected. A monospot test, liver function tests, and thyroid function tests are sometimes indicated. Heavy metal screening and red blood cell acetylcholinesterase level are required in selected cases, but these are rarely available to the emergency physician while the patient is in the department. Carboxyhemoglobin is indicated in suspected cases of carbon monoxide poisoning. A serum creatine phosphokinase and aldolase are helpful in cases of suspected myopathy.

Pulse oximetry and arterial blood gas analysis are indicated in cases of suspected pulmonary dysfunction. Pulmonary function testing, including vital capacity and maximum inspiratory force, is recommended when respiratory muscle compromise is suspected, as in patients with myasthenia gravis and Guillain–Barré syndrome. An electrocardiogram and cardiac monitoring have a low diagnostic yield in patients with generalized weakness, though they may be helpful when dysrhythmias or electrolyte abnormalities are suspected. In the elderly patient without other sources of weakness, an electrocardiogram should be obtained to assess for a cardiac source. Rarely, more specialized laboratory testing is indicated in the

evaluation of the weak patient in the ED. Lumbar puncture (LP) and cerebrospinal fluid (CSF) analysis for Gram stain and culture can be a useful diagnostic tool when suspecting infection as a cause of weakness. In the setting of a fever and headache without a source or an immunocompromised patient with unknown fever and weakness, LP may be diagnostic. If there is a suspicion of increased intracranial pressure in a patient with fever and headache, a computed tomography (CT) scan, prior to LP, should be performed to exclude an intracranial mass. The LP can also aid in the diagnosis or exclusion of specific neurologic disorders. Multiple sclerosis will typically have a pleocytosis on CSF examination, and electrophoresis may demonstrate oligoclonal bands of IgG, which is highly suggestive of the disease. Guillain–Barré syndrome characteristically exhibits fewer than 50 lymphocytes per milliliter, a normal sugar, and an elevated protein. A Tensilon test should be considered in patients with suspected myasthenia gravis.

Computed axial tomography or magnetic resonance imaging (MRI) with intravenous contrast best evaluates structural lesions in the brain or spinal canal. The CT is a useful tool to diagnose intracerebral lesions and edema as a cause of weakness, such as in tumors, toxoplasmosis, cerebral bleeds, and infarcts. Clinical history and physical examination can be used to guide the clinician on this decision. If there are no focal neurologic findings in a patient with a normal mental status and a careful fundoscopic examination reveals no signs of papilledema with adequate venous pulsations, an LP can be performed safely without a CT. CT is also useful in patients with physical examination findings suggestive of upper motor neuron disease associated with symptoms such as headache, nausea, and vomiting. Unfortunately, the CT is not as sensitive in the evaluation of spinal cord lesions such as in spinal epidural hematomas and abscesses. If a patient presents with distinct weakness and sensory deficit below a cord level with associated back pain and the diagnosis of a spinal cord lesion is considered, MRI is the test of choice. MRI is also a useful imaging modality in the diagnosis of cauda equina syndrome as a cause of the lower extremity weakness in the setting of urinary dysfunction, saddle anesthesia, and impotence. If an MRI

cannot be obtained, the patient should be stabilized and consideration given to transfer to an appropriate facility.

CRITICAL INTERVENTIONS

- The focus of the emergency physician's approach to the patient complaining of weakness is to rule out the life-threatening diagnoses, specifically those that can progress to cardiopulmonary or respiratory compromise (Table 13.5). After airway patency is established, patients should be assessed for adequacy of respiration. Certain patients, based on the history and physical examination, must be assessed for hypoxemia, hypercapnia, or carboxyhemoglobinemia. Assessment of pulmonary function with measurements of tidal volume and vital capacity may be valuable, especially in patients with suspected myasthenia gravis or Guillain–Barré syndrome; patients with a vital capacity <1.5 L are possible candidates for intubation.

TABLE 13.5
Acute Life-Threatening Causes of Weakness

Cause	History	Physical	Laboratory	Treatment
Myasthenia gravis	Chronic weakness, improves with rest	Double vision, muscle fatigue, improves with rest	Positive Tensilon test	Thymectomy, AChE inhibitors
Guillain–Barré	Recent infection, progressive weakness distal to proximal	Distal motor with/without sensory loss, absent reflexes, no visual deficits	CSF with elevated protein, <50 WBCs	Supportive care, plasma exchange, gamma globulin
Botulism	Acute onset; canned, pickled, smoked food	Blurred or double vision	None	Supportive care, equine antitoxin
Adrenal insufficiency	Acute weakness associated with stress	Hypotension, hyperpigmentation	Hyperkalemia, hyponatremia	Hydrocortisone
Organophosphate poisoning	Occupational exposure, progressive weakening	Miosis, fasciculations, muscarinic dysfunction	Decreased RBC AChE	Atropine, pralidoxime
Carbon monoxide poisoning	Occupational or social exposure	Nausea, vomiting, coma, headache, dizziness	Elevated carboxyhemoglobin	100% oxygen, hyperbaric oxygen
Hypokalemia	Familial, GI, or renal loss	Diffuse weakness	Low serum potassium	Potassium

AChE, acetylcholinesterase; CSF, cerebrospinal fluid; WBCs, white blood cells; RBC, red blood cell; GI, gastrointestinal.

- Signs of respiratory compromise that may require intubation are declining oxygen saturations, increasing hypercapnea if capnometry is available, changes in mental status such as confusion or lethargy, and the increased use of accessory muscles for the work of breathing. Upon preparation for rapid sequence intubation, careful thought should be given to the medications used. If intracerebral mass lesion is suspected, premedication with

lidocaine and fentanyl should be considered. Organophosphates decrease the amount of plasma pseudocholinesterase and prolong activation of succinylcholine at the neuromuscular junction. Using a depolarizing agent in the paralysis of a suspected myasthenic patient should be attempted with caution because of increased sensitivity and possible exaggerated response to succinylcholine. Hyperkalemia can also result from using succinylcholine in patients with multiple sclerosis or ALS and should be avoided.

- Potentially unstable patients require intravenous access, pulse oximetry, and cardiac monitoring. Regular reassessment throughout the ED stay is necessary to avoid missing deterioration in the patient's status. Specific interventions depend on the diagnosis. Both plasmapheresis and intravenous IgG have been shown to improve outcome and shorten the course of disease in patients presenting with Guillain– Barré syndrome. Sedating drugs should be avoided in anxious patients who are hypoxemic. Drugs that interfere with myoneural junction function, such as the aminoglycosides, should be avoided in patients with suspected myasthenia gravis. Hypoglycemia is treated with dextrose and hypokalemia with potassium. Hydrocortisone, 100 mg intravenously, should be given to patients with suspected adrenal insufficiency. Patients with periodic paralysis do not have a total body deficit of potassium but instead have an alteration in intra- and extracellular potassium levels. Therefore, potassium should be corrected carefully to avoid inducing hyperkalemia. Patients who are weak because of toxins require specific antidotes when available. Significant carbon monoxide poisoning is an indication for hyperbaric oxygen treatment. Organophosphate poisoning requires the use of atropine and pralidoxime. Heavy metal poisoning is treated with chelation therapy.

DISPOSITION

Patients with progressive symptoms or those with a suspected or confirmed disease that has a progressive course or risk of respiratory compromise, such as myasthenia gravis, Guillain–Barré, or botulism, should be admitted to an intensive care setting regardless of their

initial appearance. Early consultation with a neurologist or neurosurgeon is recommended, and a comprehensive management plan should be determined. Laboratory tests should not be ordered unless the results will be available before ED discharge or careful follow-up has been arranged.

Common Pitfalls

- Failure to perform a detailed history and physical examination.
- Failure to diagnose an acute stroke in a timely manner.
- Failure to obtain a thorough drug and toxin exposure history.
- Failure to suspect drug-induced myopathy, drug-induced adrenal insufficiency, or overdose.
- Failure to detect an occupational exposure and properly decontaminate the patient.
- Diagnosing a psychogenic etiology or chronic fatigue syndrome in the ED.
- Failure to recognize absent reflexes as an early manifestation of the Guillain–Barré syndrome.
- Failure to distinguish periodic paralysis from hypokalemia induced by drugs, gastrointestinal loss, or other etiologies.

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CHAPTER 14
Dizziness

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CLINICAL PRESENTATION

Dizziness is one of the most common presenting symptoms in emergency medicine (1,2). Misdiagnosis is common, even when patients are evaluated by neurologists (3). Dizziness has numerous causes and the very word "dizziness" means different things to different people. Older dizzy patients, who are becoming increasingly common in the emergency department (ED), have a higher incidence of serious central nervous system (CNS) and cardiovascular causes (4–6). Furthermore, dizziness is often caused by a variety of non-CNS or cardiovascular symptoms such as toxic-metabolic and infectious disorders. For all these reasons, correct diagnosis is important, but can be challenging. The evidence base for our understanding of the diagnosis and treatment of dizziness is weak (7), but has increased substantially in the past several years (8,9).

The traditional diagnostic approach to dizziness is based on "symptom quality," a paradigm that was first published in 1972, based on limited data from a small number of selected patients evaluated in a specialty clinic (10). The "symptom quality" method is to ask the patient, "What do you mean dizzy?" and their response will place them into one of the four categories: vertigo, presyncope, disequilibrium, or "other" nonspecific dizziness. Implicit is that each category has etiologic significance: Vertiginous patients have vestibular causes (usually peripheral), presyncopal patients have cardiovascular causes, those with disequilibrium have neurologic issues whereas nonspecific dizziness is caused by psychiatric disease.

The “symptom quality” approach has fundamental problems. The first has to do with the methods of the original 1972 paper (10). Methodologic weaknesses include small number of patients enrolled, diagnosis assigned by a single neurologist without independent verification, no brain imaging nor any long-term follow-up. Furthermore, some diagnoses known now to be common causes of dizziness (e.g., vestibular migraine), had not yet been recognized as diagnostic entities. Nevertheless, when no tests identified a specific diagnosis, the type of dizziness was used to assign the final diagnosis (e.g., vertigo was assigned a peripheral vestibular cause if no other cause was found). The paradigm of “symptom quality” has never been prospectively and properly validated.

Most ED dizzy patients would never end up in an outpatient specialist-run dizziness clinic, including those with acute cardiovascular, cerebrovascular, metabolic, infectious, and other causes. The original study was done in an era of fewer medications (propranolol was the only beta-blocker, there were many fewer antihypertensive agents) and far less polypharmacy. Thus, the patients in that 1972 study were not at all representative of patients seen in an ED in 2014.

Sensory symptoms are difficult to describe. A recent study asked patients a series of questions designed at describing their dizziness type (11). Within 10 minutes, they were asked the same questions but given the answer choices in a different sequence. Half the patients changed the category of dizziness that they had initially endorsed just a few minutes before, and most endorsed multiple dizziness symptom qualities. This fact alone seriously undercuts the “symptom quality” paradigm.

Other recent research shows that patients with cardiac causes of dizziness often use the word “vertigo” to describe what they are feeling (12). In another study of older patients presenting to an ED with dizziness, the use of the word “vertigo” (as opposed to lightheadedness or dizziness) did not predict those who had a cerebrovascular cause (13). The converse is also true. Patients with clear-cut vestibular disease often complain of vague lightheadedness or nonspecific “dizziness.”

Taken together, this literature suggests that using the "symptom quality" paradigm for the diagnosis of unselected dizzy patients has serious shortcomings. As well, they begin to suggest an alternative paradigm based on "timing and triggers." In the study showing that patients change their "type" of dizziness, their responses to issues about dizziness timing and triggers were far more reliable (11). Because the type of dizziness may not be etiologically useful and because many of the major dizziness syndromes have reliable timing and triggers patterns, an alternative paradigm based on "timing and triggers" may be more useful to the clinician.

The "timing and triggers" paradigm can be summarized using the mnemonic of **ATTEST** (see Table 14.1).

TABLE 14.1
Attest—A Method for Diagnosing Dizzy Patients

A—Associated symptoms, signs, or basic test results
Using the history (especially the HPI, ROS, and medications), vital sign, physical examination, and basic labs (e.g., finger-stick glucose or ECG) search for abnormalities that suggest a specific diagnosis or group of diagnoses
T—Timing
Is the dizziness intermittent or persistent? Did it start gradually or suddenly? If persistent, how long has the dizziness lasted and if episodic, how long do episodes last?
T—Triggers
Is there anything that triggers the dizziness (e.g., turning one's head, starting a new medication, standing up, or is it spontaneous? That is, does it "just happen" out of the blue?); distinguish "triggers" from "exacerbating factors"
ES—Exam Signs
Apply several bedside tests that can be very helpful in clinically distinguishing some dangerous from some benign causes of dizziness (oculomotor testing in AVS; in PVS, positional tests)
T—Testing
After history and physical examination with the appropriate bedside testing, there will be instances in which there is still significant diagnostic ambiguity about serious diseases. Perform whatever confirmatory testing or consultation is needed to try to resolve the ambiguity, erring on the side of patient safety

A: Associated symptoms, signs, and basic testing (such as finger-stick glucose)
TT: Timing and Triggers
ES: Exam Signs
T: Testing (if needed to confirm the clinical diagnosis)

First, the emergency physician (EP) should ask about associated symptoms that suggest a particular diagnosis or group of diagnoses (Table 14.2). For example, dizziness associated with chest pain, or vomiting and diarrhea, or acute neck pain, or fever and cough, suggest obvious possible diagnoses. Has the patient started a new medication? It is important to establish what symptoms accompany the dizziness since a large proportion of ED patients have various medical (and not vestibular or neurologic) problems that cause their dizziness (4). This step will often lead to a clear-cut limited differential diagnosis and workup for many patients (e.g., a chest x-ray for a dizzy patient with fever, cough, and green sputum).

TABLE 14.2
Associated Findings (That May Suggest a Specific Diagnosis or Group of Diagnoses)

History

Has the patient started a new medication or changed the dose of an existing one?

Has there been any recent head injury?

Does the patient have vascular risk factors or history of prior stroke or TIA?

Are coincident symptoms present?

- Headache or neck pain
- Fever
- Ear pain or discharge
- Hearing loss or tinnitus
- Chest pain or palpitations
- Dyspnea or other acute respiratory symptoms
- Abdominal pain
- Gastrointestinal blood or fluid loss (vomiting, diarrhea)
- Acute neurologic symptoms—diplopia, dysphagia, dysarthria, weakness, and any other new neurologic symptom

Physical Examination

Abnormal vital signs

- Fever
- Bradycardia or tachycardia
- Hypotension or severe hypertension
- Tachypnea or hypoxia

New murmur or gallop

New rales or wheeze

Gastrointestinal blood loss

Any new abnormality in the neurologic examination

Basic laboratory testing (as indicated)

Finger-stick glucose testing

Pregnancy testing

Urinalysis

Electrocardiogram

Next, the EP should ask questions designed to place the patient into one of four "timing and triggers" categories (see Table 14.3). These include the acute vestibular syndrome (AVS), the episodic vestibular syndrome (EVS), the positional vestibular syndrome (PVS), and the chronic vestibular syndrome (CVS). The history can be used to define the onset, duration, constancy, and triggering or exacerbating features. Patients can generally describe these features

of their histories more reliably than the "type" of dizziness (11). Each of these four categories suggests a particular differential diagnosis (see Differential Diagnosis section and Table 14.3).

TABLE 14.3
Timing and Triggers Categories for Dizzy Patients (and Differential Diagnosis of More Common Causes)[a]

Acute vestibular syndrome: Rapid onset of dizziness that persists for days and is associated with nausea, vomiting, head motion intolerance, nystagmus, and gait disturbance

Benign causes: vestibular neuritis (no auditory symptoms) and labyrinthitis (with auditory symptoms)

Serious causes: cerebellar and brainstem infarction (far less commonly, hemorrhage)

Episodic vestibular syndrome: Episodes of dizziness lasting minutes to hours without obvious trigger (occasionally shorter spells)

Benign causes: vestibular migraine, Menière syndrome (with auditory symptoms), vasovagal near syncope

Serious causes: cardiac arrhythmias, low-flow states (including PE or ACS), posterior circulation TIA)

Positional vestibular syndrome: Brief episodes of dizziness that are triggered, often lasting only seconds

Benign causes: BPPV

Serious causes: Orthostatic hypotension from hypovolemia (any cause), central positional vertigo (e.g., cerebellar tumor)

Chronic vestibular syndrome: Prolonged dizziness lasting weeks to years

Benign causes: presbylibrium, chronic bilateral vestibular failure, poorly compensated unilateral vestibular failure

Serious causes: paraneoplastic syndrome (e.g., cerebellar degeneration), posterior fossa tumor

[a]This is not meant to be an encyclopedic list, but rather a list of the more common and more serious conditions that are seen in the emergency department; there are many other causes of dizziness.

BPPV, benign paroxysmal positional vertigo; PE, pulmonary embolism; ACS, acute coronary syndrome; TIA, transient ischemic attack.

Once the category is defined, then one uses bedside and other routine tests to further narrow the differential diagnosis. Some of this testing is part of a normal physical examination. Is the patient mentating normally? Is there obvious nystagmus on primary gaze

(staring straight ahead)? Is there a murmur or signs of heart failure? Is there melena or evidence of gastrointestinal bleeding? Some of the confirmatory tests are a more detailed bedside oculomotor examination that helps to distinguish central from peripheral vestibular disorders. These tests are easy to learn to do and interpret.

Confirmation with more sophisticated (nonbedside) tests is the final step. This might mean a computed tomography angiography (CTA) of the chest if pulmonary embolism (PE) is the target diagnosis or telemetry, serial cardiac enzymes, and electrocardiograms if an acute coronary syndrome (ACS) is the concern. Many patients will not need these tests because the bedside examination findings and basic tests can establish some diagnoses (e.g., vestibular neuritis or benign paroxysmal positional vertigo or a urinary tract infection).

The "timing and triggers" paradigm frequently leads to making a specific diagnosis compared to the traditional "symptom quality" approach. The approach to patients with AVS and PVS have been studied fairly extensively (8,9,14), but it is important to acknowledge that the "timing and triggers" or ATTEST approach has not been prospectively validated or systematically studied.

DIFFERENTIAL DIAGNOSIS

Without some type of diagnostic strategy or algorithmic approach, diagnosis of the dizzy patient is an exercise in futility since dozens, if not hundreds, of individual conditions as well as side effects from nearly every medication can produce dizziness. An approach based on "timing and triggers" also suggests a differential diagnosis based on various temporal categories (Table 14.3).

For patients with an AVS, the major differential diagnosis is a peripheral vestibular process (of the eighth nerve or its end organ) versus stroke. The eighth cranial nerve has two components, the vestibular and the cochlear, that can be affected together or individually. Patients with vestibular neuritis have dizziness (but no hearing loss) (15). Patients with acute sensorineural hearing loss have diminished hearing (and no dizziness) (16,17). The term labyrinthitis is often used when both systems are affected. Because the organs of balance and hearing are colocated peripherally,

coinvolvement of dizziness and hearing generally implicates a peripheral process, but there is an important exception.

The labyrinth is supplied by the labyrinthine artery, which is a branch of the anterior-inferior cerebellar artery (AICA—itself originating from the basilar). It is, therefore, possible that an AVS or an acute sensorineural hearing loss is due to a stroke. This is probably less common than benign peripheral causes; however, with AICA strokes, both balance and hearing are usually affected (18). Although "vertigo" has been reported in patients with supratentorial stroke (19), patients with dizziness or vertigo as a prominent presenting symptom of cerebrovascular disease usually have posterior fossa strokes (20). Although vestibular neuritis accounts for the majority of patients who present with the AVS, cerebellar (or brainstem) stroke is the other important possibility that is critically important for the emergency physician to consider (21). Bedside testing can help distinguish between these groups of patients, and within the first 48 hours, may actually be better than MRI (14).

Acute intracerebral hemorrhage is a very rare cause of the AVS; almost all such patients have other neurologic symptoms or signs (22). Some older patients with a toxic–metabolic or infectious problem could present with an AVS but the frequency with which this happens is probably low ($<1\%$) (9) and many of these patients will likely be identified by attention to associated symptoms. Multiple sclerosis can also present as the AVS.

Vestibular migraine is the most common cause of the EVS. Migraine is extremely common in the general population and in one series of dizzy patients older than 65 years, 13% were found to have vestibular migraine (23). However, the EP should be cautious in diagnosing migraine in elderly patients without a prior history of migraine. Dizziness from migraine can occur with or without headache (24). Duration of attacks is often minutes to hours to days but can last seconds in 10% of patients (24). Head motion intolerance is common (24). Meniére disease is another cause of the EVS and is associated with episodic dizziness and hearing loss, tinnitus and ear fullness that last between minutes and hours (25). Meniére disease is an uncommon cause in the ED.

The major serious diagnoses that present with the EVS are transient ischemic attack (TIA) of the posterior circulation, cardiac arrhythmias, and transient low flow states such as from a PE, an ACS, or aortic stenosis. As for posterior circulation TIA, classic teaching is that other brainstem symptoms are nearly always associated with dizziness, at least in patients presenting with episodes occurring over more than 3 weeks (26). Since 1975, when the NIH published its TIA classification system (27), many authorities have recommended this definition, which stated that patients presenting with isolated vertigo, general dizziness, diplopia, and dysarthria should not be diagnosed with posterior circulation TIA. Several authors report that TIA can present with isolated dizziness (28–30). Others have reported that spells of dizziness (even over months) can herald a subsequent basilar stroke (31). More recent data clearly suggests that the symptoms above (formerly thought not to represent TIA) in fact do (32). Patients presenting with these symptoms had an odds ratio of 15 for having a vertebrobasilar territory stroke, many within the 48 hours following the transient neurologic symptoms (32). Some of these patients had isolated vertigo. Patients with vertebral stenosis and posterior circulation symptoms are at particularly high risk for subsequent stroke (33).

Patients with the PVS have a narrower differential diagnosis. BPPV is the most common benign cause. These patients have very brief episodes lasting about 15 to 30 seconds that are triggered by head movement. It is important to note that many episodes occur at night in bed and therefore some patients have difficulty precisely fixing the duration of the spells. This is one instance in which a symptom waking a patient from sleep makes a benign diagnosis more likely than a serious one. Patients with BPPV may feel an anticipation of dizziness and will sometimes report “constant” dizziness for days, but a careful history will tease out the true episodic nature of the dizziness. It is important to note that many patients with BPPV do not endorse true vertigo (34). As well, BPPV may be less well recognized in elderly patients (35). It bears reemphasis that these patients may complain of vertigo or vague lightheadedness or

dizziness that can easily be mistaken for orthostasis if symptoms occur on arising in the morning, as is often the case. The two can usually be distinguished, however, by inquiring whether the symptoms also occur on reclining or rolling over in bed, which should not occur in those with orthostatic hypotension.

More serious diagnoses that present as the PVS include orthostatic hypotension of any cause and central positional vertigo. The former can be due to any dangerous cause of hypovolemia such as gastrointestinal bleeding, fluid losses from gastroenteritis, persistent vomiting, and others including medication side effects (36). Abnormal orthostatic vital signs are very common in elderly patients especially in those who live in extended care facilities (37); this means that orthostasis is a common cause of dizziness, but also that the presence of an orthostatic blood pressure drop may be an incidental finding in an elderly patient with dizziness of another cause.

Central positional vertigo is a very uncommon BPPV mimic that can be caused by tumors, strokes, and other CNS lesions (38–40). Most of these patients will have physical examination clues during positional testing (Dix–Hallpike) that typical BPPV is not the correct diagnosis: persistent symptoms or signs lasting longer than 1 minute, downbeat nystagmus, lack of latency to nystagmus onset, and lack of therapeutic response to an Epley or other canalith repositioning maneuver (41).

Patients with the CVS whose symptoms persist longer than weeks most commonly have polysensory dizziness, degenerative neurologic disease, psychiatric syndromes, drug side effects, or drug–drug interactions, although specific data about the relative frequency for various causes are lacking. Occasionally, a patient with a slow growing posterior fossa tumor can present with the CVS.

DIAGNOSTIC APPROACH

History

The history is of paramount importance. In addition to the usual history, the following steps may help focus and supply clues that

may help pinpoint a diagnosis or at least help to narrow the list of potential diagnoses.

The ATTEST (Table 14.1) mnemonic should be used to gather the important elements of the history. Associated symptoms should be identified that may supply clues of the underlying etiology (see Table 14.2). Antecedent medication changes or head trauma may suggest a drug side effect or posttraumatic BPPV. The clinician's focus will be different with a patient who presents with severe abrupt onset headache with dizziness than with a dizzy patient who reports abdominal pain and diarrhea as associated symptoms.

A distinction should be made between "triggering" the dizziness and "exacerbating" the dizziness. "Triggered" dizziness suggests that something made a patient dizzy when they started out not dizzy. An example is a patient who is lying on a stretcher completely asymptomatic and when a Dix–Hallpike is done, the patient becomes dizzy. "Exacerbated" suggests that something increased a dizzy patient's symptoms (but they were already dizzy to start with). An example of this would be a patient with vestibular neuritis who feels dizzy at baseline while lying still in the stretcher, but on head motion, the dizziness intensifies.

This is a very important distinction and highlights a common misconception about dizziness (42). The misconception is that a patient whose dizziness worsens with head motion has a peripheral vestibular cause of their dizziness. This is not true. A dizzy patient from a stroke, multiple sclerosis, or a cerebellar tumor, will develop worse dizziness with head movement. A hypovolemic patient will also have worse dizziness upon changing position (standing up).

Next, a "timing and triggers" category should be defined by asking questions such as the following.

- "When did the dizziness start?"
- "Did it begin suddenly or gradually?"
- "What were you doing when it started?"
- "How long does the dizziness last?"
- "Is it episodic or continuous?"
- "If it's episodic, how long do episodes last?"
- "Are the episodes triggered or do they occur without warning?"

• “If they are triggered, what seems to be the trigger?”

PHYSICAL EXAMINATION

Physical examination of the dizzy patient needs to be fairly comprehensive given the long list of possible causes but always starts with considering the vital signs (factoring in the specific chief complaint). For example, if a patient has dizziness with a new fever, then the source of the fever should be sought. If the fever is associated with cough, then a chest x-ray is likely indicated. Dizziness and tachycardia should raise the suspicion of a gastrointestinal bleed or PE or perhaps just dehydration from poor PO intake as a result of a vestibular disorder.

The EP should not pigeonhole the patient too early in the evaluation and certainly not based on which word the patient uses to describe their dizziness. A patient endorsing true vertigo “like the room is spinning around” might have rapid atrial fibrillation whereas another patient complaining of “lightheadedness” might have BPPV. With the caveat that the physician has done relatively thorough general and cardiac examinations and that the vital signs do not suggest anything obvious or catastrophic, special care should be taken on the examination of the ears, eyes, and nervous system. As for the neurologic examination, the EP should test the gait, and focus on the cerebellar and oculomotor examinations.

The tympanic membrane is inspected for signs of otitis. Unilateral new hearing deficit plus dizziness suggests a peripheral cause, since hearing and balance end organs are colocated peripherally. However, in the appropriate setting (abrupt onset of symptoms in a patient with vascular risk factors), a stroke involving the AICA or its labyrinthine branch can cause acute hearing loss and dizziness.

Gait should be tested. Patients who normally use a cane or a walker should be tested using those devices to allow for a meaningful comparison with their baseline. A new gait abnormality, especially the inability to walk without falling, should suggest a central cause of dizziness or severe volume depletion. In a patient who is vomiting, having the patient try to sit up in the stretcher without holding on to the side rails (e.g., with arms crossed across the chest) will also test

for truncal ataxia. In patients with the AVS, presence of severe gait instability or truncal ataxia strongly suggests a CNS cause (21,43).

As well, in patients with the AVS, three specific bedside oculomotor tests can identify posterior circulation stroke more accurately than MRI, at least in the first 48 hours from symptom onset (14). These three tests are the horizontal head impulse test (HIT), testing for direction-changing gaze-evoked nystagmus, and alternate cover test for skew deviation (14). An important caveat to this study is that it was done by trained neuro-otologists. However, from the perspective of a practicing emergency physician, these tests are relatively easy to learn to perform and interpret. In patients presenting with an AVS, the presence of any of the worrisome findings suggests stroke (or another central cause) whereas the absence of all the worrisome findings strongly suggests a peripheral problem.

The HIT was first described in 1988 (44). Figure 14.1 shows how the test is performed and interpreted. The presence of a corrective saccade of the eyes back toward the examiner's nose is a positive test and means that the lesion is likely in the peripheral labyrinth. The maneuver tests the vestibulo-ocular reflex (VOR), which does not loop through the cerebellum or lower brainstem, that is why it is negative (no corrective saccade) in patients with cerebellar or medullary strokes. Pooled results across four studies identified as part of a systematic review showed that a normal HIT was found in 85% of patients with stroke ($n = 152$) and only 5% of patients with a peripheral vestibular problem ($n = 65$) (9). However, the HIT will be positive in some patients with brainstem stroke that affects the vestibular nerve root entry zone in the pons. Most patients with these brainstem strokes will have one of the other two eye findings on examinaton that indicates the central nature of the lesion (14). The HIT is a safe test although a single case of transient complete heart block has been described (45).

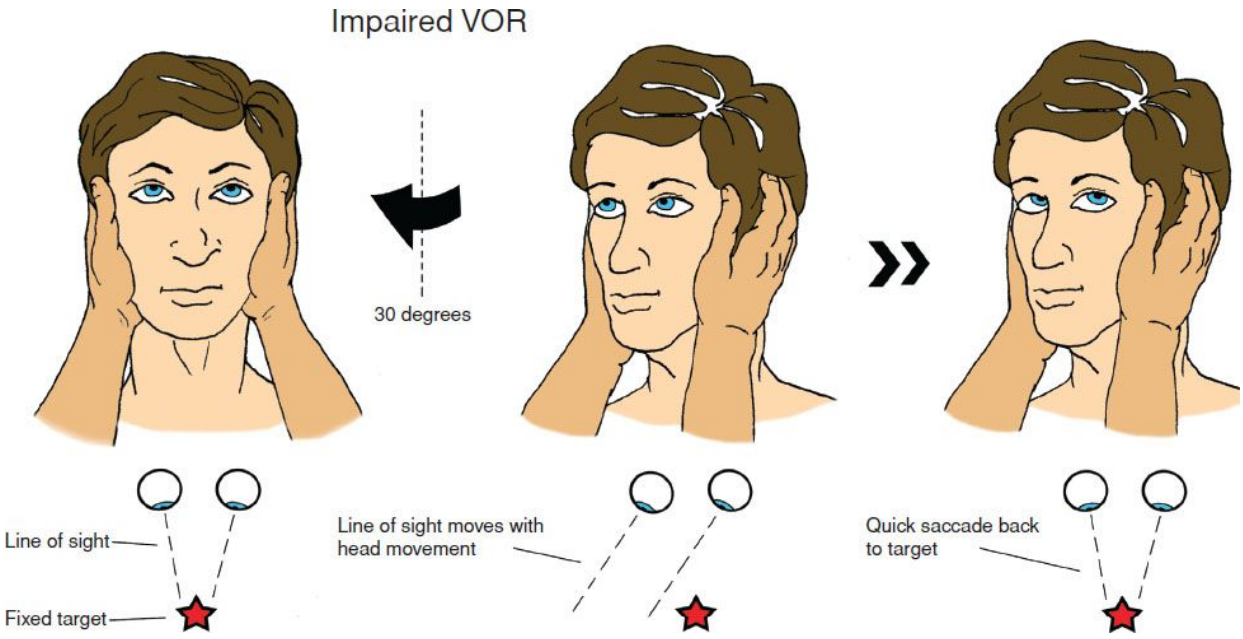

FIGURE 14.1 The head impulse test (HIT, sometimes referred to as the head thrust test) is a test of vestibular function that can be easily done during bedside examination. The HIT tests the vestibulo-ocular reflex (VOR), and can help to distinguish a peripheral process (vestibular neuritis) from a central one (cerebellar stroke). With the patient sitting on the stretcher, the physician instructs him to maintain his gaze on the examiner's nose. The physician holds the patient's head steady in the midline axis and then rapidly turns the head to about 20 degrees off the midline. **Panel 1:** The normal response (intact VOR) is for the eyes to stay locked on the examiner's nose. **Panel 2:** The abnormal response (impaired VOR) is for the eyes to move with the head, and then to snap back in one corrective saccade to the examiner's nose. The HIT is usually "positive" (i.e., a corrective saccade is visible) with a peripheral lesion (vestibular neuritis), and the test is normal (no corrective saccade) in cerebellar stroke. This occurs because the VOR pathway does not loop through the cerebellum. Occasional patients with small brainstem strokes may have a positive test because the VOR pathway does loop through the brainstem. Because it is the "positive" test that is reassuring with the head impulse test and the "negative" test that is worrisome, it is very important to only use the test in patients with the AVS. If one were to use the HIT in patients with pneumonia or with a fractured wrist, the HIT would be "negative" (worrisome for a

CNS event). Therefore, it is critical that it only be applied to patients presenting with an AVS.

There is one important issue with respect to the HIT that bears special emphasis. Because it is the "negative" or "normal" result (no corrective saccade) that is worrisome for a stroke etiology, it should only be done in patients with the AVS. For most elements of the physical examination, it is the abnormal result, which is the cause for concern, but for the HIT, it is the opposite. If one were to perform the HIT on normal individuals (or patients with pneumonia or sprained ankles), the result would be "normal" (and thus "worrisome"). Therefore, if one were to do a HIT on a patient with the EVS or the PVS, it would also be falsely "normal" and incorrectly suggest a central cause.

Nystagmus can be the clinician's friend. Patients with both vestibular neuritis and cerebellar stroke may have nystagmus. Merely reporting the presence or absence of nystagmus is not particularly useful and certainly does not distinguish benign peripheral etiologies from serious central ones. It is the nature of the nystagmus that can help to differentiate the two groups.

Patients with vestibular neuritis will have predominantly horizontal nystagmus, sometimes with a very slight torsional component (15,46). This may be present in primary gaze (patient looking straight ahead), and nearly always be present on gaze toward one side. When these patients look to the other side, they may still have nystagmus, but, if they do, the direction of the fast movement will be in the same direction as with the first side tested. The intensity of the nystagmus diminishes with fixation (46). In patients with CNS causes of dizziness, the nystagmus is usually still predominantly horizontal, but the direction of the fast component may "change direction." That is, when the patient looks to the left, the fast component beats to the left and when the patient looks to the right, the fast component beats to the right. Not very sensitive, this finding is found in approximately 20% to 50% of patients with central causes of dizziness (14,21); when present, however, it is very specific. Importantly, some normal patients will have slight

direction-changing nystagmus on extreme end gaze both right and left that resolves after a few beats and is symmetric; this is physiologic nystagmus.

Skew deviation is another relatively insensitive, but very specific finding indicating a CNS lesion in dizzy patients (14). Skew deviation is tested by performing the “alternate cover” test. With the patient instructed to focus on a fixed point, each eye is alternately covered over and then uncovered sequentially. This forces the patient to take up visual fixation first with one eye and then the other, which allows the examiner to assess whether the eyes are completely aligned. The examiner looks at the eyes to see if there is an upward or downward (hypertropia or hypotropia) correction as the eye is uncovered. This vertical misalignment is termed skew deviation. The presence of a horizontal misalignment (esophoria or exophoria) does not convey the same meaning.

Most patients with the EVS will usually be asymptomatic by the time they present to the ED; however if they are not, these same tests as above may be useful. Note however that a central localization does not necessarily mean a serious diagnosis. Migraine is a central phenomenon and patients with vestibular migraine may have findings that localize to the CNS.

In patients with the PVS, the Dix–Hallpike should be performed to test for BPPV of the posterior semicircular canal (the most common form). If this is negative and the history is strongly suggestive of BPPV, then the horizontal canal should be tested by the supine roll test (8). The Dix–Hallpike test is considered positive when there is reproduction of symptoms after several seconds of latency, with a burst of upbeat-torsional nystagmus and spontaneous resolution within 45 seconds, usually less. It should generally be positive on one side and negative on the other.

Torsional nystagmus is expected for BPPV (PVS) but pathologic in patients with the AVS. This illustrates how the “timing and triggers” category informs the “rules of nystagmus.” As well, patients with any cause of persistent dizziness, including CNS ones, will feel worse on head movements so tests producing only additional symptoms or

exacerbating pre-existing horizontal nystagmus should not be interpreted as positive.

DIAGNOSTIC TESTS

Unless a diagnosis is totally clear based on history and physical examination, and many times it will be (such as a patient with BPPV, vestibular neuritis, or hypovolemia), some basic testing probably makes sense. This is particularly true in elderly patients since the incidence of other diseases becomes increasingly common. Performing an electrocardiogram (ECG) may be useful in the dizzy geriatric patient and no obvious cause by history or physical examination. Checking the hematocrit, a basic metabolic profile including creatinine, and a stool guaiac may also be helpful. Beyond these basics, diagnostic should be targeted rather than "shotgun." If PE is the suspect diagnosis, a CT angiogram of the chest might be the best first test. If drug toxicity in a heart failure patient taking digoxin is considered, then a serum digoxin level might be an appropriate first test.

The less well a patient is able to communicate the details about their dizziness, the less well this system (or any other) will allow the physician to tailor their differential diagnosis and therefore, the subsequent testing. The important goal is to try to make a specific diagnosis. Because medication side effects are an important cause of chronic dizziness, an outpatient trial of stopping a medication might be the appropriate "test"; of course this should be coordinated with the primary care doctor.

It is very important to know the limitations of commonly used tests, especially computed tomography (CT) of the head for posterior circulation stroke (47). A recent study estimated the sensitivity of CT for acute posterior fossa stroke to be 42% (48), but studies with direct comparison to MRI scans suggest it could be as low as 16% in the first 24 hours (49). If stroke is a serious consideration, MRI with diffusion-weighted imaging is needed. Since hemorrhage is a rare cause of isolated dizziness, physicians should strongly consider starting with MRI (22). However the clinician must also be aware that even MRI is imperfect, and may miss up to 20% of posterior

circulation strokes in the first 24 to 48 hours after symptom onset (9,14).

CRITICAL INTERVENTIONS

- The treatment for BPPV is a canalith repositioning maneuver, most commonly the Epley maneuver if the BPPV is of the posterior semicircular canal (~85% of cases) (50,51). In elderly patients, one ought to make sure that the neck is sufficiently mobile to safely move the head and neck as needed; in these patients a different "side-lying" (Semont) maneuver may be used (34,52). Some patients with a typical history of BPPV will have a negative Dix–Hallpike and will not respond to an Epley maneuver. Many of these patients will have horizontal (lateral) canal BPPV diagnosed by supine roll test and can be treated with a Lempert barbecue roll maneuver (8). If a patient does not respond as expected (e.g., they have sustained nystagmus, downbeat nystagmus, no latency, bilateral positive positional test, or other new neurologic signs), the clinician should consider a rare BPPV mimic, which can be due to various CNS lesions (39).
- Patients with vestibular neuritis who present within 72 hours of symptom onset should probably be treated with steroids unless there is a contraindication (46,53). Although a vestibular "sedative" such as meclizine may be useful, its use should be limited to several days beyond which time it can impair vestibular compensation (46). As well, meclizine should not be used for BPPV, for which it has no therapeutic effect and can only potentially worsen symptoms due to its sedating side effects.
- With any peripheral cause of dizziness, it is important to ensure that the patient is well hydrated as there is a tendency for them to have become dehydrated because of nausea and decreased oral intake.
- Patients who have a posterior circulation stroke or TIA or high risk for one should be admitted to the hospital for further monitoring, vascular workup, and treatment. Treatments should be applied to prevent secondary progression or complications or

cerebellar stroke such as obstructive hydrocephalus or brainstem compression, as appropriate.

- Treatment for other specific diagnoses made are obviously based on the diagnosis made (heparin for PE, endoscopy and/or transfusion for a GI bleed, etc.).

DISPOSITION

The disposition is a function of two issues—specific diagnosis and general environmental safety. A patient with an AVS due to an ischemic cerebellar stroke requires admission both to diagnose and treat the underlying vascular lesion as well as to observe for deterioration from posterior fossa edema. Another patient with the exact same presentation but which is due to vestibular neuritis can be sent home with oral steroids and meclizine for symptomatic control. Therefore, disposition is partly a function of the underlying diagnosis. Although vascular risk factors may help stratify those at highest risk for TIA and stroke (e.g., using the ABCD2 rule) (54), care should be taken not to rely too heavily on age or related risks to exclude vascular disease—it is well documented that younger patients with vertebral artery dissection may present with dizziness or vertigo due to TIA or stroke (9) and are most likely to be misdiagnosed with dangerous consequences (55,56).

Simultaneously, the second issue is ensuring environmental safety. This is especially important in elderly dizzy patients. Dizzy patients may become dehydrated, worsening their symptoms, whatever their initial cause. Therefore, even the patient with vestibular neuritis might require admission if they are dehydrated and still sufficiently symptomatic such that they cannot keep up with fluids. Most patients with BPPV can safely go home after canal-repositioning treatment. However an elderly BPPV patient who is somewhat dehydrated, volume sensitive, and lives alone may need to some slow intravenous fluids as an inpatient prior to safe discharge. An elderly patient who has a few steps to get to the bathroom or lives with a healthy spouse may need a different disposition than another who normally has to climb a flight of stairs to do the same or lives alone.

Common Pitfalls

- Failure to identify timing and triggers to best define the category into which a patient falls.
- Failure to recognize that use of the word “vertigo” or “near fainting” does not necessarily signify a vestibular or CNS cause in the first case or a cardiovascular one in the second.
- Failure to recognize that peripheral causes of the AVS (vestibular neuritis) can closely mimic central causes (posterior circulation stroke). Posterior circulation TIA is becoming increasingly recognized.
- Failure to use bedside physical examination including gait testing and a focused oculomotor examination to differentiate peripheral from central causes of AVS. The HIT will be falsely worrisome if it is performed in patients who do not have AVS.
- Failure to categorize nystagmus differently based on syndromic category. Direction-changing horizontal nystagmus on gaze testing or predominantly vertical or torsional nystagmus is due to CNS disease in AVS, but not necessarily in PVS.
- Failure to focus more on the syndrome and examination findings than on the patient’s age or vascular risk factors—young patients have strokes too, and these are most likely to be missed.
- Failure to understand the limitations of CT scanning for cerebellar and brainstem infarction.

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SECTION III
Pain Management and Procedural Sedation

Section Editor: CARLO L. ROSEN

Medical Foramen

CHAPTER 15

Acute Pain Management

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Acute pain is the most common symptom for which patients seek emergency care, and analgesics account for one-third of all medications prescribed in US emergency departments (EDs). Studies consistently document that pain is often inadequately treated by physicians in the ED and other settings (1). Expediting appropriate and compassionate pain relief remains one of the greatest challenges in the practice of emergency medicine today (2).

Drugs used to treat pain act by reversing the underlying cause of pain (e.g., nitrates for angina) or by suppressing the symptom (i.e., the perception of pain). This chapter focuses on drugs used to treat the symptom of acute pain. Other medications that reverse the underlying cause of pain are discussed elsewhere in this book. Related discussions include the chapters on conscious sedation (Chapter 17), and chronic pain syndromes (Chapter 16).

PAIN ASSESSMENT

Current practice standards include pain assessment as the fifth vital sign. However, many challenges exist to the accurate assessment of pain in the ED.

Subjective Nature of Pain

Pain is an experience that has both physical and nonphysical dimensions. Physiologically, pain is mediated by a set of neurochemical events. At the level of consciousness, it is an event of personal suffering. The perception of pain and severity of suffering is

highly individual. These are affected by an individual's psychological and cultural conditioning, cognitive appraisal of pain, emotional state, and coping style.

The *language of pain* presents a challenge to clinical assessment. It can be very difficult for anyone to find words to convey either the quality of pain or its severity. Descriptions lack the preferred exactness of medical terminology. People resort to imagination and simile: "My back feels as if it is caught in a vise," or "My hand feels like it is on fire." Another problem is that patients and physicians use words differently. For example, a patient may use the word *sharp* to mean *severe,* whereas the physician may assume it to mean *knifelike.* Perhaps the most classic example is the patient with acute coronary syndrome who denies chest *pain* but will admit to chest *pressure* upon further questioning. Active listening and clarification yield critical information about pain severity and provide clues to etiology.

One of the most important aspects of the pain experience is the *meaning* it holds for the sufferer. Pain is often greater when its cause is perceived to be life threatening or when it is associated with emotional trauma. Conversely, pain that is perceived to offer some secondary gain can be easier to bear.

Objective Signs of Pain Are Unreliable

The emergency physician cannot rely on objective findings in estimating pain severity: The patient need not *appear* in pain to actually *be* in pain. There are no objective signs that can be used to accurately gauge the magnitude of a patient's pain. Indicators such as heart rate, blood pressure, respiratory pattern, facial expression, and body posture are not reliable. The presentation of pain may be obscured by the effects of medication such as β-blockers that blunt the adrenergic response to pain. Other medications may produce sedation but not analgesia: Drowsiness does not mean absence of pain. Pain may be underdiagnosed because of a patient's cultural bias toward stoicism or complex coping mechanisms, such as joking or maintaining a facade of being calm.

Equally unreliable is an estimate of pain severity based on its etiology. Can a toothache be more painful than salpingitis? Should

an ankle sprain hurt less than pleurisy? These questions cannot be answered, because suffering depends on each individual's pain threshold and sensitivity to a particular condition.

Utilizing the Patient's Self-Report

The subjective nature of pain means that the single most reliable method of assessing pain severity is the patient's self-report. Clinical judgment must always be guided by the patient's own assessment. This situation in which the patient knows more than the doctor is a role reversal with which many physicians feel uncomfortable. Nevertheless, accurate pain assessment must acknowledge the authority of the patient or the insight of a close family member or friend.

Asking the patient whether or not the pain is "tolerable" or "bearable" provides a straightforward assessment of treatment urgency. Patients can be assisted in conveying pain severity with a visual analog scale (VAS) or numeric rating scale (NRS); these have been validated for use in the ED (3,4) and either can be used. The VAS has been typically used for research purposes and requires the patient to physically mark a 100-cm line and the examiner to measure the mark with a ruler. The NRS is administered verbally with the examiner giving clues to the anchor points of 0 and 10. These scales need to be explained (e.g., 0 indicates no pain and 10 indicates the worst pain imaginable). Extreme ratings (e.g., 10 out of 10) should prompt clarification; these may indicate life-threatening pathology such as a subarachnoid hemorrhage or ischemic bowel, or alternatively reveal the severity of a patient's fear and anxiety. Asking a patient to relate their current pain to a past painful condition (e.g., pain of childbirth) can further assist the interpretation of pain scores.

Assessing pain in patients who are nonverbal or who have limited verbal ability is especially challenging. Numerous pain assessment scales are available that rely on behavioral indicators (e.g., grimacing and restlessness).

Distinguishing Pain-Avoiding Versus Drug-Seeking Behavior

The greatest impediment to accepting a patient's self-report of pain is the physician's concern of being manipulated into giving opioids to someone who is feigning illness. Bear in mind that *pain* is the most common reason for drug-seeking behavior. Even a legitimate patient may feel the need to dramatize distress to convince the doctor of his or her need. It may indeed be impossible to know for certain whether the patient's complaint is a sham; the gain of thwarting the possible abuser must always be weighed against the risk of withholding relief from the person who is truly suffering.

Opioid tolerance must not be misunderstood as drug-seeking behavior. Patients with chronic pain syndromes who are maintained on opioid therapy would require supplemental opioid dosing for superimposed acute pain syndromes. Methadone maintenance and combination of buprenorphine/naloxone (Suboxone) treatments for addiction do not provide analgesia and these patients would also require supplemental opioid if indicated. Patients treated with sustained-release naltrexone (Vivitrol) for alcohol or opioid dependence are a special case and require cardiopulmonary monitoring with dedicated personnel during reversal of opioid blockade for analgesia.

The diagnosis of drug abuse is based on a pattern of behavior that is often difficult to be established during a single ED encounter. Nevertheless, a few important steps can be taken: Perform a detailed history and physical examination, being alert to inconsistencies and signs of substance abuse (1); review prior ED and hospital medical records (2); obtain patient permission to confirm the medical history by contacting the personal physician or reviewing outside medical records (3); and develop an ED policy for evaluation and management of patients who raise concerns (4). This may include use of HIPAA compliant habitual patient files, criteria for urine drug testing, and developing a multidisciplinary case management system for selected patients.

Assessing Pain in Vulnerable Populations

As in any adult, pain in a child should be anticipated and aggressively treated. However, children are much less likely than adults to be given adequate analgesia for the same painful condition (5). This observation has been attributed not only to the difficulties inherent to pain assessment but to the persistent myth that young children do not experience or remember pain. Older children are generally able to describe their pain or point to pictures on a pain analogue scale. When assessing pain in younger children and infants, the quality of cry, facial expression, changes in vital signs, and impressions of the caretaker should all be taken into account.

Historically, pain has often been undertreated in older adults. Effective history-taking often requires greater time and patience. Verbal assessment may be limited due to dementia or delirium (6). Unconscious ageist bias may cause the EP to minimize or dismiss the patient's complaints.

Pain assessment depends upon communication and empathy. Medical care across lines of social difference between EP and patient poses challenges to both. Language discordance between physician and patient is an obvious impeding factor. Discordance in race, ethnicity, culture, class, gender, age, and physical ability is also significant. Studies have shown the undertreatment of pain in minoritized populations (1). Physicians must be willing to reflect on negative stereotyping and implicit biases that may interfere with accurate pain assessment, and be particularly self-aware when treating these patients.

ED MANAGEMENT

Expediting Relief

Pain relief should be timely. Unnecessary delays can often be averted. Patients often can and should be treated before a definitive diagnosis is established. Initial interventions can be nonpharmacologic (discussion follows). When the diagnosis depends solely on a laboratory or radiographic finding, there is no need for delaying analgesia while a time-consuming evaluation is proceeding.

The belief that analgesics, particularly opioids, will obscure the underlying diagnosis is generally unfounded. Although it is common to withhold such medication from a patient with abdominal pain who may need surgical evaluation, this practice is not supported by clinical studies (7,8). On the contrary, the judicious use of short-acting agents will serve the needs of both the patient and the consulting surgeon. Providing pain relief may actually enhance the patient's cooperation and improve the accuracy of the examination. Factors to consider in the administration of analgesics include severity of abdominal pain and speed of the surgical consultation (9). The emergency physician should consider administering analgesics with the target of reducing patient suffering but not obliterating the pain to allow a useful physical examination by the surgeon. Ironically, analgesics often continue to be withheld in the ED even after a decision has been made to take a patient to surgery. As the patient's most important advocate, the emergency physician must coordinate a rational and humane approach that takes into account the distress of the patient and the availability of the consultant.

Pain should be treated even if informed consent may subsequently be required. The practice of withholding all opioids from a patient who might later need to sign a consent form for surgery or other procedure is unjustified. Informed consent requires decisional capacity and voluntariness. Concern that *any* dose of opioids compromises decisional capacity is unfounded. Pain itself is distracting and mind altering; its relief can enhance rational decision making. Analgesia can be titrated without clouding consciousness; in rare cases, an opioid antagonist could be administered. The message that pain medication will be administered only after the consent form is signed is itself coercive and violates the requirement of voluntariness.

The physician should anticipate and treat pain before it develops. Good pain management involves anticipating pain prior to its onset or recurrence. Medications should be given before painful procedures (see Chapter 17). Similarly, patients should be discharged with appropriate medication for pain that may continue or recur.

Nonpharmacologic Therapy

A variety of simple and effective interventions can reduce pain.

Provide physical comfort measures. Attending to the overall physical comfort of the patient can alleviate factors that aggravate pain. This includes such actions as helping the patient find a more comfortable position, adjusting the lighting in the room, warming a patient who feels chilled, immobilizing injured extremities, and applying ice and elevation to closed bone and soft tissue injuries.

Provide psychological support. Physical suffering is amplified by fear, anxiety, and helplessness. Fear often relates to the thought that the cause of pain is life threatening or permanently disabling. New pain in a cancer patient raises the specter of disease progression. Patients with chest pain often present with a fear of myocardial infarction. A laborer may associate an acute shoulder injury with the alarming possibility of permanent loss of income. Information and appropriate reassurance may reduce the amount of analgesics needed. Supportive family members or friends should be allowed to sit with the patient. For unaccompanied patients, facilitating phone contact with a friend or family member may provide significant comfort.

It is also important to address the patient's expectations regarding pain medications. The emergency physician should let the patient know from the outset how much time it will take for the medication to work and whether to anticipate partial or complete relief. In addition, the physician can assure the patient that more analgesics can be administered as needed. This can allay a premature concern that the drug "is not working."

Distress also arises in response to the ED experience itself. Patients find themselves in a harsh and unfamiliar milieu, feeling vulnerable, dependent on strangers, and relatively helpless. Building rapport, dignifying interactions, and restoring some sense of control to patients are all essential in emergency pain management.

Pain and distress may also be helped by simple hypnosis or guided imagery techniques that relax the body and calm the mind. Videos, storytelling, and imagining favorite places or activities are distraction techniques used for pediatric patients. The role of

complementary and alternative therapies for adjunctive, acute pain management in the ED is not known. Although the overall analgesic efficacy of acupuncture has been established, limited research has been conducted on its application in the ED.

Pharmacologic Therapy

Dozens of drugs are available to treat pain. To select the best regimen for an individual patient, the emergency physician should consider the following:

1. How intense is the pain?
2. How quickly is pain relief required?
3. Can the patient take oral medications?
4. Are there contraindications to particular agents?

The answers to these questions help direct the choice of drug, dose, and route of administration.

Aspirin and Acetaminophen

Aspirin and acetaminophen are equally effective for the relief of mild-to-moderate pain. eTable 15.1 lists dosing recommendations for these drugs. Aspirin, the prototype nonsteroidal anti-inflammatory drug (NSAID), is believed to work by blocking cyclooxygenase (COX) enzymes, thereby inhibiting the synthesis of prostaglandins, which mediate both pain and inflammation. Unlike aspirin, acetaminophen lacks anti-inflammatory properties, and its central mechanism of action is poorly understood.

eTABLE 15.1
Dosing Information for Nonopioids

Drug	Dosage	Comments	Generic Formula Available
Acetaminophen (Tylenol)	650 mg q4h	No anti-inflammatory activity	Yes
	1,000 mg q6h		
Aspirin	650–975 mg q4h		Yes
Aspirin, nonacetylated (salsalate)	≤1,500 mg BID	No effect on platelet function	Yes
Choline magnesium trisalicylate	1,000–1,500 mg BID	Oral liquid available	Yes
Celecoxib (Celebrex)	400 mg initially	Selective COX-2 action	Yes
	200 mg BID	Contraindicated in sulfonamide allergy; caution in patients with cardiovascular disease	
		May offer less GI toxicity	
		No inhibition of platelet function	
Diflunisal (Dolobid)	1,000-mg load; then 500 mg BID		Yes
Diclofenac (Voltarin)	Diclofenac potassium: 50 mg TID to QID		Yes
	Diclofenac sodium: 75 mg BID		Yes
	Voltarin XR: 100 mg QD to BID		No
	Voltarin Gel: 2 g to upper joint; 4 g to lower extremity joint up to QID	Risk of dermatitis	No
			No
	Flector Patch: 1 BID	Risk of dermatitis	
Etodolac (Lodine)	200–400 mg q6–8h		Yes
Fenoprofen (Nalfon)	200–600 mg q6–8h		Yes
Ibuprofen (Motrin and others)	Oral: 400 mg q4–6h or 600 mg q6–8h or 800 mg q8h	Oral liquid available	Yes
	Parenteral: 400–800 mg IV (IM not approved). Slow infusion over ≥30 minutes.		
Indomethacin (Indocin)	25–50 mg TID	FDA approved only as an anti-inflammatory	Yes
		Frequency of adverse effects higher than other NSAIDs. Available as a suppository	
Ketoprofen	25–75 mg q6–8h		Yes
Ketorolac (Toradol, Sprix)	Oral: 10 mg PO q4–6h; max: 40 mg/day; start: 20 mg PO ×1 if <65 yo and >50 kg	Multiple black box warnings for all formulations (see text); limit to 5 days of therapy	Yes
	Parenteral: Dose: Initial 30 mg IV or 60 mg IM; then 30 mg IV/IM q6h; >65 yo or <50 kg, 15 mg IV/IM q6h, max 60 mg/day		
	Nasal: 1 spray QID		
Naproxen (Naprosyn, Aleve), Naproxen sodium (Anaprox)	500 mg initially, then 250–500 mg BID	Oral liquid available	Yes

Aspirin commonly leads to gastrointestinal (GI) distress. It very rarely causes a hypersensitivity reaction (more common among asthmatics with nasal polyps), characterized by bronchospasm, urticaria, rhinitis, and even shock. Aspirin inhibits platelet function, although salsalate, a nonacetylated aspirin product, does not have this effect. Because acetaminophen is free of these side effects and hypersensitivity risk, it is often the preferable drug. It is available as a rectal suppository for patients who cannot tolerate oral administration.

Nonsteroidal Anti-Inflammatory Drugs

At usual doses, NSAIDs are not as safe as acetaminophen but are generally better tolerated than aspirin. All six major chemical classes of NSAIDs inhibit COX but also act through nonprostaglandin-mediated pathways. Doses in the higher range are generally required to achieve anti-inflammatory effects, which may not be seen for a

few days. Although no oral NSAID has emerged as a consistently superior analgesic, it is widely believed that an individual patient may respond to one agent (or chemical class) and not another.

Nonselective Nonsteroidal Anti-Inflammatory Drugs

Older, nonselective NSAIDs inhibit COX-1 and COX-2 enzymes and may directly modulate neutrophil responses (see Chapter 304). When given as a single, full dose in the acute setting, most NSAIDs are more effective than aspirin or acetaminophen. In some situations, they provide analgesia equal or superior to certain oral opioids.

The onset of analgesia is within 1 hour for the majority of NSAIDs. For drugs with a relatively long half-life, such as diflunisal and naproxen, onset of analgesia is considerably longer but can be hastened by administration of a loading dose. For patients who cannot swallow pills, several agents are available in a liquid form eTable 15.1. For patients who are vomiting or for whom oral medications are contraindicated, rectal suppositories of naproxen and indomethacin are available; another option is parenteral ketorolac, discussed below.

Parenteral NSAIDs

Ketorolac was the first NSAID available in the United States for parenteral administration in the ED, either IM or IV. There is controversy as to whether the analgesic efficacy of parenteral ketorolac is generally comparable to that of parenteral opioids. For example, a single dose of IV ketorolac may be at least as effective as titrated, IV opioid in relieving pain in patients with renal colic (10). However, it is important to note that its efficacy in renal colic appears to be related to ureteral or renal prostaglandin mechanisms and may not be generalizable to other painful conditions. When studied in the ED setting, parenteral ketorolac does not provide superior analgesia to oral ibuprofen (11,12). Given parenterally, ketorolac does not act any faster than many oral NSAIDs: Drug effect is limited by the time to prostaglandin inhibition, not absorption. Thus, in many instances parenteral ketorolac offers no advantage

over far less expensive alternatives. Ketorolac also exists in oral and intranasal formulations.

Ketorolac is associated with the greatest adverse event potential among all NSAIDs and carries black box warnings for GI risk, cardiovascular risk, renal risk, bleeding risk, fetal risk, and risk to nursing infants. Risk increases with duration of use that should be limited to 5 days maximum for all forms of ketorolac. Dosages must be reduced in pediatric and geriatric populations.

Intravenous ibuprofen (Caldolor) carries fewer black box warnings and may be a safer alternative. It is not approved for IM administration.

Topical Diclofenac

Pharmacokinetic data suggest that topically applied NSAIDs can result in enhanced local concentrations without significant toxic systemic effects. Nevertheless, topical Diclofenac still carries black box warnings for cardiovascular and GI risks. Voltaren Gel and Flector Patch are approved for treatment of minor sprains, strains, and contusions. Patches are considered to provide more consistent dosing than gel. Both of these nongeneric preparations are expensive but do provide adequate pain relief and can be prescribed from the ED.

Selective COX-2 Inhibitors (COXIBs)

COXIBs selectively block COX-2, the form of COX that mediates inflammation, without affecting COX-1, the inhibition of which can produce gastric injury (13). They are no more effective than nonselective, less costly NSAIDs. Celecoxib (Celebrex) is currently the only COXIB available for prescription in the United States, with others withdrawn from the market owing to higher risk of cardiovascular thrombotic events. Celecoxib may have an improved gastric safety profile compared with nonselective NSAIDs but still carries a black box warning for GI risk. COXIBs do not interfere with platelet function. They may be considered for a highly select group of patients at risk for peptic ulcers who have a well-established

indication for NSAID treatment, or perhaps for patients at increased risk of bleeding.

Advantages and Disadvantages of Nonsteroidal Anti-Inflammatory Drugs

NSAIDs do not cause respiratory depression and rarely cause mental clouding. Given their anti-inflammatory properties, they treat the cause and the symptom of pain in conditions such as inflammatory arthritis or soft tissue injury. NSAIDs do not have abuse potential. NSAIDs carry black box warnings for cardiovascular and GI risks. Ketorolac carries additional black box warnings as mentioned above. The risk of cardiovascular thrombotic events increases with the presence of concomitant risk factors and duration of use. While other COXIBs may have posed the greatest cardiovascular risk, celecoxib may be associated with a lesser risk than nonselective NSAIDs (14).

Dyspepsia, the most common side effect, can be minimized by administering the drug with food or an antacid. Less commonly, NSAIDs lead to ulcers and upper GI bleeding and perforation, complications that are seen more with chronic rather than short-term use but may occur any time during treatment and without warning, especially in the elderly. NSAIDs are thus strongly contraindicated in patients with active ulcer disease and should be given with great caution to those with a history of upper GI bleeding. The incidence of GI bleeding may be dose dependent; daily doses of ibuprofen exceeding 1,500 mg are associated with increased risk. Other risk factors for GI complications include patient age older than 60 years and concurrent steroid or anticoagulant use (15). In such high-risk patients, the chance of GI bleeding can be reduced by coadministration of a proton pump inhibitor or misoprostol, at least with long-term NSAID use. The benefit these agents offer with short courses of NSAID is less well established. Other agents that were often used for prophylaxis of NSAID-related GI complications are either ineffective (antacids, sucralfate) or marginally effective (H_2 blockers). COXIBs, without gastroprotective drugs, may represent another therapeutic option in patients with risk factors for GI bleeding.

All NSAIDs, *including* COXIBs, may affect the kidneys, causing fluid retention and renal insufficiency, and possibly acute renal failure. Patients at greater risk for renal complications include those with chronic renal insufficiency, those with reduced renal perfusion (congestive heart failure or cirrhosis), and those taking diuretics or angiotensin-converting enzyme inhibitors. NSAIDs should generally be prescribed for no more than a few days in this patient population.

Because they interfere with platelet function, nonselective NSAIDs predispose to bleeding and should not be given to patients with thrombocytopenia or intrinsic clotting abnormalities. They should generally not be used in patients receiving anticoagulants and in those suspected of internal bleeding, as in the case of severe headache with possible subarachnoid hemorrhage.

Very rarely, NSAIDs cause hypersensitivity reactions such as urticaria and bronchospasm; patients who are sensitive to aspirin are at greater risk. NSAIDs are generally contraindicated during pregnancy, particularly in the third trimester, because of known effects on the fetal cardiovascular system (closure of the ductus arteriosus).

Opioid Analgesics

Opioids are usually the first-choice drugs for the prompt relief of severe, acute pain. Unlike the NSAIDs, they have no ceiling on analgesic effect. Given IV, they work within minutes, and their effect can be titrated and reversed. Many patients treated with these agents, however, do not receive adequate pain relief because of physicians' misconceptions about correct dosing, route of administration, and adverse effects.

Dosing by Titration

The effective analgesic dose varies considerably among patients; the *correct* dose of opioid is the dose that works. While some adult patients may respond to a low dose (i.e., morphine 2 mg IV), others may require higher doses for adequate pain relief. The "given" initial doses published in various references can serve only as general guidelines (16). Therefore, in the initial treatment of severe pain, it

makes sense to titrate small frequent doses to effect. In pediatrics, weight-based dosing (i.e., morphine 0.1 mg/kg/dose IV) is traditionally used to guide safe and effective initial treatment (Table 15.1 and eTable 15.2).

TABLE 15.1
Dosing Guidelines for Parenteral Opioids

Drug	Route[a,b]	Dosage	Comments
Morphine	IV	Titrate 2–5-mg increments q5–10 min Peak analgesia in 10–20 min Average = 10 mg q3–4h	Preferred first-line agent in most situations
	IM/XC	Average = 10 mg q3–4h	
Fentanyl	IV	Titrate 25–50-µg increments q2–3 min Peak analgesia in 3–5 min Duration 30–60 min	Ideal for short procedures No histamine release
	IM/SC		Not suitable for the ED
Meperidine (Demerol)	IV	Titrate 12.5–50-mg increments Peak analgesia in 5–10 min Average = 100 mg q2–3h	Risk of unique CNS toxicity with repeated dosing
	IM/SC	Average = 100 mg q3h	IM/SC injection is very irritating to tissue
Hydromorphone (Dilaudid)	IV	Titrate 0.5–1-mg increments Peak analgesia in 5–15 min Average = 1.5 mg q3–4h	High-solubility benefits SC injection
	IM/SC	Average = 1.5 mg q3–4h	
Butorphanol (Stadol)	IV	Titrate 0.5–2-mg increments Peak analgesia in 4–5 min Average = 2 mg q3–4h	Mixed agonist–antagonist May be preferred in biliary colic
	IM/SC	Average = 2 mg q3–4h	

Note: Intervals are approximate. Individual patients may require dosing either more or less frequently.
Caution: Dosing may need to be adjusted in the elderly, patients weighing <50 kg, and those with renal or hepatic insufficiency.
[a]IV route is preferred for faster onset and ability to titrate to effect.
[b]Rapid IV administration increases incidence of respiratory depression, hypotension, nausea, and itching; IV administration should be slow (over 4 to 5 minutes), with the patient recumbent.

eTABLE 15.2
Pediatric Dosing Guidelines for Drugs for Pain Management[a]

Drug	Route	Dosage (mg/kg/dose)
Morphine	IV	0.1–0.2
Fentanyl	IV	0.001–0.003
	Oral/transmucosal	0.005–0.015
Codeine	Oral	0.5–1 q4–6h
Acetaminophen	Oral/rectal	10–15 q4–6h
Ibuprofen	Oral	10 q6–8h

[a]For further pediatric dosing guidelines, see Chapter 220, "Pediatric Procedural Sedation, Anxiolysis and Analgesia."

Once satisfactory analgesia is achieved, another common pitfall is to withhold a subsequent dose until a "standard" dosing interval has elapsed. Statements about "average duration of action" provide only a rough estimate and some patients require more frequent dosing.

A common error is to mistake an inadequate dose with an ineffective agent; this is the tendency to switch opioids when the first dose does not relieve pain, rather than upwardly titrating the initial agent of choice. The upper limit of an opioid dose is determined by its side effects.

Equianalgesic Dosing and Opioid Cross-Tolerance

The potency of opioids varies widely. The emergency physician must understand how to determine the equianalgesic dosages of various agents. See Table 15.2 for dosage equivalencies.

TABLE 15.2
Oral Opioid Dosing Information

Drug	Analgesic Equivalence (mg)[a]	Usual Starting Dose (mg)[b]	Usual Interval (hrs)
Morphine (MSIR, Roxanol, others)	30	15–30[c]	3–4
Morphine: sustained release (MS Contin, Oramorph SR)	30	30[c]	8–12
Meperidine (Demerol)[d]	300	50–100	2–3
Codeine (in Tylenol #3, others)[e]	200	30–60	3–4
Oxycodone (Roxicodone, also in Percocet, Percodan, Tylox, others)	20–30	5–10	3–6
Hydrocodone (in Lorcet, Lortab, Vicodin, others)	30[f]	5–10	3–6
Hydromorphone (Dilaudid)	7.5	4–8[c]	2–3
Tramadol (Ultram)	N/A	25–50	4–6

Note: Addition of a nonopioid may allow lower dosing of an opioid. In using combination products, be careful not to exceed the allowable dose of the nonopioid constituent.
Intervals are approximate. Individual patients may require dosing either more or less frequently.
Caution: Dosing may need to be adjusted in the elderly, patients weighing <50 kg, and those with renal or hepatic insufficiency.
[a]Doses equianalgesic to IV morphine 10 mg and IV meperidine 100 mg.
[b]Doses in this column are not equianalgesic.
[c]Usually reserved for chronic, severe pain.
[d]Meperidine has a unique CNS toxicity with repeated dosing and is not recommended as a first-line agent. See text.
[e]Doses >60 mg are not recommended. See text.
[f]Limited data available.

Opioid cross-tolerance poses the critical exception to calculating equianalgesic dosing. This phenomenon is relevant to pain patients who present to the ED on chronic opioid therapy such as oxycodone. The patient will be somewhat habituated to oxycodone and more sensitive to a different opioid. Should the physician need to treat pain with a different agent—with IV morphine, for example—the calculated equianalgesic dose must be *reduced* initially by 25% to 50%.

Route of Administration

IV administration of opioids is preferable to the IM route for several reasons. Absorption is more reliable, and repeated dosing is painless. It also leads to more rapid onset of analgesia; IV morphine begins to work within 5 minutes (peaks in 10 to 20 minutes), whereas IM morphine requires 10 to 30 minutes to take effect (peaks in 30 to 60 minutes) (16). It is easier to titrate the opioid dose using the IV route. It is also important to keep in mind that the frequency and severity of several side effects, such as respiratory depression,

hypotension, histamine release, and nausea and vomiting, are related to the *speed* of IV injection. Side effects can be minimized if drugs are injected over several minutes, rather than by rapid push. See eTable 15.3 for a summary of safety guidelines for IV administration of opioids.

eTABLE 15.3
How to Administer Intravenous Opioids Safely

1. Initiate infusion of normal saline before administering opioids.
2. Keep the patient in a recumbent position.
3. Have naloxone and airway management equipment available.
4. Adjust dose downward in patients with hypotension, chronic obstructive pulmonary disease, or potential for airway compromise.
5. Give SLOWLY, over 3–5 minutes to minimize side effects.
6. Titrate to pain relief.
7. Supplement careful observation with pulse oximetry or apnea monitoring.

Major Risks

- CNS depression leading to hypoventilation or aspiration
- Hypotension

It is not clear which is the second best parenteral route for opioid administration. Subcutaneous (SC) injection is typically less painful than IM administration; however, this benefit may be offset by an even more delayed onset of action.

Oral opioids are discussed below. When both IV and oral routes are unavailable, alternatives include rectal suppository (morphine, hydromorphone, and oxymorphone), sublingual tablet (buprenorphine), and even a nasal spray (butorphanol). Studies have reported use of nebulized and intranasal administration of fentanyl in a pediatric population. Transdermal fentanyl patches are inappropriate for acute pain management since a therapeutic blood level may not be reached for 24 hours.

Adverse Effects

All opioid analgesics share certain side effects, although some occur more with one drug than another. A patient who has had a problem with one agent may be able to tolerate another opioid without difficulty.

Of all the potential adverse effects, respiratory depression is the most dangerous. Using sophisticated testing, it is possible to show that therapeutic doses of most opiates cause some degree of respiratory depression in nearly all patients. Most of the time, this is not clinically important. However, patients with diminished respiratory reserve, such as those with severe chronic obstructive pulmonary disease or massive obesity, may stop breathing after receiving these drugs. Even in those with normal reserve, removal of a painful stimulus, as occurs with the reduction of a dislocated joint, can precipitate respiratory depression. Except in the case of massive overdose, respiratory arrest does not occur suddenly but is heralded by a decreased respiratory rate and level of arousal.

Hypotension is the second major hazard of opioid use. Through a variety of mechanisms, opioids, particularly those given parenterally, may cause peripheral vasodilation. This seldom affects blood pressure in the supine patient, but the ambulatory patient may experience significant orthostatic hypotension. Volume-depleted individuals are at increased risk for hypotension regardless of body position. Hypotension from opioids generally resolves spontaneously within a few minutes; if necessary, IV fluids and possibly naloxone are effective treatments.

Opioids occasionally trigger the release of histamine from mast cells. Because this occurs through a nonimmunologic mechanism, it is technically not an allergy. Clinical consequences include itching, urticaria, bronchospasm, and hypotension, which are not responsive to naloxone. The agents most frequently implicated in these reactions are morphine, followed by codeine and meperidine. Fentanyl has practically no potential for this complication.

Rapid administration of high-dose fentanyl has been associated with muscle rigidity, including chest wall spasm, which may require treatment with IV naloxone. This is usually seen in the context of

fentanyl anesthesia and may be treated with a neuromuscular blocking agent.

Opioids commonly cause sedation and occasionally produce confusion. Therefore, ED patients should be warned not to drive vehicles or operate power tools when they take them. Opioids present a special set of problems for head-injured patients. They may interfere with the evaluation of central nervous system (CNS) function. The respiratory depressant effect of opioids is exaggerated in this group of patients, and the resultant hypoventilation may actually increase intracranial pressure, mediated by cerebral vasodilation in response to an elevated pCO_2 (16).

Opioids have other effects on the genitourinary and GI systems. They may cause urinary retention, particularly in older men with underlying prostatism. They can sometimes cause abdominal pain or dyspepsia. Nausea and vomiting can be minimized by administering the drug to the patient in the supine position and, if necessary, with an antiemetic (Jaffe 2001). GI side effects, if severe, can be reversed with naloxone. Opioids are constipating even with short-term use; when discharged on a course of opioids, patients should be warned to expect this and advised to use laxatives as necessary. Despite historic concerns over opioids raising biliary pressures, morphine appears to be safe and effective for the relief of biliary colic (17).

Opioids have the potential to mask the diagnosis of serious abdominal disease. Although they can be given safely to patients with abdominal pain who are under close observation, prescribing them for patients who are sent home with undiagnosed abdominal pain is potentially dangerous.

Polypharmacy, multiple comorbidities and an aging brain all make adverse events more likely in older adults (6). Lower initial dosing and frequency, and slower upward titration, are the rule when treating this population.

Choosing an Injectable Agent

A variety of choices of parenteral analgesic agents exist for the emergency physician. Selection is based largely on physician preference as well as the patient's condition.

Morphine is the traditional first-line parenteral narcotic. No other opioid is superior in relieving pain. It is easy to dose and titrate, is relatively inexpensive, and has a relatively long duration of action. **Fentanyl** is another ideal IV agent for performing short, painful procedures because of its very rapid onset and limited duration of action. **Hydromorphone** (Dilaudid) provides effectiveness similar to morphine with a similar side-effect profile, although a lower incidence of pruritus has been noted with its use (18).

Partial agonist and agonist–antagonist opioids were developed to provide analgesia with less sedation, respiratory depression, nausea, and addiction potential (19). Practical benefits, however, have been limited. **Butorphanol** (Stadol) and **buprenorphine** (Buprenex) are available as parenteral agents. **Pentazocine** produces psychotomimetic symptoms, including disorientation, paranoia, and hallucinations, in as many as 7% of treated patients. All drugs in this class can precipitate withdrawal when they are given to patients addicted to pure opioid agonist. These drugs offer no advantages over the strong opioid agonists, except perhaps in the management of biliary pain.

Meperidine (Demerol), another available parenteral opioid, offers few, if any, advantages over morphine. Because of multiple safety concerns, meperidine is not a recommended agent and its use has been eliminated or restricted in many hospitals. With repeated dosing, meperidine has its own peculiar CNS toxicity caused by normeperidine, an active metabolite that is excitatory and may cause mood irritability, agitation, tremors, myoclonus, and seizures. Normeperidine has a longer half-life than its parent compound, accumulating with repeated dose administration of meperidine and thus increasing the risk of CNS toxicity, especially in patients with renal insufficiency. Meperidine should not be given to patients at risk for seizure. It should also be avoided in those receiving monoamine oxidase (MAO) inhibitors because of the potential for a poorly understood interaction, characterized by delirium and hyperthermia, which may be fatal. Patients with renal or hepatic insufficiency require special considerations. See **Table e-15.3**.

Adjuvant Parenteral Agents

Historically, a number of drugs have been administered along with parenteral opioids to minimize adverse effects by reducing the amount of opioid needed to treat pain. Phenothiazines can reduce GI side effects. However, when given along with an opioid, sedative effects are increased, but analgesia is not (16).

The antihistamines hydroxyzine (50 to 100 mg IM or 1 mg/kg IM) and diphenhydramine (25 to 50 mg IM or IV) have been combined with opioids to potentiate analgesia and to provide limited antiemetic effects. Although hydroxyzine does have additive analgesic properties, this practice poses two problems. First, it requires a painful, intramuscular injection. Second, it may not, in fact, decrease adverse effects because hydroxyzine itself is a mild respiratory depressant (20). No study has examined whether the combination of an opioid plus hydroxyzine produces respiratory depression less frequently than an equianalgesic dose of opioid alone.

Choosing an Oral Agent

Table 15.2 lists dosing guidelines for a number of commonly used oral opioids. Because opioids experience a significant first-pass hepatic metabolism, a higher oral than parenteral dose is necessary to achieve the same level of analgesia. See **Table e-15.4** regarding patients with hepatic or renal insufficiency. **Table 15.3** lists DEA Drug Schedules.

TABLE 15.3
DEA Drug Schedules

Schedule	Abuse Potential	Examples
I	High; no accepted medical use	Heroin, marijuana, methaqualone
II	High; less abuse potential than schedule I drugs, with use potentially leading to severe psychological or physical dependence	Cocaine, methadone, hydromorphone, oxycodone, fentanyl, methylphenidate (Ritalin), Adderall
III	Moderate to low; abuse potential less than schedules I and II more than schedule IV	Combination products with less than 15 mg of hydrocodone/dosage unit (Vicodin), products containing less than 90 mg codeine/dosage unit (Tylenol #3 and #4), ketamine
IV	Low	Benzodiazepines (alprazolam, clonazepam, diazepam, lorazepam) and nonbenzodiazepine hypnotics (eszopiclone, zaleplon, zolpidem)
V	Lower than schedule IV	Cough preparations with less than 200 mg of codeine or per 100 mL. (Robitussin AC); diphenoxylate (Lomotil); pregabalin (Lyrica)

Data from http://www.justice.gov/dea/druginfo/ds.shtml. The United States Department of Justice—Drug Enforcement Agency Drug Scheduling.

Codeine is a poor choice of agent for many reasons, despite its widespread use. It is a relatively weak analgesic with a relatively high incidence of GI side effects, especially nausea. NSAIDs are as effective, or more effective, than standard codeine doses of 30 to 60 mg (21). At higher doses, the analgesic effect does not increase significantly, but the rate of side effects is higher. Some patients are poor CYP2D6 metabolizers of codeine and receive no analgesic benefit, whereas a significant number of patients are ultrarapid metabolizers and experience greater-than-expected analgesic effects and side effects. Codeine may have a lower addiction potential than other oral opioid agents. Preparations containing no more than 90

mg per dosage unit are classified by the DEA as schedule III that allows more liberal prescribing.

Hydrocodone is an excellent analgesic. However, similar to codeine, patients may be poor CYP2D6 metabolizers and not receive adequate analgesia, whereas others are ultrarapid metabolizers and may experience faster analgesia but increased toxicity. Preparations containing no more than 15 mg per dosage unit are classified as DEA schedule III.

Oxycodone, another excellent analgesic, is a schedule II medication because of its higher potential for addiction and abuse. It is available as a single agent or in combination with acetaminophen.

The main applications for oral **morphine** and **hydromorphone** (Dilaudid) are in cancer and sickle cell pain. Oral morphine is available in an immediate- and a sustained-release preparation. Oral transmucosal **fentanyl** (Actiq) is a rapid-acting analgesic useful in breakthrough symptoms in patients with severe chronic pain. All three are schedule II medications.

Tramadol (Ultram) is a weak opioid agonist that also inhibits reuptake of serotonin and norepinephrine. It is not a federally scheduled drug but it has abuse potential and some states classify it as a schedule IV controlled substance. It is a centrally acting synthetic analgesic compound with effects comparable to opioid analgesics, approved for the short-term treatment of acute pain in adults. The most common side effects are nausea, vomiting, dizziness, somnolence, and constipation. It does not appear to produce respiratory depression or hypotension, probably because of selective opioid receptor binding. It may or may not be as effective as codeine or hydrocodone in combination with acetaminophen (22). Tramadol is contraindicated in patients taking an MAO inhibitor, as it inhibits monoamine uptake.

Meperidine (Demerol) should not be prescribed routinely. It is a DEA schedule II drug with a short analgesic duration and unique CNS toxicity as discussed earlier in detail. Propoxyphene (Darvon, Darvocet) no longer has FDA approval due to cardiac toxicity and should not be prescribed. Pentazocine is the only oral, mixed agonist–antagonist agent. It is only available in combination with

acetaminophen and is rarely prescribed because of psychotomimetic adverse effects.

COMBINATION THERAPY

Rational pain management often involves combining analgesics of different classes. Adding acetaminophen (or an NSAID) to an opioid may produce better analgesia than a double dose of either agent alone (23). One possible explanation for this is that the drugs work by different mechanisms. Combination therapy may permit a reduction in the opioid dose and a corresponding reduction in opioid-associated side effects.

Many formulations that are commercially available combine aspirin, acetaminophen, or an NSAID with codeine, hydrocodone, or oxycodone. Close attention must be paid to the risk of acetaminophen toxicity with the increasing popularity of acetaminophen containing OTC products, including cough and cold formulations. Patients are often unaware of the acetaminophen content in these products and associated risk of liver injury with amounts exceeding 4 g/day.

Therapy does not need to be restricted to these fixed-ratio products; prescribing the constituents separately may permit greater therapeutic flexibility. For very severe pain, the opioid dose can be increased without risking toxic doses of acetaminophen or NSAIDs. Conversely, as the pain improves, the patient can taper off the opioid but continue the nonnarcotic. For the outpatient treatment of severe pain, one common regimen is ibuprofen 2,400 mg/d in divided doses, along with oxycodone 5 to 10 mg every 4 to 6 hours. An acetaminophen and codeine elixir is available for use in children.

PRESCRIBING OPIOIDS AND ADDICTION RISK

The past decade has seen a precipitous rise in opioid prescribing, opioid abuse, and opioid-related adverse events and deaths. Use of opioids in treating many *chronic* pain conditions may pose far greater risk than benefit. There is ample evidence that opioid dependence and abuse often begins with an opioid prescription. Nevertheless, opioids are an irreplaceable mainstay of acute pain management in

the ED. Patients with acute bone or visceral pain being discharged from the ED may require an opioid prescription. Current guidelines for appropriate prescribing include the following (24).

- Evidence-based use of a nonopioid whenever possible.
- Limiting opioid prescriptions to 3 days as a general rule with appropriate follow-up.
- Screening for addiction and addiction potential. Screening tools are available, such as the CAGE questionnaire adapted to include drug abuse (CAGE-AID). In some cases, prescription of an opioid may still be clinically appropriate but would require special follow-up and case management.

AGENTS FOR TREATING NEUROPATHIC PAIN

Acetaminophen, NSAIDs, and opioids are the key analgesics for treating acute pain in the ED. However, patients discharged from the ED with neuropathic pain (e.g., herpes zoster or radiculopathy) may benefit greatly from the prescription of a second agent specific to treating neuralgia. **eTable 15.4** lists typical agents commonly used for this indication.

eTABLE 15.4
Outpatient Medicines Used for Neuropathic Pain

Agent (Class)	Starting Dose	Comments
Gabapentin (antiepileptic)	300 mg TID	Main side effect is dose-dependent drowsiness that abates over time. Limiting use to bedtime only is better tolerated but less effective is better tolerated but less effective. Can also start at subtherapeutic dose of 100 mg TID and increase as tolerated to minimum effective dose of 300 mg TID
Amitriptyline (tricyclic antidepressant)	10–25 mg qHS	Main side effects are drowsiness and dry mouth. Avoid in patients with AV cardiac conduction abnormalities or prolonged QT
Transdermal lidocaine (topical analgesic/anesthetic)	Apply patch to affected area, 12 hrs on and 12 hrs off	Apply only over intact skint

Common Pitfalls

- Relying too much on “objective” signs of pain severity and not enough on the patient’s self-report.
- Confusing pain avoidance behavior with drug-seeking behavior.
- Misinterpreting sedation as pain relief.
- Delaying analgesia until a definitive diagnosis is made.
- Withholding opioid analgesia because consent for surgery or other procedure may later be necessary.
- Failing to screen for addiction potential.
- Administering opioids IM or SC when the IV route is superior.
- Infusing IV opioids too rapidly and when the patient is not supine.
- Choosing a dosage and dosing interval based on standard guidelines instead of individual patient response.

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CHAPTER 16

Chronic Pain Syndromes

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Pain is typically defined as an unpleasant sensory and emotional phenomenon associated with actual or potential tissue damage. Chronic pain is defined as a sustained painful experience that in most cases persists beyond the time in which tissue damage occurs. Although acute pain typically has a rapid onset coinciding with tissue damage, it typically resolves as tissue heals. It serves as a biologic warning of potential illness or injury, prompting the individual to protect the painful area and seek medical attention. Although distressing and anxiety provoking, it usually can be treated effectively with proper selection and use of analgesic drugs.

Chronic pain differs from acute pain in many respects (Table 16.1). In chronic pain, the symptom of pain itself often becomes more of a problem than its underlying cause, altering the patient's well-being and frequently causing both disability and depression. It has been estimated that about 30% of the US population suffers from chronic pain, and the loss of productive time as a result costs more than $60 billion a year (25); additional expenditures are also incurred from health care and litigation related to chronic pain syndromes. The treatment of chronic pain is complex and difficult. Success in treating chronic pain typically requires a multidisciplinary team approach, using various regimens of pharmacotherapy, physical therapy, and behavioral therapy to both reduce pain and restore function.

TABLE 16.1
Differences Between Acute and Chronic Pain

Acute Pain	Chronic Pain
Usually as a result of tissue damage	Often no identifiable pathology
Is related to underlying illness	Is the problem itself
Has a biologic purpose	No biologic purpose
Responds to typical analgesics	May not respond to typical analgesics
Straightforward treatment	Complex treatment
Causes anxiety	Causes depression

CLINICAL PRESENTATION

Patients with chronic pain syndromes are commonly encountered in the emergency department (ED) and often present a management challenge for the emergency physician. Some present with vague signs and symptoms and often are not definitively diagnosed on the first encounter. Treatment is typically complex, requiring several regimens of varying effectiveness. Many patients have other psychological disturbances and a protracted course of exacerbations and remissions, with failures of various therapies. They may be demanding and frustrating for the clinician, because their conditions are not easily managed. Patients may feel uncomfortable with a physician who has not been their regular caretaker. The presentation of patients requesting controlled substances for illicit means may overlap with the presentation of chronic pain exacerbations. As a result, malingering or drug-seeking behavior may inappropriately be suspected in patients with chronic pain syndromes.

In each patient with chronic pain, the development of progressive or new pathology must be considered, and the physician should not simply assume that a patient's chronic pain exacerbation is nothing more than a worsening of an already existing disease process. For example, in a patient with increasing chronic low back pain, one must consider the possibility of new spinal cord pathology. Simply providing analgesics without consideration of acute pathology may result in missing serious disease.

Chronic pain syndromes typically fall into one of the categories listed in Table 16.2.

TABLE 16.2
Categories of Chronic Pain Syndromes

Categories of Chronic Pain Syndromes
1. Pain as a result of prolonged tissue destruction as a result of malignancy or other terminal illness (e.g., AIDS)
2. Pain as a result of dysfunction of the central or peripheral nervous system (e.g., trigeminal neuralgia)
3. Pain as a result of well-known painful syndromes (e.g., fibromyalgia)
4. Pain with no objectively confirmed cause

Although patients with pain as a result of prolonged tissue destruction can be treated successfully with appropriately titrated analgesics in the ED, patients in the remaining categories should also be referred to a chronic pain management center whenever feasible, to facilitate the management of the chronic pain syndrome in a multidisciplinary manner.

Communication between the emergency and pain service physicians fosters a team approach to the management of chronic pain exacerbations. For example, a pain contract and/or specific patient care plan may be developed between the patient, the pain service, the primary care physician, and the ED regarding when the patient will be expected to present to the ED for a pain exacerbation, the analgesic that will be used after appropriate evaluation, and the quantity of analgesics to be prescribed on discharge.

Although chronic pain as a result of any cause may be exacerbated by psychological factors, the pathophysiology of chronic pain without obvious tissue pathology is still being elucidated. Prolonged noxious sensory input from the periphery may result in self-sustaining central neural activity, possibly by reducing inhibitory input into the central nervous system (CNS) and producing changes in neurontransmission at spinal neuron synapses

(27). Activation of *N*-methyl-D-aspartate (NMDA) receptors appears to be central to this process. This phenomenon, known as "windup," essentially produces a memory effect for pain perception in the CNS. These effects persist despite the lack of ongoing tissue injury. As a result, patients become increasingly more sensitive to painful stimuli.

Chronic pain commonly causes the patient to lose a sense of control over his or her environment. Allowing patients to become passively dependent on health care practitioners and medical therapy only feeds this vicious cycle of illness and the helpless victim.

Drug Abuse and Addiction

Drug abuse and addiction are unfortunate yet common problems in our society, and approximately 8% of all adult patients are actively abusing illicit drugs. Unintentional prescription opioid analgesic deaths increased more than 500% between 1999 and 2010, continues to rise, and is now higher than deaths from cocaine and heroin use combined, as well as higher than annual deaths from vehicular trauma (13). Drug abusers (whether or not they suffer from chronic pain) tend to patronize EDs on a frequent basis to obtain opioid analgesics. Because of this, ED staff members may develop a bias against many chronic pain patients. Because it may be difficult to differentiate patients with exacerbations of chronic pain from patients who are seeking drugs for abuse and there are no validated tools to help the clinician distinguish abuse from undertreated pain, many patients with real exacerbations of chronic pain are consequently labeled as drug abusers.

It is important to distinguish between opioid dependence, tolerance, and addiction. *Dependence* refers to the physical phenomenon in which sudden withdrawal of the drug results in a drug-specific withdrawal syndrome. This occurs in patients chronically using opioid analgesics, whether for legitimate or illicit purposes. *Tolerance* refers to the physical phenomenon of a decrease in drug effect at a specific dose over time, requiring increasing doses

to produce the desired effect, whether it is analgesia or euphoria. Tolerance often occurs as a result of downregulation or desensitization of opioid receptors, resulting in a physiologic resistance to opioid therapy (2). Additional physiologic changes may occur at the cellular level with chronic opioid therapy, which may result in abnormally increased sensitivity to painful stimuli.

Dependence and tolerance must be distinguished from *addiction,* which is the psychobiologic state of compulsive use despite signs of toxicity, preoccupation with obtaining and using a substance, and inability to function as a result of compulsive use. With legitimate prolonged use of opioid analgesics for chronic pain, dependence and tolerance do occur; however, addiction is uncommon. Conversely, when pain medication is withheld from patients with chronic pain, such patients may learn pain avoidance or maladaptive behaviors to obtain opioids. These drug-seeking behaviors do not imply addiction but inappropriate techniques used by patients to satisfy a physiologic need state. This phenomenon is often referred to as *pseudoaddiction.* Underdosing and giving pain medication on an as-needed basis for sustained pain (rather than around-the-clock dosing) contribute to this phenomenon, as the patient learns to express both exaggeration of symptoms and maladaptive behavior to obtain the reward of receiving pain medication.

Drug abusers may have a history of medical noncompliance, discharge from pain services, polysubstance abuse, multiple visits for treatment of various nonspecific painful conditions, an unusual reluctance to try new therapies, or a report that their primary physician is unreachable. They may have a history of selling prescription drugs (diversion), forging prescriptions, using aliases, or injecting oral preparations. The use of a state prescription monitoring program may help identify patients who exhibit these behaviors (4). Because it is not appropriate and is unethical to withhold analgesics from patients experiencing pain unless the emergency physician has clear objective evidence that the patient is a drug abuser, the patient's pain should be treated. Guidelines limiting the prescribing of opioid analgesics from the ED, while well intentioned and designed to reduce the harm of inappropriate

opioid use, have the unintended consequence of potential undertreatment of patients with exacerbations of painful conditions, some of whom have limited access to care outside of the ED. Sometimes, a known substance abuser may present with an acutely painful condition. In these cases, pain should be adequately relieved in the ED, and judicious amounts of analgesics to be taken at regular intervals should be given on discharge. The use of opioid agonist–antagonists may be useful in these patients, as they are less likely to cause euphoria. However, they should not be given to a patient physically dependent on opioids, as they may precipitate withdrawal.

ED MANAGEMENT

Although many of the concepts that apply to acute pain management (see Chapter 15) also apply to patients with chronic pain, the endpoint of marked relief may not be attainable. Exacerbations of chronic pain (breakthrough pain) are often a result of a combination of both physical and psychological factors, and the primary goal in the ED is to reduce pain to the point where the patient becomes functional, with pain service referral when appropriate. In additon, certain pain syndromes (e.g., neuropathic pain) may not be effectively treated by the usual doses of typical analgesic agents. Therefore, an understanding of both the physical and psychological pathophysiologies associated with these disorders will ensure optimal treatment.

The treatment of chronic pain includes the use of many modalities (**Tables 16.3–16.5**). Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are often employed early in the patient's course; however, many patients are unable to be adequately controlled with these agents alone.

TABLE 16.3
Therapies for Chronic Pain

Therapy	Indications
Opioid analgesics	Most causes of chronic pain; limited effectiveness in neuropathic pain
Tricyclic antidepressants, selected SSRIs, SNRIs	Most causes of chronic pain
Skeletal muscle relaxants	Chronic low back pain, fibromyalgia
Anticonvulsants	Neuropathic pain
Topical anesthetics	Neuropathic pain
Capsaicin	Neuropathic pain, arthritic pain
NMDA receptor antagonists	Neuropathic pain
Salmon calcitonin	Complex regional pain syndrome, phantom limb pain
Behavioral therapy	Most causes of chronic pain
Physical therapy	Complex regional pain syndrome, temporomandibular disorders, tension myalgia
Surgery	Refractory trigeminal neuralgia, complex regional pain syndrome, phantom limb pain

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitors; NMDA, *N*-methyl-D-aspartate.

TABLE 16.4
Opioid Pharmacotherapy for Chronic Pain

Drug	Starting Dose[a]
Morphine, extended release	15–30 mg PO q8–24 h
Oxymorphone, extended release	5–10 mg PO q12 h
Oxycodone, extended release	10–20 mg PO q12 h
Levorphanol	2 mg PO q6–8 h
Hydromorphone	2–8 mg PO q3–4 h
Fentanyl	25–100 µg/h patch q 72 h
Methadone	2.5–10 mg PO q 8–12 h

[a]Higher starting doses often required in opioid-dependent patients.

TABLE 16.5
Nonopioid Pharmacotherapy for Chronic Pain

Drug Class/Agent	Dosing
Antidepressants	
Amitriptyline, desipramine, nortriptyline	50 mg PO QHS up to 150 mg/d
Duloxetine	30 mg PO daily, increase to 60 mg daily after 1 wk
Venlafaxine	37.5 mg PO daily, increase by 75 mg each week to 225 mg daily
Doxepin	25–50 mg PO QHS
Bupropion	150 mg PO BID
Anticonvulsants	
Gabapentin	300 mg PO TID increase as necessary to maximum of 3,600 mg/d
Pregabalin	50 mg PO TID increase to 100 mg PO TID over 7 days
Carbamazepine	100 mg PO QHS[a] increase to 100 mg PO BID
Oxcarbazepine	maximum 1,200 mg/d 300 mg PO BID increase to 600 mg PO BID in 7 days
Skeletal Muscle Relaxants	
Cyclobenzaprine	10 mg PO TID
Orphenadrine	100 mg PO BID
Carisoprodol	200–400 mg qid
Chlorzoxazone	250–750 mg PO TID or qid
Methocarbamol	1.5 g qid
Baclofen	5 mg PO TID increase to 20 mg PO TID
Topical Anesthetics	
Lidocaine patch	1–3 patches for 12 HQD
Prilocaine/lidocaine	2.5 g cream or 1 g disc
Substance P inhibitor	
Capsaicin	Apply to affected area qid
NMDA Receptor Antagonists	
Ketamine	0.4–0.5 mg/kg PO or IV
Dextromethorphan	60–240 mg PO BID titrated to effect
Other Agents	
Salmon calcitonin	200 IU intranasal daily

NMDA, *N*-methyl-D-aspartate.
[a]Obtain baseline complete blood count.

Opioid analgesics are the most useful drugs in treating exacerbations of chronic pain. The agents used are discussed in the chapter on acute pain (see Chapter 15), but longer-acting preparations such as those listed in Table 16.4 may be more appropriate for the treatment of chronic pain. These agents also avoid the risk of aspirin or acetaminophen toxicity from the nonnarcotic component of combination products, which may occur when doses sufficient to provide adequate amounts of the opioid component are taken. The use of extended release preparations of oxycodone and oxymorphone has gained considerable attention as a result of its potential for abuse. In the ED, they should typically be reserved for patients with pain as a result of an advanced terminal illness such as malignancy, as alternatives can be successfully used in other patients.

Pain as a result of malignancy, although chronic in nature, may be considered sustained acute pain because it is typically associated with progressive tissue damage. Although nonnarcotic analgesics and physical therapy are often used to treat malignant pain, progressively increasing doses of opioid analgesics remain the mainstay of therapy. Despite the risk of opioid dependence, opioid analgesics should never be withheld from patients with terminal malignant pain, as pain control is the most important factor contributing to overall quality of life (16). Acute exacerbations of malignant pain must be treated as an emergency, with aggressive opioid analgesia. Higher doses of opioids titrated more rapidly than in opioid-naive patients are typically needed, and this approach is both safe and effective.

Tramadol is a centrally acting oral analgesic that activates opioid receptors in the CNS and also inhibits monoamine neurotransmitter reuptake (similar to tricyclic antidepressants [TCAs]). Tolerance and withdrawal symptoms appear to be absent with tramadol. However, it has been demonstrated to be less effective in the management of acute pain than other opioids when used alone (26) and is associated with a high incidence of side effects, including seizures. It appears to be most appropriate for adjunctive treatment in mild to moderate chronic pain.

TCAs are useful in treating chronic pain, both by controlling depression, increasing inhibitory fiber stimulation, and by altering nociceptive responses to painful stimuli, thereby altering the cerebral process in pain perception. They are effective in pain control even if no evidence of depression exists. TCAs are effective in various chronic pain syndromes, particularly neuropathic pain, facial pain syndromes, fibromyalgia, and arthritis. TCAs act synergistically with opioids in controlling chronic pain. It is likely that all TCAs are effective in treating chronic pain, but amitriptyline has been the most extensively studied. The recommended starting dose for all TCAs in managing chronic pain is half the antidepressant dose, which may be titrated up if necessary. Analgesic effects may not be evident for several days. Referral for follow-up is essential in patients started on TCAs in the ED. Available evidence suggests that other agents used for depression may be used but are less effective than TCAs in the management of most types of chronic pain (22). However, the serotonin–norepinephrine reuptake inhibitors (SNRIs), duloxetine and milnacipran, have been effectively used to treat neuropathic pain. The association between depression and chronic pain is clear, but in some patients the painful process produces depression, and in others chronic pain is a manifestation of a depressive disorder. In patients with chronic pain in whom no etiologic basis can be established, management is also focused on treating the underlying depression. In addition, depression is also known to increase opioid analgesic requirements.

Transcutaneous electrical nerve stimulation (TENS) may be effective in certain acute and chronic pain syndromes. It is used most often in chronic low back pain and complex regional pain syndrome, although the evidence for its benefit is limited by the lack of well-designed clinical trials. In addition, most patients note a decrease in the analgesic effect over time. The “gate control” theory of pain postulates that in the periphery, small unmyelinated C fibers transmit nociceptive information, and large myelinated A fibers transmit light touch and pressure sensations. Both of these fibers synapse at the substantia gelatinosa in the dorsal horn of the spinal

cord. Stimulation of the A fibers inhibits the transmission of nociceptive C fiber stimuli into the CNS, thereby “closing the gate.” By using electricity to stimulate the A fibers preferentially, the pain stimulus entering the CNS can be controlled.

In neuropathic pain syndromes, pain originates from peripheral nerve dysfunction. Therefore, anticonvulsants play a primary role in treating most of these disorders, with carbamazepine, gabapentin, and preganalin commonly used. In addition, because substance P may be the principal mediator of neuropathic pain, an effort to inhibit substance P may be beneficial. When applied topically, capsaicin, a substance derived from red chili peppers, releases substance P from primary afferent nerve fibers. With repeated application, capsaicin depletes substance P from these nerve fibers. Consequently, capsaicin may have some benefit in treating the neuropathic pain of postherpetic neuralgia, complex regional pain syndrome, metabolic neuropathy, and other chronic pain syndromes such as psoriatic and rheumatoid arthritis. Capsaicin causes skin redness and burning. This may also contribute to its analgesic effect, as peripheral counterirritation causes pain relief by a “gate-closing” effect, as described for TENS. However, this skin irritation also limits the concentration that may be used, thus reducing its potential efficacy (18). It has been postulated that in chronic pain, NMDA may play a central role in the windup phenomenon of sensitizing the CNS to a prolonged painful stimulus, possibly by recruitment of C fibers. Consequently, substances that antagonize the NMDA receptor are gaining attention as possible agents in the management of chronic pain. Ketamine, dextromethorphan, methadone, memantine, and amantadine all antagonize the NMDA receptor and have been studied as agents for chronic pain management (particularly in neuropathic pain). However, the doses needed to produce analgesia exceed the doses that cause untoward adverse effects (12).

Behavioral and physical therapy help patients cope with chronic pain and regain a sense of self-control, thus improving overall day-to-day function. The focus with these therapies is rehabilitation, not

total pain relief. However, patients must be motivated to be successful.

The most effective ways to treat these chronic pain syndromes are the multidisciplinary approaches used by pain clinics, in which combinations of the various therapies are coordinated. Thus, the emergency physician should confer with the patient's primary care or referring physician and make arrangements for follow-up before initiating or changing therapy.

SPECIFIC CHRONIC PAIN SYNDROMES

Chronic Low Back Pain

Chronic low back pain is the most common chronic pain syndrome seen in the ED. Approximately 8% of US adult patients develop nonspecific low back pain annually, and of these about 5% will continue to experience persistence after 3 months (7).

Opioid and nonopioid analgesics, including acetaminophen, remain the mainstay of therapy for chronic back pain. As with other chronic pain syndromes, tolerance and dependence can occur with prolonged opioid use, and gastrointestinal and renal damage can occur with prolonged NSAID use. Antidepressant therapy may be added to patients poorly controlled on analgesics alone. Skeletal muscle relaxants may improve range of motion, but their use is limited in chronic back pain owing to a high incidence of CNS side effects (drowsiness and dizziness).

In patients with sciatica, treatments specific for neuropathic pain may be beneficial, and trials using gabapentin or topiramate have shown modest improvement in pain relief as compared with placebo (6). Although sometimes prescribed, systemic corticosteroids have not been associated with any clinically significant benefit when compared with placebo.

Nonpharmacologic therapies have been used with varying degrees of success. Regular exercise with an emphasis on core stability appears to be important to improve function, and behavioral therapy, massage hydrotherapy, and acupuncture seem to have modest beneficial effects (5). A review of 26 randomized controlled

trials on spinal manipulative therapy concluded that this intervention results in a clinically insignificant benefit on short-term pain relief (19). The evidence of effectiveness of other therapies such as traction and TENS is lacking, with studies either showing no benefit or conflicting results (14).

Myofascial Pain and Fibromyalgia

Myofascial pain syndrome and fibromyalgia are conditions in which acute or chronic muscle pain, stiffness, and tenderness occur at specific anatomic sites ("trigger points"). A trigger point is an area within a taut band of skeletal muscle that, when palpated, produces referred pain in the area in which the patient complains of pain (a "reference zone"). It may be activated by physical trauma, other trigger points, or psychological stress.

Fibromyalgia and myofascial pain syndrome may be considered opposites in the spectrum of a single disorder (Table 16.6). Myofascial pain tends to be localized, and the involved muscle group may twitch involuntarily. Fibromyalgia pain tends to be diffuse and is associated with systemic symptoms such as chronic fatigue, sleep disturbance, headaches, vertigo, visual disturbances, and irritable bowel syndrome. Symptoms may begin after an acute viral illness, trauma, or psychological stress. Physical findings may be nonspecific, and the patient may be told that the symptoms are unexplained or psychogenic.

TABLE 16.6
Myofascial Pain Syndrome Versus Fibromyalgia

Location	Myofascial Pain Regional	Fibromyalgia Generalized
Muscular twitch	Yes	No
Systemic symptoms	No	Possible
Sleep disturbances	No	Yes
Trigger-point injection useful	Yes	Sometimes
Physical therapy useful	Yes	No
Skeletal muscle relaxants useful	No	Yes

Although it has been postulated that psychological causes may underlie the pathophysiology of fibromyalgia (e.g., patients may not respond in a normal fashion to physical or psychological stress or may have a heightened perception of bodily discomfort), elevated CSF, and levels of plasma substance P and decreased plasma levels of serotonin have been demonstrated (20). Windup due to noxious stimuli appears to be enhanced in these patients (24). Consequently, fibromyalgia patients may experience pain from stimuli that are below the painful threshold in normal patients as a result of neurochemical alteration of pain pathways. Complicating matters are that depression is a frequent result of fibromyalgia, and somatization disorders are more frequent in fibromyalgia patients than the general population. Many patients seen in the ED for exacerbations of fibromyalgia pain may have failed traditional therapies and may be using alternative treatments such as guaifenesin, magnetic therapy, diet therapy, acupuncture, herbal therapy, and zone therapy.

Other painful systemic illnesses such as systemic lupus erythematosus, polymyalgia rheumatica, polymyositis, metabolic myopathy, hypothyroidism, chronic fatigue syndrome, and irritable bowel syndrome should be considered. Because symptoms often overlap, the diagnosis is frequently one of exclusion.

The treatments of myofascial pain and fibromyalgia have certain similarities. Trigger-point injection of local anesthetics is a technique easily performed for both fibromyalgia and myofascial pain, often with rewarding results. Relief of local and referred pain and a decrease in muscle tension may be seen after injection. Topical vapor coolant sprays using fluoromethane or ethyl alcohol followed by stretch of the affected muscle may provide relief, but this mode of therapy is difficult to provide in the ED setting.

Although aerobic exercise and strength training may have some benefit in fibromyalgia, other physical techniques, such as muscle stretching, biofeedback, and exercise, are useful in myofascial pain syndrome but are of limited value in fibromyalgia (23). In fibromyalgia patients, analgesics usually provide only partial relief, and additional therapy with antidepressants or anticonvulsants is

often needed. The SNRIs, duloxetine and milnacipran, are now FDA approved for the treatment of fibromyalgia (10). TCAs are useful to improve pain, depressive symptoms, and sleep disturbances; cyclobenzaprine, a skeletal muscle relaxant chemically similar to the TCAs, may also be useful. The anticonvulsants, pregabalin and gabapentin, have shown effectiveness in the treatment of fibromyalgia and NMDA receptor antagonists may be useful (1,8,9). If these therapies are initiated in the ED, follow-up care should be ensured.

Temporomandibular Disorders

Temporomandibular disorders affect the temporomandibular joint (TMJ) and surrounding facial structures, resulting in orofacial pain and dysfunction. Patients typically report facial pain, chewing difficulties and nonspecific headache, in addition to joint noise and difficulty in joint motion. Muscular and joint tenderness and limited TMJ range of motion may be found. The disorder is similar in many respects to both myofascial pain syndrome and fibromyalgia and is often referred to as a form of myofascial pain. Many patients with TMJ dysfunction also are diagnosed with fibromyalgia or other myofascial pain syndromes.

The etiology of TMJ disorders is unclear. Some patients may exhibit signs of TMJ dysfunction but may not have troubling symptoms. Many patients have coexistent psychiatric diagnoses, and behavioral therapy is often employed to supplement medical care. Many patients show a greater sensitivity to certain noxious stimuli than do pain-free controls (21). Patients who clench or grind their teeth secondary to stress may develop masticatory muscle hyperactivity and fatigue, which can lead to pain and altered joint mechanics. Patients may present before definitive diagnosis with a complaint of nonspecific facial pain or may present during a symptom exacerbation. Facial neuralgias, myofascial pain syndrome, tension headache, and somatization disorder should be considered in the differential diagnosis.

As in other chronic pain syndromes, treatment frequently requires analgesics, antidepressants, and nonpharmacologic therapy. Physical therapy, biofeedback, and intraoral splinting help relax the afflicted muscles and reduce discomfort. Some patients improve with trigger point or TMJ joint injections; however, pain control with analgesics is usually necessary. Patients should be discharged on TCAs if the diagnosis is certain and should be referred to a maxillofacial specialist so that an intraoral splint can be fitted and physical therapy started.

Neuropathic Pain Syndromes

Patients with neuropathic pain syndromes (Table 16.7) commonly present when symptoms first develop. The pain in these syndromes develops from nerve malfunction, sometimes as a result of physical damage to the involved nerve. The pain may be described as burning, tingling, stabbing, or electric shock like. In certain neuropathic pain syndromes, the pain is exacerbated by other stimuli that also stimulate the same nerve, such as light touch, temperature changes, or emotional stress. This phenomenon is known as *allodynia.* The pain is typically described as burning in nature, and treatment is often frustrating, because the usual doses of opioid and nonopioid analgesics are typically ineffective in relieving it.

TABLE 16.7
Neuropathic Pain Syndromes

- Facial neuralgias
  - Trigeminal
  - Glossopharyngeal
- Metabolic neuropathy
  - Diabetic
  - B_{12}
- Nerve compression pain
  - Radiculopathy
  - Entrapment neuropathy
- Postherpetic neuralgia
- Complex regional pain syndrome, types I and II
- Phantom limb pain

Generally, selected antidepressants, anticonvulsants, and topical anesthetics are considered first-line therapies for neuropathic pain syndromes, with opioids considered to be second line and useful as adjunct therapy (8). Antidepressants are of modest benefit and include the tricyclics amitriptiline, nortriptyline, and desipramine and the SSRIs, duloxetine and venlafaxine; anticonvulsants that are commonly used include gabapentin, pregabalin, and carbamazepine. However, there are certain considerations unique to the management of various neuropathic pain syndromes that should be understood by clinicians in the ED.

Facial Neuralgias

Trigeminal neuralgia is a relatively common, often debilitating disorder. Typically older patients (beyond age 50) are affected, and the development of this disorder in patients younger than age 40 suggests a secondary cause, typically multiple sclerosis (11). Women develop this disorder more often than men do. The right side is more frequently involved, and bilaterality is rare. The second division of the fifth cranial nerve (V2) is most frequently affected. Attacks at the third division (V3) and first division (V1) are uncommon. The initial attacks are brief but severe and lancinating, often described as an “electric shock” sensation. Allodynia is prominent, and attacks may be triggered by touching the face, cold

air blowing against the face, eating, shaving, or talking. Unlike other neuralgias, an objective sensory deficit is atypical and if found should alert the clinician to the possibility of nerve compression as a result of malignancy. As the condition progresses, the attacks become more frequent and a background ache may develop.

Glossopharyngeal neuralgia is less common and usually less severe than trigeminal neuralgia. It affects equal numbers of men and women. About 25% of cases are bilateral. Typically, a single episode of lancinating pain along the ninth cranial nerve sensory distribution (neck, throat, and ear) occurs. Atypical facial pain may occur, which is poorly localized but frequently involves the mandible. Unlike other facial pain syndromes, it is not clearly neuropathic and consequently does not respond as well as trigeminal neuralgia to anticonvulsants.

Cluster headache, maxillary sinusitis, postherpetic neuralgia (especially with V1 distribution), dental pain, and temporomandibular disorders should also be considered. Swallowing and chewing may trigger the pain from both facial neuralgias and TMJ dysfunction. Allodynia and the absence of TMJ tenderness suggest the former diagnosis.

The mainstay of treatment for the facial neuralgias is the administration of anticonvulsants, particularly carbamazepine, oxcarbazepine, and gabapentin. Unfortunately, patients typically present in extreme pain, and anticonvulsants usually require several days before a demonstrable effect is noticed. The recommended doses for gabapentin oxcarbazepine and carbamazepine are listed in Table 16.5. Other drugs, such as baclofen and clonazepam, may also need to be added. Because carbamazepine may cause neutropenia, a baseline complete blood count should be obtained if this drug is used. Carbamazepine may also cause nausea, dizziness, or somnolence, which may limit patient compliance. Follow-up with the patient's primary care physician or a neurologist should be arranged. Patients who fail medical therapy for trigeminal neuralgia often need surgical destruction of the sensory distribution of the trigeminal nerve, either by percutaneous thermocoagulation, cryosurgery, microvascular decompression, or glycerol injection.

Postherpetic Neuralgia

Postherpetic neuralgia is the most common type of neuropathic pain as well as the most common complication from herpes zoster. It occurs in 10% of cases of herpes zoster, and it is more common in the elderly. It may begin during or after an attack of zoster; it typically persists for several weeks after the rash resolves, and it has no relation to the severity of the zoster attack. Burning pain occurs in the involved dermatome, which is most commonly thoracic (about 50%), ophthalmic (about 20%), and cervical (about 20%). Diabetic neuropathy, demyelinating polyneuropathy, radiculopathy, and alcoholic neuropathy should all be considered in the differential diagnosis.

Many treatments used in other neuropathic pain syndromes (e.g., painful diabetic peripheral neuropathy) have been recommended for the treatment of postherpetic neuralgia. However, it is difficult to determine what is truly effective because few well-designed, controlled clinical trials exist, and some cases may resolve with no treatment. The longer the condition is allowed to persist, the less likely that any one treatment will be effective.

Opioid analgesics may provide modest temporary improvement in pain, but they are typically not useful alone in the treatment of postherpetic neuralgia. TCAs are often used early in the course of therapy, and there is some evidence to suggest that preemptive treatment with antidepressants during an attack of herpes zoster may reduce the prevalence of postherpetic neuralgia (3).

Anticonvulsants reported to be useful in treating postherpetic neuralgia are primarily gabapentin, pregabalin, and carbamazepine, however, there is no clear superiority of any of these agents; phenytoin, valproic acid, and the antispastic drug baclofen are occasionally used as well. Local anesthetics have been used in IV forms, in topical preparations such as lidocaine patch (Lidoderm) and EMLA (prilocaine/lidocaine) cream, and in nerve blocks. All of these methods appear to provide additional short-term relief of pain as a result of this condition. Capsaicin appears to provide temporary but effective relief if used four times a day for 3 to 4 weeks,

however discontinuation due to skin irritation is common. Botulinum toxin, the NMDA antagonists dextromethorphan, memantine, and ketamine have also been reported to treat postherpetic neuralgia, but the data on their effectiveness is limited.

Acyclovir, valacyclovir, and famciclovir may be useful in the treatment of an acute attack of herpes zoster to decrease viral shedding and the duration of lesions. However, there is insufficient evidence to suggest that antiviral therapy decreases the incidence of postherpetic neuralgia (15). Likewise, steroids are occasionally prescribed to enhance the resolution of zoster lesions, although they are not effective in preventing or treating postherpetic neuralgia.

Complex Regional Pain Syndrome

Complex regional pain syndrome (formerly referred to as *reflex sympathetic dystrophy* and *causalgia*), is a neuropathic pain syndrome characterized by a vicious cycle of pain, disuse atrophy, and peripheral autonomic dysfunction. Patients are usually 40 to 60 years old, although children are occasionally affected. It typically occurs after major extremity trauma, but it has also been related to minor trauma, cerebrovascular accident, myocardial infarction, arthritis, infection, and local tumor infiltration. Drugs such as isoniazid, ethanol, and phenobarbital have also been implicated as causative factors. It often occurs after prolonged extremity immobilization, presumably as a result of irritation of the sympathetic ganglia.

The term *causalgia* is reserved for complex regional pain syndrome related to a major peripheral nerve injury. After nerve damage as a result of an extremity injury, a positive feedback loop develops in which sympathetic efferent neurons stimulate afferent pain fibers and vice versa. Stimuli that cause sympathetic efferent outflow, such as temperature changes, often trigger this vicious cycle. Peripheral nociceptors are sensitized, and when stimulated, they then stimulate sympathetic fibers. Thus, the cycle of pain and sympathetic overflow occurs.

The median, ulnar, and femoral nerves are most commonly affected. In patients with minor trauma, the degree of initial pain is often much greater than suggested by objective findings. The first (acute) stage occurs during the first several weeks of the disease process. Symptoms include pain, swelling, sympathetic underactivity, joint stiffness, warm skin, hypertrichosis, and edema. As the disease progresses, joint stiffness, hair loss, allodynia, sympathetic overreactivity, and muscular dystrophy occur, along with paroxysms of pain. After several months, decreased joint motion and muscle and skin atrophy occur. At this stage, the extremity appears cool, pale, shiny, and hairless. Radiographs are usually normal early in the disease and later show patchy osteopenia and erosions. The differential diagnosis for complex regional pain syndrome includes collagen vascular disease, phlebitis, degenerative arthritis, and conversion hysteria.

Treatment is difficult, and most therapies provide only temporary relief. Medications that may be helpful include salmon calcitonin, TCAs, anticonvulsants, botulinum toxin, corticosteroids, β-blockers, α-blockers, calcium channel blockers, serotonin antagonists, capsaicin, NMDA receptor antagonists, and type Ib antiarrhythmics. However, the benefit of any individual therapy is limited (28). As with other forms of neuropathic pain, opioids and NSAIDs are often ineffective. Regional blocks using guanethidine may be effective but can exacerbate the pain before it improves. Physical therapy is essential, and other nonpharmacologic therapies, such as TENS or implantable neurostimulators, may be used. Sympathetic blocks may provide only temporary analgesia but may allow aggressive physical therapy.

This disorder can be prevented by avoiding prolonged immobilization in patients with extremity trauma. Recognizing the early stages and intervening before the disease progresses is important. Patients should be referred for early physical therapy.

Phantom Limb Pain

Phantom limb pain is a poorly understood syndrome that occurs after extremity amputation. It can be debilitating and is difficult to treat. After amputation, phantom sensation is nearly universal and usually resolves in less than a year. Persistent pain is thought to be related to neural damage in the postamputation period, and mechanisms in the peripheral nerve, spinal cord, and brain all contribute to the development of phantom limb pain. It has been postulated that the last impulses received by the limb before amputation may be stored in "memory," and if these impulses are painful, the sensation may persist (17). Consequently, the incidence of phantom limb pain is decreased in patients given preoperative regional anesthesia. As with other chronic pain syndromes, psychological stress exacerbates the degree of pain experienced. The differential diagnosis includes complex regional pain syndrome, metabolic neuropathy, and neurosarcoma.

There are few well-designed studies that evaluate the various treatment regimens for phantom limb pain. Antidepressants, anticonvulsants, analgesics, anesthetics, ketamine, capsaicin, and β-blocking agents all seem to provide temporary relief. Surgical techniques such as cordotomy, stump revision, and neuroma removal have been reported, with variable degrees of success. A combination of long-term behavioral therapy and antidepressants appears to be the most useful mode of therapy.

CRITICAL INTERVENTIONS

- Use nonanalgesic interventions that are specific for particular chronic pain syndromes.
- In the ED, prescribe opioids to the endpoint of improved function.
- Facilitate referral to pain service or primary care for long-term symptom management.

DISPOSITION

Most chronic pain patients can be discharged from the ED. The primary care physician or pain clinic should be consulted before

initiating or changing long-term therapy in patients with chronic pain syndromes. Follow-up should be arranged for patients with neuropathic pain syndromes.

Common Pitfalls

- Missing acute disease by assuming that an exacerbation of chronic pain is due to pre-existing disease.
- Routinely labeling chronic pain patients who have true pain as drug seekers.
- Overrelying on analgesic drugs to treat neuropathic pain.
- Failure to appreciate the risk of aspirin or acetaminophen toxicity when using escalating doses of combination opioid products to treat chronic pain.
- Assuming that pain from fibromyalgia or temporomandibular disorders is of purely psychogenic origin.

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CHAPTER 17

Procedural Sedation and Analgesia

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The care of patients with painful conditions and the performance of painful diagnostic and therapeutic procedures are routine aspects of emergency care. Approximately half of emergency department (ED) visits are for pain-related chief complaints. Many of these conditions are also associated with anxiety. Accordingly, procedural sedation and analgesia (PSA) has become a fundamental skill of emergency physicians and an important part of emergency medicine residency training (1).

Despite the emphasis on PSA, oligoanalgesia has been well described in emergency care. Inadequate pain control has been ascribed to underestimation of patient pain, concern for patient safety, fear of delays associated with oversedation, and the alteration of physical findings (1,2). PSA can improve quality of care and patient satisfaction through the relief of pain and anxiety and the facilitation of therapeutic or diagnostic procedures such as cardioversion, incision and drainage of abscesses, tube thoracostomy, lumbar punctures, fracture reduction, complex suturing, and imaging studies (1,3–5). Many drugs used for sedation and analgesia have the potential to cause respiratory, cardiovascular, and central nervous system (CNS) depression. The introduction of protocols using shorter-acting, more effective drugs, the development of noninvasive monitoring devices, and published clinical policies for PSA have made it an extremely safe, practical procedure. The airway and

critical care expertise of emergency physicians make them ideal providers of safe PSA (1).

The wide variety of procedures and patient types requires the ability to individualize PSA. This can be achieved only through a comprehensive understanding of the drugs used and by proper patient assessment. Protocols delineating staffing responsibilities, monitoring guidelines, medications, observation periods, and discharge criteria and instructions are recommended before implementing PSA in the ED.

DEFINITIONS

The term *conscious sedation* has previously been used to describe the process of providing analgesia, sedation, and amnesia for patients undergoing painful procedures. However, this term may be misleading. A more precise and preferred term is PSA. In a recent clinical policy published by the American College of Emergency Physicians, PSA was defined as a technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedures without undue pain or anxiety while maintaining cardiorespiratory function. PSA is intended to result in a depressed level of consciousness that allows the patient to maintain oxygenation and airway control independently and continuously (1).

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO), in its 2003 Comprehensive Accreditation Manual for Hospitals, states that “the standards for sedation and anesthesia care apply when patients receive, in any setting, for any purpose, by any route, moderate or deep sedation and general, spinal, or other major regional anesthesia” (6). JCAHO has adopted the American Society of Anesthesiologists (ASA) definitions of sedation and analgesia created in 1999 to better describe the continuum of sedation and analgesia. *Moderate sedation* most closely approximates the replaced term *conscious sedation.*

Minimal sedation is primarily anxiolysis for a procedure, during which patients respond normally to verbal commands. Ventilatory and cardiovascular function remains unaffected.

Moderate sedation/analgesia is a drug-induced depression of consciousness during which the patient responds purposefully to verbal commands, alone or accompanied by tactile stimulation. Typically, no interventions are required to maintain a patent airway. Spontaneous ventilation is adequate, and cardiovascular function is maintained; therefore, this is associated with less respiratory depression than deep sedation. At this level of sedation, patients generally are amnestic, even to painful procedures, but moderate sedation should be used only when the procedure is likely to be successful on a more responsive patient rather than a deeply sedated patient (7–9).

Deep sedation/analgesia is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. Assistance may be needed to maintain a patent airway, and independent ventilation may be inadequate. Cardiovascular function is usually maintained. This level of sedation is associated with a greater degree of respiratory depression than moderate sedation but is often necessary for the successful completion of procedures for which patient relaxation and amnesia is required (9–11).

General anesthesia is a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. Independent ventilatory function is often impaired, and ventilatory and airway support is often required. Cardiovascular function may be impaired.

The response to medications can vary greatly between individuals and may be unpredictable. Therefore, it is recommended that clinicians be competent in the skills required to manage patients at least one level greater than the intended sedation (12). The management of impaired ventilatory function is a usual part of the practice of emergency medicine and represents a critical skill for the management of procedural sedation in the ED.

ED EVALUATION

Careful patient selection is necessary to provide safe and effective PSA. The comorbid illness or injury, any underlying medical

problems, patient age, the procedure, and the ability to manage the airway are important considerations in determining the indication for and the method of PSA. Not all patients or procedures are appropriate candidates for PSA and may be best served in the operating room.

The agents used in procedural sedation, to some degree, all cause hypoventilation and diminished airway reflexes. The principle complication of procedural sedation associated with significant morbidity is aspiration pneumonia from the loss of airway reflexes (3,13–15). Luckily, this is a rare complication, but a principle goal of sedation must be to avoid situations where a patient is at risk of its occurrence. Other complications include hypoxia, hypotension, and paradoxical agitation reactions from the sedative agents.

A patient's physical status can be conveniently described using the ASA's classification (Table 17.1) (16). This is frequently incorporated into the documentation of the preprocedure assessment. Patients with ASA physical status scores of 3 and 4 are more likely to have complications from hypoventilation and hypotension than patients with scores of 1 and 2, and the risk/benefit ratio of performing PSA in these patients must be considered (17).

TABLE 17.1
American Society of Anesthesiologists Physical Status Classification

I.	Normal, healthy patient
II.	Mild systemic disease
III.	Severe systemic disease
IV.	Severe systemic disease that is a constant threat to life
V.	Moribund patient, not expected to survive the procedure

A history of prior problems with anesthesia or PSA should be elicited. Particular attention should be paid to underlying hypovolemia, cardiorespiratory diseases, neurologic diseases, medications, and intoxicants. Physical examination should focus on the cardiovascular, respiratory, and neurologic systems and performing an assessment of airway difficulty. There is no evidence

to support the need for specific diagnostic testing before PSA. A discussion including the risks, benefits, and potential side effects of PSA should take place before the procedure. Written consent is recommended when possible; however, patient condition may preclude this (12).

There is insufficient literature to recommend a necessary period of fasting prior to PSA. The combination of vomiting and loss of protective reflexes during PSA causing aspiration is considered to be a rare event (13). There is no evidence that gastric emptying or antacids reduces the incidence of PSA-associated complications. It is likely, however, that increasing depth and duration of PSA is associated with an increased risk of aspiration, and it may be beneficial in patients who have recently taken more than clear liquids and require nonurgent procedures to delay until 3 hours after the last oral intake. For patients needing a procedure urgently (fracture reductions, intractable pain, etc.) recent intake should be considered in the choice of the target sedation level and duration of the planned PSA. The complimentary use of local anesthesia when appropriate, such as a regional block, can reduce the amount of sedation required. Patients at high risk for aspiration may benefit from the lightest level of sedation for the shortest amount of time that will allow successful completion of the procedure. Recent food ingestion is not a contraindication but rather a consideration when choosing the targeted level of sedation (13,17,18).

KEY TESTING

- Interactive monitoring
  - Airway assessment
  - Physical status score
  - Procedural plan
  - Sedation plan
- Mechanical monitoring
  - Capnography
  - Pulse oximetry
  - Cardiac monitor
  - Blood pressure

ED MANAGEMENT

Preparation

The necessary equipment and supplies should be gathered in an appropriate setting prior to the initiation of PSA. There does not have to be a specific dedicated area for PSA. However, the capability to provide cardiovascular and respiratory support and availability of personnel may dictate the location. Monitoring equipment, oxygen, suction, advanced life support equipment and medications, a bag-valve-mask, and intubation equipment must be readily available. IV access should be established and maintained before PSA with IV agents. The antagonists naloxone and flumazenil should be available when opioids and benzodiazepines are being used (19).

The Joint Commission and compliant institutions insist that the PSA provider demonstrate adequate training to administer the agents effectively and safely and have the skills to manage all potential complications (6). These are all within the scope of the emergency physician's expertise, especially in the unpredictable setting of the ED, which is unique to the practice of emergency medicine. There is no clear guideline in the literature or organizational policies regarding the required number of support personnel. It is essential that an individual is present who is capable of recognizing the respiratory and hemodynamic responses to the medications and is able to perform interactive monitoring without interruption throughout the procedure. The performance of a procedure often precludes the continual clinical assessment of the patient. Therefore, one individual provider not performing the procedure is usually recommended to monitor and document patient status when providing deep sedation (15). Moderate sedation using a single provider has been described (20).

The use of supplemental oxygen during PSA is somewhat controversial. Although its routine use may prevent hypoxemia in some patients, there is concern that it will delay the recognition of respiratory compromise and hypercarbia, due to its effect on the sensitivity of pulse oximetry to changes in ventilation (21,22).

Evidence supports the use of supplemental oxygen in patients undergoing PSA to reduce episodes of hypoxia; but care must be taken to use monitoring modalities other than pulse oximetry, such as close interactive monitoring, when supplemental oxygen is used (11,23).

Monitoring

The most important aspects of monitoring during PSA are the interactive observation and assessment of physiologic changes and the level of consciousness. The patient's ability to follow commands and the response to varied levels of stimulation are useful in quantifying the level of consciousness. Direct observation of the patient's airway and breathing (interactive monitoring) are likely to be the most accurate monitors of a patient's ability to maintain adequate ventilations and airway protection and to assess the safety of giving further medication to patients who have not yet achieved the desired level of sedation, and are therefore critical to the safe titration of sedatives and the avoidance of oversedation and its associated adverse effects (15,24,25). Interactive monitoring can be augmented by blood pressure, oxygen saturation, capnometry, and cardiac rhythm monitors.

The use of pulse oximetry is widely recommended in national and institutional PSA guidelines. Many studies have demonstrated its utility in monitoring oxygenation; however, there is no clear demonstration that its use during PSA affects patient outcome other than decreasing episodes of transient hypoxia (1,26). This may be as a result of the extremely low risk of morbidity and mortality during PSA when the patient's respiratory efforts and level of consciousness are clinically monitored. Furthermore, the clinical significance of transient decreases in oxygen saturation is not known (26), but we at least assume it is a marker of ventilatory depression and therefore a marker of risk for aspiration. Pulse oximetry measures oxygenation, not ventilation. A patient breathing supplemental oxygen may not exhibit changes in the oxygen saturation until several minutes after the onset of hypoventilation. In a patient breathing room air with a normal oxygenation prior to PSA, however, decreases in oxygenation

correlate with decreases in ventilatory effort. In either case, it represents useful information and should be utilized during PSA. However, it should not be a substitute for continuous clinical assessment.

Capnometry can be used to monitor ventilation. Capnographs measure expired CO_2 and display a waveform that represents the patient's ventilation. The peak of each wave represents the end-tidal CO_2, or the maximum concentration of CO_2 in the expired air. Large changes in the end-tidal CO_2 values and in the shape of the waveform have been associated with respiratory depression in sedated patients and may allow earlier identification of hypoventilation than oximetry (21,22,26,27). An increasing end-tidal CO_2 value can represent CO_2 retention from hypoventilation. A decreasing end-tidal CO_2 value can represent hyperventilation and decreasing arterial CO_2 levels, or increased mixing of room air and expired air in the upper airway owing to airway obstruction. An absent waveform on the capnograph can represent apnea or possibly upper airway obstruction if respiratory effort is present. The earlier detection of hypoventilation associated with the use of capnographic monitoring has been shown to decrease episodes of hypoxia during procedural sedation in the ED (26). Capnographic monitoring of end-tidal CO_2 improves the detection of hypoventilation, even in patients receiving supplemental oxygen, and decreases episodes of hypoxia. It should be considered in patients undergoing deep sedation who are receiving supplemental oxygen.

Blood pressure, heart rate, and respiratory rate should be assessed at regular intervals throughout PSA. Patients are at the highest risk for complications when they are at their deepest level of sedation, primarily within 90 seconds to 3 minutes of receiving IV sedatives, and when noxious stimuli are removed (immediately after the procedure). Continuous electrocardiographic monitoring is not routinely recommended. However, it should be used in older patients or those with a history of cardiovascular or pulmonary disease. Documentation of the level of sedation can be quantified using a

predefined sedation score, such as the Aldrete score or a simplified version suggested in Table 17.2.

TABLE 17.2
Assessment of Sedation

Fully awake
Arouses easily
Arouses with tactile stimuli
Arouses to vigorous stimuli
Responsive to painful stimuli
Unresponsive

Drug Selection and Administration

The ideal agent for PSA would provide analgesia, anxiolysis, amnesia, and somnolence rapidly and predictably with no adverse effects. Unfortunately this drug does not exist. As a result, multiple sedative hypnotics, opioids, and various anesthetic agents have been employed, singly and in combination, in an attempt to achieve the desired level of PSA (Table 17.3) (2). The agent selected, and its dose and route of administration, should be guided by the type of procedure and by the specific patient. Drug availability and physician experience are also important determinants.

TABLE 17.3
Agents Commonly Used in Procedural Sedation and Analgesia

Drug	Class	Effect	Side Effects	Dose	Peak	Clinical Duration
Morphine	Opioid	Analgesia Sedation	↓ Respirations N&V ↓ BP, HR ↑ Histamine	Children: IV: 0.05–0.1 mg/kg Adults: IV: 3–5 mg	IV: 20 min Oral: 60 min IM: 30–60 min	1–3 h
Fentanyl	Opioid	Analgesia Sedation	↓ Respirations N&V Chest wall rigidity	Children: IV: 1–2 µg/kg Adults: IV: 1 µg/kg	IV: 0.5–2 min	30–60 min
Midazolam	Benzodiazepine	Sedation Amnesia	↓ Respirations ↓ BP ↓ Pulse	Children: IV: 0.05 mg/kg PO: 0.5 mg/kg Adults: IV: 0.5–5 mg	IV: 1–5 min PO: 30 min	30–60 min
Diazepam	Benzodiazepine	Sedation Amnesia	↓ Respirations ↓ BP ↓ Pulse	Children: IV: 0.05 mg/kg PO: 0.2 mg/kg Adults: IV: 2.5–5 mg PO: 10 mg	IV: 5–15 min PO: 45–60 min	2–6 h
Methohexital	Barbiturate	Sedation Amnesia	↓ Respirations N&V ↓ BP ↑ Histamine	Adults: IV: 1–3 mg/kg Children: PR: 25 mg/kg (maximum 500 mg)	IV: 1 min PR: 8 min	IV: 3–5 min PR: 80 min
Pentobarbital	Barbiturate	Sedation Amnesia	↓ Respirations N&V ↓ BP ↑ Histamine	Children: IV: 2 mg/kg PO: PR: 2–6 mg/kg IM: 2–6 mg/kg Adults: IV: 100 mg PO: 100 mg	IV: 1 min	6–10 min
Propofol	Imidazole derivative	Sedation Amnesia Antiemetic	↓ Respirations ↓ BP	1–2 mg/kg bolus 50–100 µg/kg/m IV continuous infusion	0.5 min	4–8 min
Etomidate	Isopropylphenol compound	Sedation Amnesia	↓ Respirations	0.1 mg/kg	1 min	5–8 min
Ketamine	Phencyclidine derivative	Dissociation Analgesia Sedation Amnesia	↑ BP, HR Laryngospasm Increased secretions	Adults: IV: 1–2 mg/kg Children: IV: 1 mg/kg IM: 2–5 mg/kg	IV: 1 min IM: 5 min	IV: 15–20 min IM: 30 min
Nitrous oxide	Anesthetic gas	Analgesia Sedation		Self-administered 50:50 mix NO_2–O_2	1–2 min	5 min

N&V, nausea and vomiting.

Prior to PSA, patients with pain should receive pain medications titrated to pain relief. Morphine 0.1 mg/kg, followed by 0.05 mg/kg every 2 to 3 minutes until pain is relieved, is a common approach. For situations in which the patient is likely to have much less pain after PSA owing to the nature of the procedure (the reduction of a severely comminuted fracture, e.g.,), fentanyl 1.5 µg/kg followed by 0.75 µg/kg may be preferable. Fentanyl is short-acting, with a duration of action of 30 to 45 minutes (25,28). It does not cause histamine release and has minimal cardiovascular effects. Like all opioids, fentanyl is reversed by naloxone. Respiratory depression is

more likely at higher doses, when given rapidly IV push, or when combined with other CNS depressants, such as benzodiazepines or alcohol. Lower doses should be used in elderly patients and when other CNS depressants may have been previously ingested. Side effects of fentanyl include hypoxemia, apnea, vomiting, and pruritus. Hypotension is rare. Bradycardia may occur with high doses. Truncal rigidity and glottic spasm, which make ventilation difficult, are unique complications seen with doses above 10 μg/kg, or at lower doses if the drug is given rapidly.

The duration of action of these agents is often much longer than the sedatives typically used in ED PSA; therefore, their titration should be performed prior to the PSA encounter rather than as part of it. Many of the sedative agents used in PSA have amnestic but not analgesic properties, and patients may have a brief transient increase in pain during their procedure. Combining sedatives with opioids for procedural sedation, however, has been associated with an increased risk of hypoventilation (25,29–31). Furthermore, patients receiving moderate or deep sedation, are unlikely to recall the event. The physiologic significance of brief pain that is not recalled is unlikely to outweigh the risk of prolonged or deeper sedation than was intended and the associated hypoventilation (31).

Regardless of the agent used, an important principle in PSA is the titration of drugs to the desired level of sedation with the least possible respiratory depression. Drugs given IV have a rapid onset with a more predictable response than agents given orally, transmucosally, or IM (2). Drugs should be titrated slowly, because rapid administration is more likely to cause hypotension or respiratory depression (32). To avoid oversedation, it is important to allow adequate time to achieve and assess peak effect before a second dose is given. A possible exception to the preferred IV route may exist in children, in whom IV access is often difficult and the IM response to ketamine is very predictable (33,34).

Sedatives

Methohexital is an ultrashort-acting barbiturate with sedative and hypnotic effects. It produces deep sedation but provides no analgesia

(35). Methohexital produces a state of deep sedation, which may be preferred for such procedures as cardioversion, chest tube insertion, or complicated orthopedic reductions. It has a rapid onset of action of 30 to 60 seconds, a duration of action of 3 to 5 minutes, and a short recovery phase. Deep sedation is achieved with bolus doses of 1 to 2 mg/kg (35).

Intramuscular doses of 10 mg/kg produce effects that begin in 2 to 3 minutes and last almost 1 hour. Rectal methohexital has been used in children when a motionless state is needed. A dose of 20 to 30 mg/kg induces sleep within 10 minutes and lasts for about 45 to 80 minutes. Cardiorespiratory complications rarely occur with rectal administration. Adverse reactions associated with the use of methohexital include dose-dependent respiratory depression and apnea. Oxygen desaturation is especially common when concomitant respiratory depressants are used. Hypotension is uncommon but can occur, especially in patients with hypovolemia and sepsis. It is easily corrected by giving IV fluids (2). Hiccups can occur, and protective reflexes may be impaired. Methohexital induces epileptiform activity by electroencephalogram in seizure patients and should be avoided in patients with epilepsy.

Midazolam is a benzodiazepine with amnesic and anxiolytic properties. Midazolam has a more rapid onset and shorter duration of action than diazepam and rarely causes phlebitis. Its amnestic properties also appear to be superior to those of diazepam (2). It is eliminated by hepatic metabolism. The IV dose is 0.03 to 0.1 mg/kg, with a starting dose of 1 mg. Onset of sedation is within 3 to 5 minutes, and the duration of action is about 30 to 60 minutes. With IM administration, the same dose is typically used, but the onset of sedation is delayed. Its duration of action is similar to fentanyl; therefore, the two drugs are frequently used together to induce extended PSA. It is often used to provide minimal procedural sedation.

In children, oral, rectal, and intranasal routes are effective alternatives to IV sedation. Oral doses are 0.2 to 0.75 mg/kg, and sedation is achieved within 1 hour. Rectal administration is effective at doses of 0.3 to 0.5 mg/kg, but the response is variable as a result

of the unpredictable effect of first-pass hepatic metabolism and it is not well tolerated or accepted by older children. Intranasal administration can be used when an intravenous line is not needed or when sedation is necessary to establish one. Doses of 0.2 to 0.4 mg/kg result in sedation in about 10 to 15 minutes.

Lower doses should be used when analgesic agents are given concomitantly and in elderly patients. Prolonged effects may occur in elderly patients as a result of decreased metabolic clearance and decreased first-pass metabolism.

Side effects include dose-dependent hypoventilation and hypoxemia. At high doses, midazolam blunts the central respiratory center's sensitivity to hypercapnia (2). Apnea is rare, except when other CNS depressants, such as opioids, are used. Hypotension can also occur with high doses.

Etomidate is an ultrashort-acting, nonbarbiturate sedative hypnotic with no analgesic properties. Like methohexital, it causes deep sedation, has a very rapid onset of less than 1 minute, and has a duration of action of 3 to 5 minutes. Etomidate has minimal cardiac effects. Although respiratory depression can occur, it is usually transient and associated with the use of other respiratory depressants (24,36,37). In critically ill patients (ASA physical status 3 and 4), it is associated with less hypotension than propofol (17).

Etomidate is given IV (0.1 to 0.15 mg/kg) and is currently not approved for children younger than age 10. Side effects are uncommon. Transient respiratory depression can occur. Myoclonic jerking occurs in up to 25% of patients and has been mistaken for seizures (17). Adrenal suppression can occur after long-term use but is not an issue in ED PSA (1,30). Published experience with the use and safety of etomidate in the ED suggests a rate of respiratory depression similar to other agents used for moderate and deep PSA (24).

Ketamine is an anesthetic that causes a dissociation between the thalamic and limbic systems. This, in turn, hinders the perception of visual, auditory, and painful stimuli, leaving the patient in a trancelike state (13). After absorption, ketamine is rapidly distributed and taken up by cerebral tissue. Effects are maintained

until the drug redistributes into the peripheral tissues and is metabolized by the liver (34).

Ketamine can be given by multiple routes. An IV dose of 1 to 2 mg/kg, an IM dose of 2 to 6 mg/kg, a rectal dose of 5 to 15 mg/kg, or an oral dose of 6 to 10 mg/kg induces a dissociative state (34). Sedation is achieved within 1 minute when the drug is given IV, 5 minutes when given IM, and 5 to 20 minutes by other routes. The duration of action is 15 to 30 minutes for IV dosing and 30 to 40 minutes for IM dosing.

Ketamine's most common side effect is the emergence phenomenon, in which the patient wakes up hallucinating. This is more common in patients older than age 10, in females, and in those with an underlying psychiatric disorder. It is less common with IM injection and can be attenuated by the concomitant use of benzodiazepines.

Laryngospasm and emesis are infrequent complications. Patients given ketamine may develop nystagmus and muscular hypertonicity. The pharyngeal–laryngeal reflexes remain intact, although laryngospasm sometimes occurs (13). Ketamine has minimal effects on oxygen delivery. Respiratory depression may occur with high doses or rapid IM infusion. The drug stimulates tracheobronchial and salivary secretions, but this effect can be minimized by the concomitant use of an anticholinergic such as atropine. Mild-to-moderate elevations in pulse rate and blood pressure may result from ketamine's ability to block the reuptake of catecholamines, especially with IV infusion. Twitching, hypertonus, and myoclonic jerking can occur and have been mistaken for seizures. Electroencephalographic studies, however, have shown that ketamine does not cause convulsions.

Ketamine is contraindicated in patients with cardiovascular disease, chronic obstructive pulmonary disease, intracranial and intraocular injuries, and increased intracranial or intraocular pressure. It is not recommended for use in patients with a history of psychiatric illness or children younger than 3 months of age.

Propofol is a very short-acting sedative hypnotic agent, with a rapid onset of action. Propofol is given intravenously as an initial

bolus of 1 mg/kg, followed by 0.5 mg/kg bolus injections every 3 minutes until adequate sedation is achieved. It has a duration of action of 5 to 7 minutes following this dosing regimen. The duration of action of propofol increases with the quantity of propofol used, and can extend to 10 to 20 minutes after a prolonged infusion. It is metabolized by the liver and excreted by the kidneys. It is thought to have a secondary form of metabolism, because it can be used safely in patients with liver cirrhosis and renal failure. Propofol is often used in combination with analgesics such as fentanyl.

ED PSA using propofol has been evaluated in multiple studies of adults and children. Hypoxia has been reported in 5% to 30% of patients (10,15,17,28,32). The use of bag-valve-mask assisted ventilations has been reported to be necessary in 3% to 9% of adults, with a much lower rate of oral airway use (0.3% to 0.5%). Hypotension has been reported to occur in 2% to 7% of adult patients, with emesis occurring in 0% to 0.5% (17,32). These rates are not unique to propofol but are typical of moderate and deep PSA. In comparisons with etomidate and methohexital, propofol was found to have similar rates of respiratory depression (15,17,24,32,35). If hypotension occurs, it is easily reversed with fluids or by terminating the infusion. However, propofol should be avoided in patients with pre-existing hypotension or hypovolemia.

Propofol and ketamine have been combined in an attempt to make a new sedation protocol that maximizes the benefits of both drugs while minimizing their adverse events (38,39). Theoretically, by combining the medications, the dose-related respiratory depression of propofol can be avoided with smaller doses due to the effect of ketamine, whereas the dose-related vomiting and emergence phenomena of ketamine could be avoided through the effects of propofol. Combinations ranging from 1:1 to 4:1 mixtures of propofol and ketamine have been described, with research showing a trend toward less respiratory complications than propofol alone. The duration of sedation appears to be longer than propofol alone, resulting in longer patient stays in the ED. More research will be required to determine the role of this combination of medications in

the ED, but the practice appears to be a safe alternative to either agent alone.

Nitrous oxide is a colorless gas that, when used in combination with oxygen, provides analgesia and sedation. The gas diffuses rapidly across membranes, providing a rapid onset and elimination (2). The level of sedation is often disproportional to the analgesia provided. The use of analgesics in combination with nitrous oxide appears to synergistically enhance the level of sedation and pain control; however, potential side effects, such as hypoventilation, also are compounded.

Nitrous oxide is given as a 30% to 70% mixture with oxygen by a demand valve-mask or a mouthpiece, held by the patient. A variety of delivery systems are available that allow titration of the concentration of nitrous and ensure adequate scavenging of the gas. Nitrous oxide is a teratogen, and it is important to avoid exposing pregnant patients or staff to the agent. Scavenger devices and adequate room ventilation are important to minimize the escape of the gas into the air, preventing potential acute and chronic adverse effects on providers.

Because the gas rapidly diffuses into gas-filled pockets, it potentially can worsen conditions such as pneumothoraces, small bowel obstructions, decompression sickness, chronic obstructive pulmonary disease, and ear effusions (6). Nitrous oxide has the potential for abuse, and every effort should be made to safeguard against this. Many systems available currently have lock systems that allow for controlled access to the medication.

Reversal Agents

Naloxone is a competitive antagonist of opioids at the μ receptors and is used primarily for the reversal of opioid-induced respiratory depression. The initial dose is 1 to 2 mg IV. However, if the patient is opioid-dependent, a titrated dosing of 0.1 to 0.2 mg IV every 1 to 2 minutes may prevent unpleasant withdrawal symptoms. Naloxone may have a shorter duration of action than the opioid used; therefore, continued observation for delayed respiratory depression

is required. It may not reverse the chest wall rigidity occasionally associated with high-dose fentanyl.

Flumazenil is a competitive antagonist of benzodiazepines and is given in titrated doses of 0.1 to 0.2 mg IV, every 1 to 2 minutes to desired effect. It has a half-life of 45 to 100 minutes; therefore, a similar caution must be exercised when used with benzodiazepines having a longer duration of effect. Flumazenil may not be effective at reversing respiratory depression. It should be used with caution in patients with benzodiazepine dependence or a history of seizures.

Elective reversal of PSA remains controversial. It has been proposed that reversal may reduce the time required for postprocedure observation. Several factors caution against this practice. Naloxone has a clinical effect of 30 minutes, which may be shorter than the continued duration of effect for the opioid (2). Flumazenil has not been shown to be effective at reversing the respiratory depression associated with benzodiazepines (9). No effect on discharge time has been demonstrated with reversal in the ED setting. Therefore, elective reversal is not recommended.

CRITICAL INTERVENTIONS

- Assess the patient's underlying medical conditions and potential airway difficulty prior to the initiation of PSA.
- Continue to monitor the patient after the completion of the procedure until recovery to baseline. Patients may become more sedated after the removal of a painful stimulus.

DISPOSITION

Patients must be observed after PSA, and monitoring and documentation should continue until they have regained their baseline mental and physical status. Complications after this time are very rare. Discharge criteria should include regaining baseline mental and physical status when complications of PSA are no longer expected. Patients may require treatment for pain and nausea after sedation. Discharge instructions should otherwise focus on the care necessary for the disease process that necessitated the PSA.

Common Pitfalls

- Forgetting that the most important aspect of patient monitoring is interactive clinical assessment of the level of sedation and respiratory effort
- Using the "one-drug-fits-all" strategy. The selection and dosing of agents should be individualized to the patient and the procedure.
- Failure to treat pain adequately

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SECTION IV
Trauma

Section Editor: CARLO L. ROSEN

Medical Foramen

PART 1 • GENERAL CONSIDERATIONS

CHAPTER 18

General Principles of Trauma

Eric Legome and Ashika Jain

Accidental trauma is the leading cause of death in the United States in the 1- to 44-year-old age group and the fifth leading cause overall. In the United States, injuries cost an estimated $117 billion in medical expenditures each year. This represents approximately 10% of total medical spending, similar in magnitude to the medical costs associated with other leading public health concerns. These estimates do not include the lost productivity, nonmedical expenditures, insurance costs, property damage, litigation, decreased quality of life, and long-term noninjury health consequences (e.g., mental health care costs). In addition, the personal and social costs owing to premature loss of life or livelihood is immeasurable (1,2).

Optimal care of the trauma patient begins in the prehospital setting, continues throughout the emergency department (ED) course, and extends into the intensive care and rehabilitation phases. All of these parts must work in concert to provide for the best outcome. Although not always feasible, the outcome for the severely injured trauma patient is optimized when they are initially treated at, or expeditiously transferred to, a regional trauma center with expertise in and dedication to all facets of trauma care (3–5).

In addition to treatment of the individual patient, resources must be allocated to the prevention of trauma, an often underappreciated aspect of trauma care. Even minor changes in traffic safety, alcohol

and drug use, and gun safety have a tremendous potential to decrease trauma morbidity (4,6).

CLINICAL PRESENTATION

Prehospital

After extrication and immobilization, rapid transport to a trauma center is the most efficacious prehospital trauma intervention. Many prehospital interventions such as military antishock trousers for hypotensive patients have not been found to be helpful, and even interventions such as rapid-sequence intubation (RSI) in the head-injured patient, once thought invaluable, have become controversial. The use of intravenous fluids has likewise become controversial, with timing, amount, and end point a current focus of contention. Current and future studies may offer a clearer understanding of which prehospital interventions have the most utility (5,7).

There are several reasons for rapid transport to a trauma center. While community hospitals have physicians with excellent skills and training in managing trauma patients, major trauma centers evaluate a significantly higher number of major trauma patients with appropriate resource allocation. Furthermore, their personnel are more likely to have advanced skills, appropriate ancillary staffing, up-to-date technology, readily available consultants, rapid operating room (OR) capability, intensive care unit (ICU) capability, and rehabilitative care to restore a patient to full health. In addition, when compared to nontrauma centers, they have been shown to decrease death rates in the most seriously injured patients (3,5). Some areas do not have an available trauma center; for example, there are no major level 1 trauma centers in rural states such as Idaho or Montana (8). In these areas, it may be prudent to take a high-risk patient to a center with available surgical and interventional capability, even if it means bypassing a closer hospital. Often a local hospital will have to stabilize a patient prior to transfer to a convenient trauma center. Therefore, transfer agreements, routes and the mechanics of evacuation should be

worked out well in advance of the individual patient's need. These decisions are often community-specific and based on an understanding of local resources, demographics, and transport times. Regardless of the setting, most emergency physicians (EPs) will encounter both major and minor trauma throughout their career, and competence and confidence in caring for these patients is essential to the skill set of the EP.

Due to funding constraints, a number of hospitals have closed their trauma service because of an inability to support the expensive personnel and equipment needs of a 24-hour service. Moreover, lack of reimbursement, along with the risk of malpractice suits that often accompany major trauma, has discouraged many specialists from participating in trauma care. Subsequently, this has led to a crisis in the ability to deliver timely and appropriate subspecialty care (9).

Emergency Department

On arrival to the ED, trauma patients with abnormal physiologic parameters, a major mechanism of injury or a potentially serious injury should be triaged to a suitable treatment area capable of major resuscitation. It is safer to initially overestimate the degree of injury and then downgrade the patient after initial evaluation, rather than upgrade a patient to more aggressive care. Appropriate personnel should accompany the patient to the resuscitation room to ensure that adequate life-support measures are being accomplished en route. Details regarding the mechanism of injury may offer important clues in predicting potential injuries.

Mechanism of injury must always be taken seriously and is essential for injury evaluation. While a significant mechanism may not lead to major injury, and a trivial mechanism may cause severe morbidity, knowing the mechanism should heighten the suspicion for significant trauma. The most sensitive way to prognosticate major injury is to take both physiologic parameters and mechanism into consideration (Table 18.1).

TABLE 18.1
Mechanism of injury

Blunt Trauma

Motor vehicle collision

1. Estimated speed of both vehicles on impact
2. Orientation of the vehicles (e.g., head-on, broadside)
3. Location of the patient in the vehicle
4. Trajectory and extent of damage to patient's vehicle
5. Amount of intrusion into the vehicle
6. Was there an explosion or fire?
7. Was the patient restrained?
8. Were airbags deployed?
9. Was the windshield intact?
10. Was the steering wheel intact?
11. Was there an initial loss of consciousness at the scene?
12. Was any alcohol or drugs recovered from the patient or car?
13. How long did it take to extricate the patient?
14. What is the ambient temperature (potential for hypothermia)?
15. Was any person killed in the crash?

Fall

1. Estimated height
2. Possible reason for fall (e.g., electrocution; explosion; medical cause of syncope such as a dysrhythmia)
3. Was there an initial loss of consciousness at the scene?
4. Was any alcohol or drugs recovered from the patient or scene?
5. How long was the patient down?
6. What is the ambient temperature (potential for hypothermia)?

Penetrating Trauma

Stab wound

1. Description of the weapon (e.g., length, width)

Gunshot wound

1. Description of the weapon (including caliber)
2. Number of gunshots heard

Triage must take into account the immediate threat to life and limb and patient discomfort and anxiety. A variety of options exist for triage including emergency nurses, a dedicated trauma nurse and even a triage physician.

Major trauma is best evaluated by a dedicated trauma team. The team must have a captain, and the training and experience of this person may vary and should be appropriate to the specific hospital. Usually, the captain is initially an EP; given the increasing economic pressures and the decrease in number of trained trauma surgeons, there is increasing movement to involve trauma surgeons only after full ED evaluation or if urgent operation is required. EPs have also undergone advanced training in trauma care and may have joint appointments with surgical departments. This has led to ongoing controversy, and there is no widespread agreement on when or whether the trauma surgeon is needed routinely in the initial resuscitation (10–12). In some settings, an EP may be the only physician physically present in the ED (and, for that matter, in the hospital). Ideally, surgical support personnel are available within 10 to 30 minutes.

In trauma centers, surgical support is generally rapidly available within the hospital. In this system, the EP may assume the role of trauma captain for the initial assessment and resuscitation. When the attending trauma surgeon arrives, a defined transition of leadership may occur. The team concept must be maintained at all times.

If the responsibility for the major orchestration is formally handed over to the attending trauma surgeon, it does not relieve the EP of responsibility for the patient. The EP should assist until the patient physically leaves the ED for the OR, ICU, or special diagnostic study. Exceptions of course are made if there are other critical patients who demand the attention of the EP. When the EP has to leave the patient, the departure should be coordinated with the team and the team leader. The team may summon subspecialty consultations, but there must be a single person, generally the EP or trauma surgeon, in charge of the orchestration of total patient needs.

Nurses who care for trauma patients should have the requisite special knowledge and skills. In large urban centers, there is usually an abundance of physicians to perform resuscitative procedures, but in the rural ED, the trauma nurse may require technical skills ordinarily performed by physicians. Other institutions may use a

combination of midlevel providers including specially trained nurse practitioners or physician assistants. Prehospital personnel who do not need to immediately return to the field may be requested to remain in the ED so that their technical skills can be utilized.

The area of the radiology department designated for emergency patients should optimally be adjacent to the ED. As radiology has become essential to trauma management, the radiologist must be considered a member of the trauma team and should be readily available for consultation. The ability to perform portable radiographs in the trauma resuscitation room is necessary since these patients should not be moved from the area during the initial stages of evaluation. Likewise point of care ultrasound (US) has become common in trauma centers to provide immediate information at the bedside. Protocols and guidelines should be available regarding expectations of all ancillary staff. A coordinated, knowledgeable response from the blood bank, laboratory, respiratory therapy, and radiology department is vital to an effective trauma system. Social workers, clergy, and lay support should be included in the team framework.

The OR must be rapidly accessible to the ED for operative resuscitation of critically injured patients. Some centers have emphasized this by having an OR as part of the ED or by reserving a single OR for trauma use, but others have utilized a special OR in the surgical suite in which to perform the initial resuscitation.

ED EVALUATION AND MANAGEMENT

Prior to Arrival

When notice is given by EMS that a critical patient is en route, the ED should consider potential needs, for example, having blood for an exsanguinating patient. The entire trauma team should ensure standard precautions, with gloves, gowns, masks, and protective eyewear. All patients should be presumed to be potentially infectious from blood-borne or body fluid–borne diseases and should be treated accordingly until risk can be fully assessed. These precautions apply to blood and to other body fluids containing

visible blood, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid. Prior to arrival, the team captain should assemble the team and assign roles; this may include setting up for necessary procedures (i.e., airway management and tube thoracostomy).

Primary Survey

The approach to the trauma patient begins with a rapid initial examination. While the initial assessment proceeds in a stepwise approach, when performed with multiple providers, several steps may occur simultaneously. This is appropriate as long as one clinician is clearly overseeing the entire process. On arrival, the patient must be immediately undressed. Care should be taken to avoid hypothermia by placing warm blankets on the patient after the evaluation is done. The cervical spine should be immobilized until it is cleared of injury by radiographic or clinical criteria, but early relief from the back board is critical to patient comfort.

The initial trauma assessment, or the ABCs, begins with evaluation of the airway. The need for airway management is the most critical initial question in the patient with multiple trauma. Table 18.2 lists common criteria that serve as guidelines for this decision.

TABLE 18.2
Indications for Intubation

Mandatory

Inability to protect airway, oxygenate, or ventilate

Head injury with Glasgow Coma Scale <8

Penetrating injury to the cranial vault or high energy to the neck

Massive facial injuries

Blunt injury to the neck, with expanding hematoma, painful phonation, or alteration of the voice

Bilateral missile penetrating injuries of the thorax

Multisystem trauma with persistent shock

Relative Indications

Need for significant ongoing sedation/pain control

Expectation of significant worsening

Any patient with injuries impairing ventilation, e.g., flair chest, severe pulmonary contusions, deteriorating respiratory status

Need to transport long distances with potential or actual instability

Bilateral pneumothorax

Expanding hemothorax that recurs or does not respond to thoracostomy

Any patient developing severe hypovolemic shock or with extensive burns, or patients with pulmonary, facial or neck burns

The airway assessment should include patency, ability to speak clearly, and ability to control secretions. If this is not the case, the EP should search for possible obstruction in the form of foreign body or relaxed tongue that might obstruct the airway. Oxygenation of the tissues is critical, and clearing the airway is the initial step in oxygen delivery. A suction apparatus may be used to clear the upper airway. The patient with facial injuries, but no neck injuries, may be turned onto the side or sat up leaning forward to allow rapid clearing of the airway. A patient may also be turned on the backboard or while maintaining spinal immobilization (log rolling) if the condition of the cervical spine is unknown.

An oral airway may be placed in the unconscious trauma victim to allow for oxygenation but this is generally followed rapidly by intubation. In some cases of severe maxillofacial trauma or direct tracheal injury, cricothyrotomy is indicated. The need for intubation and active airway management is a clinical decision and should never be withheld pending a blood gas. Once the airway is patent, breath sounds should be rechecked.

If the patient is not breathing spontaneously or adequately, ventilation must be controlled. Initial control may be by bag-valve-mask ventilation with high-flow supplemental oxygen. Once the patient is oxygenated and hypercapnia has been corrected, intubation is less hazardous, but undertaking bag-valve-mask ventilation must be weighed against the risk of distending an already full stomach.

Major trauma victims often need early airway management, even if they are breathing spontaneously. Patients may have injuries distorting their airways (e.g., a gunshot wound to the neck). It is prudent to intubate these patients early in their course before intubation is impossible to perform such as if the neck is distorted by a large hematoma. In addition to airway protection and maintenance of anatomic function, other reasons to intubate the major trauma patient exist. Intubation will allow for multiple tests and transport in patients with serious injuries or altered mental status who may require ongoing sedation or narcotic pain control. In some cases, airway management is indicated owing to the expectation that the injuries are so severe that the patient will eventually need intubation. Patients with severe or suspected head injury with a Glasgow Coma Score (GCS) of <8 or a declining mental status should be intubated to protect the airway, prevent hypoxia, and allow for controlled breathing. Finally, because few trauma patients have an empty stomach at the time of injury, intubation can help lower the risk of vomiting and aspiration.

Oral intubation using RSI is the optimal approach in the ED. It has been very successful and has virtually eliminated the need for cricothyrotomy. The preferred approach to intubation in the patient with a possible cervical spine injury is to keep the neck immobilized by inline stabilization and perform RSI. A second pair of hands other than those of the intubator provides in-line stabilization of the head and neck, which also allows for opening the anterior collar.

Nasal intubation, which is still occasionally performed in some prehospital systems, is rarely used in the ED. Many EDs are commonly using specialized approaches to the airway, especially video-assisted laryngoscopy, often as the initial procedure (13). A

surgical airway may be necessary if there is extensive damage to the patient's larynx, complete tracheal separation, or significant midfacial or orofacial trauma or neck distortion.

Laryngeal mask airway may be used as a rescue technique in the ED but generally does not provide a long-term secure and safe airway and should be replaced as soon as possible by a secure endotracheal tube.

After evaluation and management of the airway, breathing and circulation must be assessed.

In assessing breathing, the physician should observe the chest for sucking wounds or paradoxical motion, palpate for bony crepitus or subcutaneous air, and auscultate for breath sounds. Severe dyspnea, hypoxia, subcutaneous air, or tachypnea in the presence of penetrating chest trauma should lead to the presumption of an underlying hemo- or pneumothorax.

The major causes of pulmonary dysfunction in the trauma patient are hemo- and pneumothorax. The patient may also hypoventilate owing to multiple rib fractures or underlying pulmonary contusions.

Tension pneumothorax causes shock by increasing intrathoracic pressure, shifting the mediastinum, and compressing the great veins, thereby preventing venous return. The diagnosis is probable in a trauma patient in shock who has distended neck veins and an increased resistance to bagging. An ipsilateral decrease in breath sounds may be noted and a contralateral tracheal shift. Unfortunately, these physical findings are often not present acutely and the only clues to the presence of this may be a sudden rise in pulse, a drop in blood pressure, and an increased resistance to ventilation. If tension pneumothorax is suspected in the field, it should be immediately decompressed with a large-bore over-the-needle catheter in the fifth intercostal space or the second intercostal space in the midclavicular line. Treatment of a suspected tension pneumothorax should not be delayed to obtain radiographic confirmation. The physician should needle decompress the chest or perform thoracostomy by inserting a large-bore chest tube in the fifth intercostal space, midaxillary line, to evacuate any blood or air.

After pulmonary evaluation, circulation must be rapidly assessed. Any obviously bleeding source should be controlled by pressure, and vascular access should be obtained. There is no single answer to which method of intravenous access is the best. Each patient must be evaluated individually, and the risk–benefit ratio of the chosen routes weighed. In the patient in shock or with concerning findings, it is best to insert a minimum of two large-bore (14 to 16 gauge) peripheral lines, adding more as necessary. Patients with minimal or no injuries may not require such aggressive intervention. Sometimes it may be necessary to proceed immediately to a central line or peripheral cut down to gain access. A central venous catheter may be helpful in monitoring central volume, in addition to delivering fluid and blood. Central line placement utilizing an US probe has become a much safer procedure and will not only give access with a large-bore catheter but allow successful central venous pressure monitoring. Intraosseous techniques, more common in children, may be used in adults also. This has become more common, especially in the prehospital arena when standard access is unobtainable (14).

Most traumatized adults can tolerate generous fluid infusions because they are usually young and previously in good health. Whether this is best however, is still unclear. Classic teaching has been that an initial dose of 20 mL/kg is safe and an appropriate starting point. If the patient still shows signs of significant volume deficit after administration of 50 mL/kg or 2 L of crystalloid, type-specific or O-negative blood should be started. In the patient who has an injury that obviously will produce a major volume deficit (e.g., shotgun blast with marked tissue destruction and loss), blood should be given very early. Massive transfusion protocols have become much more common, based largely on experiences in the military. While there is little prospective research showing their benefit, retrospective case control studies suggest that when performed with appropriate ratios of blood to platelets and factors, they may be effective in decreasing mortality. When massive transfusions are used, they generally should be part of a hospital wide strategy and protocol (15–17).

Both the end point and the aggressive use of fluid resuscitation are controversial. Owing to concerns, based mostly on animal studies, that aggressive fluid resuscitation to normotension in the actively bleeding patient may lead to increased mortality, a less assertive response to hypovolemia has been advocated. This mortality is due to factors such as increased bleeding from increased arterial and venous pressure, dilution of clotting factors, clot disruption, and decrease in blood viscosity. Multiple animal studies have upheld this idea of “hypotensive resuscitation.”

In clinical practice, however, it has yet to be fully proven beneficial. Few significant studies have been performed in human beings, one with penetrating and one with a combination of penetrating and blunt trauma patients. Although one study found a benefit to not actively resuscitating patients with penetrating torso trauma, there have been concerns about the methodology and validity of the study. In addition, patients with severe head injury have a worsened outcome with hypotension, making this approach unlikely to be helpful in this group of patients. However, many clinicians and academic centers believe strongly in the concept of less aggressive resuscitation. This approach should be considered as an appropriate alternative while awaiting more definitive research in this area (18–20).

The amount of fluids administered depends on continued losses, which should be minimized as much as possible. Though intra-abdominal bleeding may require definitive surgical or angiographic intervention, interventions in the ED such as proper splinting, bandaging, and avoidance of probing large soft tissue wounds will maximize hemorrhage control. The degree to which long-bone and pelvic fractures bleed is not generally appreciated; it is far more effective to administer blood when these injuries are recognized than to wait until the patient is in shock. Direct pressure should be applied to control external hemorrhage. Blind probing and clamping deep within a wound may cause further injury to vessels and nerves. A soft tissue injury, especially to the scalp, may result in large amounts of bleeding. The best treatment for hypovolemia is to locate the source of bleeding and stop the blood loss. Hemostasis

can be rapidly obtained in a scalp laceration either by the use of Raney clips (neurosurgical skin clips that can be quickly applied to the scalp laceration edges) or by placement of a 2-0 nylon running locked stitch.

While most trauma patients in shock are hypovolemic and this should be actively pursued, other options should still be considered. Cardiac causes of shock must also be in the differential diagnosis. Pericardial tamponade is rare with survivable closed-chest injuries; another source of the shock should probably be sought. It must always be considered with penetrating injuries, even if the entrance wound appears anatomically remote. The physiologic response to tamponade is to compensate for the fall in cardiac output by raising the pulse rate. The classic physical findings may be absent in the acute situation. Thus, one may not see distended neck veins if the patient is profoundly hypovolemic. Furthermore, heart sounds may be difficult to appreciate in the ED. The use of focused assessment with sonography for trauma (FAST) in the trauma bay is highly useful in evaluating for pericardial fluid. If not available in the trauma bay a pericardiocentesis can be performed. If, on the other hand, the patient has just lost vital signs an immediate thoracotomy should be performed.

Blunt cardiac injury may cause dysrhythmias. An electrocardiogram should be obtained in patients with significant anterior blunt chest trauma. Continuous cardiac monitoring is indicated. A normal EKG and period of monitoring in the ED generally rules out a significant blunt cardiac injury. Myocardial infarction may occur as a result of the stress associated with blood loss and catecholamine release, or it may have preceded the traumatic injury.

The presence of spinal cord trauma with loss of sympathetic vascular tone can be assessed by rectal examination and examination of peripheral reflexes. The extremities should be palpated; if they are cool, moist, or pale, hemorrhagic shock must be presumed.

If the patient has a cardiac arrest from hypovolemia or pericardial tamponade, immediate emergency thoracotomy may be indicated.

In general, thoracotomy in the presence of penetrating injury and a patient who arrests in the ED or just prior to arrival offers the best prognosis. Maximal benefits are obtained in the presence of low-velocity penetrating injury to the chest, particularly the heart. Blunt trauma arrests in general have an extremely poor prognosis, especially with a prehospital arrest or multiple concomitant injuries (9).

Operative intervention is part of the resuscitation of the unstable trauma victim. In the patient unable to be resuscitated from shock without an obvious source of blood loss, immediate exploration may be indicated. A chest radiograph helps determine whether the chest or the abdomen is the site of initial exploration.

Patients with penetrating trauma, in the absence of contraindications, should be rolled onto the side to ensure that there are no wounds on the back, buttocks, or in the axillae. Blood pressure determination from the field should be repeated. Although not clearly correlated with a specific blood pressure, locating a palpable pulse provides information about the perfusion pressure.

When intravenous lines are placed, blood is drawn for typing and other tests. If possible, the prehospital providers may draw blood. Though it may be more efficient to use a large, 50-mL syringe and simultaneously draw all needed blood samples and measure arterial blood gas from the femoral artery, this may also increase the possibility of needle sticks when the blood is transferred. It is the trauma captain's responsibility to ensure that blood is obtained in a timely manner.

The priorities of definitive management are still vigorously debated, and it is often necessary to perform invasive procedures without the luxury of confirmatory diagnostic studies. In general, one should attempt to approach the pathology that poses the most immediate threat to the patient's life—usually in the abdomen.

Secondary Survey

In the patient who stabilizes during resuscitation, the next priority is a complete head-to-toe examination, including repeat maxillofacial,

cardiopulmonary, abdominal, neurologic, and orthopedic examinations. In addition to the examination, further history about the timing and mechanism of the injury should be obtained with the past medical history, medications, and allergies.

If the patient is unconscious, determining the level of brainstem function and the presence of a herniation syndrome is paramount. Most trauma victims die of central nervous system–related injuries. While in the stable patient with little clinical concern the rectal examination is rarely helpful and may be misleading, in the multiple trauma patient, a rectal examination may reveal displacement of the prostate, or gross blood, and provide for neurologic assessment of the anal sphincter tone and sensation (21). The absence of tone or sensation may indicate a spinal cord injury in a patient previously assessed to have only a head injury.

It is necessary to immobilize the spinal column until its status can be ascertained, but it is not necessary to spend long periods of time trying to clear the cervical or other spinal column before dealing with more life-threatening injuries. The patient can be maintained supine with a hard collar while more immediate life threats are determined.

Open fractures should be gently irrigated (realizing that this procedure will not substitute for more effective and complete irrigation and debridement under anesthesia) and splinted to prevent further injury and reduce pain and bleeding. Open fractures should be covered with clean dressings and intravenous antibiotics administered, to provide antistaphylococcal coverage. Definitive care may have to be delayed while surgical treatment of more serious, life-threatening injuries occurs.

Laboratory and Diagnostic Studies

Laboratory analysis of the trauma patient is generally more extensive than necessary. Routine laboratory studies on preoperative patients are not useful or cost effective unless indicated by the history and physical. However, owing to the limitations in obtaining this information in the multiple trauma patient, an extensive array of tests is often completed. Though testing based on clinical

parameters has been shown to be cost effective without compromising care, most trauma centers use some type of protocol to standardize and speed the laboratory evaluation of patients (22). The patient who is fully awake and alert, who has sustained minimal trauma, and who has no distracting injuries may require no testing. Rational laboratory analysis of most patients with moderate trauma can probably be limited to a complete blood count, a basic metabolic panel, blood type and screen, and urinalysis.

Clinical screening for basic risk factors for renal insufficiency (i.e., history of renal disease or diabetes) in ED patients has been repeatedly shown to be an excellent screening tool for patients who need a serum creatinine prior to receiving intravenous contrast for CT. If risk factors are absent, an urgent CT scan should not be withheld while awaiting serum creatinine. The multiple trauma patient or one about to undergo urgent operative management may require more thorough testing. Women of childbearing age should have a pregnancy test performed.

The sequencing of radiologic studies should be prioritized in the same manner as the other components of the resuscitation. Though cervical spine imaging is essential in the patient who cannot be clinically cleared, the imaging may be delayed and the patient kept in a collar and immobilized while addressing more pressing issues. In victims of blunt trauma, chest and pelvic films should be obtained next and, if necessary, extremity films obtained thereafter. The chest radiograph should be taken as soon as possible in the patient with penetrating injury, although with proper training, the test characteristics of bedside US for lung pathology are excellent and arguably better than radiographs (23). Empiric treatment of a presumed pneumo- or hemothorax should take priority if the patient is unstable. Clinical evaluation of the pelvis without radiographic study is accurate to exclude a clinically important fracture. It is still wise to routinely obtain a study on the patient with altered mental status, hypotension or significant distracting injury and appropriate mechanism (24).

One of the most important decisions in the management of the multiple trauma patient is when and how to obtain an objective

evaluation of the abdomen. Generally a combination of mechanism, physical findings and age are the most important factors. With a major mechanism of injury even in the well-appearing patient, it is reasonable to consider further evaluation of the abdomen for occult hemorrhage. Clinical judgment, however, should be used (25). The physical examination of the abdomen is less reliable when there are multiple injuries, competing pain from skeletal trauma, or altered mental status from head injury, shock, or substance abuse. In the presence of these factors, objective evaluation should generally be obtained. Finally, in any patient who demonstrates hemodynamic instability without obvious source, it is critical to evaluate the abdomen for hemorrhage.

Objective evaluation of the abdomen is generally performed by one of two common methods: CT or US. While previously a common option, diagnostic peritoneal lavage (DPL) has largely been replaced by US (26).

DPL is highly accurate (92% to 98%); it has reliable significance when negative. However, as noted, it has largely been supplanted by CT and US, both noninvasive tests. DPL is still recommended in the unstable patient with an unclear US result or in the stable patient with a significant concern for a hollow viscous or mesenteric injury, either by examination or after an equivocal CT. The only absolute contraindication for DPL is the need for emergency laparotomy.

Ultrasonography can also be performed at the bedside. The FAST examination, a four-view, directed US examination, is able to reliably find fluid within the abdomen and within the pericardial sac. It is accurate with significant intra-abdominal hemorrhage, and as it is noninvasive, it has mostly replaced the DPL. FAST is performed on the supine patient with the examiner positioned on the right side. Four locations are scanned: (a) the right upper quadrant, (b) the left upper quadrant, (c) the suprapubic region, and (d) the pericardium. The examiner looks for unclotted blood, a black or anechoic finding on the US's screen. It is reasonably reliable, especially with enough bleeding to cause hemodynamic instability, but may need to be performed more than once if the patient is seen very soon after the trauma prior to large amounts of bleeding. The

level of accuracy is comparable regardless of whether an EP, surgeon or radiologist performs the study. The major limitation of US is that it shows fluid in the abdomen but not its source or the magnitude of injury. Therefore, a positive US in a stable patient is generally followed by a CT scan. An advantage of US is that the heart can be assessed for pericardial effusion. The bedside US has good diagnostic accuracy for long-bone fractures and hemothorax and is more accurate than supine chest radiograph for detection of a pneumothorax (23).

Though the main use for US is in blunt abdominal trauma, a positive FAST in a penetrating trauma patient has an extremely high positive predictive value for an operative lesion. A negative test cannot rule one out (27).

CT offers both quantitative and qualitative information. It is the gold standard for evaluation of the abdomen in the hemodynamically stable blunt trauma patient. It may also be used to evaluate penetrating trauma, although with greater limitations. With the advent of the multidetector CT, the test is performed rapidly with excellent accuracy. These scanners also allow for reformations of areas of concern for pathology, including the spine and aorta. The major limitation of abdominal CT is the decreased sensitivity for bowel, mesenteric, diaphragmatic, and pancreatic injury, although there is usually some direct or indirect sign of injury such as unexplained free fluid (28,29). A normal CT in trauma has an extremely high negative predictive value for operative intra-abdominal pathology and should provide clinicians with a very high probability that they are not missing an operative lesion (30). Of course, technology and those who interpret its data are not infallible. If the clinical examination still suggests the possibility of injuries not revealed on CT, the patient should undergo further testing or observation.

Additional evaluation depends on specific concerns. Gross hematuria should prompt evaluation of the genitourinary (GU) tract. Microscopic hematuria is poorly sensitive and specific for significant GU injury and, in the absence of a pelvic fracture, gunshot wound of the abdomen, or unexplained hypotension after blunt trauma, does

not mandate workup. Penetrating trauma with any hematuria should be followed by a formal evaluation of the GU tract. Gross penile bleeding should be evaluated by retrograde urethrography before passage of a Foley catheter.

Many modern EDs have a scanner either in or immediately adjacent to the ED. The speed of the newest scanners along with their proximity to the ED has allowed for safer use in patients who previously would not have been scanned owing to borderline blood pressure or concern over absolute stability. This must be done with extreme caution, however, as resuscitation is best not performed in CT. One approach that some trauma centers are now using is to perform a CT from head to pelvis, that is, the pan-scan. This may be cost effective as the extra time is measured in minutes, there is no increased use of film if the images are stored on a picture archival retrieval system, and scans of the bones can be included, obviating the need for plain films. Reformations allow for the ability to image the aorta and have essentially replaced aortography in the diagnosis of aortic injury. Radiation exposure, though not acutely dangerous, is essential to consider when making decisions about performing CT scans, especially in young patients. Although the lifetime risk of developing cancer from CT scanning remains low it is still a real concern. Therefore, a CT should not be performed as a replacement for physical examination when the patient is fully evaluable (31–33).

Interventional angiography is increasingly important in the management of trauma patients. Angiography is the definitive modality in controlling hemorrhage from major pelvic fractures. In patients with ongoing hemorrhage from major pelvic trauma, angiography with embolization has been shown to be more effective and definitive than external fixation devices or operative packing. For stable patients with intraperitoneal injuries, if an actively bleeding spleen, liver, or kidney is visualized, a dedicated angiography team may be able to embolize the lesion and avoid laparotomy. Though effective, angiography still remains resource-intensive and is not readily available at all centers (34,35).

Angiography may also be used to diagnose arterial injuries in the neck or extremities. Doppler US may reveal flow impairment in the carotid or vertebral vessels after a whiplash trauma to the neck. Arteriography is then used to define the injury. Currently, many centers have switched to CT angiography as the definitive test for vascular injury and are using catheter-based angiography only for treatment or in equivocal cases. Other centers utilize magnetic resonance angiography in the stable patient. Another place for angiography is in the patient with a penetrating wound near a large vascular structure with massive tissue damage or evidence of distal pulse deficits. If the patient is unstable, however, it is more prudent to take the patient to the OR, obtain vascular control, and perform the angiography intraoperatively. In some cases, for example, possible aortic rupture, transesophageal echocardiography is an excellent option to perform in the OR in the patient unable to tolerate CT angiography.

Though the management priorities in patients with head, chest, and abdominal injuries still present a challenge, the critical ordering should be to diagnose and treat injuries to the abdomen, head, and then chest (aorta), in that order. However, the specific patient and clinical judgment may alter this approach. In addition, the rapid speed of the multidetector CT allows for the full body scan with little additional time once the patient is on the CT gurney. The initial priority is to assess for intraperitoneal bleeding. An US study or DPL that shows blood in the abdomen does not reveal the specific organ injured or the amount of damage, and the patient may also have evidence of intracranial injury. A head CT requires transfer to the radiology suite, but the rapidity of the procedure may enable a quick assessment of the head en route to the OR for laparotomy. It also adds little time to the assessment to take cuts of the chest and abdomen. If intraperitoneal bleeding is present in the unstable patient, then management of pelvic fractures or aortic injury must be delayed until after laparotomy.

Finally, it is imperative to recognize that the trauma patient needs prompt definitive care. Time wasted in the field, the ED, or the radiology suite may increase mortality. Sometimes, the trauma

surgeon must proceed to the OR with a paucity of diagnostic information rather than have the patient continue to hemorrhage.

KEY TESTING

Laboratory *Depends on presentation and underlying concern.* *If major trauma*	Minor trauma—low suspicion Generally urinalysis and HCG for all females of childbearing age	Moderate trauma—moderate suspicion Generally urinalysis and HCG for all females of childbearing age Consider CBC, chemistries, type and screen	Severe trauma—high suspicion Urinalysis and HCG for all females of childbearing age CBC, chemistries, type and screen/cross
Radiology *Depends on presentation and underlying concern.* *If major trauma*	Minor trauma—low suspicion Consider chest radiograph FAST	Moderate trauma—moderate suspicion Chest radiograph Pelvic radiograph (unless CT planned and stable) FAST Consider CT (head/chest/abdomen pelvis depending on suspicion)	Severe trauma—high suspicion Chest radiograph Pelvic radiograph (unless CT planned and stable) FAST CT (head/chest/abdomen pelvis)

DISPOSITION

The stable trauma patient may spend a number of hours between the ED and the radiology department during the completion of diagnostic tests. During this time, the patient must be monitored to ensure that deterioration does not occur or that a quick transfer to the OR has not become necessary. This may be visual or with cardiac monitoring, depending on the clinical situation.

The patient remains the responsibility of the ED until admitted. Once admitted, overall ED care of the patient may depend on institutional policies and resources. However, the EP should assist in care of any patient who remains in the ED. Even if the trauma team monitors the patient in the radiology department, when the patient returns to the ED, it again becomes the EP's responsibility to remain involved in the care of the patient, unless pre-existing protocols are in place and the trauma service has the proper manpower to observe the patient. After careful evaluation and a period of observation, many patients can be discharged from the ED.

Transfer of the patient to another institution depends on multiple factors. If the patient is unstable, the only rationale for transfer is to achieve a level of care higher than what is available at the original treating facility. It may be necessary to care for life-threatening injury (e.g., removal or salvage of a ruptured spleen) and then transfer the patient for more sophisticated neurosurgical, orthopedic, or thoracic management.

TRAUMA SCORING SYSTEMS

Trauma scores are an imperfect but commonly used tool in trauma systems. Prehospital providers, EPs, and inpatient trauma services use these scores for planning purposes and as a quality assurance screen to monitor system performance. Regional trauma planners use these scoring systems to compare institutions and assess resource needs and as a tool for performing research on the effects of different interventions.

Economic and geographic constraints have dictated that many trauma patients cannot be cared for in a trauma center. Unfortunately, it is extremely difficult to devise a system based on inpatient data that is accurate in the prehospital setting for triaging patients. Prehospital triage protocols are complicated by factors such as drugs, alcohol, and competing injuries, and many serious injuries are often hidden until there is a catastrophic decompensation. For example, most of the trauma scores utilize the GCS as part of their scoring estimation. Although the GCS is often

applied in the field, it was not intended to be used until after all alcohol has been metabolized. As at least half of all major traumas involve patients who are intoxicated, the GCS is not likely to solely represent brain injury. It is also difficult to calculate the GCS in the intubated and paralyzed patient. Even mechanism of injury, which provides useful clues to the seriousness of the forces involved, is inaccurate because the recipients of those forces sustain such variable degrees of injury. Data suggest that physiologic criteria and altered mental status are the best predictors of the need for major interventions; however, these criteria are bound to miss serious occult injuries that may not present until later in the ED or hospital course. Even at the trauma center, the initial recognition of injury severity is often difficult, and the variations of response to what appears to be minor trauma can lead to increased morbidity or mortality.

The optimal scoring system should be easy to apply to patients and have validity and good interrater reliability. It must have easily measured and understandable criteria and should not be so complex that it is difficult to calculate or understand the outcome measurements. Most scoring systems are based on anatomic scoring systems, physiologic scoring systems or a combination of both (36).

In the prehospital system, scores may be used to monitor quality assurance and to assist in deciding whether a patient requires a major trauma center. They may also aid trauma centers in formulating their needs and levels of response prior to patient arrival. In the ED, scores may be chosen to assess the need for a trauma team response, the need for prophylactic intubation, the likelihood of occult injury, or the need for ICU admission.

Physiologic Scores

Physiologic scores are employed in prehospital decision making, to evaluate the appropriateness and efficacy of injury treatment and to prognosticate outcome.

Revised Trauma Score

The original trauma score evaluated respiratory rate, respiratory expansion, systolic blood pressure, capillary refill, and GCS. Owing to variability in assessing several of the components, a revised score was developed in 1989, using data from the Washington Hospital Trauma Center and the Major Trauma Outcome Study. The Revised Trauma Score (RTS) was broken into three components: GCS, systolic blood pressure, and respiratory rate. Numbers were assigned to each parameter, with a higher number representing improved function. As this score is based entirely on physiologic variables, there is a risk of inappropriate decision making when patients are scored early after injury. Though the RTS is a commonly used score, several factors contribute to decreasing its specificity. This score is partially driven by the GCS score. As mentioned earlier, the GCS is skewed by alcohol and drugs, but it is also skewed by how quickly the patient is evaluated after the head trauma. For example, many patients who are ultimately deemed minor head injuries would actually have a low GCS if examined immediately after being struck on the head.

Anatomic Scores

Injury Severity Score

The Injury Severity Score (ISS) was developed as an extension of the Abbreviated Injury Scale (AIS) (4), one of the original scoring systems. The AIS grade was developed by dividing the body into six regions (the thorax, abdomen, and visceral pelvis; head and neck; face; bony pelvis and extremities; and external structures) and utilizing the site with the worst injury from each region when calculating the overall score. The original ISS was devised by summing the squares of the highest AIS grade in each of the three most severely injured areas. This modified scale was shown to correlate with fatality from trauma. Death from trauma begins to rise significantly when the ISS is above 15. Unfortunately, both the AIS and the ISS can be calculated accurately only after the full extent of the patient's injuries is known. The ISS is now commonly

used as a quality assurance tool, but it has no role in decision making either in the ED or in the prehospital setting.

Other Scoring Systems

Trauma and Injury Severity Score

Though the ISS accounts for patients' injuries, prediction of mortality should take into account factors that affect likelihood of survival. The trauma and injury severity score (TRISS) methodology incorporates the patient's age and ISS into a score that predicts the chance of survival. Patients with outcomes different from those predicted by the formula may be candidates for quality assurance review. TRISSs are heavily weighted toward head injury. The W statistics, derived by comparison of a hospital's results to those from the Major Outcome Trauma Study, portray the number of excess survivors per 100 patients (8).

A Severity Characterization of Trauma System

A severity characterization of trauma system (ASCOT) was developed based on analysis of the shortcomings of TRISS seen in the Major Trauma Outcome Study. In addition to the RTS variables, ASCOT adds scoring assignments for injury to three body regions (brain–spinal cord, thorax–neck, and abdomen-major vessel). In comparison, ASCOT seems to perform better than TRISS for adults with blunt trauma. Both TRISS and ASCOT appear adequate for pediatric patients.

Clinical Judgment

After reviewing the available scores and methodologies for triaging trauma patients, the practicing physician may wish to consider the role of clinical judgment. In a large study evaluating the ability of urban EMTs to assess trauma, none of the scores were found to perform better than EMT judgment. The physician considering the use of these scores will need to consider the setting in which the scores will be used. Most urban EMTs have the ability to recognize major trauma patients (37). Depending on the purpose for which

they are being used, EDs have a number of scoring systems available for their use. The RTS may be used to monitor changes in a patient's condition during the course of the patient's initial resuscitation. Clearly, the use of mechanism of injury to activate the trauma team will lead to an overuse of that resource, but a degree of overtriage is accepted in the effort to include all potentially injured trauma patients. EMS systems commonly use the Prehospital Index or the RTS.

Common Pitfalls

- Failure to appreciate the severity of the mechanism of injury.
- Ascribing positive physical findings to a benign cause.
- Failure to anticipate patient needs prior to arrival.
- Failure to have a visible trauma captain throughout the resuscitation.
- Failure to use a well-thought-out, systematic approach to the patient.
- Chaotic and inefficient resuscitation because of poor use of team members or because too many physicians are trying to give orders.
- Focusing on subspecialty needs at the expense of real or potential life threats.
- Overemphasizing diagnostic tests in an unstable patient.

ACKNOWLEDGMENT

Authors Gratefully acknowledges the contribution of Peter Rosen to the content of this chapter.

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CHAPTER 19

Trauma Airway Management

Timothy J. Fortuna and John H. Burton

Expertise in airway management is an essential skill for the emergency physician (EP), and this is especially true of airway management in patients with multisystem trauma. Many trauma patients benefit from early control of the airway to ensure adequate oxygenation and ventilation and to protect against aspiration.

There are many special considerations to take into account when faced with controlling and maintaining an adequate airway in the trauma patient; some are listed in Table 19.1. The EP should assume the presence of cervical spine injury in most victims of blunt trauma. Owing to the common occurrence of altered mental status and hemodynamic instability, as well as the difficulty of rapidly obtaining adequate cervical spine imaging, cervical spine injury cannot typically be excluded in many trauma patients who require emergent intubation.

TABLE 19.1
Factors Complicating Trauma Airway Management

1. Inability to optimally position the airway for intubation owing to the possibility of spine injury
2. Presence of hypovolemic shock or occult hypovolemia
3. Presence of full stomach and risk of aspiration
4. Possibility of concomitant head injury
5. Known or unknown pre-existing disease states
6. Obstruction of the airway and normal anatomy owing to blood, emesis, or injury

There are many methods for predicting the difficulty of intubation in a patient (see Chapter 1). Though these are helpful as a structured approach to airway management, their application in the trauma patient is frequently limited. Coexisting facial and penetrating neck trauma may exacerbate the challenge of both the assessment and visualization of the airway. The inability to optimally position the airway in the trauma patient can be problematic for adequate laryngeal visualization during intubation.

All trauma patients should be assumed to have hypovolemia or compensated shock. Therefore, caution must be used when choosing medications to facilitate airway management to avoid hemodynamic compromise. Trauma patients should also be presumed to have a full stomach. This places the trauma patient at an elevated risk for aspiration during the initial assessment and airway interventions. Patients immobilized by cervical collar and long spine board are not always able to fully protect their airways.

Concomitant head injury alters the approach to airway management in the trauma patient. Adequate cerebral perfusion pressure should be maintained in these patients and the consequence of potentially increased intracranial pressure (ICP) should be considered for all interventions. Drugs or alcohol, which may cause altered mental status and combative behavior, complicate the determination of the presence of closed head injury and the need for emergent airway management.

INDICATIONS FOR AIRWAY MANAGEMENT IN THE TRAUMA PATIENT

The most common reasons for deciding to perform endotracheal intubation (ETI) in the acutely injured patient are for oxygenation, ventilation, and airway protection. Severe chest and pulmonary injuries, hemorrhage, traumatic brain injury, and airway obstruction may lead to the inability of trauma patients to adequately oxygenate or ventilate. Protective airway reflexes may be impaired due to depressed mental status from traumatic brain injury, severe alcohol intoxication, and upper airway trauma. Trauma patients are often combative and resistant to calming techniques as well as physical and chemical restraints. These patients may benefit from intubation in these circumstances to expedite their evaluation. The increasing frequency of elderly trauma patients, who commonly have comorbidities, may provoke the clinician to consider early airway interventions to facilitate both the assessment and treatment of their traumatic injuries.

TECHNIQUES OF AIRWAY MANAGEMENT

Orotracheal intubation (OTI), video-assisted intubation (VAI), blind nasotracheal intubation (NTI), and surgical cricothyrotomy are choices for definitive airway management in the trauma patient. Proper preparation is essential in the anticipation and execution of all airway interventions. The use of the mnemonic SOAPME may be helpful to ensure readiness (eTable 19.1).

eTABLE 19.1
Preparation for Airway Management: Mnemonic

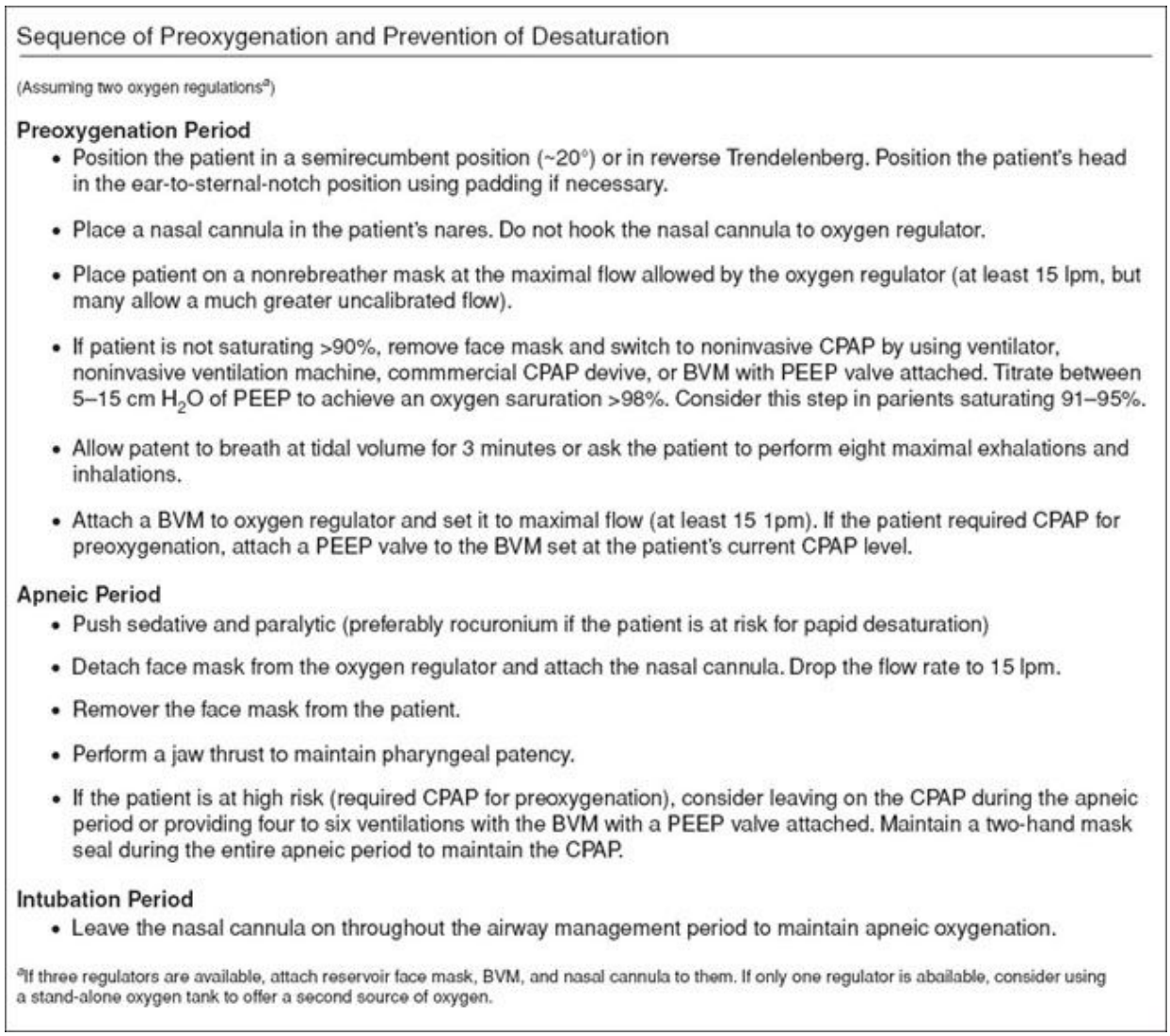
S	*S*uction should be readily available with Yankauer or tonsil tip apparatus.
O	High-flow *O*xygen with appropriate methods of delivery such as bag-valve-mask device and nonrebreathing masks should be available.
A	*A*irway supplies should be present in various sizes. These include naso- and oropharyngeal airways, endotracheal tubes with stylets, 10-mL syringes, and functioning straight- and curved-blade laryngoscopes. Airway adjuncts should be available for difficult airways including gum elastic bougie, fiberoptic intubating scope, and/or laryngeal mask airways.
P	*P*harmacology in the form of induction, sedative, analgesic, and neuromuscular blocking agents, as well as local anesthetics, should be available for immediate administration.
ME	*M*onitoring *E*quipment such as ECG, pulse oximetry, end-tidal CO_2 monitoring, and stethoscopes should be applied and in working condition.

ECG, electrocardiography.

Orotracheal Intubation and Rapid Sequence Induction

OTI may be performed in several ways, ranging from having the patient totally awake to performing OTI in conjunction with rapid sequence induction (RSI). OTI with RSI is the preferred approach to the airway management of the majority of patients with traumatic injuries. Although different pharmacologic agents may be chosen for neuromuscular blockade and induction, the major components of this intervention include preoxygenation, administration of agents that cause loss of consciousness (induction), administration of paralytics (neuromuscular blockade), and administration of postintubation analgesia and sedation.

Preoxygenation is performed to maintain hemoglobin saturation during airway management. Desaturations below 70% put patients at risk for dysrhythmia, hemodynamic decompensation, hypoxic brain injury, and death. Preoxygenation is achieved either actively or passively. A logistic flow of preoxygenation to prevent desaturation is shown in eFigure 19.1 (7).



Sequence of Preoxygenation and Prevention of Desaturation

(Assuming two oxygen regulations[a])

Preoxygenation Period

- Position the patient in a semirecumbent position (~20°) or in reverse Trendelenberg. Position the patient's head in the ear-to-sternal-notch position using padding if necessary.
- Place a nasal cannula in the patient's nares. Do not hook the nasal cannula to oxygen regulator.
- Place patient on a nonrebreather mask at the maximal flow allowed by the oxygen regulator (at least 15 lpm, but many allow a much greater uncalibrated flow).
- If patient is not saturating >90%, remove face mask and switch to noninvasive CPAP by using ventilator, noninvasive ventilation machine, commmercial CPAP devive, or BVM with PEEP valve attached. Titrate between 5–15 cm H_2O of PEEP to achieve an oxygen saruration >98%. Consider this step in parients saturating 91–95%.
- Allow patent to breath at tidal volume for 3 minutes or ask the patient to perform eight maximal exhalations and inhalations.
- Attach a BVM to oxygen regulator and set it to maximal flow (at least 15 1pm). If the patient required CPAP for preoxygenation, attach a PEEP valve to the BVM set at the patient's current CPAP level.

Apneic Period

- Push sedative and paralytic (preferably rocuronium if the patient is at risk for papid desaturation)
- Detach face mask from the oxygen regulator and attach the nasal cannula. Drop the flow rate to 15 lpm.
- Remover the face mask from the patient.
- Perform a jaw thrust to maintain pharyngeal patency.
- If the patient is at high risk (required CPAP for preoxygenation), consider leaving on the CPAP during the apneic period or providing four to six ventilations with the BVM with a PEEP valve attached. Maintain a two-hand mask seal during the entire apneic period to maintain the CPAP.

Intubation Period

- Leave the nasal cannula on throughout the airway management period to maintain apneic oxygenation.

[a]If three regulators are available, attach reservoir face mask, BVM, and nasal cannula to them. If only one regulator is abailable, consider using a stand-alone oxygen tank to offer a second source of oxygen.

eFIGURE 19.1 Logistic flow of preoxygenation and prevention of desaturation. (From Weingart SD, Levitan MD. Preoxygenation and prevention of desaturation during emergency airway management. Ann Emerg Med. 2012;59:165–175, with permission.)

A standard reservoir facemask with the oxygen flow rate set as high as possible is the recommended source of high FiO_2 in the emergency department (ED). A passive approach will allow for spontaneous respirations through this nonrebreather facemask.

Active preoxygenation techniques should be considered for patients who cannot achieve greater than 95% oxygen saturation even with high FiO_2 delivered passively. The risk categorization of

patients during preoxygenation and the means by which oxygen should be applied is shown in eTable 19.2 (7). Active techniques for oxygenation include the use of continuous positive airway pressure (CPAP) masks, noninvasive positive-pressure ventilation, or positive end-expiratory pressure (PEEP) valves on a bag-valve mask (BVM). Optimal application of a BVM for the purposes of oxygenation and ventilation in the trauma patient typically requires two medical providers: one to ensure a proper mask-to-patient seal and one to manage bag compression.

TABLE 19.2
Selected Pharmacologic Agents for Use During Trauma Airway Management

Opiates	Dose	Comments
Fentanyl	2–4 μg/kg	Onset, 1–2 min; duration, 1–2 hrs Increasing dose increases incidence of respiratory depression Chest wall rigidity rare complication associated with high doses
Sedatives	**Dose**	**Comments**
Midazolam	0.1 mg/kg	Onset, 1–2 min; duration, 1–2 hrs Respiratory depression, especially in combination with opiates or high doses May cause hypotension in patients with hypovolemia or cardiovascular instability
Thiopental	3–5 mg/kg	Onset, 1–2 min; duration, 5–10 min Respiratory depression is significant with induction dose Associated with profound hypotension, specifically with hypovolemia or patients with cardiovascular instability
Propofol	1–2 mg/kg	Onset, 1 min; duration, 4–8 min Respiratory depression is significant with induction dose Associated with profound hypotension, specifically with hypovolemia or patients with cardiovascular instability
Etomidate	0.3 mg/kg	Onset, 1 min; duration, 4–6 min Excellent choice for trauma patient induction owing to minimal effects on cardiovascular stability and head-injured patient Adrenal suppression of no known significance in trauma patient
Ketamine	1–2 mg/kg	Onset, 1–2 min; duration, 20–30 min Offers sedation, analgesia, and amnesia through interactions with cortical, limbic, and spinal opiate sites Minimal suppression of respiratory drive Use in head-injured patient is controversial Elevates mean arterial pressure and venous return via norepinephrine release

eTABLE 19.2
Risk Categorization of Patients During Preoxygenation

Risk category, based on pulse oximetry while receiving high-flow oxygen	Preoxygenation period (3 min)	Onset of muscle relaxation (≈60 sec)	Apneic period during tracheal intubation (variable duration, depending on airway difficulty; ideally <30 sec)
Low risk, SpO_2 96–100%	Nonrebreather mask with maximal oxygen flow rate	Nonrebreather mask and nasal oxygen at 15 L/min	Nasal oxygen at 15 L/min
High risk, SpO_2 91–95%	Nonrebreather mask or CPAP or bag-valve-mask device with PEEP	Nonrebreather mask, CPAP, or bag-valve-mask device with PEEP and nasal oxygen at 15 L/min	Nasal oxygen at 15 L/min
Hypoxemic, SpO_2 90% or less	CPAP or bag-valve-mask device with PEEP	CPAP or bag-valve-mask device with PEEP and nasal oxygen at 15 L/min	Nasal oxygen at 15 L/min

Risk categories are based on patient's initial response to high-flow oxygen through a tightly fitting nonrebreather mask. Patients who are already hypoxemic exhibit shunt physiology and are prone to rapid desaturation during the peri-intubation. Patients with saturations of 91% to 95% have values close to the precipice of the steep portion of the oxyhemoglobin dissociation curve and should be considered high risk. Patients with saturations greater than or equal to 96% are at low risk for peri-intubation desaturation. Patients in all risk categories should receive preoxygenation in a head-elevated position (or reverse Trendelenburg if there is a risk of spine injury).

From Weingart SD, Levitan MD. Preoxygenation and prevention of desaturation during emergency airway management. *Ann Emerg Med.* 2012;59:165–175, with permission.

Apneic oxygenation is also a key component of adequate preoxygenation. When high flow oxygen (15 L/min) is delivered through a nasal cannula after induction and during the apneic period patients can maintain oxygen saturations of more than 98% for 18 to 55 minutes (5).

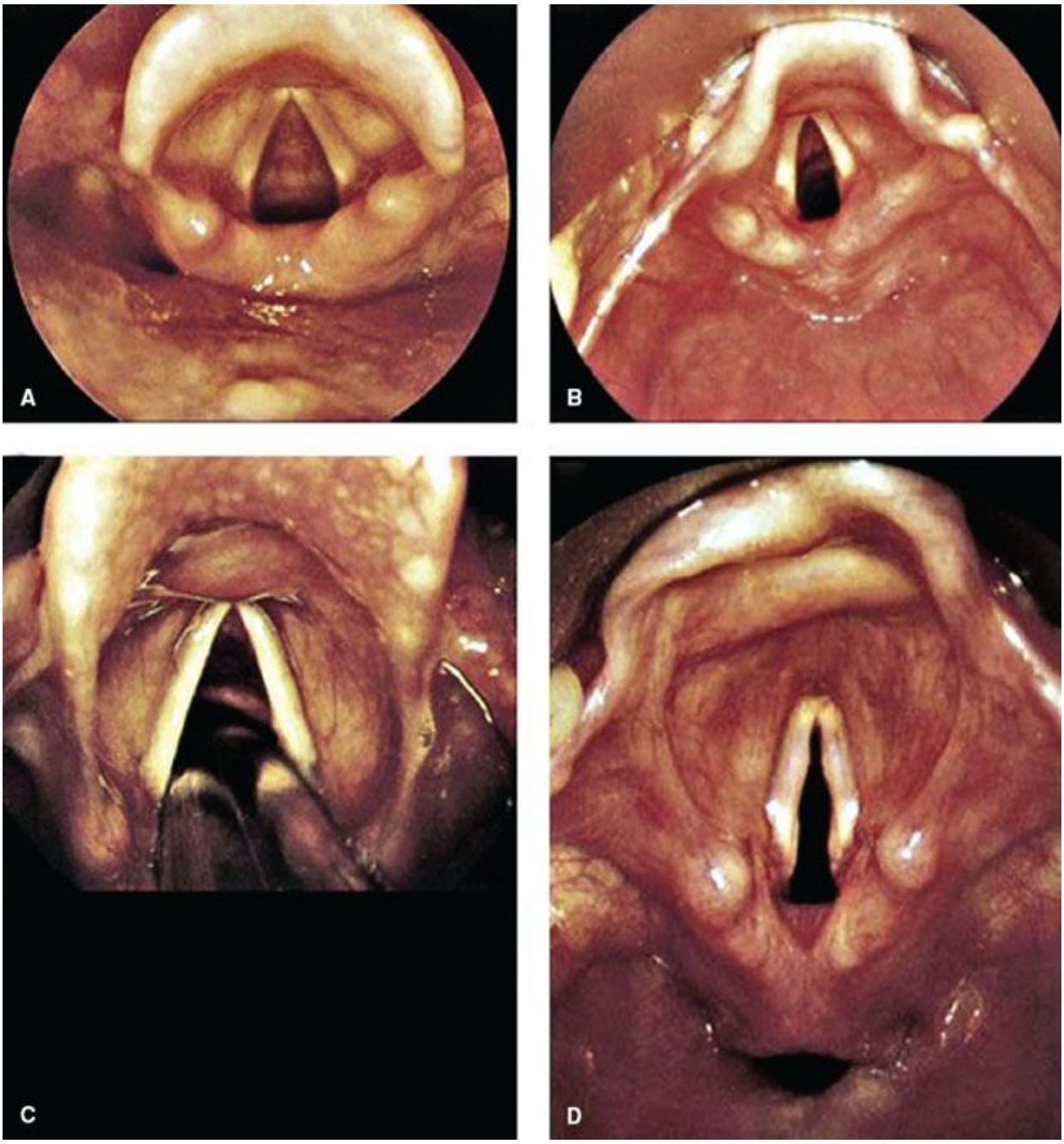
Difficulty in providing maximal preoxygenation may occur in patients with chest trauma or those with bronchospasm from pre-existing reactive airway disease or from smoke inhalation. In cases where pneumothorax is strongly suspected, consideration should be given to delaying intubation and mechanical ventilation until after performance of tube or needle thoracostomy. Artificial ventilation can result in rapid progression of a simple pneumothorax to a tension pneumothorax, even with a brief period of mechanical ventilation.

Neuromuscular blockade is performed during RSI for a number of reasons. Muscular paralysis reduces the aspiration risk by eliminating the gag and cough response to laryngoscopy. Paralysis also effectively relaxes the upper airway musculature to allow for an optimal view of the larynx. It prevents patient movements that might complicate efforts to visualize the airway during intubation. Caution should be exercised in the use of paralytic agents if difficulty ventilating the patient via BVM is anticipated.

Rescue airway adjuncts, as well as cricothyrotomy equipment, must be immediately available at all times during RSI of trauma patients. In cases where a difficult airway is anticipated, a modified approach may be used to provide adequate sedation or anesthesia to allow for airway intervention without the use of neuromuscular blocking agents.

Video-Assisted Intubation

Video-assisted devices are becoming more commonplace in EDs, particularly in the training environment. There have been many studies to date that have shown users obtain better laryngeal visualization and have a higher first-pass success rate in the difficult airway patient (6). There are many commercially available video laryngoscopes and all require some added training. Even in the hands of novice video laryngoscopy improves visualization and visual confirmation of proper tube placement (eFig. 19.2). Intubation can be performed by passing a tube over a flexible fiberoptic scope while visualizing the vocal cords or using a rigid video laryngoscope, such as the Glidescope or Storz video system. The same principles of RSI apply when using a video device.



eFIGURE 19.2 Larynx appearance with videolaryngoscope. A: Preintubation view of an adult airway. B: Preintubation view of a pediatric airway. C: ETT passing between the vocal cords. D: The larynx and hypopharynx (note the horizontally oriented space below the laryngeal inlet, which is the esophagus). (From Nagdev A. Airway, breathing, circulation: Normal airway. In: Greenberg MI, Hendrickson RG, Silverberg M, et al., eds. Greenberg's Text-atlas of

Emergency Medicine. Philadelphia, PA: Lippincott Williams & Wilkins; 2004, with permission.)

The utility of the video-assisted device is limited in certain trauma situations particularly when visualization is impaired by blood, vomit, secretions, or direct trauma to the airway. As with any intubation attempt proper preparation should include having backup plans for failed attempts, this includes the ability to perform direct laryngoscopy and the tools for a surgical airway.

Blind Nasotracheal Intubation

NTI has several drawbacks and few advantages when compared to other techniques that are readily available for emergency airway management. Nasotracheal intubation requires a clinician who is experienced in the technique, a cooperative patient who is spontaneously breathing, and proper preparation of the nasal mucosa. This technique has largely fallen out of favor because it is more time consuming, has a larger failure rate, a higher complication rate, and requires a smaller tube size than other techniques. Despite these drawbacks NTI is still an important skill because it may be useful in certain situations such as limited mouth opening or severe oral trauma. The safety of NTI in patients with significant midface trauma has been suggested in clinical experience and the literature (13).

If NTI is attempted, oxygen should be administered by high-flow delivery throughout the procedure to improve oxygenation. The larger nostril should be chosen for placement of the endotracheal tube. The nasal mucosa should be prepared using a topical anesthetic and vasoconstrictive agent such as 4% lidocaine and 1% phenylephrine. Mild or moderate sedation may improve patient cooperation and decrease patient movement. Endotracheal tubes specifically designed for NTI are helpful as well, including tubes in which the tip can be manipulated anteriorly by a proximal trigger, thus enhancing the success of tracheal placement.

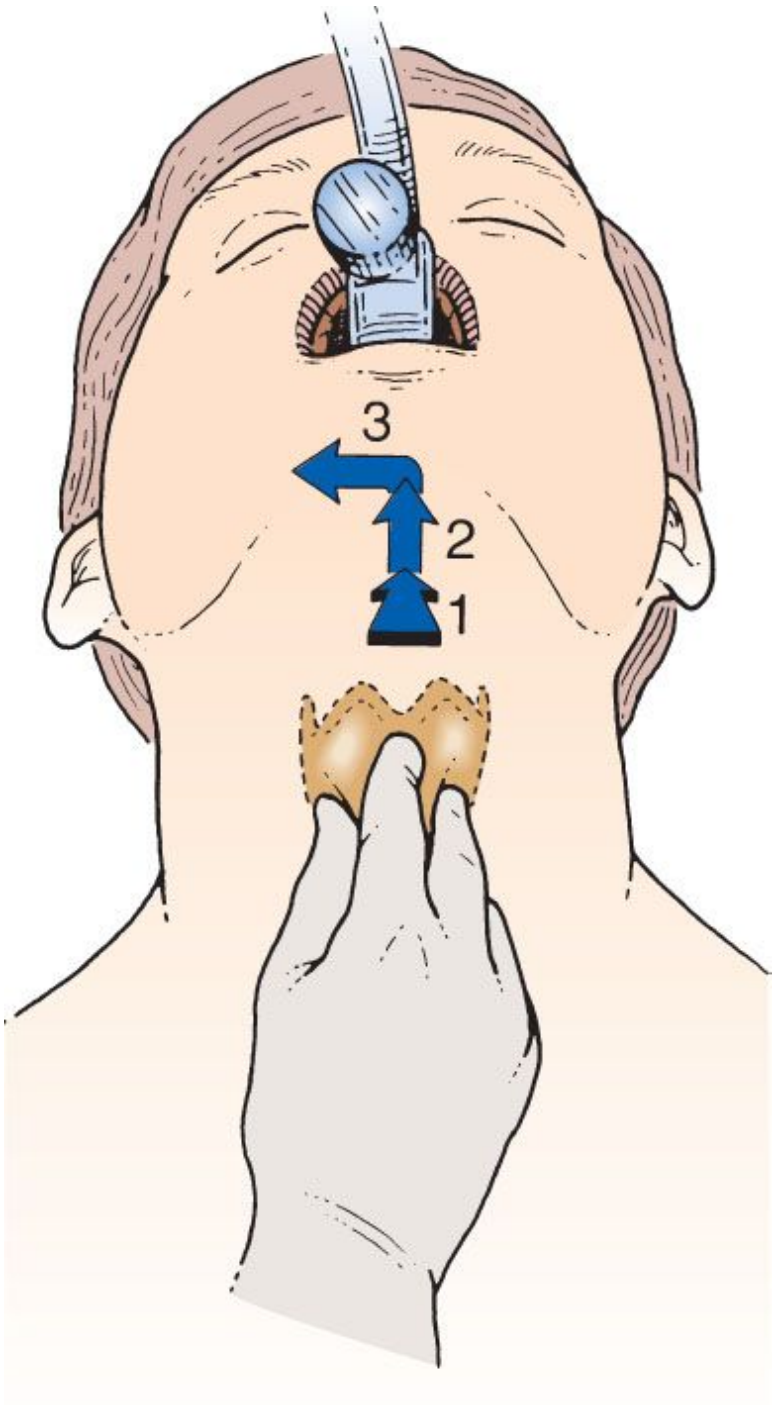
Surgical Airway Management

Cricothyrotomy equipment should be immediately available for any trauma patient undergoing emergent airway interventions, including RSI. The major indication for cricothyrotomy is failure of other methods of intubation with the simultaneous inability to ventilate and oxygenate the patient via BVM. Many cricothyrotomies involve patients with significant facial trauma or upper airway hemorrhage.

Patients with anterior neck trauma (penetrating and blunt) deserve particular consideration since they have a relative contraindication to cricothyrotomy. In addition, there will always be a small percentage of patients whose oral anatomy or body habitus renders intubation by any means very difficult and limits the feasibility of using airway adjuncts for more than a very limited amount of time. Perhaps the greatest mistake regarding the use of cricothyrotomy is its timing, as it is frequently used too late in the course of management when the patient is already severely hypoxemic.

Special Maneuvers and Intubation Adjuncts

Displacement of the thyroid cartilage *B*ackward against the cervical vertebrae, *U*pward or as superiorly as possible, and laterally to the *R*ight (the BURP maneuver) has been described and demonstrated to improve the view of the glottis during laryngoscopy (eFig. 19.3) (22). The mechanism by which BURP improves visibility may lie in the ability to move the glottis into the line of vision given that laryngoscopy tends to push the tongue and possibly the larynx toward the left. Application of the BURP maneuver may require a third provider in addition to the laryngoscopist and individual holding inline stabilization of the neck.



eFIGURE 19.3 Diagram of application of the BURP maneuver to improve the glottic view during laryngoscopy. The thyroid cartilage is moved Backward against the cervical vertebrae, Upward or as superiorly as possible, and laterally to the Right.

Several airway adjuncts can aid in the intubation process or are designed to temporarily substitute for intubation if it cannot be performed (3,14). These devices should be included as part of the difficulty airway algorithm for trauma airway management. The lighted stylet and gum elastic bougie, allow blind placement (placement without visualization of the vocal cords) of an endotracheal tube (12). Ventilation and oxygenation adjuncts for temporary airway support in the sedated or unconscious patient include the laryngeal mask airway (LMA), the combitube, and the King airway. LMAs are increasingly utilized as rescue airway devices for the failed intubation patient and often provide excellent airway management until intubation can be achieved. LMAs that allow for intubation through the lumen of the device have been developed and should be considered for their potential to achieve airway management as a blind intubation technique.

Pharmacologic Agents

Pharmacologic agents are chosen to accomplish several goals including topical anesthesia, sedation, analgesia, amnesia, and paralysis. Judicious use of these agents may facilitate intubation while avoiding such complications as increases in ICP and emesis. Selection of the proper agent in the trauma setting is essential to avoid complications such as prolonged paralysis with inability to ventilate, rises in ICP, or cardiovascular deterioration. There is very little published data from the acute care setting upon which to base and evidence-based practice for trauma airway management. As a result, preference for specific agents is based largely on theoretical principles as well as extrapolation of data from other settings. There is no pharmacologic agent that has been proven to offer a comprehensive advantage without limitations when compared to other selections.

Local Anesthetics

Lidocaine is an amide that can be used topically, locally, or intravenously to aid in airway management. Maximum doses are 3 to 4 mg/kg. When applied topically in a 4% solution, lidocaine may be

used with topical vasoconstrictors to aid in NTI. Nebulization of a 4% solution to a spontaneously breathing patient can produce complete topical anesthesia of the oro- and nasopharynx and the vocal cords in 5 to 7 minutes (4). When given intravenously, in a dose of 1.5 to 2 mg/kg 2 to 3 minutes prior to intubation, lidocaine may attenuate the hemodynamic and cough reflex–mediated rise in ICP (20). This application remains controversial with debatable advantages and few drawbacks other than complicating the RSI approach by addition of another agent.

Induction Agents

Sedatives, hypnotics, and potent opioid analgesics may be used as pharmacologic adjuncts to achieve states ranging from light sedation to complete loss of consciousness (Table 19.2). There is a balance between the risks and potential benefits for each of these agents in the trauma setting. The hemodynamic effects of each agent should be a primary consideration. Additional considerations include the following factors: (a) the agent's reliability of induction at a given dose, (b) the need to maintain spontaneous respiration, (c) the likelihood of a traumatic brain injury, and (d) the patient's pre-existing physiologic state including comorbidities.

Although adverse effects on respiration can be countered in most instances with artificial ventilation, there is no simple maneuver to counteract the cardiac dysfunction that may be produced by these agents in the trauma victim.

Barbiturates

Thiopental and methohexital are very short-acting sedative, hypnotic agents with no analgesic properties. Their onset of action is within 1 minute with duration of clinical effects between 5 and 10 minutes (21). The benefits of these agents are their induction reliability and rapidity of onset.

The major disadvantage of barbiturates is their effect on cardiovascular stability in the hemodynamically compromised patient, primarily due to significant reductions in venous return and contractility (21). While these effects are typically not a major

consideration in the nontrauma patient, their use in the hypovolemic or unstable trauma patient may result in sudden, profound hypotension as well as reduction in cerebral perfusion pressure. Given the principle that all acutely injured trauma patients should be assumed to have injuries rendering them unstable from a cardiovascular standpoint, the use of barbiturates in this population should be approached with caution. If barbiturates are to be utilized, meaningful reductions in induction dosages should be employed with thiopental doses ranging from 0.5 to 1 mg/kg are generally recommended (21).

Propofol

Propofol is a substituted isoprophylphenol that is highly lipophilic and capable of producing profound sedation, hypnosis, and amnesia, with no analgesic properties (21).

A unique characteristic of propofol is its rapid metabolic clearance and redistribution, which is approximately 10 times faster than thiopental. Clinical recovery is rapid, occurring within 4 to 8 minutes, with little residual sedation.

Caution must be exercised if propofol is used in the undifferentiated trauma patient, particularly owing to the hemodynamic effects on venous return that often result in clinically observed decreases in blood pressure. Propofol should be avoided in patients at high risk for hemodynamic compromise and instability due to hemorrhage or hypovolemia.

The primary use of propofol in the trauma setting is as a postintubation sedative with continuous infusion. The brief duration of clinical effects associated with propofol allows for rapid recovery of neurologic status and levels of consciousness. This advantage is often cited as a benefit in the trauma patient who may undergo recurrent neurologic assessments over an extended time period.

Etomidate

Etomidate is a carboxylated imidazole induction agent with no analgesic properties (21). In doses of 0.3 mg/kg, induction is reliably produced in <1 minute, and the duration of action is between 6 and

8 minutes. Etomidate has several properties that make it attractive for use in the multisystem trauma patient. When given in single induction boluses, etomidate causes minimal changes in heart rate and cardiac output compared with equipotent doses of thiopental (21). This is particularly advantageous in patients with hypotension or compensated shock, as well as in those with pre-existing myocardial dysfunction.

Etomidate also causes significantly less respiratory depression than barbiturate agents, although transient apnea may occur when it is given rapidly. Etomidate may in fact stimulate ventilation. For this reason it may be advantageous when maintenance of respiration is desirable, such as during sedation with NTI or modified RSI.

Although etomidate occasionally causes side effects, there are no contraindications to its use as a single injection in the trauma patient. Side effects include transient burning on injection, transient myoclonus after administration in up to 40% of patients, and transient suppression of endogenous cortisol production for up to 12 hours after single bolus administration. The temporary suppression of cortisol production has not been demonstrated to affect outcome in the trauma patient and should not limit the use of etomidate in this population (15,21).

Ketamine

Ketamine is a phencyclidine derivative that produces dissociative anesthesia. It is the only agent commonly used for induction in the ED that possesses sedative, hypnotic, analgesic, and amnestic properties (21). Ketamine provides the most cardiovascular and respiratory support of any agent. Although it is a direct myocardial depressant, heart rate and blood pressure are usually maintained or increased owing to centrally mediated sympathetic stimulation via increases in norepinephrine. Central sympathetic stimulation also results in transient bronchodilation.

The major advantage of ketamine, in comparison to other agents, lies in the setting of the hypovolemic patient (21). Its onset of action is within 1 minute when given intravenously (1 to 2 mg/kg), with a duration of action ranging from 5 to 15 minutes. Ketamine may also

be given intramuscularly (4 mg/kg), with the onset of action delayed by several minutes.

Because it is a phencyclidine derivative, ketamine can cause an emergence delirium. Though this is a concern during procedural sedation, it should not prohibit its use as an intubation adjunct in a critically ill trauma patient. Intubated trauma patients are typically kept sedated and paralyzed for many hours after their initial presentation, and emergence delirium at that time is rare (21). Continued sedation with benzodiazepines virtually eliminates this issue as a concern.

The primary concern with the use of ketamine in the trauma population is its potential to affect ICP owing to its ability to increase cerebral blood flow by 30% to 60% (21). Even though the cerebral metabolic rate is increased with ketamine, cerebral blood flow is probably sufficient to meet demand. There is evidence that this increase in cerebral blood flow does not increase ICP (11). In fact, there is evidence that ketamine is neuroprotective in the setting of head trauma because it is an *N*-methyl-D-aspartate receptor antagonist (19). The use of ketamine may be warranted in the setting of head injury when induction is required in a hypotensive patient. Any reduction in MAP has greater potential to worsen cerebral ischemia than to affect clinical outcome from a transient rise in ICP.

The routine use of ketamine in the trauma patient remains an area of controversy. Its use in the hypotensive patient appears to be a reasonable decision given the relative concerns for other agents in this setting.

Benzodiazepines

Benzodiazepines (diazepam and midazolam) have been used alone, and in combination with opioids, as induction agents. They provide good anxiolysis and amnesia, but no analgesia is provided. Large doses are usually needed to produce predictable states of induction equivalent to those of the agents discussed above (21). Midazolam is currently the most commonly used benzodiazepine for airway management. An induction dose of midazolam (0.1 mg/kg) takes effect within 1 to 2 minutes and has a duration of action between 30

and 60 minutes. Even at doses of 0.1 mg/kg, induction is not always predictable.

Benzodiazepines can be accompanied by side effects such as severe respiratory depression. Significant decreases in venous return, MAP, and cardiac contractility can also occur, especially in patients with hypovolemia or heart disease (1). All of these effects are more pronounced when opioids are given simultaneously.

Subinduction doses (0.03 to 0.05 mg/kg) of midazolam are not commonly associated with these complications and can serve as valuable adjuncts in providing continued sedation for patients after intubation.

Opiates

Synthetic opioid agonists including fentanyl, sufentanil, and alfentanil are 100, 500 to 1,000, and 20 times more potent than morphine, respectively (21). These agents are fast acting, having an onset of action of <1 minute, with a duration of action between 15 and 60 minutes.

Fentanyl results in little or no histamine release, and its cardiovascular effects in the normal host are minimal. At higher doses, however, small but potentially significant decreases in blood pressure may occur (21). Depending on the existing state of consciousness and the presence of drugs such as alcohol, the dose necessary to produce unconsciousness can range from 2 to 20 μg/kg or more. The effect of fentanyl on ventilation varies, but doses >2 μg/kg result in a high incidence of respiratory depression in "normal" subjects (2). This incidence is even higher when used together with other agents such as midazolam.

Fentanyl is often used as a preinduction adjunct for intubation of the head-injured patient owing to its ability to attenuate the hemodynamic response to intubation. However, when given in doses sufficient to achieve this effect, 2 to 3 μg/kg given 2 to 3 minutes before laryngoscopy, increases in ICP may occur that may negate any advantage to its use in the setting of traumatic brain injury. Decreases in MAP were also noted to occur after administration of fentanyl at these doses. Coupled with the potential for producing

premature hypoventilation and apnea, this makes the routine use of these agents as induction or preinduction agents in the setting of multisystem trauma controversial. An additional role for these opiates is to provide postintubation sedation and analgesia to attenuate the hyperdynamic responses from pain and intubation and for patient comfort.

In summary, despite the most careful use of pharmacologic agents, any induction agent may result in sudden and profound hypotension unresponsive to simple fluid boluses. In cases of head injury, hypotension, even if transient, can result in prolonged cerebral hypoperfusion (16).

Neuromuscular Blocking Agents

The use of neuromuscular blocking agents to facilitate intubation has become widespread in emergency airway management. These agents are classified as depolarizing and nondepolarizing agents.

Depolarizing Agents

Succinylcholine (1.5 to 2.0 mg/kg) is the agent of choice during emergent RSI. No neuromuscular blocking agent has a faster onset (<1 minute) or is of shorter duration (4 to 6 minutes). Succinylcholine can also be given intramuscularly (4 mg/kg), but its onset is delayed by 2 to 4 minutes.

The disadvantages of succinylcholine in the trauma patient population are relatively few and should not preclude its use in the acutely injured patient. Fasciculations, hyperkalemia, and transient rises in intragastric, intraocular, and ICP may occur (9). Succinylcholine-induced hyperkalemia in burns and crush injuries does not occur in the acute setting. If fasciculations and elevated intraocular, intragastric, and ICP are major concerns, administration of a defasciculating dose of a nondepolarizing agent (i.e., vecuronium 0.01 mg/kg) 2 to 3 minutes before succinylcholine administration has been demonstrated to prevent these occurrences (21). If a defasciculating dose of a nondepolarizing agent is used, the dose of succinylcholine should be increased to 1.5 to 2 mg/kg to maintain its rapidity of onset.

Nondepolarizing Agents

There are several nondepolarizing neuromuscular blocking agents in current use. Vecuronium and rocuronium are the major nondepolarizing agents used in trauma airway management. The advantages of these agents are that they are longer acting, cause no fasciculations, and cause no reported increase in intraocular, intragastric, or ICP. These agents also have little effect on the cardiovascular system (9,21).

The standard dose of vecuronium for paralysis is 0.15 mg/kg. This results in complete paralysis within 2 to 3 minutes, with a duration of action of 30 to 40 minutes. The onset of action of rocuronium (0.9 mg/kg) approaches that of succinylcholine, although its duration of action is similar to that of vecuronium (25 to 40 minutes) (21).

A major disadvantage of vecuronium and rocuronium in the trauma patient is the relatively slower onset of clinical effects, taking up to 2 to 3 minutes for a full clinical effect. Large doses of vecuronium (0.25 mg/kg) and rocuronium (1.2 mg/kg) may be used as an initial bolus to achieve more rapid paralysis within 60 to 90 seconds. However, this strategy lends an extended period of duration of paralysis, lasting as long as 90 minutes. The duration of action of nondepolarizing agents is longer relative to succinylcholine, creating significant problems if intubation attempts are unsuccessful.

Nondepolarizing agents can be reversed to some extent by drugs that block cholinesterases, such as neostigmine, edrophonium, and pyridostigmine. The routine use of these reversal agents in the acutely injured patient is not advised owing to the potential for cardiovascular complications.

SPECIAL CONSIDERATIONS

Cervical Spine Injury

OTI utilizing RSI is now the preferred procedure to achieve definitive airway control in patients with suspected cervical injury (17). As positioning the airway in this setting is limited, use of a straight laryngoscope blade may be preferable to a curved blade because it will lift the epiglottis directly. The use of VAI has also been shown to

be of particular benefit in these patients with an improved first-pass success rate (6).

Removal of the front of the cervical collar while maintaining in-line immobilization (not traction) significantly improves the view of the larynx during intubation and should be a routine component in airway management of the trauma patient (8). When manual immobilization is being performed, an applied cervical collar offers no significant advantage.

Regardless of approach, airway management in the setting of potential cervical spine injury is optimally performed with at least three people: one as the laryngoscopist, one to provide in-line immobilization of the cervical spine, and one to perform cricoid pressure. Rational use of airway adjuncts such as special laryngoscopes, the gum elastic bougie, and the LMA may be indicated based on the experience of the operator.

Penetrating Neck Trauma

In cases of penetrating neck trauma with possible altered upper airway anatomy or signs of airway obstruction, OTI with RSI is the procedure of choice when injuries do not impair OTI visualization (18). Administration of paralytics may be strategically deleted if proper sedation and upper airway anesthesia are provided.

Use of induction agents with less effect on ventilation (etomidate and ketamine), along with intravenous or nebulized lidocaine, will aid in reduction of gagging and further hemorrhage and anatomic distortion of the neck. Ketamine without paralysis is an alternative as it preserves respiratory drive. This may be essential for intubating patients who have anatomic distortion owing to an expanding hematoma. The presence of anterior neck trauma is a relative contraindication to cricothyrotomy.

Head Injury

The pathophysiology of traumatic brain injury is complex and involves a combination of mechanical and biochemical events initiated by the trauma itself, followed by secondary injury in the

form of ischemia. The most preventable forms of secondary brain injury are systemic hypoxemia and hypotension. Because most head injuries occur in association with multisystem trauma, a reasonable approach would be to administer agents that cause a predictable loss of consciousness, cause no increase in ICP, and maximize the chance to maintain MAP.

Traditional approaches to the head trauma victim requiring intubation assumed that the brain had lost some degree of its ability to autoregulate its blood flow. The MAP minus the ICP determines cerebral perfusion pressure and hence cerebral blood flow in this setting. Emphasis has been placed on blocking the rise in ICP during intubation with the use of agents such as barbiturates. However, maintaining the mean arterial pressure in these circumstances is critical given that cerebral blood flow is directly related to perfusion.

Although an attempt to block the rise in ICP during intubation of the head-injured patient is of theoretical benefit, this concern has not been demonstrated to affect outcome in controlled studies. Attempts to manage ICP during intubation must be carefully balanced with the pharmacologic agent's effect on blood pressure, as lowering mean arterial blood pressure may lower cerebral blood flow and cause secondary ischemic brain injury (16).

Facial Trauma

Patients with facial injuries represent an airway management challenge, especially when there is severe upper airway hemorrhage. The airway management technique of choice depends on several factors, including the patient's level of consciousness, level of oxygenation, amount of upper airway hemorrhage, and risk of other injuries such as cervical spine injury. The availability of one or more large-volume suctioning devices is critical if upper airway hemorrhaging is present. OTI with RSI remains the best approach in the majority of facial trauma cases.

Airway adjuncts should be readily available in all trauma patient encounters, particularly in those patients with facial injuries. If OTI is unsuccessful, placement of the esophageal tracheal combitube or LMA can reverse hypoxemia and temporarily protect the airway

while cricothyrotomy is performed. Fiberoptic laryngoscopy may be of limited use in these patients as blood and other secretions render visualization of the glottis a challenge.

SUGGESTED APPROACHES

In most emergent trauma airway management scenarios, OTI with RSI using in-line cervical stabilization is the preferred approach. This approach should be followed with continued sedation and analgesia. The immediate concerns in this population are the prevention of hypoxemia and hypotension.

- The physician should assume that every trauma patient is hypovolemic, even if there are no signs of shock during the initial evaluation.
- The clinician should assume that all victims of blunt trauma have suffered an intracranial injury, with loss of cerebral blood flow autoregulation.
- All patients should be treated as if a cervical spine injury is present.
- The patient should not experience further decreases in MAP secondary to administration of medications or airway maneuvers.
- The patient should not develop premature apnea or hypoventilation.
- The patient should not develop large increases in ICP.

Figure 19.1 outlines intubation algorithms that will meet the needs of the majority of severely injured trauma patients.

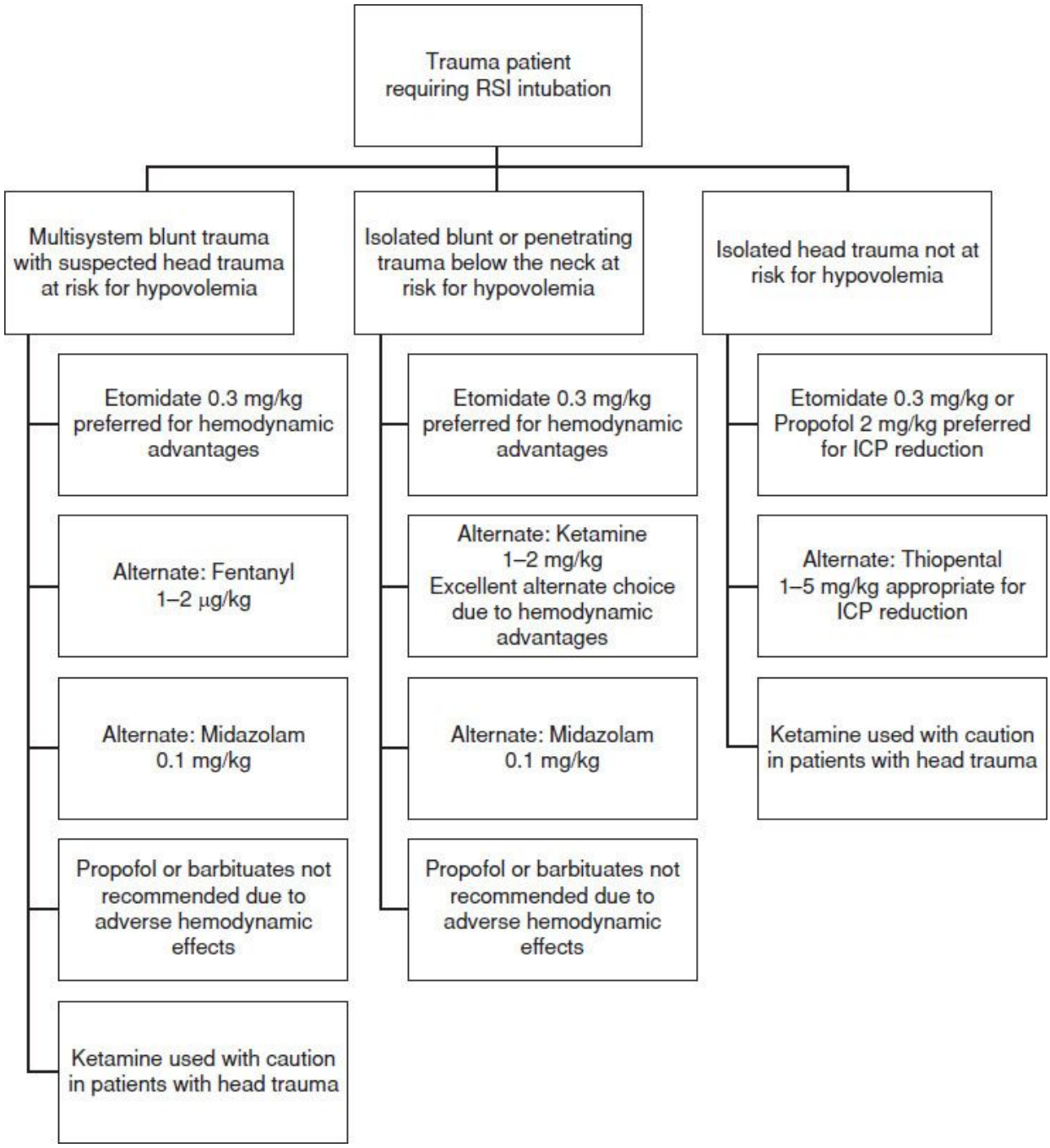


FIGURE 19.1 Algorithm for selection of induction agent in trauma airway management with preferred induction agent and alternate choices.

After intubation, small, frequent doses of midazolam (1 to 3 mg) and fentanyl (50 to 100 μg) are appropriate for sedation and are not

typically associated with major side effects. Longer-acting agents such as lorazepam and morphine may also be used.

Once significant hemorrhage or hemodynamic instability has been ruled out, more easily titrated agents such as propofol can be used in a continuous infusion for sedation. Continued paralysis while simultaneously providing analgesia and sedation, may be required to optimize resuscitation and diagnostic workup. Early removal of patients from spine immobilization boards, proper splinting of fractures, and application of local anesthetics to wounds significantly decrease the patient's discomfort.

Common Pitfalls

- Failure to consider occult hypovolemia, shock, and pre-existing disease states when choosing induction agents.
- Failure to maintain cervical spine stabilization during intubation in patients with suspected cervical spine injuries.
- Failure to have airway rescue adjuncts available for difficult airway situations.
- Failure to have a preplanned and prepared sequence of alternative airway approaches in case of failure of initial intubation attempts.
- Failure to provide adequate ongoing postintubation sedation and analgesia.

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CHAPTER 20

Traumatic Shock

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Shock is the ultimate consequence of inadequate tissue perfusion, which may be manifested clinically by hemodynamic disturbances or organ dysfunction. At the cellular level, shock initially results from the insufficient delivery of required metabolic substrates, principally oxygen, to sustain aerobic metabolism. In the setting of trauma, shock is most often related to loss of circulating blood volume caused by hemorrhage, although inadequate oxygenation, cardiac dysfunction, neurologic dysfunction, or mechanical vascular obstruction may be either primary or contributing factors.

There are four general pathophysiologic types of shock: (a) hemorrhagic or hypovolemic, (b) cardiogenic, (c) neurogenic or vasogenic, and (d) septic. Hemorrhagic shock involves the loss of circulating intravascular volume caused by blood loss internally, externally, or both. Cardiogenic shock indicates a process that prevents the normal pumping of the heart and can be caused by pericardial tamponade that prevents normal ventricular filling, tension pneumothorax with vena caval compression and reduction in venous return to the heart, or direct cardiac damage with loss of contractile force (myocardial contusion).

Neurogenic or vasogenic shock may result from spinal cord injury with loss of peripheral vascular resistance. Major spinal cord injury results in acute vasodilatation but generally does not cause impaired tissue perfusion unless other injuries are present. Spinal cord injuries result in a loss of sympathetic tone and are, therefore, accompanied by bradycardia (spinal shock). Septic shock refers to a hyperdynamic response (elevated cardiac output and low systemic vascular

resistance), followed by decreased cardiac output and increased systemic vascular resistance, eventually resulting in organ function deterioration associated with the inflammatory mediators accompanying infection.

If the acute stress of the traumatic shock state is sufficiently severe or prolonged, organ dysfunction may also develop, including acute kidney injury (AKI), adult respiratory distress syndrome (ARDS), and multiple organ failure (MOF). These entities can develop within a few hours to several weeks after the acute injury.

Shock is a common and potentially treatable cause of death in injured patients. Traumatic shock usually results from one or more of the following mechanisms: (a) acute blood loss from solid organ injury, rib fractures, major vascular injury, pelvic fracture, or multiple long-bone fractures; (b) cardiac dysfunction from blunt cardiac injury, tension pneumothorax, or pericardial tamponade; (c) hypoxemia caused by airway compromise or pulmonary contusion; or (d) loss of vasomotor integrity (distributive) caused by neurologic injury and late overwhelming infection.

The pathophysiology of traumatic shock is largely related to an imbalance in oxygen supply and demand. In the early phase of acute trauma, this imbalance is often caused by hypoperfusion, although low arterial blood oxygen saturation may be a significant contributing factor. Aggressive resuscitation with fluids having low or no oxygen-carrying capacity in the setting of severe and ongoing hemorrhage may lead to a critically low hemoglobin concentration that further contributes to tissue oxygen debt.

Acute blood loss elicits compensatory hemodynamic changes that serve to maintain vital organ perfusion. These changes include increased heart rate and vasoconstriction primarily in the peripheral circulation and splanchnic vascular beds. The term *compensated shock* refers to varying degrees of tachycardia and peripheral vasoconstriction that maintain adequate critical organ perfusion. Arterial blood pressure in compensated shock states may be moderately low or within the normal range. The term *uncompensated shock* indicates inadequate vital organ perfusion.

Vasoconstriction in response to acute blood loss is a protective response that preserves perfusion to the vital organs at the expense of peripheral and abdominal organ perfusion. In the hypoperfused tissues, oxygen demand exceeds oxygen delivery, and the numerous cellular processes that depend on oxidative metabolism and subsequent production of adenosine triphosphate (ATP) begin to fail. Acidosis results when aerobic metabolism slows, as protons cannot be used to synthesize ATP from adenosine diphosphate (ADP); lactate cannot be converted to pyruvate and, therefore, lactate increases. If the pathologic processes are not corrected, cellular dysfunction and eventually organ failure result.

CLINICAL PRESENTATION

Initial findings in a patient with traumatic shock may include tachycardia, hypotension, signs of poor peripheral perfusion, and alteration in mental status. In response to a loss of circulating volume, the heart rate will increase to sustain normal cardiac output. Continued blood loss will eventually result in a decrease in blood pressure. Peripheral vasoconstriction and central venoconstriction shunt blood centrally and result in a narrowed pulse pressure. Clinically, decreases in peripheral perfusion manifest as cool, pale, clammy extremities with prolongation of capillary refill (Table 20.1).

TABLE 20.1
Classes of Hemorrhagic Shock

Class	Blood Volume Lost	Heart Rate (beats/min)	Systolic Blood Pressure	Respiratory Rate (breaths/min)	Central Nervous System/Mental Status
I	750 mL (15%)	<100	Normal	14–20	Slightly anxious
II	750–1,500 mL (15–30%)	>100	Normal	20–30	Mildly anxious
III	1,500–2,000 mL (30–40%)	>120	Decreased	30–40	Anxious, confused
IV	>2,000 mL (>40%)	>140	Markedly decreased	>35	Confused, lethargic

From American College of Surgeons Committee on Trauma. *Advanced Trauma Life Support: Providers' Manual.* Chicago, IL: American College of Surgeons, 2007.

The skin may become mottled in appearance, but cyanosis is not a common finding. The narrowed pulse pressure can make the pulse quality weak or thready. Alterations in mental status caused by hypoperfusion may be subtle initially and can be difficult to distinguish from associated head injury or intoxication. Therefore, altered mental status on presentation or a subsequent decline in mental status, especially in patients without head trauma, should raise concern of systemic hypoperfusion and impending circulatory collapse.

Shock may be present even in the setting of “normal” vital signs. Young, healthy patients with substantial blood loss may maintain a blood pressure within the normal range by compensatory vasoconstriction and increased heart rate. Heart rate can occasionally be in the upper normal range. In such patients, signs of peripheral hypoperfusion and subtle changes in mental status may be the only warning signs preceding rapid hemodynamic decompensation. Elderly patients may not develop a tachycardic response to blood loss because of pre-existing medical conditions or medications. In fact, a bradycardic response may occur with rapid blood loss that is believed to be vagally mediated. Conversely, hypotension and tachycardia may be exacerbated in a pregnant trauma patient for a given degree of blood loss caused by compression of the inferior vena cava by the gravid uterus, resulting in decreased venous return.

Decline in urine output caused by renal hypoperfusion and renal fluid reabsorption is an important manifestation of shock physiology. Monitoring urine output may be useful in the emergency department (ED); later, it is a critical parameter in the surgical intensive care unit. Therefore, a urinary catheter should be placed in patients who exhibit evidence of shock, and the bladder should be drained to begin urine-output monitoring and to check for hematuria.

DIFFERENTIAL DIAGNOSIS

The most common cause of postinjury shock is hemorrhage-induced hypovolemia. However, several pathologic entities must be considered as either potential contributors or primary causes of shock. These entities are listed in Table 20.2.

TABLE 20.2
Causes of Shock

Causes of Shock
Hemorrhage
Cardiac tamponade
Tension pneumothorax
Blunt cardiac injury
Myocardial infarction
Spinal shock
Toxicologic or pharmacologic agents
Air embolism

Pericardial tamponade is classically described as exhibiting the Beck triad of hypotension, distended neck veins, and muffled heart sounds. A pulsus paradoxus of >10 mm Hg may also be seen. However, not all of these markers may be present or detected. In a hypovolemic patient, the neck veins may be flat. Muffled heart sounds may be difficult to distinguish in a busy trauma resuscitation room, and detection of a pulsus paradoxus is not reliable. Pericardial tamponade should be considered whenever there is penetrating chest trauma, when there are rib fractures near the heart, or when there has been significant blunt trauma to the chest. The immediate availability of ultrasonography or echocardiography offers the best potential for rapid and accurate diagnosis.

A large pneumothorax or hemothorax can usually be detected by diminished breath sounds, although auscultation can be unreliable. Ultrasound (US) is useful for confirmation with a chest radiograph warranted if the US is equivocal. A tension pneumothorax may also result in deviation of the trachea away from the affected side, cardiac displacement, and hypotension related to inferior vena caval compression that limits venous return to the heart. However, tracheal deviation and cardiac displacement are late findings and may be difficult to detect by physical examination. Hypoxemia may be an earlier sign of a tension pneumothorax than hypotension. If a patient is hypotensive and has clinical evidence of a pneumothorax, placement of a chest tube before diagnostic imaging is appropriate.

Blunt cardiac injury (formally referred to as *myocardial contusion*) resulting in significant contractile dysfunction is a difficult diagnosis to make in the ED unless echocardiography is immediately available. Blunt cardiac injury should be suspected when blunt trauma involves the sternum and anterior left chest, particularly if ventricular ectopy, dysrhythmias, or electrocardiographic demonstration of ST-segment elevations (especially in the anterior precordial leads) are present. In addition, blunt trauma can result in valvular disruption and coronary artery dissection. Evidence of cardiogenic shock (hypotension, tachycardia, elevated central venous pressure) should alert the physician to the possible presence of a blunt cardiac injury or pericardial tamponade.

Spinal cord trauma with neurogenic shock may present with hypotension caused by loss of peripheral vascular resistance. In addition, because of the loss of sympathetic tone, these patients will not have the usual tachycardic response to hypotension but often demonstrate bradycardia instead. In this setting, the presence of neurologic deficits and lack of signs of peripheral vasoconstriction should arouse suspicion for this entity. Such patients generally have warm extremities and good urine output. Volume status must be carefully monitored, because excess fluid administration in patients with spinal shock may be detrimental.

Signs of shock in a trauma patient may not be a direct consequence of the injury. For example, a myocardial infarction may be the cause of a motor vehicle collision, or the physiologic stress associated with trauma may precipitate myocardial ischemia in a patient with underlying coronary artery disease. History, physical examination, or electrocardiographic findings consistent with myocardial infarction should arouse suspicion of combined medical and surgical processes. Another rare medical cause of hypotension in a trauma patient is anaphylaxis that may have preceded the trauma. Pharmacologic agents such as β-adrenergic blockers and recreational agents, such as ethanol and cocaine, may also significantly affect the clinical picture in the setting of acute trauma.

ED EVALUATION

The initial step in managing shock in the injured patient is prompt recognition. Effective management of the acutely injured patient exhibiting signs of shock requires that initial assessment and treatment begin simultaneously (1) with an emphasis on the airway, breathing, and circulation (ABCs). Assessment of airway patency, adequacy of ventilation (respiratory excursion and lung auscultation), hemodynamic status (pulse rate, central and peripheral pulse quality, blood pressure), and evidence of controllable hemorrhage should be immediately linked with interventions to (a) secure the airway while protecting the cervical spine, (b) enhance oxygenation, (c) provide ventilatory assistance, (d) limit further hemorrhage, (e) gain intravenous access, (f) initiate volume replacement, (g) obtain blood for laboratory and blood bank testing, and (h) perform US screening of the chest and abdomen (Fig. 20.1).

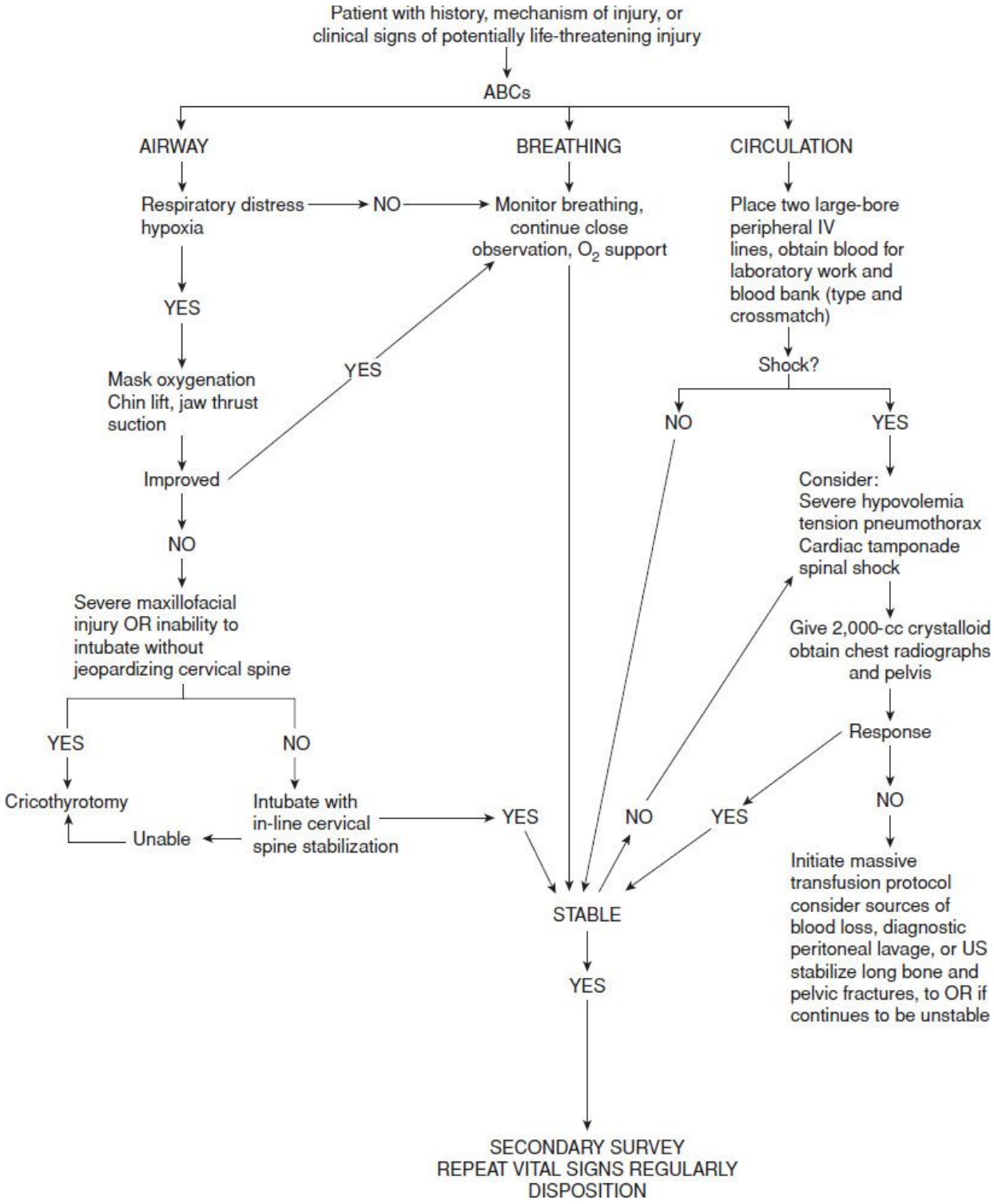

FIGURE 20.1 Treatment algorithm for traumatic shock.

After the primary assessment and initiation of treatment, a thorough secondary assessment should be conducted to identify

potential injuries to the head, neck, chest, abdomen, pelvis, back, extremities, neurologic, and vascular system. Hypothermia can depress hemodynamics and aggravate coagulopathy and should be aggressively treated. Acute trauma is a highly dynamic disease process that requires frequent and careful reassessment of ventilation, hemodynamic status, and physical examination to optimally adjust therapeutic interventions and identify evolving pathologic processes.

Initial laboratory studies in patients with major trauma should include (a) complete blood count (CBC); (b) arterial blood gases (base deficit); (c) electrolytes; (d) coagulation studies; (e) type and cross match for four units of packed red blood cells (PRBCs); and (f) toxicologic studies (Table 20.3). Urine should be obtained and checked for blood. Base deficit is a reliable early index of the magnitude of shock (2). Serum lactate has been advocated by some as an early predictor of morbidity and mortality, particularly in burn patients (3), but it appears to lag behind base deficit in the first 12 hours after injury (4).

TABLE 20.3
Initial Laboratory and Radiographic Studies in Major Trauma

Laboratory
Complete blood count
Arterial blood gases
Electrolytes (including BUN, creatinine, glucose)
Coagulation studies (Thermoelastography [TEG])
Type and crossmatch for four units of blood
Toxicologic studies (as indicated)
Serum lactate
Urinalysis
Ultrasound
Thorax
Pericardium
Abdomen
Radiographs
Chest x-ray, portable AP
Pelvis x-ray,[a] AP view

[a]In the stable patient who will undergo pelvic CT, pelvic x-ray is not needed.
BUN, blood urea nitrogen; AP, anteroposterior.

Initial radiographs have previously included the lateral view cervical spine, chest, and pelvis. With a number of studies suggesting that computed tomography (CT) scanning of the cervical spine is superior to plain films for detecting fractures (5), most centers are forgoing plain films of the cervical spine and going straight to CT. X-rays of the pelvis do not generally play a significant role in most trauma patients. Many of these patients will be getting a CT scan of the abdomen and pelvis and do not need a plain film unless they are unstable and may need to go directly to the operating room. In the unstable patient, a pelvic x-ray can determine the need for pelvic stabilization (by a bed sheet tied around the pelvis), as the patient is resuscitated initially or transferred to the operating room.

The initial chest radiograph will identify pneumothorax, hemothorax, pulmonary contusion, or a widened mediastinum, and the initial pelvic radiograph will identify major pelvic fractures as a potential cause of hypotension. Any patient with suspected spinal fractures or spinal shock should undergo radiographic evaluation once stabilized. The thoracic and lumbar spine can be evaluated by

CT scanning of the chest and abdomen, if these studies are indicated. Otherwise CT scans of the spine are appropriate in most situations.

US is part of the initial evaluation of the trauma patient. During the initial resuscitation, the focused assessment with sonography for trauma (FAST) examination should be performed to obtain views of the heart and abdomen to assess for pericardial effusion and intraperitoneal bleeding. Serial US examinations can be performed to increase the sensitivity for detecting intraperitoneal bleeding. In addition, US can be used for prompt detection of a hemothorax or pneumothorax. An alternative means of detecting intraperitoneal bleeding is diagnostic peritoneal lavage (DPL). The unstable trauma patient should undergo DPL when US is not available or if the US results are equivocal.

Monitoring of heart rate, respiratory rate, blood pressure, temperature, and pulse oximetry are important. Early placement of central venous pressure lines should be considered in patients who do not stabilize hemodynamically or are suspected of having cardiogenic or neurogenic shock components. Placement of a nasogastric or orogastric tube for decompression reduces the chances of aspiration and may improve ventilation if the stomach is distended with air.

A urinary drainage catheter should be placed after a search for potential urethral injury has been performed.

Urethral injury should be suspected in patients with pelvic fractures in the area of the symphysis pubis, anterior lacerations on rectal or vaginal examination, or abnormal position of the prostate gland. As noted, urine output becomes an important indicator of the adequacy of organ perfusion.

Quantitative end-tidal carbon dioxide ($ETCO_2$) monitoring is useful in intubated or sedated patients. $ETCO_2$ can help avoid hypoventilation, prevent excessive therapeutic hyperventilation, and detect decreases in cardiac output. Sequential assessment of hemoglobin/hematocrit and arterial blood gases during therapy for traumatic shock may be useful. These results should be interpreted together in terms of oxygen-carrying capacity and blood-oxygen content. In the trauma patient, the presence of metabolic acidosis in

the early phase of resuscitation indicates poor tissue perfusion and should be considered an indicator of inadequate volume resuscitation or ongoing hemorrhage.

Constant reassessment of ventilation and oxygenation, hemodynamic response to volume replacement therapy, and physical examination findings is crucial to detect clinical deterioration, adjust therapy, and identify previously missed injuries. Trauma resuscitations involve multiple individuals performing numerous tasks. During the process of resuscitation, tubes and catheters can become dislodged or disconnected, pneumothoraces can develop or enlarge, external or internal injuries may bleed again as blood pressure increases, pulmonary congestion or contusion may develop in response to volume therapy, core temperature may drop substantially in an exposed patient receiving large amounts of intravenous fluids, or the previously benign abdomen may become distended or rigid. These are examples of significant changes that can occur rapidly during the trauma resuscitation. Careful and constant attention with frequent reassessment is crucial to ensure optimal outcome.

KEY TESTING

- Type and cross
- Base deficit
- Thermoelastography (TEG)
- US of the thorax, pericardium, and abdomen
- Chest x-ray

ED MANAGEMENT

Walter Cannon wrote in 1923, “Since acidosis in shock indicates a deficient delivery of oxygen to active tissues, the rational move is not to treat the effect, but the cause, that is, to provide a better supply of oxygen by early and permanent improvement of the circulation” (6). This approach remains prudent today and is reflected in the ABCs. Initial treatment in traumatic shock occurs concurrently with initial evaluation and is focused on restoring adequate oxygen delivery.

Oxygen should be administered to all major trauma patients, regardless of presenting pulse oximetry readings. Early control of the airway in the patient with traumatic shock may be lifesaving and should take priority over all other interventions. Insertion of oral or nasal airways with assisted ventilation and endotracheal intubation are key components of the initial trauma resuscitation.

Gaining intravenous access rapidly is essential to begin volume replacement and support the hemodynamics of the patient in traumatic shock. The antecubital fossa is an excellent site to initiate intravenous access. Large-bore catheters (14 or 16 gauge) and high-flow intravenous tubing should be used to maximize delivery rate of fluids. At least two intravenous sites should be secured. If adequate intravenous access cannot be established within a few minutes, percutaneous femoral venous access, ankle venous cutdown, greater saphenous–venous cutdown at the proximal thigh, subclavian/jugular venous access, or intraosseous access should be considered.

Fluid therapy in trauma is an area of ongoing controversy. Intravascular volume replacement to compensate for blood loss and restore tissue perfusion has been accepted standard therapy for many years. The historical justification for aggressive intravenous fluid resuscitation was to maintain organ perfusion and improve survival. The enthusiasm for the approach was generated from experimental work employing controlled hemorrhage models and for decades, crystalloid loading to normalize blood pressure and heart rate was the standard. However, the Houston randomized clinical trial in 1994, showing no advantage to aggressive preoperative crystalloid resuscitation for penetrating torso wounds and reduced survival for cardiac wounds, prompted a reassessment of the resuscitation of the severely injured trauma patient. This often-cited clinical trial suggested higher survival rates in patients who underwent delayed fluid resuscitation at the time of operative intervention, instead of immediate fluid resuscitation starting in the field, but the benefit was limited to patients with pericardial tamponade (7). Although this trial initiated significant additional research and healthy debate, subsequent clinical trials have not been able to replicate the

advantage of hypotensive resuscitation found in the Houston study. Other studies have also suggested that aggressive fluid resuscitation in patients with uncontrolled or ongoing hemorrhage (prior to operative control) may increase blood loss and ultimately mortality. Research has questioned which intervention should take priority, reversal of hypovolemia or control of hemorrhage, when both cannot be achieved simultaneously. Restoring blood volume before active hemorrhage is controlled may result in increased blood loss caused by clot disruption, hemodilution, and loss of clotting factors. Although some studies have criticized aggressive fluid administration as being ineffective (8), others suggest that limited volume replacement, termed *hypotensive resuscitation,* which maintains minimally adequate organ perfusion, may result in improved outcome (9). The threshold for clot disruption appears to be about 90 mm Hg (10). It is important to remember that most clinical trials evaluating fluid administration have involved penetrating trauma victims. Whether the same principles can be applied to blunt trauma victims is not clear. In fact, this approach may be detrimental to blunt trauma patients with traumatic brain injury (TBI), because hypotension increases mortality in these patients (11). A clear endpoint of fluid therapy, in terms of an optimal blood pressure, has not been defined. Based on the current literature, it appears reasonable to have a goal of a systolic blood pressure of approximately 90 mm Hg for penetrating trauma patients and 100 mm Hg for blunt trauma patients with suspected TBI.

The optimal type of fluid for volume replacement has also been the subject of considerable debate. Crystalloid solutions, such as normal saline or lactated Ringer solution, have long been considered the standard. While hypertonic saline (HTS) is an appealing resuscitative agent, the recent large multicenter Resuscitation Outcomes Consortium (ROC) trial was terminated because of safety issues (12).

Replacing a significant percentage of the patient's blood volume with fluids that have not been warmed ("room temperature" is significantly cooler than body temperature) can render a patient hypothermic very quickly. Fluids may be warmed ahead of time or be administered through a fluid warmer. In an average-sized adult

showing signs of shock, infusion of 2 L of crystalloid and immediate reassessment of hemodynamics is a reasonable course of action (see Chapter 245 for pediatric resuscitation). The point in volume resuscitation at which blood transfusion is initiated has not been well defined. Factors that influence the decision to start blood transfusion include severity of shock, initial response to crystalloid, and anticipated ongoing bleeding. In general, if hemodynamics do not improve after administration of 3 L of crystalloid (or about 50 mL/kg) given rapidly, further volume replacement with blood should be considered. Certain patients may also require transfusion based on their initial injuries, such as those with major pelvic trauma.

The value of colloids in the treatment of traumatic shock remains to be established. Colloids, such as albumin, hetastarch, and dextran, can effectively increase intravascular volume and maintain plasma oncotic pressure at more normal levels compared with crystalloids. However, substantial data demonstrate that crystalloid and colloids are equally effective in resuscitation from hemorrhagic shock (13), and colloids have not been shown to improve outcomes despite higher cost. Furthermore, some evidence suggests that resuscitation with colloids may have deleterious effects. One study found that albumin was associated with significantly worse outcomes in patients with TBI (14) and another trial suggested starches might increase the risk of coagulopathy and AKI (15). Therefore, until well-designed clinical trials are performed showing an advantage to another approach, crystalloids remain the fluid of choice for the resuscitation of trauma patients in hemorrhagic shock (16).

Red blood cell (RBC) substitutes consisting of hemoglobin that has been modified by polymerization and biochemical alteration have been extensively studied in both animal and human trials. Studies have suggested that these RBC substitutes, with their ability to carry oxygen, may be superior to the current, more conventional methods of resuscitation from hemorrhagic shock (17). The USA Multicenter PolyHeme Resuscitation Trial enrolled 720 patients in 32 centers, but the results fail to demonstrate a clinical benefit (18).

Typed and cross-matched PRBCs are the best choice for blood transfusion, although this usually takes at least 30 minutes to obtain.

If transfusion is required more urgently, type-specific blood (usually available in 10 to 20 minutes) is an appropriate alternative. Type-specific blood has ABO compatibility with the patient's blood type but has not been tested for antibody compatibility. If traumatic shock is severe and immediate transfusion is critical, type O Rh-positive blood for males and type O Rh-negative for girls and women of childbearing age should be used until type-specific or typed and cross-matched blood is available. Type O Rh-negative blood should be immediately available in the trauma room, if there is appropriate prehospital notification.

If early blood transfusion is required to manage profound hypovolemia or if there is ongoing massive hemorrhage, fresh-frozen plasma (FFP) and platelets may be needed to restore the coagulation system. If a massive transfusion is anticipated (persistent hypotension with presumed active torso hemorrhage), some clinical studies have suggested a preemptive FFP:RBC ratio of 1:1 although a survival benefit has not been clearly defined. Others have suggested a 1:2 ratio may be more effective (19). A suggested definition of massive transfusion is 10 or more units of RBC in a 12-hour period. Initial large studies have suggested a significant survival benefit, but the role of tranexamic acid (TXA) remains controversial and the clinical benefit has not yet been clearly established (20). Conventional coagulation studies (PRR, INR) and platelet counts generally do not reflect the coagulation status of the critically injured. Point of care measurements, such as thermoelastography (TEG), that allow for early diagnosis of primary fibrinolysis, are now being implemented (21). Recombinant factor VIIa is a hemostatic agent originally developed to treat bleeding in hemophiliacs. Several authors have suggested that factor VIIa may be beneficial in severely bleeding trauma patients. However, two large randomized clinical trials have failed to identify a benefit (22).

Pneumothorax or hemothorax should be managed by the placement of a chest tube (18 French for pneumothorax, 28 French for hemothorax) in the lateral chest with the tube oriented toward the apicoposterior chest wall. While traditionally large chest tubes have been used in these situations, some authors have argued the

smaller pigtail catheters (14 French) perform just as well, even for a traumatic hemothorax (23). If a tension pneumothorax is suspected and the patient is hypotensive, the chest tube should be placed immediately even if a drainage system is not available.

If pericardial tamponade is suspected and the patient is hypotensive and worsening despite volume resuscitation, pericardiocentesis is indicated. A pericardiocentesis needle is inserted in the left subxiphoid area and directed 45 degrees toward the left shoulder or sternal notch, whereas suction is maintained through an attached syringe. Although the subxiphoid approach has been described as the "classical" approach for performing pericardiocentesis, the para-apical or parasternal approach with US guidance has been advocated in more recent studies (24). No controlled trials have compared the approaches in trauma patients. If a particular view by US (subxiphoid or parasternal) offers evidence of significant fluid accumulation, it is prudent to take that approach with the pericardiocentesis needle. Blood in the pericardium often forms clots, thus limiting the value of pericardiocentesis, particularly with right ventricular or atrial injuries. If the patient is profoundly hypotensive or has lost a detectable blood pressure in the trauma bay, an emergency left lateral thoracotomy should be performed to open the pericardium. Patients who have not shown signs of life after sustaining blunt trauma are poor candidates for ED thoracotomy (25).

Intra-abdominal injury is a common source for postinjury shock. The clinical presentation and response to initial therapy dictate the subsequent assessment of the abdomen. Hemodynamically unstable patients with physical examination or US evidence of abdominal injury should undergo exploratory laparotomy. Patients with suspected abdominal trauma who have exhibited transient hemodynamic instability should undergo a FAST examination, which can identify free intra-abdominal fluid. DPL is an alternative method of detecting intraperitoneal hemorrhage, if US is not available. Hemodynamically stable patients with potential abdominal trauma are candidates for abdominal CT scanning.

A quick maneuver to treat the hypotensive pregnant trauma patient is to place the patient in the left lateral decubitus position or tilt the backboard up 15 degrees on the right to move the gravid uterus off the inferior vena cava. This positioning improves venous return and may normalize the blood pressure.

In general, vasopressors and inotropic agents are not used in the ED management of traumatic shock except for cases of neurogenic or vasogenic shock (e.g., spinal cord injury) in which peripheral vasodilatation causes or contributes to hemodynamic instability. Agents such as dopamine or norepinephrine may be useful after fluid resuscitation. From the ED perspective, shock rarely occurs from isolated head trauma except in the young child. In cases of myocardial infarction associated with trauma or significant myocardial contusion, inotropic support may be appropriate.

CRITICAL INTERVENTIONS

- Recognize and treat shock aggressively before hypotension develops. Remember that shock may exist in a patient with "normal" vital signs.
- Wrap potentially unstable pelvic fractures with a sheet prior to transfer or extended diagnostic testing.
- When possible, place the hypotensive pregnant trauma patient in the left lateral decubitus position to relieve possible compression of the inferior vena cava.
- Isolated head trauma rarely causes hypotension; search for other causes.

DISPOSITION

Definitive management of the patient with traumatic shock often requires emergency surgery. Consultation with a surgeon should be initiated as soon as possible in all victims of significant trauma who might require operative or critical care interventions. If information from prehospital care providers indicates potentially serious injury, the surgeon (or trauma team) should be notified before the patient arrives in the ED. If transfer to another hospital is required, early

mobilization of resources (ambulance, staff, or air medical transport service) should be initiated concurrently with assessment and stabilization.

The criteria for transfer to a trauma center include lack of an experienced trauma surgeon, lack of adequate critical care or support services, and lack of adequate resources to manage a patient's injuries. The use of scoring systems such as the Trauma Score (TS), Revised Trauma Score (RTS), and the Glasgow Coma Scale (GCS) for triage may be helpful in identifying patients with severe injury. Patients with a TS <12, an RTS of ≤ 8, or a GCS <10 generally have serious injuries and should be managed within an organized trauma system. The emergency physician must determine which interventions and diagnostic studies are essential before transfer. These decisions are affected by mode of transport, distance to the trauma center, and the capabilities of the referring hospital. For example, delaying transfer to obtain a head and abdominal CT scan or plain radiographs is of no benefit if there is no neurosurgeon, general surgeon, or orthopedist available or if no immediate intervention will take place at the referring hospital. On the other hand, if a head, chest, or abdominal CT scan is indicated and can be obtained while waiting for the ambulance or helicopter to arrive (and will not cause a delay in transfer), it is best to proceed with these studies.

Common Pitfalls

- Failure to recognize shock; normal vital signs can be misleading.
- Failure to realize that altered mental status is a sign of shock, particularly when there is no evidence of head trauma.
- Failure to monitor trauma patients carefully and to perform serial examinations to detect changes in clinical status and response to interventions. An initial favorable response to volume replacement should not mislead the physician to be less vigilant, as adequate initial resuscitation can temporarily mask significant ongoing hemorrhage.
- Delaying surgical consultation or transfer to a trauma center.

- Missing subtle injuries, especially in patients with severe multisystem trauma.

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CHAPTER 21 Wound Management

Judd E. Hollander and Adam J. Singer

Nearly 9 million patients with traumatic lacerations are treated annually in emergency departments (EDs) in the United States (1). The ultimate goals are to restore the physical integrity and function of the injured tissue in a cosmetically pleasing manner and to reduce the risk of infection. Treatment of these wounds involves a series of decisions that determine the methods of evaluation, wound preparation, wound closure, and postoperative care most likely to help attain these goals.

CLINICAL PRESENTATION

Lacerations occur predominantly in young adults; the majority of patients with lacerations are males (2). Most wounds are located on either the head or neck (50%) or the upper extremity (35%), usually involving the fingers or hands. The most common mechanism of injury is application of a blunt force, such as bumping the head against a coffee table. Such contact crushes the skin against an underlying bone, causing the skin to split. Other causes of injury include sharp instruments, glass, and wooden objects (2). While mammalian bites continue to receive much attention, they are a relatively infrequent cause of puncture wounds and lacerations (2).

ED EVALUATION

Evaluation of the patient with a traumatic wound begins with an expeditious, comprehensive assessment of the patient. This assessment can be divided into primary and secondary surveys, following advanced trauma life support algorithms. Unless the

wound compromises the ABCs, formal wound evaluation and management occur during the secondary survey and management phase of the trauma evaluation.

Proper wound management begins with a thorough patient history. It is important to determine hand dominance and occupation. Host factors such as the extremes of age, diabetes mellitus, chronic renal failure, obesity, malnutrition, and the use of immunosuppressive medications all increase the risk of wound infection and can impair wound healing. Wound healing can also be impaired in the presence of inherited and acquired connective tissue disorders. The tendency of patients to form keloids should be ascertained because the development of keloids can result in a scar with less than acceptable cosmesis. Black and Asian populations are more prone to keloid formation (3).

Identification of the mechanism of injury is essential to help ascertain the presence of potential wound contaminants and foreign bodies that might result in chronic infection and delayed healing (3). Failure to diagnose foreign bodies in wounds is a leading cause of litigation against emergency physicians. Missed tendon and nerve injuries and failure to prevent infection are other common wound-related causes of litigation. In patients with scalp lacerations, a history of loss of consciousness and any neurologic complaints should be obtained. In patients with hand injuries, a history of neurologic deficits should be obtained to help predict the presence of tendon or nerve injury.

A careful history can also predict the likelihood of foreign bodies. Most organic and inorganic components of soil potentiate infection. However, sand grains are relatively innocuous. The black dirt on the surface of highways appears to have minimal chemical reactivity.

Crush injuries that tend to cause greater devitalization of tissue are more susceptible to infection than are wounds resulting from the more commonly seen shearing forces. Impact injuries with low energy levels may not result in division of the skin; they can, however, disrupt vessels and produce a hematoma and ecchymosis.

The presence of allergies to local anesthetics, latex, and antibiotics should be determined. The tetanus status of all patients should be

assessed, and patients should receive immunization in accordance with current Centers for Disease Control and Prevention recommendations (Table 21.1). Before inspecting the wound, the emergency physician should question the patient regarding the time and mechanism of injury. The amount of time elapsed since the accident may influence treatment decisions.

TABLE 21.1
Recommendations for Tetanus Prophylaxis

	Clean Minor Wounds		All Other Wounds	
History of tetanus immunization	Td	TIG	Td	TIG
<3 or uncertain doses	Yes	No	Yes	Yes
≥3 doses				
Last dose within 5 yrs	No	No	No	No
Last dose within 5–10 yrs	No	No	Yes	No
Last dose >10 yrs ago	Yes	No	Yes	No

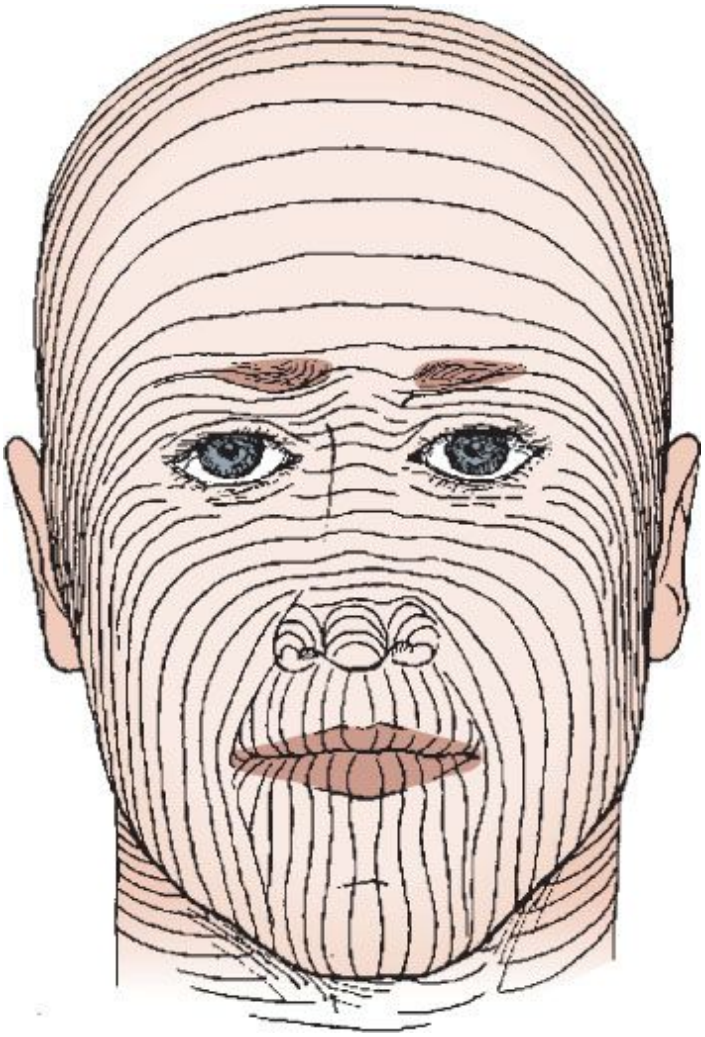
Td, tetanus–diphtheria toxoid; TIG, tetanus immune globulin.
Note: For example, contaminated wounds, puncture wounds, avulsions, burns, crush injuries.
From Singer AJ, Hollander JE, Quinn JV. Evaluation and management of traumatic lacerations. *N Engl J Med*. 1997;337:1142–1148.

Adequate wound examination should always be conducted in a field where bleeding has been controlled. One way to minimize the possibility of missing an injury to a vital structure is to start the wound examination with a careful neurovascular assessment of pulses, motor function, and sensation distal to the laceration. Finger tourniquets or a blood pressure cuff may then be used to obtain a bloodless field, but they should not be used for more than 30 to 60 minutes.

Moist areas of the body, such as the axillae, perineum, toe webs, and intertriginous areas, harbor millions of bacteria per square centimeter. Lacerations of the oral cavity are usually heavily contaminated with facultative species and obligate anaerobes. Wounds with fecal contaminants run a high risk of infection despite therapeutic intervention.

Wounds located on highly vascular areas, such as the face and scalp, are less likely to be infected than are wounds located in less vascular areas, such as the extremities (2). Lacerations of the scalp and face have a very low infection rate regardless of the intensity of cleansing (4).

Wound location also contributes to the cosmetic appearance of the scar by affecting static and dynamic skin tensions (eFig. 21.1). Lacerations over joints are subject to large, dynamic skin tensions and will have a wider scar than will similar lacerations subject to less tension. Wounds that run perpendicular to the lines of minimal skin tension will also be prone to the development of wider and more visible scars.



eFIGURE 21.1 Langer lines of least skin tension.

eTABLE 21.1
Advantages and Disadvantages of the Common Wound-Closure Techniques

	Advantages	Disadvantages
Suture	Time-honored	Requires removal
	Meticulous closure	Requires anesthesia
	Greatest tensile strength	Greatest tissue reactivity
	Lowest dehiscence rate	Highest cost
		Slowest application
Staples	Rapid application	Less meticulous closure
	Low tissue reactivity	May interfere with some older-generation imaging techniques (CT, MRI)
	Low cost	
	Low risk of needlestick	
Tissue adhesives	Rapid application	Lower tensile strength than sutures
	Dehiscence over high-tension areas (joints)	Not useful on hands
	Resistant to bacterial growth	Cannot bathe or swim
	No need for removal	
	Low cost	
	No risk of needlestick	
	Patient comfort	
Surgical tapes	Least reactive	Frequently falls off
	Lowest infection rates	Lower tensile strength than sutures or adhesives
	Rapid application	
	Patient comfort	Highest rate of dehiscence
	Low cost	Requires use of toxic adjuncts
	No risk of needlestick	Cannot be used in areas of hair
		Cannot get wet

CT, computed tomography; MRI, magnetic resonance imaging.

eTABLE 21.2
Characteristics of Nonabsorbable Sutures

TABLE 21.2
Properties of Commonly Used Local Anesthetics

Agent	Trade Name	Local Anesthetic Class	Concentration	Maximal Safe Dose	Onset	Duration
Procaine	Novocaine	Ester	0.5–1%	7 mg/kg	2–5 min	15–45 min
With epinephrine				9 mg/kg		30–90 min
Lidocaine	Xylocaine	Amide	0.5–2%	4.5 mg/kg	2–5 min	1–2 hrs
With epinephrine				7 mg/kg		2–4 hrs
Bupivacaine	Marcaine	Amide	0.125–0.25%	2 mg/kg	2–5 min	4–8 hrs
With epinephrine				3 mg/kg		8–16 hrs

Suture	Knot Security	Tensile Strength	Tissue Reactivity	Workability
Nylon (Ethilon)	Good	Good	Minimal	Good
Polypropylene (Prolene)	Least	Best	Least	Fair
Silk	Best	Least	Most	Best

eTABLE 21.3
Characteristics of Absorbable Sutures

TABLE 21.3
Suture Selection Based on Anatomic Location

Location	Suture Size[a]
Face	6-0 or 7-0
Oral mucosa	4-0 or 5-0
Scalp	4-0
Chest	3-0 or 4-0
Back	3-0 or 4-0
Forearm	4-0 or 5-0
Fingers	4-0 or 5-0
Hand	4-0 or 5-0
Lower extremity	4-0 or 5-0
Foot	4-0 or 5-0

[a]Larger suture sizes may need to be used for wounds with higher tension.

Suture	Knot Security	Tensile Strength	Wound Security (50% Tensile Strength)	Tissue Reactivity
Surgical gut	Poor	Fair	5–7 d	Most
Chromic gut	Fair	Fair	10–14 d	Most
Poliglecaprone (Monocryl)	Good	Fair	10–14 d	Least
Polyglactin (Vicryl)	Good	Good	30 d	Minimal
Polyglycolic acid (Dexon)	Best	Good	30 d	Minimal
Polydioxanone (PDS)	Fair	Best	45–60 d	Least
Polyglyconate (Maxon)	Fair	Best	45–60 d	Least

KEY TESTING

- The majority of lacerations require no diagnostic testing besides a history and physical examination.
- Depending upon the likelihood of a retained foreign body or fracture from the injury, radiography, ultrasound, or computerized tomography may be necessary.

ED MANAGEMENT

Aseptic Technique

The use of sterile gloves makes common sense, despite the lack of clinical evidence supporting their use (5,6). Though the practice of universal precautions is recommended in all patients, double gloving is recommended when caring for patients who can transmit serious infections (human immunodeficiency virus or hepatitis) to the healthcare provider.

Latex Allergy

Severe reactions in latex-sensitive individuals have resulted in fatalities. Populations that appear to be at increased risk for allergic reactions to latex include patients who have undergone multiple

operations, patients with atopic disease, children with spina bifida, and medical personnel with frequent latex exposures.

Wound Examination

Wound examination should always be conducted under optimal lighting conditions and with bleeding in the field controlled. Wound examination should begin with a neurovascular assessment of pulses, motor function, and sensation distal to the laceration.

Bleeding should be controlled with direct pressure. When lacerations continue to bleed despite reasonable pressure, placement of a sphygmomanometer cuff proximal to the injury, with inflation to a pressure greater than the patient's systolic blood pressure, will help contain bleeding to allow proper examination. Palpation of the bones adjacent to the injured site may detect tenderness, a defect, or instability consistent with an underlying injury. Radiography should be used to detect fractures. Detection of an open fracture will dictate a change from usual management because it will require the administration of systemic antibiotics and may require irrigation in the operating room. Wounds occurring adjacent to a joint should be carefully evaluated for joint violation. If in doubt, sterile fluid should be injected into the joint, and the physician should look for communication to verify violation of the joint space.

Amputated parts should be cared for as outlined in the chapters on hand injuries and replantation emergencies (Chapters 41 and 47). Digits should be covered with a protective saline-soaked dressing, placed within a waterproof bag, and then placed in a container of ice water for preservation and consideration of future reattachment.

Complicated injuries involving most open fractures, joint penetration, flexor tendon injuries, nerve injuries, or arterial injuries are often treated in the operating room. In most other cases, wound repair will occur in the ED.

The ultimate appearance and function of a scar can be predicted by the static and dynamic skin tensions on the surrounding skin (see eFig. 21.1). The most aesthetically pleasing scar occurs when the long axis of the scar is parallel to the direction of minimal tension, because the static skin tensions continually pull on the wound edges

even after wound closure. The ultimate width of the scar is proportional to the magnitude of the static skin tensions.

An appreciation of the effects of various dynamic tensions can be used to determine the need for tension-relieving absorbable sutures in addition to the nonabsorbable skin closure.

Wound Anesthesia

Most lacerations will require some form of anesthesia prior to wound closure. All visibly contaminated wounds and wounds that will require anesthesia for closure should receive anesthesia prior to cleansing so that adequate mechanical removal of bacteria, soil, and other debris can be more readily accomplished.

Local Infiltration

The most common form of anesthesia for traumatic injuries is local infiltration. Unfortunately, local anesthesia is painful. To reduce the pain associated with local infiltration, several strategies can be employed. The addition of sodium bicarbonate to lidocaine (pK_a, 7.9) in a 1:9 ratio increases the ratio of uncharged to charged ions and results in more rapid diffusion of anesthetic agent into nerve endings. It reduces the pain associated with local infiltration without altering the ability of host defenses to prevent infection (7). The use of warm anesthetic solutions, small needles, slow rates of infiltration, injection through the wound edges in noncontaminated wounds, and pretreatment with topical 4% tetracaine or lidocaine, epinephrine, and tetracaine (LET) are additional strategies that can be used to decrease the pain of infiltration (3,8).

For injection of local anesthesia, a 27- to 30-gauge needle attached to a 10-mL syringe should be used. The needle should be passed into the wound edge rather than the intact skin because wound edge injections are less painful. Full anesthesia to pinprick is present 5 to 6 minutes after subdermal injection. The local anesthetic agent should be instilled slowly to decrease the pain that accompanies tissue infiltration. The needle should be passed through the dermal tissue initially; then the anesthetic agent can be injected as the

needle is slowly withdrawn. This technique minimizes distention and pain by providing a potential space for the anesthetic solution. Aspiration of the syringe before injection is recommended to prevent inadvertent intravascular injection.

Because the duration of local anesthesia induced by bupivacaine is nearly four times longer than that of lidocaine, bupivacaine (0.25%) should be used when longer durations of anesthesia are desirable (Table 21.2).

Vasoconstrictors such as epinephrine can be used as adjuncts to the local anesthetic agents. They will reduce bleeding and oozing within the laceration, which will make exploration and closure easier to accomplish. The addition of epinephrine also delays systemic absorption and increases the therapeutic window. Clinical studies have not found that the vasoconstriction associated with epinephrine use results in differences in infection rates. While traditionally these agents have been avoided in fingers, toes, and the penis owing to the risk of vasospasm and subsequent necrosis, more recent evidence suggest that their use is safe (9).

Regional Anesthesia

When the nerve supply to a wound is easily accessible, a regional nerve block is a valuable alternative to local anesthesia. The use of regional nerve blocks will prevent distortion of the wound edges, facilitating approximation and increasing the likelihood of an excellent cosmetic result. Regional nerve blocks can be accomplished by only one or two needle passages through skin proximal to the injury site. Regional nerve blocks of the supraorbital, infraorbital, and mental nerves are useful for facial lacerations; however, they are more painful and less reliable than local infiltration (10). Median, radial, and ulnar nerve blocks may be useful for lacerations of the hand. Digital or metacarpal nerve blocks can be used for finger lacerations. Regional nerve blocks can also be used for lacerations of the feet. Field blocks can be considered for more proximal extremity injuries.

A 27- or 25-gauge needle is preferred to a 30-gauge needle for a regional nerve block, because either one is more resistant to

deflection during passage through tissue. The duration of sensory analgesia can be significantly prolonged when epinephrine (1%) is added to the anesthetic solution. When the needle puncture site is the mucous membrane, anesthetizing the mucous membrane with a topical anesthetic agent makes the introduction of the needle painless.

Topical Anesthesia

Topical anesthesia eliminates needle use and the risk of inadvertent needle sticks while allowing the application of painless anesthesia. Various combinations of lidocaine (1% to 4%), adrenaline (1:1,000 to 1:2,000), and tetracaine (0.5% to 2.0%) are as effective as eutectic mixture of local anesthetic cream (EMLA) (11,12). An EMLA has a slower onset of action, is more expensive than LET, and is not approved for use on injured skin; therefore, it is not recommended for use in the ED.

Preparation of Skin

Removal of the hair surrounding a laceration may facilitate meticulous wound closure. Because many bacteria normally reside in hair follicles, shaving the hair prior to repair may increase wound infection rates. Reduced damage to hair follicles may be achieved by using hair clippers instead of a razor. Removal of the eyebrow hair should be avoided because it does not always grow back. Additionally, the presence of hair serves as a guide to approximation of wound edges during laceration repair.

The skin surrounding the wound should either be cleansed with normal saline or disinfected with an iodophor (such as Betadine) or chlorhexidine; the physician should avoid contacting the wound itself with disinfectant. A recent study in the operating room demonstrated significantly reduced wound infection rates after skin preparation with chlorhexidine (13). Although these agents can reduce the bacterial concentration on intact skin, they appear to damage wound defenses, making the wound more susceptible to

development of infection. Consequently, any contact of these agents with the wound should be avoided.

Debridement

Appropriate debridement is an important factor in the management of contaminated wounds. Retained devitalized soft tissue, fat, muscle, and skin can damage wound defenses and increase the likelihood of infection through the promotion of bacterial growth and the inhibition of phagocytosis. Identification of the exact limit of devitalized tissue in wounds may be difficult. Evaluation of the color, consistency, contraction, and circulation is useful.

In some anatomic sites, such as the trunk, debridement is best accomplished by complete excision of the skin and deep tissues. Heavily contaminated wounds with serpiginous defects in these regions can be converted to clean wounds by more generous tissue excision. When a heavily contaminated wound contains specialized tissues, such as the nerves or tendons that perform important physical functions, complete excision often is not feasible. In such instances, mechanical wound cleansing followed by excision of all fragments of tissue that are not clearly viable is indicated.

The benefits of debridement must be weighed against the consequences of excision of the tissue. Debridement of skin and underlying tissue leaves a significant soft tissue defect that makes reapproximation more difficult.

Assessment for Foreign Bodies

Metal, bone, teeth, pencil graphite, certain plastics, glass, gravel, sand, some fish bones, some wood, and some types of aluminum are visible on plain radiographs. Almost all glass fragments 2 mm or larger are visible on radiographs (14). If the wound was caused by metal or glass and no foreign body is found on wound exploration or on plain films, it is unlikely that a foreign body exists. Computed tomography (CT) and magnetic resonance imaging (MRI) are useful for identifying and locating objects that have densities similar to soft

tissue. Sonography may also be useful, particularly for wooden foreign bodies.

Cleansing the Wound

The two basic methods of wound cleansing are hydraulic forces (irrigation) and direct contact (scrubbing).

Irrigation

Some debate exists over both the optimal method of irrigation and the preferred solution. The efficacy of wound irrigation is correlated with the pressure at which the irrigant is delivered to the wound. High-pressure irrigation (>7 pounds per square inch) successfully cleans wounds of small particulate matter, such as bacteria and soil. Such cleansing has reduced the infection rate of experimentally contaminated wounds. In contrast, low-pressure syringe irrigation, even with large volumes of fluid, demonstrates negligible capability for removing small particles (bacteria) but removes large particulate matter, such as detached devitalized tissue.

High wound impact pressures can be easily obtained using a 30- to 60-mL syringe and a 19-gauge needle or Zerowet splash shield (15). However, it must be noted that sustained high- pressure irrigation can result in tissue damage. As a result, at very high pressures, infection rates may actually increase.

For relatively clean wounds in highly vascularized areas containing loose areolar tissue, such as the eyelid, high pressures should be avoided. In fact, high-pressure irrigation has not been found to offer any advantages for cleansing clean, noncontaminated facial lacerations (4). Conversely, high-pressure irrigation is clearly indicated for contaminated wounds of the lower extremity. The choice of irrigation solution is relatively straightforward. Normal saline compares favorably with more expensive, less readily available alternatives. Because of their tissue toxicity, detergents, hydrogen peroxide, and concentrated forms of povidone–iodine should not be used to irrigate wounds. Irrigation of wounds with tap water results in comparable infection rates versus irrigation with sterile saline (16). Irrigation volume should be individualized based on patient

characteristics and such wound characteristics as location and etiology. Use of a device designed to reduce splatter will minimize the healthcare provider's risk of exposure to potentially infectious materials.

Scrubbing

Direct scrubbing of the wound with gauze or a sterile surgical brush helps remove both bacteria and particulate matter, which potentiate the risk of wound infection. However, scrubbing also contributes to the tissue damage and reduces the ability of the wound to resist infection. Therefore scrubbing should be reserved for highly contaminated wounds.

Use of Drains

The potential benefits of the use of surgical drains in a clinical setting must be weighed against its harmful effects. Drains evacuate potentially harmful collections of pus and blood from wounds. When no definite localized fluid collection exists, drains must be considered prophylactic, and their potentially harmful effects become more important. The general use of drains is not indicated in the management of most wounds in the ED.

Open Wound Management

The technique of wound closure largely depends on whether the wound has lost tissue and the risk of wound infection. With *primary closure,* the wound is immediately closed. Primary closure results in a reduction in healing time in comparison with other closure methods. It also may reduce the bleeding, inconvenience, and discomfort often associated with open wounds. *Secondary wound closure,* in which the wound is left open and allowed to close on its own, is particularly well suited for highly contaminated or infected wounds. Though this method may reduce the risk of infection, it is relatively slow and uncomfortable. *Delayed primary* (or *tertiary*) *closure* combines the advantages of both primary and secondary closures. The wound is left open for a period of 3 to 5 days, after which it may be closed if no infection supervenes. For wounds with associated significant

tissue loss, grafts or flaps are often required to close the defect. These procedures are usually performed in the operating room.

Though there is a direct relationship between the time interval from injury to laceration closure and the risk of subsequent infection, the length of this "golden period" is highly variable (3). A study of forearm lacerations found that closure within 4 hours had a lower infection rate than later closure (17). A large series of pediatric patients (2,834 patients) with lacerations did not find a difference in infection rate for lacerations closed within or >6 hours from the time of injury (18). Facial lacerations healed well regardless of the time to closure. In contrast, trunk and extremity lacerations exhibited lower rates of healing if they were closed more than 19 hours from the time of injury (63% to 75%) as compared to earlier (75% to 91%) (19).

On the basis of these data, it seems appropriate to consider each laceration separately, taking the time from injury until presentation into account, along with laceration location, degree of contamination, risk of infection, and importance of cosmetic appearance, before deciding whether to perform primary wound closure. Wounds that are not closed primarily owing to a high risk of infection should be considered for delayed primary closure after 3 to 5 days, when the risk of infection decreases.

Wound Closure

Careful handling of tissues and judicious use of electrocautery are necessary to reduce further trauma that may lead to poor cosmetic outcome (20). The optimal wound-closure technique varies with the clinical situation. Sutures are the most commonly employed wound-closure technique. Tissue adhesives can be used in up to one-third of ED laceration repairs. Staples and surgical tapes can be used in selected situations. The advantages and disadvantages of various wound-closure techniques are summarized in Table 21.4.

TABLE 21.4
Advantages and Disadvantages of the Various Suture Techniques

Suture Type	Advantages	Disadvantages	Frequent Uses
Interrupted percutaneous	Excellent approximation	Time-consuming May strangulate tissues	Low-tension wounds May be used with deep sutures for high-tension wounds
Continuous percutaneous	Rapid closure Accommodates edema	Less meticulous closure than interrupted sutures If a single knot unravels the wound may dehisce (if no deep sutures placed)	Percutaneous closure in conjunction with deep sutures
Interrupted dermal	Reduces tension on wound surface Allows early removal of percutaneous sutures avoiding hatch marking May reduce scar width	May increase infection in contaminated wounds	High-tension wounds Closure of dead space
Continuous dermal	Rapid Reduces tension on wound surface Allows early removal of percutaneous sutures avoiding hatch marking May reduce scar width	Technically difficult Less accurate approximation than interrupted sutures If a single knot unravels, the wound may dehisce	High-tension wounds require interrupted dermal sutures Closure of dead space
Vertical mattress	Excellent wound edge eversion Combines advantages of deep and superficial sutures	May cause tissue strangulation	Thin or lax skin with little dermal or fascial tissues High-tension areas (e.g., extremities)
Horizontal mattress	More rapid than simple interrupted sutures Excellent wound edge eversion	May cause tissue strangulation	Bleeding scalp wounds Initial approximation of high-tension wounds
Half-buried horizontal mattress	Less compromising to flap perfusion	Time-consuming Technically difficult	For corner stitches and flaps

Sutures

The choice of suture technique should be determined by the configuration and biomechanical properties of the wound, in combination with an assessment of its risk of infection. Percutaneous sutures pass through the epidermal and dermal layers of the skin. They are used alone for low-tension lacerations and in combination with deep dermal sutures for higher tension lacerations. The dermal suture reapproximates the divided edges of the dermis without penetrating the epidermis. Often, dermal and percutaneous sutures are used together.

Most often, percutaneous sutures are performed with nonabsorbable sutures, such as nylon and polypropylene. Both nylon and polypropylene retain most of their tensile strength for more than 60 days and are relatively nonreactive (3). Removal of nonabsorbable sutures is required. Percutaneous sutures of either monofilament nylon or polypropylene exert the least damage to the wound defenses.

Nonabsorbable sutures made from natural fibers potentiate infection more than synthetic nonabsorbable sutures, correlating with the reaction of tissue to these sutures in clean wounds. The incidence of infection in contaminated tissue containing

monofilament sutures is lower than in those containing multifilament (braided) sutures. Although use of absorbable sutures is generally reserved for dermal closures, more rapidly absorbing forms can be used to close skin in children and avoid the discomfort and inconvenience of suture removal.

Dermal closures are generally accomplished with absorbable sutures. Chromic gut lasts for up to 2 weeks, but it is associated with increased tissue reactivity. Polyglactin (Vicryl) and polyglycolic acid (Dexon) maintain tensile strength for 20 to 28 days and have less tissue reactivity. Some synthetic absorbable sutures, such as polydioxanone (PDS) and polyglyconate (Maxon), retain their tensile strength for as long as 2 months. They are particularly useful in areas with high static and dynamic tensions. These sutures should be used only in the deeper areas, because they can become extruded after long periods of time. Antibiotic-impregnated absorbable sutures (such as Vicryl Plus and Monocryl Plus) have in vitro antibacterial actions against a wide variety of bacteria. They should be considered especially in contaminated wounds.

The use of dermal sutures relieves skin tension, decreases dead space and hematoma formation and, theoretically, should improve cosmetic outcome. Research in experimental animal models has found that deep sutures increase the risk of infection in highly contaminated wounds, but they do not do so in clean, noncontaminated lacerations (3). Deep sutures should not be placed in adipose tissue and in contaminated wounds. No studies of traumatic lacerations have demonstrated any benefit to the use of deep sutures (21). Many practitioners prefer to use deep sutures in gaping lacerations and in cosmetically important lacerations despite a lack of evidence. Deep sutures should not be used in the hand as they may inadvertently cause damage to important structures such as nerves and tendons.

Undermining the wound margin decreases the forces required for wound closure. Theoretically, it should limit the width of the ultimate scar. However, this benefit must be weighed against its potential damage to the skin blood supply, which may increase the likelihood of infection. Consequently, undermining should be

reserved for clean, noncontaminated wounds subjected to strong static and dynamic tensions.

The magnitude of the suture's damage to the local tissue defenses is related to the quantity of the suture within the wound. As a result, the narrowest diameter suture (5-0 or 6-0) that is strong enough to resist disruption of the skin should be used (Table 21.3). Approximation of the midportion of the laceration first, with subsequent bisection of the remaining portion, will enable the use of the least amount of suture. Interrupted dermal sutures placed in each quadrant of the wound subjected to strong static and dynamic skin tensions may provide sufficient strength to permit early suture removal.

Careful attention to the following details may help ensure proper wound edge eversion and an optimal cosmetic outcome after suturing. The needle should enter the wound at an angle of 90 degrees. This will result in a wider "bite" at the depth of the wound than at its surface, helping to achieve wound eversion. This is best accomplished by maximally pronating the hand that is holding the needle holder. It is also important to match corresponding layers of the skin on either side of the wound by taking equally sized bites.

The choice of a particular suture technique is based upon the specific wound, its location, tension, and advantages and disadvantages of the various suture techniques (Table 21.4). *Simple interrupted* sutures are commonly used for low-to-moderate tension wounds. For long linear lacerations, *continuous* sutures may be used to save time and distribute the tension more evenly. *Continuous subcuticular* (or *intradermal*) sutures can be used instead of percutaneous sutures to avoid the need for suture removal. However, this method is more time-consuming and technically challenging. A *half-buried horizontal mattress* suture (or *corner* stitch) is most appropriate for narrow corners and flaps, as it does not compromise tissue perfusion. *Vertical mattress* sutures help achieve maximal wound edge eversion, but they may result in tissue strangulation. They are best reserved for closure of high-tension wounds in thin skin where placement of deep dermal sutures is difficult. Whatever method is used, the sutures should be tied tightly enough to achieve

complete apposition of the wound edges. However, care should be taken not to tighten the suture too tightly, as this may compromise perfusion and result in necrosis and sloughing of the wound edges.

Topical Skin Adhesives

The only topical skin adhesives that are strong enough to close wounds are the cyanoacrylate polymers. A growing number of butylcyanoacrylate, octylcyanoacrylate, or combination topical skin adhesives are now available. The topical skin adhesives also have the advantage of forming a microbial barrier to prevent wound contamination (22).

Several clinical studies have compared the use of 2-octylcyanoacrylate to 5-0 and 6-0 sutures. Quinn et al. (23) found the long-term cosmetic outcomes to be equivalent. The use of 2-octylcyanoacrylate was faster and less painful than the use of sutures. The largest study to date enrolled 818 patients who were randomly assigned to receive skin closure with either 5-0 or 6-0 sutures or 2-octylcyanoacrylate (24). Of the 818 patients enrolled, 333 had subcuticular or subcutaneous sutures placed prior to laceration closure. Comparing the group of patients who received 2-octylcyanoacrylate with the group of patients who received skin closure with sutures, the 3-month cosmetic outcomes, short-term infection rates, and wound dehiscence rates were all similar. The time to wound closure was reduced by more than 50% in the group treated with 2-octylcyanoacrylate. Subgroup analysis of patients from both adult and pediatric EDs found equivalent 3-month cosmetic outcomes (25,26).

Although in vitro and in vivo studies have found that cyanoacrylate tissue adhesives possess gram-positive antimicrobial properties, it is imperative that clinicians adhere to standard wound preparation and wound-cleansing procedures. Meticulous wound cleansing is essential regardless of wound closure method. Although wound cleansing can sometimes be accomplished without the use of local anesthesia, the decision to close wounds with tissue adhesives should not, in and of itself, lead the clinician to avoid the use of anesthesia when needed for wound cleansing.

The application of tissue adhesives is rapid and relatively painless. Adhesives also have the advantage that they do not require later removal, as do sutures. They will usually slough off in 5 to 10 days as the keratinized layer of epithelium sloughs. They should be used only topically, not placed within the wound margins. The topical skin adhesives are needleless alternatives to sutures for the closure of most facial lacerations, providing an excellent cosmetic appearance, comparable to that provided by sutures.

Topical skin adhesives can be used in locations that could otherwise be closed with 5-0 or 6-0 nonabsorbable sutures. Topical skin adhesives should only be used in higher-tension areas if subcutaneous or subcuticular absorbable sutures are placed to relieve tension on the skin. They should not be used over high-tension areas or areas involved in repetitive movement, such as joints, unless the wound is splinted and tension-relieving sutures are used. When tissue adhesive application leads to a suboptimal wound edge apposition, antibiotic ointment, petroleum jelly, or bathing can be used to accelerate removal.

For the repair of very small facial lacerations, the butylcyanoacrylates are equivalent to 5-0 and 6-0 sutures or octylcyanoacrylates. In general, the butylcyanoacrylates are more brittle and friable than octylcyanoacrylates and do not allow the same degree of movement and flexibility of the skin.

Staples

Staples can be applied more rapidly than sutures. Staples are associated with a lower rate of foreign body reaction and a lower infection rate. In general, staples are considered particularly useful for scalp, trunk, and extremity wounds (3). They can also be used when time is limited, such as in situations of mass casualties or multiple trauma. On the other hand, they do not allow as meticulous a skin closure as sutures, and their use is limited when cosmetic appearance is of utmost importance. They are slightly more painful to remove than sutures. In experimental animal models, staples have shown lower rates of bacterial growth and lower infection rates than

sutures, although these effects appear to have limited clinical significance.

Adhesive Tapes

Linear wounds in skin subjected to minimal static and dynamic tensions are easily approximated by tape. The relatively lax skin of the face and abdomen is amenable to wound closure by tape. With tape closures, patients are spared the discomfort of suture removal and the development of suture puncture scars. An additional benefit of this technique is that patients need not be subjected to the painful injection of the local anesthetic agent required for suturing.

Surgical tapes are intrinsically less reactive than staples. However, adhesive tapes require the use of adhesive adjuncts (e.g., tincture of benzoin), which are tissue toxic. Although the various surgical tapes have different degrees of adhesion, porosity, breaking strength, and elasticity, tapes alone will not maintain wound integrity in areas subject to tension. They are seldom recommended for primary wound closure in the ED but are often used after suture removal to decrease tension on the wound until they fall off. The outcome of highly select, small, short, linear, low-tension facial lacerations that are closed with surgical tape is comparable to closure with a tissue adhesive (27).

Complex Issues in Wound Care

Bite Wounds

An estimated 1 to 2 million animal bites are treated each year in the United States. The most frequent complication from bites is infection. Dog bites have an infection rate of 1.4% to 30%, cat bites 15.6% to 50%, and human bites 9% to 18% (14). Most bite wounds are minor. Local wound care always begins with a thorough evaluation of the injury. The location, number, type, and depth of wound are noted. The wound is also assessed for signs of infection. Bite wounds are frequently puncture wounds. Meticulous examination is of utmost importance, as they are notoriously deceptive and may be more

extensive than they initially appear to be. The physician should evaluate all bite wounds for injuries to deep structures such as tendons, joint capsules, blood vessels, nerves, and bone. Local or regional anesthetic should be used to facilitate wound exploration, and a proximal tourniquet may be used when necessary to create a bloodless field. If bony involvement or foreign body is suspected, a plain radiograph should be obtained. Meticulous cleansing, irrigation, and debridement are the essential components of all bite wound care. Irrigation of puncture wounds is controversial. Their small openings do not allow the irrigant solution to drain out appropriately. This may result in infiltration of the tissue. Surgical debridement may be necessary to remove compromised or necrotic tissue that may contain embedded organisms, soil, and clots that cannot be removed by irrigation alone.

Primary closure generally should not be performed for human or extremity bites. Primary closure of dog bite wounds is controversial. Recent studies support primary closure of selected dog bite wounds (28). In one study, 145 head and neck dog bite wounds underwent primary closure without the use of antibiotics, and the wound infection rate was only 1.4% (29). Dog bite wounds to the head and neck that are more than 1.5 cm long can be closed primarily with sutures. Small bite wounds (<1.5 cm) behave like puncture wounds and should be left open to allow for drainage. Patients with bite wounds that require reconstructive surgery should be immediately referred to the appropriate specialist. Hand wounds should be managed without primary closure. However, for cosmetic reasons, facial wounds should be repaired. Other bite lacerations can be closed using delayed primary closure techniques. All injured extremities should be immobilized and elevated. Bites are tetanus-prone wounds, and the recommendations for immunoprophylaxis should be followed (Table 21.1). Domestic and wild animal bite victims should be assessed for the need for rabies postexposure immunoprophylaxis (see Chapter 375).

Puncture Wounds

The feet are the most common site for puncture wounds. There are many different views on the management of plantar puncture wounds (14,30). Some physicians prefer expectant therapy, reacting to complications as they develop. Others pursue invasive exploration for and removal of foreign bodies with subsequent antibiotics in the hope of preventing unusual but devastating infections that can develop.

Infections of plantar wounds can often have serious consequences and lead to disability or amputation. Osteomyelitis, osteochondritis, and septic arthritis are the worst of the complications. *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the most common isolates from plantar puncture wound infections. *Pseudomonas* infections are associated with puncture wounds through tennis shoes.

Exploration of plantar puncture wounds for foreign bodies is technically difficult. Foreign bodies that penetrate the plantar fascia are almost impossible to locate through a narrow puncture wound. Irrigation of deep puncture wounds may not be beneficial because the irrigant does not completely drain out of the wound. Some authors recommend enlarging the puncture wound to allow for deeper irrigation and exploration, especially if bone or joint involvement is suspected. Others believe that removing a block of tissue down to the subcutaneous layer allows adequate visualization of accessible foreign bodies and removal of most of the contaminated tissue. Still others simply trim jagged epidermal skin edges. Blind probing and grasping have unknown false-negative rates and may force foreign bodies deeper into the wound. If a wound infection is present, the risk of foreign body is very high, and imaging or exploration is mandated.

Another controversy involves the use of prophylactic antibiotics for this type of injury. Many experts do not recommend the use of antibiotics for new plantar puncture wounds. They argue that antibiotics will not compensate for inadequate initial wound care, they are ineffective in wounds with retained foreign bodies, they may contribute to a gram-negative infection, and wound infections that do not have a retained foreign body respond quickly to initiation of antibiotics. Owing to the difficulty of cleaning and exploring

plantar puncture wounds, physicians should reevaluate these wounds for infection within 2 to 3 days of initial presentation. If infection develops, they should be aggressively explored for a foreign body.

Facial Lacerations

Owing to their cosmetic significance and proximity to important structures, several points concerning the repair of facial lacerations are noteworthy. Because of their rich vascular supply, facial lacerations have a relatively low rate of infection. The risks of high-pressure irrigation (edema making it more difficult to perfectly approximate wound edges) should be weighed against the benefits (cleansing), and individual decisions regarding the use of wound irrigation should be made accordingly. For example, an upper eyelid laceration resulting from a blunt impact with the corner of a table requires minimal irrigation, whereas a contused cheek laceration resulting from a fall onto a rough and dirty surface requires larger volume irrigation.

Whether nongaping facial lacerations require deep sutures is a subject of ongoing debate, but at least one study suggests that nongaping lacerations do not benefit from layered closure (21). Gaping lacerations as well as those in which underlying muscle are involved should be repaired in multiple layers. Meticulous wound approximation should follow important anatomic landmarks such as the forehead or nasolabial creases, the eyebrow, and the vermilion border. When these structures are within a laceration, initial placement of key sutures aligning the landmarks is crucial. Eyebrows should never be removed because they may not grow back.

With lip lacerations, it is important to exclude any underlying dental injuries. If a fractured tooth is not found, careful exploration of the lip wound should be performed to rule out an embedded tooth fragment. Through-and-through lacerations of the lips should be closed in three layers. The first layer should be placed within the oral labial mucosa using a 4-0 or 5-0 absorbable suture. The laceration should then be recleansed now that it is sealed off from the oral flora. The second layer should be placed in the muscle using a 5-0 absorbable suture, and the third layer should be placed in the skin

using a 6-0 nonabsorbable suture. The first suture in the skin should be placed at the vermillion border. Patients should be advised to eat a soft diet and carefully rinse out their mouth after each meal. Prophylactic use of oral antibiotics for lacerations of the oral mucosa that cover oral anaerobes is recommended.

With ear lacerations, it is important to identify any underlying injuries to the cartilage. A field block performed at the base of the ear is helpful with extensive ear injuries. With simple lacerations, primary repair of the overlying skin, ensuring complete coverage of the cartilage, suffices using nonabsorbable 6-0 sutures. Large or gaping lacerations of the cartilage may be closed with a 6-0 monofilament nonabsorbable suture. Any hematoma beneath the skin needs to be evacuated, and a compressive dressing should be placed to ensure adequate contact between the skin and the cartilage. Due to its relative avascularity, necrosis of the cartilage with subsequent formation of a "cauliflower" ear may result if the cartilage is deprived of its vascular supply. With exposure of cartilage, prophylactic oral antibiotic coverage for staphylococcus and pseudomonas is recommended.

With eyelid lacerations, it is crucial to exclude any injury to the lacrimal duct or the tarsal plate. These lacerations, as well as those involving the lid margins and inner surface, should be repaired by a specialist. Bulging of subcutaneous fat suggests violation of the tarsal plate and, along with the presence of ptosis, should always prompt referral. See Chapter 25.

Post Repair Wound Care

Post repair wound care should optimize healing. It must be tailored to both the type of wound and method of wound closure. Sutured or stapled lacerations should be covered with a protective nonadherent dressing for 24 to 48 hours until enough epithelization takes place to protect the wound from gross contamination. Maintenance of a moist wound environment increases the rate of reepithelization. When possible, the site of injury should be elevated above the patient's heart to limit the accumulation of fluid in the wound interstitial spaces.

Topical antibiotic ointments may help reduce infection rates and prevent scab formation. Patients whose lacerations are closed with topical skin adhesives should not have topical ointments applied. They will loosen the adhesive and result in dehiscence.

Prophylactic systemic antibiotic administration should not be used as a regular adjunct to wound care. Several studies and a meta-analysis have found no benefit in prophylactic antibiotics for routine laceration repair (31). Use of antibiotics should be individualized on the basis of the degree of bacterial contamination, the presence of infection-potentiating factors (e.g., soil), the mechanism of injury, and presence or absence of host predisposition to infection. In general, decontamination is far more important than antibiotics. Antibiotics should be used in most human, and extremity bites; intraoral lacerations; open fractures and open joints; or tendon lacerations (3). Additionally, patients with soft tissue lacerations who are prone to the development of infective endocarditis, patients with prosthetic joints and other permanent “hardware,” and patients with lymphedema should receive antimicrobial therapy. Intravenous antibiotics can be given prior to wound care in patients at high risk for systemic complications of infected soft tissue injuries.

Sutured or stapled wounds should be kept clean but can be washed (14). Patients with tissue adhesives may shower, but they should avoid bathing and swimming; prolonged moisture may loosen the adhesive bond. Gentle blotting should be used to dry the area, as wiping could result in dehiscence. Splinting may prove helpful in areas subject to high tension (e.g., in lacerations across joints). Patients should be instructed to observe the wound for erythema, warmth, swelling, and drainage, as these findings, as well as fever, may indicate infection. Use of standardized wound care instructions improves patient compliance and understanding.

Sutures or staples in most locations should be removed after approximately 7 days (Table 21.5). Facial sutures should be removed sooner (within 3 to 5 days) to avoid the formation of unsightly sinus tracts. Sutures subject to high tension (e.g., in joints, hands) should be left in for 10 to 14 days. When tissue adhesives are used, patients should be advised to avoid picking or scrubbing the area and to

avoid exposure of the wound to water for more than brief periods until the previously noted times. When tissue adhesives remain on the skin for prolonged periods, antibiotic ointment, petroleum jelly, or bathing can accelerate removal. Acetone can be used when more rapid removal is required. Patients should be told when and with whom to follow up for suture removal or wound examination. Most wounds do not require scheduled wound checks as patients can be told to watch for the signs and symptoms of infections.

TABLE 21.5
Optimal Time from Placement of Sutures Until Suture Removal

Location	No. of Days
Face	3–5
Oral mucosa	3–5
Scalp	7
Chest	8–10
Back	10–14
Forearm	10–14
Fingers	8–12
Hand	8–10
Lower extremity	8–12
Foot	10–12

Abraded skin and wounds may develop permanent hyperpigmentation after exposure to the sun. Consequently, they should be protected with a sun-blocking agent for at least 6 to 12 months after injury.

Prevention of Tetanus

Two-thirds of the recent tetanus cases in the United States have followed lacerations, puncture wounds, and crush injuries. Proper immunization plays the most important role in tetanus prophylaxis. Recommendations on tetanus prophylaxis are based on the condition of the wound and the patient's immunization history. A summary guide to tetanus prophylaxis of the wounded patient, as recommended by the Centers for Disease Control, is outlined in Table

21.1. As noted, passive immunization with tetanus immunoglobulin is indicated only under specific conditions.

The only contraindication to tetanus and diphtheria toxoids is a history of neurologic or severe hypersensitivity reaction after a previous dose. Local side effects do not preclude repeated use. Local reactions, generally erythema and induration with or without tenderness, are common after the administration of vaccines containing diphtheria, tetanus, and pertussis antigens. These reactions are usually selflimited and require no therapy. If a systemic reaction is suspected to represent allergic hypersensitivity, immunization should be postponed until appropriate skin testing is undertaken. If the use of a tetanus toxoid is contraindicated, passive immunization against tetanus should be considered in a tetanus-prone wound. In those patients who have not completed a primary tetanus immunization series, appropriate follow-up should include referral to a physician who can complete active immunization.

CRITICAL INTERVENTIONS

- Obtain a tetanus immunization history and administer tetanus toxoid if it has not been given within the past 10 years (5 years if the wound is tetanus prone).
- Perform and document a neurovascular assessment distal to the laceration.
- Perform and document a careful wound exploration to exclude foreign bodies and tendon lacerations.

DISPOSITION

The appropriate surgical specialist should be consulted for patients with open fractures of long bones, nerve or vascular injuries, flexor tendon disruptions, repair of specialized structures such as the parotid or lacrimal duct, replacement of skin loss by a flap or graft, or extensive debridement.

Few patients with lacerations will require admission to the hospital. Even those patients requiring surgical intervention can

often be discharged with appropriate follow-up arrangements. Often, definitive repair can be accomplished via same-day surgery.

If the initial receiving hospital does not have the appropriate emergency or surgical specialist, transfer is necessary. The patient should be transferred in the most expeditious manner possible.

Common Pitfalls

- Failure to detect sensory, motor, and vascular complications or injuries to specialized tissues.
- Failure to detect and remove foreign bodies.
- Removing hair with a razor, because it may increase the infection rate.
- Using antiseptic agents such that there is contact between the agent and the wound.
- Using drain placement as a replacement for meticulous hemostasis; drains should be reserved for removal of harmful collections of fluid.
- Using tissue adhesives without appropriate cleansing and exploration.
- Using tissue adhesives in high-tension wounds or over joints.

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PART 2 • SPECIFIC INJURIES

CHAPTER 22 Head Injuries

James F. Holmes and Cindy H. Chang

Traumatic brain injury (TBI) is the most common trauma-related cause of death and disability. Blunt head trauma results in more than 5 million emergency department (ED) visits annually, with more than 500,000 of these patients ultimately hospitalized. Although males of age 15 to 40 make up nearly half of all ED visits for blunt head trauma (1), the prevalence of TBI is bimodal, with peaks in the young and in the elderly (1). Traffic accidents (40%) and falls (30%) are the most common mechanisms. Medical and surgical improvements during the past 30 years have resulted in reduced mortality from TBI. Nevertheless, TBI continues to place a heavy cost burden on society (>$60 billion/year) as well as family and caregivers, because surviving patients of moderate to severe TBI frequently require long-term care.

TBI is typically categorized as primary or secondary brain injury. Primary brain injury refers to the irreversible brain damage occurring at the time of initial impact. Injury prevention and education are the primary tools to reduce the incidence of primary brain injury. These interventions include motorcycle and bicycle helmet laws, seatbelt laws, and alcohol preventive measures. Secondary brain injury includes the insults that occur following the initial impact, such as tissue ischemia, hypoxia, reperfusion injuries, and infection that occur minutes to days later. Both prehospital and hospital interventions are designed to prevent or limit the degree of secondary brain injury.

CLINICAL PRESENTATION

The Glasgow Coma Scale (GCS) is the standard method to describe head-injured patients (Table 22.1). The GCS was initially described in 1974 as a tool to standardize the intensive care unit (ICU) description of patients with significant TBI. This scale has subsequently been modified, including the use of a summation score and application in both prehospital and ED evaluations. Intubated patients should be assigned a "T" in the summation score (e.g., GCS = 7 T) to reflect the inability to assign a verbal score. Patients are categorized by their GCS into mild (GCS 14 to 15), moderate (GCS 8 to 13), and severe (GCS <8) head injury classifications. Some authors include a GCS score of 13 in the mild head injury category, but this is more appropriately categorized as moderate head injury, with up to 25% of patients having TBI on cranial computed tomography (CT). The GCS score is crude and current work is aimed at better classification of patients with TBI (2).

TABLE 22.1
Glasgow Coma Scale

Best Eye Opening	
Spontaneously	4
To verbal command	3
To painful stimuli	2
None	1
Best Verbal Response	
Alert and oriented	5
Disoriented	4
Inappropriate words	3
Incomprehensible sounds	2
No response	1
Best Motor Response	
Follows verbal commands	6
Localizes pain	5
Withdraws from pain	4
Flexure (decorticate) posturing	3
Extension (decerebrate) posturing	2
No movement	1

Patients with TBI frequently have additional injuries that require prompt diagnosis and treatment. Patients should be maintained in cervical spine immobilization until such injury is ruled out. Patients with TBI are at increased risk of having “delayed diagnosis” of their nonhead injuries, as the physical examination is not reliable. Thus, liberal radiographic evaluation is often warranted in those patients with decreased GCS scores.

Epidural hematomas (EDHs) most often occur following damage to an epidural artery (often the middle meningeal artery), typically adjacent to a skull fracture. Injuries to the middle meningeal vein, diploic veins, and venous sinuses can also cause EDH, but these mechanisms are less common. EDH appears as a convex collection of blood on CT scan, resulting from blood dissecting the dura from the inner skull table (Fig. 22.1). The clinical presentation is classically that of a patient who sustains a blow to the head with a brief loss of consciousness (LOC) followed by an awake, lucid interval and then a progressive decline in mental status as the EDH expands. This classic scenario is the exception rather than the rule, however. Patients with EDH require prompt neurosurgical evaluation. Although small EDHs may be managed conservatively with very close observation, symptomatic EDHs require prompt drainage. Morbidity and mortality increase as neurologic symptoms occur.

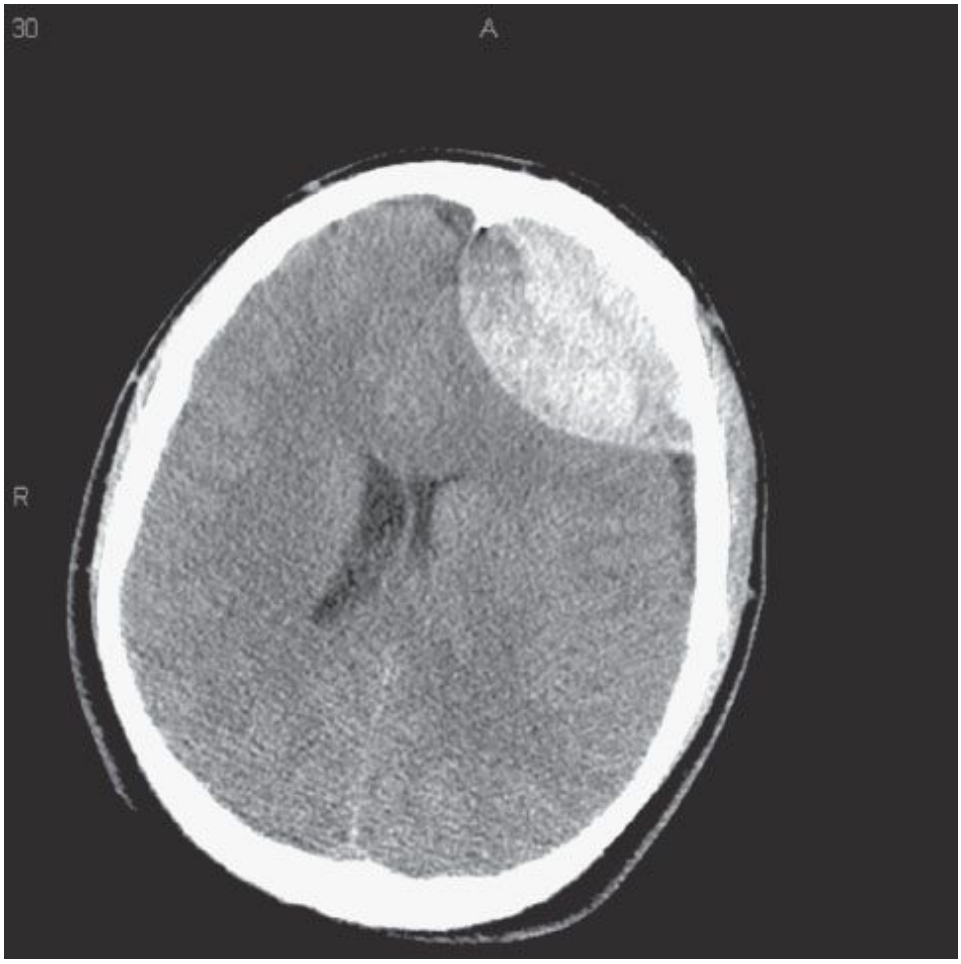

FIGURE 22.1 Left frontal epidural hematoma appears convex as it is restrained in its expansion by the dural membrane. This patient presented with a decreased mental status and decreased movement of his right side.

Subdural hematomas (SDHs) occur with greater frequency than EDHs. The injury is a collection of blood in the subdural space, appearing concave on cranial CT scan (Fig. 22.2). Patients with brain atrophy (particularly alcoholics and the elderly) are at increased risk for SDH because the bridging veins in the subdural space are stretched as brain size decreases. These "stretched" bridging veins are at risk of injury even with minor head trauma. Of all TBIs, SDHs are most likely to have delayed presentations (Fig. 22.3A,B) or present without a history of a significant traumatic event. Some SDHs are managed conservatively, but symptomatic SDH requires

prompt evacuation of clot. As with most TBIs, mortality from SDH increases with increasing patient age. On CT scan, fresh blood from an SDH (and other injuries) appears hyperdense in comparison to brain tissue. From 7 to 14 days after the event, blood becomes isodense with the brain tissue and may be missed if the CT scan is not carefully studied (Fig. 22.3A). Older SDHs appear hypodense compared to brain tissue (Fig. 22.3B).

FIGURE 22.2 Right subdural hematoma appears concave as it tracks below the dural membrane. Note the compression of the right lateral ventricle and the mass effect exhibited by the hematoma as it shifts the brain structures to the patient's left.

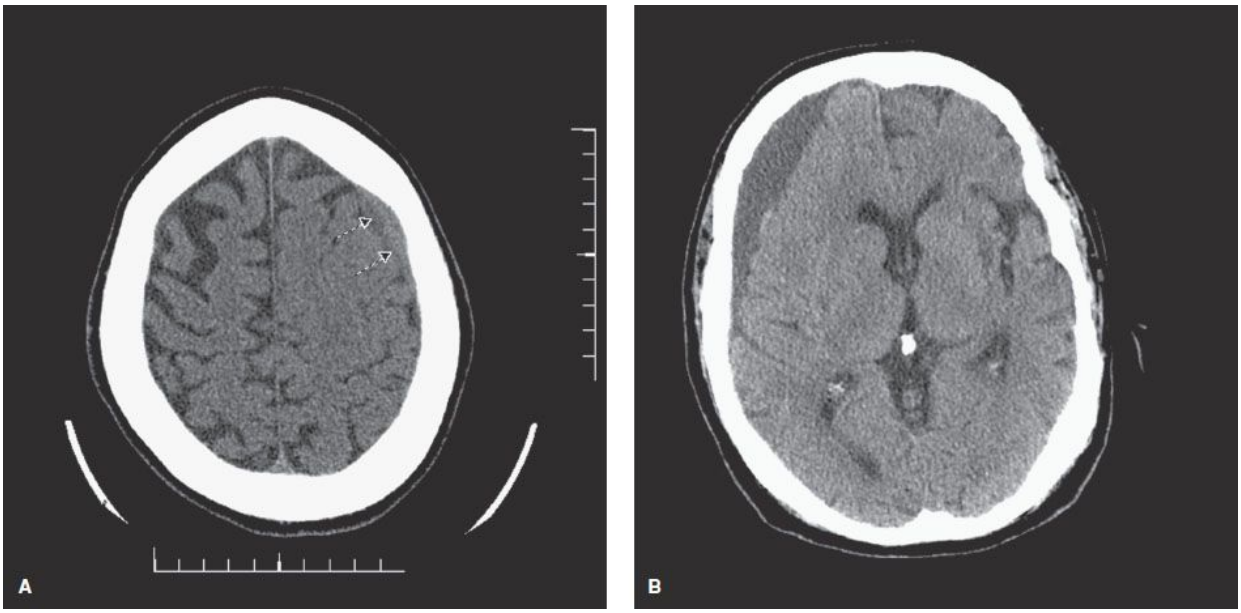

FIGURE 22.3 **A:** Subacute subdural hematoma. The *arrows* outline the isodense collection of blood in the subdural space. Blood becomes isodense on CT scan 1 to 2 weeks after injury. This finding is easily missed if the CT scan is not carefully inspected. **B:** Chronic subdural hematoma. The hypodensity in the right frontal region represents a chronic subdural hematoma. Blood becomes hypodense on CT scan 2 weeks after the injury. Note the small area of hyperdensity within the chronic subdural hematoma. This area represents acute hemorrhage within the chronic subdural hematoma.

Parenchymal contusion is the most common traumatic finding on CT scan following head trauma (1). Contusions are highly variable in size, location, and consistency. They are located anywhere in the brain but are most common in the frontal, temporal, and occipital regions where the skull base has an irregular contour. Size ranges from punctuate (1 mm) hemorrhages to areas several centimeters in diameter. The consistency of the contusion may vary from edematous tissue to necrotic brain tissue to frank hemorrhagic contusion. Contusions frequently evolve throughout time, such that the initial CT scan may show minimal to no contusion, but repeat cranial CT imaging demonstrates the development of a substantial contusion (Fig. 22.4A,B). In addition, contusions can develop over the opposite side of skull impact; these are termed *contrecoup* injuries.

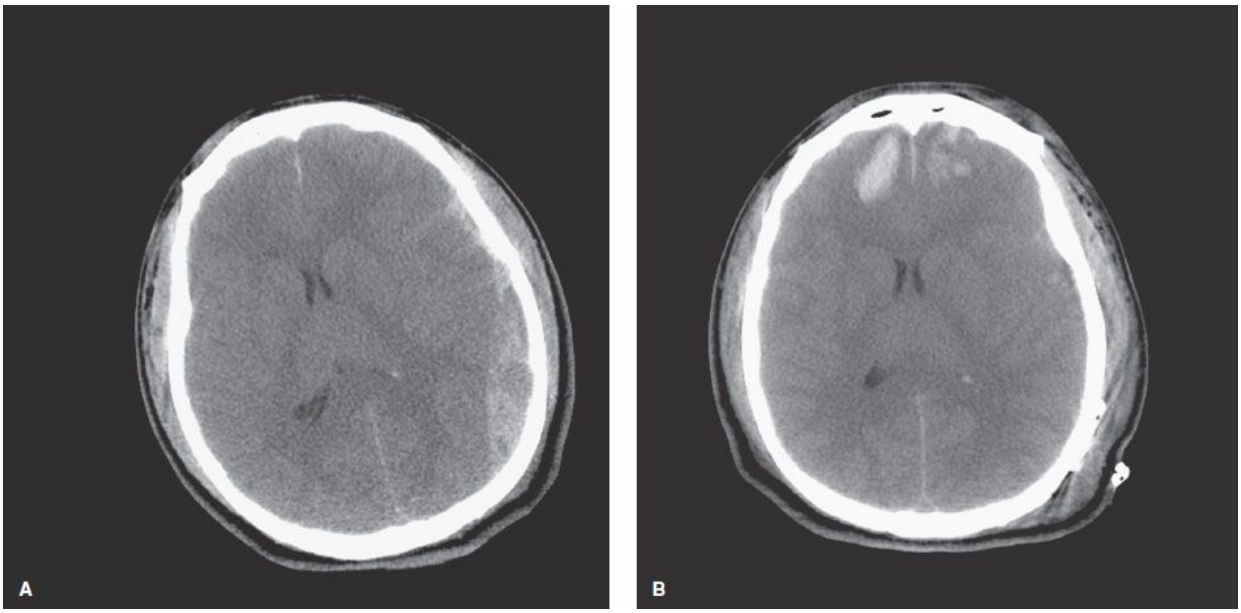

FIGURE 22.4 **A:** Initial cranial CT scan in the ED after acute injury. There is an epidural hematoma (EDH) adjacent to the posterior temporal bone that compresses portions of the left lateral ventricle. **B:** Repeat cranial CT scan in the ICU after craniotomy. The image taken 11 hours after the initial cranial CT scan reveals new bilateral frontal parenchymal hemorrhagic contusions. The previously noted EDH was drained by neurosurgery. Hemorrhagic contusions frequently evolve throughout the initial 24 hours after injury.

Subarachnoid hemorrhage (SAH) is the second most common traumatic finding on CT scan (1). Because the blood disperses within the subarachnoid space, this injury does not usually result in a mass effect. However, coexisting TBIs are frequently present, and the presence of SAH increases the likelihood of morbidity and mortality from these injuries. Cerebral vasospasm occurs 2 to 3 days after traumatic SAH but is generally less frequent and less severe than vasospasm following spontaneous SAH.

Diffuse axonal injury (DAI) occurs when deceleration and rotational shearing forces disrupt axons in the white matter of the brain. The clinical presentation ranges from brief LOC without other clinical symptoms of head injury to coma. This injury is underdiagnosed, as the CT scan is often normal, although cerebral edema and loss of the gray/white junction may be identified.

Magnetic resonance imaging (MRI) is better at characterizing the extent of the injury, although it too may underestimate the degree of injury if there is only limited edema. DAI can be devastating, and no specific treatment beyond supportive care is currently available.

Intraventricular hemorrhage (IVH) is rare and occurs when blood collects within one of the ventricles. In isolation, this injury is unlikely to have clinical implications and can be observed without intervention.

Skull fractures occur after direct blows to the skull and are best identified on CT scan when viewed using a bone window setting (Fig. 22.5). Skull radiographs also demonstrate such fractures, but this radiologic technique has become obsolete with the introduction of CT scanning. Skull fractures are commonly divided into linear, depressed, and basilar types. Basilar skull fracture encompasses the spectrum of fractures occurring along the skull base and is often a clinical diagnosis as CT scanning frequently does not demonstrate the fracture. The temporal bone is the most commonly involved bone, and fractures may be best identified by thin-cut CT scanning. Patients with basilar skull fracture extending into the carotid canal are at increased risk of carotid artery injuries, and CT angiography is thus warranted in these cases. Skull fractures frequently present with associated pneumocephalus (air within the skull) (Fig. 22.5); however, pneumocephalus on cranial CT does not require specific intervention.

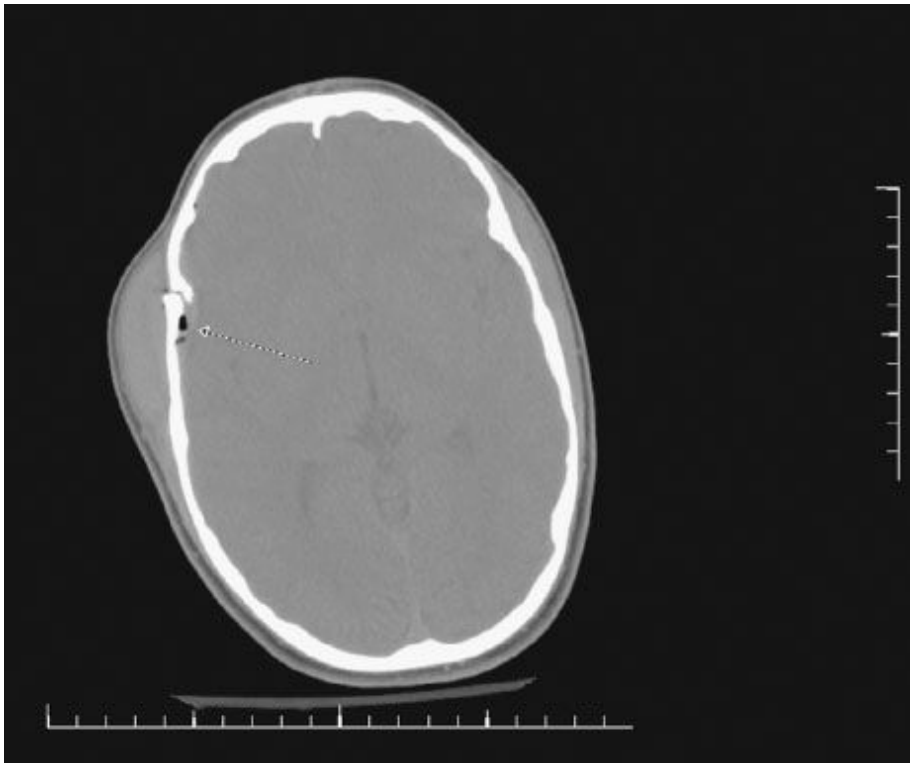

FIGURE 22.5 Cranial CT scan viewed with bone windows. A large cephalohematoma is visible in the right temporal region. The *arrow* identifies a slightly depressed skull fracture and pneumocephalus below the cephalohematoma. The presence of skull fractures and pneumocephalus are best identified with bone windows.

Concussion is the most common type of head injury, often occurring during sports activities. The diagnosis is often given to patients with signs or symptoms of TBI but normal cranial CT scans. Concussive symptoms include traumatic amnesia, headache, nausea, blurry vision, vertigo, sleep disturbance, emotional lability, and difficulty concentrating. Postconcussive syndrome refers to the continuation of these symptoms and may last from weeks to months. The American Academy of Neurology has developed a grading scale and treatment regimen for athletes with concussions (Table 22.2) and recently expanded and updated their recommendations regarding concussion (3). It is imperative that patients sustaining a concussion avoid further head trauma, because repeated concussions pose additive risks. In addition, the Centers for Disease Control

recently developed detailed care plans for patients with concussions (4).

TABLE 22.2
Grading and Treating Concussions in Athletes

	Clinical Description	Treatment
Grade I	Transient confusion, no LOC	
	Concussive symptoms last <15 min	Athlete may return to action once no symptoms for 15 min
Grade II	Transient confusion, no LOC	
	Concussive symptoms last >15 min	Athlete can no longer play in game, may return to contact if no symptoms for 1 wk
Grade III	LOC of any duration	Requires ED evaluation; for brief LOC (<1 min), may return to contact if no symptoms for week; if LOC is prolonged (>1 min), must wait 2 wks without symptoms before return to contact

LOC, loss of consciousness; ED, emergency department.
Adapted from Giza CC, Kutcher JS, Ashwal S, et al. Summary of evidence-based guideline update: Evaluation and management of concussion in sports: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2013;80(24):2250–2257 and Practice parameter: The management of concussion in sports (summary statement). Report of the Quality Standards Subcommittee. *Neurology.* 1997;48(3):581–585.

Traumatic sinus thrombosis is a rare occurrence after injury. Traumatic sinus thrombosis is suspected based upon cranial CT findings and confirmed with MRI and magnetic resonance angiography (MRA). Treatment is controversial but includes heparin if there are no contraindications to such therapy.

Brain herniation is an ominous finding. Transtentorial herniation occurs when a space-occupying mass depresses brain tissue (usually the uncus) below the tentorium. The third cranial nerve is also compressed, resulting in pupillary dilation (“blown pupil”) on the side of the lesion. Subfalcine herniation involves midline shift of the cingulate gyrus, compressing the anterior cerebral artery and producing brain ischemia.

Penetrating head injury occurs most frequently with firearms. Immediate cranial CT scanning is imperative to identify the path of the penetrating object and associated injuries. Shock waves associated with high-velocity bullets damage tissue beyond the bullet's actual path, requiring careful observation for further swelling of the tissue around the tract. Mortality from gunshot wounds to the head is >50% and increases significantly if the bullet crosses the midline. Objects such as knives and nails that are impaled into the skull require cranial CT scanning and neurosurgical consultation to determine the appropriate location for removal (operating suite vs. the ED).

DIFFERENTIAL DIAGNOSIS

The ED presentation of patients with TBI is usually straightforward. Standard protocols for the evaluation and management of the trauma patient are followed, but one must always consider the contribution of underlying medical illnesses to the patient's presenting condition. Careful consideration of both traumatic and nontraumatic causes for decreased mental status will minimize the risks of failing to reach a correct diagnosis. Stroke, seizure, hypothermia, hyperthermia, hypoglycemia, electrolyte disturbances, alcohol intoxication, and drug overdose may all result in decreased mental status and mimic TBI, especially if the patient has some evidence of head trauma. Furthermore, the physician should always consider a medical cause as the precipitant of the traumatic event. Frequently, a complete and reliable history cannot be obtained, and proper management requires maintenance of a broad differential diagnosis and systematic exclusion of medical conditions through appropriate and thoughtful diagnostic testing.

ED EVALUATION

The evaluation of head injured patients starts with prehospital management and transportation to an appropriate facility. The Brain Trauma Foundation developed guidelines for the prehospital management of patients with TBI (5). Prehospital providers typically institute spinal immobilization, oxygenation, and immediate

transport. Although intravenous (IV) access and fluid resuscitation is controversial in the hypotensive patient with penetrating trauma, the hypotensive patient with a blunt mechanism should receive fluid resuscitation to support the blood pressure and minimize secondary brain insults. Prehospital airway management is controversial, as evidence is conflicting (5–8). Reasons for adverse outcomes with prehospital intubation include a combination of hypoxic episodes during intubation attempts and hyperventilation or hypoventilation after definitive airway establishment (7,8). Prehospital rapid sequence intubation is not recommended for patients with short transport times who are spontaneously breathing and are not hypoxic (5). Those prehospital systems electing to include prehospital intubation in trauma protocols must ensure that paramedics have adequate airway experience and that end-tidal CO_2 monitoring is not only available but followed to assure normocarbia.

Prehospital triage protocols should function to match patient needs with the resources available at the destination hospital. Patients with prehospital GCS scores <14 require transportation to the nearest designated trauma center. The hospital destination for patients with minor head injuries (GCS ≥ 14) is more controversial. At a minimum, these patients require transportation to a center with immediate CT scanning capabilities and the ability to rapidly transport if neurosurgical consultation is needed but not available.

Initial ED trauma evaluation centers on the primary and secondary trauma surveys. Proper assessment of the airway, breathing, and circulatory status is critical, as a single episode of hypotension (systolic blood pressure <90 mm Hg) nearly triples the mortality risk and an episode of hypoxia (O_2 saturation $<90\%$) doubles this risk (9). Thus, aggressive evaluation and treatment is essential to prevent complications related to hypotension and hypoxia. Hypotension secondary to brain herniation is an ominous finding and suggests impending death. Cushing reflex (hypertension with bradycardia) also suggests impending death and indicates the need for rapid treatment. Neurologic components assessed in the primary survey include an initial GCS score and identification of any obvious motor deficits (i.e., confirming movement in all extremities).

A detailed head examination and neurologic examination is performed and documented in the secondary survey, although it may not be possible to perform these well in severely injured patients. Care is taken not to delay diagnosis and treatment to perform a detailed examination. However, findings pertinent to patients with head injuries should be documented, including all abrasions and lacerations, violations of the galea and/or the skull, contusions and hematomas, and findings suggestive of basilar skull fracture. Basilar skull fracture is primarily a clinical diagnosis confirmed by the presence of raccoon's eyes (periorbital ecchymosis), Battle sign (mastoid ecchymosis), hemotympanum, or cerebrospinal fluid (CSF) drainage from the nares. Battle sign, and to a lesser degree, raccoon's eyes, are late findings that generally appear 12 to 24 hours after injury. CSF is often difficult to differentiate in patients with epistaxis. The "halo test" aids in the identification of CSF rhinorrhea. Bloody fluid from the nares is dropped on a sheet of filter paper, and a positive "halo test" occurs if a clear halo forms around this fluid, suggesting the presence of CSF. Neurologic examination includes pupillary size and response to light, cranial nerve function, motor and sensory function, deep tendon reflexes, and proprioreception. A focal neurologic deficit suggests a space-occupying brain lesion (Fig. 22.1). All penetrating injuries are identified and documented, as this aids in determining the trajectory of the object. Determining entrance and exit wounds is difficult and does not alter initial patient care.

Brainstem function should be tested in patients with coma. The corneal reflex is tested by lightly brushing the cornea with a sterile cotton swab. Patients with an intact brainstem blink, whereas no response indicates absence of brainstem function. The oculovestibular reflex is tested using the cold caloric test. Injecting ice water against an intact tympanic membrane induces nystagmus; if the eyes fail to move, the brainstem is not functioning.

The secondary survey also includes a detailed history. Alternative sources (family, friends, other witnesses, and paramedics) are sought when the history is not obtainable from the patient. Certain events (e.g., syncope, seizure) may guide the need for a medical evaluation

in addition to the trauma evaluation. The identification of potential risk factors for TBI and thus the need for CT scanning are sought from awake patients and include traumatic amnesia, LOC, headache (location and severity), nausea, seizure, vomiting, neurologic complaints, and visual changes. The patient's past medical history is critical and must include current medications, especially the use of anticoagulants. Patients who take anticoagulants, especially clopidogrel and warfarin, are at increased risk of TBI and its complications. Prompt evaluation, laboratory testing, and cranial CT scanning are critical in all patients on clopidogrel or warfarin, regardless of how minor the head trauma may appear (10). Physicians should be aware of new oral anticoagulants available (Dabigatran, Rivaroxaban, and Apixaban), as the risk for intracranial hemorrhage after blunt head trauma is believed increased but not formally studied.

Radiographic evaluation is central to the ED evaluation and treatment of patients with head injuries. Cranial CT scanning allows rapid identification of TBI and skull fractures so that educated management decisions can be made. The prevalence of TBI on cranial CT scan increases as the GCS decreases, ranging from 2% to 5% in patients with GCS scores of 15% to >90% in patients with GCS scores of 3. There are several CT grading scales, but the Marshall CT grading system is most commonly used and predicts mortality when combined with age and the GCS score (11).

Trauma cranial CT scanning is performed without IV contrast. Thus, cranial CT scanning is obtained prior to any contrast study (chest CT, abdominal CT, angiography), as residual IV contrast mimics SAH on CT. A 4- to 6-hour delay after a contrast study is recommended before undergoing a noncontrast cranial CT scan. However, if the patient's mental status rapidly deteriorates cranial CT should not be delayed, as large space-occupying masses are identified regardless of prior contrast administration.

The indications for cranial CT scanning after blunt head trauma have been the subject of significant research efforts in recent years. Appropriate selection of patients for CT should decrease both the rate of missed TBI and the rate of negative cranial CT scanning.

Cranial CT has inherent risks including radiation-induced malignancy, time, and cost, although these risks should not limit its use in the patient at risk for TBI. Patients with GCS scores <15 require immediate cranial CT scanning. Although some have suggested that selective cranial CT scanning be employed in those with GCS scores of 14, these patients have a risk of TBI on CT scan that approaches 15% and should thus undergo immediate cranial CT scanning (12).

Cranial CT scanning in patients who have GCS scores of 15 is more controversial. The New Orleans Cranial CT rule was developed in patients with ED GCS scores of 15 and a history of LOC (13). This rule had a sensitivity of 100% (95% CI 95, 100%) for TBI on CT scan but a specificity of only 25% (95% CI 22, 28%). The rule's criteria for obtaining a CT scan included headache, vomiting, age >60, drug or alcohol intoxication, deficits in short-term memory, and physical evidence of trauma above the clavicles. The variable "physical evidence of trauma above the clavicles" was the least helpful, and most patients with this variable as their only abnormal finding did not benefit from CT scanning. The Canadian Cranial CT rule was developed on a multicenter population of patients with initial ED GCS scores ≥ 13 and a history of LOC or traumatic amnesia (14). The "moderate risk" criteria using this rule consist of failure to reach a GCS score of 15 within 2 hours, open skull fracture, evidence of basilar skull fracture, vomiting two or more episodes, age ≥ 65, amnesia before impact >30 minutes, and a dangerous mechanism of injury. The rule had a sensitivity of 98% (95% CI 96, 99%) and specificity of 50% (95% CI 48, 51%) for predicting clinically important TBI on CT scan. The dangerous mechanism of injury variable consists of 10 descriptive mechanisms, making it difficult for the busy clinician to remember and use. The NEXUS Cranial CT rule was derived on a multicenter population of patients undergoing cranial CT scanning in the ED (15). This rule was designed to identify a population at such low risk for TBI that cranial CT scan is *not* indicated. The rule consists of age <65, no evidence of skull fracture, no scalp hematoma, no neurologic deficit, normal alertness, normal behavior, no coagulopathy, and no persistent vomiting. The

rule had a sensitivity of 98% (95% CI 97, 99%) and a specificity of 14% (95% CI 13, 14%). Validation of these rules has been difficult but the Canadian CT rule appears to perform best. Unfortunately, implementation of these rules has been challenging and has the potential to increase rate of cranial CT scanning.

KEY TESTING

Together, these and other studies suggest that patients undergo cranial CT scanning in the ED for the following high-risk findings:

- GCS <15
- Head trauma on anticoagulation (i.e., clopidogrel, warfarin)
- GCS of 15 with LOC/amnesia and any of the following
  - Vomiting
  - Age >60
  - Abnormal mental status
  - Evidence of any type of skull fracture

Patients who have a GCS score of 15 and a LOC/traumatic amnesia are also considered for CT scanning, as there is still a small but increased risk of TBI if the patient has any of the following:

- Headache
- Deficits in short-term memory
- Dangerous mechanism of injury
- Alcohol intoxication

With the introduction of CT scanning, skull films have fallen out of favor because of the high false-negative rate and are now limited only to the youngest patients. MRI provides more detail about the extent of TBI, especially parenchymal contusions, DAI, and brainstem and posterior fossa injuries. CT scanning provides better definition of SAH and skull fractures, but MRI is otherwise more sensitive. MRI is more time consuming, expensive, and complicated, and thus it is not routinely used in the ED evaluation of head-injured patients.

Investigators have recently attempted to identify neuro-biomarkers to aid in both appropriate cranial CT utilization and predicting adverse outcomes in those with TBI. S-100B, a protein produced by certain astrocytes, is most studied and levels <0.1

μg/L within 4 hours of injury suggest a very low risk of intracranial hemorrhage on CT. It has, however, failed to demonstrate improvement from clinician judgment and currently, along with other neuro-biomarkers, remains experimental.

ED MANAGEMENT

A definitive airway with a cuffed endotracheal tube is required for patients who are unable to maintain their airway or who have GCS scores ≥ 8. Recommendations for airway management in TBI patients include the use of potentially cerebroprotective agents. Fentanyl and defasciculating dosages of paralytics are recommended, although fentanyl may carry a small risk of inducing hypotension in patients with tenuous volume status. Pretreatment with lidocaine (1 mg/kg IV) to blunt the rise in intracranial pressure (ICP) associated with laryngoscopy and succinylcholine administration is controversial, but the downside of this intervention is minimal (16,17). Oxygenation should be maximized by preoxygenating the patient prior to intubation and providing supplemental oxygen to those who are not intubated. The ventilated patient requires close monitoring of tidal volumes to prevent hypercapnia and hypocapnia; CO_2 levels can be followed with end-tidal CO_2 monitoring or arterial blood gas measurements.

The patient's volume status should be continuously assessed, and fluid resuscitation with crystalloid and blood is provided to support blood pressure. Normal saline is preferred, as lactated Ringer solution is hypo-osmolar and might theoretically worsen cerebral edema. Hematocrit measurements and blood transfusion are indicated to maximize the patient's oxygen-carrying capacity. Recent evidence suggests a target hemoglobin level of 9 to 10 g/dL is warranted in TBI patients. Additional laboratory measurements should include platelet count, coagulation studies, a chemistry profile, ethanol level, toxicologic screen, type and screen, and rapid glucose assessment.

The Brain Trauma Foundation provides evidence-driven treatment guidelines for patients with significant TBI (18). Medical and surgical

treatment in patients with TBI should maximize cerebral perfusion pressure (CPP), which is calculated as mean arterial pressure (MAP) minus ICP (CPP = MAP − ICP). Ideally, CPP is maintained between 50 and 70 mm Hg. Unfortunately, ICP is not initially available in the ED, and treatment must thus be based on clinical findings and cranial CT scan results. Once ICP monitoring is established, treatment is guided by the CPP.

Mannitol is an osmotic diuretic that can be used to reduce ICP. The dosage ranges from 0.25 to 1 g/kg IV as a bolus (not a continuous infusion because of the risk of concentrating mannitol in brain tissue and subsequent worsening of cerebral edema). Mannitol's positive effect on ICP is twofold: (a) immediate plasma expansion, with improvement in red blood cell membrane deformability and subsequent increased cerebral blood flow and (b) increased plasma osmolarity and an osmotic diuresis, leading to a decrease in cerebral edema that is noted by 30 minutes after administration and lasts 90 minutes to 6 hours. Indications for mannitol prior to CT or ICP monitoring include signs of transtentorial herniation or progressive neurologic decline from TBI. Because of its osmotic effect and the risk of hypotension, mannitol should not be administered in patients whose volume status has not been optimized.

Patients with TBI have an increased risk of both early ($\geq$7 days) and late (>7 days) posttraumatic seizures. The prevalence of early posttraumatic seizures ranges from 4% to 25%. Seizures increase ICP and cerebral metabolism, and prophylaxis is thus recommended to prevent their occurrence. Risk factors for posttraumatic seizures include a GCS score <10, EDH, SDH, cortical contusion, and depressed skull fracture. Patients with significant TBI should receive a 7-day course of antiseizure medications. Phenytoin (18 mg/kg IV load), levetiracetam (1 g IV), and carbamazepine (100 mg orally [PO] tid) are preferred instead of valproic acid because of concerns of higher mortality with valproic acid in TBI patients. Seizure prophylaxis is not recommended for the prevention of late posttraumatic seizures, as studies have not shown that it confers a benefit.

Recognition and prompt treatment of coagulopathy, either preexisting or as a result of brain injury, is critical in TBI patients. Patients on warfarin with TBI on cranial CT scan require immediate treatment with plasma once the diagnosis is made. Many centers now administer low-dose recombinant factor VIIa (40 μg/kg IV) or prothrombin complex concentrates to immediately reverse coagulopathy in TBI patients. Trauma-induced coagulopathy occurs in nearly 20% of patients with TBI, as thromboplastin that is released from damaged brain tissue activates the clotting cascade (19). Patients with moderate to severe TBI are at increased risk of coagulopathy, and careful monitoring and aggressive treatment, if necessary, are warranted to prevent progression of the intracranial hemorrhage.

Adequate analgesia and sedation are important in patients with severe TBI. Options include morphine (4 to 10 mg/h), fentanyl (2 to 8 μg/kg/h), midazolam (2 to 5 mg/h), and propofol (20 to 75 μg/kg/min). Propofol improves ICP but has not been shown to improve mortality or 6-month outcomes. Barbiturate coma is only recommended for patients who fail standard medical and surgical treatment.

Isolated linear skull fractures can be observed and may not require hospitalization. Depressed skull fractures may require operative therapy to elevate the depressed bone fragment, and thus neurosurgical consultation is indicated for these injuries. Fractures that are depressed more than the thickness of the skull bone are most often repaired. Basilar skull fractures involving the temporal bone require ears, nose, and throat (ENT) consultation, as the auditory bones may be disrupted, resulting in varying degrees of hearing loss. Meningitis is a rare complication ($<5\%$) in these patients; prophylactic antibiotics are not believed to be effective. Direct measurement of the ICP through a ventriculostomy catheter is recommended in patients with GCS ≥ 8 and traumatic findings on cranial CT scanning although a recent trial questions the benefit of ICP monitoring (20). Some centers employ ICP monitoring in comatose patients with normal cranial CT if the patient is >40 years, has neurologic posturing, or is hypotensive. Treatment is instituted

when ICP is >20 mm Hg. There is no evidence that prophylactic antibiotics at the time of catheter insertion prevent infection. The procedure can be performed in the ED by experienced personnel.

Craniotomy can be lifesaving in patients with TBI. Indications for craniotomy include an expanding mass lesion (EDH or SDH), significantly depressed skull fracture, or penetrating injuries with signs of preserved brain function. Patients with EDH or SDH who have decreased mental status (GCS <13), focal neurologic findings, clinical signs of herniation, or shift on CT require emergent craniotomy for hematoma drainage. Signs predicting the need for craniotomy in TBI patients with an initial GCS score of 15 include vomiting, restlessness, a decline in GCS, severe headache, confusion, and temporal bone trauma (21).

Hyperventilation was once a standard initial therapy for patients with severe TBI because it causes a decrease in ICP. More recent evidence suggests that hyperventilation can be harmful. Routine hyperventilation to a partial pressure of arterial carbon dioxide ($PaCO_2$) of 25 mm Hg is thus no longer recommended, and hyperventilation is avoided during the initial 24 hours of resuscitation. Currently, hyperventilation is recommended only as a final effort to control ICP after other interventions have failed. Steroids have long been used to treat malignancy-induced cerebral edema. However, multiple studies, including a large randomized controlled trial of 10,008 patients (22), have demonstrated increased mortality in TBI patients who receive steroids.

Studies evaluating prophylactic hypothermia for severe TBI have yet to identify a population or specific regimen that reduces morbidity or mortality. Current evidence suggests that hypothermia must be maintained for at least 48 hours followed by slow rewarming to have an impact on mortality. Rapid rewarming is to be avoided as it causes cerebral edema. Additional research is required before this treatment can be accepted. Use of hypertonic saline (3% to 7.5% saline) may improve outcomes in head-injured patients, but a large randomized controlled trial demonstrated no benefit when given in the field. Thus, definitive recommendations await further investigation. Hypertonic saline causes an osmotic shift of free water

from brain tissue, thus potentially reducing cerebral edema in patients with intact blood–brain barriers. Finally, recent work failed to show benefit of administering progesterone in patients with moderate to severe TBI. An ongoing multinational study is currently evaluating tranexamic acid in patients with GCS scores <13 or TBI on CT scan.

CRITICAL INTERVENTIONS

- Determine the need for cranial CT in patients with minor head trauma.
- Establish and maintain a definitive airway, and prevent hypoxia (maintain O_2 saturation $>90\%$) in patients with severe head injury.
- Use adequate volume resuscitation to maintain systolic blood pressure >90 mm Hg.
- Maintain cervical spine protection, and perform appropriate radiologic evaluation (CT scan).
- Administer seizure prophylaxis in patients who are at risk.
- Obtain immediate neurosurgical consultation, and ensure appropriate disposition of patients with significant TBI.

DISPOSITION

Patients with intracranial hemorrhage on their cranial CT scan warrant surgical consultation. The elderly (>65 years) and those with GCS scores <15 are hospitalized in ICUs for close neurologic observation. Disposition of patients <65 years with GCS scores of 15 and intracranial hemorrhage on CT, however, is highly variable (23). Risk for intervention in this population is very low and many can be managed with ward admission or in an ED observation unit, thus saving intensive care resources. Facilities without neurosurgical capabilities must safely transfer patients with intracranial hemorrhage on CT to appropriate treating facilities. Such patients should be transferred expeditiously and should not undergo extensive diagnostic testing that may delay their transfer. Cranial CT scan images, if obtained, must be sent with the patient at the time of

transfer. With expanded electronic and Internet capabilities, cranial CT images can now be digitally transferred to neurosurgeons at the accepting facility.

Patients with mild head injury may be safely discharged home following normal cranial CT scans (24). Appropriate discharge instructions for head-injured patients are essential, especially if the patient is on warfarin or has not undergone CT scanning. Because of the risk of delayed hemorrhage, the most conservative trauma centers may admit patients on warfarin for close observation despite normal cranial CT scans, although the risk of delayed hemorrhage is less than 1% (10). Appropriate ED discharge involves assessing how well the patient can be observed outside the ED and how reliably he or she can be returned to the ED if signs and symptoms of TBI develop. Both the patient and the caretaker should be made aware of the signs and symptoms of progressing TBI (e.g., increasing headache, vomiting, alterations in mental status, and seizure).

Appropriate information and follow-up should be provided to patients with concussions. Athletes with concussions are advised to follow up with a physician and must be asymptomatic for at least 1 week before they are allowed to return to contact sports (Table 22.2) (3,25).

Common Pitfalls

- Failure to recognize the need for cranial CT scanning in patients with minor head injury who are at risk for TBI.
- Failure to identify other causes for decreased mental status in the trauma patient, including alcohol or drug (narcotic) intoxication, medication overdose, hypoglycemia, seizure, hypothermia, hyperthermia, electrolyte disturbances, and stroke.
- Inadequate airway protection in patients with moderate to severe TBI and failure to appropriately fluid resuscitate the hypotensive or marginally stable head-injured patient.
- Inappropriate hyperventilation of patients with TBI. Hyperventilation is a last-ditch effort after other interventions have failed.

- Failure to give appropriate discharge instructions to patients with minor head injury.

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CHAPTER 23 Maxillofacial Injuries

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There is substantial regional variation in the etiology of facial trauma, and in the developed world interpersonal violence has surpassed motor vehicle collisions (MVCs) as the most common cause of facial fractures (1). The use of seat belts as restraint devices in vehicles has been repeatedly shown to result in a decreased incidence of facial lacerations and fractures, whereas the protective effect of airbags is less clearly established in facial trauma (2). Other causes include falls, sports injuries, and gunshot wounds, with gunshot wounds and MVCs resulting in the highest injury severity (1). The most frequently fractured facial bones in descending order are the nasal bones, orbital floor, zygomaticomaxillary complex, maxillary sinuses, and mandibular ramus (1).

CLINICAL PRESENTATION

The presentation of maxillofacial trauma depends largely on the mechanism of injury; understanding the mechanism of injury can aid in predicting the severity and risk for associated injuries. Patients who sustain significant blunt trauma (e.g., MVC) often suffer multiple injuries, and their initial evaluation and stabilization should follow a standard trauma protocol. Neglecting potentially serious chest, abdominal, or pelvic injuries in the multiple-trauma patient with distracting facial deformity is a dangerous error. Facial injuries in women in particular are a marker for intimate partner violence, which is underreported and should be investigated when taking the patient's history. Studies estimate between 1/3 and 2/3 of women who present with facial trauma are victims of intimate partner

violence (IPV), and the most common injuries are to the midface (3). Overall, assaults most frequently involve young males as the perpetrators with alcohol being the main contributing factor. Mandibular, orbital floor, nasal, and zygomaticomaxillary complex fractures most commonly result from assault, whereas MVCs tend to cause more complex midface injury patterns (1).

Victims of penetrating maxillofacial trauma are less likely to have serious injuries to distant organ systems but may experience injury to the globe, brain, or neck. High-velocity injuries have a high rate of airway compromise, with nearly a third requiring urgent airway control, either intubation or a definitive surgical airway (4). The emergency physician must be particularly attuned to both central nervous system (CNS) and vascular injury in penetrating trauma as well.

Airway compromise and management of hemorrhage are the most urgent concerns in maxillofacial injury. Airway problems can result from a posteriorly displaced tongue, dislodged teeth, oral hemorrhage and vomitus, or injury to the soft tissues surrounding the airway. A decision for definitive airway control is based on the patient's level of consciousness, severity of injury, risk for aspiration or airway obstruction by delayed edema, and hematoma formation (5). Clinicians who elect to perform blind nasotracheal intubation should be aware of the rare risk of intracranial placement of the endotracheal tube (6). The risk of delayed airway compromise has prompted some authors to recommend intubating patients who present with significant intraoral blood or moderate-sized hematomas in the neck or face, although definitive support in the literature is lacking (7). For patients who require transfer for definitive care, the emergency physician should consider the risk of developing airway compromise en route to the trauma center and complications may increase with the length of transport. When in doubt, it is best to obtain a definitive airway prior to transport. Given the significant vascularity of facial structures, maxillofacial trauma may infrequently result in enough blood loss to cause hypotension and, rarely, exsanguination. The incidence of severe hemorrhage ranges from 1% to 11%, with the highest incidences

occurring in patients with midfacial fracture (8,9). The tamponade effect of the facial musculature combined with the relative accessibility for direct pressure makes life- threatening hemorrhage in adults relatively uncommon.

DIFFERENTIAL DIAGNOSIS

The sometimes dramatic appearance of facial trauma may distract the examining physician from more serious injuries. Once the airway is ensured and brisk facial bleeding controlled, other life threats must be quickly and systematically excluded. Then, the emergency physician should attempt to specifically address bony and soft tissue facial injuries.

Brain injury is the most common associated injury, occurring in up to 79% of patients with single facial fracture, and 88% of patients with two or more facial fractures (10). Previously, some suggested that facial fractures may decrease the risk for intracranial injury. Recent evidence supports the contrary, noting that patients with facial fractures, especially involving the midface, actually have an increased risk of traumatic brain injury (10). This link suggests that the clinician should have a low threshold for performing head computed tomography (CT) in patients with any facial fracture, especially those who have altered mental status, neurologic deficit, or perhaps a worrisome mechanism of injury. The converse is also true. In one study, 10% of comatose blunt trauma victims had significant unsuspected facial bone fractures that were diagnosed by routine facial CT (11).

The incidence of concomitant cervical spine fracture in the setting of facial fracture is not insignificant, reports range from 1% to 8% with that number increasing with number of facial fractures (10,11). The use of the Nexus or Canadian Cervical Spine Rules provides evidence-based guidelines for cervical radiography and the presence or absence of a facial fracture alone should not determine the need for cervical spine imaging unless it is considered a “distracting injury.” See Chapter 28, “Cervical Spine Fractures” (12). There is some data to suggest that facial fracture is a risk factor for injury to the carotid or vertebral vessels, which is more frequent in blunt

trauma than previously recognized. Recent guidelines recommend imaging (CT angiography) to screen for cerebrovascular injury if the patient has displaced midface or complex mandibular fractures (13).

Loss of vision is another significant concern, occurring in as high as 6% of maxillofacial trauma. Visual testing and red color perception are the most useful tests but not always possible in the unconscious patient. Pupillary size and shape, reactivity to light, lid lacerations and globe tension to palpation may also reveal important clues to ocular or periorbital injury (14,15).

ED EVALUATION

Aside from airway concerns, maxillofacial injuries are seldom life threatening. However, other organ system injuries carry significant morbidity and potential mortality. *After* resuscitation and addressing significant injuries to other organ systems, the emergency physician should perform a thorough and directed examination of the face. Anatomic complexity, swelling, lacerations, pain, and altered level of consciousness pose challenges to an optimal physical examination. A systematic approach can help surmount these challenges.

A complete history, including specifics about the mechanism of injury, should be obtained, ensuring that certain injuries are not overlooked. High-yield general questions include the presence of loss of consciousness, facial numbness, weakness, and visual disturbances. Specifically, for periorbital injuries, the emergency physician should ask about blurred vision, pain on extraocular motion, and diplopia. Monocular diplopia indicates a problem with the lens or retina in a single eye; binocular diplopia that involves eye movement suggests nerve palsy, muscle injury, or entrapment. For midface and jaw injuries, ask about dental malocclusion and trismus.

The emergency physician should begin with inspection and evaluate the patient from multiple perspectives. This should include both the “bird’s eye view” as well as the “worm’s eye view,” which involves inspection from above and below to reveal subtle facial asymmetries. Loss of contours, edema, ecchymosis, and hemorrhage are clues to soft tissue and underlying bony injuries (eFig. 23.1). Facial elongation in the frontal plane can occur with high-grade Le

Fort fractures (“donkey” facies) (16). Ecchymoses around the eyes (raccoon eyes) and over the mastoid areas (Battle’s sign) are associated with basilar skull fractures. Raccoon eyes, which usually take several hours to develop, are nonspecific and may be associated with nasoorbitoethmoid (NOE) injuries, Le Fort, orbital, and frontal bone fractures. Facial function is tested by examining the muscles of facial expression. Patients should be asked to close their eyes tightly, raise their eyebrows, purse their lips, smile, and frown. Fractures of the temporal bone may be associated with a posttraumatic Bell palsy with weakness of the facial muscles on the affected side (16). Difficulty with opening and closing the mouth may be secondary to jaw muscle spasm, or it is less commonly associated with fractures of the mandible, zygoma, or maxilla. Evaluating extraocular motions is just as important as testing facial function. Inability to gaze upward or downward, exophthalmos, or enophthalmos can be associated with periorbital fractures. Pain with extraocular movements suggests an occult periorbital fracture. The eye examination should encompass visual acuity, examination of the anterior chamber and pupil, extraocular motions, ptosis, periorbital sensation, and the swinging flashlight test to assess for a Marcus Gunn pupil (see Chapter 25). The ear canal is inspected for any lacerations or clear fluid leak that may represent cerebrospinal fluid (CSF). Using an otoscope, the tympanic membrane is examined for evidence of rupture or hemotympanum, seen as a purplish bulge of the membrane. This finding is associated with basilar skull fracture and fractures of the mandibular condyles. The external ear is examined for otohematomas, which can result in chronic deformity called “cauliflower ear.” In the nose, the most important findings include septal hematoma and CSF rhinorrhea. A septal hematoma is a bluish colored, bulging septal mass that is tender and boggy to palpation.

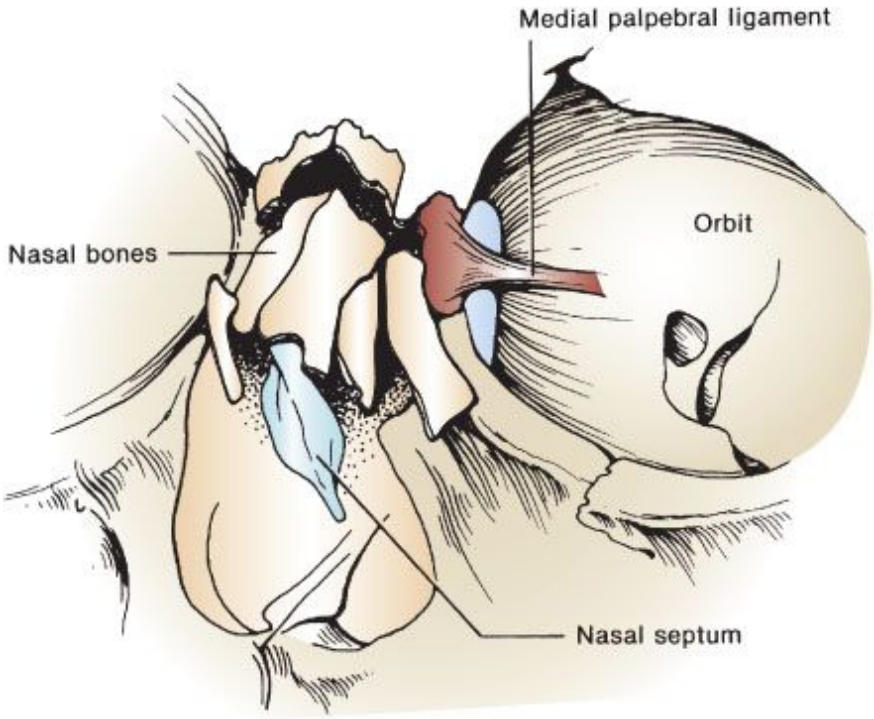
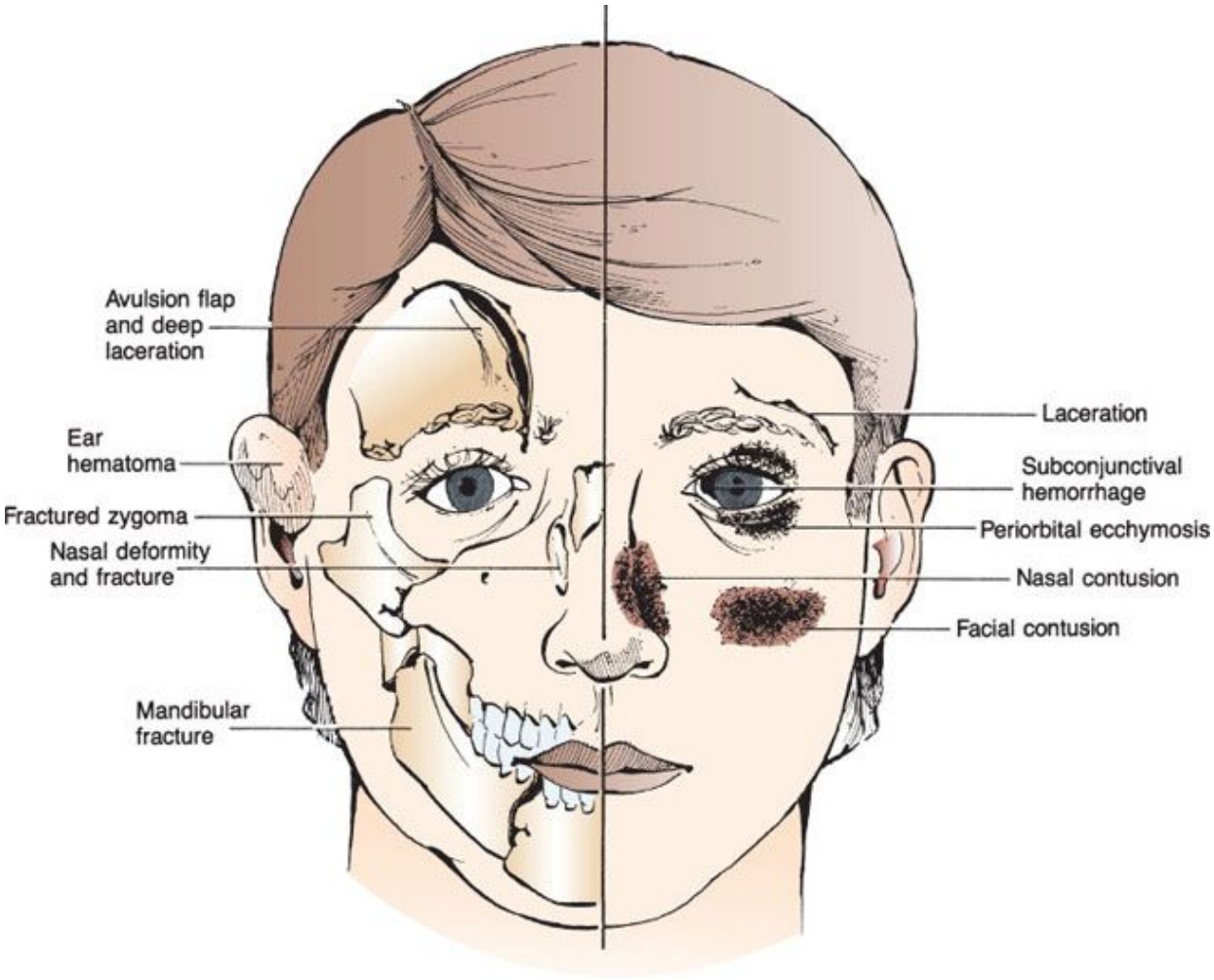


FIGURE 23.1 Nasoethmoidal fractures.



eFIGURE 23.1 Superficial facial injuries provide important visual clues to underlying soft tissue and bony injuries.

The emergency physician should consider testing bloody nasal discharge for CSF. A drop of the bloody fluid containing CSF will demonstrate a target or "halo sign" when placed on a paper towel or bed sheet, because the CSF migrates farther and faster than blood. This test can produce false-negative results with non-CSF fluids mixed with blood, whereas glucose and β-2 transferrin testing are more specific for CSF (10).

Palpation is another important part of the physical examination. The entire face should be palpated for tenderness, step-offs, bony crepitus, and subcutaneous air (often present with fractures involving the sinus). Facial stability is tested by placing a gloved hand in the

patient's mouth, grasping the hard palate, and rocking back and forth while the other hand simultaneously palpates the central face. The physician should be careful to not rock the teeth themselves if dental trauma exists, as dental avulsion may occur.

The final part of the examination of the face is a test for sensation. The branches of the trigeminal nerve are commonly disrupted or contused during facial injury and can cause sensory deficits to the face. The V1 branch of the trigeminal nerve is particularly susceptible to injury in the supraorbital notch. Damage to this nerve can result in anesthesia of the upper nose, eyebrow, and forehead. The infraorbital nerve can be disrupted as it courses through the floor of the orbit and is frequently damaged with orbital or zygomatic fractures. This results in ipsilateral numbness of the lower eyelid, side of the nose, upper lip, gums, and hard palate. Finally, the mental nerve can be injured when there is a mandibular injury resulting in ipsilateral anesthesia to the chin. The presence of facial anesthesia does not necessarily confirm a facial fracture; contusion to the nerve alone can produce similar numbness.

While plain radiographs (e.g., a Waters view, or occipitomental view, for midface fracture) may be effective as a screening tool for some facial fractures, there has been a gradual shift away from this modality (17). Ultrasound has been shown to have diagnostic value, recognizing its limitations with nondisplaced and complex fractures, especially in posterior orbital floor and mandibular condyle where sensitivity is especially low. Data is most impressive for nasal bone fractures, with a sensitivity of 90% to 100% and specificity of 98% to 100% with ultrasound (18). CT, however, is the gold standard for imaging in cases where there is concern for facial fracture with superior sensitivity, speed, cost, and utility in surgical planning (17). Interestingly, several studies have shown that the noncontrasted head CT ordered primarily for ruling out intracranial trauma, has the added advantage of evaluating for orbital, maxillary, and zygomatic fractures, citing sensitivities of 90% to 100% (19,20). The decision to add facial CT to a patient already undergoing head CT can be augmented by specific physical examination findings. Aid in the decision to add a facial CT to a patient's planned head CT may come

from the knowledge that 12% of trauma patients who require a head CT will have facial fractures as well as the fact that complicated orbital fractures may not be fully delineated on isolated head CT (21).

KEY TESTING

- Airway assessment and attention to hemorrhage take precedent, vision-threatening injury should also be evaluated with an ocular examination.
- If suspicion for facial fracture exists based on physical examination, facial CT is the gold standard imaging modality (17).
- Ultrasound shows promise in the diagnosis of facial fracture, in particular there is data showing nasal bone fractures, orbital fractures, anterior maxillary wall, and zygomatic arch fractures can be readily detected (18).
- Head CT should be strongly considered in any patient with facial fracture given the high incidence of concomitant intracranial injury.
- Facial fracture is also a marker of increased risk for cervical spine fracture in trauma, adherence to clinical decision rules is appropriate to determine need for cervical spine imaging.
- CT angiography (16-slice scanner) is recommended to screen for cervical vessel injury with displaced midface and complex mandible fractures (13).

ED MANAGEMENT

Fractures, bleeding, edema, and foreign bodies (such as loose teeth) may occlude the airway and distort anatomy minutes to hours after injury. Thus, it may be prudent to prophylactically secure the airway in patients with evidence of progressive swelling using rapid-sequence orotracheal intubation or an awake intubation. In patients with significant facial trauma, equipment for “backup” cricothyrotomy should be readily available as several factors may qualify them as “difficult airways.” These factors should be assessed

prior to any intubation attempt, including the potential for poor mask seal precluding effective bag-valve-mask ventilation, cervical spine immobilization, and loss of normal landmarks with bony, soft tissue, and vascular injury.

The patient's position on the stretcher dramatically affects the airway. Sitting up and leaning forward is the "position of life" as it clears the airway of blood and displaces any fractured bones or loose tissue forward. The patient can even self-suction blood with one or two Yankauer suction catheters. However, this position is not an option if there is significant concern for cervical spine injury.

Maxillofacial trauma can compromise the airway at the nasal, oropharyngeal, or laryngeal level. If collapse of the nasal airway results from posteroinferior displacement of maxillary fractures, definitive control may be achieved by pulling the face forward using anterior traction on the maxilla (38). The maxillary arch should be grasped above the front teeth to avoid pulling them out of their loosened sockets. If a prolapsed tongue is occluding the oropharyngeal airway (often seen in central mandibular fractures), the tongue can be pulled forward with a traction suture or towel clip. Maxillofacial trauma may also occur in conjunction with direct trauma to the neck, causing airway collapse at the level of the larynx. Cricothyrotomy is possible if the level of injury is above the larynx. In patients with injuries at or inferior to the larynx, endotracheal intubation under direct laryngoscopy may be attempted, but emergency tracheostomy may be necessary. If tracheal injury is inferior to a level at which tracheostomy will provide an adequate airway, emergent consultation with an ENT or thoracic surgeon is warranted (22).

Once the airway is secure and breathing is stabilized, the "C" of the trauma ABCs must be addressed. Although some patients with maxillofacial trauma may be hypotensive, isolated facial injuries rarely cause shock (8). Hemodynamic compromise should be ascribed to other injuries until proven otherwise. The blood supply to the face involves both branches of the external and internal carotid arteries with several anastomoses between each. Generally, if there is ongoing hemorrhage, direct pressure should be applied both

internally to the anterior nares and externally where indicated. Immediate manual reduction of fracture fragments or dislocations may also slow the bleeding. If there is continued blood loss despite these maneuvers, particularly if there is massive nasopharyngeal bleeding, hemorrhage control may be achieved by using posterior nasal packing with either gauze, Foley catheter, or a commercially available nasal balloon (8). Care should be taken with posterior nasal packing to avoid the risk of intracranial placement. The McKesson prop, which is a rubber stopper placed in between the upper and lower teeth to push the midface upward, has also been proposed as a temporizing measure to tamponade bleeding from severe midface fractures (17). Seldom, with maxillary fractures, the posterior pharynx may need to be packed after endotracheal intubation. If hemorrhage continues, arterial ligation or embolization should be pursued (8).

Frontal Bone Fractures

The frontal bone is the strongest bone in the face, consisting of a thick anterior wall that can tolerate as much as 2200 lb of force, and a relatively thin posterior wall. Two-thirds of frontal bone fractures involve both anterior and posterior tables, and given the tremendous amount of force required to break these bones, the incidence of concomitant intracranial and other facial injury is high. These fractures also carry significant potential for infection (23). Therefore, patients with known or strongly suspected frontal bone fractures should undergo head CT scanning and meticulous evaluation for associated injuries, including orbital, nasal, and ethmoid fractures (24).

Frontal sinus injuries are often not obvious; suspicion is based on mechanism of injury (person's head hits the dash of a car or assault with a heavy blunt object such as a brick). On inspection, the emergency physician should look for any depression of the forehead. Glabellar depression indicates fracture of the anterior wall of the frontal sinus. The presence of subcutaneous air indicates sinus disruption, and the supraorbital rims should be palpated for step-off or deformity. Palpation with a sterile gloved finger can help detect

fractures that underlie open wounds. Though rare, posterior wall fractures may result without an anterior wall fracture (24). When testing sensation, it is important to realize that numbness in the distribution of the supraorbital nerve (forehead) may herald an occult fracture. CSF rhinorrhea, if present, indicates involvement of both the posterior wall and meninges (24). Some patients may present with postnasal drip as CSF may preferentially enter the oropharynx. Finally, all patients with frontal bone fractures deserve a thorough ophthalmologic examination due to high rate of concomitant injury.

Although plain films such as Waters and Caldwell views of the face can screen for fracture, if there is significant concern for fracture, axial and coronal CT is indicated to delineate the status of the posterior table and the nasal frontal outflow tract (14). Pneumocephalus is another significant finding which indicates dural violation (25).

Repair of the anterior wall of the frontal sinus can often be delayed; however, fracture of the posterior table requires urgent neurosurgical consultation. When the frontal sinus is fractured, prophylactic antibiotics are generally given. Commonly prescribed antibiotics include first-generation cephalosporins, erythromycin, trimethoprim–sulfamethoxazole, and amoxicillin-clavulanate. However, choice of antibiotics and when to start them is often left to the consultant. In addition, the presence of CSF rhinorrhea associated with frontal bone fractures usually prompts antibiotic prophylaxis by the consultant, although there has been conflicting evidence to the utility of this practice.

Orbital Fractures

Trauma to the orbital regions may range from simple soft tissue swelling around the eye to blindness. Immediate blindness from trauma is rare and is generally permanent, but delayed loss of vision is possible (15). A majority of blindness results from globe rupture; however, damage to the optic nerve (directly or indirectly) and retinal detachment can also lead to a loss of visual acuity. In addition, direct ocular trauma can produce a traumatic iritis. Injuries

occurring as a result of trauma to the globe are discussed in detail in Chapter 25.

Fractures of the orbit are either “pure” or “impure.” Pure fractures affect only the internal orbit without orbital rim involvement, whereas impure fractures include the orbital rim. The blow-out fracture (eFig. 23.2) is a pure internal orbital fracture, usually involving the floor and medial portion of the orbit (24). These fractures occur with either direct force to the orbital rim or when a blunt force strikes the globe. Blow-in fractures consist of fractures and collapse of the orbital roof, which are strongly indicative of intracranial injury. If the fracture propagates to the orbital apex, it can place the optic nerve in jeopardy. This is called *orbital apex syndrome* and is an emergency if there are clinical or radiographic signs of optic nerve impingement (23).

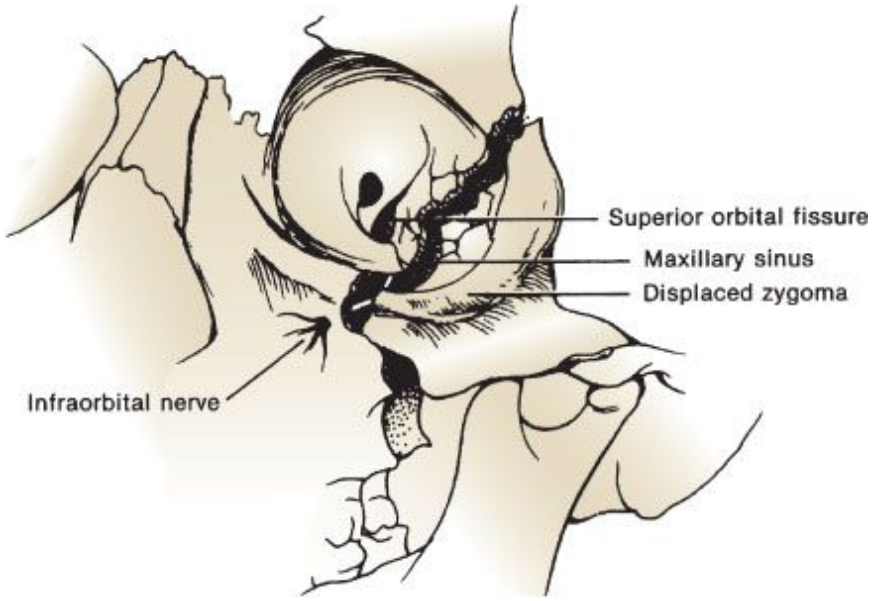
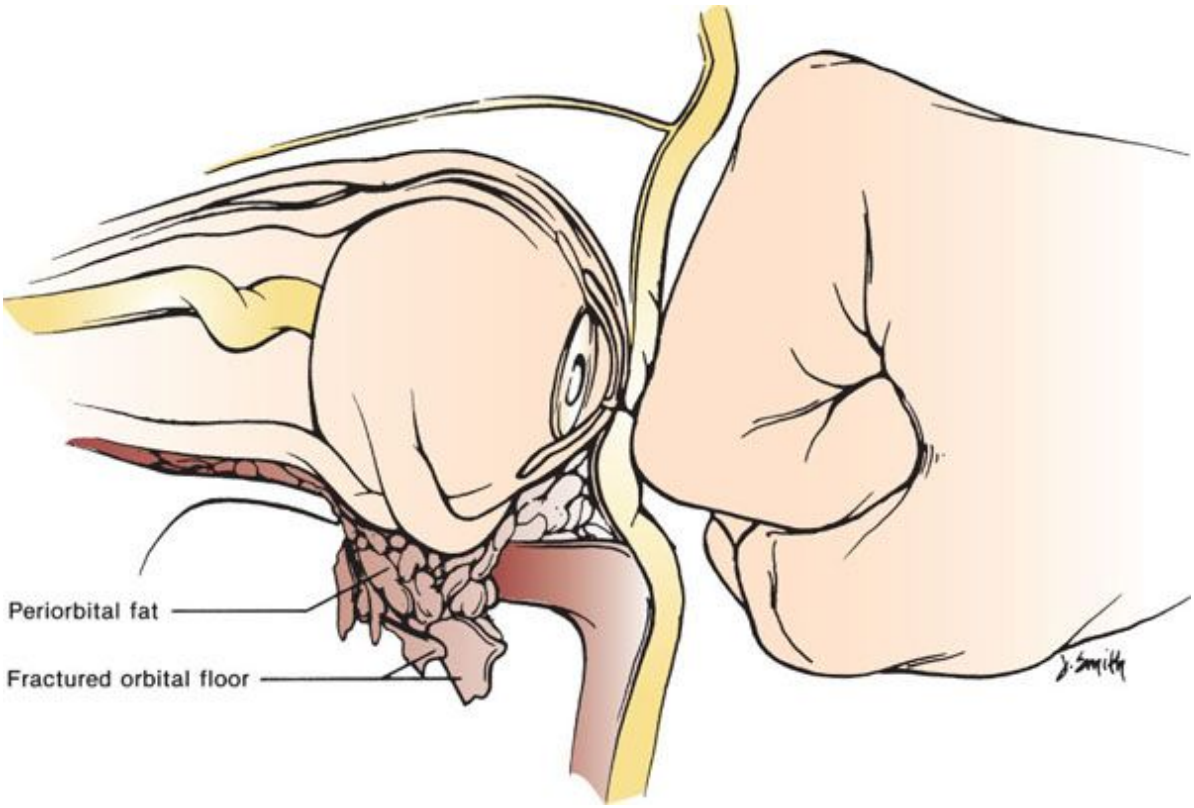


FIGURE 23.2 Zygomaticomaxillary complex fractures.



eFIGURE 23.2 Blow-out fracture.

The patient's orbital region should be inspected for eyelid edema, lacerations, ecchymosis, enophthalmos (sunken globe), hypoglobus, proptosis, or obvious inability of the patient to deviate the involved eye. If the patient cannot look up or complains of diplopia on upward gaze, inferior rectus muscle entrapment associated with orbital blow-out fractures should be considered (26). However, most diplopia is a result of muscle hematoma or nerve injury and not a result of true muscle entrapment. The orbital rims should be palpated for bony step-offs or crepitus, which may indicate a fracture involving the sinuses. When palpating for irregularities, the unaffected side should be palpated for comparison, because the supraorbital and infraorbital nerve foramina can masquerade as fractures (24). Finally, the patient should be asked about numbness of the cheek, maxillary teeth, or upper lip. Paresthesias in these areas suggest a contusion or disruption of the infraorbital nerve (24). When there are findings consistent with fracture in the orbital region, the emergency physician's first step is a meticulous

evaluation of the globe. The ocular examination takes precedence because certain injuries (e.g., globe rupture) benefit from early diagnosis and management, and an adequate examination may be impossible as swelling progresses. In a patient with acute orbital trauma, the two most important ophthalmologic functions to evaluate are visual acuity and extraocular muscle mobility. If the eyelid is too swollen to allow for retraction and therefore an evaluation of visual acuity, light perception should be documented to ensure optic nerve integrity. When in doubt, involvement of ophthalmology is prudent. Retrobulbar hematoma, or more rarely, subcutaneous emphysema creating ocular compartment syndrome, must also be addressed emergently if a tense proptotic globe with decreasing visual acuity is identified. Lateral canthotomy should be performed in consultation with an ophthalmologist to prevent optic nerve ischemia, and mannitol, acetazolamide, and steroids may further decrease the possibility of optic nerve ischemia in the presence of increased intraocular pressure (26). Once ocular injuries have been identified, attention shifts to imaging of the orbital region. Plain radiographs are no longer recommended as screening tools as CT is the preferred test (27). Classic radiologic signs include the "hanging teardrop," which appears when orbital fat herniates into the maxillary sinus, and air/fluid levels in the maxillary sinus.

Management of orbital blow-out fractures remains controversial but phone consultation with plastic surgery on call provides crucial follow-up. In addition to consultation, the following guidelines provide a reasonable basis for decision making in the emergency department (ED). In cases associated with minimal displacement, no entrapment, and no diplopia, the patient may be treated as an outpatient with head elevation, ice, pain medication, and surgical follow-up within several days (28). Absolute indications for surgery include acute enophthalmos, hypophthalmos, or muscular entrapment with mechanical gaze restriction, even despite lack of extraocular muscle entrapment on CT (23). Contraindications for urgent surgery include hyphema, retinal tears, and globe perforation, as soft tissue injuries of the eye may be aggravated by surgery for blow-out fractures. Timing of surgery is also controversial especially

in the multiply injured patient and is a decision to be made by the consultant(s). Patients should be refrained from nose blowing, which can increase the risk for rare, but significant, orbital subcutaneous emphysema (29). If there is significant subcutaneous emphysema or other evidence of fracture into the maxillary sinus, some physicians prescribe prophylactic antibiotics against sinus pathogens, although the utility of this practice has not been studied in a prospective manner (23). First-generation cephalosporins, trimethoprim–sulfamethoxazole, or amoxicillin–clavulanate are often employed.

Nasal Fractures

Nasal bone fractures are the most common facial fracture, and can result in chronic deformity and nasal obstruction (30). Isolated nasal bone fractures typically do not require emergent treatment unless there is significant epistaxis or septal hematoma. A more severe injury involves trauma to the bridge of the nose and includes fractures of the medial orbital wall. This is termed a *NOE fracture* and can involve disruption of the cribriform plate with associated CSF rhinorrhea or intracranial injury (22).

Evaluation begins with a detailed history. The patient should be asked about previous nasal fractures and whether the nose looks normal, as nasal deformity can be secondary to either old or new trauma. Another important question regards difficulty breathing through the nose.

The nose should be inspected for swelling, ecchymoses, and deformity and palpated for crepitus. The emergency physician should move the nasal pyramid to both sides to detect any mobility. Using a nasal speculum inside each naris, the physician should note the position of the nasal septum and examine for lacerations and septal hematoma, which will appear as a bulging blue mass that is boggy to palpation with a finger or cotton swab. Any fluid from the nose should be tested for CSF.

Nasal bone fractures are often diagnosed by history and physical examination alone. Nasal bone radiographs have no clinical utility as they do not affect management (31). If there is no misalignment of the nose, the only treatment includes ice packs and analgesia. If the

patient presents immediately with deformity and significant swelling has not developed, closed reduction using local anesthesia and manual pressure with or without forceps can be attempted according to the comfort and experience of the emergency physician. More often, soft tissue edema precludes adequate examination and the patient should be referred to ENT or plastic surgery as an outpatient. Often, open or closed reduction will be performed within 5 to 7 days, after swelling has subsided. Indications for immediate treatment include CSF rhinorrhea, the presence of septal hematoma, and lacerations with exposure of the underlying bony or cartilaginous elements (30).

Septal hematomas, if not drained in the ED, can lead to abscess formation or necrosis of the nasal cartilage, with resultant saddle nose deformity especially if the hematoma is bilateral. To drain a septal hematoma, the nasal mucosa is anesthetized with a topical anesthetic, and a no. 11 blade is used to make a mucosal incision through the inferior portion of the hematoma, excise a small amount of mucosa. The clot should be suctioned and the area irrigated before the nostril is packed in similar fashion to that for anterior epistaxis. The patient should be put on broad spectrum antibiotics and packing can be removed when there is no hematoma for 24 hours (32).

Nasoorbitoethmoid Fractures

NOE fractures result from significant forces to the bridge of the nose or medial orbital wall and rarely occur as isolated events. These injuries involve the central portion of the midface (the nasal bones, frontal processes of the maxilla, and ethmoid bones) (Fig. 23.1) and may result in a fracture of the cribriform plate with subsequent CSF leakage (22). In addition, these fractures may be associated with dural tears or lacrimal disruption.

A thorough history of the mechanism of injury can be helpful in making the diagnosis typically this will be high-energy blunt trauma. On examination, asymmetry or widening of the nasal bridge between the eyes should be noted (telecanthus) as this is the most troublesome permanent defect resulting from these fractures. The distance between the medial canthi is normally about half the

interpupillary distance (approximately 32 to 35 mm for Caucasians). An increase in this distance suggests an NOE fracture. Also characteristics of NOE fractures are a flattened nasal bridge, enophthalmos, and epiphora (tears pouring over the eyelid) (33). These findings are increasingly difficult to detect as swelling progresses. Palpation of the medial orbital rim especially at the medial canthus may reveal crepitus, tenderness, or movement of bony fragments.

Plain radiographs are not useful in the diagnosis of NOE fractures because of thin bones and complex anatomy. Radiographic assessment should be performed with a facial CT scan with fine-cut axial and coronal images.

The emergency physician's role in management of the patient with an NOE fracture is to make the diagnosis and to rule out associated lacrimal system injury or dural tear. NOE fractures should be repaired no later than 10 to 14 days, but if an NOE injury is identified, the patient will generally be admitted by a facial surgeon.

Zygomatic Fractures

The zygoma is a prominent bone in the lateral portion of the facial skeleton that attaches to the maxillary, frontal, and temporal bones. Occasionally, the zygoma is fractured exclusively through its body. However, because of the thickness of this bone, fractures often extend through weaker areas of the orbit and maxilla. Fractures through the suture lines where the zygoma attaches to the three adjacent bones are termed *tripartite, tripod,* or *zygomaticomaxillary* fractures, whereas fracture through the arch of the zygoma are termed (not surprisingly) *zygomatic arch fractures* (Fig. 23.2).

History and physical examination reliably detect most zygomatic fractures. The mechanism of this injury is usually a direct blow to the cheek with a bat or fist. The patient may complain of pain with, or difficulty in, opening the mouth, which can be a result of impingement of the bone fragment on the temporal muscle or coronoid process The patient's range of mouth opening should be >30 mm; if it is less than this or there is cheek pain with jaw movement, a zygoma fracture should be suspected (26). Inspection of

patients with zygomatic injuries may reveal flattening of the cheek or a downward orbital tilt secondary to disruption of the lateral canthal ligament. Lateral subconjunctival hemorrhage may be an important clue to an associated zygoma injury. Further examination may reveal binocular diplopia secondary to damage of the extraocular muscles or entrapment. Up to 90% of patients with blunt zygoma trauma will have hypesthesia in the infraorbital nerve distribution (26,34). Palpation of the zygomatic arch is accomplished by the intraoral approach (the index finger is placed along the outside of the upper rear molars to palpate the arch intraorally). A crushed arch may not permit an examining finger to slip under the arch on the involved side as compared to the opposite side (26).

If an isolated arch fracture is suspected, a submentovertex view, or "jug-handle" radiograph, may aid in diagnosis. If a tripod fracture or other complex fracture is suspected, a facial CT with fine cuts through the maxilla and orbit is indicated. Surgical consultation for possible open reduction and internal fixation should be obtained for these fractures, but treatment is often delayed until swelling has subsided and a complete evaluation can be preformed. In patients with isolated fractures of the zygomatic arch, ED management is limited to analgesia and surgical follow-up within several days. All patients with suspected fractures of the zygoma should avoid nose blowing to decrease the incidence of subcutaneous emphysema (26).

Maxillary Fractures

Maxillary fracture is the most common finding in patients who sustain penetrating facial trauma. In blunt trauma, maxillary fractures are often associated with other significant traumatic injuries, as these bones require considerable force to break. The Le Fort classification system is used to describe maxillary fractures and by definition all involve the pterygoid plate. In actual practice, pure Le Fort fractures are much less common than unilateral or bilateral mixed maxillary fractures (e.g., left Le Fort I with right Le Fort II).

- Le Fort I
  - Transverse line separates the hard palate from the surrounding bone (Fig. 23.3).

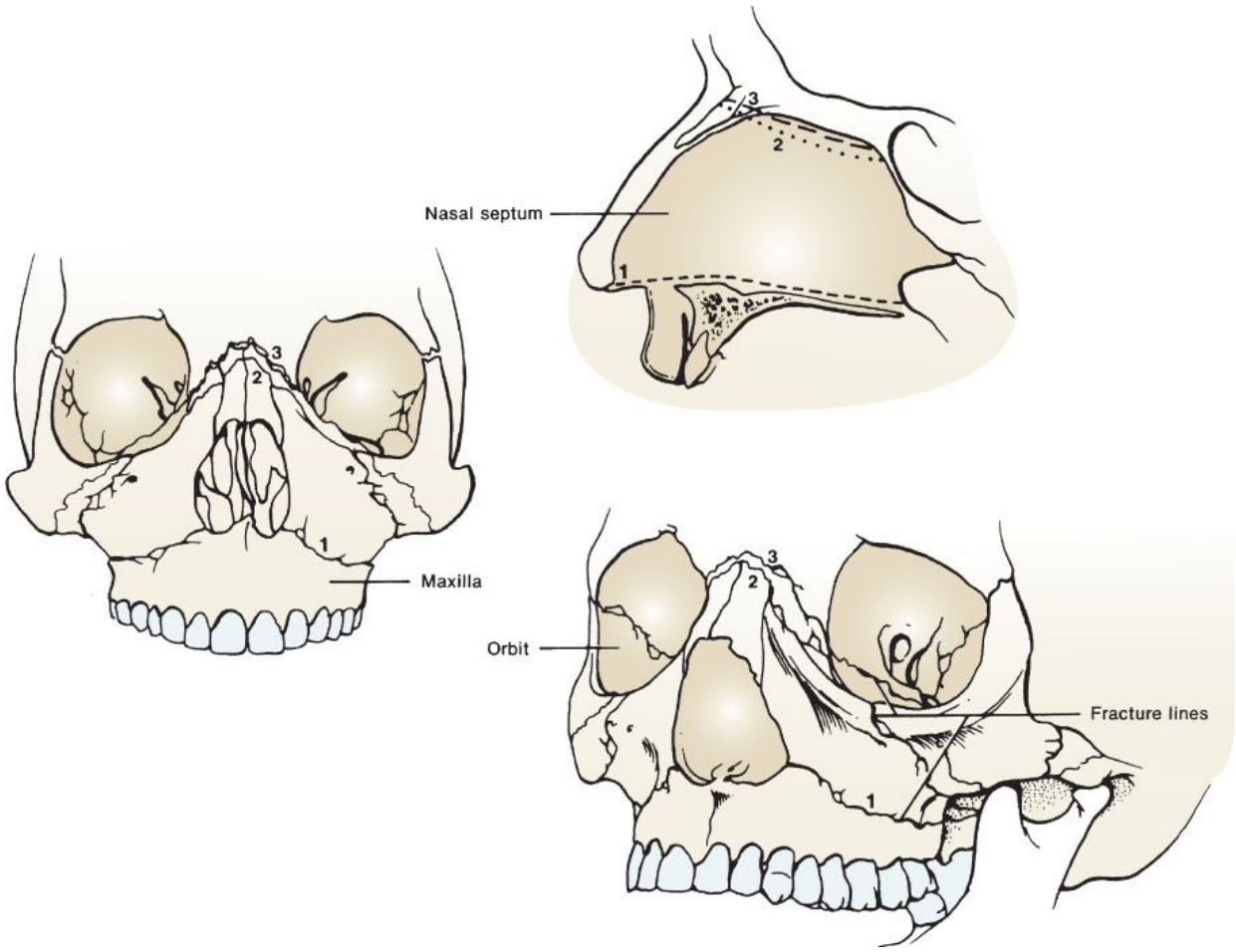


FIGURE 23.3 Lines of fracture in Le Fort I, Le Fort II, and Le Fort III fractures are shown from different views.

- "Floating palate," may involve dental mobility but nose does not move.

- Le Fort II
  - Pyramidal fracture line extends into the orbital floor and inferior orbital rim, separates central maxilla and palate from the rest of the face
  - Mobility of maxilla and hard palate is appreciable.
- Le Fort III (Craniofacial dysjunction)
  - NOE, zygomas, and maxilla are separated from calvarium.
  - Maxillary excursion reveals facial mobility, globes are kept in place by the optic nerve.
- Le Fort IV

• Le Fort III with associated frontal bone fracture.

Fractures of the maxilla are often associated with significant facial edema and bleeding, which may make diagnosis by inspection difficult. The emergency physician should note any asymmetry or loss of contour; an elongated oval or donkey face may be seen with high-grade maxillary fractures. Orbital ecchymosis, lengthening, and edema of the middle third of the face, and malocclusion are also present with Le Fort type II and III fractures. Facial nerve injury may also accompany maxillary fractures, with resultant facial muscle paralysis, and sensory deficits in the infraorbital distribution should be noted. When there is trauma to the lateral midface, the physician should carefully examine cheek wounds for clear or pink fluid leakage (saliva), representing possible parotid duct damage. Alternatively, blood may be expressed from the parotid duct located adjacent to the maxillary molars when the parotid gland is massaged. Providers should also be vigilant for CSF leaks presenting with rhinorrhea with Le Fort type II and III fractures.

Palpation of the maxillary structures follows inspection with special attention given to bony crepitus and abnormal mobility of the face upon stress maneuvers. To stress the face, the examiner firmly grasps the upper palate and rocks back and forth, checking for abnormal midface mobility with the other hand (eFig. 23.3). In patients with facial mobility, the fracture is further characterized by delineating the mobile portions of the face.

eFIGURE 23.3 Checking for abnormal midface mobility.

Severe epistaxis is commonly associated with maxillary fracture, with the internal maxillary artery being the most frequent culprit. Anterior and posterior nasal packing and fracture reduction can often decrease facial hemorrhage, although care should be taken with posterior nasal packing as intracranial placement of a Foley or commercial packing material could occur (2). If basic measures to tamponade have failed and life-threatening hemorrhage continues, arterial ligation or transcatheter arterial embolization are the next steps to address ongoing hemorrhage (8).

CT scan is required to delineate the extent of bony and soft tissue injury if there is suspicion for midface fracture, plain films are not sufficient. Penetrating trauma to the midface can involve injury to the brain and major vascular structures in the head and usually requires CT of the brain and occasionally diagnostic angiography. Multislice CT angiography have been recommended in cases of

displaced midface fracture to screen for cerebrovascular injury (13). Surgical specialists should be consulted early when significant maxillary fractures are identified, early versus late repair will be determined by coexistent injuries.

Mandible Fractures

After nasal bone fractures, the mandible is the most commonly fractured facial bone. Because of its ring shape, the mandible is frequently broken in more than one place; one series found that more than half of mandibular fractures occur in at least two locations (35). Areas of the mandible that are most commonly fractured are the mandibular condyle, body, and the angle (Fig. 23.4).

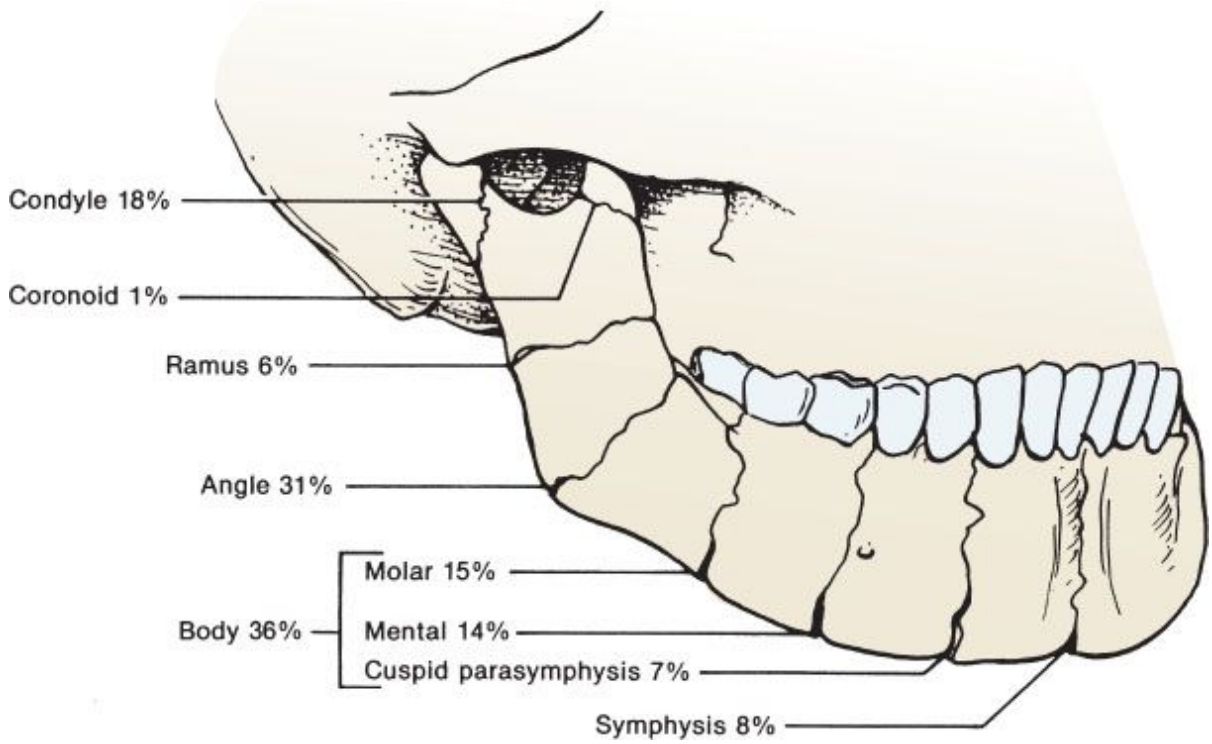
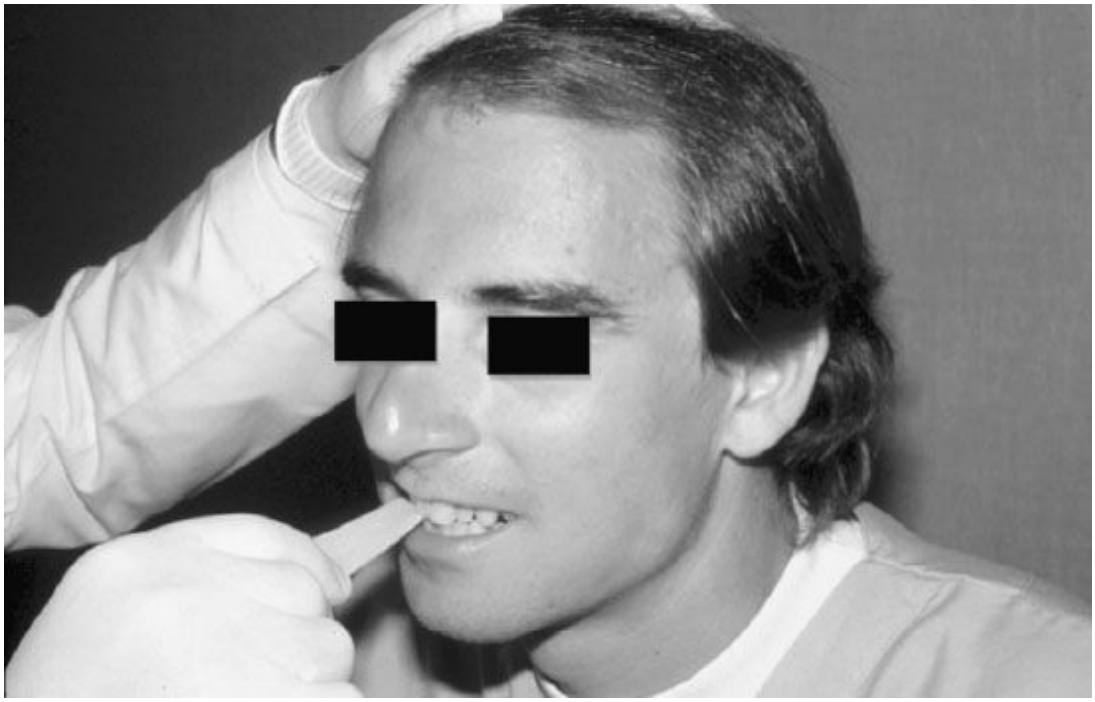


FIGURE 23.4 Mandible fractures: sites and incidence.

Patients should be asked whether their teeth fit together normally, as many fractures of the mandible or maxilla result in malocclusion. The proprioceptive receptors of the teeth allow for detection of as little as 1 to 2 mm of bite discrepancy (34). Then, the patient should be asked whether there is jaw pain with opening or closing of the

mouth, and sensation should be assessed in the mental nerve distribution of the lower lip and chin. During the physical examination, the patient's jaw is inspected for asymmetry. When a fracture is present, the chin is often deviated toward the injured side; with a unilateral dislocation, the jaw is deviated away from the injured side. Traumatic dislocation from acute blunt trauma is rare; fractures are far more common. Edema, bleeding, and hematomas can also provide evidence of fracture. Particularly, preauricular swelling or bleeding from the external auditory canal may indicate a condylar fracture, which can be notoriously difficult to identify on plain radiographs. A careful intraoral examination is of paramount importance to evaluate for open fracture, including any tenderness or irregularities in the contour of the mandible or altered dentition. A sublingual hematoma, although not common, is strongly suggestive of mandibular fracture. Normal condylar excursion should be assessed by placing the examiner's fingers into the external ear canals and instructing the patient to open and close the mouth. In the patient with pain but without obvious fracture, the tongue depressor test has been shown to be a useful clinical tool to rule out mandible fracture with a sensitivity of 95% (36). A positive test, suggestive of possible fracture, is elicited when the patient reflexively opens his mouth when a tongue depressor clenched between the teeth on the side of the fracture is twisted by the examiner. Normally, a patient should be able to break the tongue blade when it is twisted between the teeth (eFig. 23.4).



eFIGURE 23.4 Tongue blade test.

CT scan has surpassed plain radiographs as the gold standard for diagnosis of mandibular fractures and have been shown to have greater sensitivity and utility in operative planning (14,37). The panoramic radiograph (Panorex) still holds some utility in defining dentition even after CT. Although evidence for prophylactic antibiotics in mandibular fractures is poor, standard practice is to give intravenous antibiotics for open mandibular fractures to cover oral pathogens (38). Penicillin G (2 to 4 million units IV) is the drug of choice, with clindamycin (600 to 900 mg IV) and first-generation cephalosporins serving as alternatives. Open fractures require admission for operative treatment, whereas most closed mandibular fractures can be treated on an outpatient basis with open reduction and internal fixation 3 to 5 days after injury to allow for swelling to decrease if patient comfort allows. A Barton bandage (Ace bandage wrapped around the head and jaw) and soft or liquid diets are helpful in cases of delayed repair.

Mandibular Dislocations

The temporomandibular joint is also subject to dislocation; this may occur during yawning, singing, or other movements that involve opening the mouth very widely. Dislocation can also occur during seizures, dystonic drug reactions, dental procedures, or more rarely after blunt trauma. Dislocation is often recurrent.

With mandibular dislocation, the history is often difficult to obtain because the patient has difficulty speaking. During inspection, asymmetry of the jaw is a clue to the diagnosis. A unilateral dislocation will often cause deviation of the mandible away from the affected side. A bilateral dislocation of both condyles will give the patient an underbite appearance (bottom teeth more anterior than upper teeth). The teeth will not occlude normally, and speech is often affected. Often there is significant masseter muscle spasm that can make reduction difficult.

Mandibular dislocations can be reduced by the emergency physician, sometimes requiring benzodiazepines or local anesthetic to relax the masseter or pterygoid muscles. Occasionally, conscious sedation may be required. There are two simple reduction techniques that are most often employed. In the first technique, the clinician faces the patient with thumbs wrapped in gauze to avoid being bitten. The physician's thumbs are then placed under the posterior molars or on the mandibular ridge and the inferior surface of the mandible is grasped placing downward pressure on the molars. This will free the condyles and allow them to be pushed forward into place (28). In the second technique, the clinician stands behind the patient with gauze-wrapped thumbs on the posterior molars and fingers grasping the mandible anteriorly. Pressure is exerted downward and forward until the joint snaps into place (eFig. 23.5). An alternating rocking motion between right and left sides may help in reduction.

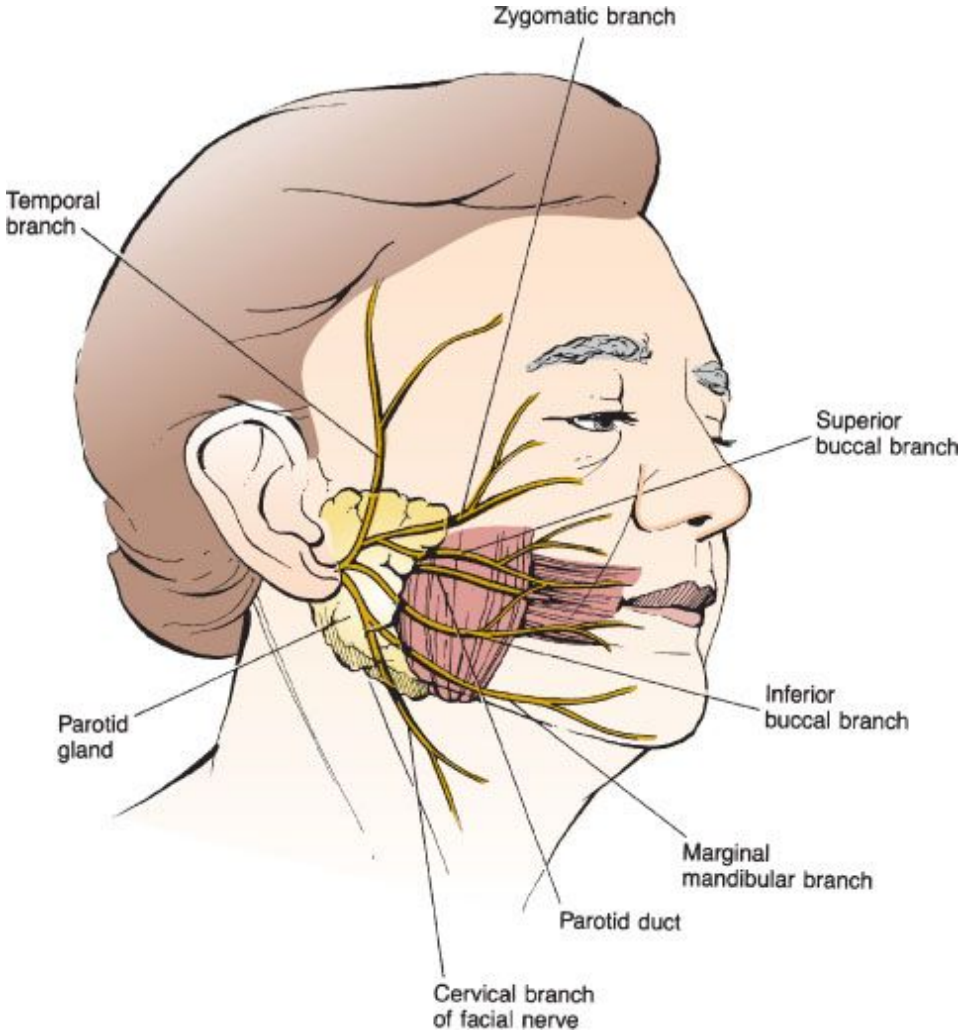


FIGURE 23.5 Important soft tissue structures of the face.

eFIGURE 23.5 Method for reduction of a mandible dislocation from behind.

Rarely, neither of the foregoing techniques will work, and reduction under general anesthesia may be required. Once reduction is accomplished, the patient's jaw should be wrapped in a Barton bandage, and the patient should be instructed to avoid opening the mouth widely to prevent repeat dislocation. Though some physicians obtain x-rays to confirm the relocation of the condyles and to exclude any fractures that occurred during reduction, others do not find this necessary (16,22).

Soft Tissue Injuries

Many patients with facial fractures have associated cutaneous injuries. These do not routinely need to be closed in the patient who will undergo surgical evaluation in the ED, as the opening may be used for examination or repair. Rapid suture ("whip stitching") is appropriate to achieve hemostasis in some cases, as the sutures can be easily removed by the consultant. Wound repair is important as cosmesis is of paramount importance to the patient. Laceration repair

is discussed in Chapter 21. In addition to lacerations, oral, ocular, salivary, lacrimal, otologic, or neurologic injuries may be associated with maxillofacial trauma (Fig. 23.5).

Any dental appliances present should be removed to prevent their aspiration from compromising the airway. These appliances should be saved, as they are expensive and may provide important guides to pretraumatic oral alignment.

The significant incidence of ocular injuries associated with various facial fractures necessitates meticulous ophthalmologic evaluation in all patients sustaining maxillofacial trauma. Injuries to the lacrimal system, with associated findings such as epiphora, may be present in patients with midface fractures. Lacrimal disruption is rare in blunt trauma, even in patients with significant craniofacial injury. These injuries are discussed in Chapter 25.

Clear or pink fluid leakage from the cheek suggests parotid gland laceration or Stensen duct damage. Lacerations that cross an imaginary line drawn from the tragus of the ear to the corner of the lip may traverse the parotid duct or facial nerve. Parotid lacerations do not require repair, as commonly occurring salivary fistulas resolve spontaneously in less than a month. Stensen duct may be repaired by suturing the ends together over a stent; this is most appropriately performed by a surgical consultant.

Tympanic membrane rupture can occur when there is significant force applied to the condyles that fractures the temporal bone. They generally heal spontaneously, but referral may be necessary in those with large disruptions.

CRITICAL INTERVENTIONS

- Secure the airway in patients with evidence of progressive swelling or airway obstruction using rapid sequence orotracheal intubation. Consider “awake” intubation for those patients who are likely to be difficult to intubate but who are currently maintaining their airway.
- Have equipment for “backup” cricothyrotomy readily available when managing the airway of a patient with significant maxillofacial trauma.

- Include evaluation for vision-threatening injury with the initial assessment of facial trauma, including pupillary size and shape, reactivity to light, lid lacerations, globe tension, and visual acuity.
- Perform facial CT as the initial radiologic study if mechanism or physical examination findings are concerning for facial fracture.
- Perform cranial CT scanning in patients with significant facial fractures to rule out intracranial injury, especially with loss of consciousness or neurologic abnormalities. Cervical spine CT and CT angiography for cervical vessel injury should also be considered.
- Obtain urgent neurosurgical consultation for patients with posterior table fractures of the frontal sinus.
- Obtain urgent surgical or ophthalmologic consultation for patients with orbital fractures who have paralysis of extraocular motions, ptosis, and periorbital anesthesia (superior orbital fissure syndrome) or visual loss.
- In mandibular fractures, perform a thorough examination to evaluate for open fracture.
- Administer intravenous antibiotics (penicillin or clindamycin) to patients with open facial fractures.

DISPOSITION

In the vast majority of patients with maxillofacial trauma, the emergency physician can perform the initial resuscitation and stabilization without the need for consultation with maxillofacial specialists. The role of emergent surgical consultation in patients with airway compromise or refractory facial hemorrhage has been discussed.

Involvement of the appropriate surgical specialist is now recommended at a time earlier than had been standard in the past for patients with severe facial fractures. Delays in treatment have been shown to result in suboptimal outcome in some facial injuries (13).

Patients with CSF leak must be evaluated by a neurosurgeon in addition to a facial specialist. Although prophylactic antibiotics may

be ordered by some consultants, in general they are not recommended as their use is not supported by the literature (39).

The surgical therapy for maxillofacial trauma is a rapidly evolving field. Patients with significant injuries should be transferred to referral centers if local consultants lack expertise in treating the injury in question. Before transfer, the patient who requires definitive care of maxillofacial injuries must be evaluated for other life- or limb-threatening injuries. Even in the setting of isolated maxillofacial trauma, the potential for airway deterioration may be present, and pretransfer stabilization in these instances may include intubation. The potential for airway compromise, as well as the high frequency of significant associated injuries, dictates a high level of training for personnel involved in the prehospital or interhospital transport of patients with significant maxillofacial trauma.

Common Pitfalls

- Failure to manage the airway aggressively with intubation or cricothyrotomy when indicated. Waiting too long in the presence of progressive swelling or hemorrhage may convert an urgent procedure into an emergent one.
- Failure to consider the presence of subtle or physically remote injuries. Particular attention should be paid to the neurologic and ophthalmologic examinations.
- Failure to realize that frontal bone injuries are associated with intracranial injury as well as infection.
- Failure to screen for and recognize intimate partner violence in patient presenting with facial trauma.

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CHAPTER 24 Dental Injuries

Kip Benko

Complaints pertaining to the teeth are common and patients frequently present to the emergency department (ED) for initial care. Complaints range in scope from simple chipped teeth to odontogenic deep space infections or complex maxillofacial injuries. Estimates are that 3 million ED visits for dental-related complaints occurred in the United States between 1997 and 2000 (17). Recent data indicate that these numbers have continued to grow, with more than 830,000 visits in 2009 alone, an increase of 16% compared with 2006 estimates (25). The age group with the highest frequency of dental-related complaints is 18 to 35 years old; however, traumatic dental emergencies are more likely in patients 18 years old and younger (17). The frequency of dental-related visits is expected to increase over the next several years as a larger segment of the population becomes uninsured or underinsured. Although these patients can be frustrating and challenging, the emergency physician (EP) should be equipped to diagnose and treat basic traumatic dental conditions until definitive dental evaluation can be obtained.

CLINICAL PRESENTATION

Dental injuries in the younger population are often related to falls or accidents as new motor skills are developing. Frequently cited causes of injury to the permanent dentition include assaults, falls, motor vehicle collisions, and sports-related mishaps (7,22). Traumatic dental injuries presenting to the ED usually involves the permanent dentition and most commonly the anterior teeth. Dentoalveolar injuries in adults are also found in association with mandibular and

facial fractures. Patients with dental injuries usually present with pain, although bleeding and swelling may be associated with these injuries. Patients may also complain of abnormalities of occlusion or of loosened teeth.

A thorough understanding of dental anatomy allows not only proper ED diagnosis and treatment, but also a more concise and accurate discussion with dental consultants. The adult dentition consists of 32 teeth of which there are four distinct types: incisors (8), canines (4), premolars (8), and molars (12). Starting in the midline, each quadrant has central incisor, lateral incisor, canine (cuspid), two premolars (bicuspids), and three molars, the last of which is the wisdom tooth (Fig. 24.1). The adult teeth are numbered from 1 to 32 as noted in Figure 24.2, although it is more important that the EP be able to describe the tooth involved (i.e., upper left quadrant wisdom tooth) rather than remembering the actual tooth number. Teeth of primary dentition (baby teeth) are, likewise, best described by location and type. The earliest teeth to erupt in a child are the central incisors, usually at 4 to 8 months. The child usually has a full complement of primary teeth by the end of the third year of life. The primary teeth are not numbered but rather lettered as shown in Figure 24.2. The permanent teeth usually start replacing the primary teeth at approximately 5 years of age and this process begins with the incisors (Table 24.1).

TABLE 24.1
Teeth Eruption Times

Baby (Primary) Teeth		
Tooth Designation	**Name of Tooth**	**Appearance in the Mouth (mos)**
A	Central incisor	4–14
B	Lateral incisor	8–18
C	Canine tooth	14–24
D	First molar	10–20
E	Second molar	20–36
Adult (Permanent) Teeth		
Tooth Designation	**Name of Tooth**	**Appearance in the Mouth (yrs)**
1	Central incisor	5–9
2	Lateral incisor	6–10
3	Canine tooth	8.5–14
4	First premolar (bicuspid)	9–14
5	Second premolar (bicuspid)	10–15
6	First molar (6-yr molar)	5–9
7	Second molar (12-yr molar)	10–15
8	Third molar (wisdom tooth)	17–25

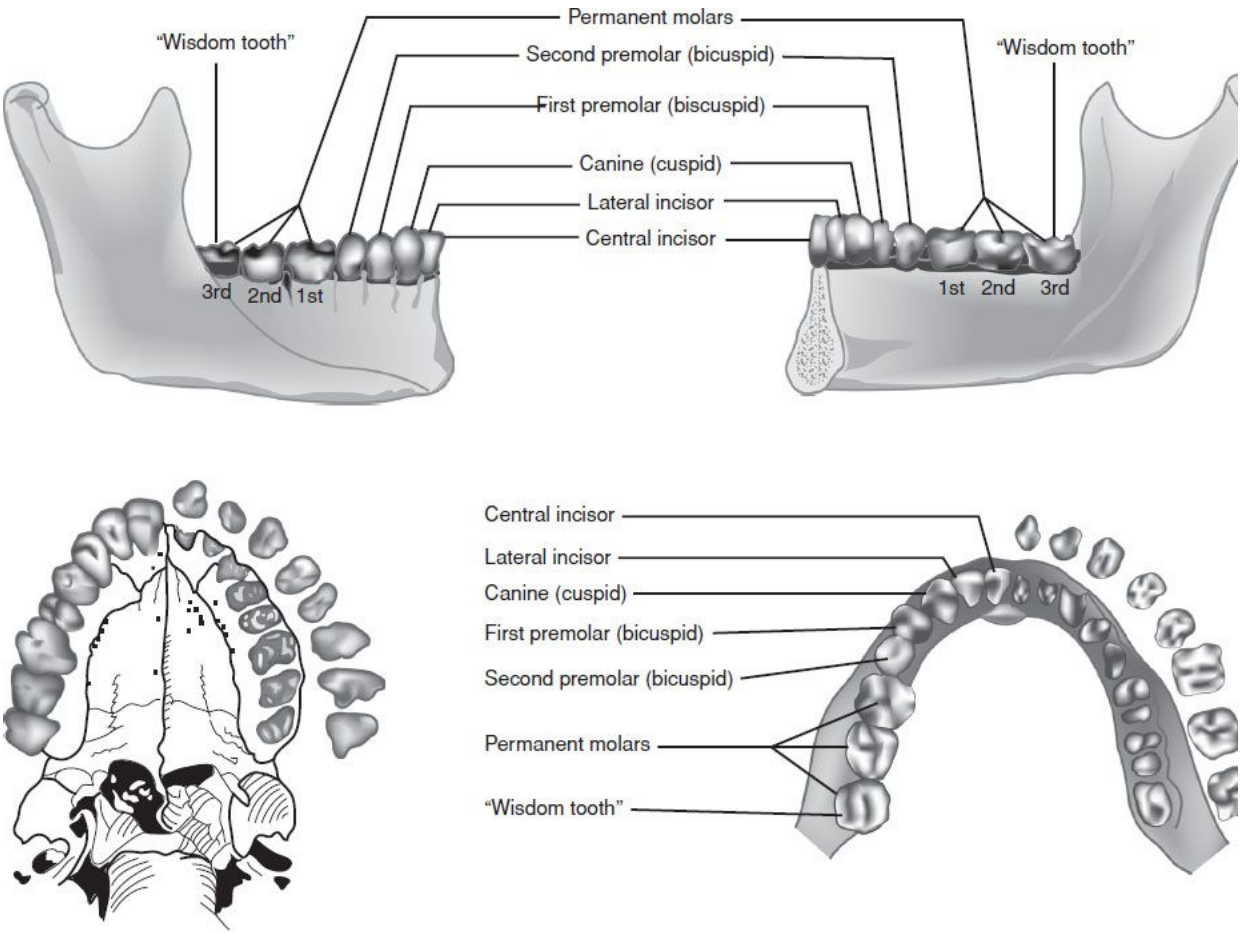


FIGURE 24.1 Classification of teeth.

A tooth consists of the central pulp, the dentin, and the enamel (Fig. 24.3). The pulp contains the neurovascular supply of the tooth that carries nutrients to the dentin, a microporous layer that consists of a system of microtubules. The dentin serves to cushion the tooth during mastication and makes up the majority of the tooth. The enamel is the visible portion of the tooth and is considered the hardest part of the body. The tooth may also be described in terms of its crown or root. The crown is that portion covered in enamel and the root anchors the tooth to the alveolar bone.

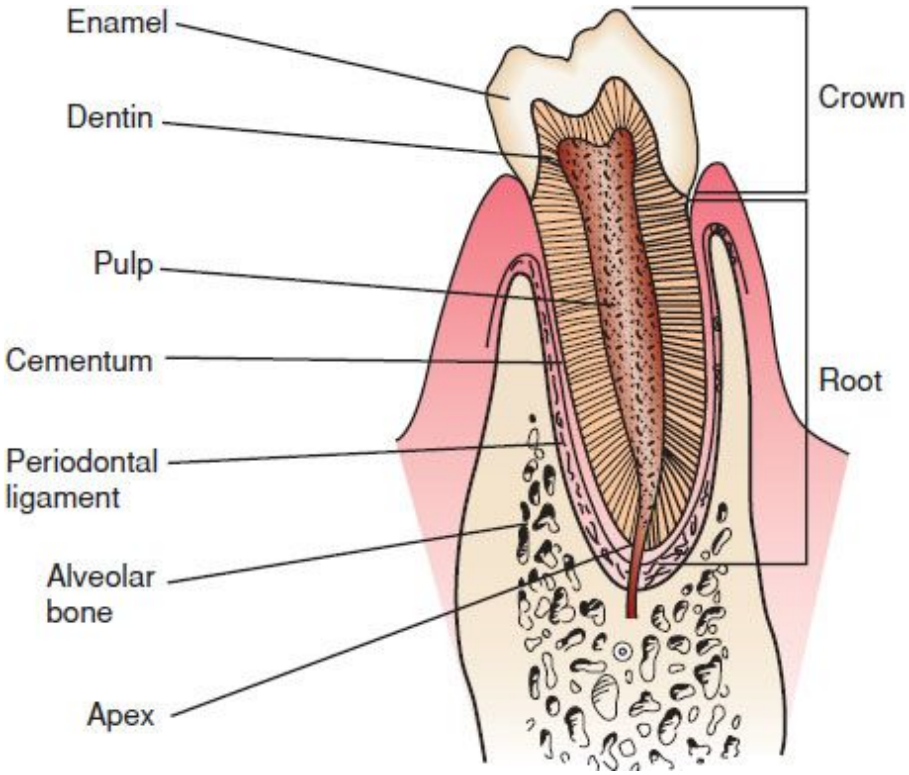


FIGURE 24.3 The dental anatomic subunits.

The following terms are used to identify the different anatomic surfaces of the tooth and are helpful when describing a specific tooth injury to a consultant.

Facial: Refers to the surface of the tooth that is seen when a person smiles. This is a general term, is applicable to all the teeth, and is sufficient to use when describing an injury, however, the following is more specific and precise.

Labial: Refers to the facial surface of the canines and incisors.

Buccal: Refers to the facial surface of the molars and premolars.

Oral: Surface that faces the tongue or the palate. This is also a general term and is applicable to all the teeth, but the following is more precise.

Lingual: Toward the tongue, the oral surface of the mandibular teeth.

Palatal: Toward the palate, the oral surface of the maxillary teeth.

Approximal /interproximal: The contacting surfaces between two adjacent teeth.

Mesial: The interproximal surface facing anteriorly or closest to the midline.

Distal: The interproximal surface facing posteriorly or away from the midline.

Occlusal: The biting or chewing surface of the premolars or molars.

Incisal: The biting or chewing surface of the incisors and canines.

Apical: Toward the root of the tooth.

Coronal: Toward the crown or the biting surface of the tooth.

The attachment apparatus, or periodontium, consists of two major subunits and is necessary for maintaining the integrity of the normal dentoalveolar subunit.

The *gingival* subunit consists of the visible junctional epithelium and the gingival tissue.

The *periodontal* subunit includes the periodontal ligament, alveolar bone, and the cementum of the root of the tooth.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of traumatic dental injuries is fairly straightforward. The primary concerns are whether the existent trauma could potentially cause airway compromise. Mandibular, maxillary, or alveolar ridge fractures may leave the tongue unsupported or the midface unstable. Each scenario may lead to difficultly when performing intubation or ventilation with a bag-valve-mask. Tongue and mucosal lacerations may cause bleeding severe enough to compromise the airway. It is also important to evaluate potential associated injuries such as traumatic brain injuries, other maxillofacial injuries, or cervical spine injuries.

Trauma to the teeth usually consists of fracture, intrusion, subluxation, (loose, nondisplaced teeth), luxation (displaced teeth), or complete avulsion. Fractures involving segments of teeth usually involve the alveolar ridge as well. The final diagnosis is primarily determined by a meticulous physical examination, accounting for each tooth, portion of the tooth, and integrity of buccal and gingival mucosa. Radiography usually serves a confirmatory role (Table 24.2).

TABLE 24.2
Differential Diagnosis of Orofacial Trauma

Dental fractures
Enamel fractures
Dentin fractures
Pulp fractures
Dental subluxation, luxation, intrusion, and avulsion
Facial fractures
Alveolar ridge fractures
Soft tissue lacerations
Traumatic ulcers
Mandible/maxilla fractures
Mucosa/tongue lacerations

ED EVALUATION

The evaluation of dental complaints in the ED consists of a focused, but meticulous, history and physical examination. Important historical information with regard to traumatic injuries includes the following:

When did the incident occur? The timing of the incident is important when evaluating avulsed permanent teeth, as the decision to reimplant the tooth is largely based on the duration that the tooth was out of the socket.

Were any teeth found at the scene? Did the patient experience any coughing or gagging after the injury? This may be suggestive of aspiration of a tooth.

Has the patient been drinking alcohol or using any other drugs, which may alter their level of consciousness (including recreational drugs)? These drugs may increase the likelihood of aspiration, especially if the gag reflex is diminished.

Was there a loss of consciousness?

Does the patient complain of pain? Do the teeth feel as if they are meeting normally? Is the pain associated with occlusion? Mandibular fractures are often worsened with jaw movement and patients will also complain that their teeth do not meet normally. Pain from temporomandibular joint (TMJ) injuries is often referred to the ear.

Pain from fractured teeth is made worse with the inspiration of air or contact with hot or cold substances. Alveolar ridge fractures are made worse with any movement of that segment.

Did the patient apply any substance to the teeth to decrease the pain? Over-the-counter anesthetics and topical analgesics can cause sterile abscesses if applied to the pulp or the dentin (12).

Does the patient have a history of dental work with regard to the traumatized tooth?

Is the tooth a primary or secondary tooth? Traumatized primary teeth are managed differently than permanent teeth.

Does the patient have a history of bleeding disorders or allergies to medicines?

A meticulous physical examination is important. Injuries to the dentition and mucosa are easily missed during a casual examination or if the examiner is distracted by more obvious physical findings. The many nooks and crannies of the mouth can easily hide fairly significant sized lacerations, tooth fragments, and other foreign bodies.

The examination should begin with observation and simply talking to the patient; muffling, drooling, and voice change may signify airway involvement. Individuals with mandible dislocations or fractures often talk with a partially open mouth without pursing their lips. External inspection should be performed next. Mandibular dislocations and fractures are associated with asymmetry, deformity, or swelling of the face. The EP should visualize the face from multiple angles to note subtle asymmetries. The opening and closing of the mouth should be smooth and full, with no limitations or hesitations. The face is palpated for crepitus, tenderness, or step-offs. The mandible and entire midface should be palpated with particular attention being paid to the maxilla, zygomas, mandibular condyles, and coronoid processes. The TMJs should be palpated throughout the entire range of motion. There should not be any pops, clicks, or complaints of pain.

The physician should palpate the neck with special attention to the area beneath the mandibular body and assess for swelling or tenderness, and examine the skin for bruising. The oral cavity should

be inspected for bleeding, swelling, or tenderness. Each tooth should be accounted for. A tongue blade can be used to visualize the entire mucobuccal fold region. Often, when the buccal mucosa is redundant or if there is swelling secondary to trauma, a two-tongue blade technique is necessary to visualize the entire oral cavity. Using a gloved hand, the EP should palpate the buccal mucosa and the floor of the mouth. Each tooth should be percussed with a tongue blade for sensitivity and palpated with fingers for mobility. Blood in the gingival crevice (where the enamel contacts the tooth) is suggestive of a traumatized tooth or a mandibular or maxillary fracture. The teeth should meet evenly when biting and the patient should be able to exert firm pressure on a tongue blade with his or her molars. The inability to crack a tongue blade bilaterally when it is twisted between the molars (tongue blade twist) is suggestive of a mandibular fracture (1).

The basic evaluation and treatment of most dental emergencies can be performed without any radiographic or laboratory evaluation. Unlike definitive care in the specialist's office, the ED treatment of tooth and alveolar ridge fractures is usually not changed by information gained from x-rays. Radiographs should be obtained if a tooth fragment is missing and thought to be aspirated or otherwise lodged in the lip or buccal mucosa. Similarly, intruded teeth are not always apparent and x-rays can help distinguish between an intruded and an avulsed tooth.

A panorex and a Towne view are probably the most useful and cost-effective views to obtain when evaluating mandibular trauma in the ED (8,12). The panorex of the mandible shows the mandible in its entirety and demonstrates fractures in all regions, including the symphysis; however, it can rarely miss overriding anterior fractures (18). An occlusal view or CT scan is indicated if this is likely. The Towne view allows slightly better visualization of the condyles and should be used if the condylar regions cannot be visualized adequately with a panorex (8). Coronal CT scanning is more precise and definitive and is often used in the preoperative evaluation, however, CT scanning is usually unnecessary in the ED evaluation. CT scanning should be obtained if multiple facial fractures are

suspected or if clinical suspicion is high and standard radiographs are negative or equivocal. If the patient is unable to sit still in the panorex machine or is immobilized, then CT scanning or standard lateral mandibular films should be obtained. Lateral mandibular films have the disadvantage of not visualizing the symphysis well and occlusal films may be required to better evaluate this part of the mandible.

Laboratory work is not necessary for the routine evaluation of dental and and maxillofacial trauma but should be considered on an individual basis. Likewise, bleeding times and coagulation profiles are unnecessary in most individuals, but should be considered if the patient is anticoagulated or the history is compatible with a bleeding disorder.

KEY TESTING

- Radiographs should be obtained if a tooth or tooth fragment is missing and thought to be either aspirated, intruded, or lost in the buccal or gingival tissue.
- An initial panoramic radiograph should be obtained if there is a suspicion of mandibular fracture
- A Towne radiograph should be obtained if there is suspicion of a mandibular condyle fracture and the initial panorex is negative or inconclusive.
- CT scanning should be considered if there is suspicion of multiple facial fractures or the panorex is negative and suspicion remains high for mandibular fracture.
- CT or lateral mandibular films can be used to evaluate mandibular injury if the patient is immobilized.
- Bleeding times and coagulation profiles should be considered if the patient exhibits ongoing bleeding and the history is suggestive of anticoagulation or a bleeding disorder.

ED MANAGEMENT

Table 24.3 lists the equipment that EDs should have for taking care of dental-related injuries. There are several key principles which

apply to the management of dental trauma in the ED.

TABLE 24.3
Dental Equipment Needed in the ED

Packing gauze
Dental roll gauze
Calcium hydroxide paste or glass ionomer cement or zinc oxide cement
Dry socket paste or eugenol
Topical anesthetic gel (20% benzocaine or 5% lidocaine)
Periodontal paste (Coe-Pak) or self-cure composite
Bupivacaine cartridges with epinephrine
EMT Toothsaver Preservation system, Save-A-Tooth or fresh milk
Zinc oxide/eugenol temporary cement (Temrex) or other dental cement
Ringed injection syringe
Stainless steel spatula and mixing pads
Oral surgery tray with arch bars and ligature wires
Tongue blades and cotton-tipped applicators
Disposable electrocautery (optional)

The EP should identify all fracture fragments as well as loose teeth and note if a mandibular fracture is open or closed. Radiographs should be taken if there is any suspicion of intrusion into the alveolar bone or surrounding mucosa. A chest x-ray (CXR) is obtained if a patient with a missing tooth does not recall the location of the tooth. Lack of pulmonary complaints cannot be counted on to rule out an aspirated tooth.

Over-the-counter topical tooth remedies and analgesics should be avoided as their use can lead to the development of sterile abscesses and soft tissue irritation (14).

It is much easier to repair the dentition if the tooth can be manipulated without causing significant discomfort. Dental block anesthesia and tooth and supraperiosteal injection should be a part of the EP's armamentarium. Dental blocks, topical and injectable anesthetics and regional oral anesthesia should be used to treat pain and to provide anesthesia for manipulation and temporary repair of the injured tooth. Narcotic and nonnarcotic alternatives, although

helpful after treatment is completed, do not usually offer the patient the comfort required to do most dental manipulations.

Tetanus vaccine should be administered if indicated.

Dental Fractures

Maxillary central incisor injury accounts for between 70% and 80% of all fractured teeth (20). The associated morbidity of fractured teeth can be considerable and includes failure to complete eruption, abscess, loss of space in the dental arch, color change of the tooth, ankylosis, abnormal exfoliation, and root resorption.

The ED management of acute tooth fractures depends upon the extent of fracture, the degree of development of the apex of the tooth, and the age of the patient. There are many systems for classifying dentoalveolar injuries and, in particular, tooth fractures. The Ellis classification system is one classification system often cited in the EM literature. An Ellis Class I fracture is only through the enamel. An Ellis Class II fracture involves the dentin as well as the enamel and an Ellis Class III, the most severe, is a fracture through the pulp, dentin, and enamel. Many dental specialists, however, do not use this nomenclature and, therefore, the most widely understood and recognized method of classification is based on description.

Crown Fractures

Crown fractures may be divided into complicated and uncomplicated categories. Uncomplicated crown fractures involve the enamel alone or the dentin in combination with the enamel.

Fractures that involve only the enamel are considered uncomplicated and are usually not sensitive to forced air, temperature extremes, or percussion and generally pose no threat to the dental pulp. They are characterized by the loss of some portion of the normal contour of the tooth edge. Immediate ED treatment is not necessary but may consist of smoothing the sharp edge of the tooth with an emery board or a rotary disk sander if the patient is very uncomfortable because of the sharp edges of the fractured tooth. The

patient should be reassured that the tooth can be restored to its pretraumatic state by a dentist using composite bonding materials. Follow-up is important, as pulp necrosis and color change occasionally do occur after these fractures (Fig. 24.4A,B) (3,7).

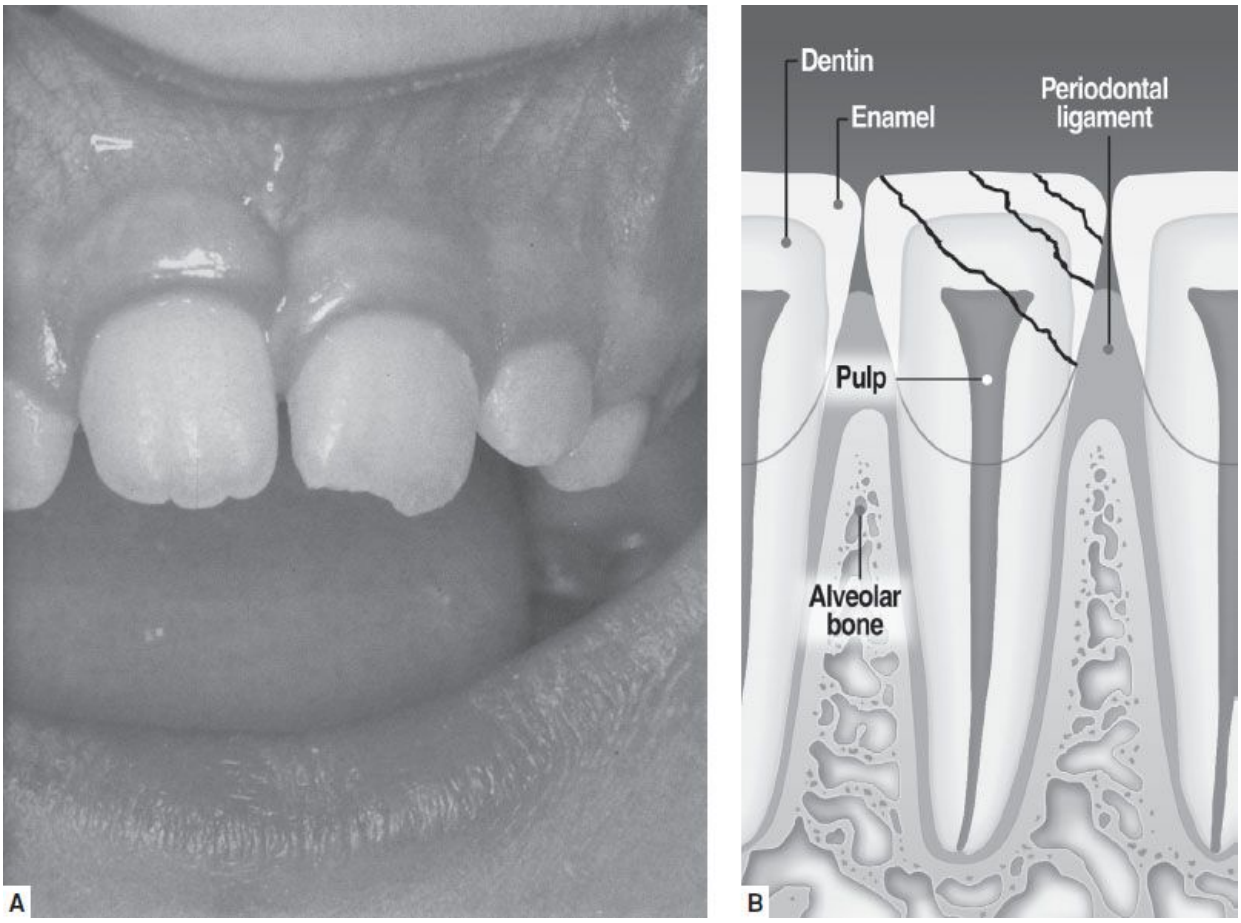


FIGURE 24.4 Fractures of the crown should be described as through the enamel, the dentin, or the pulp. Fractures through the enamel and dentin are uncomplicated, and fractures through the pulp are considered to be complicated.

Uncomplicated Fractures through the Enamel and Dentin

Fractures that extend into the dentin are at a higher risk of pulp contamination with subsequent abscess development and possible pulp necrosis. They are also more likely to have an associated periodontal ligament injury because of the force sustained in creating the injury. The overall prognosis of dentin fractures depends upon

the extent of dentin exposed and the overall injury to the Periodental Ligament (PL) (10). The risk of pulp necrosis in these patients is 1% to 7%, but this increases as treatment time extends beyond 24 hours (7). Patients often complain of sensitivity to extremes of temperature, forced air, or palpation. The physical examination reveals the yellow tint of the dentin as contrasted to the white hue of the enamel. (Fractures that are closer to the pulp cavity reveal a pink tinge to the dentin.) The dentin's porous quality allows passage of bacteria from the oral cavity to the pulp, which may result in inflammation and infection of the pulp chamber. The inflammatory response occurs usually after 24 hours, but may occur sooner if the level of injury is closer to the pulp. Younger patients less than 12 years of age have a pulp/dentin ratio larger than in the mature adult and are at increased risk of pulp contamination. They should be treated aggressively and should be seen within 24 hours (15).

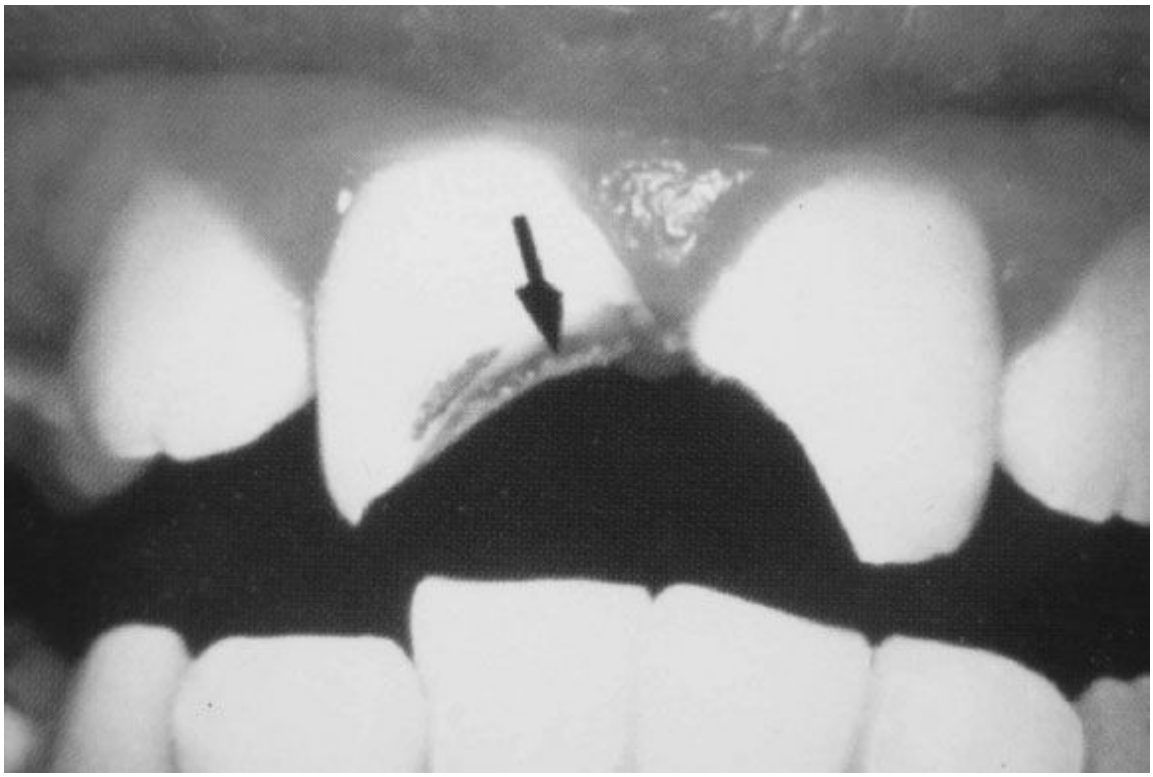
There are two goals in treating dentin fractures in the ED. The exposed dentin should be covered to prevent secondary contamination or infection, and the clinician should provide pain relief. After a fracture is covered emergently in the ED, a dentist can later rebuild it with modern composites, often directly over the appropriate dressing applied by the EP, provided the pulp is in good condition. A supraperiosteal injection performed prior to covering allows manipulation of the tooth and increased patient cooperation. Surface coverings include calcium hydroxide, dentinal sealants, bonding agents, and glass ionomer composites (2,14,18,20). Topical agents that are applied by a dentist or dental professional are often not realistic for use in the ED. Likewise, composites that are used in the dental office are often cured with a bonding light and are beyond the scope of most emergency practice. The ease of applicability of calcium hydroxide paste, the long shelf life and the fact that it can be used easily by itself make it attractive for ED use (5,20). Topical skin adhesives are among the many topical dressings often applied to teeth in the ED, however, they are not approved for intraoral use and are broken down by salivary enzymes before the patient can be seen in follow-up. Many patients sustaining a fracture through the dentin will eventually require a root canal or other definitive endodontic

treatment. The timely application of an appropriate dressing in the ED, however, may prevent contamination of the pulp and make root canal unnecessary. As with any trauma to the anterior teeth, it should be explained to the patient that disruption of the neurovascular supply is possible and that long-term complications such as pulp necrosis, color change, and root resorption may occur.

Complicated Fractures of the Crown Involving the Pulp

Complicated fractures of the crown that extend into the pulp are true dental emergencies as they result in pulp necrosis in 10% to 30% of cases, even with appropriate initial treatment (7). They are distinguished from fractures of the dentin by the pink or red color of the pulp. The fracture surface of the tooth should be wiped off with gauze and observed for frank bleeding or a pink blush, which indicates exposure of the pulp (Fig. 24.5 and eFig. 24.1). These fractures are usually exquisitely sensitive, however, occasionally there is a lack of sensitivity secondary to a concussion of the nerve supply of the tooth (2).

FIGURE 24.5 A fracture through the pulp. Acute fractures through the pulp usually bleed.



eFIGURE 24.1 A pulp fracture.

Management includes referral to a dentist, oral surgeon, or endodontist and usually a pulpectomy (complete removal of the pulp) or, in the case of primary teeth, a pulpotomy (partial removal of the pulp) is the definitive treatment (3,6). The longer the pulp is exposed, the greater the chance of contamination and abscess formation. If a dental consultant cannot see the patient immediately, then the EP should attempt to relieve the pain and cover the exposed pulp. Supraperiosteal injection (dental block) should be performed if significant pain is present and the tooth should be covered with one of the dressings described in the previous section.

There is currently no literature that addresses the issue of whether or not antibiotics should be prescribed for fractured teeth seen in the ED. Patients who present to the dentist and then undergo definitive treatment do not usually receive antibiotic prophylaxis (6,20). In the ED, patients must be treated under the following assumptions. First, it is uncertain as to whether the patient is going to be able to secure follow-up care, and second, the status of the patient's underlying

dentoalveolar health is not always known. Delayed fracture care and poor gingival health increase the risk of pulp necrosis and, potentially, periapical abscess. These factors suggest to some that tooth fractures involving the dentin or pulp should receive antibiotic prophylaxis, unless follow-up is certain and is within a reasonable time period (i.e., several days).

Luxation, Subluxation, Intrusion, and Avulsion

Subluxation refers to teeth that are mobile but not displaced and luxation refers to teeth that are displaced, either partially or completely from their sockets. Luxation injuries are further divided according to the direction of the displacement. Extrusive luxation refers to displacement of the tooth in an axial direction (eFig. 24.2). Intrusive luxation occurs when the tooth is displaced apically (toward the root) and is often accompanied by crushing or a fracture of the apex of the tooth (eFig. 24.3).

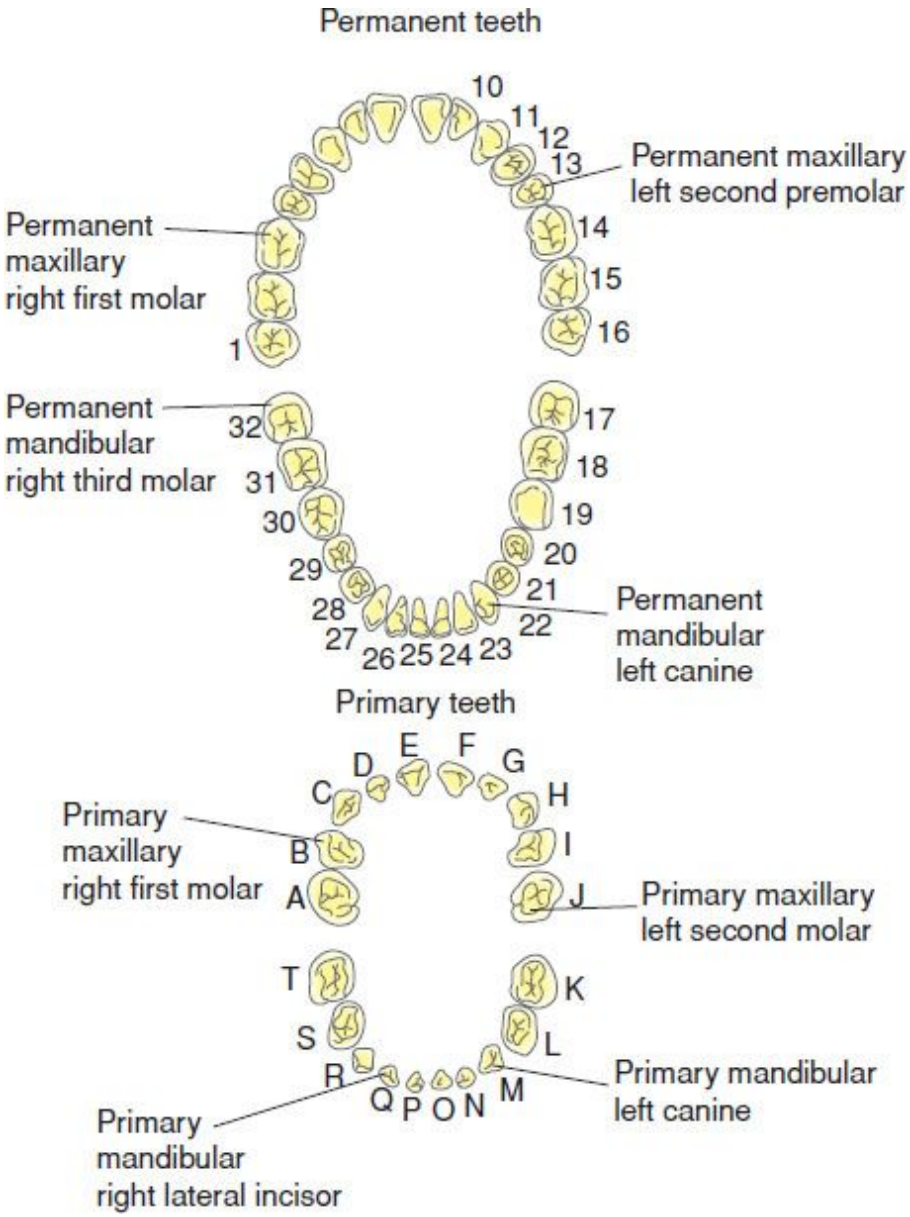
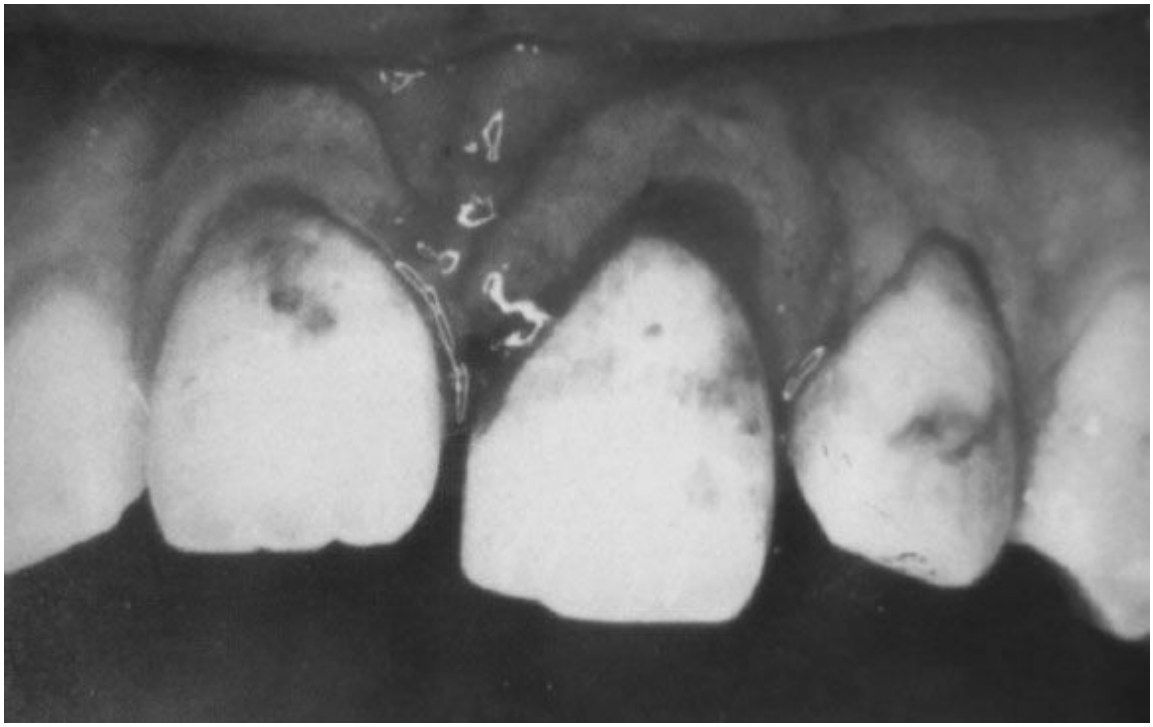
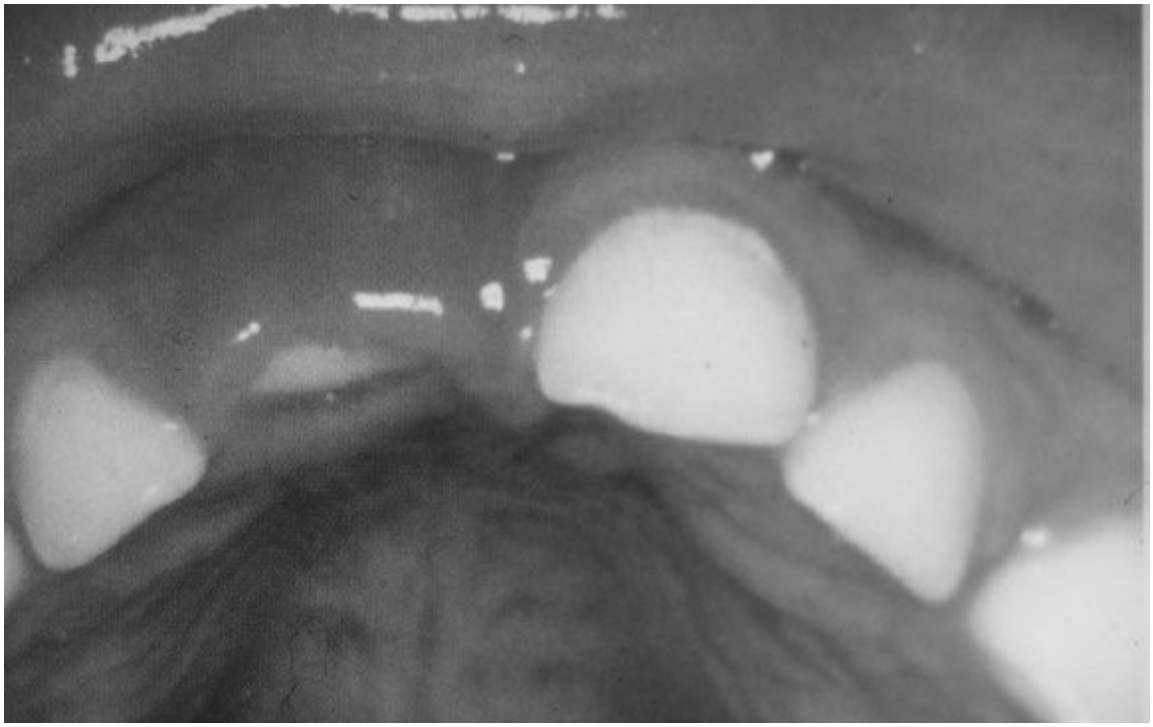


FIGURE 24.2 Identification of teeth.



eFIGURE 24.2 Extrusive luxation. Extruded teeth are displaced coronally.



eFIGURE 24.3 Intruded teeth. Intruded teeth are displaced apically.

Lateral luxation occurs when the tooth is displaced facially, mesially, lingually, or distally. Fractures of the alveolus frequently accompany lateral luxation injuries. Complete luxation, also known as complete avulsion, occurs when the tooth is entirely lost from the socket.

Teeth that are minimally mobile and not displaced do very well with conservative treatment only. As the periodontal ligament reattaches to the alveolar bone, the tooth will tighten up in the socket without intervention and the vascular supply of the tooth will reestablish itself. Patients should be instructed to eat a soft diet for 1 to 2 weeks and follow-up with their dentist as soon as possible.

Grossly mobile teeth require stabilization in the ED. Fixation is best performed by the dental specialist with bonding materials or wire ligation. Temporizing splinting techniques suitable for use by EPs include periodontal paste and self-cure composite. A commercially available periodontal paste is Coe-Pak, a moderately sticky clay-like dressing that becomes firm after application. Self-cure composite is another splinting option in the ED. This composite does not require acid etching or a bonding light and is applied only to the enamel surface of the tooth. Both periodontal paste and self-cure composites are easy to remove by the dentist during formal restoration.

Intruded teeth have been forced apically into the alveolar bone and often result in a disruption of the attachment apparatus or fracture of the supporting alveolar bone. Intruded teeth are usually immobile and do not need stabilization in the ED, but often do require later endodontic treatment because of root necrosis. X-rays should be obtained any time there is uncertainty as to whether a tooth is intruded or avulsed. Permanent teeth need to be repositioned the majority of the time as they are often associated with alveolar bone fracture, but primary teeth are usually given a trial period to erupt on their own before any intervention is taken (10,11).

An avulsed tooth is a true dental emergency. The first goal is to find the tooth. Missing teeth may be lost, intruded, aspirated, swallowed, fractured, or embedded in the oral mucosa somewhere. Radiography should be considered to find the lost tooth or

fragments. Management in the ED is based on patient age, time since avulsion, presence of other maxillofacial trauma such as alveolar ridge fractures, and the overall health of the periodontium (4). Primary teeth are not replaced because they can fuse to the alveolar bone and potentially cause craniofacial abnormalities or infection and they may prevent normal eruption of the permanent teeth (9,11). There are a few reports of successful reimplantation of primary teeth by dentists, however, most resources do not recommend it be performed by dentists, family members, or EPs (9). Parents can be reassured that prosthetic replacements can be worn, if desired, until the permanent teeth erupt.

Time is the essential consideration when deciding to replace an avulsed tooth. The longer the tooth is out of the socket, the higher the incidence of periodontal ligament necrosis and subsequent failure of reimplantation (4). Periodontal ligament cells begin to die within 20 minutes outside of the oral cavity and cell death is usually complete within 60 minutes if the tooth is not placed in appropriate transport medium (15). Various transport media, including milk, Hanks balanced salt solution (HBSS), water, saliva, and Gatorade have all been studied. Certain cell culture media have also been developed that cause periodontal cells to proliferate and remain viable, but milk and commercially available HBSS products (known as EMT Toothsaver or Save-A-Tooth) are currently best for prehospital transport and ED storage (19). HBSS has been shown to maintain PL cell viability for 24 hours and is currently recommended by the American Association of Endodontists. If such a product is unavailable, milk should be used as the storage media until reimplantation can be performed. The pH and osmolarity of milk have been shown to maintain PL viability for up to 4 hours (26). Saline or the patient's saliva can be used at the scene if nothing else is available as both will maintain PL viability for up to 2 hours. The use of water as a transport medium should be discouraged as the low osmolarity causes PL cell disruption. Likewise, the transporting of the tooth in the oral cavity or under the tongue should be discouraged because of the risk of aspiration of the tooth as well as physical trauma which can occur to the PL from structures in the mouth.

Antibiotics are controversial in the management of avulsed and fractured teeth. Human trials have not shown any significant effect of systemic antibiotics on the outcome of avulsed teeth reimplantation, but animal study data suggests that antibiotics may decrease resorption of the tooth root and increase the likelihood to successful tooth reimplantation. Recent dental association guidelines recommend oral antibiotics be administered until conclusive data is obtained (27,28). The goal of the EP in any tooth avulsion or injury or fracture is to keep the native tooth if possible. Therefore, it is of utmost importance that the tooth be stored in an appropriate storage media until the EP can prepare the socket for reimplantation. Once reimplanted, the tooth usually loses the majority of its blood supply and undergoes pulp necrosis, but it remains a functional tooth if the PL stays intact.

Alveolar Bone Fractures

Fractures to the alveolus, which is the tooth-bearing portion of the mandible or maxilla, often occur in multitooth segments but will vary in the number of teeth involved, the amount of displacement, and the amount of mobility of the affected segment. The diagnosis is confirmed by noting a segment of mobile teeth that are misaligned. Dental bitewing x-rays confirm the diagnosis and panorex or facial films may show a fracture line apical to the roots of the involved teeth.

The treatment of alveolar ridge fractures involves rigid splinting of the affected segment, which should be performed urgently by an oral surgeon or a dentist. The urgency is dependent upon the mobility, the displacement, and the extent of the segment. This ideally should be done within 24 hours. The role of the EP is to identify the injury as well as any avulsed or fractured teeth and preserve as much of the alveolar bone and surrounding mucosa as possible. Alveolar bone that is lost, debrided, or missing is difficult for the specialist to restore properly (5).

Soft Tissue Trauma

It is imperative for the EP to carefully inspect the mucosa of the perioral region and determine the presence of any foreign bodies, lacerations, or tooth fragments. The repair of injured mucosa should generally take place after the repair of the dentition as soft tissue manipulation can result in damage to sutures already placed in the soft tissue.

The rates of infection of intraoral lacerations are extremely small, and most heal uneventfully without antibiotic coverage. One prospective study showed a trend toward decreased infections in intraoral lacerations treated with prophylactic penicillin, however, the results were not statistically significant (22). It is reasonable to use antibiotics if the wound contains a large amount of devitalized tissue or is through and through.

Buccal Mucosa Injuries

Most lacerations and abrasions of the oral mucosa heal quickly and do not require definitive repair. Large lacerations (>1.5 cm) should generally be repaired using 4-0 or 5-0 chromic sutures. Absorbable sutures should be placed so that the knots are buried. Silk is an acceptable alternative, but used much less commonly as it requires removal. It is also more reactive. Nylon should be avoided as it is sharp and irritating to the tissues.

Through and through lacerations require a meticulous physical examination to rule out foreign bodies, damage to Wharton or Stenson ducts, or damage to the facial nerve. Guidelines for closure are controversial but, in general, larger lacerations (>1 cm) should be closed (23). The mucosa is repaired as described and the skin is closed with 6-0 nylon, prolene, or rapidly absorbable suture. The mucosa is closed first so as not to damage the skin layer. It is reasonable to close only the skin layer if the mucosal laceration is very small. Large lacerations, through and through lacerations, or lacerations with large amounts of devitalized tissue should be rechecked in 2 days. Facial sutures should be removed in 4 to 5 days. Saline rinses and a soft diet should be prescribed.

Gingival Injuries

Most small injuries over the maxillary or mandibular gingiva usually heal uneventfully without intervention. If the laceration is large, gaping, if a flap is present or if there is bone exposed, the edges should be approximated with 4-0 or 5-0 absorbable suture. If difficulty arises because there is little soft tissue underneath the gingival to anchor your suture, the practitioner can wrap the suture around the teeth and use them as anchors for your suture. Periodontal paste, which is used for stabilizing loose teeth, can also be used to repair gingival lacerations without the need for sutures. When placed over nongaping gingival lacerations, it protects the mucosa and allows the laceration to heal uneventfully. The paste is removed in 7 to 10 days by a dentist.

Frenulum Injuries

Lacerations of the frenulum rarely require suturing except in complex lacerations which extend into the surrounding mucosa or gingiva. In these cases, the mucosa should be tacked down and approximated with absorbable suture. Wounds of the frenulum are very uncomfortable and analgesia should be prescribed even if suturing is not required.

Tongue Lacerations

Tongue lacerations that are <1 cm in length and whose edges are not gaping seldom require repair. Gaping lacerations require repair as the edges will epithelialize leaving a grooved or bifid appearance. Likewise, wounds that are bleeding profusely, are flap shaped, or are on the edge of the tongue should be sutured. Small avulsions heal without intervention.

Repair should be initiated with anesthesia via local infiltration or by lingual block. Absorbable sutures, 4-0 are ideal, but silk can be used as well as it is easy to work with. It has the disadvantage of having to be removed in 5 to 7 days.

CRITICAL INTERVENTIONS

- Identify all teeth and consider aspiration of fractured or avulsed teeth. Inspect all lacerations for possible foreign bodies or tooth fragments.
- Cover all fractures of the dentin or pulp, unless dental consultation is available immediately.
- Splint all moderately or severely loosened teeth.
- Place avulsed teeth in an appropriate storage medium, such as milk, EMT Toothsaver or Save-A-Tooth until reimplantation is possible.
- Do not replace primary teeth.
- When performing a dental block, aspirate before performing injecting local anesthetic.
- Obtain x-rays if there is any suspicion of intruded teeth, alveolar ridge, mandible fractures, or oral foreign bodies (such as tooth fragments).
- Repair tongue lacerations that are gaping or that involve the tongue margin.

DISPOSITION

The disposition of most dental injuries is somewhat dependent upon what treatment is provided in the ED. Any fractured tooth should receive follow-up as even small chip fractures through the enamel can result in pulp necrosis. Fractures through the dentin and pulp should both be seen as soon as possible, preferably within 24 hours, if tooth salvage is to be an option. If the dentin/pulp is covered with CaOH, the 24 hour window is lengthened somewhat, the patient will be more comfortable and abscess may be less likely. A fracture through the pulp should be seen as urgently as can be arranged. Luxated or reimplanted avulsed teeth, if stable, can also be seen in 24 to 48 hours. If a luxated tooth, reimplanted tooth, or alveolar ridge fracture remains unstable and splinting by the EP is not possible, dental or oral surgery consultation should be obtained immediately. Intruded teeth should be seen within 24 to 48 hours for evaluation of possible alveolus fracture and realignment. Mobile or open alveolar ridge fractures require immediate consultation. Any mucosal or tongue laceration which is extensive or will require

plastic surgery repair should receive appropriate consultation or be transferred to facility where repair is possible.

Common Pitfalls

- Failure to replace an avulsed tooth assuming that the patient can get an implant. It is always better to have a functional native tooth if possible.
- Replacing primary teeth. They may cause problems later on. The tooth should be left out and the patient referred to the dentist.
- Failure to consider that the patient aspirated a tooth or that it may be embedded in the oral mucosa.
- Failure to close a significant tongue laceration, which can be debilitating and creates a more difficult delayed repair.
- Failure to use proper anesthesia, such as a dental block, prior to manipulating a fractured tooth. The patient's pain makes it very difficult to complete the procedure properly. Dental blocks with long-acting anesthetics control pain very effectively (Table 24.3).

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CHAPTER 25

Eye Trauma

Kevin J. Knoop and William Dennis

Eye trauma accounts for approximately 1% of annual ED visits, with more than 2 million ocular injuries yearly (1). Of these, 60,000 require admission, and lasting visual impairment results in approximately 50,000. The emergency physician (EP) has an important role in the diagnosis, management, and referral of eye injuries. Thus, the EP must be cognizant of the spectrum of ocular trauma to preserve vision and prevent disability.

CLINICAL PRESENTATION

A rapid, focused history must direct the EP early in the evaluation. Surrounding context and events as well as injury mechanism and presenting symptoms should be elicited. For example, elderly patients frequently present after falls and may have additional systemic injuries and an underlying condition that may have precipitated the fall. There are four mechanisms of ocular trauma: abrasion, blunt force, laceration or penetration with a foreign body (FB), and burn. Prognosis may be linked to mechanism, as lacerations generally have better outcomes than blunt trauma that may contuse or rupture the globe (2).

ED EVALUATION

When evaluating eye trauma, the EP should consider concomitant nonocular injuries. Rapid primary assessment of airway, breathing, circulation, and disability before conducting a systematic and comprehensive eye evaluation will address this possibility. After

determining patient stability, ocular trauma is addressed as immediate treatment is imperative in many instances. The chemically burned eye must be irrigated immediately and continuously for at least 30 minutes with 2 L of saline, lactated Ringer, or another neutral solution, until the measured pH reaches physiologic neutrality (7 to 7.4). If the pH is normal after initial irrigation, a recheck of pH every 15 minutes ensures neutral pH. Traumatic endophthalmitis usually presents as pain and inflammation out of proportion to the penetrating injury preceding the infection. It requires immediate ophthalmologic consultation for injection of intravitreal antibiotics.

Visual Acuity

Visual acuity is the single most important predictor of visual outcome and is documented as soon as possible. It is helpful if a baseline acuity can be obtained by history or medical records. The EP should test one eye at a time while covering the opposite eye, beginning with the affected eye. Corrective lenses are worn when possible; if not available, a piece of paper with multiple pinholes (pinhole acuity) can be used. Contact lenses should not be placed in an injured eye. The EP should test routine distant visual acuity at 20 ft from a Snellen chart. Emergent assessment of visual function includes an assessment of light perception, hand motion, finger counting, ability to read print (the distance should be noted), and formal near vision (14 in from a Rosenbaum card). Children require some special consideration. From age 6 months to 3 years, fixing on a moving light source corresponds to 20/40 vision. From age 3 years to 6 years, Allen pictures are used or the “E” chart for those who cannot read. Formal visual acuity should never delay important therapeutic interventions such as eye irrigation (3).

Lids and Other Periorbital Structures

The lids and periorbital structures should be examined for injury (Fig. 25.1). When there is any suspicion of an open globe secondary to blunt or penetrating trauma, no pressure or object is applied to

the globe thereafter for any part of the examination. An exception is bedside ultrasonography (no pressure applied) performed by an experienced examiner in selected patients. The EP should inspect for swelling, ecchymosis, proptosis, enophthalmos, ptosis, lacerations, and FB. If the eye is swollen shut, ultrasonography or lid retraction is used to assess the globe and underlying structures. Ptosis suggests contusion or laceration of the levator palpebrae, Horner syndrome, or third nerve palsy. Upper lid lacerations should be explored for penetration of the tarsal plate, the muscle, or the entire structure (through and through). All three indicate significant force and raise concern for globe injury. Any visible surface FBs should be removed. Penetrating FBs should be left for an ophthalmic surgeon to address. The EP should palpate the orbital rim and soft tissues and the zygomatic arch area, noting point tenderness, step-offs, and subcutaneous emphysema.

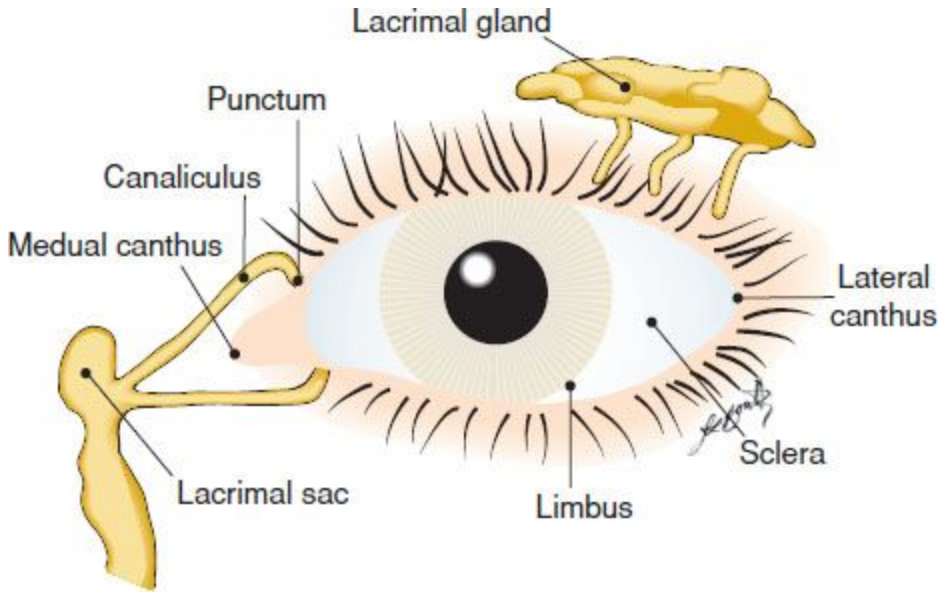


FIGURE 25.1 Periorbital structures.

Anterior Segment

The anterior segment of the eye includes the sclera, conjunctiva, cornea, anterior chamber, iris, and lens (Fig. 25.2). A topical anesthetic is used to examine this part of the eye, generally two drops are adequate, but may be augmented with one to two

additional drops. The EP should inspect for globe laceration, FBs, subconjunctival hemorrhage, chemosis, limbal edema, lid laceration, and contact lenses (these should be removed). Nonadherent FBs should be evacuated as soon as they are identified. The EP should perform a slit-lamp examination to evaluate each anterior chamber component separately: globe, lid margins, cornea, anterior chamber, iris, and lens. A cobalt light and fluorescein dye will highlight abrasions on the cornea and are necessary to perform Seidel test for leaking aqueous.

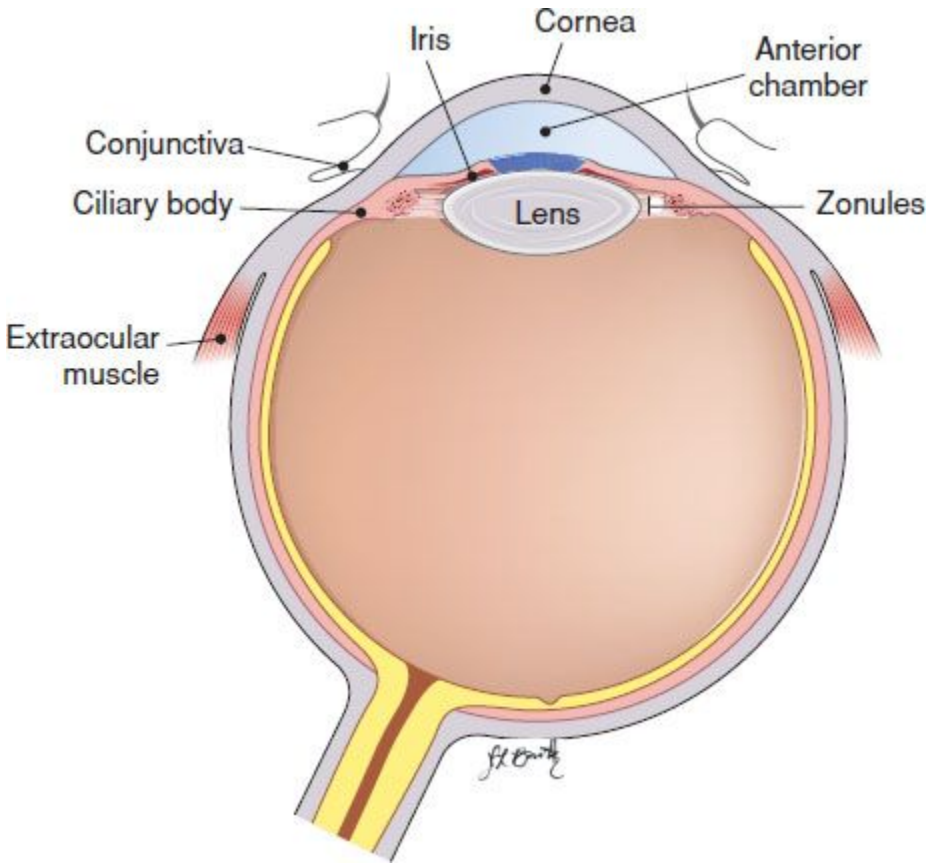


FIGURE 25.2 Cross section of the eye.

Pupils

Pupils provide information via their size, shape, and reaction. The EP should inspect for anisocoria and pupillary distortion. *Anisocoria* is defined as a disparity in size >0.3 to 1 mm. If pupils react briskly and the degree of anisocoria is unchanged with and without bright

light, the anisocoria is physiologic. A distorted pupil suggests globe rupture, iridectomy, or synechiae. In a ruptured globe, the pupil is tear shaped, with the apex of the teardrop pointing toward the rupture. A relative afferent pupillary defect (RAPD) suggests one or more of the following: efferent third nerve damage, glaucoma, iris incarceration, massive internal derangement of the eye (trauma to the eye so severe that light pathways are disrupted), optic chiasm or tract damage, optic nerve damage, retinal detachment, traumatic mydriasis, or vitreous hemorrhage. To test for RAPD, the EP should observe pupil symmetry and size of the unaffected eye while swinging a bright light from eye to eye. When the light strikes the unaffected eye, the pupil constricts. When the light strikes the affected eye, the pupil of the unaffected eye paradoxically dilates.

Extraocular Muscles

Extraocular muscles are tested in the six cardinal positions of gaze. Lateral rectus is innervated by cranial nerve (CN) VI, superior oblique by CN IV (LR6 SO4), and the remainder by CN III. Keys, a light, or toys should be used with infants. Binocular diplopia is seen with an abscess, cellulitis, CN palsy, hematoma compressing the globe or anterior chamber (retro-orbital hematoma or a large external eyelid hematoma), orbital edema, orbital floor or wall fracture with muscle entrapment, or retrobulbar hemorrhage. Monocular diplopia is seen in conditions that distort structures through which light must pass (corneal irregularity, dislocated lens [natural or implant], iridodialysis, or retinal detachment).

Posterior Segment

The posterior segment consists of the optic nerve, retina, and vitreous. Direct ophthalmoscopic examination yields limited but important information. Pupillary dilation is not necessary. Absence of the red reflex or inability to visualize the fundus suggests cataract, hyphema, lens rupture, retinal detachment, or vitreous hemorrhage. Visual field testing by confrontation is sufficient in the ED. Optic nerve function is assessed by testing for RAPD. If the

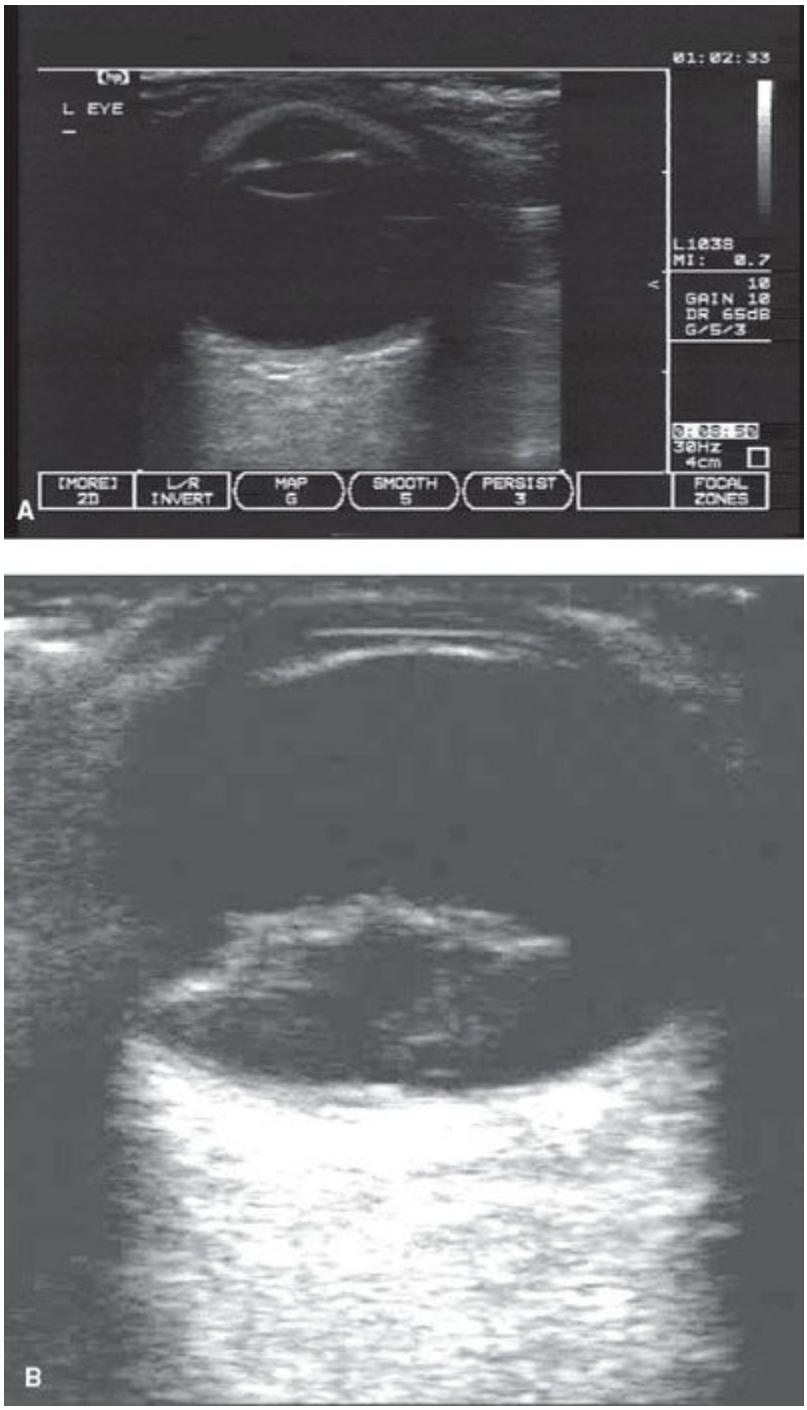
pupils are nonreactive or irregular, red desaturation testing is a suitable substitute. To test red desaturation, the EP should ask the patient to view a bright red object with each eye separately and compare the two images. If the optic nerve is damaged in one eye, the image coming from that eye will appear gray or washed out in comparison to the unaffected eye.

Intraocular Pressure

The intraocular pressure (IOP) may be elevated (>22 mm Hg) in several conditions, including acute glaucoma, globe rupture, hyphema, lens dislocation or swelling, suprachoroidal hemorrhage, and retrobulbar hemorrhage. Normal pressure ranges from 10 to 20 mm Hg (4). IOP measurement is contraindicated if a globe penetration is suspected. When the pressure is <5 mm Hg, penetration of the globe is likely.

Imaging of the Eye

Spiral computed tomographic (CT) scan with axial and coronal cuts is the preferred study when there is suspected injury to the orbit or globe. Plain x-ray has been replaced by CT as the primary radiologic diagnostic tool, as x-ray is unreliable for detecting small (0.2 to 1.5 mm) and nonmetallic FBs (60% false-negative rate), nor is it precise in determining the location of an FB. CT can also identify choroidal detachment, endophthalmitis, fracture, extraocular hemorrhage or hematoma (<3 days old), lens luxation or subluxation, globe rupture, orbital cellulitis, subperiosteal hematoma, vitreous hemorrhage (<3 days old), and retinal detachment. Bedside ultrasound performed by EPs with training and experience has been shown to be highly accurate and useful in diagnosing ocular pathology including FBs (as small as 0.2 mm), retinal detachment, lens dislocation, and vitreous hemorrhage (eFig. 25.1) (5).



eFIGURE 25.1 Emergency bedside ultrasonography of the eye is obtained with minimal pressure on the eye. A: A normal eye is shown with lid, anterior chamber, iris, lens capsule, and vitreous clearly seen. B: A retinal detachment is seen as a hyperechoic area anterior to the retina.

KEY TESTING

Physical examination

- Visual acuity
- Lids and periorbital structures
- Anterior segment
- Pupils
- Extraocular muscles
- Posterior segment
- IOP

Imaging

- CT for detecting FBs and orbital injuries
- Ultrasound for detecting retinal detachment, lens dislocation, and vitreous hemorrhage

ED MANAGEMENT

Subconjunctival Hemorrhage

Typically, an isolated subconjunctival hemorrhage is flat and involves a small portion of the bulbar conjunctiva without any break in the membrane. The history may reveal a related Valsalva maneuver or rubbing of the eye but often does not explain the event. There may not be a history of anticoagulant use, blood dyscrasia, or recurrent subconjunctival hemorrhage. No treatment is necessary as the condition is not threatening to the orbit or globe and will resolve over approximately 14 days. Bulging circumferential bloody chemosis after trauma should alert the EP to the possibility of a ruptured globe.

Simple Eyelid Lacerations and Periorbital Contusion

Eyelid laceration or periorbital contusion mandates a thorough evaluation to rule out involvement of the globe or associated structures. Periorbital contusion is generally managed with ice packs. Concurrent intracranial injury must be ruled out based on history and examination. Instructions for head injury and visual changes are given. Resolution of a simple contusion can take 2 to 3

weeks, whereas hemorrhage into the levator palpebrae may produce ptosis that can last for months. A *simple* eyelid laceration involves neither underlying structures nor the lid margin and can be repaired by the EP. Contaminated wounds must be irrigated without force against the underlying globe. No tissue should be debrided, owing to the excellent blood supply of the eyelid and desire for cosmetic and functional integrity. Wound closure is accomplished with single interrupted sutures of 6-0 or 7-0 nonabsorbable material, which are removed in 5 days. For contaminated wounds, parenteral antibiotics to cover *Staphylococcus* and *Streptococcus* are administered in the ED and oral antibiotics prescribed for 7 to 10 days. Unless trauma was minimal, the patient requires referral to an ophthalmologist for follow-up evaluation.

Complex Eyelid Lacerations and Other Penetrating Trauma

At the first evidence of globe penetration, the EP should document visual acuity, shield the eye, and consult an ophthalmologist. Any protruding penetrating objects are left in place and protected from manipulation until an ophthalmologic surgeon assumes management of the injury. Penetrating wounds near the eye are assumed to have penetrated the globe until proven otherwise.

Isolated lacerations of the conjunctiva are benign; however, laceration of the sclera or full thickness of the cornea is regarded as a penetrating injury. When the cornea is injured, the iris plugs the wound and distorts the pupil into a teardrop shape, with the apex of the drop pointing toward the wound (Fig. 25.3). When there is doubt regarding globe penetration, Seidel test is performed. Fluorescein is instilled onto the eye and observed for a fluid stream leaking from the globe under cobalt light. Parenteral antibiotics should be administered prophylactically to help prevent endophthalmitis. All penetrating eye wounds require an emergent ophthalmologic consultation.

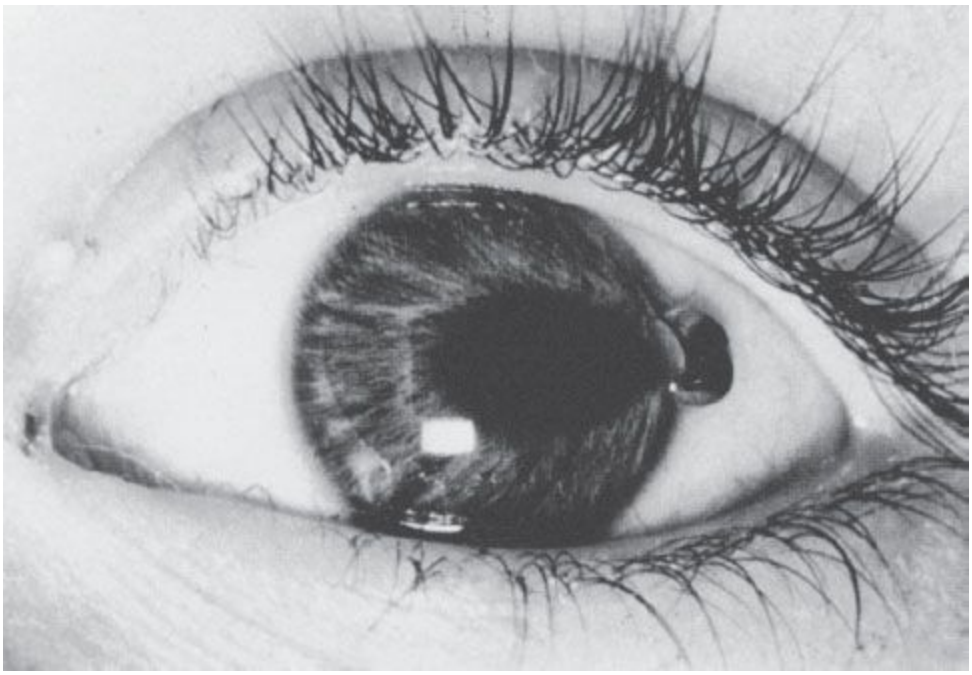


FIGURE 25.3 Penetrating corneal foreign body with entrapment of the iris, forming a teardrop pupil.

Complex eyelid lacerations should be repaired by an ophthalmologic surgeon. These wounds are characterized by exposed orbital fat, globe penetration, muscle laceration, nasolacrimal system damage, tarsal plate laceration, or through-and-through laceration. With any periorbital wound, it is imperative that the lids be retracted to rule out globe penetration. Injury to the *nasolacrimal duct system* is considered when wounds are in close proximity to the anatomic location in the medial eyelids, extending laterally 5 to 7 mm from the medial canthus. Medial to the canthus, the system runs vertically into the nose. A parenteral antibiotic to cover *Staphylococcus* and *Streptococcus* should be administered prophylactically. Wounds should be covered with a sterile saline dressing to keep the tissues moist until the ophthalmologist arrives.

Blowout Fractures and Other Facial Fractures

When a ball, fist, or other object larger than the orbital rim strikes the eye, a blowout or other facial fracture may result. Suggestive complaints and findings are diplopia, enophthalmos, epistaxis,

inferior displacement of the globe, ipsilateral numbness of the cheek and the upper lip, point tenderness of the orbital rim or maxilla, palpable step-off, periorbital ecchymosis, swelling, or even subcutaneous emphysema when sinuses are affected. Plain films have been used for diagnosis but can be falsely negative (≥60%) or falsely positive (≥46%) (6). A spiral CT scan with coronal cuts is preferred for diagnosis. Most blowout fractures involve the inferior or medial walls of the orbit. Involvement of the roof of the orbit signals that considerably more force was sustained and suggests violation of the cranial vault with associated injury to the brain.

Facial injuries such as Le Fort, tripod, and nasal fractures may have an associated eye injury. At the minimum, for an apparently uninvolved eye, the EP should document visual acuity, extraocular movement, the absence of any obvious trauma, and absence of visual symptoms. See Chapter 23 for further discussion of facial trauma.

Management consists of oromaxillofacial and ophthalmologic referral, antibiotics (to cover *Staphylococcus* and *Streptococcus*) for 10 to 14 days, ice packs, nasal decongestant spray, and avoidance of blowing the nose. Surgical repair may be delayed for up to 14 days. The vast majority of blowout fractures will resolve without surgical intervention (7). Urgent ophthalmology referral is indicated for injuries with entrapment or obvious injury to the globe or anterior chamber. Close ophthalmology follow-up is indicated for all others so that occult injuries can be identified.

Burns

Chemical, electrical, infrared, thermal, and ultraviolet (UV) burns may affect the eye. Chemical burns are irrigated immediately with saline for at least 30 minutes. “Time is sight,” and irrigation at the scene is often inadequate. Triage and registration should not further delay immediate and thorough irrigation upon ED presentation. Copious irrigation should continue uninterrupted for at least 20 minutes in the ED. The local poison control center should be contacted for assistance in characterization of the chemical in

question, its pH, and its potential to cause ocular damage. After irrigation is completed (defined as normal serial pH testing of the affected eye for at least 10 minutes after irrigation has stopped), the EP should then examine the eye. *Alkali burns* are particularly devastating. They destroy tissue via *liquefaction necrosis* and are classified by four grades of involvement:

1. Corneal epithelial damage similar to a corneal abrasion with a good prognosis.
2. Cornea hazy but the details of the iris are seen and up to one-third of the limbus is ischemic (whitened). The prognosis is still good.
3. Corneal epithelium is destroyed, and the details of the iris are blurred; one-third to one-half of the limbus is ischemic. The prognosis is guarded.
4. Cornea is opaque, and the details of the iris and pupil are obscured; more than half of the limbus is ischemic. The prognosis is poor.

Acid burns are classified with the same severity grades; however, they tend to produce less extensive damage, as strong acids precipitate proteins via *coagulation necrosis,* which may form a barrier to further spread.

For severe chemical burns, all foreign matter should be removed prior to irrigation by sweeping the fornices with a moistened cotton-tipped applicator. *Calcium hydroxide* tends to cake and may be easier to remove if the applicator is moistened with 10% ethylenediaminetetraacetic acid (EDTA). Minimal irritation and lack of symptoms after irrigation require no further follow-up. Moderate irritation with persistent symptoms requires instillation of antibiotic ointment and referral to an ophthalmologist in 24 hours. Any injury producing more than moderate irritation and having associated significant changes in vision mandates immediate consultation with an ophthalmologist.

Electrical burns are rare; however, the injury may be indirect. Nine percent of patients experiencing electrical injuries involving the head develop cataracts 6 to 12 months after the injury. *Infrared radiation* can produce keratitis, macular damage, or “glassblower’s

cataract" (a heat injury that damages the anterior lens capsule of unprotected glassblowers) after prolonged exposure to heat. *Thermal burns* are rare, as the light of a heat flash reaches the eye faster, producing the upward rotation reflex of the globe (Bell phenomenon), which protects the cornea from damage. Thermal corneal injury occurs when hot objects, such as lighted matches, spitting grease, or car radiator steam, are propelled into the eye. These burns rarely involve more than the corneal epithelium and heal in a few days. Treatment involves the application of cold compresses for up to 2 hours. For partial-thickness burns of the lids and surrounding skin, ophthalmic antibiotic ointment is applied. Minor burns of the cornea are managed similarly to a corneal abrasion. For more severe burns, an ophthalmologist is consulted immediately. *UV radiation* from the sun, tanning salons, or a welder's arc produces acute, diffuse, superficial punctate keratitis of the corneal epithelium about 6 to 12 hours after exposure. The amount of UV radiation is enhanced by reflection off of water, rocks, or snow and at altitudes above 8,000 ft (2,438 m). Prolonged exposure may damage the retina, particularly the fovea, and visual changes may manifest up to 1 to 2 days later (8). Management is similar to that of a corneal abrasion. A nonsteroidal anti-inflammatory medication and narcotic-containing analgesic are prescribed. Ophthalmologic follow-up for all burns of the eye is essential unless the injury is minimal.

Corneal and Conjunctival Injuries

The corneal epithelium is 4 to 6 cells thick, and abrasions generally heal in 12 to 36 hours, sometimes longer, depending on the injury. Full-thickness injuries require prompt surgical repair. Further examination is deferred. Evidence of full-thickness injuries may include a positive Seidel test, an irregular pupil with or without iris prolapse, shallow anterior chamber, cataract, hyphema, or microhyphema. Infection is a risk with any wound, and a retained FB heightens that risk. Consider tetanus prophylaxis for susceptible wounds. Iron-containing FBs will leave a rust ring deposit after

being in place for a couple of hours. Rust rings extrude to the surface over 48 hours, where they are easily removed with an ophthalmic burr.

Corneal abrasions usually present as an FB sensation. Often, there is a history of something striking the eye. Exposure to high-speed particles raises the suspicion for a penetrating eye injury. In addition to an FB sensation, symptoms include blepharospasm, blurred vision, eye pain, halos around lights, photophobia, red eye, and tearing. Visual acuity is mildly decreased. The eye is hyperemic, eyelids mildly swollen, and an anterior chamber reaction (cells or flare) is sometimes noted. Abrasions are highlighted by fluorescein and are best seen on slit-lamp examination. A handheld cobalt light in a darkened room may be used for minor abrasions but will miss more subtle findings such as anterior chamber reaction or corneal microperforation. Soft contact lenses should be removed prior to fluorescein instillation. The EP should evert the upper lid to examine for FBs. Low-mass, low-speed particles largely produce insignificant trauma without anterior chamber reaction; therefore, the IOP does not need to be measured. When larger objects, such as a finger, fist, or ball, strike the eye, the IOP should be measured. After instilling anesthetic ophthalmic drops, removal of an FB is accomplished by either gentle irrigation, a saline-moistened cotton-tipped applicator (brush off), an ophthalmic burr, or a 25-gauge needle held tangential to the corneal surface (pick off). Rust ring removal is accomplished with an ophthalmic burr. The EP should consider instilling a short-acting cycloplegic (one to two drops) to reduce ciliary muscle spasm and synechiae formation secondary to inflammation. Patching is not shown to improve healing rates or reduce pain and thus are generally not used (9). Despite a lack of supporting evidence, ophthalmic antibiotics are often prescribed. Analgesics include a nonsteroidal anti- inflammatory medication (daily dosing for 3 days) and a narcotic as needed. Patients who wear contact lenses or those with large or centrally located abrasions are followed up closely by an ophthalmologist, usually at 1-day interval, until healed. EPs can follow up these corneal

abrasions, but referral to an ophthalmologist the next day is advisable.

Contact lens usage can lead to a corneal symptom complex similar to corneal abrasions. Contact lens–related corneal abrasions, due to overwear or improper fit, result from hypoxic injury, toxic deposits under the lens, or trauma related to insertion or removal of the lens. Infectious keratitis with gram-negative bacterial organisms, particularly *Pseudomonas,* and protozoa, specifically *Acanthamoeba,* may occur as well. Chemical irritation may result from preservatives such as thimerosal and chlorhexidine and inadequate rinsing of lenses after enzyme use. *Tight lens syndrome* occurs within 2 days of placement of the offending lens. The lens appears "sucked-on," leaving a conjunctival imprint after lens removal. Other complications of contact lens use include corneal ulceration, superficial punctate keratitis, anterior uveitis, and infrequently, hypopyon. Treatment begins with removal of the contact lens; fluorescein will permanently stain the lens. An antipseudomonal ophthalmic antibiotic preparation should be prescribed. A cycloplegic should be used if needed. The patient should follow up with an ophthalmologist within 24 hours. (See Chapter 57.)

Conjunctival and *subconjunctival* injuries are minor when the underlying sclera remains intact because the conjunctiva does not provide any structural support to the eye. Visual acuity is usually unaffected. There may be an associated corneal injury, exhibiting the usual corneal symptoms. All conjunctival wounds, with or without an associated FB, must be examined under magnification for scleral penetration. The EP should anesthetize the eye and tease the wound with a cotton-tipped applicator, observing for exposed white scleral tissue. Seidel test can provide additional information. If there is any doubt regarding penetration of the sclera, the injury is managed as though there has been violation of the globe, and an ophthalmologist is consulted immediately. The EP should remove FBs from the fornices by handheld irrigation or forniceal sweeping with a saline-moistened cotton-tipped applicator after anesthetizing the eye. Although commonly practiced, there is no evidence to

support empiric antibiotic treatment. The patient should be referred to an ophthalmologist for next day follow-up.

Other Anterior Segment Injuries

Blunt and penetrating forces inflame, contuse, lacerate, rupture, stretch, and tear the tissues of the anterior segment of the eye, resulting in various injuries such as hyphema, glaucoma, lens displacement, and cataracts. When these conditions are suspected, an ophthalmologist should be consulted immediately.

Traumatic iritis occurs in up to 18% of eye trauma (10). Synonyms for this condition are *anterior chamber reaction, anterior uveitis, uveitis,* and *iridocyclitis.* Inflammation in the anterior segment of the eye results in symptoms of blurred vision, impaired visual acuity, pain, photophobia, hyperemia, and tearing; symptoms vary from mild to severe. The pain of ciliary spasm is exacerbated by light shining in either eye (photophobia) or with accommodation, which increases ciliary muscle contraction (11). When light strikes the unaffected eye, the consensual response exacerbates the pain (consensual photophobia). Protein and white blood cells are visible by slit lamp in the anterior chamber. The limbus is injected. In severe reactions, there may be hypopyon (a layer of white blood cells seen in the anterior chamber). The IOP may be increased or decreased. Treatment includes a short-acting cycloplegic, a nonsteroidal anti-inflammatory medication (for 3 days), and a narcotic analgesic. The patient should be referred for ophthalmologic follow-up within 36 hours.

Hyphema may be microscopic (cells visualized only by slit lamp) or gross (characterized by the percentage of the anterior chamber that is filled) (Fig. 25.4). If blood fills the chamber entirely, it is commonly called an “eight-ball” hyphema. Symptoms include pain, red eye, and blurred vision. Treatment begins by shielding the eye and elevating the head to 30 degrees. Medications, other than those for pain and nausea, are administered only at the direction of an ophthalmologist. Rebleeding occurs in approximately 30% of cases. Outpatient management may be appropriate for some

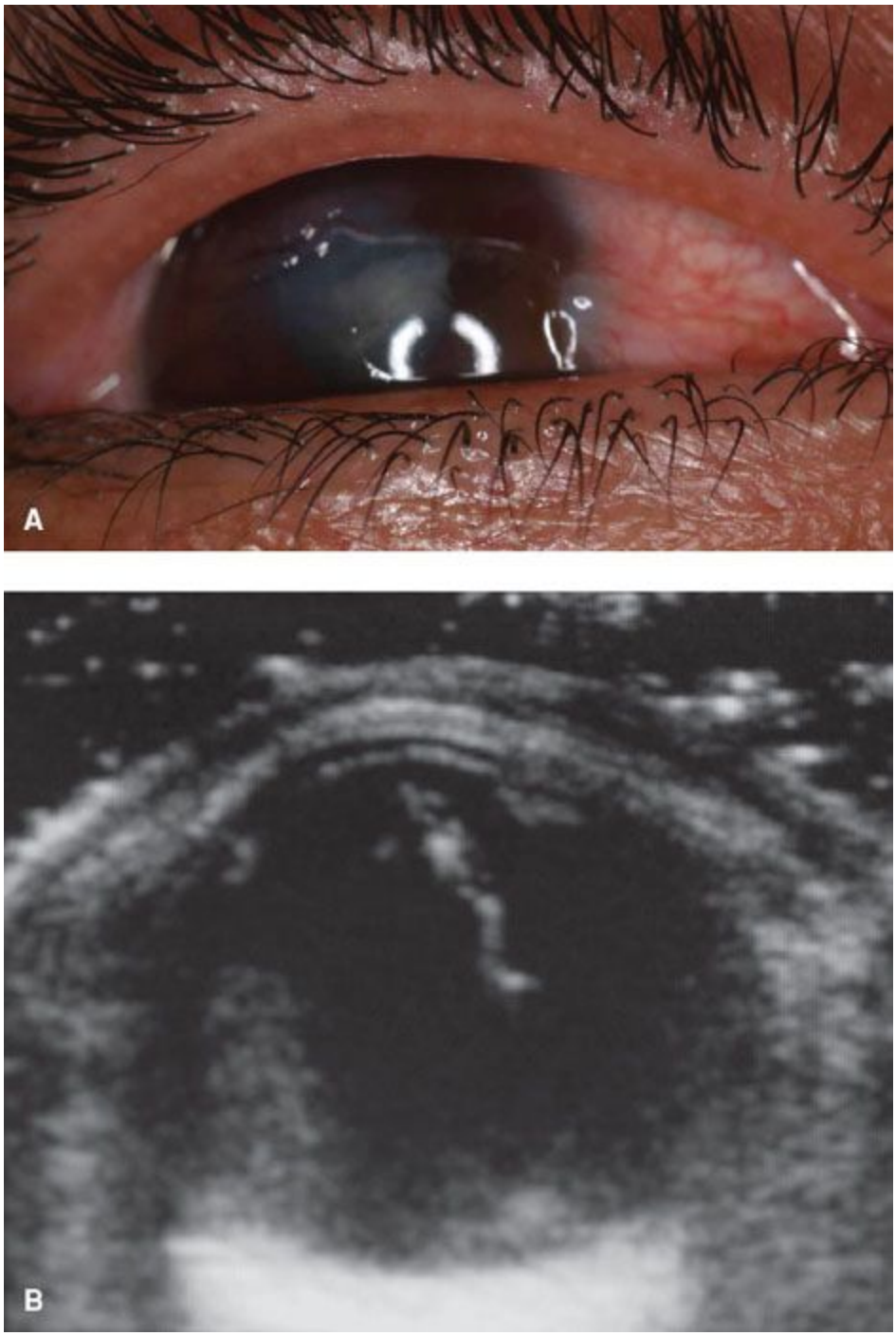
microhyphemas and in compliant patients with good follow-up and no risk factors for complications (e.g., sickle cell disease or bleeding diathesis). Which patients to hospitalize is controversial and should be discussed with an ophthalmologist. Many ophthalmologists manage uncomplicated small hyphemas (<25% of the anterior chamber) without hospital admission. When there is a history of sickle cell disease or trait and IOP is >25 mm Hg, the anterior chamber may need to be washed out (12).

FIGURE 25.4 Traumatic hyphema (20%) with blood layering in the anterior chamber, subsequent to blunt trauma.

Traumatic glaucoma occurs when the trabecular meshwork is disrupted or obstructed by blood or inflammatory debris. Glaucoma may develop acutely over hours or may be delayed for months to years. Medications employed acutely include topical β-blockers, acetazolamide, mannitol and, occasionally, miotics. Lens displacement varies in degree, as do associated symptoms, including myopia, monocular diplopia and, most commonly, blurred vision. Signs include decreased visual acuity, anterior chamber asymmetry, a displaced lens, quivering of the iris (iridodonesis) or the lens

(phacodonesis) after rapid eye movement, visibility of the lens edge, and the presence of vitreous in the anterior chamber.

Traumatic cataracts can occur secondary to blunt trauma (*contusion cataracts*) or penetrating trauma, irrespective of direct injury to the lens capsule, though violation of the lens capsule tends to accelerate the process. Symptoms include blurred vision, glare from lights (particularly headlights), and reduced color vision. Signs include decreased visual acuity, an indistinct retina, lens opacity, and a reduced red reflex (eFig. 25.2). In acute trauma, the eye is shielded as soon as any of these conditions are identified or suspected. Outpatient ophthalmology follow-up is indicated for all patients at risk for traumatic cataract.



eFIGURE 25.2 A: Traumatic cataract (white pupil) after penetrating injury. B: Ultrasound shows a collapsed anterior chamber and foreign body track through the lens and vitreous.

In *traumatic iridodialysis,* the iris is pulled away from the ciliary body along a portion of the circumference (eFig. 25.3). A secondary

"pupil" is formed, causing diplopia. There may be an associated hyphema or dislocated lens. The EP should refer patients with isolated injuries to an ophthalmologist for outpatient follow-up.

eFIGURE 25.3 The iris has been pulled away from the ciliary body (traumatic iridodialysis).

Intraocular Foreign Bodies

Eighty percent of all intraocular FBs enter the eye through the cornea. An obvious penetrating FB of the eye is easy to diagnose. However, there are also more subtle presentations suspected in certain circumstances, including a history of hammering metal on metal (grinding usually does not lead to penetration), a child with eye pain and a history of something sharp near the eye, and a history of head trauma with the eye(s) swollen shut. Metal splinters produced by hammering metal on metal and glass splinters produced by shattering glass can penetrate the eye painlessly (13). Plain films can be helpful but do not differentiate intraocular from extraocular FBs. Some FBs are not intraocular but are intraorbital. In

this circumstance, damage to the globe must be ruled out. The imaging study of choice for detecting intraocular FBs is spiral CT. Intraocular FBs that remain in the eye can produce varying degrees of inflammatory reaction. Copper, iron, steel, vegetable matter, and wood produce severe reactions. Aluminum, nickel, mercury, and zinc produce mild reactions. Carbon, coal, glass, gold, lead, plaster, plastic, platinum, porcelain, rubber, silver, and stone are inert. Iron, nickel, and steel are magnetic. Inflammatory reactions put the eye at risk for endophthalmitis.

Globe Luxation or Subluxation

Luxation of the globe is rare (eFig. 25.4). Visual acuity in the involved eye may vary from being mildly reduced to no light perception. Immediate globe reduction is mandated to relieve symptoms and to minimize visual impairment. If an ophthalmologist cannot be present within 20 minutes to reduce the globe, the EP should attempt reduction by applying gentle pressure to the globe while retracting the eyelids. Attempts at reduction are contraindicated when there is obvious globe rupture. Admission is mandatory for further ophthalmologic management.

eFIGURE 25.4 Globe luxation occurred in this patient from lid traction during contact lens insertion.

Globe Rupture from Blunt Trauma

The globe is ruptured in up to 3.5% of patients with blunt eye trauma (14). Ruptures typically occur at the weakest areas of the globe—the equator (an imaginary line equally dividing the globe into anterior and posterior halves), the limbus, and muscle insertions. Another site of rupture is the globe portion opposite the point of impact. The conjunctiva often remains intact after rupture, and bleeding occurring beneath the conjunctiva produces circumferential bloody chemosis (Fig. 25.5). When severe eye hemorrhage (hemorrhagic chemosis, hyphema, vitreous hemorrhage) or severe periocular hemorrhage has occurred, the presence of one of the following four signs predicts rupture with a sensitivity of 100% and a specificity of 98.5%: (a) a visual acuity that demonstrates light perception or less, (b) an anterior chamber

that is abnormally deep or shallow, (c) an IOP ≥ 5 mm Hg, or (d) an opacity that prevents fundus visualization (15).

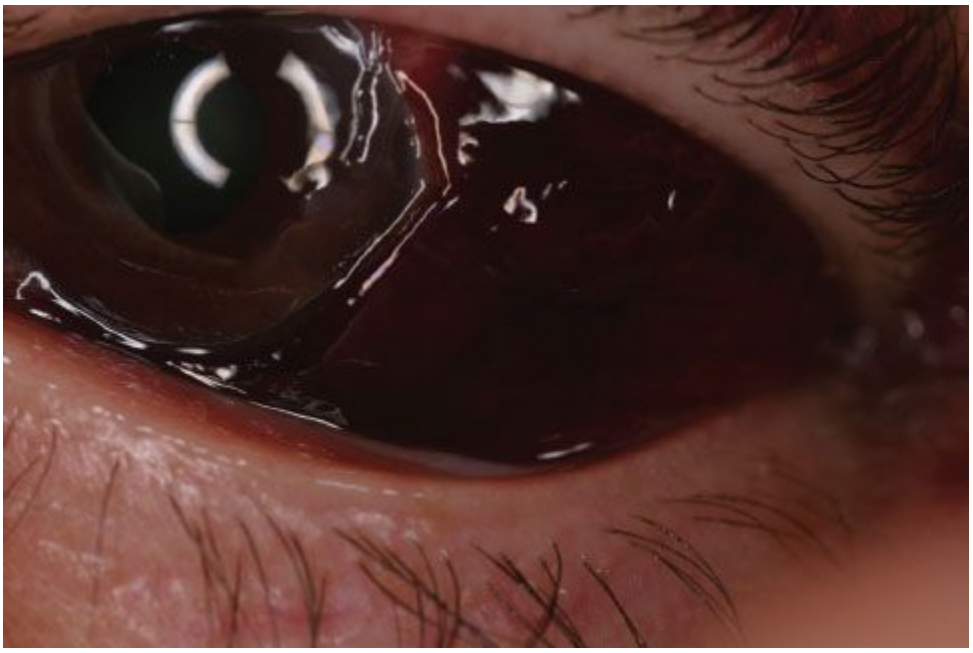


FIGURE 25.5 Large subconjunctival hemorrhage with bloody chemosis associated with blunt trauma.

As soon as a ruptured globe is suspected, the EP should shield the globe using a Fox shield, paper cup, Styrofoam cup, or similar device and consult an ophthalmologist (Fig. 25.6). Parenteral antibiotics (gentamicin plus vancomycin or clindamycin) are administered prophylactically to help prevent endophthalmitis. Bed rest with the head of the bed elevated and antiemetics are indicated to lessen the occurrence of stresses that might increase IOP. When intubation is necessary, the use of succinylcholine should be avoided, if possible, because it raises extraocular muscle tone and will increase IOP. However, the clinical significance of the increase in IOP has been questioned (16).

FIGURE 25.6 Teardrop pupil seen in this patient represents an open globe, and is easily mistaken for a superficial injury.

Posterior Segment Injuries

The posterior segment consists of the choroid, optic nerve, retina, and vitreous. Any indication of injury mandates an immediate ophthalmologic consultation. The choroid, retina, and vitreous may be detached, hemorrhagic, ruptured, or torn. The optic nerve may be injured along its course by direct or indirect mechanisms.

Symptoms are often lacking, or they are nonspecific. They include blurred vision, curtain of darkness, flashes of light, floaters, pain, and red eye. Important signs are blurring of fundus detail, decreased acuity, and RAPD. Anatomic findings are not necessarily apparent on direct fundoscopy performed in the ED, even with dilatation. They are best identified by an ophthalmologist using dilated indirect fundoscopy. EP performed ultrasonography may be helpful in identifying posterior segment injuries at the bedside (17).

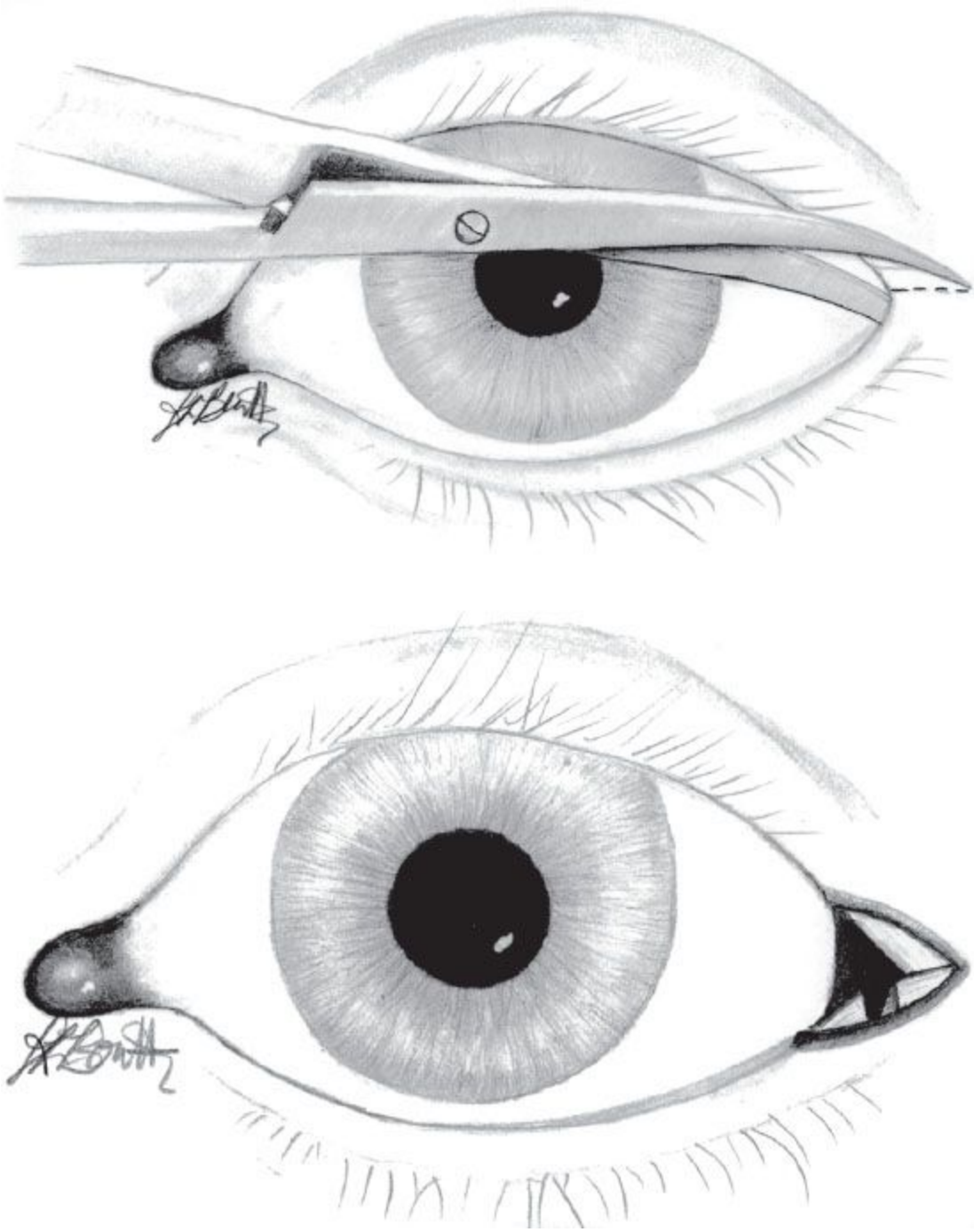
Retrobulbar Hematoma

Retrobulbar hematoma (*orbital compartment syndrome*) is a very rare condition. It is associated with intraoperative retrobulbar injections

and occurs postoperatively. It is less often associated with trauma (eFig. 25.5). Signs and symptoms include severe eye pain, nausea, vomiting, decreasing vision, diplopia, RAPD, decreased ocular motility, hemorrhagic chemosis, proptosis, and resistance to retropulsion of the globe. The retina can withstand total ischemia for only about 90 minutes before damage may be permanent, so rapid treatment without any delays is required. Initiating conservative management (head elevation, ice packs, acetazolamide, mannitol, timolol) while preparations are underway (including consultation) is appropriate, as long as the definitive treatment is not delayed.

eFIGURE 25.5 Retrobulbar hemorrhage demonstrating dramatic proptosis and subconjunctival hemorrhage after a fist strike in a man on warfarin.

Definitive treatment is decompression of the eye by lateral canthotomy and cantholysis to maximize the chance of preserving vision. After local injection with an anesthetic agent, this is performed by crushing the lateral canthus with a small hemostat to reduce bleeding, then incising 1 cm into the tissue with scissors, taking care to avoid injury to the globe. The inferior arm of the lateral canthal tendon is cut to release the globe (eFig. 25.6). An ophthalmologist should be consulted as soon as this condition is suspected.



eFIGURE 25.6 Lateral canthotomy and cantholysis. The inferior arm of the lateral canthal tendon has been incised to release the globe. (Adapted from Cullom RD Jr, Chang B (eds). The Wills Eye Manual. Philadelphia, PA: Lippincott–Raven Publishers; 1994.)

Complications of Eye Trauma

Eye trauma and eye surgery predispose to *endophthalmitis* (25% and 62% of cases, respectively). It develops in 8% to 13% of patients with eye trauma when there is a retained FB. The percentage rises to 26% if the FB is organic material from a rural setting. The onset is sudden and begins from hours to 2 months after the injury. *Bacillus cereus* infection has been reported to develop within 24 hours, streptococci within 2 days, and Staphylococcus epidermidis within 4 days (18). Treatment is intravitreal injection of vancomycin and amikacin by an ophthalmologist. Delay in treatment of even a few hours, particularly with *Bacillus* species, can lead to the loss of an eye. There is an association between *B. cereus* infections, metallic intraocular FBs, and injuries related to soil. Symptoms include blurred vision, fever, a red eye, and severe pain. Signs are anterior chamber reaction, markedly decreased acuity, cells and opacities in the vitreous, conjunctival hyperemia, decreased red reflex, hypopyon, increased IOP, and proptosis. The EP should consider endophthalmitis in any patient presenting with these signs and symptoms and a history of previous eye trauma. Early diagnosis is imperative for the best outcome.

Sympathetic ophthalmia is an immune-mediated inflammatory condition that occurs in the uninjured eye days to years after severe trauma to the opposite eye. After a penetrating or rupturing injury, antigens in the injured eye are exposed, and an immune response is mounted against the uninjured eye. The incidence is 0.2% after penetrating eye trauma and 0.01% after routine eye surgery. Sixty-five percent of cases begin between 2 and 8 weeks after the insult and 90% within 1 year. The signs and symptoms in the sympathetic eye begin as a mild anterior uveitis, which progresses over time to anterior and posterior uveitis. Enucleation of a severely traumatized eye, with no hope for useful vision, appears to eliminate the risk of sympathetic ophthalmia.

CRITICAL INTERVENTIONS

- Document the best-corrected visual acuity. Failure to improve with pinhole suggests a posterior segment injury.

- In patients with chemical burns, continue eye irrigation in the ED until pH is normal and the injury has been assessed.
- Obtain a history of contact lens use (corneal ulcer) or striking metal on metal (globe perforation) in patients with suspected corneal abrasion.
- Protect the eye when globe penetration is suspected; confirm with Seidel test.
- Perform a lateral canthotomy or obtain immediate ophthalmology consultation in patients with retrobulbar hematoma.

DISPOSITION

Disposition of patients with ophthalmologic trauma is arranged on a case-by-case basis. Immediate consultation in the ED or transfer to an appropriate center when an ophthalmologist is not available should take place for patients with globe penetration (or suspicion thereof), complex eyelid lacerations, penetrating FBs, orbital fracture with entrapment, ocular burns, anterior chamber injuries, hypopyon, hyphema (>25% of anterior chamber, associated with increased IOP or blood disorders), globe luxation, orbital compartment syndrome, and traumatic endophthalmitis. All but the most trivial of ocular injuries should be discussed with an ophthalmologist and appropriate outpatient follow-up and care arranged; even apparent trivial injuries may harbor significant occult injury.

Common Pitfalls

- Failure to test visual acuity.
- Using nitrazine paper (measures pH only up to 7.4) to assess alkaline injuries.
- Inadequate visualization of the eye on examination; a slit lamp should be used for best magnification.
- Failure to evert the upper lid to diagnose FB.

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CHAPTER 26
Blunt Neck Trauma

Edward Ullman

The majority of blunt neck trauma occurs in conjunction with significant injuries to the head, cervical spine, and face (1). The most commonly reported injury is the "padded dash syndrome." This occurs when the unrestrained driver decelerates against the steering wheel or dashboard. There have been case reports of isolated neck trauma due to a "clothesline" mechanism in motorcycle, jet ski, snowmobile, and all-terrain vehicle users (2,3). Strangulation occurs from hanging, ligature suffocation, and manual manipulation. Other etiologies include blunt impact secondary to a punch, kick, strike by a baseball bat or other object.

CLINICAL PRESENTATION

There is a wide range of presentations in patients with blunt neck trauma; patients may be asymptomatic, have minimal symptoms, or present in extremis. Therefore, it is critical to recognize that a lack of obvious soft tissue trauma does not rule out a significant injury (2).

Airway injuries can present with hoarseness, stridor, subcutaneous emphysema, hemoptysis, or respiratory distress (4). Laryngotracheal injuries include vocal cord damage or disruption, dislocation of the arytenoid cartilage, tracheal transection, and fractures of the thyroid or cricoid cartilage or hyoid bone (Fig. 26.1) (5). Patients with any alteration in voice should be assumed to have a laryngeal injury. Development of a soft tissue hematoma or edema can externally compress the airway and cause respiratory

compromise. Therefore, continuous airway reassessment is required in patients with blunt neck trauma. Palpation of the thyroid and cricoid cartilages will often reveal tenderness and crepitus as an indication of injury, especially in men, as these landmarks are prominent. If there is loss of definition or deviation of these structures, the likelihood of underlying injury is high.

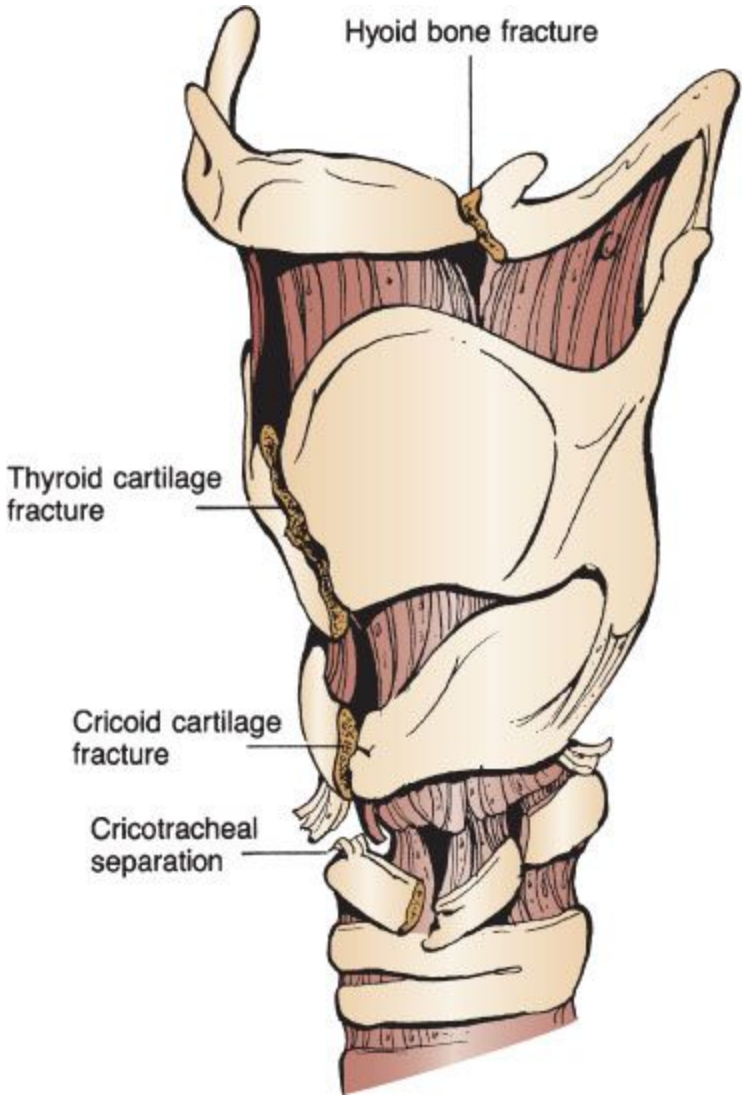

FIGURE 26.1 Types of laryngeal injuries: hyoid bone fracture, thyroid cartilage fracture, cricoid cartilage fracture, cricotracheal separation.

The incidence of vascular injury in blunt trauma patients is 0.08% to 1% (6). As a result, blunt vascular injuries to the carotid or

vertebral arteries are often diagnosed after admission (7). The majority of these injuries occur at the carotid bifurcation or higher and involve multiple vessels (8). Carotid injuries include intimal tears, hematoma, thrombosis, and pseudoaneurysms. Injuries that cause hyperextension and rotation can stretch the carotid artery and compromise the vessel. Acute flexion injuries may crush the carotid artery between the mandible and the cervical spine, leading to thrombosis or intimal damage. An intraoral blow to the soft palate can cause carotid thrombosis, especially in the pediatric population. This usually occurs when a child has an object in his or her mouth and falls, forcing the object into the soft palate. Carotid injuries can present with isolated ipsilateral cerebral findings that include contralateral hemiplegia, sensory loss, and aphasia (9). The presence of a bruit can indicate partial disruption of the carotid by either intimal dissection or thrombus formation. Patients may also present with Horner syndrome (ipsilateral miosis, ptosis, and anhidrosis) owing to disruption of the thoracic sympathetic chain that encircles the carotid artery.

The incidence of vertebral artery injury has increased (10). However, vertebral artery involvement remains difficult to diagnose. Many patients remain asymptomatic owing to an extensive collateral circulation (11). Those who have some deficit complain of vague symptoms such as dizziness, visual disturbances, nausea, and vertigo. Furthermore, because the vertebral artery connects to the basilar artery, an embolic event from trauma could affect either the ipsilateral or contralateral posterior circulation. This can leave the patient with a variety of neurologic deficits without an apparent vascular source.

Several studies recommend evaluation for vascular pathology if any of the following injuries are noted upon trauma evaluation: Horner syndrome; cervical spine fracture that involves the transverse foramen or a facet joint dislocation; Le Fort 2 or 3 fracture; and neurologic deficit not explained by a cervical spine fracture or abnormal head computed tomograph (CT) (12).

DIFFERENTIAL DIAGNOSIS

The existence of other associated injuries and the lack of external neck findings make vascular injuries difficult to diagnose. Neurologic deficits are often delayed; only 10% of those with vascular injury have initial findings. The diagnosis should be suspected in patients with neurologic deficits not explained by head CT and in hemiparetic patients without alteration in mental status. In a series of 66 patients, 34% of those with neck vascular injuries had incongruent neurologic findings (6). The emergency physician should consider this diagnosis in patients with basilar skull fractures and marked external cervical trauma, as associated vascular injuries are often present. The diagnosis should also be considered in patients with anterior neck soft tissue injury such as abrasions, edema, or hematoma.

There are only 10 reported cases of isolated gastrointestinal injury in blunt neck trauma (13). The majority of these injuries occur in conjunction with laryngotracheal injury. Gastrointestinal injury should be considered in patients with pain on swallowing or subcutaneous emphysema; the latter group has a higher incidence of airway compromise.

ED EVALUATION

Because of the difficulty in diagnosing vascular, airway, and gastrointestinal injuries in blunt neck trauma, a systematic evaluation is critical. Table 26.1 lists signs that should raise the suspicion of a vascular injury. In the patient without signs of vascular injury the Denver Modification of Screening Criteria should be used to identify patients at high risk for injury who likely need imaging (14) (Table 26.2). These criteria have been used by the Eastern Association for the Surgery of Trauma (15).

TABLE 26.1
Signs and Symptoms of Vascular Injury

Decreased level of consciousness
Hemiparesis without CT-scan evidence of pathology
Neurologic deficit
Neck hematoma
Horner syndrome
Carotid bruit
Vomiting and dizziness

TABLE 26.2
Risk Factors for Asymptomatic Blunt Cerebrovascular Injury

Glasgow coma scale less than 8
Petrous bone fracture
Diffuse axonal injury
Cervical spine fracture: C1–C3 and fracture through the foramen transversarium
Cervical spine fracture with subluxation or rotation
Le Fort 2 or 3 fracture

In the patient with acute findings (Table 26.1), there is an increasing body of literature that supports the use of multidetector CTA as a screening modality (16,17). While there is earlier data that raises concern in using CTA, that data used 4-slice CTA compared to current 64-slice MDCT CTA (18). Although there is conflicting data, many trauma centers are using CTA for initial evaluation of vascular injuries. Benefits include that it is readily available, noninvasive, and can image other involved anatomy. In those patients with a negative CTA but high concern for vascular injury, angiogram is recommended (16). Magnetic resonance angiography has a reported sensitivity as high as 95% (8). However, difficulty in obtaining this modality in an acute trauma setting limits its usefulness in the ED.

Previously, standard of care for vascular evaluation of blunt cerebrovascular injury was four-vessel digital subtraction angiography. It has a reported sensitivity that approaches 99%. However, there are risks involved with its use. There is a reported 0.5% risk of stroke (19) with another 0.5% risk of hemorrhage and hematoma. Furthermore, it is difficult to obtain off-hours, is invasive, resource demanding, and more expensive.

In the asymptomatic patient or those who have sustained a low-risk event (minor trauma without evidence of acute findings), color-flow Doppler ultrasonography (US) may identify arterial dissection. It has been shown to have sensitivities as high as 92% to 100% in detecting *penetrating* injuries. However, given that the "miss rate" for US in detecting carotid injury is reported to be as high as 8% in the literature, when evaluated retrospectively (9), it is difficult to recommend US as the sole diagnostic modality.

Evaluation of the airway is crucial in patients with blunt neck trauma. Fiberoptic visualization of the endolarynx allows for identification of function and pathology. Plain films have limited values but may indicate evidence of subglottic narrowing of the air column, prevertebral soft tissue swelling, fractured calcified larynx, or the presence of subcutaneous air. CT is effective for identification of cartilage disruption and defines anatomical relationships (20).

Although isolated esophageal injuries after blunt neck trauma are rare, those patients with signs of gastrointestinal injury (Table 26.3) require additional examination. Gastrografin swallow is often the initial study of choice owing to less pleural irritation if extravasation occurs. Barium provides a more sensitive study but has an increased risk of pulmonary complications. Recently, several studies have shown endoscopy as an adequate modality to evaluate for perforation (21).

TABLE 26.3
Signs and Symptoms of Gastrointestinal Injury

Pain on swallowing
Subcutaneous air
Blood in saliva

KEY TESTING

- CT cervical spine in the initial trauma evaluation
- CT angiography for the initial evaluation when there is a concern for vascular injury

- Digital subtraction angiography is reserved for patients with a high concern for vascular injury and a negative CTA

ED MANAGEMENT

Blunt trauma can create difficult airway situations. Evidence of air hunger, stridor, or sonorous respirations should be addressed immediately. The emergency physician should prepare all airway management equipment upon recognition of possible airway compromise. If time permits, anesthesiology or otolaryngology should be alerted owing to the potential for a difficult airway. The current literature indicates that orotracheal intubation is the first-line airway management technique for all blunt neck trauma patients requiring airway control (2). Surgical or needle cricothyrotomy is relatively contraindicated in the presence of bruising, hematoma over the cricothyroid membrane or suspected laryngotracheal injury. In these cases, emergency tracheotomy is recommended to avoid the risk of converting a partial cricotracheal disruption into a complete one. The development of subcutaneous emphysema and a large air leak after intubation and initiation of positive-pressure ventilation indicates a tracheal injury distal to the cuff of the endotracheal tube. This situation requires immediate tracheotomy and, in some cases, median sternotomy to regain control of the distal tracheal segment. Nasotracheal intubation is relatively contraindicated given the high rate of failure and the possibility of worsening an already difficult airway by extending the laryngeal injury.

In patients with marked laryngeal injuries, bleeding and edema can obscure landmarks (22). In those with complete laryngeal transection, use of neuromuscular blockade can make endotracheal intubation nearly impossible. Upon paralysis, the muscles that provide internal stabilization become relaxed, which may result in the endotracheal tube creating a false lumen in the soft tissues of the neck (23). Given this concern, oral-awake intubation is an alternative to rapid sequence intubation, especially in the presence of an anterior neck hematoma. Owing to the increased incidence of

cervical injury in blunt neck trauma patients, careful in-line stabilization should be performed with any airway management technique.

Fiberoptic laryngoscopy has replaced direct laryngoscopy as the standard method of evaluating upper airway injuries. It is useful in assessing airway patency, vocal cord mobility, and the presence of endolaryngeal lacerations or hematoma without causing movement of the cervical spine. Fiberoptic bronchoscopy permits additional visualization of the subglottic airway and may be used to facilitate endotracheal intubation.

It is rare for patients with blunt neck trauma to have life-threatening hemorrhage. However, concern for expanding neck hematoma should always be addressed. This requires aggressive, early airway management as well as otolaryngology or general surgery consultation. In the case of suspected gastrointestinal injury, broad-spectrum antibiotics with anaerobic coverage should be administered.

As the majority of vascular injuries result in luminal narrowing and thrombosis, anticoagulation is the recommended therapy; it results in improved neurologic outcomes in patients with blunt neck trauma (24). As the majority of blunt cervical vascular injuries are high in the internal carotid artery, surgical repair is difficult. Furthermore, in one study, the majority of injuries were “long dissections” not amenable to surgery (12). There is growing evidence that endovascular repair of pseudoaneurysms produces favorable results. This may prove to be a rational approach in patients with cervical vascular injuries (25).

CRITICAL INTERVENTIONS

- Perform early orotracheal intubation in blunt neck trauma patients with evidence of airway compromise.
- Perform CTA in patients who are at high risk for vascular injuries.
- In patients with suspected blunt laryngeal injury, order a neck CT to elucidate the injury pattern.

- Administer broad-spectrum antibiotics to patients with esophageal injuries to help prevent abscess formation.

DISPOSITION

Patients with evidence of blunt neck trauma that involves the airway, vascular, or gastrointestinal systems should be admitted or carefully observed. For these patients, early consultation with an otolaryngologist or general surgeon should be obtained. If the patient is asymptomatic and has a negative workup, discharge is recommended. Comprehensive instructions are critical for patient education in discharged patients. Symptomatic patients should be admitted or transferred to a trauma center where an otolaryngologist and general surgeon are available. It is critical to secure the airway in those symptomatic patients who are transferred, given the potential for respiratory compromise.

Common Pitfalls

- Failure to secure the airway early and failure to prepare for a difficult airway that may require specialty intervention.
- Failure to recognize potential vascular injury in the patient with neurologic deficits and a normal head CT.
- Failure to recognize that vascular injuries frequently have a delayed presentation.

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CHAPTER 27

Penetrating Neck Trauma

Julie Mayglothling

Penetrating wounds of the neck present a therapeutic and diagnostic challenge to the emergency physician. Mortality among patients who suffer penetrating neck injuries in the civilian population approaches 6%. Fatality rates for major vascular injuries may reach 50% (1). Successful management of a penetrating neck wound demands an understanding of the regional anatomy and those structures vulnerable to injury, familiarity with the options for proper airway management, and appreciation of the evolving concepts in the diagnosis and treatment of significant injuries. Even the most benign-appearing wound may belie serious pathology, and extreme vigilance is essential to avert catastrophic airway, vascular, neurologic, and gastrointestinal complications.

A number of anatomic factors predispose structures within the neck to serious injury in the setting of penetrating trauma. Vital components of the respiratory, vascular, neurologic, and gastrointestinal systems course through the neck. Dense musculature and the structural integrity of the cervical spine afford some protection to these structures posteriorly, but the lack of similar shielding anteriorly exposes them to significant injury. Moreover, the majority of the vital structures of the neck are contained within dense, tightly confined fascial compartments, rendering them vulnerable to distortion and compression when bleeding occurs within the deep tissues (Fig. 27.1). For these reasons, penetrating wounds to the neck are best approached conceptually with regard to the site of external penetration, the depth of the wound, and the potential pathway of injury within the deeper compartments.

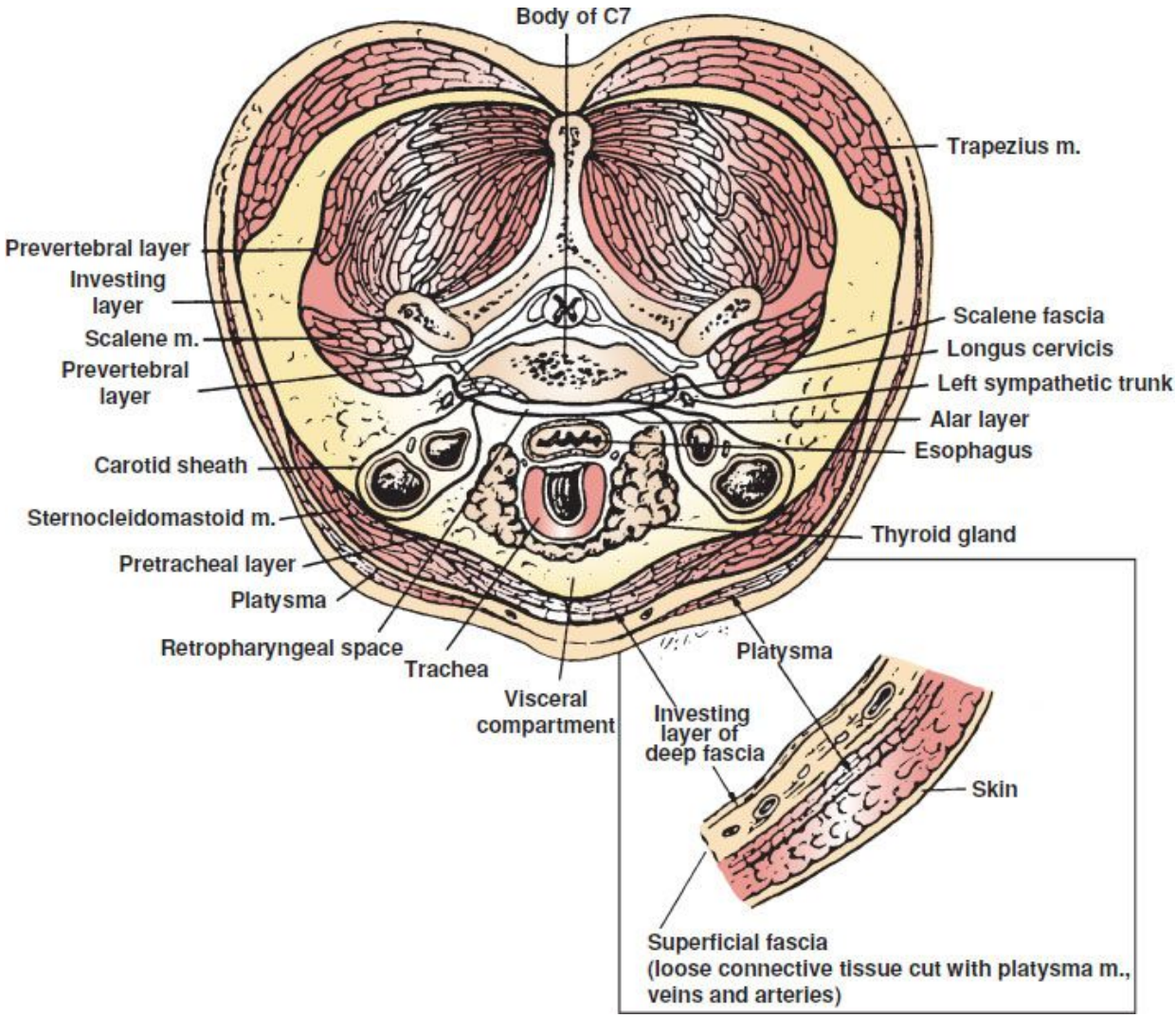

FIGURE 27.1 Cross-sectional anatomy of the neck. (From Gray SW, Skandalakis JE, McClusky DA. *Atlas of Surgical Anatomy*. Baltimore, MD: Williams & Wilkins; 1985, with permission.)

Most sources concur in dividing the external neck anatomically into *posterior* and *anterior* triangles. The *posterior triangle* connotes an area bordered by the posterior aspect of the sternocleidomastoid muscle anteriorly, the anterior edge of the trapezius muscle posteriorly, and the clavicle inferiorly (Fig. 27.2). The defining sides of the *anterior triangle* consist of the mandible superiorly, the anatomic midline anteriorly, and the anterior aspect of the sternocleidomastoid posteriorly. The anterior triangle is further subdivided into three zones, with penetrating injury to each zone

and its underlying structures carrying distinct and important implications for diagnostic evaluation and clinical management (Fig. 27.3).

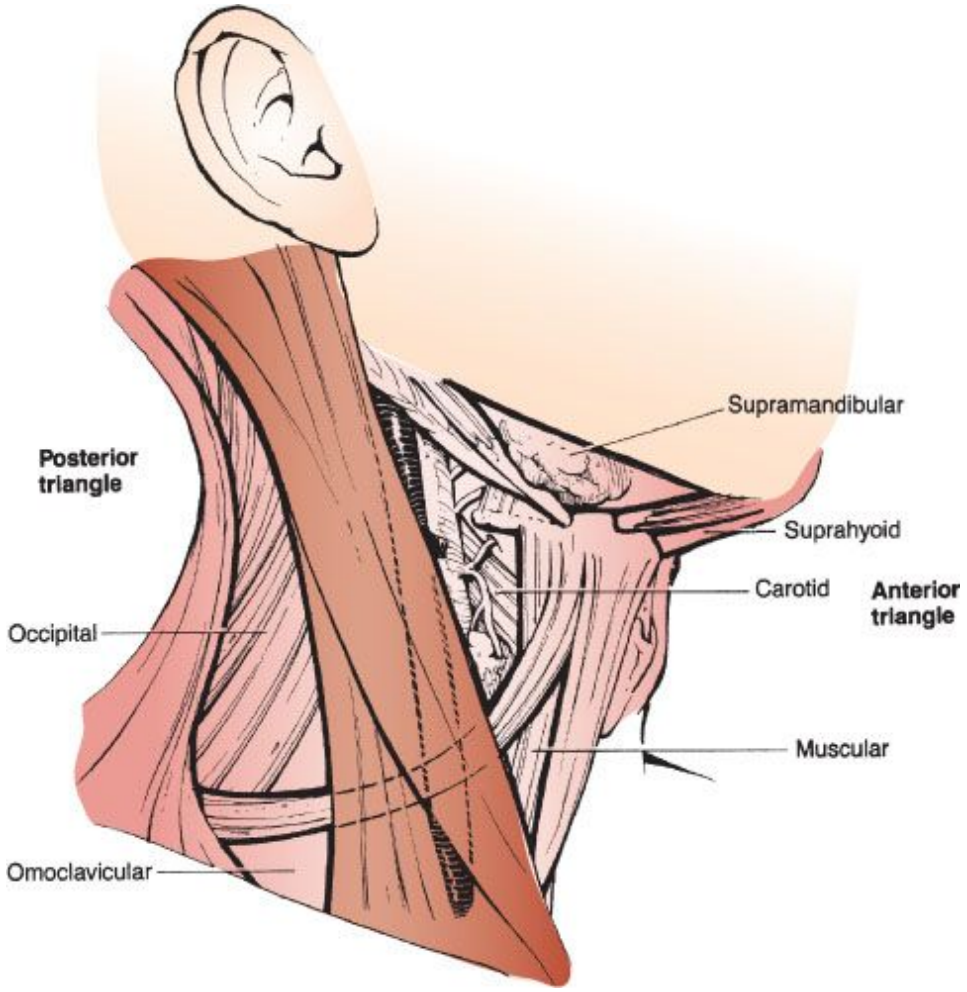

FIGURE 27.2 Anatomy of the neck: anterior and posterior triangles.

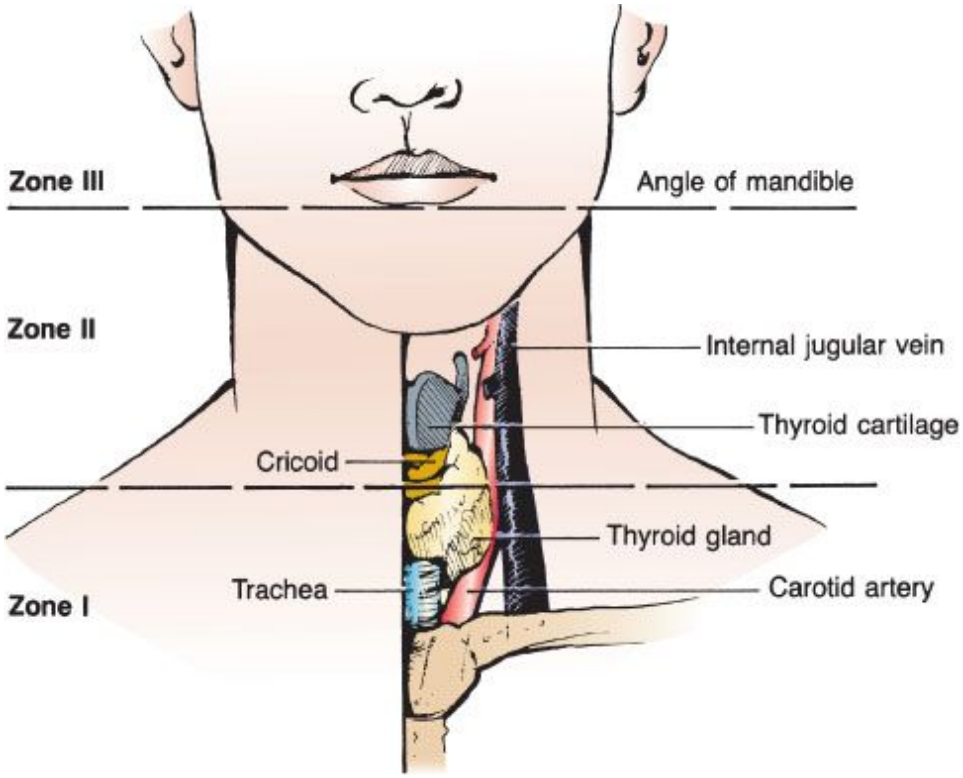

FIGURE 27.3 Anatomy of the neck: zones I, II, and III.

Zone I defines the region between the clavicles and the inferior rim of the cricoid cartilage. Vital structures susceptible to injury after penetrating trauma to zone I include the proximal common carotid, vertebral, and subclavian arteries, the thoracic outlet, the apex of the lung, the trachea, the esophagus, the thoracic duct, and the thyroid. Mortality rates for penetrating wounds to zone I are the highest of the three zones because of the inherent inability to achieve rapid proximal control of vascular injuries and the overall difficulty in gaining exposure to injuries within the thoracic cavity (2).

Zone II spans the distance from the superior edge of the cricoid to the angle of the mandible. Injuries to zone II threaten the carotid and vertebral arteries, the jugular veins, the vagus and recurrent laryngeal nerves, the cervical spinal cord, the trachea and larynx, and the esophagus. As the most exposed anatomic region of the neck, zone II injuries are the most common penetrating wounds in most series (3).

Zone III extends superiorly from the angle of the mandible to the base of the skull. Vulnerable structures in this region include the distal carotid and vertebral arteries, the salivary and parotid glands, the pharynx, the spinal cord, and cranial nerves IX to XII. As with zone I, management of zone III wounds may be problematic because of the difficulty in gaining surgical access to injured structures and control of bleeding vessels.

Within the anterior neck, the superficial fascia lies immediately beneath the skin and envelopes the platysma, a thin sheet of muscle that extends upward from the upper thorax over the clavicles to cover the entirety of the anterior triangle as well as the anteroinferior portion of the posterior triangle. As it extends cephalad, the platysma crosses the mandible to merge with the musculature of the face. This superficial structure has historically been an important landmark in gauging the potential severity of a wound—violation of the platysma by a penetrating mechanism signifies injury to vital underlying structures until proven otherwise.

CLINICAL PRESENTATION

Penetrating neck trauma is most commonly the result of a violent attack. This is reflected in the fact that the majority of victims are young adult males, and that most victims have ingested alcohol or other abusive substances immediately prior to the trauma (4). Other mechanisms of injury include unintentional impalements and bites from animals such as dogs. In most societies, stabbings outnumber gunshot and other wounds as the most common cause of penetrating neck trauma. In the United States, however, gunshot wounds account for an increasing proportion of injuries, particularly among the pediatric and young adult population (3).

Low-energy penetrations occur through such injuries as stabbings with knives or other cutting instruments, impalements, or wounds inflicted by air guns, low-caliber handguns, or shotguns at long range. High-energy mechanisms include discharges from rifles and shotguns at close range as well as shrapnel from explosive devices.

Stab wounds to the neck are typically unilateral and more frequently involve the left side because of the higher likelihood of

right hand dominance in a facing attacker. As the most exposed portion of the anterior neck, zone II is the area injured most frequently, accounting for 50% to 80% of stab wounds to the neck (1). Information relating to an assault, such as the size of the instrument and the angle of the attack, may yield some insight into the potential depth and tract of a wound. Nevertheless, the external appearance of a stab injury to the neck correlates poorly with its underlying severity, and even the most superficial-appearing injury should be approached as potentially life threatening.

Because of the higher kinetic energy imparted to the tissues by an offending missile, approximately 50% of gunshot wounds to the neck results in injury to vital structures (1). As with stab wounds, the depth and pathway of injury of a gunshot wound to the neck can be difficult to predict based upon its external appearance, particularly when it is secondary to a low-velocity projectile. When the wound traverses the anatomic midline of the neck, however, the likelihood of significant injury doubles (5).

DIFFERENTIAL DIAGNOSIS

Penetrating trauma to the neck demands consideration of potential injury to vital respiratory, vascular, neurologic, and gastrointestinal structures (Table 27.1). This differential diagnosis should guide the clinician through an initial evaluation that is rapid yet thorough. Moreover, subtle signs of significant injury may not be appreciable initially and can evolve rapidly. Frequent reevaluation of the patient for developing clinical signs and symptoms is therefore essential to avoiding a disastrous outcome.

TABLE 27.1
Signs and Symptoms of Specific System Injuries

Vascular	Aerodigestive	Neurologic
Hematoma	Respiratory distress	Altered sensorium
Persistent hemorrhage	Stridor	Hemiplegia/quadriplegia
Neurologic deficit	Cyanosis	Respiratory paralysis
Pulse deficit	Hemoptysis	Brown-Séquard syndrome
Horner syndrome (carotid injury)	Tracheal deviation	Extremity paresis or sensory loss
Hypovolemic shock	Subcutaneous emphysema	Horner syndrome (stellate ganglion)
Vascular bruit or thrill	Pneumothorax	Hoarseness (recurrent laryngeal nerve)
Altered sensorium	Sucking wound	Cranial nerve deficit (VII, XI, and XII)
Harsh, machinery-like precordial murmur (venous air embolism)	Dysphonia, aphonia, hoarseness	
	Dysphagia	
	Odynophagia	

Respiratory Injuries

Structures of the respiratory tract that are vulnerable to penetrating neck wounds include the oropharynx, larynx, trachea, and lung apices. Assessment for airway and respiratory compromise takes the highest priority during the initial and subsequent evaluations, and obvious signs of injury include dyspnea, cyanosis, and stridor. Air bubbling at the wound site, subcutaneous emphysema, pneumomediastinum, hemoptysis, voice change, tenderness over the larynx, and unilaterally diminished breath sounds are other important indications of respiratory injury.

Vascular Injuries

Vascular injuries are present in approximately one-fourth of patients and are the leading cause of mortality in the setting of penetrating neck trauma (1). Death results most often from exsanguination secondary to arterial injury, venous injury, or both. Unequivocal or "hard" signs of a major vascular insult include the following:

- Shock either with or without active hemorrhage

- An expanding or pulsatile hematoma
- Carotid bruit or thrill
- Absent radial or ulnar pulses
- Any focal neurologic deficit consistent with hemispheric stroke

Other indications of vascular injury may include diminished pulses in the temporal or facial arteries, decreased breath sounds as a consequence of hemothorax, bleeding within the oropharynx, and signs of venous air embolism such as hemodynamic collapse unresponsive to standard resuscitative measures or the presence of a loud, machinery-like murmur over the precordium.

Gastrointestinal Injuries

Violation of the pharynx and esophagus is frequently unrecognized during the initial evaluation of the patient with a penetrating neck injury, yet the consequences of such an injury can be devastating. Extravasation of saliva, gastric acid, digestive enzymes, and bacteria through a penetrating wound can ignite an aggressive necrotizing inflammatory reaction within the neck and mediastinum. Mortality and morbidity increase sharply when there is a delay in diagnosis and treatment in this setting (6). Pertinent signs and symptoms include dysphagia, odynophagia, hematemesis, and air within the soft tissues as manifested by subcutaneous emphysema or radiographic free air within the retropharyngeal space or mediastinum.

Nervous System Injuries

A number of neurologic injuries can manifest as distinct clinical syndromes after penetrating neck trauma. Gunshot wounds and, occasionally, stabbings that enter the spinal canal from a posterior orientation can partially or completely transect the spinal cord. Complete transection of the cord above the level of C5 may cause acute respiratory failure because of paralysis of the diaphragm. Transection at a lower point will cause paraplegia and loss of upper extremity function according to the level of injury. Hemisection of the spinal cord, or the Brown-Séquard syndrome, yields ipsilateral

hemiplegia, loss of tactile and proprioceptive sensation, contralateral loss of pain, and temperature sensation. Injury to the cervical sympathetic ganglia can present with the ipsilateral ptosis and myosis of Horner syndrome. Damage to the recurrent laryngeal nerve as it courses in the groove between the trachea and the esophagus impairs vocal cord movement, resulting in dysphonia or hoarseness. Cranial nerve transection may result in ipsilateral drooping of the corner of the mouth (CN VII), inability to shrug the shoulders (CN XI), or tongue deviation (CN XII). Injury to a nerve root as it travels from the vertebral foramen to the brachial plexus causes sensory and motor deficits in the corresponding upper extremity.

Cervical Spine Considerations

There is controversy as to whether cervical spine immobilization should be routinely performed in victims of gunshot wounds to the neck. Although such injury is unlikely to result from a stab wound, high-energy projectiles such as bullets can cause injuries that destabilize the cervical spine. The reported incidence of cervical spine injury as a result of gunshot wound ranges from 2.7% to 22% (7). Victims of gunshot wounds to the cervical spine may suffer neurologic deficit either from direct injury to the spinal cord by a transecting bullet or as a consequence of the concussive force imparted to the cord by a projectile passing in close proximity. Victims of gunshot wounds to the neck who do not manifest a neurologic deficit, on the other hand, are very unlikely to have an unstable cervical spine.

A retrospective review of over 45,000 patients using the National Trauma Data Bank (NTDB) found that 0.08% of patients with penetrating trauma would have potential benefit from cervical spine immobilization (7). However, the small potential benefit of routine cervical spine immobilization for penetrating wounds to the neck must be weighed against its dangers. Stabilization devices deprive the clinician of direct visualization and easy palpation of the neck, thus increasing the likelihood that signs of life-threatening complications of injury might be missed. Moreover, cervical spine immobilization may make visualization of the vocal cords more

difficult, further complicating an already challenging intubation. The NTDB review found that prehospital spine immobilization is associated with higher mortality in penetrating trauma and recommends against its use. For these reasons, the Prehospital Trauma Life Support (PHTLS) course and textbook, recommend that spine immobilization is not indicated in patients with penetrating trauma to the head, neck, or torso without neurologic deficit or complaint (8). Thus, the most recent recommendations promote selective spine immobilization in penetrating trauma only for patients with altered mental status, cervical spine tenderness or an abnormal sensory or motor examination.

ED EVALUATION

Attention to airway patency and protection is the central focus of the initial evaluation of any patient with penetrating neck trauma. Vigilance for signs of actual or impending airway compromise begins with the initial patient contact in the prehospital setting and must continue throughout the victim's ED evaluation.

Although several acceptable options for establishing definitive airway control in this clinical setting exist, each possesses inherent challenges and the risk of failure or complication. The emergency physician must therefore be familiar with and capable of quickly implementing an array of airway management techniques when confronted with the victim of a penetrating neck wound. At the same time, rapid and thorough assessment of the patient's circulatory status, the need for emergent operative intervention, and the potential for injury to the major structures of the neck is essential.

In the prehospital setting, all patients with penetrating neck trauma should be considered to have a life-threatening injury. If circumstances allow, prehospital personnel can gather pertinent information such as the circumstances related to the trauma, the character and size of the weapon responsible for the injury, the position of the attacker relative to the patient, and an estimation of the amount of blood lost at the scene.

Immediate airway management in the field is indicated for any patient with acute respiratory distress, stridor, or cardiopulmonary

arrest. If transport to an appropriate trauma center will be rapid, attempts at intubation may otherwise be deferred until arrival in the emergency department (ED). High-flow oxygen should be provided, but ventilation via bag valve mask should be avoided if possible because of its potential to force air through a tracheolaryngeal wound and into the surrounding tissues, distorting neck anatomy and further compromising the airway. Direct pressure should be applied to sites of hemorrhage, and at least one large-bore IV catheter should be placed at a site contralateral to any potential vascular injury.

Upon arrival to the ED, the primary survey must be quickly and thoroughly repeated. Indications for emergent airway stabilization include acute respiratory distress or persistent stridor, copious blood or secretions threatening the airway, extensive subcutaneous emphysema, visible expanding hematoma or tracheal shift, and altered mental status. When such frank signs of airway compromise are absent, however, the emergency physician must remain vigilant for subtle indications of airway compromise such as voice change or odynophagia. Early airway management is warranted, as deterioration can be rapid and catastrophic.

Due to potential damage to surrounding structures causing edema and distortion of airway anatomy, airway management in the patient with a penetrating neck injury should be managed as a difficult airway. Many institutions have difficult airway algorithms or carts which should be available for these situations. A number of options exist for appropriate airway management after penetrating neck trauma. Intubation over a fiberoptic bronchoscope in the awake patient may allow for effective visualization of the vocal cords and passage of an endotracheal tube despite the presence of airway distortion or excessive blood and secretions. It may also identify specific laryngotracheal injuries. Its disadvantages include the need for specialized equipment and expertise and the potential to induce gagging and coughing.

In most EDs, rapid sequence intubation (RSI) using a neuromuscular paralytic agent is the primary modality of airway management in trauma (9). Some authors recommend using caution with RSI in this setting, however, arguing that a decrease in muscle

tone following paralysis holds the potential to worsen airway distortion and thus invite airway disaster. Appropriate caution and, more importantly, preparation for an alternative means of airway management in the event of failure are therefore essential before attempting RSI after penetrating neck trauma. The increased use of videolaryngoscopy may be particularly useful in situations where visualization of the glottis is difficult, as it has been shown to improve first pass success rates and decreased complications compared to direct laryngoscopy (10). To date, there are no studies specifically evaluating the use of videolaryngoscopy in patients with penetrating neck trauma. Similar to fiberoptic bronchoscopy, significant bleeding or copious secretions may limit visualization using such adjuncts.

The establishment of a surgical airway is the most commonly used rescue technique for airway management after failed RSI among patients with penetrating neck injuries (11). Cricothyroidotomy should be performed with a vertical incision to allow for extension of the incision if the cricothyroid membrane is not easily identified initially. Significant hematoma overlying the cricothyroid membrane is a contraindication to cricothyroidotomy because of the potential to convert a partial cricotracheal separation into a complete disruption. Emergent tracheostomy is warranted in this setting.

When the patient is stable, the wound itself should be inspected *but never probed* to determine if it has violated the platysma. Wounds that do not penetrate the platysma may be irrigated and closed. Otherwise, a thorough secondary assessment for the signs and symptoms of significant vascular, respiratory, neurologic, and gastrointestinal injury described previously should proceed to determine further appropriate evaluation and management in the ED.

All patients with penetrating trauma to the neck should receive an upright or supine (if cervical spine precautions are being maintained) chest radiograph. Potentially life-threatening injuries such as pneumothorax or hemothorax can be rapidly diagnosed with chest radiograph. In addition, subcutaneous air that may not be appreciated on physical examination may be visualized on plain

radiograph and may signify injury to the aerodigestive system. Although it may be difficult to distinguish air from an esophageal or tracheobronchial injury from air tracking through a penetrating wound, any positive finding should prompt strong consideration of and further evaluation for these injuries.

The evaluation and management of all penetrating injuries to the neck has changed with the increasing availability of computed tomography (CT), particularly multidetector CT angiography (CTA). The technology is available in most centers around the clock, and it provides rapid information about the vascular, aerodigestive, soft tissue, and bony cervical spine with high resolution (12). In addition, CT, even one performed without contrast, can provide information regarding the trajectory of the penetrating missile and potential injuries from its path (13). Wounds concerning for vascular injuries that were previously evaluated with arteriography, are now evaluated with CTA with equal sensitivity (1,11). All patients who do not have indications for emergent surgical management, and in whom further testing is warranted, should undergo CTA as a first diagnostic modality.

Duplex ultrasonography, or color flow Doppler imaging, is a modality used for diagnosis of arterial injuries and has been demonstrated to have sensitivities of 85% to 92% and specificity of 100% (14). Specifically in zone I and zone III injuries, duplex ultrasonography may be limited due to bony artifact. However, in situations where CTA may be equivocal due to metallic fragments causing difficulty in visualization of the vessels, ultrasonography may be helpful.

Arteriography used to be the gold standard and used frequently for evaluation of vascular injuries in penetrating trauma. However, given the use and sensitivity of CTA, arteriography has been used mostly as a confirmatory test in equivocal CTA's or as a therapeutic modality for those patients necessitating embolization or thrombolytic therapy for vascular injuries (1,15).

Evaluation of the digestive system is imperative in patients with a missile trajectory that is adjacent to the oropharynx or esophagus. Most frequently, patients are found to have an injury on CTA that

either crosses the mediastinum or comes dangerously close to the digestive structures, and requires further testing with either contrast esophagography (usually with either barium or a high osmolality contrast agent such as Gastrografin or Hypaque) or esophagoscopy (endoscopy). Both modalities have been found to have adequate sensitivity and specificity to be used alone and both do not need to be performed (1,16,17).

Diagnostic laryngoscopy and bronchoscopy are used to evaluate injuries of the larynx and trachea. Most airway system injuries can be initially diagnosed by either physical examination or CT, and endoscopic studies are performed for further evaluation or management of these injuries. CT scans without concern for airway injuries do not need routine evaluation with laryngoscopy or bronchoscopy.

KEY TESTING

- Chest radiography
- Multidetector CTA
  - First diagnostic modality for patients who do not have indications for emergent surgical management
- Duplex ultrasonography, or color flow Doppler imaging
- Either contrast esophagography (usually with either barium or a high osmolality contrast agent such as Gastrografin or Hypaque) or esophagoscopy (endoscopy) for evaluation of the digestive system
- Diagnostic laryngoscopy and bronchoscopy are used to evaluate injuries of the larynx and trachea

ED MANAGEMENT

Historically, surgeons advocated mandatory operative exploration of all penetrating neck wounds because of the high mortality and morbidity associated with delays to diagnosis and treatment observed during the First World War. For much of the 20th century, this practice was extended to wounds suffered by the civilian populace as well. As effective adjunctive diagnostic modalities have

emerged, selective operative management for victims of penetrating neck trauma based on clinical assessment and supplementary diagnostic imaging has become standard (1).

Thorough clinical examination is essential for differentiating those patients in need of operative intervention from those who may be observed and further evaluated without immediate surgery. The “hard signs” of vascular injury mentioned above, (active or pulsatile hemorrhage, shock unresponsive to volume resuscitation, expanding hematoma, presence of a bruit or thrill, diminished distal pulses, and a focal neurologic deficit) are clear indications that immediate operative management is required. In addition, air bubbling from a wound, hematemesis, odynophagia, subcutaneous emphysema, or blood in the saliva or aspirate can be signs of injury to the aerodigestive system and also warrant immediate surgical exploration.

Those patients who do not present with signs mandating immediate surgery may be divided into two groups: those who are asymptomatic and those with findings or symptoms concerning for vascular, neurologic, or aerodigestive injury. The specific zone of injury determines the approach to further evaluation and management for patients in either group.

Patients with zone I injury who do not proceed emergently to surgery should undergo further diagnostic evaluation regardless of whether they manifest any of the vascular, neurologic, or aerodigestive symptoms described previously. Asymptomatic patients may harbor occult injury to the structures of the lower neck and upper thorax that may not become apparent until catastrophic decompensation occurs. CT with angiography should be obtained in these patients to evaluate for significant injury. For any trajectory that traverses the mediastinum or passes in the vicinity of the aerodigestive system, evaluation with esophagoscopy or esophagography should then be performed. If the trajectory of the injury is unable to be determined by CT, evaluation of the esophagus should still occur, given the high morbidity associated with missed injury.

Zone II injuries have received the most scrutiny and rigorous study in the past decade. The Eastern Association for the Surgery of Trauma reviewed the literature on penetrating zone II injuries and published Practice Management Guidelines (PMG) in 2008, looking specifically at the management of Zone II injuries (1). A synopsis of their evidence-based recommendations is as follows.

1. Selective operative management for patients without hard signs of injury is recommended to minimize unnecessary operations.
2. High resolution CTA is the initial diagnostic study of choice when available. Arteriography is no longer necessary to rule out an arterial injury.
3. CT of the neck (even without CTA) can be used to rule out a significant vascular injury if it demonstrates that the trajectory of the penetrating object is remote from vital structures.
4. Either contrast esophagography or esophagoscopy can be used to rule out an esophageal perforation.

One question addressed by the PMG that is more controversial is whether the sensitivity of physical examination is high enough to rule out both vascular and aerodigestive injuries. Based on several studies that suggest that physical examination is $>95\%$ sensitive for detecting significant injuries, the EAST PMG gave a level III recommendation that asymptomatic patients with zone II injuries and a normal physical examination do not need imaging studies or operative exploration and may be safely observed for serial physical examinations. However, given the potential morbidity of missed injury, the ease of obtaining CT, and the time commitment needed for serial physical examinations, most clinicians have a low threshold for obtaining imaging studies.

Zone III injuries are evaluated and treated similarly to penetrating head trauma. Patients who are stable but manifest signs of vascular or neurologic injury should receive further diagnostic imaging, most commonly CTA of the neck and head, to evaluate the extent of injury and assist in determining the optimal method of surgical repair. Similar to zone II, although the safety and cost effectiveness of observation in asymptomatic patients with zone III injuries has been reported (3), the increasing use and ease of CT has made most

practitioners evaluate these patients radiographically, regardless of the presence or absence of symptoms. In patients with hard signs of vascular injury, arteriography may be an alternative to operative management. Because of the difficulty of obtaining surgical access, injuries diagnosed by arteriography may be amenable to embolization, thrombolytic therapy or even observation (15).

CRITICAL INTERVENTIONS

- Perform early airway management for patients with acute respiratory distress, stridor, copious blood or secretions, extensive subcutaneous emphysema, expanding hematoma, tracheal shift, or altered mental status.
- Apply direct pressure to active bleeding sites.
- If direct pressure fails to control hemorrhage, insert and inflate a Foley catheter balloon within the wound to tamponade bleeding.
- Evaluate all patients with penetrating neck wounds for vascular, esophageal, and airway injuries.

DISPOSITION

Patients with wounds that do not violate the platysma should receive standard wound care, after which they may be discharged safely. All patients with injuries deep to the platysma must receive emergent surgical consultation and should undergo systematic evaluation as described previously. Even the most benign-appearing wound that violates the platysma in an asymptomatic patient must either be investigated radiographically or be observed for 12 to 24 hours. Patients with negative imaging can safely be discharged from the ED.

Common Pitfalls

- Failure to appreciate the potential severity of a small or “trivial” penetrating neck wound.
- Failure to appreciate subtle signs and symptoms of impending airway compromise.
- Delaying definitive airway management until airway distortion or respiratory compromise have rendered intubation exponentially

more difficult.
- Failure to anticipate difficulties in airway management and implement effective alternative strategies.
- Failure to complete a thorough physical examination to detect subtle vascular, aerodigestive, and neurologic injuries.
- Failure to obtain studies evaluating esophageal or tracheal injury when the trajectory of the penetrating missile is in close proximity to the mediastinum.

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CHAPTER 28

Cervical Spine Fractures

William R. Mower and Jerome R. Hoffman

Each year, U.S. emergency physicians evaluate nearly 1 million patients for cervical spine injury (CSI). Two to three percent of these patients actually have spine injuries, including nearly 11,000 who suffer catastrophic injury and permanent paralysis. Lifetime medical care exceeds $3 million per injury victim, and the cost of annual nationwide care for these patients exceeds $2 billion (1). Medical costs reflect only a portion of the burden produced by catastrophic cervical spine injuries. Affected patients also encounter severe limitations on activity and mobility, loss of income, productivity, and independence and increased rates of medical illness, depression, and suicide (1–3).

CLINICAL PRESENTATION

CSI most frequently occurs after blunt trauma and is often accompanied by other significant injuries, particularly head injury. CSI may be severe and life threatening and may require immediate attention (1). Conversely, unstable CSI can present with subtle clinical findings. Though truly occult injury rarely if ever occurs, patients may be unaware of a serious neck injury if they are intoxicated, have another painful injury that distracts their attention, or have an altered level of alertness that impairs their ability to appreciate the spine injury (4). Though CSI should be suspected in the setting of new-onset neurologic impairment, a normal neurologic examination does not preclude a serious and potentially unstable spine injury (4).

Classification Based on Mechanism

The specific injuries associated with a given force reflect compressive, tensile, and rotatory stresses generated by the force. In general, compressive forces produce failure (fracture) in osseous elements, whereas distractive or tensile forces can result in failure of either ligament or bone, depending on the strength of the involved bone and the rate of loading (ligamentous failure is more likely at high rates of loading) (5). For example, forced flexion generates compressive stress along the anterior spine and posterior tensile or distractive stresses. The anterior compression can produce mechanical failure of the vertebral body resulting in wedge compression and flexion teardrop fractures, whereas the posterior tensile forces can cause stretching and tearing of the posterior ligament complex, as seen in anterior subluxation, or failure across the spinous process, as found in clay shoveler's fractures. Severe flexion forces may destroy the entire posterior ligament complex, obliterate all middle and anterior support, and produce bilateral interfacetal dislocation (6).

Hyperextension and lateral flexion also produce forced curvature of the spine, generating compressive stresses along the concave side of the curvature and tensile stresses along the convexity. Alternatively, pure vertical compression generates only compressive stresses, whereas some combined actions (rotation coupled with hyperflexion or hyperextension) produce relatively complex force distributions. Each of these mechanisms generates specific stress patterns and is associated with a particular family of injuries (5,6).

It is not possible to classify all CSIs in terms of specific applied forces. Injuries involving the occipital articulation and atlantoaxial complex, such as occipitoatlantal and atlantoaxial dissociation, as well as fracture of the dens, appear to have multiple etiologies (5,6). These injuries indicate the application of significant forces capable of producing other spine injuries and should prompt a careful search for additional lesions.

Classification Based on Stability

Functionally, the spine is considered stable if it is able to support physiologic loads without developing displacement or structural changes that cause irritation of the spinal cord or nerve roots or incapacitating deformity or pain (5). Although this definition is relatively straightforward, determining the stability after specific spine injuries can be extremely difficult. Consequently, general principles have been developed to aid in assessing stability (5).

The two-column concept of the spine is particularly useful in understanding pathophysiology and assessing stability of injuries to the lower cervical spine (base of the second cervical vertebra through first thoracic vertebra) produced predominantly by flexion or extension. This construct divides the spine into anterior and posterior columns based on anatomic elements. The anterior column consists of the posterior longitudinal ligament and all anatomic elements anterior to it, including the vertebral body, annulus fibrosus, intertransverse ligaments, and anterior longitudinal ligament. The posterior column consists of all elements posterior to the posterior longitudinal ligament, including the facet and capsular ligaments, the lamina and ligamentum flavum, and the spinous process and interspinous and supraspinous ligaments (5). Biomechanical studies demonstrate that clinical stability is preserved if all of the elements from one column and any single element from the other column remain intact (i.e., all of the anterior elements plus one posterior element or all of the posterior elements plus one anterior element) (7,8).

The two-column concept is not useful in assessing stability for injuries involving the occipital articulation and atlantoaxial complex, and it is of limited utility in assessing injuries associated with lateral flexion (5,6). With a very limited number of exceptions (fractures to the posterior arch of atlas, small avulsion fractures of the anterior arch, and type I dens fractures), consultation with an experienced spine specialist is recommended to determine the stability of these injuries.

Table 28.1 summarizes the injury mechanism and clinical stability associated with common cervical spine injuries. This table presents a conservative interpretation of clinical stability in that many of the

injuries described as unstable may actually have stable variants, but the detailed considerations required for a definitive assessment are beyond the scope of this text. Consultation with an experienced spine specialist is recommended in cases of uncertainty. Table 28.2 describes the specific injuries that characterize common cervical spine fractures.

TABLE 28.1
Injury Mechanism and Clinical Stability of Common Isolated Cervical Spine Injuries

Forced Flexion

Spinous process fracture (Clay shoveler's fracture) (S)
Anterior subluxation (D)
Wedge compression fracture (D)
Bilateral interfacetal dislocation (U)
Flexion teardrop fracture (U)

Extension

Avulsion of anterior arch of the atlas (S)
Fracture of posterior arch of atlas (S)
Laminar fracture (S)
Traumatic spondylolisthesis (hangman's fracture)
  Nondisplaced: type I (S)
  Displaced: types II and III (U)
Extension teardrop fracture (U)
Hyperextension dislocation (U)
Hyperextension fracture dislocation (U)

Vertical Compression

Jefferson burst fracture (U)
Vertebral body burst fractures (U)

Hyperflexion and Rotation

Unilateral interfacetal dislocation (U)
Unilateral interfacetal fracture dislocation (U)

Hyperextension and Rotation

Pillar fracture (S)
Unilateral pedicolaminar fracture separation (S)
Bilateral pedicolaminar fracture dislocation (U)

Lateral Flexion

Unilateral occipital condyle fracture (U)
Unilateral fracture of the C1 lateral mass (U)
Uncinate process fracture (U)
Transverse process fracture (U)

Injuries Due to Multiple or Poorly Understood Mechanisms

Torticollis (atlantoaxial rotatory displacement or fixation) (S)
Dens fractures
  Type I (S)
  Type II or high (U)
  Type III or low (U)
  Os odontoideum (U)
Occipitoatlantal subluxation or dislocation (U)
Occipitoatlantal dissociation (U)
Atlantoaxial rotatory dissociation (subluxation or dislocation) (U)
Atlantoaxial dissociation (U)
Occipital condyle fractures (U)

S, stable injury; D, initially stable, but delayed instability possible; U, unstable or potentially unstable injury, consider consultation with experienced spine specialist.
Modified from Harris JH Jr, Mirvis SE. *The Radiology of Acute Cervical Spine Trauma.* 3rd ed.

TABLE 28.2
Pathophysiologic Lesions Associated with Common Cervical Spine Injuries

Injury	Pathophysiology
Occipitoatlantal dislocation	Separation or disruption of the craniovertebral junction
Burst fracture of the atlas (Jefferson burst fracture)	Fracture of the anterior and posterior arches of the atlas (C1) that may be accompanied by disruption of the transverse atlantal ligament. Unilateral and bilateral variants exist
Dens fractures (odontoid fractures)	Fractures of the axis (C2) involving the dens
	Subclassification is based on fracture location with respect to the dens and has important implications to stability and treatment
Type I	Fracture of the superolateral odontoid process
Type II	Fracture at the base of the dens
Type III	Fracture of the axis body caudal to the junction with the dens
Traumatic spondylolisthesis (hangman's fracture)	Bilateral fractures of the pars interarticularis of the axis (C2). Subclassification is based on displacement of the posterior ring of the axis and disruption of the C2–C3 disk space and reflects important mechanistic and therapeutic implications
Type I	Minimal (hairline) displacement of fracture fragments with preservation of the disk space
Type II	Displacement between anterior and posterior fragments with abnormal disk space
Type III	Displacement between anterior and posterior fragments with bilateral interfacetal dislocation of C2 and C3
Vertebral body burst fractures	Compressive fracture of the vertebral body producing circumferential dispersion of bone fragments
Flexion teardrop fracture	Fracture of the anteroinferior corner of the vertebral body, with associated disruption of the anterior and posterior longitudinal ligaments and intervertebral disk
Extension teardrop fracture	Avulsion fracture of the anteroinferior corner of the vertebral body of the axis (C2)
Wedge compression fracture	Impaction and angulation of the superior endplate and anterior cortical margin of the vertebral body
	Frequently accompanied by injuries to the posterior ligament complex
Bilateral interfacetal dislocation	Disruption of the posterior ligament complex, posterior longitudinal ligament, and intervertebral disk, with bilateral anterior dislocation of the articular masses
Unilateral interfacetal dislocation	Unilateral rotation and dislocation of the articular mass (perched or locked facet); usually accompanied by disruption of the articular capsule and posterior ligament complex but may also involve disruption of the contralateral articular capsule
Hyperextension dislocation	Disruption of both anterior and posterior longitudinal ligaments and disruption or detachment of the intervertebral disk frequently reduces

DIFFERENTIAL DIAGNOSIS

Neck pain and tenderness are common findings among trauma patients, but significant CSI is rare. Most patients have minor strains and contusions that require no specific therapy. As such, it is not necessary to identify specific soft tissue injuries in most cases but rather to exclude serious injuries that could result in permanent dysfunction or catastrophic disability.

Injury to the spine and spinal cord should be suspected in any trauma patient presenting with a new-onset neurologic deficit. At the same time, it is important to recognize that these same deficits can be due to a variety of other etiologies outside the cervical spine, such as vascular injury, intracranial injury, lower spine injury, or injury to one or more peripheral nerves (4,6). Respiratory distress in blunt trauma patients may also be due to a variety of causes, including upper CSI. The neck contains a remarkable number of vital structures, including the spinal cord, carotid and vertebral arteries, jugular veins, trachea, and esophagus. All are susceptible to injury and may produce pain indistinguishable from that produced by CSI. It is important to note that trauma patients frequently have multiple injuries, and identifying a specific injury does not preclude the presence of other injuries. Spine injuries in particular provide evidence of significant axial forces and should prompt clinicians to evaluate affected patients for secondary CSIs as well as injuries to other axial elements, including the lower spine.

ED EVALUATION

Once vital functions have been ensured, blunt patients should undergo a meticulous examination to detect other injuries and ascertain baseline function. Patients should be assessed for mental status changes that may limit the reliability of clinical evaluations. Careful attention should be placed on assessing the face and calvarium. Many of the force vectors that cause CSIs originate in the head, and meticulous evaluation may disclose such injuries as well as provide information relating to potential spine injuries. The neck

and spine should be examined to detect areas of pain and swelling. A detailed neurologic examination is essential and should include an assessment of reflexes and pathologic findings associated with spine injury (bulbocavernosus reflex, priapism, decreased rectal tone). Sensory innervation follows dermatomal distributions and is particularly helpful in localizing lesions in patients with cord injuries (Table 28.3). Similarly, deficits in motor function are associated with specific nerve root levels and may also prove informative in determining injury levels (Table 28.3). Any patient with suspected spine injury should also undergo a careful evaluation of the remaining axial anatomy.

TABLE 28.3
Sensory and Motor Examination

Spinal Cord Level	Sensory Distribution	Functional Ability
C4	Neck	Spontaneous breathing
C5	Shoulder and arm	Shrug shoulders
C6	Thumb	Elbow flexion
C7	Third digit	Elbow extension
C8	Fifth digit	Flexion of fingers

Because CSI can be permanent and devastating, all trauma patients should be evaluated for potential CSI. Radiographic imaging provides the definitive means of assessment but is unnecessary in many cases. Clinical assessments based on decision guides such as the NEXUS low-risk criteria (4) and Canadian C-spine rule (CCR) (9) allow clinicians to identify patients who are at very low risk of CSI and can be safely spared the expense and radiation exposure associated with imaging. Although these instruments reliably detect injury (high sensitivity) and preclude injury in patients deemed “low risk” (high negative predictive value), they exhibit poor positive predictive value, and the majority of “non–low-risk” patients do not have a CSI.

The NEXUS criteria are based on five historical and physical examination findings. Patients are at low risk and may safely be

spared radiographic imaging provided they exhibit *all* of the following criteria: (a) no posterior midline cervical spine tenderness, (b) no evidence of intoxication, (c) normal level of alertness, (d) no focal neurologic impairment, and (e) no distracting painful injuries. The criteria are subject to interpretation by individual physicians. Although they are not precisely defined, each criterion is further clarified as follows (10).

- Midline posterior bony cervical spine tenderness is present if the patient complains of pain on palpation of the posterior midline neck from the nuchal ridge to the prominence of the first thoracic vertebra or if the patient has pain with direct palpation of any cervical spinous process.
- Patients should be considered intoxicated if they have either of the following: (a) a recent history by the patient or an observer of intoxication or intoxicating ingestion or (b) evidence of intoxication on physical examination such as odor of alcohol, slurred speech, ataxia, dysmetria or other cerebellar findings, or any behavior consistent with intoxication. Patients may also be considered to be intoxicated if tests of bodily secretions are positive for drugs (including but not limited to alcohol) that affect level of alertness.
- An altered level of alertness can include any of the following: (a) Glasgow Coma Scale (GCS) score of 14 or less; (b) disorientation to person, place, time, or events; (c) inability to remember three objects at 5 minutes; (d) delayed or inappropriate response to external stimuli; or (e) other evidence of cognitive impairment or altered alertness.
- Any focal neurologic complaint (by history) or finding (on motor or sensory examination).
- No precise definition for distracting painful injury is possible. This includes any condition thought by the clinician to be producing pain sufficient to distract the patient from a second (neck) injury. Examples may include, but are not limited to (a) any long-bone fracture, (b) a visceral injury requiring surgical consultation, (c) a large laceration, degloving injury, or crush injury, (d) large burns, or (e) any other injury producing acute

functional impairment. Physicians may also classify any injury as distracting if it is thought to have the potential to impair the patient's ability to appreciate other injuries; conversely, no injury should be considered distracting in a given patient simply because it is frequently so among a group of patients. Thus, not all fractures are distracting; it is as always a matter of judgment for the clinician to decide whether a given injury is likely to impair a given patient's ability to appreciate other (e.g., cervical spine) injuries.

The CCR excludes patients from risk classification if they (a) are younger than 16 years, (b) have a GCS score <15, (c) have grossly abnormal vital signs, (d) were injured more than 48 hours previously, (e) have penetrating trauma, (f) present with acute paralysis, (g) have known vertebral disease (ankylosing spondylitis, rheumatoid arthritis, spinal stenosis, or previous cervical surgery), as determined by the examining physician, (h) are returning for reassessment of the same injury, or (i) are pregnant (9).

According to the CCR, among patients suitable for risk classification, imaging is mandatory for those aged 65 years or greater, those with a dangerous mechanism of injury (fall from a height of 3 ft or greater, or 5 stairs; axial load to the head such as from diving; motor vehicle collision involving speed of 100 km/h or greater; motor vehicle accidents involving rollover, ejection, or a recreational vehicle; or a bicycle collision). Patients who do not meet these high-risk criteria require further risk assessment based on range of neck motion. Prior to assessing range of motion, clinicians must first determine whether a patient can safely undergo rotational assessment. Patients for whom rotational assessment can be safely completed include (a) those with a rear-end motor vehicle collision (excluding those pushed into traffic, those hit by a large vehicle such as a bus or truck, and those hit by high-speed vehicles); (b) those in a sitting position in the ED; (c) patients who were ambulatory at any time; (d) patients whose neck pain was delayed in onset (neck pain not immediately following event); or (e) those who have no midline cervical spine tenderness. Imaging should be obtained on patients who cannot safely undergo assessment of range

of motion, as well as all patients who are unable to actively rotate neck 45 degrees to the right and left (9).

Patients who fail to meet low-risk classification based on clinical assessment, should undergo imaging that is individualized according to the patient's clinical presentation and potential for CSI. Plain radiographs frequently fail to identify important cervical spine injuries, and are not highly sensitive for CSI—including for some clinically important injuries—so they should not even be considered in patients with at least a moderate prior probability of injury. These include the elderly (in whom it is often difficult to evaluate plain films because of the common presence of concomitant osteoarthritis), those in whom any movement is impossible or contraindicated, those already scheduled for computed tomography (CT) scanning for some other reason, and those with a truly high prior probability of injury (11). On the other hand, in a reasonably young patient who requires imaging merely because of failure to meet low-risk criteria, but in whom the prior probability of CSI is truly low, and it is likely that clearly interpretable plain films can be accomplished, an adequate three-view series has an extraordinarily high-negative predictive value if it can be read as clearly negative (12).

Noncontrast CT provides the most definitive means of evaluating the bony cervical spine and is the current standard for evaluating the cervical anatomy of most blunt trauma patients, including most adults and older pediatric patients (12,13). Such an imaging is highly sensitive in detecting the presence of CSI as well as the specific form of injury (12). CT imaging may miss fractures of the dens as well as injuries in the plane of the scanner such as dislocations and subluxations, particularly if imaging is completed using early-generation scanners (14). The cross-table lateral radiograph provides a reliable means for detecting these potential missed injuries and, consequently, still plays a role in the initial evaluation of blunt trauma patients undergoing radiographic imaging when reconstructions are inadequate (6,13).

Radiation exposure is an important concern on younger children, and x-ray imaging that includes an anteroposterior (AP), lateral, and

open-mouth odontoid still plays an important role in screening this population for injury (13). Plain radiography requires correct exposure and positioning; injury cannot be reliably excluded if images are incomplete or inadequate. Abnormal radiographs should also cause concern, even though no specific injury is evident. Misalignment of spine elements and changes in soft tissue contours may indicate the presence of serious injuries. The interpretation of plain radiographs can be difficult and requires comprehensive knowledge of the subtle findings that may indicate significant injury as well as a detailed understanding of the normal variants that may simulate injury patterns (6). The inexpert interpretation of inadequate cervical spine radiographs is a recipe for disaster. Noncontrast CT imaging is indicated for children with demonstrated cervical spine injuries, and for those who cannot be safely cleared on the basis of x-ray imaging (13).

Imaging, whether CT or x-ray, must be of high quality, with complete visualization of the spine and soft tissues from the base of the skull to the top of the first thoracic vertebra. High technical quality is essential, with proper patient positioning, removal of foreign bodies, and avoidance of motion artifact (6).

Magnetic resonance imaging (MRI) offers an effective and discriminating means for assessing the soft tissues of the cervical spine. Bony injuries are frequently missed on MRI; hence, it is not an adequate substitute for CT or x-ray imaging. MRI is most useful in assessing injuries to the cord, intervertebral disks, and paracervical tissues, including supporting ligaments. Use of this modality should be limited to patients with posttraumatic myelopathy or radiculopathy, patients with pain disproportionate to their physical and radiographic findings, and those with demonstrated occipitoatlantal subluxation, and to assess the acuity of anterior subluxations. MRI and MR angiography may also be valuable in assessing the vertebral arteries, particularly in patients who have pedicolaminar fracture separations (6,13).

Flexion–extension radiographs have been advocated in the acute evaluation of suspected anterior subluxation when plain films are nondiagnostic. However, this type of imaging is known to miss

acute anterior subluxations, presumably because of reflex cervical spasm, and has not been shown to enhance the early detection of this initially stable injury (15,16). Consequently, the value of flexion–extension imaging is questionable in the emergency setting and may provide false security to patients with missed injuries. A better approach to the diagnosis and management of patients with suspected anterior subluxation would be to employ MRI to evaluate patients with typical imaging findings or those with neurologic symptoms such as radiculopathy. The remaining patients appear to be best evaluated by delayed flexion–extension imaging once their spasm has resolved (13,15,17).

Motion fluoroscopy has been used to assess spine stability in selected patients, particularly those who cannot cooperate with flexion–extension imaging. Use of this modality, particularly passive fluoroscopy, is controversial because of its potential to produce permanent cord injury. Currently, there are no emergent indications for the use of this imaging (13,18).

KEY TESTING

- Use clinical judgment to initially assess whether a blunt trauma patient is truly at risk of a CSI.
- Apply a decision instrument to determine whether radiologic imaging is indicated.
- High-quality x-ray imaging provides appropriate radiologic evaluation for children and lower-risk young adults.
- CT imaging should be used in assessing high-risk individuals, and older patients.
- MR imaging is inappropriate for most patients. It is inadequate for assessing bone integrity and should be used selectively in assessing vascular and soft tissue structures.

ED MANAGEMENT

The primary goal of the emergent treatment of spine injury is to prevent further injury and disability. Although CSI can be devastating, initial management must focus on ensuring other vital

functions, including adequate airway, breathing, and circulation. Trauma patients should always be presumed to have an unstable spine injury until proven otherwise, and their entire spine should be protected until an appropriate evaluation can be completed.

Special care must be exercised in managing patients who require mechanical ventilation. Although all methods of securing an adequate airway, including surgical approaches, can produce movement of the cervical spine, this should not result in neurologic deterioration if performed appropriately and, of course, ventilatory support should not be delayed because of concerns related to spine injury. Inadequate ventilation not only places other organ systems at risk but increases the potential for ischemic and hypoxic injury to the spine.

The airway should be secured using familiar techniques that are least likely to require repeated attempts. Most patients can be orotracheally intubated, whereas those with extensive neck and facial injuries may require a surgical airway. If time, resources, and skilled practitioners are present, fiberoptic bronchoscopy offers an alternative means of intubation that may confer theoretical advantage, but has yet to be shown to improve neurologic outcomes (19). Adequate preparation and equipment are essential, as is a careful technique. An assistant who can help stabilize the spine and ensure anatomic alignment may prove particularly helpful. Axial traction may produce harmful distractive forces and is contraindicated (19).

Protecting the spine from additional mechanical injury is essential. Cervical spine “precautions” should be used to maintain an anatomically neutral position. Immobilization may include the use of various collars, backboards, and supplemental devices such as braces and sandbags. However, the use of these devices should be directed toward the primary goal of maintaining appropriate spine alignment. Ill-fitting collars and poor patient positioning may actually produce further injury, despite the fact that the spine is immobilized. Backboards and cervical collars can be removed as soon as the spine has been cleared in patients who are uninjured or

as soon as alternative measures have been initiated to provide support for patients with spine injuries.

Specific treatments for spinal cord injuries are currently limited. Meticulous supportive care, including optimization of ventilatory and circulatory support, is essential and plays a substantial role in the preservation of neurologic function. Injury to the spinal cord may produce loss of sympathetic and vasomotor tone and subsequent neurogenic shock. Intravenous crystalloids should be administered as initial treatment, and patients should be carefully assessed for other sources of hypotension, particularly other traumatic injuries. Vasopressors may be required to attain adequate perfusion pressures, but these agents should be used carefully, with an appreciation of their ability to temporarily mask the hypovolemia produced by coexisting injuries. Neurogenic shock may also be complicated by bradycardia, which may require specific pharmacologic treatment if accompanied by circulatory embarrassment.

Corticosteroids and G_{M1} gangliosides have been advocated in the treatment of acute cord injuries, but there is insufficient evidence to support the use of either agent. They are recommended as options in the treatment of spinal cord injuries but have no demonstrated benefit. Treatment with methylprednisolone in particular appears to be more likely to produce harmful side effects as opposed to clinical benefit (20).

CRITICAL INTERVENTIONS

- Suspect CSI in all trauma patients. Though CSI frequently occurs in the setting of multisystem trauma, presentation can be subtle. Geriatric patients are particularly at risk of injury after relatively minor trauma such as ground-level falls (21).
- Support the airway, ensure ventilation, and treat other life-threatening injuries. Assume cervical spine injuries are present in all blunt trauma patients until they are sufficiently stable to permit a thorough evaluation.

- Maintain normal cervical anatomy (cervical immobilization). Provide physical support for the spine to prevent further injury.
- Perform an adequate diagnostic evaluation. Obtain complete and adequate radiographic imaging in any cases in which injury cannot reliably be excluded on the basis of clinical evaluation. Ensure that the images are interpreted by clinicians familiar with the subtle radiographic findings associated with many cervical spine injuries.

DISPOSITION

Patients who have a minor spine injury, including those with a cervical strain, or an isolated stable fracture that does not require further specific intervention, may be discharged with analgesia and instructions to avoid uncomfortable or painful activities. A soft cervical collar is frequently dispensed to such patients but has little proven benefit (19,22).

An experienced spine specialist should be involved in the care of all patients with evidence of neurologic injury, those with a clinically unstable or potentially unstable spine injury, a fracture that is displaced or otherwise interferes with normal function, and those whose injury status is uncertain. Rigorous protection from additional injury is indicated in all cases involving an unstable fracture or a neurologic deficit. Consultation with a spine specialist should be initiated as soon as the patient's condition permits.

Common Pitfalls

- Failure to suspect injury, particularly in patients without localized tenderness or neurologic deficits, and among intoxicated patients, those with altered levels of alertness, and those with other painful or distracting injuries.
- Performing an inadequate physical examination. Clinical clearance is impossible in patients who cannot cooperate with a detailed examination (intoxicated patients and those with altered mentation or other painful distracting injuries). Detailed and

complete neurologic examination is essential with careful attention to dermatomal function and pathologic reflexes.

- Performing inadequate radiographic evaluation. Imaging must be of high technical quality with complete visualization of the spine from the base of the skull to the cervicothoracic junction. Images must be free of foreign bodies and motion artifacts.

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CHAPTER 29

Thoracolumbar Spine Fractures

Amy Kaji and Robert S. Hockberger

Thoracolumbar spine (TLS) injuries are relatively uncommon in the United States; however, of all blunt trauma patients presenting to the emergency department (ED), the rate of TLS injury is up to 15% (1). Although there are only approximately 40 cases per million population in the United States, spinal cord injury (SCI) predominantly afflicts productive young adults. Between 1973 and 1979, the average age at injury was 28.7 years, but as the median age of the general population has increased, the average age of injury has also increased (2). Since 2005, the average age at injury is 41. Over 80% of SCI occur among males, and the total annual cost to society from medical expenses and lost productivity is estimated to be over $5 billion. Statistics from the National Spinal Cord Injury Database (NSCID) reveal that motor vehicle–related collisions account for 39.2% of all SCI, followed in frequency by falls, and intentional acts of violence, such as gun shot wounds (2). At its peak, violence caused 24.8% of SCI between 1990 and 1999, but since 2005, it accounts for only 14.6% of SCI. Sports-related injuries have also decreased over time.

The human spine consists of 33 bony vertebrae: 7 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 4 coccygeal. In the adult, the spinal cord ends at the level of the L1 vertebrae and then continues as the cauda equina. Due to its highly exposed location above the torso and its inherent flexibility, the cervical spine is the most commonly injured part of the spinal column (see Chapter 28). In contrast, the

thoracic spine is rigidly fixed. The thoracic ribs articulate with the respective transverse processes and sternum, and a great amount of force is necessary to damage the thoracic spine. The middle of the thoracic spine is a vascular watershed area; thus, a vascular insult may lead to spinal cord ischemia. The second most commonly injured spine region is the thoracolumbar junction. The transition zone from thoracic to lumbar vertebrae is vulnerable to injury because of the juxtaposition of a rigidly fixed thoracic spine against a flexible lumbar spine. The spinal column also changes from a kyphotic curve to a lordotic curve at this level, and of all TLS injuries, 90% of the fractures occur in the region between T11 and L4. Allowing for more flexion and extension, the thoracolumbar junction facet joints are oriented differently when compared to other vertebral levels, and this is thought to concentrate greater forces at this level. Since the spinal canal is relatively wide at this level, however, thoracolumbar junction injuries rarely result in complete cord lesions and more commonly result in incomplete cord lesions (3).

CLINICAL PRESENTATION

Classification

White and Panjabi first described the concept of spinal instability, which they defined as the inability of the spine to maintain the anatomical relationships between vertebrae necessary to prevent neurologic injury or compromise (4). Since then, numerous classification schemes for TLS injuries have been reported. Utilizing results from a retrospective review of over 400 TLS injuries, Denis delineated a means to assess stability of vertebral fractures in which he divided the spinal column into three columns: anterior, middle, and posterior. The anterior column includes the anterior longitudinal ligament, the annulus fibrosus, and the anterior half of the vertebral body; the middle column comprises the posterior longitudinal ligament, the posterior annulus fibrous, and the posterior half of the vertebral body; whereas the posterior column includes the supraspinous and interspinous ligaments, as well as the facet joint

capsule (Fig. 29.1) (4). According to this scheme, the stability of the spine is based upon the integrity of two of the three spinal columns, although Denis stipulated that the stability of the middle column determined the integrity of the spine. Denis used his three-column theory to distinguish major and minor TLS fractures. Spinal instability can also be inferred from plain radiographs as a loss of 50% vertebral height or an angulation at the thoracolumbar junction of greater than 20 degrees (5). The spine is also considered to be unstable in the presence of a neurologic deficit, since the spinal column has failed to protect the cord. In general, a stable fracture pattern in a neurologically intact patient may be treated nonoperatively.

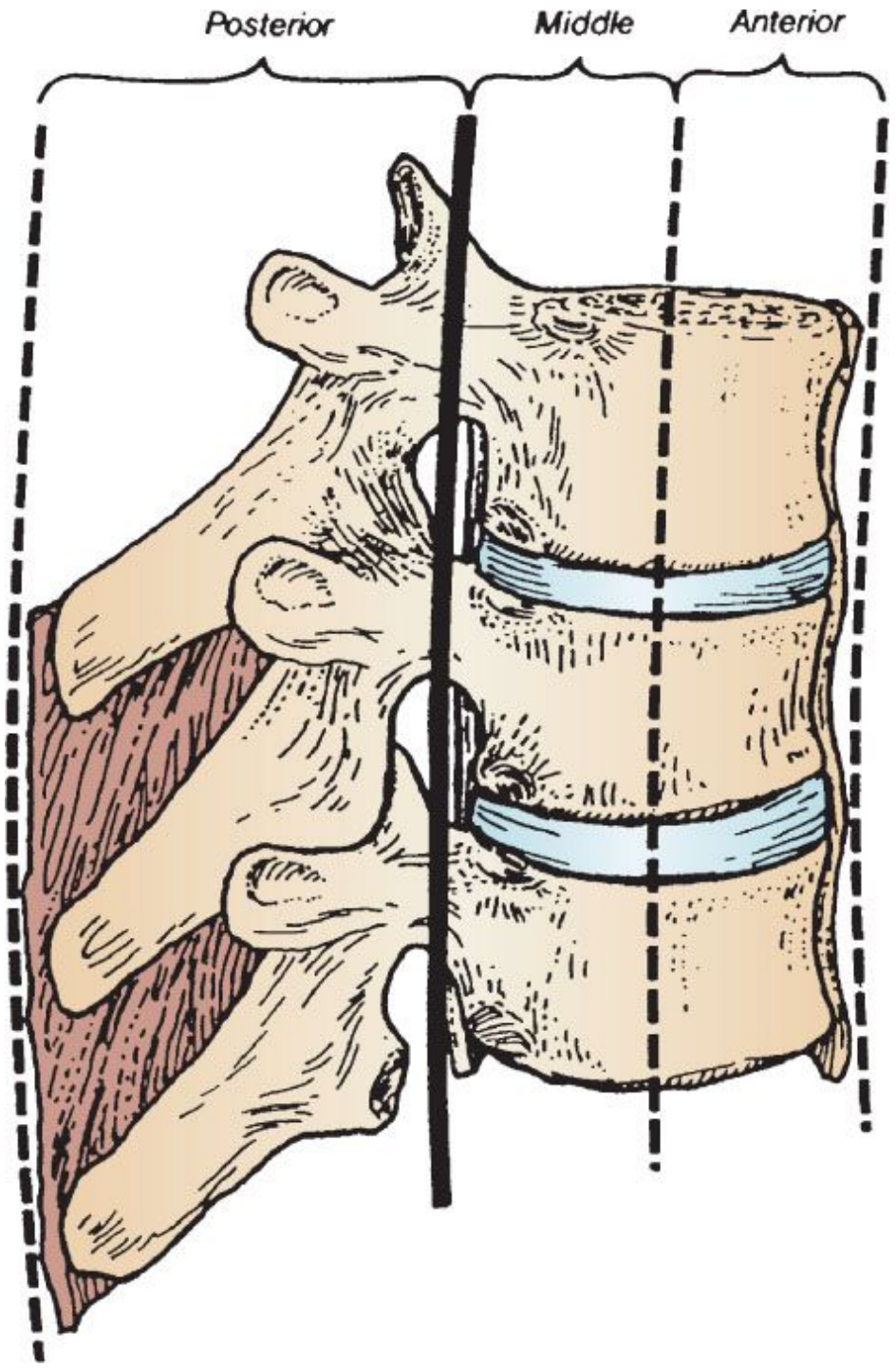

FIGURE 29.1 The three-column concept used to classify thoracic and lumbar spine fractures. (From Galli RL, Spaite DW, Simon RR. Fractures, dislocations, and major ligamentous injuries. In: Galli RL, Spaite DW, Simon RR, eds. *Emergency Orthopedics: The Spine.* Norwalk. Appleton and Lange; 1989, with permission.)

McAfee subsequently classified TLS injuries into five different patterns: wedge compression fractures, chance fractures, stable and unstable burst fractures, flexion–distraction injuries, and translational injuries. All of these fractures result from one or more of the three mechanisms of injury: axial compression, axial distraction, and translation (6). McAfee distinguished stable and unstable burst fractures based upon the integrity of the posterior ligament complex (6). A combination of Dennis' division of major and minor fracture patterns and McAfee's fracture–dislocation scheme is currently widely accepted and utilized (Table 29.1).

TABLE 29.1
Thoracolumbar Spine Injury Classification

Acute TLS Injury	
Major fracture/dislocation	Minor fracture
Wedge compression fracture: Isolated anterior column fracture	Transverse process fracture
Chance fractures: Horizontal vertebral avulsion injury with center of rotation anterior to vertebral body	Spinous process fracture
Stable burst fractures: anterior and middle column compression failure with posterior column intact	Pars interarticularis fracture
Unstable burst fractures: Compressive failure of anterior and middle columns with disruption of the posterior column	
Flexion–distraction injuries: Compressive failure of anterior column with tensile failure of the posterior column	
Translational injuries: Disruption of the spinal canal in the transverse plane, usually due to a shear mechanism	

More recently, the Spine Trauma Study Group collaborated to create the Thoracolumbar Injury Classification and Severity Score (TLICS), which identifies three major injury characteristics to describe TLS injuries: injury morphology, posterior ligamentous complex integrity, and neurologic status (Table 29.2) (7). The injury morphology is categorized as one of the following four injury

patterns: compression, burst, translational/rotational, or a distraction pattern (these are detailed further later in the chapter). The integrity of the posterior ligament complex, which consists of the supraspinous ligament, interspinous ligament, and facet joint capsules, can be assessed from plain radiographs, CT scans, and MRI. The neurologic status is graded in increasing order of severity as: neurologically intact, nerve root injury, complete SCI and incomplete SCI or cauda equina. Each characteristic is assigned a score and then summed to yield the TLICS. A score ≥ 5 suggests the need for operative treatment due to significant instability, whereas a score ≥ 3 suggests nonoperative treatment. A score of 4 may be treated either operatively or nonoperatively. The TLICS has yielded $>90\%$ agreement in the management of thoracolumbar trauma (8,9).

TABLE 29.2
Thoracolumbar Injury Classification and Severity Score Scale

Category	Points
Injury Morphology	
Compression	1
Burst	1
Translational/rotational	3
Distraction	4
Neurologic Status	
Intact	0
Nerve root	2
Cord, conus medullaris	
Incomplete	3
Complete	2
Cauda equina	3
Posterior Ligamentous Complex	
Intact	0
Injury suspected/indeterminate	2
Injured	3

Wedge Compression Fractures

Wedge compression fractures account for 50% to 70% of all TLS fractures and usually result from compressive failure of the anterior column after an axial load is applied in flexion. Simple wedge fractures are defined as demonstrating less than 10% compression, and there is generally no neurologic impairment since the middle column remains intact. Simple wedge fractures are stable, since pure flexion injuries do not disrupt the posterior ligament complex, and an additional rotational force is necessary to cause an unstable fracture pattern. However, if there is severe compression (>50%), kyphosis greater than 20 degrees, multilevel compression fractures, or a rotational component to the injury, then the posterior ligamentous complex may fail and progress to involve the middle column, resulting in spinal instability (6).

Wedge compression fractures generally result from falls, motor vehicle collisions, and occasionally generalized tonic–clonic seizures. Bilateral calcaneal fractures should alert the emergency physician to the possibility of a TLS fracture due to axial compression from a vertical plunge (4). Associated injuries are common, and fractures frequently coexist at other spinal levels. It is important to image patients older than 75 who complain of back pain, even after apparently minor injury, since 25% of this age group sustains osteoporotic compression fractures. In conscious patients who have no major distracting injury, there is invariably pain or tenderness at the site. While neurologic deficits are rare, wedge compression fractures are associated with a high incidence of intestinal ileus (3).

Best seen on lateral radiographs, simple wedge compression fractures demonstrate anterior compression of the vertebral body without any disruption of the posterior cortex (Fig. 29.2). The AP radiograph may demonstrate a subtle increase in the interspinous distance if there is a kyphotic deformity. Of note is that there is no vertebral subluxation, and thus, acute neurologic injury almost never occurs with a simple, single wedge compression fracture. It is important to ascertain that the posterior elements remain intact, since the integrity of the posterior cortex is the key feature that distinguishes the wedge compression fracture from an unstable burst fracture. However, standard radiographs may not be adequate to

evaluate the integrity of the posterior vertebral cortex. In an analysis of 67 thoracolumbar radiographs reviewed by two radiologists and two orthopedists, 20% of the CT-confirmed burst fractures were initially misdiagnosed as wedge fractures (10). Thus, CT scan should be considered when plain radiographs demonstrate what appears to be a wedge compression fracture with any possible involvement of the posterior cortex, since plain radiographs are not accurate in determining involvement of the posterior wall of the vertebral body. Once an injury is identified, CT is better at delineating the bony structures and helps to demonstrate the integrity of the middle column, the degree of canal compromise, as well as subluxations and fractures of facets and lamina.

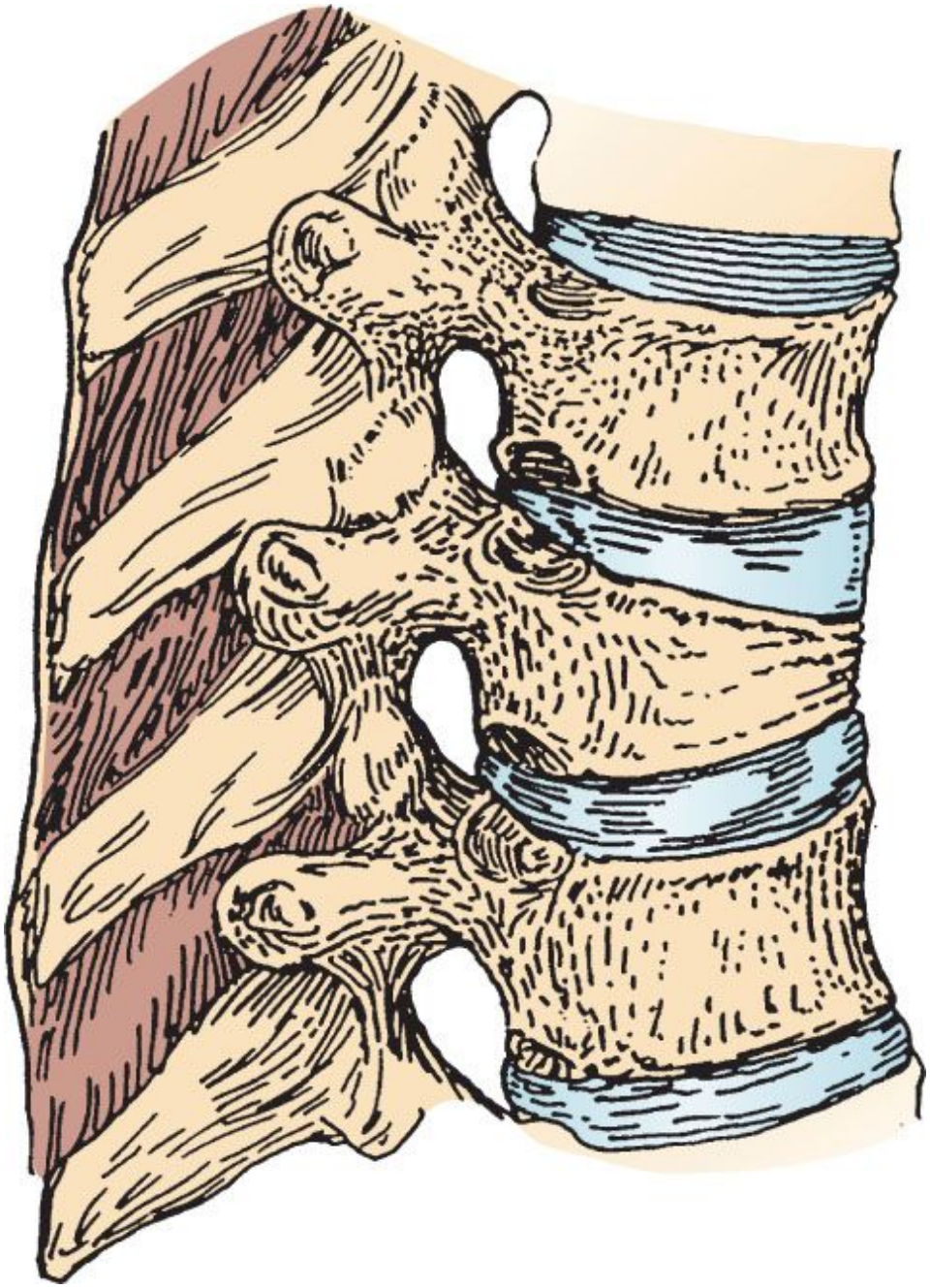

FIGURE 29.2 An anterior wedge fracture due to flexion in the thoracic region (ribs removed for visualization). (From Fractures, dislocations, and major ligamentous injuries. In: Galli RL, Spaite DW, Simon RR, eds. *Emergency Orthopaedics the Spine.* Appleton and Lange; 1989, with permission.)

Chance Fractures

Chance fractures account for only 5% of all TLS fractures and result primarily from a mechanism of distraction although there may be a minor component of flexion. The axis of flexion is anterior to the nucleus pulposus and the anterior longitudinal ligament. If the distraction forces are great enough, both the middle and posterior columns may be disrupted.

Chance fractures are usually seen in victims of automobile or airplane accidents who are wearing lap seat belts (3). Examination may reveal ecchymosis of the lower abdomen and tenderness at the fracture site, but the absence of these signs does not preclude the diagnosis. Although neurologic deficits occur in less than 5%, Chance fractures are commonly associated with intra-abdominal injuries, such as intestinal perforations, hematomas, and contusions.

Chance fractures are best seen on a lateral radiograph, which demonstrates a horizontal disruption through the spinous process, laminae, transverse process, pedicles, and the vertebral body (4). The height of the vertebral body is increased, and the distance between the spinous processes above and below the injury may appear to be widened (Fig. 29.3). The AP view may demonstrate an increased interspinous distance and a schism in the transverse processes. Routine axial CT scans of the spine frequently miss these fractures, since the image cuts are parallel to the level of the injury. Thus, sagittal reconstruction of CT images is recommended if a Chance fracture is suspected (4).

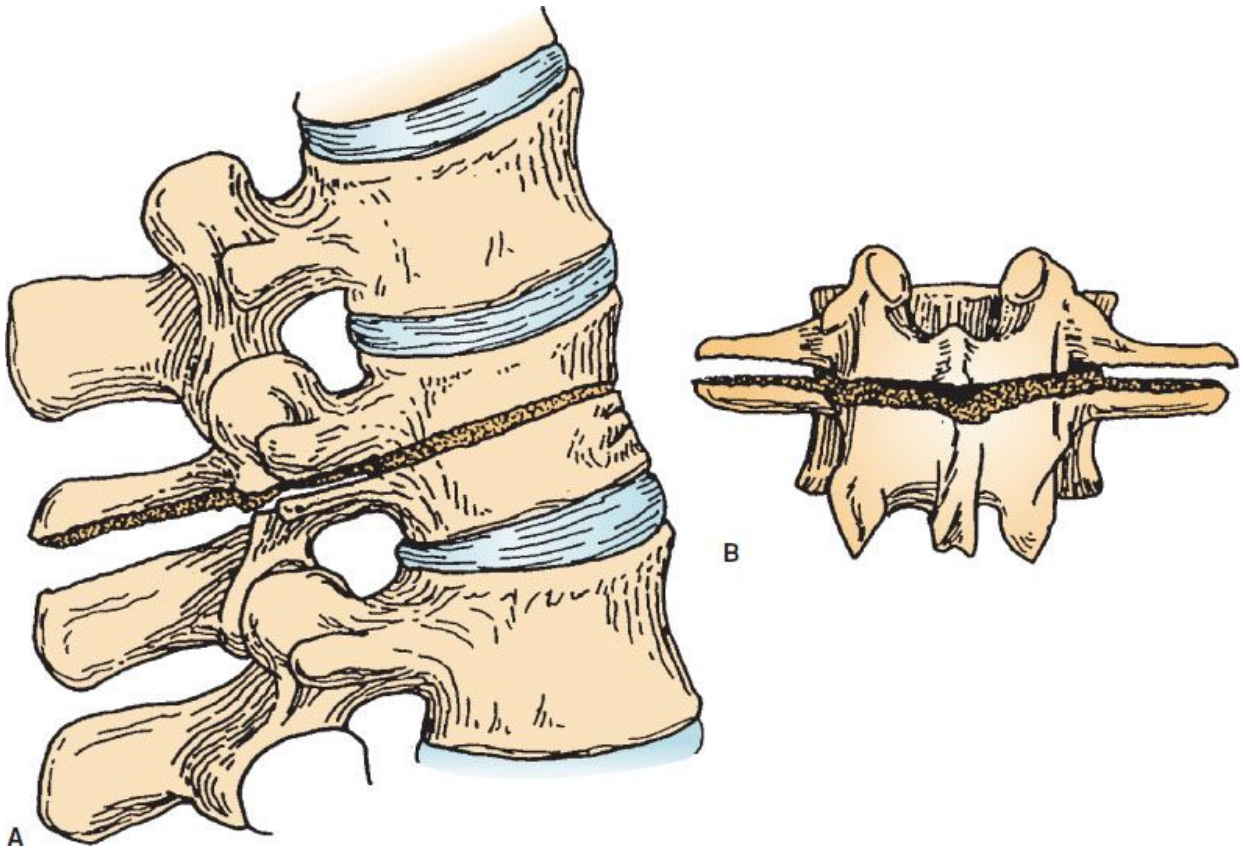

FIGURE 29.3 A "Chance" fracture created by a distraction mechanism. **A:** Lateral view. **B:** Posterior view. (From Fractures, dislocations, and major ligamentous injuries. In: Galli RL, Spaite DW, Simon RR, eds. *Emergency Orthopaedics the Spine.* Appleton and Lange; 1989, with permission.)

Burst Fractures

Burst fractures comprise 14% of all TLS injuries and result from a compressive force causing a fracture of the endplate, pressure of the nucleus pulposus on the vertebral body, and bone fragments being retropulsed into the spinal canal. Burst injuries with and without posterior element injuries occur in equal proportions, and those with posterior element involvement are at higher risk for neurologic deficits (11).

Burst fractures are most commonly associated with falls and motor vehicle accidents. All burst fractures should be considered unstable, since standard radiography misses a significant number of posterior

element fractures, and neurologic deficits are seen in 42% to 58% of these patients (11).

On lateral radiographs, a burst fracture demonstrates a loss of anterior and posterior vertebral height, and there may be a distorted posterior longitudinal ligament line (Fig. 29.4). Anteroposteriorly, there may be widening of the interpedicular distance (greater than 1 mm difference between the vertebrae above and below). Since retropulsed bone fragments often occur at the level of the pedicles, burst fractures may be difficult to visualize by plain radiography. Unstable burst fractures are, therefore, often misdiagnosed as stable anterior wedge fractures. Campbell et al. (12) demonstrated that of 53 thoracolumbar radiographs reviewed by 6 experienced radiologists, only 30 of 39 (83%) burst fractures were correctly identified. Thus, CT imaging is recommended if a burst fracture is suspected.

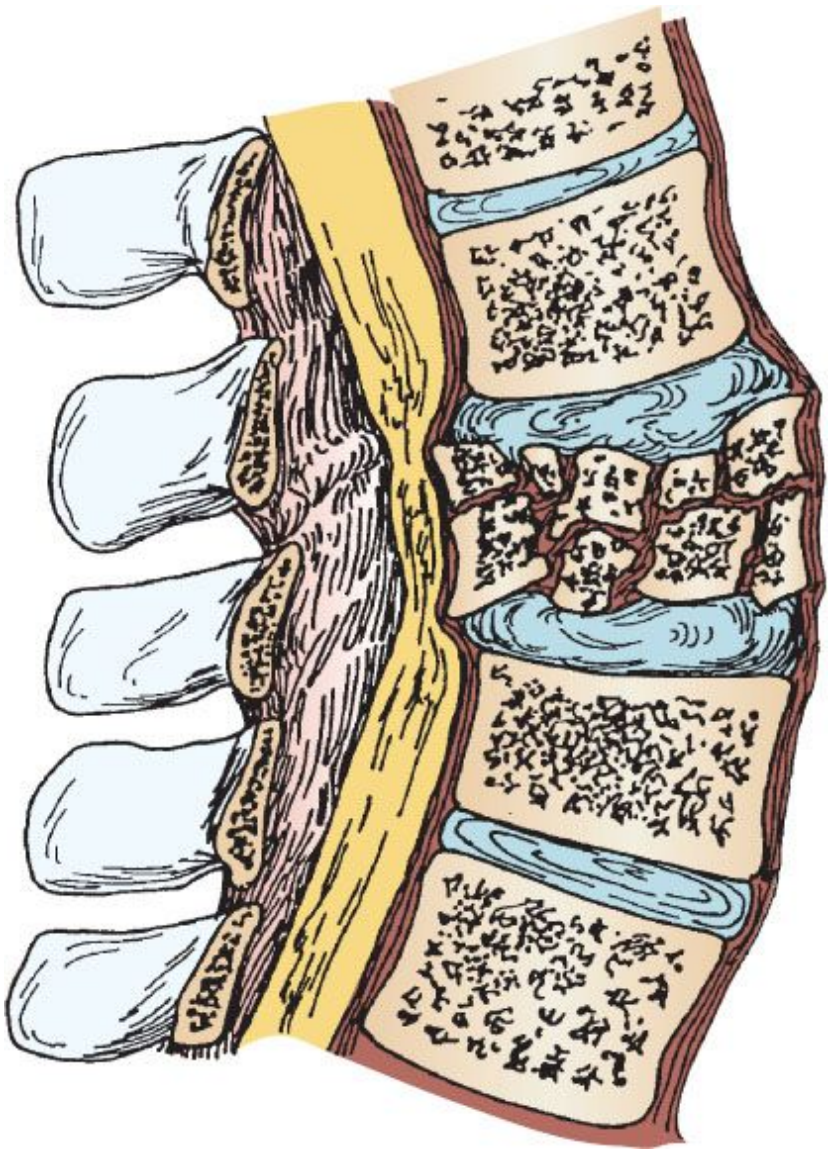

FIGURE 29.4 Burst fracture without posterior element disruption. Note retropulsion of bone fragments posteriorly into the spinal canal with cord injury. (From Fractures, dislocations, and major ligamentous injuries. In: Galli RL, Spaite DW, Simon RR, eds. *Emergency Orthopaedics: The Spine.* Appleton and Lange; 1989, with permission.)

Flexion–Distraction Injuries

Flexion–distraction injuries account for 10% of all TLS injuries. The forceful flexion component of the injury causes compressive failure of the anterior and middle columns and a tear in the posterior

longitudinal ligament. Since both middle and posterior columns are disrupted, this fracture pattern is unstable. Pure ligamentous disruptions also occur and account for 10% to 25% of flexion–distraction injuries (3).

Flexion–distraction injuries most frequently result from lap belt injuries in major motor vehicle collisions and airplane accidents, and thus, this injury is more commonly referred to as a seatbelt injury. While neurologic deficits are rare, associated intra-abdominal injuries, such as small and large intestinal perforations, are common.

Radiographic findings include anterior impaction with compression fractures of the vertebral body and increased posterior interspinous spaces caused by distraction. The hallmark finding is an increased length of the vertebral segment as a result of a distractive force. Because there is no significant rotational or translational component, displacement is unusual. As with Chance fractures, flexion–distraction injuries are frequently missed on routine axial CT scans since the disruption is oriented in the horizontal plane. Thus, it is important to obtain sagittal reconstructions of CT images if a flexion–distraction injury is suspected (4).

Translational Injuries

Translational injuries result in failure of all three columns from massive direct trauma to the back. This mechanism results in several injury patterns including the “slice” fracture, rotational fracture–dislocations, shear injuries, and pure dislocations.

The classic mechanism that creates flexion–rotation forces on the TLS, often resulting in a “slice” fracture, is a fall ending in the “tuck and roll” landing. The majority of these injuries occur at the level of the thoracolumbar junction (T-10 to L-2), and examination usually reveals tenderness at the fracture site. There may be significant kyphosis and a widening of the spinous processes at the level of the dislocation (4). Those with shear fractures in the lumbar region may present with large contusions in the lumbosacral area due to direct trauma. Patients with a complete vertebral dislocation usually have sustained massive trauma, and their examination will invariably demonstrate neurologic deficits.

Among patients who are rendered paraplegic from TLS trauma, the majority have sustained a fracture–dislocation injury. In fact, 60% to 80% of these injuries result in permanent neurologic deficits, and most patients also sustain serious trauma to other organ systems (3). Shear fractures and pure dislocations also result in severe neurologic sequelae, with complete paraplegia occurring in nearly all patients.

With plain radiographs, the classic "slice" fracture is best seen on the lateral view and appears as the superior segment being anteriorly subluxed on the inferior segment with a slice through the upper portion of the vertebral body below it. The spinous processes will appear widened due to posterior ligament rupture. If there is also a rotational component, the alignment of the spinous processes will be distorted (4). Pure dislocations are generally not subtle and appear as a complete displacement of the superior vertebrae on the one below it. CT scan is very helpful in evaluating these injuries, since it demonstrates and objectively quantifies the extent of spinal canal compromise and cord impingement.

Minor Spinal Fracture Patterns

Minor spinal fracture patterns account for 14% of all TLS injuries and include isolated transverse process fractures, spinous process fractures, facet or laminar fractures, bipedicular fractures, and fractures of the pars interarticularis.

Most minor spinal fractures occur in the lumbar region and are usually caused by direct blows, but sudden contraction of the psoas muscles may also result in avulsion of the transverse processes. While transverse process fractures are considered to be stable, it is important to realize that in high-velocity trauma, transverse process fractures frequently do not occur in isolation. In one retrospective analysis of 28 patients who initially appeared to have isolated transverse process fractures by plain radiographs, three patients were subsequently found to have compression and burst fractures by CT scan (13). In addition, high thoracic fractures may be associated with injury to the brachial plexus, and lumbar and sacral fractures may result in injury to the lumbosacral plexus. To ensure the appropriate

diagnosis and management of SCI, CT should be considered when transverse process fractures are seen on plain radiographs.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in any patient who presents with back pain after trauma includes vertebral fractures, SCI, epidural hematoma, paraspinous hematoma, “lumbar strains” and “sprains,” spinal cord injury without radiographic abnormality (SCIWORA), major aortic disruptions (intimal tear or rupture of a preexisting aneurysm), retroperitoneal hematoma, intra-abdominal injury, and simple contusions. However, in patients on corticosteroids, those with metastatic cancer to the spine, or in the elderly who are at risk for compression fractures related to osteoporosis, the absence of a history of trauma should not dissuade the physician from considering a diagnosis of a TLS fracture. In addition, the most difficult diagnostic task for the emergency physician may be to correctly classify each of the fracture patterns and to assess spinal stability.

ED EVALUATION

TLS injuries should be suspected in victims of motor vehicle collisions, falls, and sport-related injuries who complain of mid to lower back pain, and in all trauma victims with a suggestive mechanism of injury who cannot be clinically assessed because of an altered mental status or other associated painful injuries (3). To assess for TLS injury, the back should be visually inspected for contusions, lacerations, and abrasions. The spine should then be palpated for evidence of deformity, tenderness, and muscle spasm. Palpation of the spine may reveal an interspinous gap, which may indicate posterior ligamentous disruption. The back should also be visually inspected for contusions, lacerations, abrasions, and open wounds over the spine. Next, the neurologic status of the patient should be determined and any associated neurologic findings and potential cord syndromes carefully documented. The neurologic examination should include a quantitative evaluation of motor function, and sensory testing must include an evaluation of the sacral dermatomes and an examination of anal sphincter tone. Dorsal and

ventral cord function should also be assessed, and serial examinations should be performed whenever deficits are found to identify patients exhibiting progressive neurologic dysfunction.

Although there has been much work done with regard to the clinical clearance of the cervical spine, there has been relatively little research into establishing guidelines for diagnosing and imaging TLS fractures. Stanislas et al. (14) have demonstrated that thoracic and lumbar spine fractures are missed in patients who sustain a high-velocity injury, have a decreased Glasgow Coma Scale (GCS) on admission, have an associated head injury, and have a pelvic or lower extremity injury. The presence of one vertebral fracture mandates radiographic evaluation of the entire spine, since there is a 5% to 15% risk of a second noncontiguous fracture (15). In the latest edition (ninth) of the Advanced Trauma Life Support (ATLS) manual, the authors state, “the indications for screening radiography of the TLS are the same as those for the cervical spine,” without stating explicitly which criteria. However, where available, CT scanning of the thoracic and lumbar spine can be used as the initial screening modality. AP and lateral plain radiographs with thin-cut axial CT scans through suspicious areas can detect more than 99% of unstable injuries (16).

A summary of the current literature reveals that TLS imaging is indicated for those who have sustained a high energy mechanism of injury (a fall greater than 10 ft (3.048 m), high-speed motor vehicle collisions, etc.) PLUS any of the following: (1) back pain or midline back tenderness; (2) abnormal neurologic signs; (3) any other spine fracture; (4) GCS <15; (5) major distracting injury; or (6) alcohol or drug intoxication (4,11,16,17). One case-control study demonstrated that in addition to cervical and lumbar spine injuries, the presence of rib fractures was found to also be positively associated with thoracic spine fractures (18).

Due to its less-accurate test characteristics, plain films are being used less frequently and the role of plain films may be limited to patients with minor trauma. In fact, there is now literature to support utilizing CT as the initial and only mode of imaging, rather than plain radiography in the severely injured blunt trauma patient

(19), as defined by a high-energy mechanism of injury (a fall greater than 10 ft, high-speed motor vehicle collision, auto vs. pedestrian, motorcycle collision, etc.). The advantages of CT over plain radiography include superior fracture-detection rates, spinal canal evaluation, paravertebral soft tissue assessment, and reduced manipulation of the patient. The sensitivity and specificity of CT for thoracolumbar spine fracture is excellent at 100% and 97%, respectively, whereas plain radiographs are 73% sensitive and 100% specific (1). In a retrospective observational study, Antevil et al. compared the diagnostic sensitivity, time required for radiographic imaging, costs, charges, and radiation exposure. CT was found to be obtained at a similar cost to plain radiographs, was more rapid, sensitive, and involved lower levels of radiation exposure (20). As noted above in the section on wedge compression and burst fractures, CT scan is recommended for all patients in whom spinal instability is in question, as plain radiographs do not adequately evaluate the posterior vertebral body cortex. If plain radiographs are obtained, unclear fractures or displacements on standard radiographs should be further evaluated by a CT scan. In addition, it has recently been noted that if a CT of the chest, abdomen, and pelvis has been ordered, there is no need to order reconstructions or a dedicated CT of the spine unless an abnormality is found on the nonreconstructed CT scan that warrants further elucidation (21).

Magnetic resonance imaging (MRI), with its superior resolution and definition of the spinal canal, multiplanar capabilities, and lack of ionizing radiation, has become the optimal imaging modality in the general evaluation of spinal disease. The primary advantage of MRI is its ability to directly image nonosseous structures, including ligamentous injuries, and intramedullary and extramedullary spinal abnormalities. However, plain films and CT are superior to MRI in evaluating osseous anatomy and fractures, particularly posterior-element fractures. MRI is also not universally available, and there are numerous contraindications to its use, such as the presence of a pacemaker, cerebral aneurysm clips, and metallic foreign bodies. Although there are no clear evidence-based indications for MRI after spinal injury, MRI should be considered in patients with neurologic

signs and symptoms and those with intractable pain that cannot be accounted for by osseous disruption on plain radiographs and CT (22).

KEY TESTING

- Perform a careful history and physical examination, including a thorough skin, musculoskeletal, and neurologic examination.
- Perform radiographic imaging of TLS in patients who have sustained a high mechanism of injury, PLUS any of the following: (1) midline spine tenderness; (2) neurologic deficits; (3) any other spine fracture; (4) GCS <15; (5) distracting injury; or (6) intoxication.
- Obtain a CT in cases where plain radiographs demonstrate and abnormality, or are inadequate.
- Rather than plain films, CT should be considered as the primary imaging modality, given its superior sensitivity and specificity for the detection of fractures especially in high-mechanism trauma.
- Obtain MRI if there are concerns about ligamentous injuries or intramedullary and extramedullary spinal abnormalities.

ED MANAGEMENT

The patient who has sustained TLS trauma has typically been subjected to high-energy forces, and initial resuscitation efforts should focus on the evaluation and treatment of life-threatening injuries. Stabilization of the patient's airway and hemodynamic status should precede any treatment to secure adequate oxygenation and tissue perfusion. A Foley catheter should be inserted, since patients with vertebral fractures commonly develop urinary retention. However, it is important to assure that resuscitative maneuvers do not compromise neurologic function. Patients should remain immobilized on a spine board with a rigid cervical collar until neurologic and radiographic evaluation can be performed.

Hypotension in a trauma victim may be due to SCI causing neurogenic hypotension, but this should be a diagnosis of exclusion. Other causes of hypotension, such as hemorrhagic shock, cardiac

tamponade, and tension pneumothorax must first be excluded. Neurogenic hypotension results in vasodilation and bradycardia, and mild cases (generally seen with TLS injuries) most often respond to fluid resuscitation, but occasionally require vasopressor support.

When treating a thoracolumbar spine fracture, the primary goals are to protect the spinal cord and prevent deformity and instability, and surgical management can often facilitate rehabilitation and decrease hospital length of stay. Neurosurgical consultation, if available, should be obtained promptly when neurologic deficits are present or when spinal instability is suspected. TLS fractures are rarely treated as an operative emergency, however, unless there is evidence of progressive neurologic dysfunction, or in the presence of a significant epidural hematoma with cord or cauda equina compression. In addition to instability, other indications for surgery include neurologic deficit, as well as kyphosis greater than 25 degrees. A TLICS score ≥ 5 also is an indication for operative intervention, and would also, therefore, warrant a neurosurgical consultation (8,9).

Pharmacologic agents, such as glucocorticoids, naloxone, thyrotropin-releasing hormone, insulin-like growth factor, dimethyl sulfoxide, calcium channel blockers, tirilazad mesylate, and GM-1 gangliosides have been found to improve neurologic outcome in experimentally induced SCI (23). Of these, only methylprednisolone was previously routinely used, and it is the only therapy shown to have efficacy in a randomized controlled trial (23). Although the National Acute Spinal Cord Injury Study (NASCIS) Group has published several studies showing that the administration of high-dose methylprednisolone improves neurologic outcome after blunt SCI, if it is administered within 8 hours, other studies have reported worse outcomes and higher rates of respiratory and gastrointestinal complications (24). In fact, the current ninth edition of ATLS (16) states, “at present, there is insufficient evidence to support the routine use of steroids in spinal cord injury.” Thus, in general, steroids cannot be recommended for routine use. Still, there is a great deal of practice variation among emergency physicians and

neurosurgeons, and this is indicative of the continuing controversy (25).

Intestinal ileus is common following TLS injury, and a nasogastric tube may be required to prevent gastric dilation. Urinary bladder atony, due to autonomic dysfunction, is also common. Thus, placement of a Foley catheter will help prevent bladder distension and monitor fluid balance. Since gastrointestinal bleeding from stress ulcers occurs in up to 20% of spinal trauma patients, ulcer prophylaxis is indicated. Denervated skin is especially susceptible to pressure necrosis, so the spinal immobilization backboard should be removed, or pressure points padded, as soon as possible. Frequent patient repositioning should be instituted if the patient is insensate and immobilized. Prophylaxis against deep venous thrombosis should also be provided.

CRITICAL INTERVENTIONS

- Provide spinal immobilization until an unstable fracture is excluded.
- Perform a thorough baseline neurologic examination followed by serial examinations.
- Order and interpret appropriate radiographs, CT scans, and MRI scans.
- Obtain prompt neurosurgical consultation if there is evidence of spinal instability (e.g., TLICS ≥ 5) or neurologic deficits.
- Provide adequate analgesia.
- Institute nasogastric suction if an ileus is present.
- Order Foley catheter drainage to help with fluid management.

DISPOSITION

Patient disposition depends primarily upon fracture stability. If a TLS fracture is deemed unstable, neurosurgical consultation is mandatory, and if not available onsite, immediate transfer must be arranged to a center that can provide these services. Patients with these fractures have commonly sustained multisystem trauma, and the extent of these other life-threatening injuries often determine

whether they need to be admitted to an intensive care unit or a monitored setting.

If plain radiographs demonstrate minor spinal fracture patterns and there is no neurologic deficit or associated ileus, then outpatient management may be possible. Treatment should include analgesics, and follow-up care should be arranged in all instances because even minor spinal fractures may be associated with prolonged disability. If there is any ambiguity regarding the extent of osseous injury or spinal stability on plain radiographs, a CT scan or MRI should be obtained to evaluate the extent of injury and need for neurosurgical consultation.

Common Pitfalls

- Failure to suspect thoracolumbar spine fractures in a multitrauma patient due to inability to evaluate neurologic deficits or back tenderness.
- Failure to appreciate the high false-negative rate of plain radiographs in diagnosing unstable burst fractures, along with failure to obtain a CT scan in questionable cases.
- Failure to obtain a complete spinal radiograph when a fracture at one spinal level is demonstrated.

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CHAPTER 30

Spinal Cord Injuries

Brian D. Mahoney

The clinical spectrum of spinal cord injury varies from the awake patient complaining of pain, paresthesias, numbness, weakness, or paralysis to the unconscious patient (usually due to associated head injury) unable to give any clues about the severity of his or her injuries. In the United States, most spinal cord injuries are due to motor vehicle collisions (37%), followed by falls (29%), violence (14%), sports and recreational activities (9%), and other causes (11%) (10). Males comprise 81% of these patients with an average age of injury of 43 (10). In the United States, the annual incidence of spinal cord injuries is approximately 40 per million population (10). Many patients with spinal cord injury die soon after their injury because of either high cord injury or other associated traumatic injuries. Life expectancy is significantly below that of patients without spinal cord injury (10). Of those who survive their initial injury and hospitalization, illnesses with the greatest impact on life expectancy are pneumonia and sepsis (10). Direct lifetime expenses for a 25-year-old patient at the age of injury with high quadriplegia exceeds $4.5 million (10).

Normally, the spinal column ensures stability and protects the cord, the spinal roots, and the cauda equina from injury. Panjabi and White (11) defined spinal stability as “the ability of the spine, under physiologic loads, to maintain the relationships between vertebrae such as there is neither damage nor irritation to the spinal cord or roots, nor incapacitating deformity nor pain due to structural changes.” Injury can render the usually protective spinal column a threat to the cord and its roots. The cord can suffer injury through

compression, crush, laceration, penetration, stretch, inflammation, infection, hypoxia, or ischemia. In unusual circumstances, the spinal column can be rendered unstable by infectious or inflammatory causes, such as atlantoaxial dislocation in patients with rheumatoid arthritis or inflammation associated with pharyngeal infections.

The most mobile segments of the spinal column (C4, C5, C6, L1, L2) place the adjacent segments of the spinal cord at higher risk for injury. Spinal cord injury at discharge is as follows (10): incomplete quadriplegia 41%, incomplete paraplegia 19%, complete paraplegia 18%, complete quadriplegia 12%, complete neurologic recovery less than 1%.

The ribs buttress the thoracic spinal column, providing a relatively safe environment for the cord. However, when there is thoracic bony displacement or soft tissue swelling, the cord injury is usually devastating. The spinal canal is relatively narrow here, and the thoracic cord is an area of watershed circulation. At L2, the spinal cord ends and the spinal canal is filled with the cauda equina—a collection of spinal nerves passing from the cord to their respective lumbar and sacral foramina. Though certainly at risk for acute cauda equina syndrome, these peripheral nerves are relatively resistant to injury compared to the spinal cord.

CLINICAL PRESENTATION

The patient may describe pain or tenderness at the level of injury and weakness, numbness, or paresthesias distal to the injury level. Paresthesias at the time of injury are a sign that the cord or roots have been compressed. Late paresthesias may be a sign of instability of the spinal column and should lead to a comprehensive search for instability. History and physical examination establish motor (eFig. 30.1), reflex, or sensory deficits (eFig. 30.2 and eFig. 30.3), as well as fecal incontinence or urinary retention. Urinary retention may present as oliguria with overflow stress incontinence. Careful mapping of the level of sensory loss (including attention to areas around the anus for lower segmental reflexes and for sacral sparing) identifies the level of cord injury and the level at which radiologic studies should be focused (Fig. 30.1).

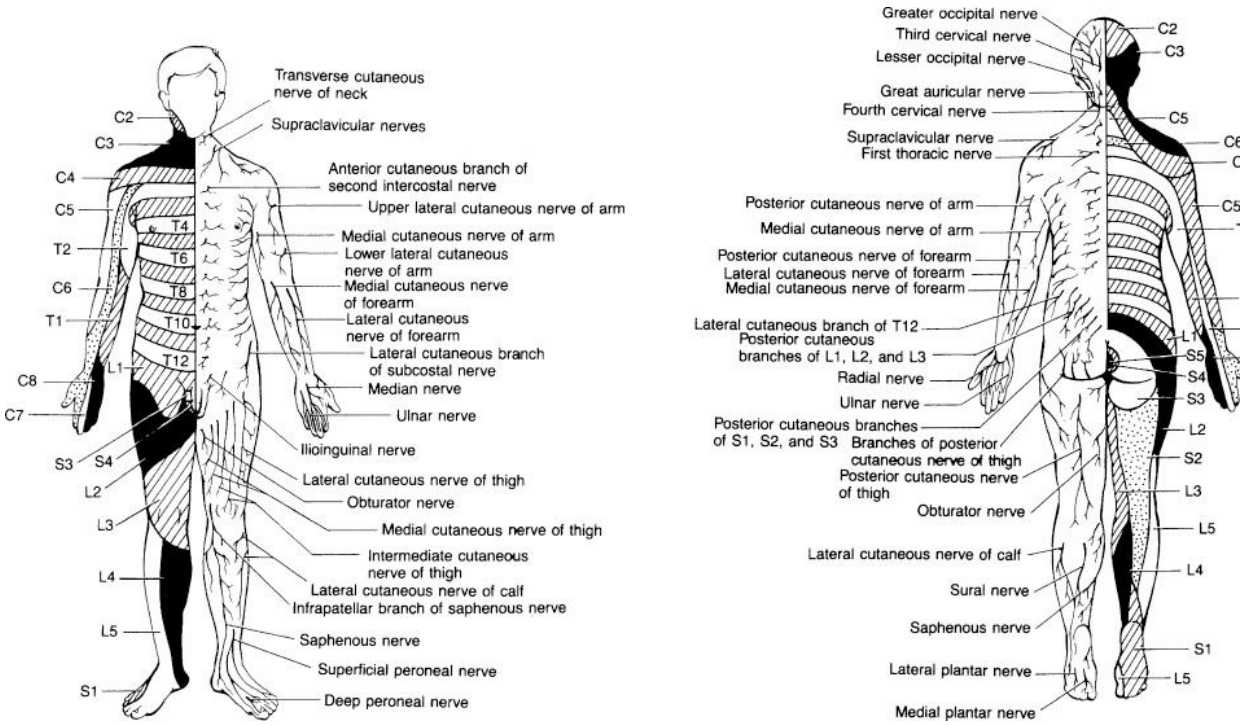
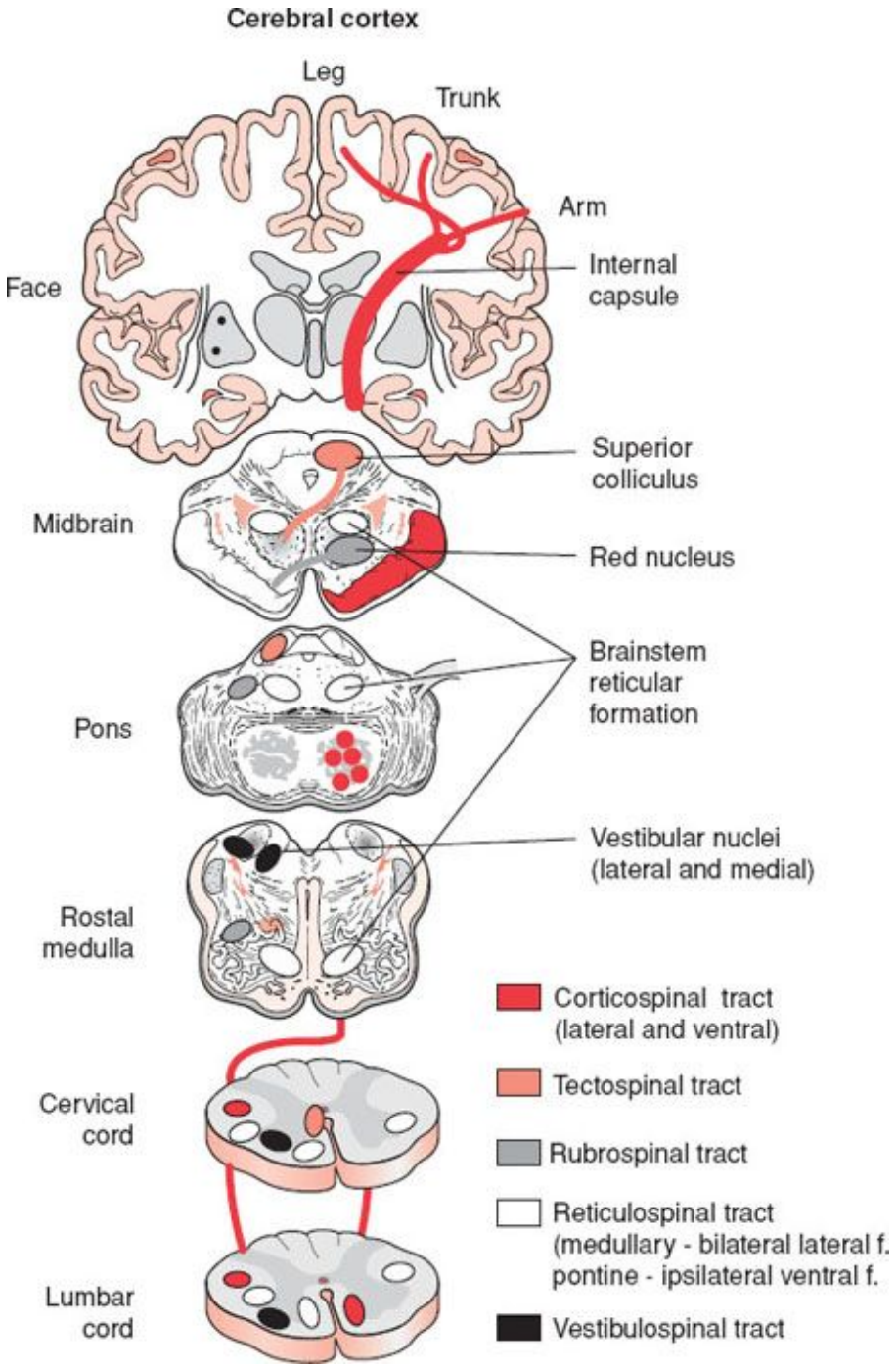
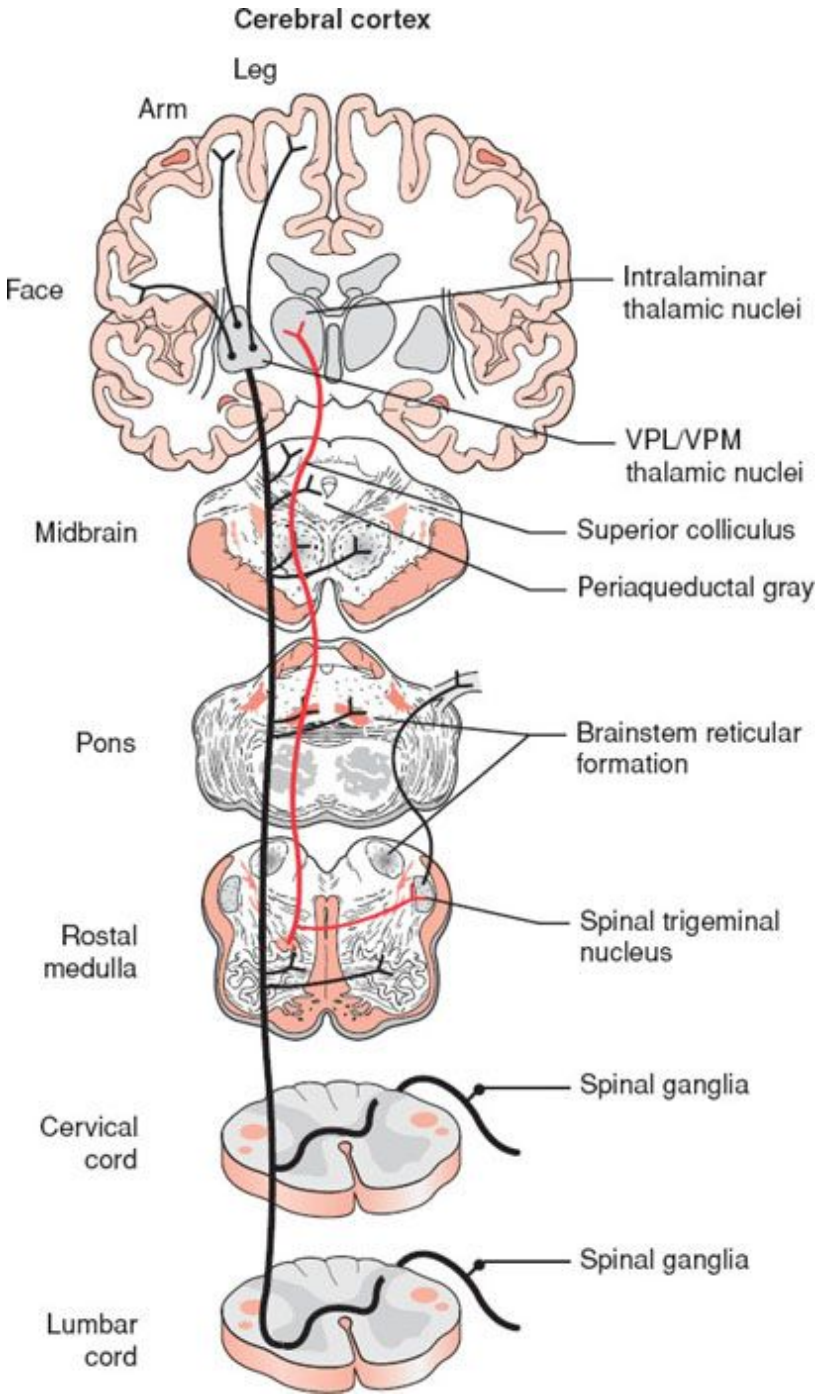


FIGURE 30.1 Sensory dermatomal segments: anterior view **(left)** and posterior view **(right)**. IDAMS Asset Name: 4766.101.001.tif Credits. (From Harwood-Nuss A, Wolfson, AB, Linden CH. *The Clinical Practice of Emergency Medicine.* 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.)

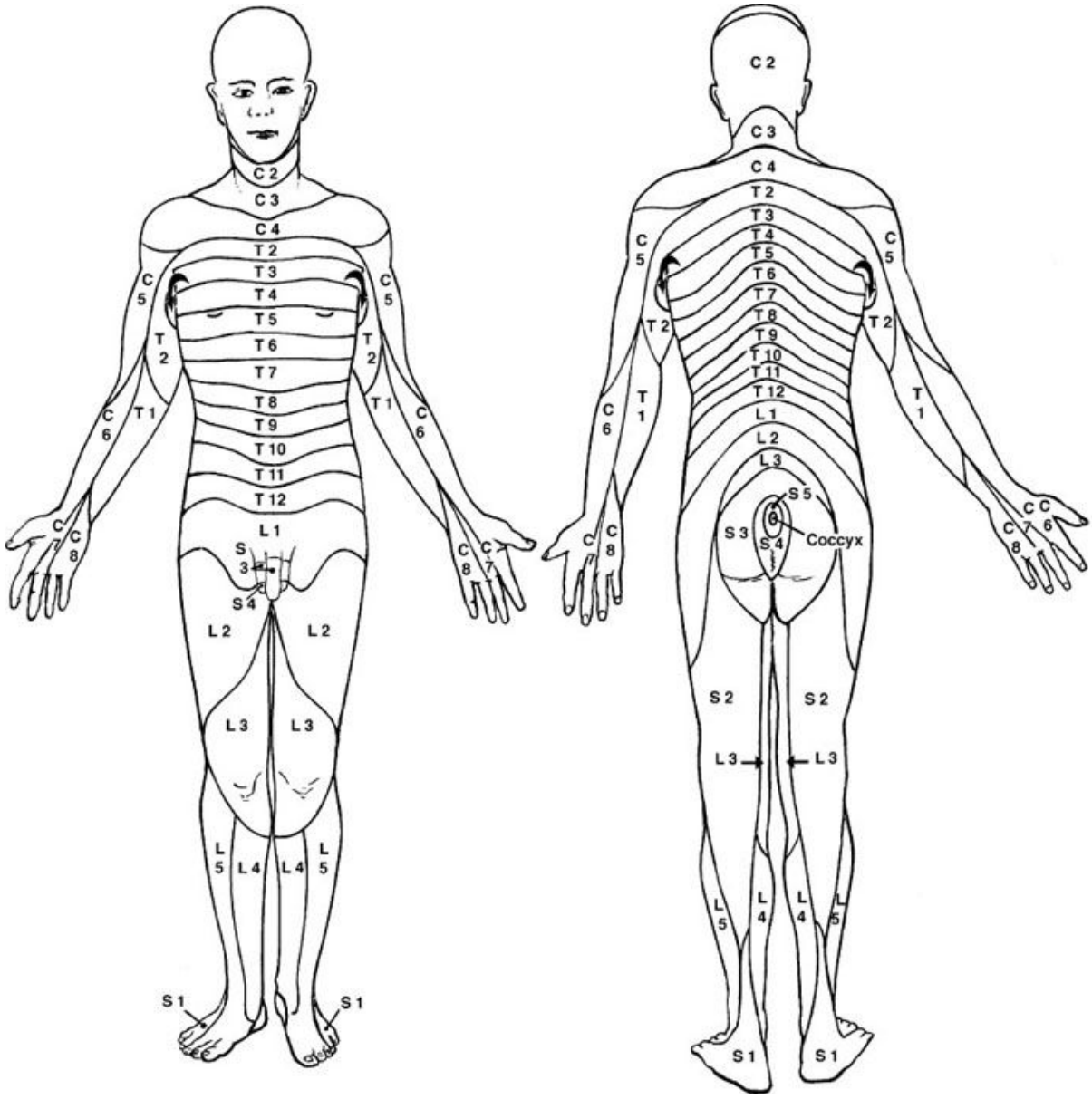


eFIGURE 30.1 A diagrammatic representation of the main descending motor pathways connecting the brain to the spinal cord for one side of the body. Approximately 90% of the corticospinal axons cross at the spinomedullary junction and comprise the lateral corticospinal tract. The remaining 10% form the ipsilateral ventral corticospinal tract. Axons from cells in the contralateral superior colliculus pass through the brainstem and enter cervical levels of the

spinal cord in the tectospinal tract. The red nucleus sends axons to the contralateral spinal cord in the rubrospinal tract. Neurons from many levels and both sides of the reticular formation form the reticulospinal tract. The medial and lateral vestibular nuclei send axons to the spinal cord in the vestibulospinal tract. This is mainly and ipsilaterally projecting pathway. (From Schwartz ED, Flander AE. *Spinal Trauma: Imaging, Diagnosis, and Management.* Philadelphia, PA: Lippincott Williams & Wilkins; 2007.)



eFIGURE 30.2 The transmission of pain from the body to the brain occurs in the spinothalamic tract. Axons of the anterolateral system terminate in the several regions including the reticular formation throughout the brainstem, superior colliculus, periaqueductal gray, and several thalamic nuclei.

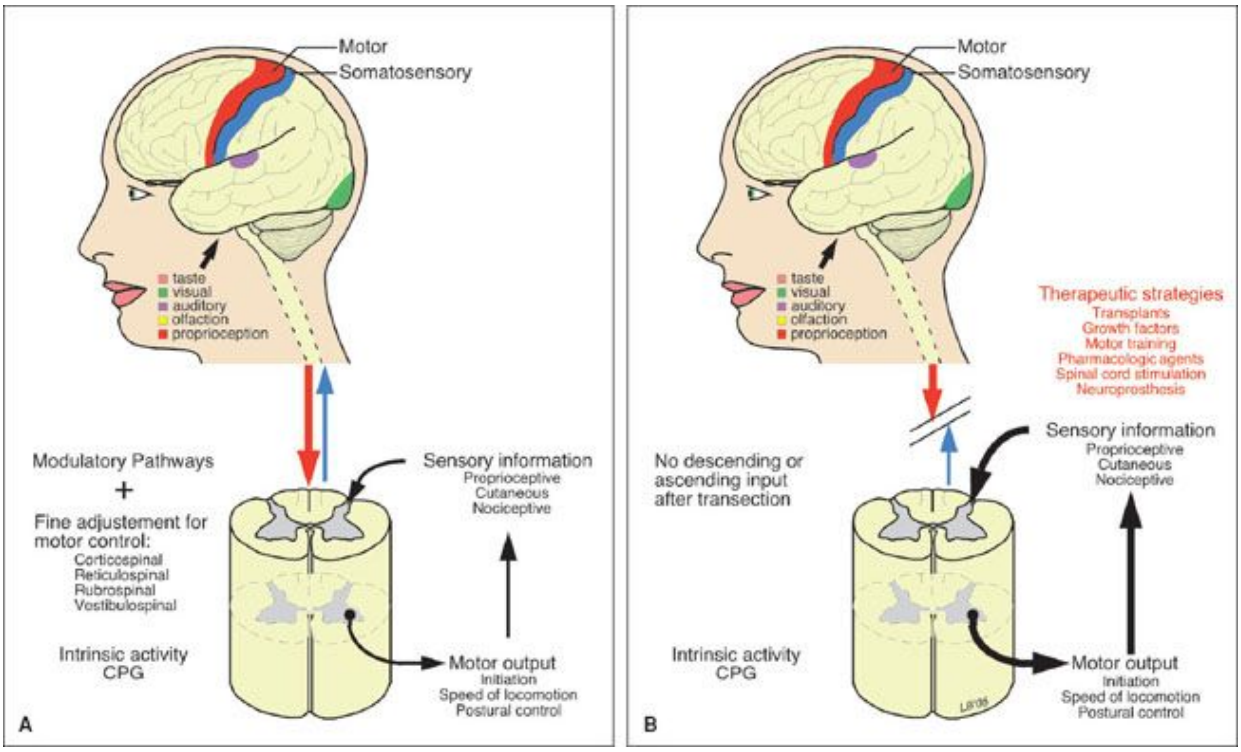


eFIGURE 30.3 Dermatomes represent the cutaneous distribution of territories innervated by spinal nerves. (From Schwartz ED, Flander AE. *Spinal Trauma: Imaging, Diagnosis, and Management*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.)

When the patient has no function of any segment of the cord below the level of injury, the injury is physiologically complete. Such a circumstance carries with it a grim but not hopeless prognosis for meaningful recovery. It is nearly impossible to accurately diagnose a permanent physiologically complete cord injury in the emergency

department (ED) because spinal shock may be a concurrent factor. *Spinal shock* is the temporary loss of spinal reflex activity that accompanies the motor and sensory losses. Males may exhibit priapism. Ditunno et al. (4) describe four phases of spinal shock lasting a variable amount of time, from a day to weeks.

- Phase 1: Flaccid paralysis, areflexic, lasts about 1 day.
- Phase 2: Return of polysynaptic reflexes, e.g., bulbocavernosus, 2 to 3 days.
- Phase 3: Return of monosynaptic deep tendon reflexes.
- Phase 4: Hyperreflexic spastic paralysis (eFig. 30.4).



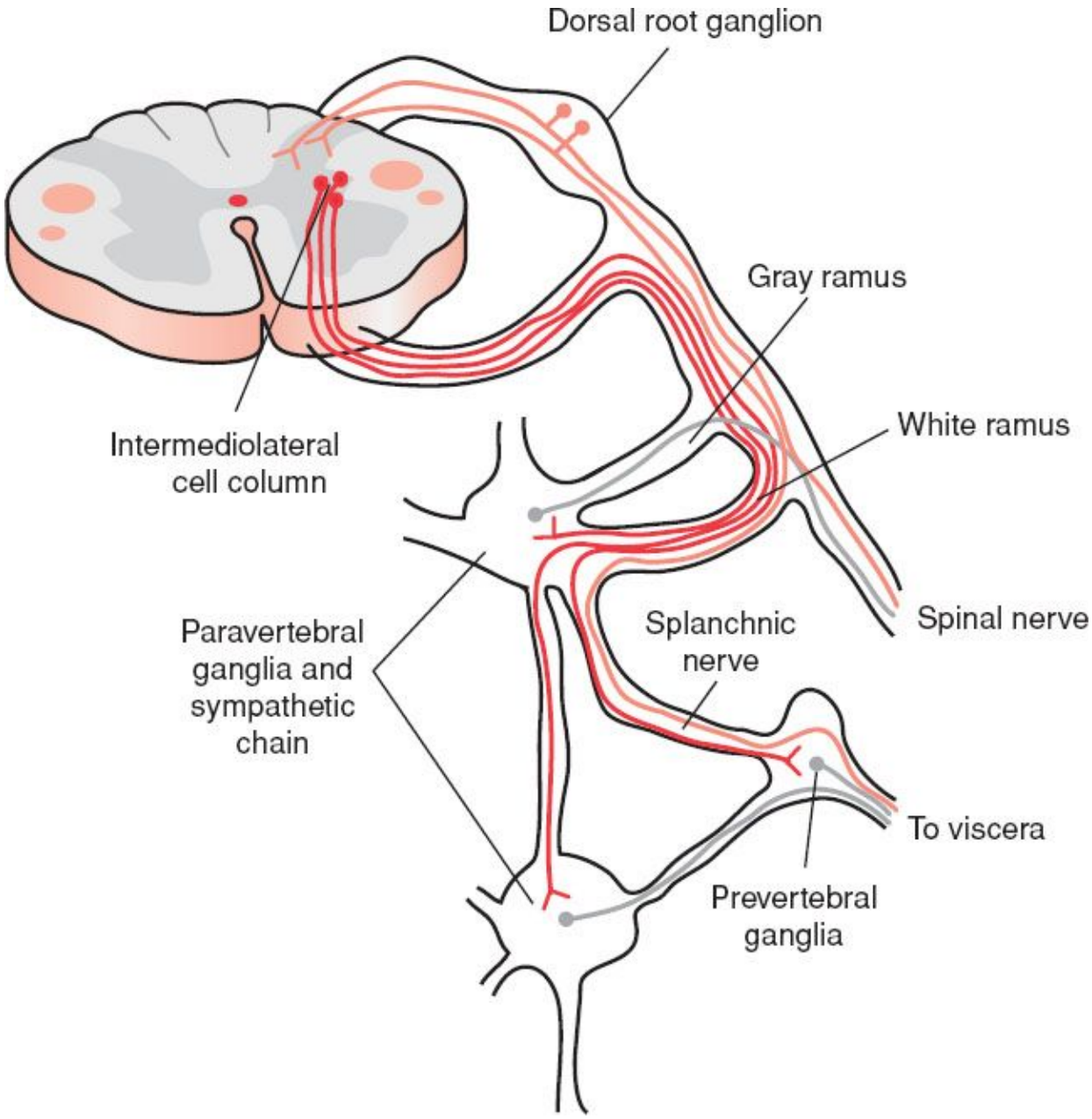
eFIGURE 30.4 Spinal transection creates a new spinal cord. Spinal transection results in considerable modification of the circuitry caudal to the lesion. Some of these changes may contribute to the deficits, while others may provide opportunities for therapeutic interventions. A: The intact spinal cord receives control and modulation from supraspinal systems and sensory input from primary afferents, which determines the activity of spinal circuits, including the central pattern generator. B: After SCI, descending pathways are lost, their denervated receptors up regulate, and

afferent pathways are enhanced, leading to hyperexcitable reflexes and spastic paralysis. Strategies targeting independent mechanisms are the bases of potential treatments. (From Schwartz ED, Flander AE. *Spinal Trauma: Imaging, Diagnosis, and Management*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.)

The bulbocavernosus reflex is elicited when squeezing or tugging on the glans penis causes reflex contraction of the anal sphincter. Some patients who initially appear physiologically completely paralyzed and have spinal shock may go on to remarkable recoveries after the initial phases of spinal shock have passed.

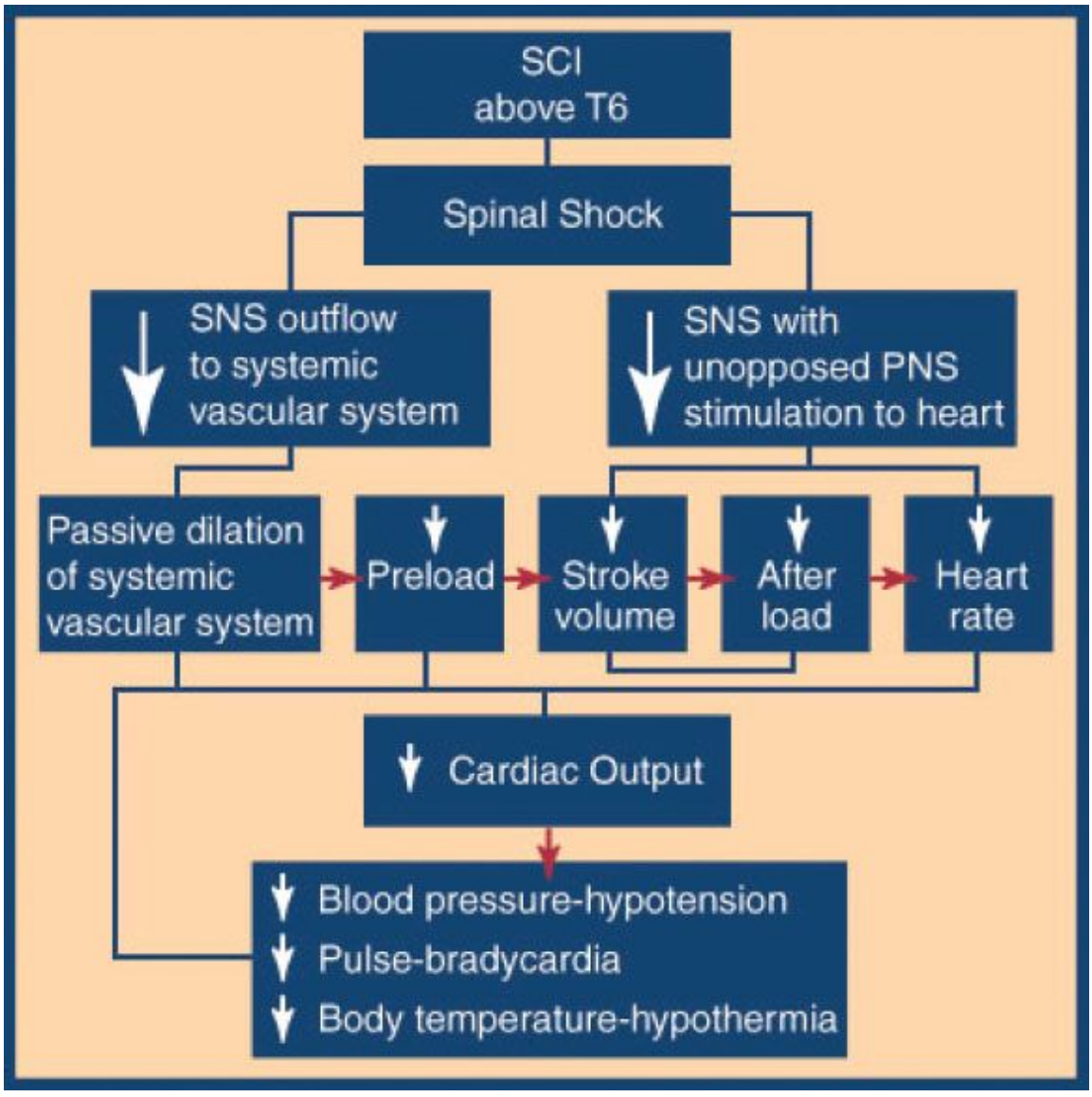
The patient with a cervical or high thoracic cord injury above T6 may present with relative hypotension due to the sudden loss of sympathetic tone below the level of the lesion (eFig. 30.5). The patient has warm, dry skin; normal capillary refill; and a paradoxical bradycardia. Labeling this condition *spinal neurogenic shock* (eFig. 30.6) helps to differentiate it from the aforementioned spinal shock. Spinal neurogenic shock in the patient with multiple injuries may be difficult to differentiate from other causes of shock. Hemorrhagic shock classically presents as hypotension, tachycardia, cool and moist skin, and delayed capillary refill. The hypotensive patient should be assumed to have hemorrhagic shock until all external bleeding is controlled and the search for occult hemorrhage in the chest, abdomen, retroperitoneum, and pelvis is complete. This search should include, at a minimum, chest x-ray, FAST cardiac and abdominal ultrasonography, urinalysis, and pelvic x-ray or abdominal and pelvic computed tomography (CT). After this survey is complete and no other explanation for shock is found, the hypotension may be attributed to spinal neurogenic shock. At that point, after adequate initial volume resuscitation of the vasodilated patient, fluid administration should be kept at maintenance levels and the hypotension should be treated with pressors as necessary to maintain perfusion of the brain and spinal cord. Excessive fluids may cause pulmonary edema and contribute to worsening spinal cord edema. Ischemia is a significant contributor to the ultimate degree of spinal cord injury. Unfortunately, there are no prospective controlled

human studies to determine what the optimal blood pressure is to maintain spinal cord perfusion and thus limit secondary injury to cord tissue. Typically, the patient is maintained at a blood pressure sufficient to sustain intact mentation and urinary output. Animal studies show that hypotension worsens neurologic outcome. For this reason it is recommended that systolic blood pressure below 90 mm Hg be avoided or corrected as soon as possible and that the mean arterial pressure be maintained at 85 to 90 mm Hg for the first 7 days (13).



eFIGURE 30.5 The sympathetic nervous system and its relationship to the central nervous system. Sympathetic preganglionic neurons (red) are located in the intermediolateral cell column of the thoracic spinal cord. Their axons leave the spinal cord via the ventral root and enter paravertebral and sympathetic chain ganglia on the ipsilateral side of the body through the white communicating ramus. Some fibers synapse within ganglia at the same segmental level, others travel up and down the sympathetic chain to other ganglia. Postganglionic sympathetic fibers arising from cells in the

paravertebral or sympathetic chain ganglia (green) join a spinal nerve by passing through a gray communicating ramus. These supply smooth muscle and glands of the body wall. Other postganglionic fibers travel through a splanchnic nerve to innervate viscera of the body cavities. Axons from sensory (pain) neurons (blue) supplying an internal organ may pass through autonomic ganglia, but they originate from neurons in the dorsal root ganglia. (From Schwartz ED, Flander AE. *Spinal Trauma: Imaging, Diagnosis, and Management*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.)



eFIGURE 30.6 Spinal neurogenic shock. Spinal cord injury above T6 impairs sympathetic nervous system activity caudal to injury and leaves unopposed parasympathetic nervous system activity.

In the past 20 years, the percentage of patients with complete spinal cord injuries has fallen while incomplete spinal cord lesions have increased. This has been attributed to improved management at the scene and in the hospital. There are several important partial cord syndromes (Fig. 30.2).

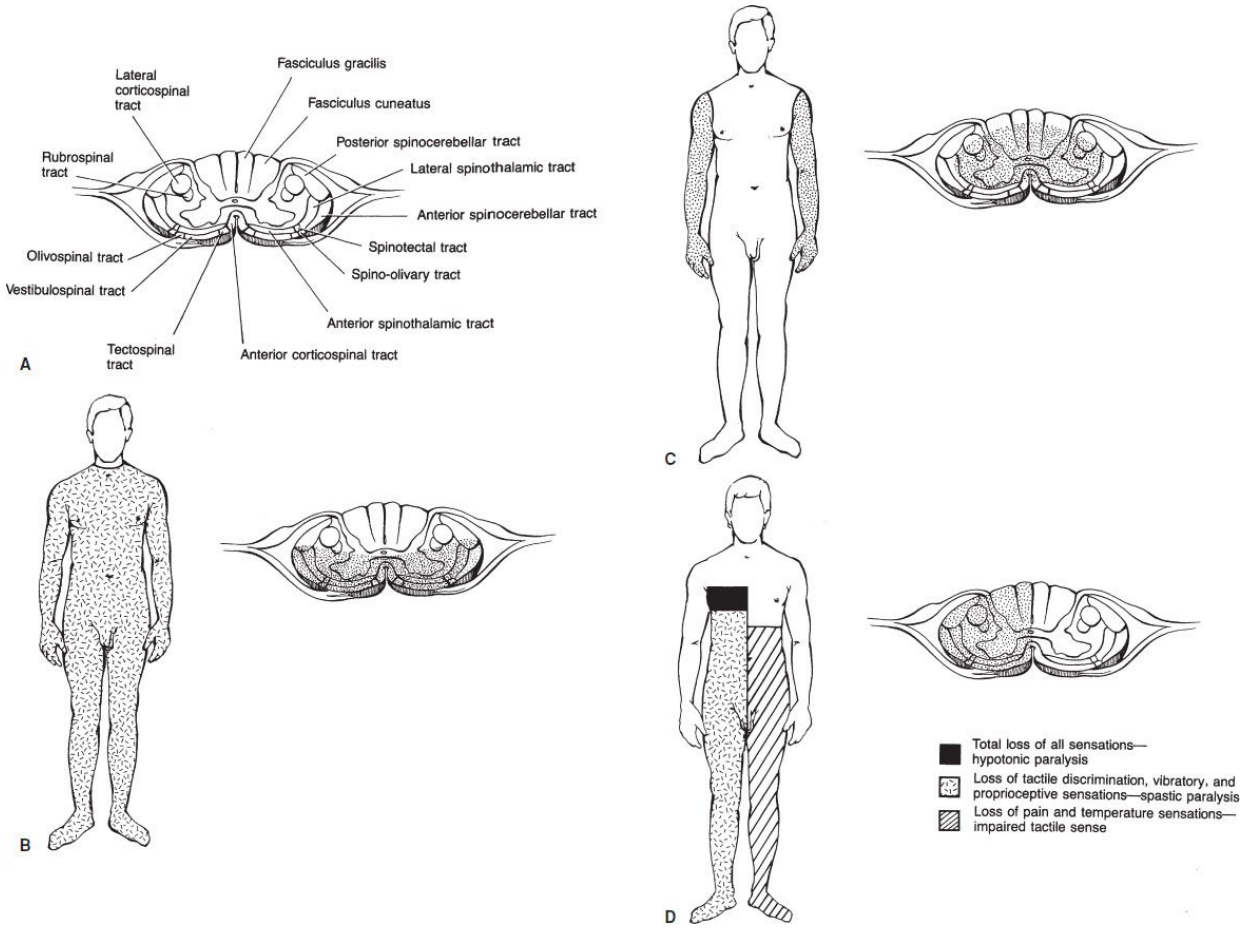


FIGURE 30.2 Transverse section of the spinal cord at the cervical level: the ascending and descending tracts **(A)**, tracts that may be damaged in the anterior spinal artery syndrome **(B)**, tracts that may be damaged in the central cord syndrome **(C)**, involved tracts and the superimposed areas of deficit from an injury at T4 **(D)**, resulting in the Brown-Séquard syndrome.

Anterior spinal cord syndrome (Fig. 30.2B) is the result of either direct blunt injury to the cord itself or compression of the anterior spinal artery by disc, bone, or hematoma, causing ischemic damage to the anterior cord. The patient presents with a loss of motor and pain sensation bilaterally below the level of the lesion, but posterior column function is preserved. Posterior column function is tested with a tuning fork for vibratory sensation or by plantar flexing and dorsiflexing the great toe to assess for gross proprioception. Early closed reduction is an important treatment option in the awake patient (6). After CT, in cervical cases, the patient may have an urgent attempt at reduction and reestablishment of the normal diameter of the spinal canal. This is typically performed by the neurosurgeon using Gardner–Wells tongs applying inline traction guided by serial x-rays and serial neurologic examinations after each incremental addition of weight. Endpoints are successful reduction, any sign of distraction that can cause additional cord injury, or the neurosurgeon's acceptable maximum weight limits for the level of the injury. Magnetic resonance imaging (MRI) or CT myelography may follow to assess for possible soft tissue masses, such as an extruded disc or hematoma that may continue to exert extrinsic pressure on the spinal cord or anterior spinal artery. If this is found, the neurosurgeon may attempt to relieve it by laminectomy. Unfortunately, the prognosis for recovery after this injury is poor.

The acute *central cord syndrome* (Fig. 30.2C) usually afflicts patients with a narrowed spinal canal. This may be due to degenerative spine disease causing bony ridges and thickened ligaments in the spinal canal, a congenital stenotic canal, acute fracture, or disc herniation. Degenerative spine disease is more common in the elderly but also may be present in younger patients. The mechanism of injury is usually hyperextension. The hallmark of this lesion is greater damage to the central portion of the cord than to the periphery. This leads to a variable sensory loss and bladder dysfunction but a predictable motor loss, with motor function of the upper extremities below the level of the lesion more impaired than that of the lower extremities. This is because the motor fibers in the lateral corticospinal tract lie in a lamellar fashion; cervical segments

are most medial and hence more damaged, and thoracic, lumbar, and sacral motor fibers are progressively more lateral. The diagnosis is confirmed by MRI. Management of this injury is usually nonoperative, although surgical decompression may be chosen by the neurosurgeon. There is a relatively good prognosis for recovery of at least partial neurologic function. Three-fourths of these patients are walking at 1 year; however, there is usually much less recovery of hand function.

The *Brown-Séquard syndrome* (Fig. 30.2D) is a hemicord injury that presents with a crossed sensory and motor deficit. Motor function is lost ipsilateral to the cord lesion, but sensory function is preserved on the ipsilateral side. Sensory function is lost on the contralateral side, where motor function is preserved. The crossed lesion is explained by the decussation of motor fibers in the medulla and the decussation of sensory fibers about two segments above the segment at which their sensory root enters the spinal cord. Causes include penetrating injuries, tumor, hematoma, and disc disease. The prognosis is poor with penetrating injuries.

DIFFERENTIAL DIAGNOSIS

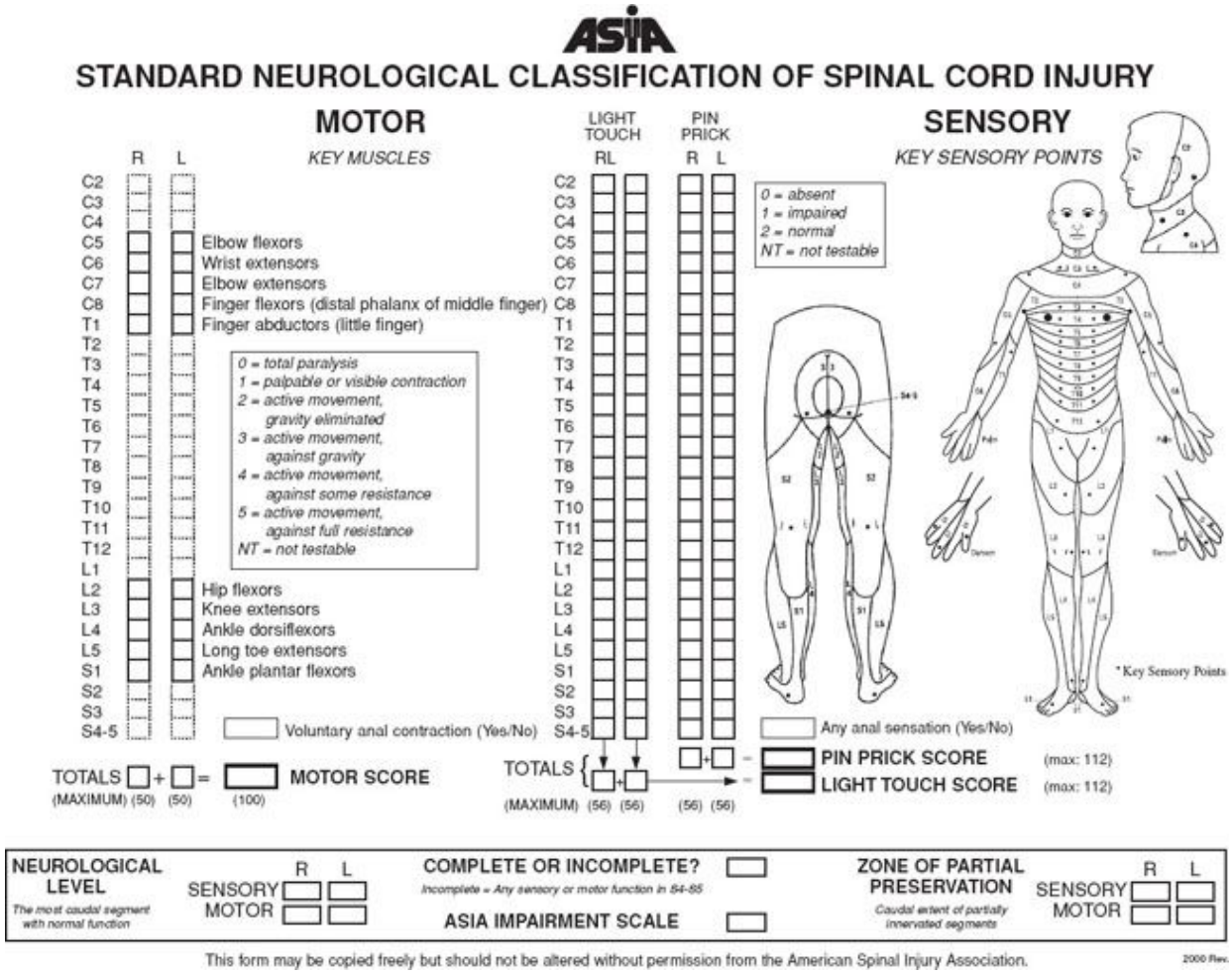
Determination of a cord injury is straightforward in the patient with acute quadri- or paraplegia. It becomes more difficult in patients with partial cord syndromes, particularly in those with acute central cord syndrome. This is due to both the patchy nature of the sensory loss and preservation of at least some motor function in the lower extremities. Evaluation for cord injury is also difficult in the unconscious patient. Most patients who present to the ED with complaints of neck or back pain or tenderness are found to have muscular strains or ligamentous sprains and no associated cord injury. The clinician should not be fooled by the absence of a fracture. A third-degree ligamentous sprain can render the spinal column unstable, allowing motion between vertebral bodies and subsequent cord or spinal root injury. In addition, mostly children, but also adults, may have *spinal cord injury without radiographic abnormality*. It is recommended that these patients have an MRI and external immobilization until spinal stability is confirmed by a

negative MRI followed by flexion–extension views; in addition, they should avoid high-risk activities for up to 6 months (12). See Chapter 28. The SCIWORA diagnosis was more common when diagnosis was based on x-rays. Now this diagnosis is less common since the MRI will often show an abnormality.

ED EVALUATION

The principles of evaluation are the same for all significantly injured patients. Initial attention should be paid to airway, breathing, circulation, disability, exposure, and environment (the ABCDEs), with simultaneous resuscitation involving high-flow oxygen, two large-bore intravenous lines delivering 20 cc/kg of crystalloid to the hypotensive patient, and a Foley catheter. Serial vital signs, bedside ultrasound of the inferior vena cava, urinary output, and pulmonary auscultation should be used to assess for the need of additional crystalloid. It is important to consider that excessive crystalloid may cause pulmonary edema. Early in their course, spinal cord–injured patients often have an atonic bladder. A Foley catheter is used to monitor urine output during the resuscitation and to prevent damaging distention of the bladder. Early in the hospitalization, the Foley catheter is removed and replaced by intermittent catheterization to decrease the chance of developing an ascending urinary tract infection. The patient is given nothing by mouth in anticipation of paralytic ileus. Physical and occupational therapy and psychological counseling are begun early during hospitalization.

In the critically injured patient, the primary survey should be followed by imaging (chest and pelvis films, as indicated), FAST ultrasound of the heart, lungs, inferior vena cava, and abdomen, and the secondary survey. In many trauma centers, the spinal cord–injured patient will have emergent CT of the head, entire spine, chest, abdomen, and pelvis. During the secondary survey, a careful neurologic examination must be performed. This examination is carefully recorded following the American Spinal Injury Association Scale (1, eFig. 30.7) so that an ascending lesion or deterioration in function can be identified by serial examinations. Motor function for all muscle groups is tested and recorded on a 0 to 5 scale.



eFIGURE 30.7 Standard neurologic classification form for spinal cord injury. (From: American Spinal Injury Association. *International Standards for Neurological Classification of Spinal Cord Injury*. Chicago: American Spinal Injury Association; Revised 2002, with permission.)

- 0: No voluntary muscle contraction
- 1: Flicker or trace of muscle contraction
- 2: Muscle activity apparent but cannot overcome gravity
- 3: Can overcome gravity but not active resistance
- 4: Active motion against mild to strong but reduced resistance from normal
- 5: Full normal active motion against resistance

The level of sensory loss is plotted to identify the level on which to concentrate radiographic imaging. Gross proprioception or vibratory function is measured to examine posterior column function. Deep

tendon reflexes, anogenital reflexes (bulbocavernosus, anal wink), and perianal sensation are elicited to identify spinal shock or sacral sparing. One common diagnostic error is performing an inadequate neurologic examination and specifically failing to examine for posterior column function (gross proprioception or vibratory sensation). A second error is failing to examine for sacral sparing, which is needed to differentiate a partial cord lesion from a physiologically complete injury. Serial neurologic examinations are performed to identify any important change in functional status, which would have a profound influence on the management of the patient by the neurosurgeon or orthopedic surgeon. Deterioration of function despite vertebral alignment implies the need for an MRI or CT myelogram to check for the presence of an extrinsic soft tissue mass compressing the cord, which might be surgically correctable. No specific laboratory studies aid in this evaluation.

After the history and physical examination have identified the level of the lesion, plain films, CT, and MRI help characterize the lesion. For a complete discussion of managing multiple trauma, x-rays, and spinal fracture management, see Chapters 21, 28, and 29.

KEY TESTING

- History and physical examination-–motor, sensory, reflexes, rectal tone and sensation, gross proprioception or vibratory sensation, urinary retention
- Search for occult hemorrhage—FAST, CXR, UA, pelvic x-ray or CT abdomen and pelvis
- CT of whole spinal column
- MRI when patient is able, if cause of patient's findings or deterioration not clearly defined on CT

ED MANAGEMENT

In the patient with a spinal cord injury, the immediate focus should be on identifying and managing life-threatening injuries, while avoiding secondary injury. The patient should remain supine in a semirigid collar using spinal precautions without applying traction

until after films carefully define the lesion. Traction that causes distraction on the cord or roots may cause severe, possibly irreparable neurologic damage. The first priority is to ensure that the patient survives, by attending to the ABCDEs. The second priority is to prevent secondary injury through unnecessary motion, hypoxia, hypotension, or infection.

The physician must not allow or cause the patient to have unnecessary motion of the unstable spinal column. However, at times, such motion may be necessary to preserve the patient's life, such as in the patient with an obstructed airway who needs immediate management when initial maneuvers have been proven unsuccessful. Inline immobilization with the Sellick maneuver should be used, allowing only as much motion as is needed to successfully control the airway. The physician should prepare to logroll and suction if the patient regurgitates, while keeping the patient's spinal column as straight as possible. Although x-ray studies show that logrolling is associated with some motion of the thoracolumbar spinal column, it must be done to prevent aspiration and obstruction in the patient who regurgitates without a protected airway. Later when such an immediate airway threat is not an issue, then multiple person vertical lifting and sliding techniques can be used to transfer the patient with less thoracolumbar spinal motion (14).

Prehospital spinal immobilization is moving toward a greater recognition of the risk–benefit of this therapy. There are no randomized controlled trials of spinal immobilization. Both the C-collar (16) and backboard (18) have come under critical review. This controversy will continue into the future. The American Association for Neurological Surgeons and the Congress of Neurological Surgeons 2013 Joint Guidelines (17) support the use of field triage to determine the need for immobilization of the awake patient with a known or suspected cervical spine injury using the five NEXUS criteria. They further support the use of C-collar and board with blocks for patients not passing those NEXUS exclusion criteria. The NAEMSP and ACSCOT position statement concludes the benefits of backboards are largely unproven, endorses the use of field triage as above and the use of spinal precautions using a rigid collar and

securing the patient to the EMS stretcher, rather than a board, if the patient is ambulatory, there is a long transport, or for those patients in whom the backboard is not otherwise indicated (18). Sundstrom et al. (16) question whether the C-collar should be used. They state its use should be rare such as during extrication and then be removed once the patient is on a spine board in blocks, and if unconscious without a protected airway, rolled into a left lateral position with the left arm raised above the head. Their extensive critical review found little evidence to support the use of a C-collar and an equal or greater amount of evidence opposing its use. They report studies that indicate it may contribute to neurologic injury higher in the cervical column, airway compromise and aspiration especially when used in conjunction with a spine board, and that C-collars raise intracranial pressure which may worsen outcomes in patients with significant traumatic brain injury.

Many patients will arrive immobilized with a long board and semirigid collar. The emergency physician should immediately perform the ABCDEs of the primary survey and resuscitation. Current practice is that the semirigid collar can be opened in a supine, immobilized patient, as needed, to examine the neck. When this examination is complete, the collar is replaced. It should otherwise be left on until clinical evaluation or imaging shows the cervical spine to be stable. The patient is removed from the spine board at the end of the exposure phase. The patient is managed with spinal precautions such as a sliding board, multiple person vertical lift, or logrolling after this.

The NEXUS study provides a reliable decision instrument to help the physician decide if the patient needs cervical x-rays after blunt trauma (8). The five NEXUS criteria are as follows: no posterior midline cervical tenderness; no focal neurologic deficit; the patient must be alert; the patient must not be intoxicated; no distracting painful injury. If the patient meets all five exclusion criteria, then the physician can reliably continue the evaluation without performing cervical spine x-rays. When the patient has none of these indications for cervical x-rays, the physician may remove the collar and gradually have the patient move the neck to assess for pain with

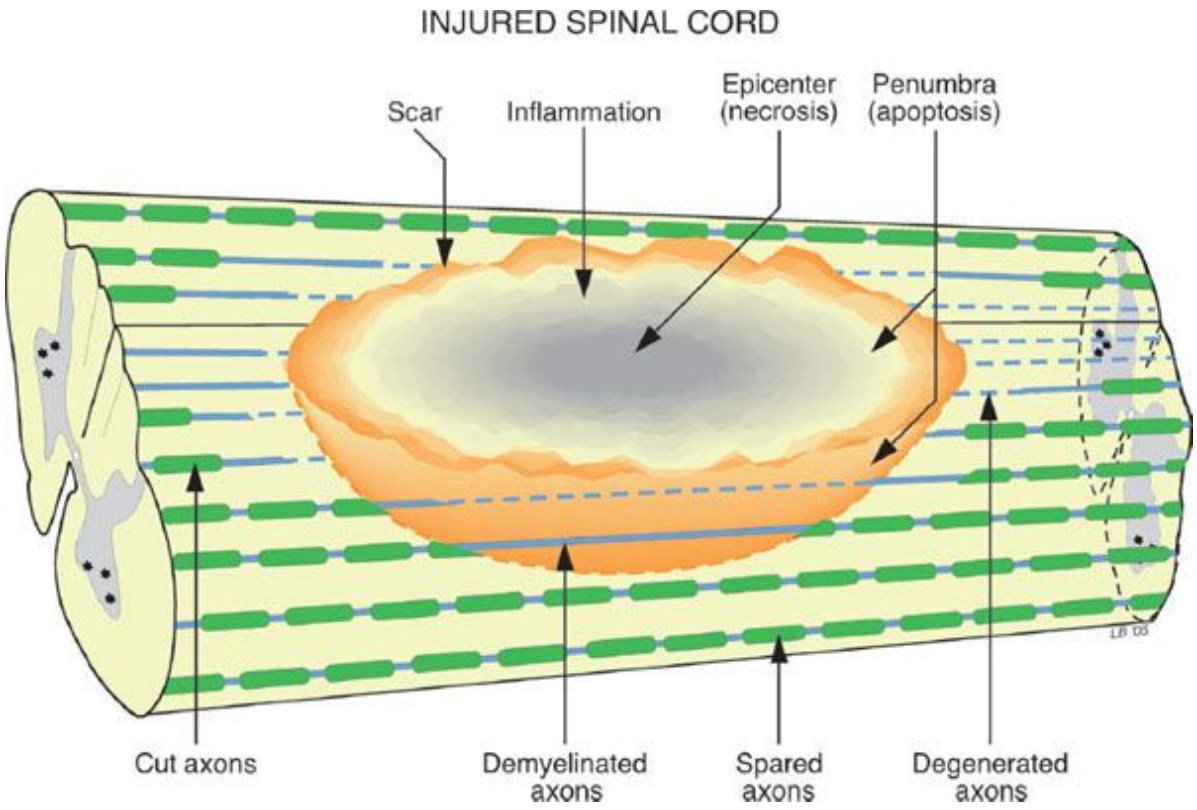
range of motion. An untoward amount of pain with motion should lead to replacing the collar and obtaining films. No similar national multicenter study has defined exclusion criteria for thoracic and lumbar spine x-rays. Domeier (5) used criteria similar to those of NEXUS above for a prehospital spinal injury assessment protocol applied to the entire spine. In it posterior midline tenderness was replaced by spinal pain or tenderness and distracting painful injury by suspected long bone fracture. Using those five criteria no patient without spinal immobilization had a spinal cord injury for lack of immobilization. An alternative approach for use in alert and stable trauma patients is to follow the Canadian cervical spine rules (14); see Chapter 28. Spinal immobilization of victims of isolated penetrating injury is not recommended (15,17,18).

Typically as the last step in the exposure phase, the patient is logrolled to examine the back. The backboard is then removed but the semirigid collar is left in place until either clinical evaluation or imaging has demonstrated stability. Further movement of the patient is accomplished using spinal precautions to move the patient as a unit, using sliding boards, logrolling, or multiple person vertical lifts. The long board is an important tool in immobilizing and protecting the spinal cord especially during early transportation. However it also can deliver significant forces to the spinal column potentially causing second injury to the spinal cord and serious complications such as aspiration, impaired ventilation, and decubitus ulcers. For these reasons, the patient should be removed from the long board as soon as is practical and other spinal precautions should be put in place.

The patient must be protected against unnecessary movement until the history, physical examination, and, if indicated, radiologic studies are complete that show that the spinal column is stable. The physician should not be fooled into thinking films are unnecessary by the fact that the patient was walking after the injury. If such a patient presents, the NEXUS or Canadian C-spine rules should be used to determine if the patient needs x-rays.

The phrenic nerve, providing motor innervation to the diaphragm, arises from the C3 through C5 segments of the spinal cord. An

otherwise healthy patient can maintain adequate long-term ventilation with diaphragmatic breathing alone. However, if a traumatic lesion affects C3 to C5, or if the level of the lesion ascends, as sometimes happens due to edema (eFig. 30.8), the patient may become ventilator dependent. In addition, the patient may need intubation and ventilation early on, despite preserved diaphragmatic breathing, if there are additional injuries that combine with the cord injury to make oxygenation or ventilation inadequate.



eFIGURE 30.8 Diagram of spinal cord following a contusion injury. A contusion injury induces hemorrhage. The epicenter is characterized by necrotic cell death and the lesion expands (secondary injury) into a penumbra region, with additional cell death due to apoptosis. The secondary injury is associated with entry of inflammatory cells and toxicity from dying spinal cord cells. Ultimately, the area of injury is surrounded by a dense glial scar. The injury destroys some axons, and damages others, leading to demyelination. Cut axons often retract (dieback). Some axons are usually spared by a contusion injury. (From Schwartz ED, Flander

AE. *Spinal Trauma: Imaging, Diagnosis, and Management*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.)

The ultimate outcome of any spinal cord injury is determined by a combination of the initial mechanical injury and a cascade of secondary injuries. Timely reduction of the displaced column is vital to achieve decompression of the spinal cord. Timely reduction has been associated with recovery from otherwise devastating spinal cord injury (2). The secondary vascular and biochemical injuries are the subject of numerous animal and human studies of their mechanism of injury and treatment. Various monotherapy and combination therapy protocols attempt to interrupt this cascade of injury at various points in its course. Pharmacologic therapy for acute spinal cord injury has been controversial for many years. The 2013 American Association of Neurologic Surgeons/College of Neurosurgeons (AANS/CNS) Guidelines state as a Level I recommendation that the "administration of methylprednisolone for the treatment of acute spinal cord injury is not recommended…" and that "high-dose steroids are associated with harmful side effects including death" (9). High-dose methylprednisolone is not indicated after penetrating spinal cord injury. There is insufficient data to support its use in children, or in patients with cauda equina, or spinal root injury.

CRITICAL INTERVENTIONS

- Ensure patient survival by attending to the ABCDEs and initial resuscitation.
- Perform inline immobilization for airway interventions.
- In the hypotensive patient with suspected spinal neurogenic shock, after completing a negative search for occult hemorrhage, use volume resuscitation and then pressors if needed to raise mean arterial pressure to between 85 and 90.
- Identify other injuries in the anesthetic or hypoesthetic patient. Because the patient cannot feel pain or tenderness below the lesion, common historical and physical examination findings will

be absent. The patient requires a very thorough examination, and areas with significant bruises should be imaged. Perform complete CT scans if available.

- Remove the patient from the backboard, while maintaining spinal precautions, as soon as practical to avoid decubitus ulcerations, pain, impaired respirations, and limit the risk of aspiration that results from being immobilized supine.
- Record an accurate baseline motor, reflex, sensory, posterior column, and rectal tone examination. Changes in these may lead to MRI or CT myelography (may be done if MRI not possible) and possible decompressive surgery.

DISPOSITION

The emergency physician must decide if a spinal column or cord injury exists. Next, the physician must decide whether the column is stable. Consultation should be obtained once cord or spinal nerve root injury is identified by physical examination or radiologic studies. The timing of consultation is urgent; it should be obtained while the patient is in the ED. It should be requested after attention is focused on the primary survey and initial resuscitation.

Patients are admitted if there is a cord injury or unstable column injury, for pain control, or for an anticipated complication such as the association of ileus with a thoracolumbar compression fracture. Patients with cord or unstable column injuries are admitted to the intensive care unit; rotating frames, or serial inflating beds are used to protect from pressure sores. Deep vein thrombosis is very common early in the hospital management of patients with acute spinal cord injury. Prophylaxis includes pneumatic compression stockings, as well as heparin when other injuries allow its safe administration, or an inferior vena cava filter.

Patients discharged home should be instructed to return immediately for a recheck if there is any sign of worsening, such as the development of numbness, weakness, hyperesthesia, paresthesias, cauda equina syndrome with urinary retention, fecal incontinence, or saddle hypoesthesia. Paresthesias are a sign of potential instability.

The patient should be transferred to a specialized trauma facility if the trauma team cannot meet all the special requirements for extensive rehabilitation and specialized care of the cord-injured patient. Deteriorating or unstable internal injuries are best managed before transfer. Transport personnel should be, at a minimum, Advanced Life Support Certified. For the emergent transfer, the patient should lie supine with a semirigid collar and moved using spinal precautions.

Common Pitfalls

- Applying cervical spine traction instead of immobilization. The patient is at the highest potential risk for traction injury during prehospital placement on a spinal board or during intubation when inline immobilization, not traction, should be used. Video laryngoscopy can facilitate intubation during inline immobilization.
- Attributing hypotension solely to spinal neurogenic shock without completing the search for occult injury.
- Attributing the subtle findings of partial cord syndrome to psychological, pharmacologic, metabolic, and infectious etiologies.
- Misreading x-rays or accepting inadequate films and failure to identify an unstable spinal segment.

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CHAPTER 31

Blunt Chest Trauma

Richard L. Byyny

Blunt chest trauma (BCT) is a common emergency department (ED) presentation. The trauma can range from the most minor chest wall contusion to catastrophic and fatal intrathoracic injury. BCT is involved in nearly one-third of admissions to trauma centers and accounts for about 25% of all trauma-related deaths in the United States (1). Most of these injuries are the result of motor vehicle collisions or pedestrians who are stuck by automobiles. Unlike penetrating injuries, BCT usually occurs when a large force is applied to a relatively larger area. Injury kinetics include acceleration and deceleration forces as well as transmission of blunt force to internal structures. BCT is often associated with multiple system trauma; including injury to the abdomen, head, spine, and extremities. Therefore, BCT must be evaluated in the context of these other injuries and, at times, more imminent life threats.

CLINICAL PRESENTATION

Chest Wall Injuries

Chest wall contusions and rib fractures account for the majority of blunt chest wall trauma (2). Rib fractures make breathing painful and can increase the patient's morbidity and mortality by adversely affecting ventilation. Fractures typically occur at the site of the impact or the posterior angle where the rib is structurally the weakest. Fractures are more common in adults than children because of the relative inelasticity of the mature thorax. In fact the presence of rib fracture in children should raise the suspicion of child abuse

and heighten the concern for coexisting intrathoracic injury (3). Elderly patients have a higher morbidity and mortality associated with rib fractures than younger patients with each additional fracture increasing the risk of death by 19% and increasing the risk of developing pneumonia by 27% (3). Although the fourth through the ninth ribs are most commonly involved, there is a fourfold increase in splenic injuries with left-sided rib fractures 9 to 11 and a threefold increase risk of liver injuries in right-sided rib fracture 9 to 11 (4). Multiple rib fractures or the presence of a flail chest wall segment may be associated with intrathoracic injury, usually a pulmonary contusion.

Clinical findings typically include pleuritic pain, tachypnea, splinting, and point tenderness intensified by deep breathing or coughing. Bony crepitus may be palpable. Anteroposterior compression of the thorax produces referred pain to the fracture site; if fracture is absent, there should not be referred pain to the localized area of tenderness.

Sternal Fractures

Sternal fractures usually result from high-energy forces to the midanterior chest wall. This force most commonly occurs from motor vehicle collisions in which the chest strikes the steering wheel, dashboard, or shoulder belt at high velocity. This force may result in a sternal fracture or costochondral separation and, in rare instances, an anterior flail chest when the sternum is disarticulated from the ribs. Patient may have point tenderness on their sternum, hematoma, or deformity.

Flail Chest

Flail chest occurs when three or more ribs are fractured in two or more places. In a patient who is breathing spontaneously, the negative intrathoracic pressure with inspiratory effort results in a paradoxical movement of the chest wall (the flail segment moves in during inspiration and out during expiration). There is usually no significant ventilatory compromise caused by the flail segment *per se*.

In these patients, respiratory compromise is related to the degree of pulmonary contusion, which almost inevitably occurs when force is significant enough to cause a flail chest. However, in patients with large flail segments, the normal thoracic physiology is disrupted, causing respiratory failure requiring mechanical ventilation. All patients experience significant pain secondary to the respiratory movement of multiple rib fracture fragments and will often have tenderness, crepitus, and paradoxical movement of the chest wall. In some patients who are splinting or in those on positive-pressure ventilation, the flail segment may not be readily apparent. Palpation of the chest can help detect the injury. It is notable that in patients with flail segments the morbidity and mortality are increased when compared to patients with a similar numbers of fractures without a flail segment (5).

Pulmonary and Pleural Injuries

Blunt trauma may result in pneumothorax, hemothorax, or hemopneumothorax, usually secondary to a rib fracture penetrating the visceral pleura and lung parenchyma. Hemothorax usually results from disruption of an intercostal artery (see Chapter 32).

Pulmonary Contusion

The most common injury to the pulmonary parenchyma in BCT is pulmonary contusion. Among severely injured (ISS >15) blunt trauma patients approximately 27% had pulmonary contusion (6) and in children pulmonary contusion represents a large proportion of thoracic injuries (7). This injury results from transthoracic transmission of kinetic injury to the pulmonary parenchyma causing an alveolar–capillary membrane disruption and subsequent pulmonary edema. This injury results in areas of the lung that are perfused but not ventilated (i.e., a ventilation perfusion mismatch), resulting in hypoxia, hypercarbia, and acidosis.

Depending upon the extent, this injury results in minimal to life-threatening symptoms. A patient with a pulmonary contusion usually presents with dyspnea and tachypnea. There may be tenderness or

obvious ecchymosis and deformity over the injured chest wall. Large pulmonary contusions are associated with tachycardia, hypotension, cyanosis, and low oxygen saturation. Patients with multiple rib fractures or flail segments of the chest wall are more likely to have associated pulmonary contusion.

Tracheal and Bronchial Injuries

Tracheal and bronchial injuries are rare accounting for only between 0.1% and 2% of patients who present to the ED (8). The majority of these injuries occur within 2 cm of the carina or at the origin of the lobar bronchi (9). Symptoms are usually related to the size of the defect in the airways and whether there is communication with the pleural space. Occasionally minimal symptoms may occur, even with severe tracheal or bronchial injury. Hemoptysis may occur in up to 25% of cases and subcutaneous emphysema or pneumomediastinum is present in 35% to 85% of cases (8). Patients can also present with dyspnea, hoarseness, or aphonia. This injury should be considered if there is a persistent air leak from a properly positioned chest tube and difficulty in fully reexpanding the lung.

Blunt Cardiac Injuries

By virtue of its location in the chest, the heart is susceptible to injury from compression of the chest wall and upper abdomen and from deceleration forces. It is the cause of death in up to 20% of automobile collisions. There is no gold standard to make the diagnosis of blunt cardiac injury; therefore, the true incidence is unknown and evaluating literature on the topic is difficult with different authors using different diagnostic standards. Therefore, there is a wide range of reported incidence from 20% to 76% of blunt thoracic trauma patients.

The right ventricle is the most commonly injured portion of the heart because of its relatively vulnerable position immediately behind the sternum; however, injuries to multiple chambers occur in 50% of cases (10). Blunt cardiac injury encompasses a spectrum of

injuries including myocardial concussion, myocardial contusion, myocardial infarction, and myocardial rupture.

Myocardial concussion (*commotio cordis*) is a ventricular dysrhythmia or asystole secondary to a direct blow to the myocardium without pathologic evidence of cardiac injury. Myocardial concussion is the most common cause of sudden death in young athletes (11). Those patients who survive a myocardial concussion usually have little or no long-term sequelae from their blunt cardiac injury.

Myocardial contusion is characterized by localized edema and hemorrhage into cardiac muscle. This trauma may involve segments of the cardiac conduction system, most commonly the right bundle branches.

Traumatic myocardial infarction is rare but can occur from disruption of the coronary artery intima and subsequent thrombosis. The most severe form of blunt cardiac injury is cardiac rupture, which is a rare injury. These patients will present with hypotension or *in extremis* and usually have a right atrial or ventricular injury.

Physical findings in blunt cardiac injury may be nonspecific. Chest pain from either chest wall trauma or ischemia may be present. Seventy percent to 80% of patients with blunt cardiac injury have external signs of chest trauma including contusions, abrasions, palpable crepitus, and flail segments. The presence of a fractured sternum, once thought to be a marker for blunt cardiac injury, has not been shown to reliably correlate with the presence of a blunt cardiac injury (12). The most common vital sign abnormality is persistent sinus tachycardia after other causes have been treated. Hypotension is a serious sign and should raise the possibility of pericardial tamponade, myocardial rupture, or rupture of an internal cardiac structure such as a chordae tendineae or valve.

Great Vessel Injuries

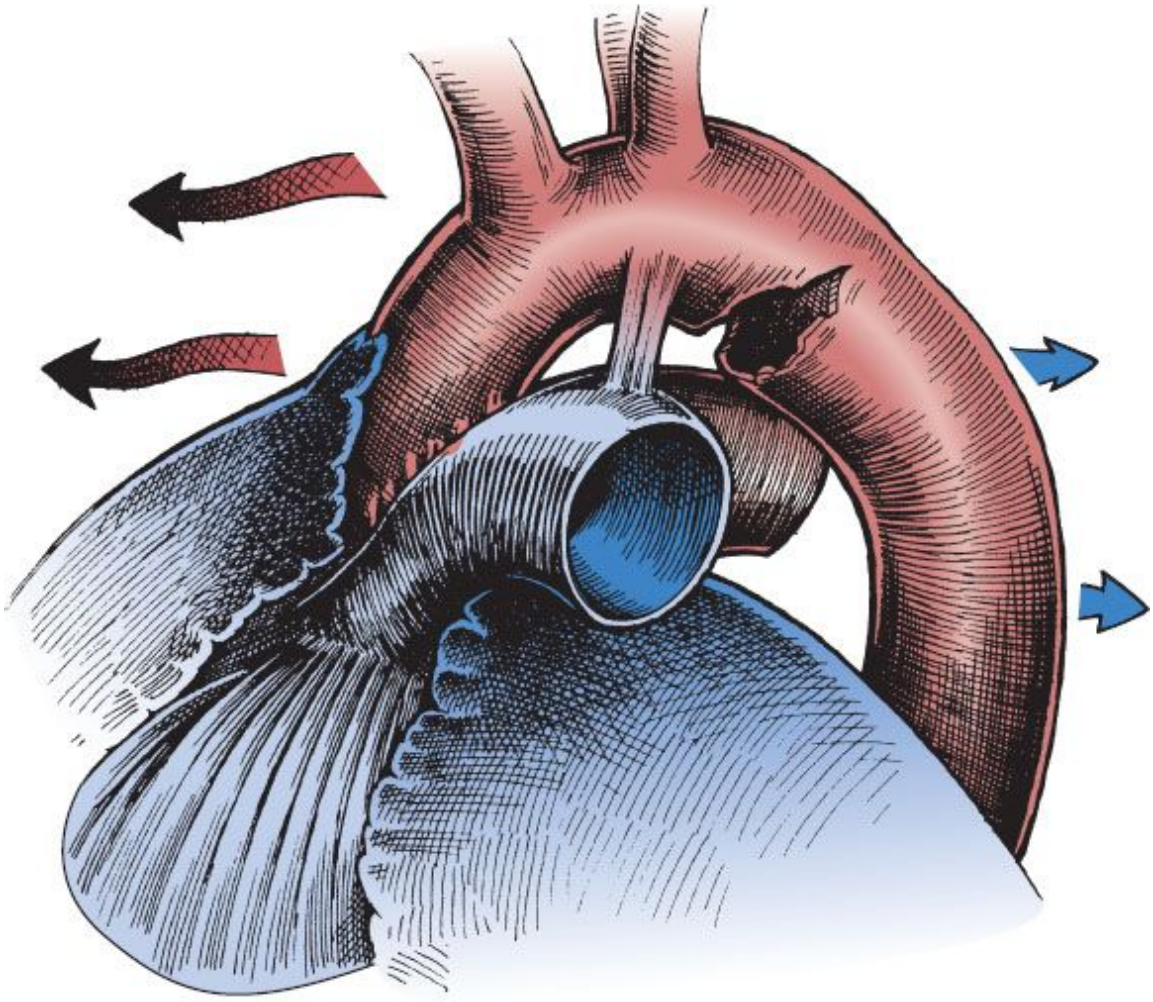
Blunt aortic injury accounts for approximately 8,000 deaths per year in the United States, and up to 15% of automobile fatalities are caused by traumatic disruption of the aorta (13). Eighty percent of patients with aortic injuries die in the field. The tear of the aorta is

usually a circumferential transverse laceration that disrupts the physical integrity of the intima and muscularis layers of the aorta. If the tear is complete, involving all three layers, this results in death caused by immediate exsanguination. In survivors, the adventitia remains intact, and blood is contained by a false aneurysm formed by the adventitia and surrounding mediastinal structures. If this injury is unrecognized, there is a significant risk of a free rupture and sudden death in the hours to days following this injury.

Disruption of the great vessels usually results from high-speed motor vehicle collisions, falls from a height, or ejection from motorcycles or other vehicles (13). The classic mechanism is a head-on motor vehicle collision, although the injury can occur after side or rear impacts. In seat-belted motor vehicle victims, descending thoracic tears are more common. Ascending aortic disruption is seen more often in unrestrained drivers or those who are ejected or fall from a height and experience vertical deceleration forces (14). Most often, these injuries involve the aorta but can involve the brachiocephalic artery and inferior vena cava. Patients with rupture of the vena cava have a poorer outcome because of continued, ongoing, significant blood loss and difficulty in controlling the bleeding and repairing the defect at surgery.

Several mechanisms have been postulated to explain aortic injuries. First, rapid horizontal deceleration produces shearing forces at the aortic isthmus just distal to the origin of the left subclavian artery. Ninety percent of traumatic aortic tears originate at this site. Anatomically, this frequency can be explained by the fact that the descending aorta is tethered by the ligamentum arteriosum and the intercostal arteries. The ascending aorta is relatively mobile and, during deceleration, continues to move forward while the descending aorta is held in place, resulting in shearing forces that cause a rent in the aorta (eFig. 31.1). The second proposed mechanism is that of the “water hammer” effect where a propagated wave of blood causes a surge in intraluminal pressure. Although the aorta may withstand intraluminal pressures of up to 350 mm Hg, this pressure may be surpassed leading to aortic injury (15). The final, and most likely, proposed mechanism is the “osseous pinch” model in which the aorta

is pinched between the sternum and the vertebral column, resulting in shearing forces that cause injury to the aorta (16).



eFIGURE 31.1 Rapid deceleration injury causing a tear in the thoracic aorta. The ascending (anterior) aorta tends to continue moving forward, while the more fixed descending aorta is held stationary. The rupture occurs just distal to the ligamentum arteriosum at the level of the isthmus.

The symptoms and signs of traumatic great vessel disruption are often absent or missed because of coexisting, significant injuries to the head, spine, abdomen, pelvis, and extremities. The most frequently recorded complaints are chest pain, dyspnea, and back pain. However, it is of note that only 25% of patients present with retrosternal pain or pain radiating to the upper back which is

considered typical of nontraumatic aortic dissection. Other symptoms include dysphagia, hoarseness, and ischemic pain of the extremities. Physical examination may reveal ecchymosis, abrasion, or tenderness of the anterior chest wall consistent with the impact of this area on a steering wheel. Thirty-one percent of patients with an aortic disruption present with the pseudocoarctation syndrome. In these cases, upper-extremity hypertension is present with decreased or absent femoral pulses because of compression of the aortic lumen by surrounding periaortic hematoma. Reflex stretching of the cardiac sympathetic fibers at the aortic isthmus may account for the observation that 72% of patients with aortic rupture manifest a relative hypertension (average blood pressure 152/98 mm Hg) (17). A harsh systolic murmur over the precordium or interscapular area (thought to be because of turbulent flow across the area of transection) has been reported to be present in 26% of cases (18). Unfortunately, the presence of great vessel injury cannot be confirmed or ruled out based on physical examination or history.

In confirmed cases of traumatic aortic injury, one-third to one-half of the patients have no external evidence of chest injury on initial presentation to the ED. Therefore, this injury should be suspected, even in the absence of these signs or symptoms, whenever there has been major acceleration–deceleration forces involving the chest (i.e., significant ejection mechanisms, falls from heights >10 ft, and motor vehicle collisions with speeds >30 mph, and a lack of proper vehicle restraints).

Diaphragmatic Injuries

Blunt traumatic diaphragmatic injury results from violent compression of the lower chest and upper abdomen and has an incidence between 0.5% and 8% of blunt trauma victims (15). Sixty percent to 90% of traumatic rupture of the diaphragm from blunt trauma occurs on the left side (19). Blunt trauma typically produces diaphragmatic defects of >10 cm on average and has a higher mortality rate than penetrating injury to the diaphragm because of the higher incidence of serious associated injuries to abdominal and chest structures.

Signs and symptoms of diaphragmatic rupture are highly variable depending upon the size of the defect, the mechanism, the abdominal viscus that herniates through the defect, and the degree of cardiopulmonary compromise. Common symptoms include cough, dyspnea, nonspecific chest or abdominal pain radiating to the shoulder, and the perception of peristalsis in the chest. Signs include an immobile left hemithorax, decreased breath sounds, and tympany or borborygmi in the left chest. Significant herniation of abdominal viscera into the thoracic cavity usually results in severe respiratory distress and may be clinically confused with a tension pneumothorax. A tension viscerothorax (gastrothorax) occurs when the resulting increase in intrapleural pressure causes shift of the mediastinum and hemodynamic collapse. Therefore, great care should be taken when performing a thoracostomy to verify a free pleural space before inserting the chest tube.

Esophageal Injuries

Esophageal injuries secondary to blunt trauma are rare occurrences yet critical to diagnose secondary to the high morbidity and mortality when treatment is delayed. They have been reported from sharp blows or when force is applied to the upper abdomen in which air and gastric contents are violently forced into the esophagus causing a perforation in the distal esophagus similar to those that results from retching and vomiting (i.e., Boerhaave syndrome). Injuries to the esophagus can also occur with compression of the esophagus against the spine, producing longitudinal tears in the upper thoracic esophagus and can be associated with laceration in the membranous (i.e., posterior) portion of the trachea, resulting in traumatic tracheoesophageal fistulas. Injuries to the esophagus can also occur from barotrauma, because the esophagus is a hollow, air-containing organ. An example of this is forceful insufflation of the esophagus from inhalation of aerosol cans, air compressors, or inflation devices or in children from the biting of inner tubes, and eruption of bottled carbonated beverages into the esophagus. Perforations of the esophagus can result from alkali ingestion, button

batteries, foreign bodies, and iatrogenic misplaced tubes or endoscopes.

Signs and symptoms of esophageal injury are subcutaneous emphysema (especially in the neck or supraclavicular fossa), unexplained tachycardia, dyspnea, dysphagia, odynophagia, cyanosis, pneumomediastinum, pneumothorax, pleural effusion (particularly on the left), and hematemesis.

Traumatic Asphyxia

Traumatic asphyxia occurs when the thorax is squeezed between two objects for a prolonged period of time. This results in compression of the vena cava with resultant prolonged increased venous pressure to the neck and head. This prolonged squeeze and compromised venous return results in intense cyanosis of the upper chest, neck, and face as well as petechiae and subconjunctional hemorrhage. Some patients may have retinal hemorrhage and loss of consciousness because of cerebral hypoxia. Sometimes there are associated chest wall and pulmonary parenchymal injuries such as pulmonary contusion and hemopneumothorax.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of chest wall injuries includes rib fractures, flail chest, sternal fracture, costochondral separation, and chest wall contusion.

After blunt trauma, the differential diagnosis for pulmonary and pleural injuries includes pulmonary contusion, pneumothorax, hemothorax, hemopneumothorax, pulmonary contusion, tension pneumothorax, and acute pericardial tamponade. Tension pneumothorax must be differentiated from acute pericardial tamponade because both cause tachycardia, hypotension, and an elevated central venous pressure (CVP). In patients with tension pneumothorax breath sounds are absent or markedly diminished and pericardial ultrasound is normal.

The differential diagnosis of tracheal and bronchial injuries includes other traumatic causes of pneumomediastinum, such as a

ruptured esophagus or an iatrogenic perforation of the esophagus, posterior pharynx, or pyriform sinus during attempts at endotracheal intubation.

In patients with blunt cardiac injury, rupture of the valves or chordae tendineae may result in acute cardiac failure. In rare instances, blunt cardiac injury may cause acute pericardial tamponade. This injury can be differentiated from tension pneumothorax by the presence of a pericardial effusion on ultrasound, as well as by bilaterally equal breath sounds on physical examination.

The majority of patients who suffer from blunt thoracic aortic injury have coexisting serious injuries. These include fractures of the sternum and ribs, hemothorax, pneumothorax, hemopneumothorax, tracheobronchial disruption, diaphragmatic rupture, esophageal perforation, acute pericardial tamponade, and blunt trauma to the myocardium.

Traumatic rupture of the diaphragm can be confused with a pneumothorax or a tension pneumothorax when abdominal viscera have herniated into the thoracic cavity resulting in respiratory distress and diminished or absent breath sounds, usually on the left side.

ED EVALUATION

Chest Wall Injuries

After a history and physical examination including pulse oximetry, chest wall trauma can be evaluated with chest radiography. However, chest radiographs may not be necessary in isolated, localized chest wall trauma when there are no physical findings and no respiratory distress manifested by tachypnea or decreased oxygen saturations. Up to 50% of rib fractures are missed on the initial chest radiographs; 10% do not visualize radiographically for 1 to 2 weeks after the injury regardless of the views taken. Specific rib views are unnecessary and much of the time the presumptive diagnosis can be made without radiography. A chest radiograph is valuable when looking for complications of rib fractures such as hemothorax,

pneumothorax, pulmonary contusion, atelectasis, and pneumonia. Because elderly patients have a greater morbidity and mortality from complications of rib fractures, there should be a lower threshold for evaluating these patients with a chest x-ray and rib films (15).

Consideration should be given to observation, performance of the focused assessment with sonography in trauma (FAST) examination, or abdominal computed tomography (CT) in the presence of 9th through 11th rib fractures given the heightened risk for spleen or liver injury. Pain referred to either shoulder may indicate the presence of either hemothorax or pneumothorax or subdiaphragmatic hemorrhage from injury to the spleen or liver. Patients who present several days after their initial trauma with increasing pain, dyspnea, or fever following chest wall trauma should have a chest x-ray to ascertain if there are any late complications such as atelectasis or pneumonia.

Flail Chest

Patients with evidence of a flail chest on physical examination should be evaluated with oxygen saturation monitoring and a radiograph of the chest to detect the presence of underlying pulmonary contusion, pneumothorax, or hemothorax. Parenteral analgesics or regional nerve blocks are necessary for adequate analgesia.

Pulmonary and Pleural Injuries

Clinical signs of tension pneumothorax or massive hemothorax (decreased breath sounds or subcutaneous emphysema in association with hypotension, tachycardia, and respiratory distress) mandate initial placement of a needle or tube thoracostomy prior to obtaining chest radiography. Tension pneumothorax should be a clinical diagnosis and should not be captured on a chest x-ray. The extended focused abdominal ultrasound in trauma (E-FAST) has been more widely utilized to assist in the diagnosis of pneumothorax. In addition to usual components of the FAST examination (evaluation of the right upper quadrant, left upper quadrant, pericardium, and

retrovesicular space) the E-FAST also includes ultrasonography of the pleural surface using the high-frequency linear probe. It has been shown to have superior sensitivity to the supine chest x-ray and can expedite the diagnosis of pneumothorax (20). If the patient is hemodynamically stable, a portable chest radiograph is the initial study of choice; this will demonstrate hemothorax, pneumothorax, and pneumomediastinum.

Pulmonary Contusion

Radiographic evidence of pulmonary contusion may not be evident initially on the chest x-ray because these injuries tend to get worse over the ensuing hours following injury with the peak not being present until 72 hours after injury (6). Radiographic findings usually lag behind the clinical findings. A contrast-enhanced helical CT scan of the chest will detect the presence of pulmonary contusions before they become visible on standard chest radiographs. CT scans may be used to measure the extent of the pulmonary contusion and to determine the prognosis (6). All patients should be placed on oxygen and have continuous oxygen saturation monitoring. If the oxygen saturation is low, an arterial blood gas can be obtained to calculate an alveolar–arterial gradient and followed serially to determine subsequent therapy.

Tracheal and Bronchial Injuries

These injuries should be suspected when there is a persistent air leak despite the proper placement of a tube thoracostomy on the involved side. All patients should have a chest x-ray to rule out associated pneumothorax and to confirm that all the holes on the chest tube are within the thoracic cavity. Consideration should also be given to diagnostic studies that rule out the presence of an esophageal disruption (discussed later in this chapter). Surgical consultation should be obtained so that bronchoscopy can be performed for definitive diagnosis.

Blunt Cardiac Injuries

All patients in whom this injury is suspected should have cardiac rhythm and oxygen saturation continuously monitored. An electrocardiogram (ECG) should be obtained to ascertain the presence of any dysrhythmia, bundle-branch block, or new changes on the ECG (15). An initial ED ultrasound of the pericardium to detect the presence of pericardial effusion and to determine, if possible, the quality of cardiac wall motion should be performed. New murmurs or acute congestive failure after chest trauma should raise the suspicion of a ruptured interventricular septum, valve leaflet, or chordae tendineae. Traumatic ventricular septal rupture presents with a pansystolic murmur heard throughout the entire precordium, especially at the left sternal border. This murmur may not be appreciated until the patient has been resuscitated to a euvolemic state. In patients exhibiting hemodynamic instability and clinical signs of cardiac failure, a formal echocardiogram should be obtained to look for the presence of pericardial tamponade, valvular or chordae tendineae disruption, and to determine cardiac output.

Chest radiographs are not helpful in diagnosing cardiac trauma *per se* but may be helpful in identifying other thoracic injuries. Although nondiagnostic, multiple ECG abnormalities have been described that range from persistent sinus tachycardia to ST- and T-wave changes and bundle-branch blocks (the most common being right bundle-branch block). If ECG abnormalities are present, the patient should be admitted for 24 to 48 hours of continuous cardiac monitoring. The presence of a normal ECG confers a negative predictive value of 95% in ruling out myocardial contusion (12). Troponin I is helpful in making the diagnosis and in the stratification of those at risk for life-threatening conditions. If the troponin is not elevated at 4 to 6 hours post injury and the ECG is normal, the patient may be discharged from the ED conferring a negative predictive value of 100% (12). Neither nuclear testing nor echocardiogram is useful in diagnosing myocardial contusion.

Great Vessel Injuries

In patients with a major traumatic mechanism, a chest x-ray is a helpful screening tool in detecting not only great vessel injuries but

also other associated thoracic abnormalities. There are multiple radiographic features of great vessel injury (Fig. 31.1). The most sensitive finding in patients with aortic injury is a wide mediastinum (>6 cm upright and >8 cm supine anteroposterior view) (13). However, only 10% of patients with a wide mediastinum will end up having an aortic injury; other causes include sternal, rib, or spine fractures, and the supine radiography. Sitting the patient up after the cervical spine has been cleared will decrease the incidence of a wide mediastinum. Despite the many radiographic signs of traumatic aortic injury that have been described, in 7% to 28% of cases of aortic injury the chest radiograph is normal (eTable 31.1) (14). Therefore, it is prudent to consider further diagnostic studies, if there is a significant mechanism, even in the presence of a completely normal upright chest x-ray (13,21).

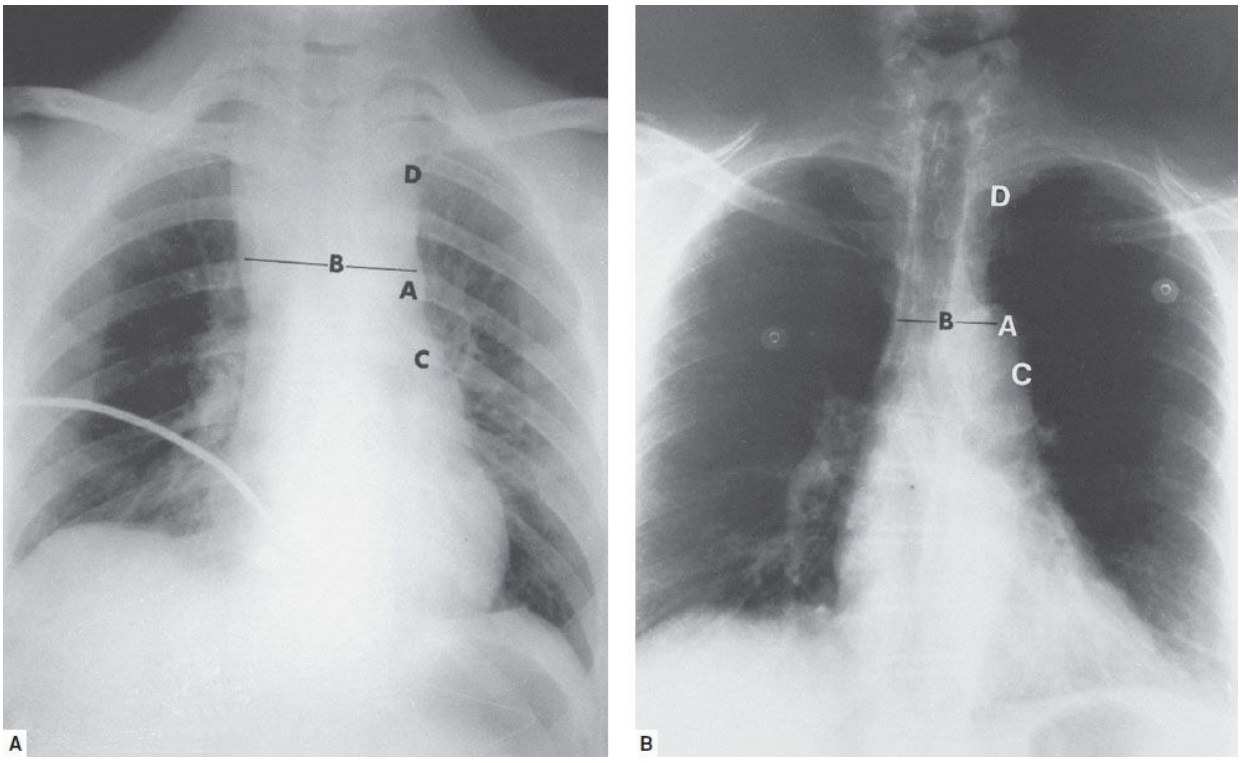


FIGURE 31.1 Upright posteroanterior chest radiographs of a 20-year-old man involved as a driver in a head-on motor vehicle collision (A) compared with that of a normal person (B). The first radiograph has several abnormalities suggestive of a great vessel disruption. A: Loss of detail of aortic knob with blurring of the aortic

outline. B: Widened mediastinum (mediastinal width to chest width ratio >0.28). C: Opacification of the clear space between the aorta and pulmonary artery (aortopulmonary window). D: Obliteration of the medial aspect of the left upper field. The aortogram revealed rupture of the aortic arch. (Radiographs courtesy of the Department of Radiology, St. Luke's Hospital, Milwaukee, WI.)

eTABLE 31.1
Radiographic Features of Great Vessel Injury

Widening of the superior mediastinum at the level of the aortic knob on an upright radiograph
Mediastinal width–chest width ratio of more than 0.25
Deviation of the trachea or endotracheal tube to the right
Deviation of the nasogastric tube (representing the esophagus) to the right
Narrowing of the carinal angle
Depression of the left mainstem bronchus
Irregularity of the aortic knob contour
Left apical cap
Opacification of a clear space between the aorta and pulmonary artery ("aortic pulmonary window")
Widening of the left or right paraspinous stripe
Hemothorax, sternal, or rib fractures

CT scanning of the chest with contrast has become the procedure of choice when the diagnosis of mediastinal great vessel injury is considered, with reported sensitivity and specificity of 96% to 100% and 98% to 100%, respectively (22,23). An added benefit to CT is the detection of other thoracic injuries. Furthermore, CT is noninvasive and can be completed in a short period of time. Contrast-enhanced CT of the chest should be performed in those patients who have any findings on chest x-ray associated with traumatic aortic injury, are hemodynamically stable, and have sustained significant acceleration–deceleration blunt-force chest trauma such as high-speed motor vehicle collisions or falls from a significant height. Positive criteria for the diagnosis of great vessel

injury include periaortic hematoma, an irregular aortic contour, change in caliber of the aorta, and intraluminal irregularity (intimal flap).

Transesophageal echocardiography (TEE) is reported to have a sensitivity and specificity comparable to helical CT in the diagnosis of blunt aortic injury (23). In contrast to CT, TEE can be performed at the bedside in an unstable patient. However, in contrast to helical chest CT, its availability is limited in most EDs. TEE may be performed in an ICU setting or the operating room to diagnose aortic injury in unstable patients and those with other life-threatening injuries. This technique is contraindicated in patients with esophageal injury or unstable cervical spine injuries.

Aortography was once considered the gold standard for making the diagnosis of traumatic aortic injury, but it is now only used in a small number of cases with equivocal findings on helical CT, when planning the surgery in some selected cases, and interventional radiographic endovascular stenting is being increasingly used to treat patients with aortic injury (24).

Diaphragmatic Injuries

An immediate chest x-ray should be obtained when blunt traumatic rupture of the diaphragm is suspected by the clinical examination (i.e., decreased or absent breath sounds on the involved side, bowel sounds audible in the chest, severe respiratory distress), and the patient has sustained major blunt-force trauma to the lower chest or upper abdomen. In most instances of blunt traumatic rupture, the left hemidiaphragm is not visualized on the radiograph, and stomach or bowel is often visualized in the left hemithorax. Small diaphragmatic tears may not be obvious on initial chest x-ray but may be diagnosed with contrast-enhanced abdominal CT.

Esophageal Injuries

The presence of particulate matter in chest tube drainage as well as the presence of pneumomediastinum should lead the physician to consider esophageal perforation. This diagnosis has a very high

morbidity and mortality if not recognized early and treated aggressively. When this diagnosis is suspected, it is imperative to move rapidly to a definitive diagnostic study to rule out this entity. The choice of the initial diagnostic procedure is somewhat controversial and is dependent upon the suspected injury. Some authors advocate esophagography, and others advocate esophagoscopy. Contrast esophagography has the disadvantage of potentially introducing contrast material into the mediastinum or peritoneum. Therefore, this study should first be performed with a water-soluble contrast material (i.e., Gastrografin), which has a much lower risk of mediastinitis or peritonitis than does barium. However, care should be taken in patients at risk for aspiration, as the entry of water-soluble contrast into the tracheobronchial tree can lead to pulmonary edema. If this study is negative, it can be followed by esophagoscopy, because Gastrografin will not obscure visualization of the lining of the esophagus. Ultimately, a barium esophagram may be needed to detect the presence of very small perforations.

Traumatic Asphyxia

Because these patients can sustain rib fractures and pulmonary contusions, one should consider chest CT to evaluate these injuries. Also, any patient with a neurologic deficit should have a CT of the head.

KEY TESTING

Test	Indication
ABG	• Pulmonary contusion for risk stratification
Troponin	• Suspected cardiac contusion
EKG	• Suspected cardiac contusion
Bedside ultrasonography	• Suspected pneumothorax or hemothorax
	• Suspected pericardial effusion
	• Rib Fracture 9–11 to assess for hemoperitoneum
Echocardiography	• Suspected valvular injury
	• Suspected injury to ventricular or atrial septum
Chest x-ray	• Focal tenderness
	• Chest wall crepitance
	• Pain with lateral or AP compression of the chest
	• Hypoxia
	• Absent or decreased breath sounds unilaterally
	• Paradoxical chest movement
	• Ejection from a motor vehicle
	• Falls >10 ft
	• Lack of Seatbelts
	• MVC at speeds greater than 30 mph
Chest CT	• Suspected pulmonary Contusion on CXR
	• Major mechanism accident
	• Ejection from a motor vehicle
	• Falls >10 ft
	• Lack of seatbelts
	• MVC at speeds greater than 30 mph
Esophagram	• Suspected esophageal injury
CT head	• Traumatic asphyxia with focal neurologic deficit
Bronchoscopy	• Continued air leak despite adequate chest tube placement
Aortogram	• Mediastinal hematoma on CT
	• Aortic irregularity on CT

ED MANAGEMENT

Chest Wall Injuries

Chest wall contusions and rib fractures with no underlying pulmonary parenchymal injury should be managed with adequate analgesics as well as careful aftercare instructions encouraging the patient to cough and deep breathe every hour while awake to

prevent the complications of atelectasis and subsequent pneumonia. Patients may be discharged with a spirometer to aid them in following these instructions. Consideration can be given to regional nerve blocks for multiple rib fractures, but these may only give significant pain relief for up to 12 hours. Admission, for pulmonary toilet and pain control, should be considered in the elderly especially those over 65 with rib fractures (3).

Flail Chest

Pain can be controlled with administration of narcotics, regional nerve blocks, or in severe cases, epidural anesthesia. Intubation should be considered if there is respiratory distress or ventilatory failure as manifested by a partial pressure of arterial oxygen (Pao_2) of <60 mm Hg on a nonrebreather bag reservoir mask at sea level or low oxygen saturation. In elderly patients with flail chest, the physician should have a lower threshold for intubation, as the patients' cardiac and pulmonary reserves are limited.

Sternal Fractures

Patients with suspected sternal fractures should have a standard posteroanterior (PA) and lateral chest x-ray. The lateral chest x-ray is the best view to determine if a fracture is present.

Pulmonary and Pleural Injuries

Tension pneumothorax, pneumothorax, and hemothorax should be treated emergently with tube thoracostomy (see Chapter 32). Patients with clinical evidence of tension pneumothorax should undergo immediate chest decompression prior to chest x-ray. Although this can be performed with a 14- or 16-gauge needle, in up to 30% of patients a standard needle will not reach the pleural space in the anterior second intercostal space and up to 18% of patient it will not reach the pleural space in the midaxillary line (25). Therefore, preference should be given to rapid decompression of the chest in the midaxillary line with eventual placement of a 28- to 36-French chest tube for adults or a 16- to 24-French chest tube for

children. Alternatively clinicians can also place a pigtail catheter (26,27). Small (<15%), simple pneumothoraces or those visualized on CT only (occult pneumothorax) can often be observed and treated without thoracostomy (15). Patients with occult pneumothorax who will undergo transfer in an ambulance or helicopter are at risk for development of a larger pneumothorax (or tension pneumothorax), clinicians should consider tube thoracostomy. Although positive-pressure ventilation was once considered an absolute indication for tube thoracostomy, there exist more recent literature suggesting that it may be possible to observe patient with occult pneumothorax (28).

Patients with pulmonary contusions should be placed on continuous, high-flow oxygen via a nonrebreather bag reservoir mask, and their oxygen saturation should be continuously monitored. Patients with more severe injury can undergo a trial of noninvasive positive-pressure ventilation; however, those patients who exhibit falling oxygen saturations or hypercarbia should be considered for rapid sequence intubation (RSI) and positive-pressure ventilation (6). Independent lung ventilation with low tidal volume and positive end-expiratory pressure (PEEP) has been reported to be efficacious in the treatment of unilateral pulmonary contusions.

Patients with an initial thoracostomy tube output of >20 mL/kg or an ongoing blood loss of >7 mL/kg/h are candidates for operative thoracotomy.

Tracheal and Bronchial Injuries

In a patient who clinically has a major airway disruption or problems maintaining adequate oxygen saturation, endotracheal intubation should be performed. In some instances, selective intubation of the nontraumatized mainstem bronchus is indicated. All tracheobronchial lacerations and disruptions require a surgical consultation, further diagnostic studies (bronchoscopy), and definitive management.

Blunt Cardiac Injuries

All patients should be on oxygen and monitored for dysrhythmias. Any dysrhythmias should be treated per advanced cardiac life support (ACLS) guidelines. Care must be taken not to fluid overload patients with myocardial contusion as their compromised cardiac output may lead to pulmonary edema. Patients who remain hemodynamically compromised after adequate volume resuscitation may benefit from pressor support with dobutamine. Unstable patients with pericardial tamponade require pericardiocentesis or ED thoracotomy. Patients with abnormalities detected on echocardiography such as chordae tendineae or valvular disruption should be referred to a cardiac surgeon for definitive repair of these lesions. In those rare instances where blunt cardiac trauma results in myocardial infarction from intimal disruption and thrombosis of the coronary artery, patients should undergo emergency angioplasty because the use of thrombolytics is contraindicated. The last option for refractory cardiogenic shock is placement of an intra-aortic balloon pump. The prognosis for patients with blunt cardiac trauma is most closely correlated with the severity and number of other associated injuries, as most patients who have an isolated myocardial contusion do well.

Great Vessel Injuries

In patients in whom a traumatic aortic injury is strongly suspected or proven via CT scan of the chest, blood pressure should be controlled via the use of a β-blocker (usually intravenous [IV] esmolol) and an afterload-reducing agent (usually IV nitroprusside) (13). β-blocking agents are usually started first. The objective of lowering blood pressure is to decrease the shearing forces of the pulse pressure, thus decreasing the possibility of free rupture. Using nitroprusside without a β-blocking agent may result in a reflex tachycardia and increased intraluminal pressure. The systolic blood pressure should be maintained between 100 and 120 mm Hg with a heart rate of 55 to 65 beats/min. In patients with bleeding and associated hypotension, judicious resuscitation to a mean arterial pressure between 65 and 80 mm Hg is adequate. All patients must be emergently referred for definitive therapy. Although all of these

patients have traditionally been treated surgically, endovascular stent placement using interventional radiographic techniques has been used successfully as well; it appears to have a lower risk of complications, and in some centers it has replaced open thoracotomy for the repair of aortic injuries. The decision on which therapy is best for the individual patient should be made in consultation with a surgeon and interventional radiologist. Many patients with aortic injury have associated life-threatening injuries that require management before repair of the aorta.

Diaphragmatic Injuries

A nasogastric tube should be placed and emergent surgical consultation for operative repair of the diaphragm should be obtained. Some of these patients may require RSI intubation, sedation, and mechanical ventilation if there is significant respiratory compromise. Unstable patients with tension viscerothorax should undergo careful tube thoracostomy placement. It is advisable to place the thoracostomy tube at a higher intercostal space to avoid injury to the bowel or introduction of the tube below the diaphragm.

Esophageal Injuries

Once the presence of an esophageal injury is confirmed by a contrast study of the esophagus or by esophagoscopy, surgical consultation for definitive surgical repair and drainage should be obtained to minimize the subsequent morbidity and mortality of this lesion. IV antibiotics should be administered preoperatively.

ED Thoracotomy

For patients with blunt trauma who sustain cardiac arrest prior to arrival in the ED, an ED thoracotomy is a futile procedure. Those patients who arrest after arrival in the ED and undergo ED thoracotomy have a 1.4% survival rate and thus are potential candidates for ED thoracotomy. Patients with isolated cardiac or pulmonary injuries have the best chance of survival after ED thoracotomy (29).

CRITICAL INTERVENTIONS

- Perform tube thoracostomy immediately for patients with clinical signs of tension pneumothorax or massive hemothorax (decreased breath sounds or subcutaneous emphysema in association with hypotension, tachycardia, and absent breath sounds).
- Obtain an ECG in patients with a mechanism consistent with potential myocardial contusion.
- Obtain an echocardiogram in unstable patients with clinical signs of cardiac failure to detect pericardial tamponade and valvular or chordae tendineae disruption.
- Administer esmolol, then nitroprusside, to control blood pressure in patients in whom a traumatic aortic injury is strongly suspected or proven by CT scan.

DISPOSITION

Patients with contused ribs and isolated rib fractures may be discharged from the ED. Patients should be instructed to return if they develop any increasing shortness of breath, fever, chills, cough, or other new symptoms. Patients with multiple rib fractures should be admitted for continued monitoring, observation, and, in some selected circumstances, consideration of epidural anesthesia for pain. In particular, elderly patients with rib fractures should be admitted for pain control and appropriate management to prevent pulmonary complications.

All patients with flail chest should be admitted to the hospital and carefully monitored via continuous oxygen saturation for an evolving pulmonary contusion, which almost always accompanies this injury. In addition, these patients have significant pain and usually require parenteral analgesics and consideration of regional or epidural nerve blocks.

Patients with fractures of the sternum sometimes need admission for analgesics because of associated injuries to the bony thorax and intrathoracic cavity. If the fracture is displaced, surgical reduction may be required. However, patients with isolated nondisplaced

sternal fractures may be discharged after appropriate measures have been taken to rule out the presence of other thoracic injuries.

Patients with pneumothorax, hemothorax, hemopneumothorax, and tension pneumothorax should be admitted to the appropriate inpatient surgical service for continued observation and treatment. Most patients with a pneumothorax and hemothorax only require a tube thoracostomy and do not require subsequent thoracotomy. However, in those patients in whom active, continued bleeding occurs or a persistent air leak is present, additional studies and surgery may be necessary.

All patients with a suspected or proven pulmonary contusion should be admitted to the hospital for continued monitoring and treatment because most pulmonary contusions will gradually worsen over the first 24 hours.

Patients with tracheal and bronchial injuries must be admitted and often require surgical repair if the injuries do not spontaneously resolve.

Patients who have sustained blunt anterior chest trauma, who have no associated injury necessitating admission, and who have a normal ECG may be discharged from the ED. The prognosis of patients with blunt cardiac injury is related to the magnitude of the initial trauma, the preexisting condition of the heart, the size and location of the cardiac injury, and the patient's other traumatic injuries; thus, those who are elderly or have coronary artery disease, significant dysrhythmias, a positive troponin, or any new abnormality on an ECG should be admitted for continuous monitoring for 12 to 24 hours. Patients with operable blunt trauma to the heart, such as myocardial and valve rupture or acute pericardial tamponade, need early and aggressive cardiac surgical treatment.

Traumatic disruption of the great vessels is potentially immediately life threatening; as soon as the diagnosis is suspected or confirmed, trauma or vascular surgery and interventional radiology should be consulted. After other more immediate life threats have been treated, these lesions should receive definitive surgical or interventional radiographic repair.

All patients with diaphragmatic injuries must be admitted to a trauma surgeon for definitive repair of the tear in the diaphragm as well as repair of associated intra-abdominal and intrathoracic injuries that often accompany these injuries.

Patients with confirmed esophageal perforation require antibiotics, admission, and immediate surgical consultation. Patients should be transferred to an appropriate surgeon and facility if resources for this definitive management are not available.

Those patients who have sustained traumatic asphyxia but have no evidence of significant chest wall, intrathoracic, or neurologic injury may be discharged home. Those patients with associated intrathoracic or neurologic injury should be admitted for continued observation and treatment.

Patients who must be transferred to another trauma facility for definitive treatment or critical care management should undergo a chest x-ray prior to transfer. Tube thoracostomy should be performed prior to transfer in patients with pneumothorax, hemothorax, or those with an occult pneumothorax detected only by CT. Patients with significant chest wall trauma or flail chest, especially the elderly, should be intubated prior to transfer. Any BCT patient with suspected aortic injury should be transferred to a trauma center.

Common Pitfalls

- Failure to appreciate a serious deceleration mechanism of injury.
- Failure to recognize the potential morbidity of rib fractures in the elderly.
- Delaying transfer of a patient to an appropriate level trauma center for definitive management of aortic injury.
- Failure to consider esophageal perforation in any patient with mediastinal emphysema.
- Insertion of a chest tube into an abdominal viscus in patients with a ruptured diaphragm.
- Overzealous fluid administration in patients with pulmonary or myocardial contusions.
- Failure to provide adequate analgesia and pulmonary care to patients with rib fractures, leading to the development of

atelectasis and pneumonia.

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CHAPTER 32

Penetrating Chest Trauma

Stephen J. Wolf

Although it is occasionally the result of mechanical accidents or impalements, penetrating trauma to the chest is often the result of interpersonal violence. Given the nature of the weapons encountered in the civilian population, injuries will typically be limited to tissues within the direct course of the penetrating implement. In military settings, penetrating trauma generally results in tissue injury as a result of transmitted compression waves or the formation of temporary cavities that are associated with higher-energy ballistics. These are all distinct from the shear injuries caused by acceleration–deceleration mechanisms and from the contusions and crush injuries resulting from forces dispersed about large contact areas, as seen in blunt thoracic trauma.

CLINICAL PRESENTATION

Pneumothorax

A common injury in penetrating thoracic trauma, *pneumothorax* is the collection of air in the potential space between the parietal and visceral pleura. The precise incidence varies across series and is largely dependent upon mechanism but has been reported to be significantly more common in penetrating trauma than blunt trauma (1). The clinical presentation depends on the patient's overall condition as well any underlying illnesses. Although multiply injured patients or those with decreased mentation may not report cardiopulmonary symptoms, the typical presentation includes pleuritic chest pain, dyspnea, and air hunger. Physical examination

may reveal tachypnea, tachycardia, and hypoxia, as well as the classic findings of decreased breath sounds and hyperresonance to percussion. Vital signs may deteriorate as the size of the pneumothorax increases. *Simple* pneumothoraces—confined collections of air within the pleural space—often result from direct injury to the pulmonary parenchyma and escape of air from bronchioles and alveoli. It has traditionally been thought that simple pneumothorax is likely to progress in the setting of positive-pressure ventilation, although the frequency of this occurrence has since been questioned. *Open* pneumothoraces result from an injury mechanism that creates a continued external communication to the pleural space. If the chest wall defect affords less resistance than the upper airways, air moves preferentially through the defect and gas exchange is impaired. *Tension* pneumothorax results from an expanding collection of intrapleural air. In the setting, increased intrathoracic pressures result in pulmonary collapse on the ipsilateral side first through direct pressure, then the contralateral side through mediastinal shifting. As a result tidal volume is compromised considerably. Ultimately, there is a significant decrease in venous return due to the compressive forces with resultant decreased cardiac output. Simple or open pneumothorax may progress to this grave clinical state if air continues to enter the pleural space from an external or bronchopulmonary source and is unable to escape. Clinical findings may include progressive tachypnea and tachycardia with hypotension and hypoxia. Physical examination may reveal jugular venous distention and absent breath sounds ipsilaterally. Tracheal deviation is a late finding and suggests impending cardiopulmonary collapse.

Tracheobronchial Injuries

Most tracheobronchial injuries occur superior to the thoracic inlet within the cervical trachea, where this structure is more superficial and in a relatively unprotected position. Although blunt trauma is a more common cause of tracheobronchial injuries, a penetrating mechanism is often associated with injury to other vital mediastinal structures (2). Pneumomediastinum is frequently seen and may be

associated with pleuritic chest pain, dyspnea, or Hamman sign—a "crunching" sound on cardiac auscultation. Other concerning clinical presentations are hemoptysis or an air leak from a penetrating neck wound. Injury to a bronchus may lead to a bronchopulmonary fistula and pneumothorax. In this case, tube thoracostomy reveals a large air leak and may exacerbate respiratory distress because of an increased loss of inspired air (2). Concomitant disruption of a bronchus and a major vessel may result in venous air embolism.

Hemothorax

Hemothorax is a common finding in penetrating thoracic trauma and is often associated with pneumothorax. Direct injury to intercostal vessels, pulmonary parenchyma, mediastinal structures, great vessels, and the internal mammary artery are possible etiologies. The presentation is occasionally subtle, with no associated pneumothorax and minimal associated blood loss. More significant injuries result in respiratory distress and symptoms consistent with hemorrhagic shock or tension physiology, as up to 1.5 L of blood can accumulate in the hemithorax. Physical examination may reveal abnormal vital signs, dullness to percussion, and diminished breath sounds dependently. The presence of these findings has an excellent positive-predictive value for hemothorax in penetrating trauma, but physical examination has been demonstrated to be insensitive for this injury, and the absence of these findings does not exclude a clinically significant hemothorax (1).

Mediastinal Injuries

The mediastinum has a dense arrangement of critical structures, and penetrating trauma to this anatomic region can result in profound injury. The presentation may vary from only local physical complaints to full traumatic arrest. Penetrating mediastinal injury holds the potential for serious delayed complications.

Esophageal Injuries

The majority of penetrating injuries to the esophagus occur in the cervical region (see Chapter 27, Penetrating Neck Trauma). Thoracic esophageal injuries may present with subtle clinical findings yet can potentially progress rapidly to mediastinitis. The clinical presentation is often dominated by injuries to adjacent vital structures, but isolated esophageal injuries may produce odynophagia, dysphagia, and hematemesis. Progression to mediastinitis is associated with fever and worsening chest pain over time. Physical examination frequently reveals no specific findings of esophageal injury, but Hamman sign is classically described.

Cardiac Injuries

Penetrating wounds to the heart are commonly fatal. The majority of patients sustaining these injuries are hemodynamically unstable as a result of hemorrhage, cardiac tamponade, or a mixed pathophysiology. Up to 80% of cardiac stab wounds present with cardiac tamponade, but the majority of critical patients with cardiac gunshot wounds present in hemorrhagic shock (3). The specific location of the cardiac injury, as well as the presence or absence of associated injuries to the great vessels and pericardium, determines the course of the disease. Because of the position of the heart within the chest, the right side of the heart is most often injured (ventricle > atria), followed by the left-sided chambers (ventricle > atria). Major coronary arteries are also at risk for injury, presenting with regional electrocardiographic abnormalities, dysrhythmias, tamponade, or hemothorax. Cardiac injuries associated with defects in the pericardium that are small or effectively obstructed by epicardial fat or clot are more likely to progress to tamponade physiology, and injuries of the higher pressure chambers are associated with a more rapid progression to clinical instability. Hemorrhage of as little as 50 to 100 mL into the pericardium may result in decreased stroke volume and cardiac output. Tachycardia and hypotension are common in both hemorrhage and tamponade, but the patient with cardiac tamponade may demonstrate a pulsus paradoxus and jugular venous distention. A small proportion of patients may be hemodynamically stable at presentation, with only

local symptoms and without evidence of cardiopulmonary compromise.

Great Vessel Injuries

Although only a minority of victims of penetrating thoracic trauma sustain injuries to the great vessels, up to 90% of injuries to the major thoracic vessels are the result of penetrating trauma (4). The associated mortality rate has been reported to be as high as 92%, with poorer outcomes associated with delayed recognition (5). In contrast to blunt mechanisms, most injuries are to the subclavian vessels, with associated mortality rates of 65% (4). Thoracic aortic injuries carry a high rate of associated vascular and nonvascular injuries. The clinical presentation depends on the degree of vascular disruption and the tissues supplied by the injured vessel, ranging from prehospital arrest to minimal local symptoms with a normal neurovascular examination.

Venous air embolism is an important complication of the disruption of any major vein that is in contact with a source of air. An example is a fistula between the pulmonary vein and a main bronchus. Valsalva or positive-pressure ventilation, may establish a pressure gradient that favors entry of air into the venous circulation, which then travels to the heart or more distal targets. In venous injuries other than those to the pulmonary vein, air emboli are confined to the right heart and pulmonary vascular bed in the absence of a preexisting right-to-left shunt. The presenting signs and symptoms may include hemoptysis, chest pain, evidence of end-organ ischemia (e.g., central nervous system deficits, myocardial ischemia), and cardiovascular collapse. Dramatic findings of “frothy” arterial blood gas samples and a machine-like murmur on auscultation have also been reported.

Diaphragmatic Injuries

Injury to the diaphragm must be considered in all thoracoabdominal gunshot wounds and in all stab wounds between the umbilicus and intermammary line anteriorly and up to the inferior tips of the

scapulae posteriorly. Suspected injury to the diaphragm mandates consideration of both intra-abdominal and thoracic pathology. Contrary to previous teaching, recent reports suggest that diaphragmatic injury may be more common in penetrating rather than blunt trauma, with an incidence as high as 42% in patients with penetrating wounds to the left thoracoabdominal region (6). Concomitant injuries—cardiothoracic, intra-abdominal, neurologic, and musculoskeletal, in decreasing frequency—are the norm. Herniation of intra-abdominal structures into the thorax is a complication of diaphragmatic injury and may occur acutely, subacutely, or even years after an identifiable traumatic insult. This delayed presentation occurs because of the difficulties in diagnosing diaphragmatic injury, as well as the poor rate of healing of diaphragmatic defects because of the pressure gradient across this structure.

In an acute traumatic injury to the diaphragm, the clinical presentation is most often dictated by associated injuries to adjacent thoracoabdominal structures but may be associated with minimal symptoms. Referred shoulder pain may be reported, as well as respiratory distress from herniation of abdominal contents into the left hemithorax. There may be ausculatory findings of decreased breath sounds or borborygmi in the chest. A large herniation may result in a tension viscerothorax (shift of the mediastinum and hemodynamic collapse) and may be difficult to distinguish from tension pneumothorax.

The delayed presentation of diaphragmatic injury is associated with upper abdominal pain occasionally radiating to the shoulder. The signs and symptoms vary depending upon the segment of hollow viscus that has herniated. Classic signs and symptoms of bowel obstruction develop only with distal small bowel and colonic herniation. Delayed recognition and development of strangulation or incarceration is associated with significant morbidity and mortality.

DIFFERENTIAL DIAGNOSIS

The initial differential diagnosis in penetrating chest trauma is broad. Simple pneumothoraces are frequently detected; they are associated

with local symptoms and may produce respiratory distress. Progression to tension pneumothorax is associated with worsening respiratory difficulty, hemodynamic instability, and the late finding of tracheal deviation. Findings of immobility of the chest wall, decreased breath sounds, and hyperresonance to percussion may aid in the diagnosis. Hemothorax, which often accompanies a pneumothorax, should be suspected when significant dullness to percussion is appreciated in the dependent portions of the thorax. Significant hemothorax can be associated with hemodynamic compromise and hemorrhagic shock.

Tracheobronchial injuries are most common with concomitant penetrating injuries to the neck or with missile trajectories that pass into the cervical region. Suspicion for this condition may be increased by findings consistent with pneumomediastinum (Hamman sign), hemoptysis, or a large persistent air leak after chest tube placement. Injuries to the mediastinal esophagus may also be associated with a “crunching” sound on cardiac auscultation but are likely to result in hematemesis or bloody output from suctioning of oral secretions or from a gastric tube.

Cardiac tamponade is classically associated with Beck triad of hypotension, jugular venous distention, and muffled heart sounds. Beck triad is present in less than half of patients with tamponade, however. Detection of pulsus paradoxus may contribute to a bedside evaluation for suspected tamponade, but it lacks sensitivity and specificity and may be present in a number of cardiopulmonary disorders. In the patient with hemodynamic instability and the possibility of a transmediastinal injury, however, hemopericardium and tamponade remain the diagnostic entities of greatest concern.

The emergency physician must consider injury to structures outside the confines of the thoracic cavity. The dome of the diaphragm extends superiorly to the nipple line, placing this structure, as well as intra-abdominal structures, at risk for injury from penetrating trauma. Injuries to the vertebral spine and associated neurologic injury must be considered (see Chapter 30). Finally, it must be emphasized that the trajectory of missiles is

remarkably unpredictable; thoracic entry wounds may be associated with exit wounds in the abdomen, neck, and extremities.

ED EVALUATION

Physical Examination

Assessment begins with a primary survey of the airway, which is performed as continuous cardiac monitoring and pulse oximetry are instituted. Sinus tachycardia—although potentially secondary to pain—is a common and early finding in injuries causing hemodynamic compromise. The physician should direct attention to the thorax, noting chest wall asymmetry or the use of accessory muscles of respiration and listening for the presence and equality of breath sounds. Palpation of the chest wall may reveal crepitus, focal tenderness, or obvious instability. Thoracic wounds should not to be probed, as this is of uncertain diagnostic value and may cause further injury. Cardiac auscultation should be performed to discover muffled heart sounds or murmurs associated with direct cardiac injury. Jugular venous distention is an indicator of the elevated right-sided pressures seen in pericardial tamponade. Conversely, flat jugular veins are more consistent with hemorrhage and hypovolemia. A careful abdominal examination should also be performed, given the possibility of associated abdominal and diaphragmatic injuries. An extremity pulse deficit or focal neurologic deficits may indicate great vessel injury to the subclavian or common carotid arteries, respectively. Finally, there must be a thorough inspection to identify wounds to the thorax, abdomen, and extremities, as well as the axillae and gluteal cleft.

Unfortunately, physical examination is insensitive for hemo- and pneumothorax, and abdominal tenderness is reportedly lacking in a significant proportion of patients with documented diaphragmatic injury (1).

Chest Radiography

Chest radiography remains a critical tool in the evaluation of patients with penetrating thoracic trauma. An initial examination is most

often performed anteroposteriorly (AP), at the bedside, in a supine or sitting patient. This examination may reveal large hemo- or pneumothorax and may provide information regarding missile trajectory by showing the location of a foreign body relative to external wounds (as indicated by radio-opaque markers). At least 200 mL of blood must be present for a hemothorax to be reliably detected on this examination, and small pneumothoraces are commonly missed. Larger pneumothoraces may be detected by a "deep sulcus sign" in the costophrenic angle (Fig. 32.1), but a normal study offers little reassurance because up to 67% of traumatic pneumothoraces are missed with this technique (7). A traditional posteroanterior (PA) film with an accompanying lateral view has a higher diagnostic yield; expiratory views may help in detection of small pneumothoraces. Traditionally, a negative initial chest radiograph was repeated after 6 hours to rule out the development of pneumothorax. However, literature now supports using a 3-hour repeat chest radiograph, or an immediate computed tomography (CT), to exclude occult injury (8). CT is recommended for select cases of significant diagnostic uncertainty (9).

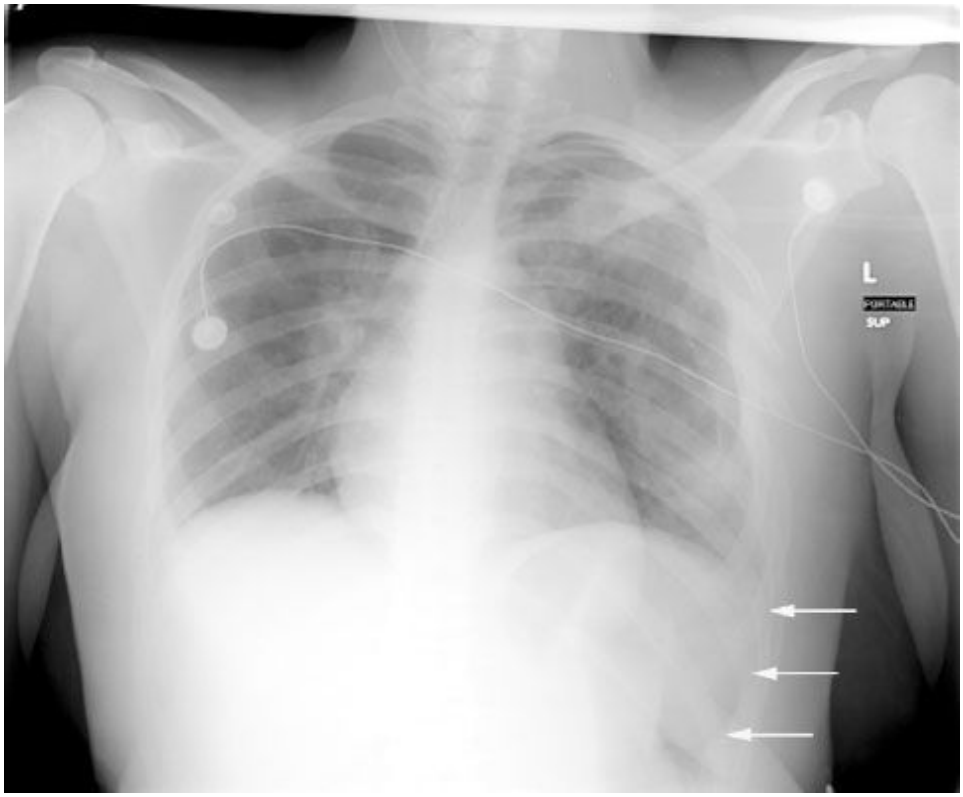
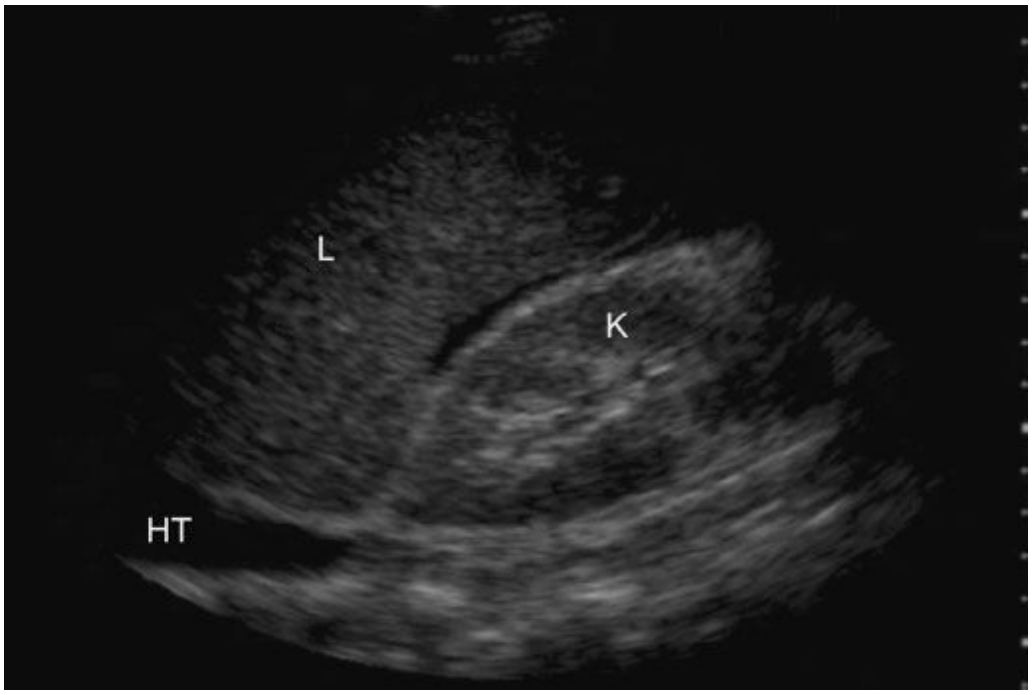


FIGURE 32.1 Chest radiograph. Portable, supine anteroposterior chest radiograph in a patient with thoracic trauma demonstrating a deep sulcus sign on the left. The relative lucency visualized over the left hemidiaphragm (indicated by white arrows) is suggestive of a pneumothorax. (Image courtesy of James F. Holmes, MD.)

Ultrasonography

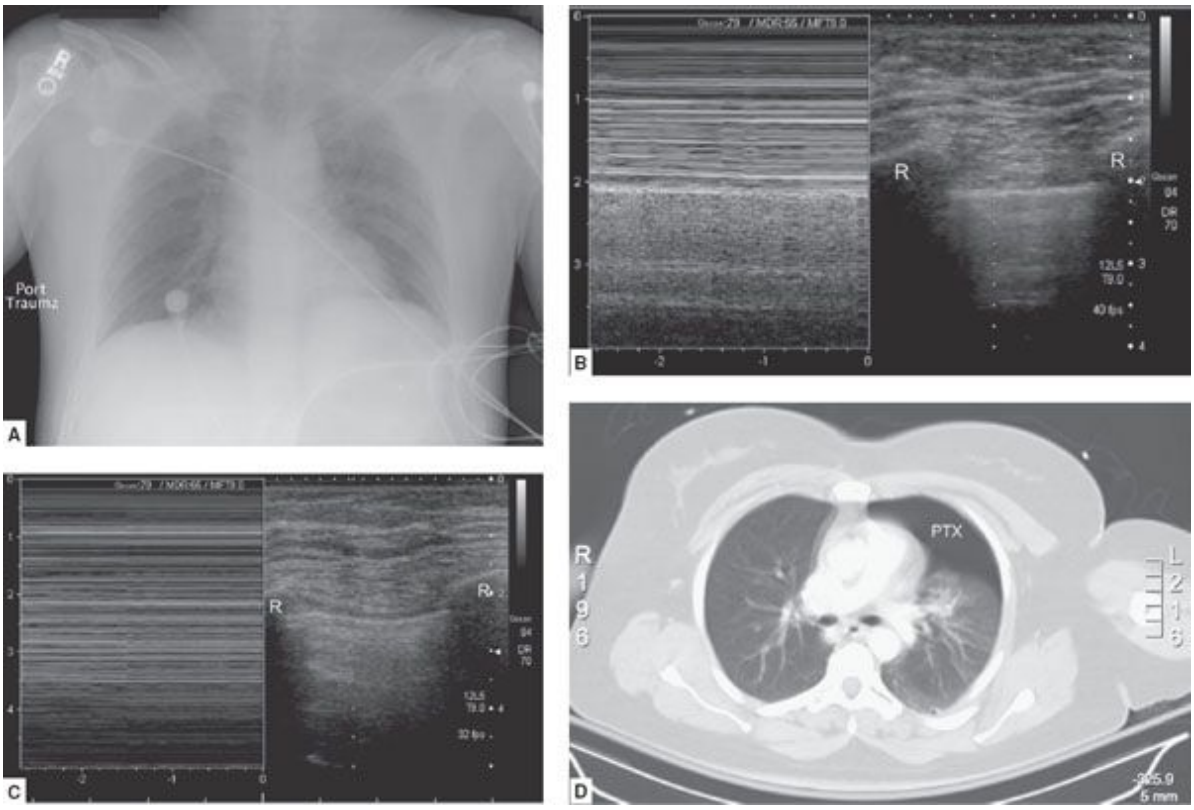
The *focused assessment with sonography in trauma* (FAST) provides the clinician with a rapid, noninvasive, repeatable diagnostic study that can detect intraperitoneal, intrathoracic, or pericardial fluid. The *extended FAST (eFAST)* examination is described to include evaluation for pneumothorax in addition. In unstable patients with injuries at or below the nipple line, or who have missile trajectories that cause concern for peritoneal violation, use of the FAST examination allows the clinician to determine whether hemorrhage into the peritoneum is responsible. Furthermore, bilateral upper quadrant windows visualize the most dependent portions of the

thorax (eFig. 32.1) and provide greater sensitivity than chest radiography for the detection of hemothorax (10).



eFIGURE 32.1 Focused assessment with sonography in trauma (FAST). Right upper quadrant coronal plane imaging liver (L) and right kidney (K) with anechoic wedge of hemothorax (HT) visualized just cephalad, in the most dependant portion of the thorax. Morison pouch is also positive, with a small anechoic stripe present between the liver and kidney.

Bedside ultrasound is accurate in the detection of intrapleural air (7,11). It is of particular utility in identifying occult pneumothoraces —those not apparent on initial plain radiography but detected on serial plain films or subsequent CT. Small anterior pneumothoraces in the supine trauma patient are particularly at risk for going undetected on supine AP plain radiographs (eFig. 32.2).



eFIGURE 32.2 Chest radiograph (A) of a patient with thoracic trauma demonstrating left clavicular fracture but no evidence of pneumothorax. Bedside ultrasound during real-time imaging demonstrated the absence of pleural sliding and comet tail artifacts on the left anterior thorax. M-mode displayed to the left of each image: B: normal-appearing right thorax with a granular—or sandy—appearance deep to level of the pleural interface that courses between ribs (R). C: Note this granular appearance is lost on the left thorax, consistent with the presence of a pneumothorax. D: Chest CT confirming anterior pneumothorax.

An early bedside cardiac ultrasound allows for rapid evaluation for hemopericardium and some cardiac injuries. It has become the preferred initial diagnostic modality. Emergency physicians and trauma surgeons trained in the use of bedside ultrasound can detect hemopericardium (Fig. 32.2) with excellent sensitivity and specificity (12). As little as 20 mL of fluid may be detected on this examination, but the presence of epicardial fat, associated hemothorax, or clotted blood in the pericardial space may lower the specificity for less

experienced users. Nevertheless, the use of bedside ultrasound reduces the time to diagnosis and is associated with a reduction in morbidity and mortality associated with penetrating chest trauma (13).

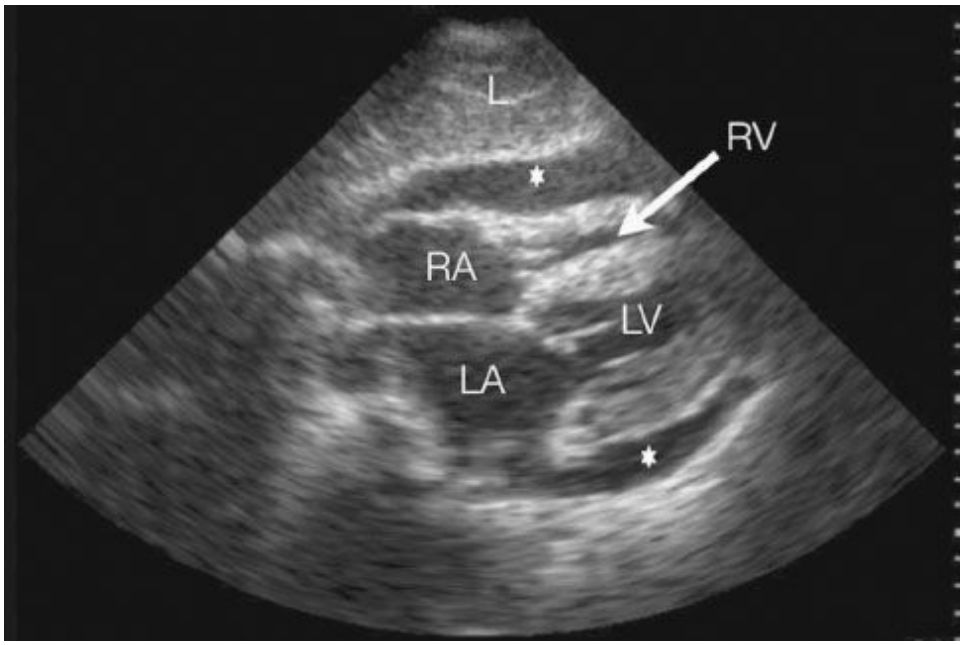


FIGURE 32.2 Cardiac ultrasound. Subxyphoid window imaging through acoustic window of the liver (L) demonstrating four-chamber view (RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle) and moderate, circumferential hemopericardium denoted by asterisks (*).

Limitations to the use of ultrasound in the setting of penetrating chest trauma include operator dependence, decreased sensitivity for small amounts of intraperitoneal free fluid, clotted hemorrhage, and inability to reliably assess for diaphragmatic or bowel injury.

Computed Tomography

Between 2006 and 2011, the use of chest CT scan in the evaluation of patients with penetrating thoracic trauma increased 3.5-fold (9). However, there is debate regarding its added benefit, particularly when balancing competing concerns of cost and radiation exposure against the benefit of diagnostic accuracy. When mediastinal

structures are not felt to be at risk, its conservative use is reserved for patients with abnormal chest radiography (initial or 3-hour repeat), serial physical examinations, or eFAST examination (9). In mediastinal penetrating trauma, authors propose that CT be used as an initial screening examination in hemodynamically stable patients (14).

While chest CT is excellent for the detection of hemo- and pneumothoraces, its role in other thoracic injuries remains to be defined. Esophageal and tracheobronchial injuries can be identified, as can some secondary findings suggestive of injury, but the sensitivity has not been established. Although hemopericardium is generally assessed with echocardiography, CT has been reported as an alternative diagnostic evaluation in the hemodynamically stable patient at risk for cardiac injury (15). Diaphragmatic injuries are inconsistently identified and evaluated on CT because of the position of the dome within the imaging plane.

Bronchoscopy

Bronchoscopy remains the diagnostic modality of choice for tracheobronchial injuries that are suspected because of pneumomediastinum, significant air leak on tube thoracostomy, persistent pneumothorax, hemoptysis or injuries to adjacent structures. Indirect signs of injury that may be identified on CT include chest wall discontinuity, endotracheal tube misplacement, paratracheal air, and pneumomediastinum. However, the overall sensitivity of CT for tracheobronchial injuries is unacceptably low.

Esophagography

Because of the profound morbidity and mortality associated with delayed recognition of esophageal injury, a high level of clinical suspicion must be maintained. Chest CT may identify direct evidence of esophageal injury, but its role in excluding injury or in precisely characterizing injury has not been established. When there are suggestive findings on physical examination, chest radiography, or CT, further evaluation may begin with esophagography. Because of

the potential for introduction of contrast material into the mediastinum, initial examinations should be performed with water-soluble contrast. This can be followed by barium contrast (at the discretion of the interpreting radiologist), if the initial study is negative.

Esophagoscopy

Identification and characterization of esophageal injuries may be accomplished with direct endoscopic visualization. The sensitivity of this examination approaches 100% and should be undertaken despite a negative contrast study when the pretest probability of injury is high.

Angiography

The gold standard for the diagnosis of great vessel injuries is contrast angiography. In the case of direct or indirect signs of injury on CT, angiography may be required to further characterize the defect in the aorta or other great vessels. Although transesophageal echocardiography has a role in blunt aortic injury and in detecting nontraumatic aortic pathology, it does not visualize the ascending aorta and major aortic branches well enough to make it as useful in penetrating thoracic trauma.

Diagnostic Peritoneal Lavage

With increased use of FAST and CT in the assessment of trauma patients, DPL is performed less and less frequently. Diaphragmatic injuries are detected with poor sensitivity when the traditional diagnostic threshold (100,000 RBC/mm^3 of lavage fluid) is used. Sensitivity is improved by decreasing the threshold to 5,000 RBC/mm^3, but some injuries will still be missed, and the rate of false-positive evaluations is higher.

KEY TESTING

- Pulse oximetry
- Hemoglobin/hematocrit

- Chest radiography
- eFAST
- Computed tomography of the chest (when indicated)
- Bronchoscopy (when indicated)
- Esophagography (when indicated)
- Esophagoscopy (when indicated)
- Angiography (when indicated)
- Diagnostic peritoneal lavage (when indicated)

ED MANAGEMENT

Patients with penetrating thoracic trauma often present in extremis, requiring rapid resuscitation with diagnostic and therapeutic interventions occurring in parallel. The clinician must be prepared to identify and effectively manage respiratory failure, cardiopulmonary collapse, tension pneumothorax, cardiac tamponade, and hemorrhagic shock.

Airway Management

Definitive airway management is indicated in a significant portion of patients presenting with penetrating thoracic trauma. Alteration of mental status, excessive secretions, or associated injuries to the face and neck may impair the patient's ability to protect the airway. Impending respiratory failures due to disturbance of chest wall mechanics, massive hemo- or pneumothorax, or cardiopulmonary collapse are also indications for endotracheal intubation. Other factors that may contribute to the decision to intubate include mental status depression, agitation, polytrauma, significant comorbidities or advanced age, hemodynamic instability, and the need for imminent operative intervention. Following intubation and the establishment of positive-pressure ventilation, the clinician must anticipate progression of any disease process associated with injury to the respiratory system. Simple pneumothoraces may progress to a tension pneumothorax, and airway injuries adjacent to venous disruptions may result in venous air emboli once sufficient pressure gradients occur.

Needle Decompression

Percutaneous decompression of the chest is indicated for a pneumothorax sufficient to cause impending respiratory failure or if there is hemodynamic compromise associated with tension physiology. This may be accomplished using a 14-gauge angiocatheter and is performed at the second intercostal space in the midclavicular line; the fourth or fifth intercostal space in the anterior to midaxillary line is an acceptable alternative and may be preferable based on body habitus. A rush of air confirms appropriate placement, although failure to reach the pleural space and kinking of the catheter after removal of the needle are both potential causes of a failed procedure. Alternatively, if the equipment is readily available, tube thoracostomy can be performed.

Tube Thoracostomy

In contrast to blunt thoracic trauma in which $<20\%$ of patients will require tube thoracostomy, up to 85% of patients with penetrating thoracic injuries will undergo this procedure (16). Successful performance of tube thoracostomy drains intrapleural air and blood, allowing for lung reexpansion and improved ventilation. It also provides an assessment of the degree of blood loss into this space and may decrease further blood loss via pressure applied to the source by the reexpanded lung parenchyma. The procedure is performed via a sterile incision in the fourth or fifth intercostal space in the midaxillary line, directing a 32- to 40-French catheter posteriorly toward the apex.

The complication rate for tube thoracostomy approaches 25% (17). Complications include improper placement into the pulmonary parenchyma, subcutaneous tissues, hilum, or intra-abdominal organs; failure to adequately drain intended collections; and infections such as empyema. Proper technique and maintenance of sterile technique will decrease this complication rate. Despite this over 3% of tube thoracostomies for penetrating chest trauma develop a posttraumatic empyema. A recent systematic review found that infectious complications are almost three times less likely to develop when

antibiotic prophylaxis is administered to patients with thoracic injuries requiring chest drains after penetrating injury (18). A first-generation cephalosporin should be used to target gram-positive organisms.

For isolated, simple pneumothoraces, there is increasing use of smaller bore thoracostomy tubes (28 to 32 French) as well as percutaneous catheter introduction kits. The latter may be placed anteriorly in the second intercostal space if the location of the pneumothorax and body habitus allow. Neither technique is appropriate for hemopneumothoraces, because maximal internal diameter is essential for adequate drainage in these scenarios.

Traditionally, massive hemothorax—defined as initial thoracostomy output of 1,500 mL, persistent output of 250 mL/h, or associated hemodynamic instability—has indicated operative thoracotomy. Persistent hemothoraces may be addressed by placement of a second tube thoracostomy. In the case of suspected organization of the hemorrhage, operative thoracotomy may be indicated. However, studies suggest thoracoscopy may provide an effective alternative associated with a shorter length of stay and decreased costs (19).

Pericardiocentesis

Pericardiocentesis is not an ideal diagnostic modality because of its poor test characteristics and the increasing availability of bedside ultrasound for detection of hemopericardium. Application of this procedure for therapeutic purposes in trauma is a temporizing measure, at best, and should be performed in coordination with aggressive resuscitation and preparation for definitive operative intervention. When possible, ultrasound guidance should be used to identify the maximal collection of blood and determine the appropriate needle course.

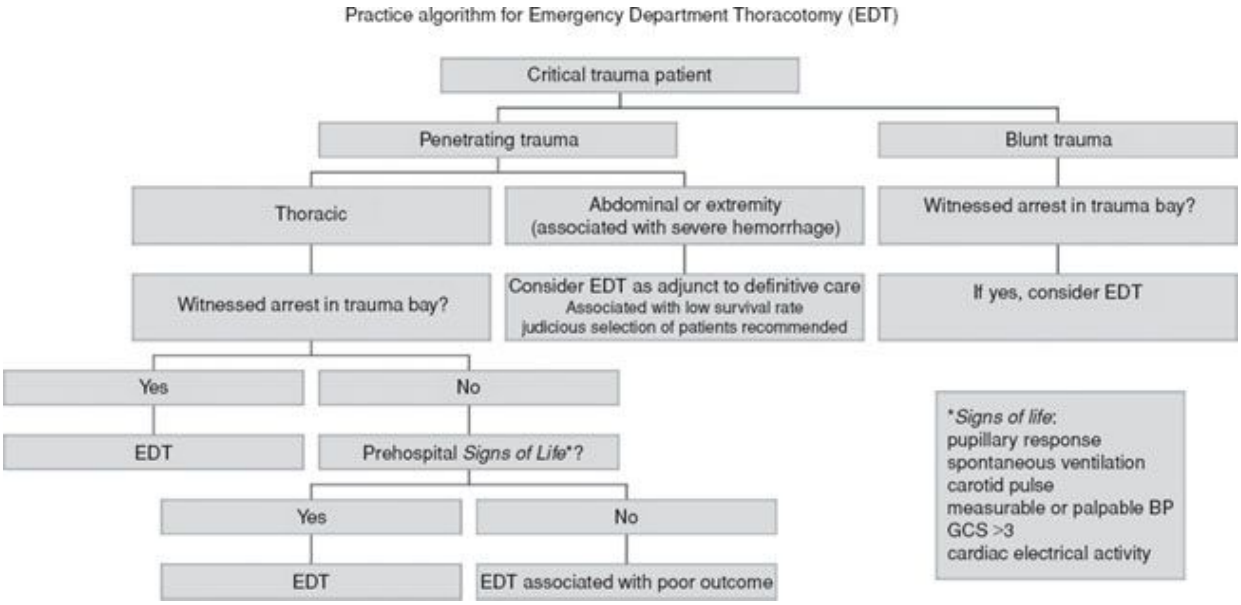
Central Venous Access

If the patient is persistently hypotensive or does not have sufficient peripheral venous access, then placement of a central venous

catheter may be necessary. Depending upon type and location of catheter placement, advantages include the ability to administer rapid resuscitative fluids as well as detection of the central venous pressure (CVP). In the event that bedside ultrasound is unavailable, an elevated CVP in an unstable patient with penetrating thoracic trauma also may support the diagnosis of hemopericardium and tamponade. If concern exists for great vessel injury, attempts at central venous access should be established via the femoral vein; otherwise placement should be established on the ipsilateral side to the penetrating injury to minimize the risk of additional injury to the lung.

Emergency Department Thoracotomy

Emergency department thoracotomy (EDT) is a potentially life-saving procedure utilized in moribund trauma patients. This procedure is historically associated with a poor rate of functional neurologic recovery. Furthermore, the procedure may place healthcare providers at risk for potential infectious exposure. The reported survival rates of EDT range from 1% to 35% in a recent report, with mechanism of injury and physiologic status of the patient strongly correlated with outcomes (20). The American College of Surgeons Committee on Trauma (ACS-COT) performed a comprehensive review of the literature on EDT, reporting survival rates of 7.8% overall and 11.2% in the setting of penetrating trauma (21). The highest rate of survival was documented in patients with penetrating cardiac injury (31.3%). Besides the type of injury, the patient's physiologic status during the prehospital course and upon emergency department presentation has a direct correlation with outcomes; those with witnessed signs of life in the ED have the greatest chance for survival following EDT (22,23). Despite this data, there is a lack of consensus on the indications for EDT. eFigure 32.3 presents a clinical approach consistent with the recommendations provided by the ACS-COT, considering mechanism and physiologic status of the patient.



eFIGURE 32.3 Practice guidelines for emergency department thoracotomy. (Adapted from recommendations by the American College of Surgeons Committee on Trauma (2).)

Several critical interventions are possible during a thoracotomy. After exposure is achieved, pericardiotomy should be performed to relieve tamponade. Delivery of the heart from the pericardium allows inspection and identification of cardiac injury. Direct pressure may be applied to control small, simple myocardial defects. More significant lacerations may be amenable to approximation with skin staples or pledgeted sutures. Extensive injuries may be challenging to approximate with these measures, and a Foley catheter may be placed through the defect into the corresponding cardiac chamber. After inflation of the catheter's balloon with saline, gentle traction may be applied in an attempt to prevent further hemorrhage as long as the inflated balloon does create an obstruction to chamber filling or cardiac output. This technique should be performed as a temporizing measure. Completion of a purse string suture may be attempted around the catheter and tightened concurrently with deflation and removal. Definitive repair then occurs in the operative suite.

Noncardiac intrathoracic injuries may be directly addressed via EDT. Significant arterial bleeds may be controlled with direct

pressure or vascular clamps. In the event of severe pulmonary parenchymal destruction, hemorrhage, or venous air embolism, the hilum may be clamped pending definitive repair. The descending aorta may be cross-clamped to address distal hemorrhage in polytrauma patients, increasing afterload and cardiac and cerebral perfusion.

Resuscitation may be continued once EDT has been performed. Internal cardiac massage provides more effective circulation than external, closed cardiopulmonary resuscitation (CPR) and should be initiated after delivery of the heart from the pericardium. Direct defibrillation or cardioversion may also be performed using internal paddles. Intracardiac administration of resuscitation medications is an acceptable alternative and likely offers improved drug delivery compared to peripheral intravenous access. If central venous access has been established, drug administration via this route is equally acceptable and avoids introduction of another sharp instrument into the field.

Mediastinal Injuries

The evaluation of suspected mediastinal injuries has traditionally involved an investigation including chest radiography, esophagography and esophagoscopy, aortography, and bronchoscopy, given the morbidity associated with delayed diagnosis of injuries to these structures and the frequent absence of localizing signs and symptoms on presentation. The potential for more selective evaluation using chest CT as a screening modality was discussed previously.

Tracheobronchial injuries are often managed nonsurgically with endotracheal intubation and broad-spectrum antimicrobials including anaerobic coverage. Careful consideration of the nature of the injury, patient condition, and associated delayed complications are factors in determining the need for urgent operative intervention.

Suspected esophageal injuries should be treated with early antimicrobial therapy—broad spectrum, including anaerobic coverage—in an attempt to prevent the complication of mediastinitis. The diagnosis is based on contrast or endoscopic examinations.

Operative intervention follows adequate characterization of the injuries.

Penetrating trauma with injury to the aorta or great vessels often manifests during the initial assessment and resuscitation, with evidence of abnormal vascular examinations or hemodynamic collapse. In cases necessitating EDT, the source of hemorrhage may be identified directly, guiding further management. Great vessel injury can be controlled locally with vascular clamps pending operative repair. Patients with aortic or great vessel injuries identified by or suspected on physical examination or cross-sectional imaging often require evaluation with angiography, as the role of CT angiography has yet to be defined as a definitive diagnostic modality. Open, operative repair remains the standard approach, although the application of endovascular techniques is reported in traumatic injuries to the thoracic aorta and great vessels (24).

Diaphragmatic Injuries

Management of penetrating wounds to the diaphragm is particularly challenging in the diagnostic phase. Herniation of abdominal contents into the thorax and tension gastrothorax may be identified in the resuscitation bay. The physician should consider diaphragmatic injury in the right clinical situation and be careful when performing tube thoracostomy to avoid intraperitoneal placement. However, diaphragmatic injury with herniation of abdominal contents is far more common after blunt trauma or as a delayed presentation after penetrating injury. Because of the difficulties in accurate diagnosis as described previously, definitive diagnosis may require laparoscopy or thoracoscopy. In the setting of penetrating trauma to the left thoracoabdominal region and nondiagnostic imaging, laparoscopy is the preferred diagnostic modality. This technique may also allow minimally invasive repair (25).

CRITICAL INTERVENTIONS

- Perform rapid primary and secondary surveys, including complete exposure and thorough inspection for wounds.
- Decompress tension pneumothoraces immediately—without radiographic confirmation—by needle thoracostomy or standard tube thoracostomy.
- Perform early endotracheal intubation using Rapid Sequence Intubation (RSI) in patients with hemodynamic instability, impending respiratory failure, depressed mental status, or multiple trauma.
- Perform tube thoracostomy in a patient with a small pneumothorax who will undergo positive-pressure ventilation or transfer in an aircraft.
- Perform an emergency department thoracotomy on any patient with a chest stab wound who loses vital signs en route to the ED or in the trauma bay.

DISPOSITION

While many patients with penetrating thoracic trauma are admitted to the hospital, those with isolated stab wounds to the chest who have a negative initial evaluation may be observed in the ED. If repeat chest radiography is negative at 3 hours after initial examination in a patient who remains asymptomatic and has normal vital signs, pneumothorax can be excluded, and the patient can be discharged home with follow-up within 48 hours (9). Patients with identified hemo- or pneumothoraces should be admitted. In the case of small, simple pneumothoraces, these patients may be observed with cardiopulmonary monitoring and serial chest radiography. Pneumothorax with associated hemothorax requires tube thoracostomy.

Suspected mediastinal injuries should be admitted to the hospital. Cardiac, great vessel, and aortic injuries require further diagnostic evaluation and, typically, operative repair (14). Tracheobronchial injuries often require bronchoscopy and operative intervention but are occasionally successfully managed medically; however, this requires inpatient observation and parenteral antibiotics. A suspicion of esophageal injury should prompt admission for parenteral

antibiotics, serial examinations, and a full diagnostic workup. Patients with confirmed or suspected diaphragmatic injury should be admitted; laparoscopy may be required for definitive diagnostic evaluation.

Common Pitfalls

- Failure to provide early definitive airway management via endotracheal intubation.
- Failure to expeditiously recognize and treat tension pneumothorax.
- Failure to investigate for diaphragmatic and intra-abdominal injuries, particularly with injuries sustained below the nipple line or the inferior border of the scapula.
- Failure to decompress a pneumothorax adequately by needle thoracostomy or failure to follow this procedure with tube thoracostomy.
- Failure to administer prophylactic antibiotics for emergency department tube thoracostomy.
- Attempting to probe a penetrating thoracic wound.
- Underutilization of bedside ultrasound in the diagnosis of hemopericardium, hemothorax, and pneumothorax.

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of Lee W. Shockley and Seric S. Cusick to the content of this chapter.

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CHAPTER 33

Blunt Abdominal Trauma

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Blunt abdominal trauma (BAT) accounts for a minority of all traumatic deaths but represents an important source of morbidity. The variety of clinical presentations, limitations of the physical examination, and the absence of consistent clinical markers make patients with BAT a particularly challenging population. Death owing to abdominal injury may be prevented by early recognition of intra-abdominal hemorrhage. After initial resuscitation, one of the primary objectives of the emergency physician (EP) is to decide which patients require early intervention and timely consultations. Although injuries to solid organs are most frequently involved after BAT, the clinician must also search for the more subtle injuries to the bowel, mesentery, and pancreas. The history and physical examination continue to be essential components of the evaluation, however, a significant portion of patients will require imaging. *Focused assessment with sonography for trauma (FAST)* and abdominal computed tomography (CT) scanning are paramount in both ruling in and excluding intra-abdominal pathology and planning definitive treatment.

CLINICAL PRESENTATION

The signs and symptoms of BAT are highly variable, and obtaining a complete and accurate history and physical examination may be unreliable due to concomitant head injury, medications, substance abuse, multisystem trauma, distracting injuries, spinal cord injuries, or shock. Though historical factors and physical findings should

guide decision making, the presence or absence of many findings is neither sensitive nor specific (1,2).

Although hypotension in the field or on arrival increases the likelihood of severe bleeding, vital signs may be normal upon presentation to the emergency department (ED). Injuries that produce minimal bleeding, for example, diaphragm perforation, and those isolated to the retroperitoneum typically result in a paucity of physical findings.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of injury in BAT includes both intra-abdominal and extra-abdominal etiologies. The most common intra-abdominal concerns are the solid organ injuries of the spleen or liver. Next most commonly injured are the hollow viscous organs, that is, the small and large bowel. These comprise less than 10% of intra-abdominal injuries. The gallbladder, pancreas, or vascular structures may also be injured, although these injuries are infrequent and are usually found in combination with hollow or solid viscous injuries. Occasionally there is an isolated injury to the bowel mesentery.

In addition to these intra-abdominal injuries, there may be extra-abdominal findings that mimic intra-abdominal injury. These include muscle strains, contusions, or rectus sheath hematomas. Muscle injuries tend to cause pain mainly over the involved muscular area and do not lead to hemodynamic instability; the pain may intensify when palpation is performed on the contracted muscle. However, these findings may coexist with an intra-abdominal injury and the presence of these findings cannot exclude an intra-abdominal injury.

ED EVALUATION

The assessment of the blunt trauma patient must be performed within the context of the patient's hemodynamic status and potential for life- or limb-threatening injuries. The ABCs of resuscitation are rapidly performed on arrival. The secondary

survey, including the abdominal examination, proceeds after the primary survey is complete. In general, the more critically injured the patient, the faster the EP must determine the need for laparotomy, blood transfusion, or angiography, and obtain early surgical consultation.

History

Upon arrival, a brief history is obtained. One common approach is the AMPLE format (*a*llergies, *m*edications, *p*ast medical history, *l*ast meal, and *e*vents surrounding the injury). In addition, the patient should be questioned about specific areas of pain. Obtaining the history also allows the EP to judge the patient's mental status.

Other valuable sources of information are the prehospital care providers and witnesses or passengers who may arrive with the patient. After a description of the mechanism and events of the injury, most paramedic reports indicate mental status changes, vital signs, evaluation of the ABCs, significant complaints, and interventions. Certain historical factors, such as prehospital vital signs and mechanism of injury, have classically been associated with a greater chance of serious injury. Mechanism alone tends to be poorly predictive of the need for operative intervention or advanced therapeutic maneuvers (3–5). On the other hand, a history of prehospital hypotension, a requirement for significant volume resuscitation, declining mental status, the presence of a femoral fracture, or the need for either prehospital or ED intubation increases the likelihood of intra-abdominal injury (6–8).

Physical Examination

Despite the necessity of a directed physical examination, the EP must be aware of its limitations. The physical examination is not sensitive enough to diagnose all patients with operative intra-abdominal injuries, nor is it specific enough to rule in an injury, even in patients with guarding and rigidity. The literature has cited a wide variability in the physical examination. For example, one study found the examination to be 65% accurate in the setting of

BAT, whereas another trauma center reported abdominal examination alone as adequate in only 35% of patients (4,9). A recent systematic review suggested that the physical examination alone is probably insufficient for excluding intra-abdominal injury; however the presence of rebound tenderness, distention, and a seat-belt sign can increase the likelihood of BAT (1).

To perform the physical examination, the patient should be completely undressed and life threats addressed first. Concomitant evaluation and therapeutic interventions of the airway, breathing, and circulation are the first priority. The abdominal examination should begin with inspection for abrasions or ecchymosis. Ecchymosis over the lower abdomen in a lap-belt distribution is suspicious for hollow viscous injury and vertebral fractures. Although Cullen sign (ecchymosis around the umbilicus) and Turner sign (ecchymosis of the flanks) are associated with retroperitoneal bleeding, they are highly insensitive and often take hours to manifest. Auscultation for bowel sounds has not been formally studied but probably has no utility in the initial examination.

Palpation of the abdomen begins with examination of the lower chest. Lower rib fractures, especially with high-energy trauma, are associated with a significant rate of associated intra-abdominal injury (10,11). The abdomen should be carefully palpated, paying particular attention to the right and left upper quadrants (RUQs and LUQs). The finding of Kehr sign (pain in the shoulder unrelated to shoulder tenderness or range of motion) is associated with the presence of blood irritating the diaphragm and is often secondary to splenic or liver injury.

Pelvic stability is assessed by palpating and applying distraction and compressive forces over the iliac crest and over the symphysis pubis. Care should be taken not to use excessive force to avoid disrupting an unstable fracture and increasing bleeding. Patients with pelvic fractures have a significant incidence of intra-abdominal injury, ranging from 30% to $>$50% in those with severe or unstable fractures (12).

Rectal examination is rarely useful in blunt trauma patients. It may provide some added information in seriously injured patients

with pelvic fractures or concern for gastrointestinal disruption; however, it is highly unlikely to be helpful, and its inaccuracy may confuse the clinical picture. It may demonstrate a high-riding or boggy prostate in patients with urethral disruption. Gross blood on rectal examination may indicate gastrointestinal rupture and mandates surgical consultation. Stool evaluation for occult blood has not been shown to be predictive of traumatic injury (13). In addition, trauma patients find the rectal examination the most uncomfortable part of the physical examination, so if performed, it should be limited to those patients with a reasonable expectation of pathology (14). The external genitalia should be inspected for blood at the meatus, scrotal hematoma, or urethral outlet bleeding, which may signify a bladder or urethral injury. The patient should then be log-rolled with palpation of the lumbar and thoracic area. Lumbar fractures, particularly those in conjunction with the seat-belt sign, are markers of hollow viscous injury.

Plain Radiographs

The plain abdominal radiograph has no utility in the evaluation of BAT. It is not reliable in diagnosing intra-abdominal pathology and therapeutic interventions should not be planned on the basis of the results. A chest radiograph should be performed to assist in evaluating the aorta, lungs, and rib cage. It may show evidence of a ruptured diaphragm in anywhere from 20% to 80% of patients with this injury (15,16). Pelvic films should be obtained based on the reliability of the examination and on physical findings. The current evidence shows that in the stable and alert blunt trauma patient without distracting injuries, a normal clinical examination can rule out a clinically important pelvic fracture (17–19). On the other hand, a patient with hemodynamic instability or in whom there is a reasonable suspicion of a fracture by examination or mechanism should have one performed early in the course. In stable patients with no evidence of instability who will be rapidly undergoing a CT scan of the abdomen and pelvis, it is reasonable to forego the plain film for the more sensitive CT.

Laboratory Tests

Laboratory analysis of most trauma patients is generally more extensive than necessary and rarely offers insight into diagnosing an occult injury. Though laboratory testing based on clinical parameters is cost effective without compromising care, most trauma centers use some type of protocol to standardize and speed the laboratory evaluation of patients. The patient who is fully awake and alert, has sustained minimal trauma, and has no distracting injury may not require any testing. Rational laboratory analysis in most patients with BAT can be limited to a complete blood count, basic electrolytes, blood type and screen, and urinalysis. Women of childbearing age should have a pregnancy test performed.

The hematocrit value is influenced by many factors, including the rate of blood loss, dilutional effects of intravenous fluids, fluid shifts from the interstitium to the intravascular space, and preinjury level. Though an initial low hemoglobin <8 g/dL may be useful to prognosticate major injury and outcome (20), the main value is as a baseline blood count. Leukocytosis may be present but is a nonspecific finding. Baseline chemistries provide information regarding blood glucose, creatinine, and evidence of acidosis. Gross hematuria is significant and should prompt evaluation of the genitourinary (GU) tract. The presence of microscopic hematuria is of less clear significance, as it has been found to be poorly sensitive or specific for significant GU injury and, in the absence of a pelvic fracture or unexplained hypotension, does not mandate workup (21).

Other studies to consider, mostly for the severely injured patient or elderly patient, include liver function studies, coagulation profiles, arterial blood gas, and alcohol and drug screening. Liver enzymes that are significantly elevated to two to three time normal may represent hepatic injury, although it is unclear how much they add to objective radiologic testing based on mechanism and physical examination (22). Coagulation studies are useful in anticoagulated patients, those with a history or stigmata of liver disease, pregnant

patients, or those with the possibility of disseminated intravascular coagulation owing to shock.

Analysis of the arterial or venous blood gas may provide diagnostic and prognostic information in the major trauma patient. Those patients with base deficits less than –6 (i.e., –7 or greater) have an increased risk of intra-abdominal hemorrhage. High initial lactates have been associated with significantly increased mortality in several trauma database reviews (23). Serial base deficits or serial lactates indicate trends in patient status. Monitoring the deficit for improvement or normalization helps discern whether ongoing resuscitation is effective. The failure to normalize a base deficit by several hours predicted a significantly greater morbidity and mortality in one study (24,25).

Serum amylase and lipase are inaccurate for pancreatic injury. One study showed that 53% of BAT patients had at least one elevation during an initial or subsequent measurement, yet $<2\%$ had a pancreatic injury. Other studies have confirmed the lack of utility of a screening amylase or lipase in the blunt trauma patient (26).

Ethanol levels and drug screens may provide additional information about the reliability of the physical examination.

Diagnostic Peritoneal Lavage

Diagnostic peritoneal lavage (DPL) is a rapid and accurate test for determining the existence of intraperitoneal blood. Although it is invasive, DPL has a low ($<1\%$) complication rate of bleeding, perforation, or infection. Once part of the standard evaluation of BAT patients, it has been largely replaced by CT scan in the stable patient and by ultrasound for the unstable patient. DPL still has utility in the unstable patient with an unclear or indeterminate ultrasound result or in the stable patient with a significant concern for a hollow viscous or mesenteric injury, either by examination or after an equivocal CT scan. DPL also plays a major role when CT scan and ultrasound are not available, and therefore remains an important diagnostic tool for the EP.

The two main techniques are open and closed. The *closed* technique is faster and is not associated with a significant increase in complication rate. The *open* technique relies on direct visualization and incision of the peritoneum, whereas the closed technique is performed using the Seldinger technique after skin incision. Though generally performed in the infraumbilical area, a supraumbilical approach should be performed in patients with pelvic fractures or previous surgical scars and in the pregnant patient. In some cases, a *semi-open* technique may be performed. With this technique, the skin, and sometimes the fascia, is incised, and the catheter (placed over a trocar) is inserted blindly into the peritoneal cavity. Most centers perform either the open or the closed technique. The sensitivity and specificity of DPL for intra-abdominal blood are both in the 95% to 99% range, with accuracy ranging between 92% and 98%. The specificity of DPL for predicting the need for a therapeutic laparotomy is somewhat lower, and it should be interpreted in light of the overall clinical picture. A positive DPL in a hemodynamically stable patient should not automatically lead to laparotomy. It had previously been estimated that up to 30% of grossly positive lavages lead to nontherapeutic laparotomies. With the advances in nonoperative management of solid organ injuries, this number is probably higher. The lavage is insensitive for retroperitoneal injuries, is not specific for site and extent of injury, and may diagnose injuries that do not require operative intervention. The only absolute contraindication for DPL is the need for emergency laparotomy.

Criteria for a positive test after blunt trauma include an initial aspirate of >10 mL of blood (grossly positive lavage) or $>100{,}000$ RBC/mm^3 in the lavage fluid. Patients with a grossly positive lavage (initial aspiration of 10 mL of blood) who are unstable should undergo immediate laparotomy. If <10 mL is aspirated, this amount of blood should be added back into the peritoneal cavity and counted toward the final lavage fluid red blood cell (RBC) determination. Generally, patients with RBC counts between 25,000 and 100,000 RBC/mm^3 should undergo CT scan and patients with counts $>100{,}000$ RBC/mm^3 should be seriously considered for CT

scanning if they remain hemodynamically stable. However, this is more of a historical remnant as most of these patients today would have had a CT as the primary test rather than a DPL. Other lavage criteria based on the leukocyte count and amylase are less sensitive and more controversial and should be interpreted in light of the clinical examination. Gross bile or fecal material should be considered a positive lavage.

Computed Tomography

CT scan of the abdomen and pelvis is the best method for radiographic evaluation of the stable patient. Owing to limitations in the physical examination of the trauma patient, most patients except the minimally injured will require some sort of diagnostic test or observation. The CT offers the ability to perform, in a relatively rapid fashion, a quantitative and qualitative diagnostic test.

Abdominal CT after blunt trauma is indicated in patients with an unreliable physical examination. This includes patients with altered sensorium, spinal cord trauma, or distracting injuries or when general anesthesia is planned for another injury and there is a concern for intra-abdominal injury. CT also evaluates for suspected retroperitoneal, small bowel, renal, or pancreatic injury. It also provides excellent visualization of pelvic and spinal fractures. CT images may also reveal a pneumothorax or hemothorax and rib fractures missed on initial plain radiograph. With each generational improvement in CT scanners, image reconstructions are greatly enhanced with thinner slices, higher spatial resolution, and increased speed. Artifacts caused by motion, respiration, and pulsations are significantly decreased.

Multidetector CT (MDCT) images more anatomic area as the IV contrast material travels through the body, resulting in better detail of structures. Thus, because of the greater anatomic coverage during optimal IV contrast material opacification, vascular structures and parenchymal organs are imaged more effectively, and the ability to construct 3D reformations is greatly enhanced (27,28). A common

approach some trauma centers are using is to perform a CT from head to pelvis, that is, “the pan scan,” in the multitrauma patient. Though seemingly cost prohibitive, it may actually be less expensive given that the extra time to perform the scan takes minutes, there is no increased use of film when images are stored on a picture archival retrieval system, and scans of the bones can be included, obviating the need for plain films. This approach, however, must be balanced by the radiation load incurred and the long-term potential, although low, for radiation-induced carcinomas (29). Currently, this approach remains controversial as clinicians attempt to balance the cost, radiation, and resource utilization with the efficiency of the “pan scan” (30).

Some controversy remains regarding abdominal CT and the need for oral contrast medium to opacify the bowel. Although the major disadvantages (the delay to scan and possibility of aspiration) are very small, it remains unclear exactly how much it contributes to care. It can assist in diagnosing bowel and pancreatic injury, although the incidence of injury to these structures is low. Extravasated contrast is a pathognomonic finding; however, it has a low sensitivity. Contrast improves the ability to see bowel wall thickening, although most patients with this finding alone do not need intervention. Although several reviews and studies have led to mixed conclusions and its use remains an institutional preference, increasingly the evidence suggests that it is probably not needed (31,32). The most recent American College of Radiology Appropriateness criteria also agrees with this approach, no longer recommending oral contrast in CT studies of BAT (33). Given its limited assistance, if oral contrast is administered, CT should not be delayed while waiting for passage of the contrast material, unless there is a strong suspicion for bowel or pancreatic injury and the patient is stable.

Another major limitation of abdominal CT scan is the decreased sensitivity for bowel, mesenteric, and pancreatic injury. Hollow viscous injury has historically been one of the most elusive diagnoses to make by CT in trauma. It is found in approximately 1% to 5% of patients with significant BAT and may be higher with

certain mechanisms such as a seat-belt injury. Air, extravasated contrast, active mesenteric bleeding, or bowel injury with mesenteric hematoma are indications for surgical intervention. Unfortunately, these are relatively insensitive and rare findings. The significance of isolated free intraperitoneal fluid is more controversial. Several studies have found a high likelihood of bowel or mesenteric injury and others document a low likelihood (34,35,37). In general, it should probably be taken seriously, and the EP should strongly consider admitting or observing the patient with this finding in addition to obtaining surgical consultation. Findings such as mesenteric infiltration or hematoma or bowel thickening are often seen in patients with less serious lesions; these patients may often be safely observed. In the past, reported sensitivities for diagnosing bowel injury with CT were as low as 41%. The newer scanners have improved resolution and provide better diagnostic accuracy (32,36).

Pancreatic injury remains a difficult diagnosis. Elevations of amylase or lipase are inaccurate for detecting this injury. Though the incidence of pancreatic injury in BAT patients is $<1\%$ and the need for operative intervention is even lower, CT is only 50% to 78% sensitive and tends to underestimate the extent and magnitude of the injuries. These patients, however, often undergo exploration for other concomitant injuries (39).

Diaphragmatic injuries, though relatively uncommon, remain diagnostic dilemmas. Studies of helical CT in diaphragmatic injury have found it better in the acute phase and with visceral herniation. Pathognomonic signs for this injury include the “collar sign”—a waist like constriction of the abdominal viscera, intrathoracic herniation of abdominal contents, and discontinuity of the diaphragm. In one small study of helical CT, these signs were highly specific, with a moderately high sensitivity; CT detected approximately 80% of left-sided and 50% of right-sided herniations. The newer scanners have improved sensitivity and specificity, with values reaching 84% and 77%, respectively, using coronal and sagittal reconstructions. Familiarity and greater use of MDCT should improve the ability to make this diagnosis in the acute phase (38).

CT is the diagnostic test of choice in the stable patient with a high suspicion for intra-abdominal injury or with an unreliable examination. It is also being used with increasing frequency in the patient who is moderately stable (i.e., the patient who is able to maintain vital signs, although they may be fluctuating, or the patient with ongoing hemorrhage who can be adequately resuscitated) in whom nonoperative management is still a possibility. A multi-institutional prospective study of 2,774 patients with suspected BAT found that a negative CT scan has a negative predictive value of 99.63%. This has tremendous implications for cost savings. A patient without other significant injuries, pain or social concerns with a normal abdominal CT can be safely discharged. The chance of a missed significant abdominal injury is extremely low (39). Despite the high sensitivity of CT scanning BAT patients, recent studies and ACEP guidelines have focused on identifying a population of patients with BAT who are at low risk of adverse outcomes, in whom CT scanning may increase radiation dose without adding valuable clinical information (1). These patients are those who have no abdominal tenderness, hypotension, altered mental status, costal margin tenderness, abnormal chest radiograph, hematocrit under 30%, and hematuria. The clinical prediction rule has yet to be externally validated but may help limit CT usage on BAT patients with a low likelihood of intra-abdominal injury.

While the pendulum has swung in the last decade toward increasing use of CT scan with BAT to provide efficient clinical care with a high sensitivity for all intra-abdominal injuries, research is now looking to help define the patient populations in which historical and physical factors can safely exclude important BAT without imaging.

Ultrasound

The advent and increasing usage of ultrasound represented a paradigm shift in the evaluation and management of the blunt trauma patient. The FAST examination is a directed assessment of

the abdomen and pericardium with the goal of detecting hemoperitoneum or pericardium. Although operator dependent, it is a rapid bedside test that can be done at the bedside with the secondary survey. The FAST examination is performed on the supine patient with the examiner positioned on the patient's right side. Four locations are scanned: (a) the RUQ, (b) LUQ, (c) the suprapubic region, and (d) the pericardium. The examiner looks for unclotted blood, which appears black or anechoic on the ultrasound screen. The RUQ view is generally the initial view. This view detects blood in Morison's pouch, a dependent space between the kidney and liver. Although this location has the greatest yield, the addition of all abdominal views has been found to significantly increase the sensitivity by up to 40%. The LUQ is examined next, specifically looking for blood in the splenorenal space. Either view of the upper quadrants may also reveal a hemothorax or pneumothorax. Trendelenburg positioning may improve the sensitivity of either of these views. The suprapubic view evaluates the cul-de-sac between the rectum and bladder (the pouch of Douglas), and the heart and pericardium are examined by a subxiphoid view. The suprapubic view should be performed before the Foley catheter is placed, as the full bladder acts as an acoustic window and enhances visualization of peritoneal fluid (40,41).

The FAST examination has become a standard part of the EP and trauma surgeon's evaluation of the blunt trauma patient. In many centers it is considered the first-line diagnostic study to identify or exclude significant hemoperitoneum. Clear benefits of ultrasound are that it is rapid, noninvasive, inexpensive, repeatable, and relatively portable. The test can be performed in conjunction with resuscitation, usually takes <5 minutes, and has a relatively steep learning curve. Its sensitivity and specificity range from 81% to 98% and 94% to 98%, respectively. The sensitivity and specificity vary somewhat depending on the amount of free fluid present and the expertise of the examiner (42,43). Though ultrasound is moderately sensitive for as little as 100 to 200 mL of fluid, sensitivities increase to $>90\%$ with volumes of fluid close to 700 mL. In other words, ultrasound is highly sensitive in patients with enough blood loss to

cause hemodynamic instability, although one cannot fully exclude an intra-abdominal lesion based on a negative ultrasound in an unstable patient. The sensitivity of the FAST examination also increases when serial examinations are performed, separated by 30 minutes. Accuracy has been reported to range between 96% and 98% (34). The level of accuracy is independent of whether an EP, surgeon, radiologist, or ultrasound technician performs the study; they all have comparable results. Though there is controversy over the exact number of studies and instructional time needed for proficiency, current studies appear to support that several hours of instruction, and roughly 20 hands-on studies lead to excellent accuracy in defining hemoperitoneum (44–46).

In US, FAST has largely supplanted DPL, especially in unstable patients, and has been used as a diagnostic adjunct in the stable patient in conjunction with physical examination or, more commonly, CT scan. Compared to DPL, ultrasound allows for a quicker, safer, and noninvasive test without interference with other resuscitative procedures. Unlike DPL, it does not require extra time or modification for the pregnant patient or patients with pelvic fractures, previous surgery, or coagulopathy.

Most centers use some variation of the algorithm from Denver published in 1997 (47). The initial test in all BAT patients is the ultrasound. If the patient is unstable and the FAST is positive, immediate laparotomy is performed. In the unstable patient, if the FAST is negative or equivocal and intra-abdominal injury is a concern, a DPL is performed. A CT scan follows a positive ultrasound in a stable patient. A negative ultrasound is followed by a CT scan or by serial ultrasounds, physical examinations, and a 6-hour hematocrit. A concerning change in physical examination, ultrasound findings, or significant drop in hematocrit is followed by either a CT scan or laparotomy. Although outcome studies are limited, literature has shown that implementation of point-of-care sonography protocol can limit CT scans, and minimize the time to definitive intervention in BAT patients (47,48). This must be balanced, at least in the Denver study, with the increased time of observation of the patients who were observed after ultrasound.

Though ultrasound clearly is valuable in the unstable patient, it has some disadvantages compared to CT scan in the stable patient. Although highly sensitive for large amounts of hemoperitoneum, it is less so with small amounts, and it is not reliable at providing a qualitative assessment of a solid organ injury. The sensitivity of ultrasound for identifying solid organ injury is approximately 30% when performed by sonographers trained for limited bedside ultrasound. It also does not provide information about bowel or pancreatic injury or evaluate the retroperitoneum (34). Patients at significant risk for intraperitoneal injury such as those with abdominal abrasions, lower rib fractures, multiple traumatic injuries, pelvic or long-bone fractures, or inability to be clinically followed up may be poor candidates for ultrasound as the only modality for evaluation. At a minimum, these patients should not be evaluated using a single examination at a single point in their course.

Overall, ultrasound provides a very useful initial test in BAT. Though it can potentially predict the need for surgical repair based on the amount of fluid observed, its main utility has been in the unstable patient as a replacement for DPL. As it does not reliably grade or even diagnose solid organ injury, it is most valuable as an adjunct to CT in the stable patient. In most centers, given the increasing availability of CT and the high negative predictive value, a negative or equivocal ultrasound is often followed by abdominal CT scanning. However, from the beginning of the resuscitation, ultrasound alerts the team to the presence of intraperitoneal injury within seconds to minutes and can be used to rapidly triage patients to the operating room or radiology suite. In addition, owing to its portability and accessibility, ultrasound can be repeated to detect hemoperitoneum if the hemodynamic status of the patient changes.

Angiography

Interventional angiography is increasingly important and more frequently employed in the treatment of hemodynamically stable BAT patients. As the technology of CT improves, active hemorrhage

is increasingly identified faster and more accurately. If an actively bleeding spleen, liver, or kidney is visualized and the patient is clinically stable, a dedicated angiography team may be able to intervene to rapidly embolize the lesion and avoid laparotomy. Angioembolization, along with close observation and serial examinations, has been shown to increase the effectiveness of nonoperative management of BAT patients. The precise population of BAT patients who will benefit from nonoperative management, and specifically, angiography, has yet to be fully elucidated (28,49,50).

KEY TESTING

- Type and screen/cross match.
- Liver function testing, amylase, lipase rarely useful. Serial hematocrits more useful than single.
- CT imaging for stable BAT patients with suspicion of injury or unreliable examination.
- FAST examination for unstable BAT patients.

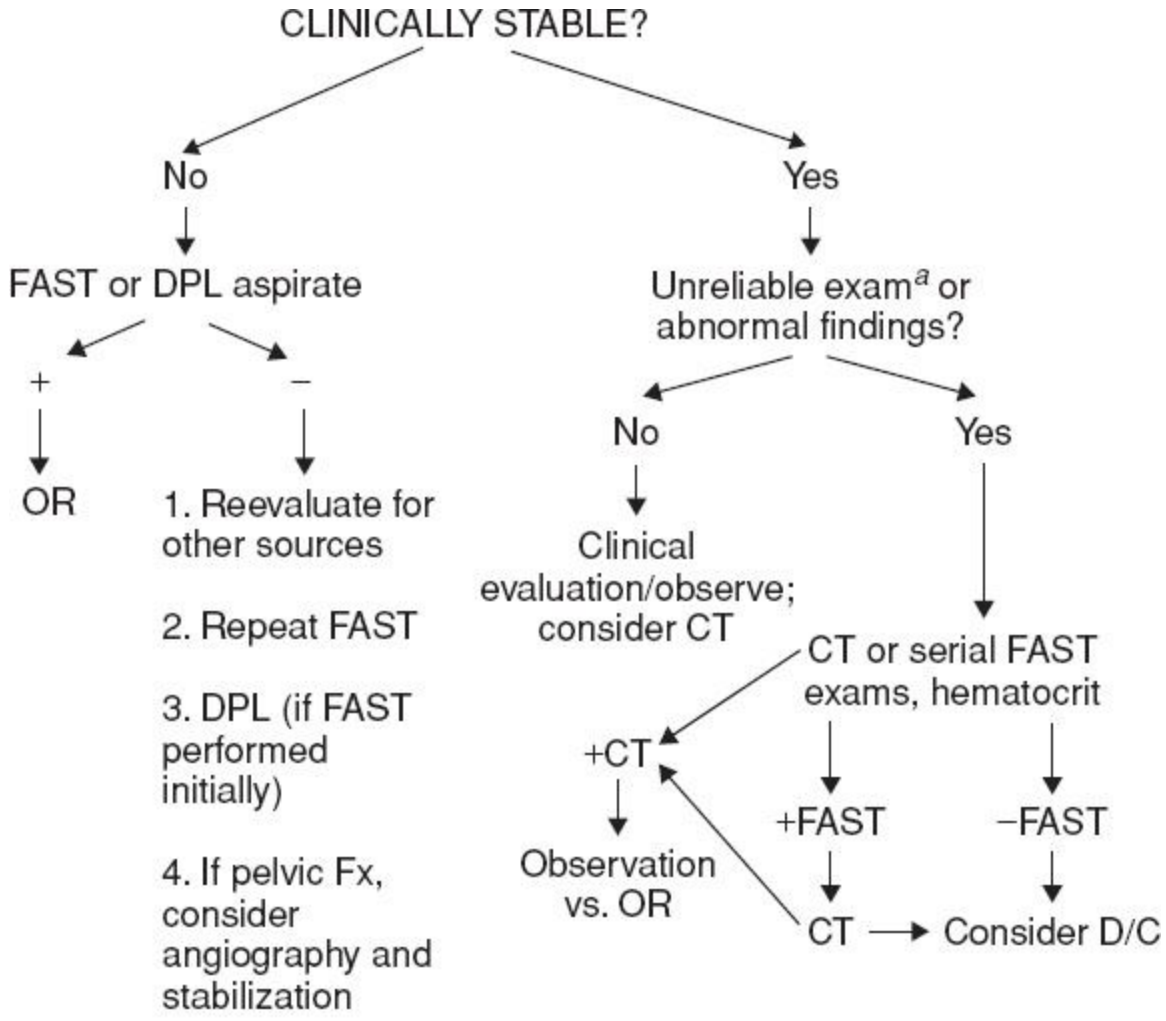
ED MANAGEMENT

In level I trauma centers, prehospital criteria such as vital signs, level of consciousness, and mechanism of injury will alert a trauma team before arrival of the patient. In most hospitals, however, the EP is solely responsible for initial trauma management. The *seriously* injured patient with BAT should undergo standard advanced trauma life support resuscitation.

Unstable Patients

In the hypotensive or tachycardic patient, the cause must be presumed to hemorrhagic until proven otherwise. Vascular access with large-bore intravenous lines should be inserted, and the patient should receive crystalloid bolus as a temporizing measure while the source of hemorrhage is sought and blood products are ready to be administered. Although beyond the scope of this chapter, the proper balance between avoidance of prolonged hypoperfusion and

overshooting an appropriate BP end point and exacerbating hemorrhage is still an ongoing debate (51). The optimal ratios of blood product administration is still unclear, but evolving research supports an approach of a balanced ratio between packed red cells, platelets and clotting factors, approximating the constituents of whole blood. A nasogastric or orogastric tube should be inserted as well as a Foley catheter, after ensuring that there is no urethral injury. Patients with hemodynamic instability in whom an abdominal injury is clearly the source, such as an injury with a traumatic bowel wall hernia and abdominal wall ecchymosis, should be taken directly to the operating room. For unstable patients, particularly those with multisystem trauma in whom intra-abdominal injury is a possibility, the primary method of evaluating the abdomen should be FAST, however, DPL or laparotomy remain important options in the indeterminate study or negative study where there remains a high suspicion of intra-abdominal hemorrhage. Special consideration should be given to the unstable patient with significant pelvic fractures (52) (eFig. 33.1).



eFIGURE 33.1 Blunt abdominal trauma algorithm.

For unstable patients in whom a FAST examination is not available, the peritoneal aspirate component of the DPL remains a primary tool for investigation. An initial aspirate of >10 mL of blood is an indication for surgery. Despite the improved speed of the current generation of scanners, CT does not have a role in the persistently unstable victim of BAT.

Though the ranking of priorities in patients with head, chest, and abdominal injuries is still very difficult, there are some advantages from the modern spiral or MDCT scan speed. The speed of the newer CT scan may allow a few quick cuts of the head and chest to screen for obvious pathology. The time of the scan is now often measured

in seconds to minutes. This may enable a quick assessment of the head en route to the operating room for laparotomy. In general, the critical ordering is to manage injuries to the abdomen first, and then the head, and then aorta but, obviously, decisions must be colored by the actual pathologies present.

Stable Patients

For the hemodynamically stable patient with BAT, the approach to management is guided by several factors. Victims of BAT who are awake and alert with a reliable, benign abdominal examination can be followed up clinically with serial examinations. For stable patients with positive abdominal findings, an unreliable examination, significant distracting injuries, or possible retroperitoneal injury, abdominal CT is the diagnostic test of choice. Some patients with a significant mechanism of injury may undergo CT or a period of observation, in spite of negative clinical findings.

Although an initial FAST examination should generally be performed, a subsequent CT is indicated in most patients. Some centers, however, follow up patients with serial ultrasounds, physical examinations, and hematocrits. CT can often help determine whether underlying injury can be managed nonoperatively. CT in patients with a negative FAST examination may identify significant injuries that have not resulted in significant intra-abdominal bleeding such as bowel injury. In addition, it will detect injuries in the retroperitoneum, pelvis, spine, and lower chest.

CRITICAL INTERVENTIONS

- Address the basic ABCs of resuscitation prior to examination of the abdomen.
- In stable patients with significant pain, tenderness, or an unreliable examination, perform a CT scan or serial physical examinations and ultrasounds.
- In unstable patients, perform an ultrasound to evaluate for intra-abdominal hemorrhage.

- Obtain surgical consultation early in hemodynamically unstable patients or those with intra-abdominal pathology by examination, ultrasound, or CT scan.

DISPOSITION

For stable patients who require evaluation by CT, disposition can be made based on a combination of historical factors, physical findings, and some combination of imaging modalities. Patients with a normal CT scan and a brief period of observation in the ED can be safely discharged from the ED (28). Patients who are awake and alert, have a reliable, benign abdominal examination, and are not candidates for CT can be followed up clinically with serial abdominal examinations in the ED over a 4- to 6-hour period. Those with low mechanism who are fully alert and appropriate can most likely have a shorter evaluation period, although the optimal time is not clear from the literature.

Operative delay is the primary cause of preventable deaths in patients with BAT. At a very early stage, the EP should evaluate the services available at his or her institution and determine whether a patient is a candidate for transfer. It is imperative that a patient is initially resuscitated prior to transfer with careful attention paid to the airway and hemodynamic status. In consultation with the receiving institution, a decision is made to have a patient transferred on the basis of the primary and secondary surveys alone. Multiple diagnostic studies at the transferring hospital will only delay care; therefore, only essential tests should be ordered. Two large-bore intravenous lines and a Foley catheter should be placed in most patients with reasonable suspicion of serious injury. A chest x-ray should be obtained and chest tubes placed for hemothorax or pneumothorax.

Common Pitfalls

- Failure to obtain early surgical consultation in the unstable patient.

- Attributing hypotension to extra-abdominal causes, such as chest trauma, spinal shock, or external blood loss.
- Failure to evaluate the abdomen in the patient with an unreliable physical examination. All patients who have multiple injuries, altered mental status, or a distracting injury should be considered to have an unreliable examination.
- Performing an abdominal CT scan in the hemodynamically unstable patient.
- Relying on a negative ultrasound to rule out intraperitoneal injury.
- Delaying transfer while performing unnecessary studies.

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CHAPTER 34

Penetrating Abdominal Trauma

Michael J. Breyer

Penetrating trauma to the abdomen continues to be a major cause of trauma and mortality in the United States. Death resulting from trauma is greatest in 15- to 34-year-old African Americans closely followed by Hispanics of the same age and is usually the result of homicide. In 2010, the Centers for Disease Control and Prevention reported homicide was the second leading cause of death in the 15- to 24-year-old age group and remains in the top four leading causes of death in all reported age groups from 1 to 44 years old (1).

Stab wounds (SWs) are three times more frequent than gunshot wounds (GSWs); however, GSWs account for approximately 90% of the deaths related to penetrating abdominal injury. A GSW carries significantly greater force, with injury and cavitation extending along the missile tract. Although bullets are the most common missiles, flying glass objects, lawn mowers, severe weather, and grenades can also create missiles.

During the US Civil War, conservative management was the treatment of choice, with laparotomy reserved for penetrating wounds with evisceration. In World War I, surgical exploration became standard of care, resulting in a survival rate of 75% for patients with GSWs to the abdomen. However, by the middle of last century, surgeons began to employ selective laparotomy with serial observation in some patients sustaining penetrating abdominal trauma. Since then, conservative management, coupled with certain diagnostic procedures, notably ultrasound (US), computed

tomography (CT), diagnostic peritoneal lavage (DPL) and local wound exploration (LWE) have gained widespread acceptance in the medical community.

The primary goals for managing penetrating abdominal injury center on expedience and accuracy. Because of the wide range of scenarios and possible injuries, the emergency and trauma teams play critical roles in the treatment of these patients, carefully integrating clinical gestalt, history, physical examination (PE), DPL, LWE, US, and CT. Notably, the evaluation, resuscitation, and method of diagnosis depend on the type of penetrating injury, the zone of penetration, and, most importantly, the hemodynamic status of the patient.

CLINICAL PRESENTATION

Patient assessment is frequently complicated by the presence of alcohol or drugs, which can mask important signs and symptoms even in the presence of major injury. Furthermore, other systems may also be involved and contribute to vital sign abnormalities. For these reasons, the American College of Surgeons (ACS) advises a 50% overtriage rate to maintain a 10% undertriage rate with studies noting 12% of patients triaged to trauma centers suffer serious injury (2). Often, prehospital providers obtain valuable information regarding the type of implement used to inflict the wound, the number of shots heard, and the position of the patient during the assault. These vital parts of the history, coupled with familiarity of the pathophysiology for penetrating abdominal trauma, can help guide Emergency Department (ED) evaluation and treatment.

There are four anatomic zones of the abdomen: anterior abdomen, low chest, flank, and back. The anterior abdomen is demarcated by the anterior axillary lines from the costal margins to the groin creases. Approximately one-third of penetrating trauma in this zone will violate the peritoneum. The low chest or thoracoabdominal area is defined by the nipple line/fourth intercostal space anteriorly and the inferior scapular tips/seventh intercostal space posteriorly to the inferior costal margins. The flank lies between the inferior

costal margins and the iliac crests between the anterior and posterior axillary lines bilaterally. The back is bordered by the inferior scapular tips and the iliac crest between the posterior axillary lines (3).

Penetrating abdominal injuries can be divided into three subtypes: SWs, GSWs, and shotgun wounds (SGWs). In patients suffering SWs, the most commonly injured organs are the liver and small bowel. Knives, ice picks, coat hangers, and screwdrivers can all be used to create SWs. Typically, SWs occur in the upper abdominal quadrants, and, as most assailants are right handed, the patient's left side is violated more frequently. In 20% of cases there are multiple wounds, and 10% of patients may have SWs involving the chest. This complicates the clinical approach as wounds in the lower chest region have a high incidence of diaphragm injury, as well as a 15% rate of intra-abdominal injury. Flank SWs injure peritoneal structures in 44% of the time, whereas back SWs cause intraperitoneal injury in 15% of patients. Nevertheless, the practitioner must remain diligent to the possibility of serious bodily injury with SW in any area of the patient's abdomen and torso.

GSWs impart a large amount of energy which generates increased tissue destruction and potential for organ injury. The most commonly injured organs are the small bowel, colon, and liver. Tissue resistance and viscoelasticity, combined with missile stability, velocity, and distance all affect the pathology created by GSWs. At medium (1,100 to 2,000 ft/sec) and high ($>$2,000 ft/sec) velocities, such as those imparted by AK-47 guns, there is an additional explosive effect of the missile. Diagnostic confusion can be caused by the closure of the tract immediately after passage, thus obscuring injured areas, as well as fragmentation of the bullet which can create additional trajectories.

SGWs differ from GSWs in velocity and missile trajectory. There is an initial rapid decrease of velocity of the pellets; thus, long-distance SGW injuries are associated with a lower morbidity and mortality. Pellet size and number, powder type, and length of the choke barrel combine to determine the potential for injury. At a range of 10 yards, 19% of pellets will cluster in a 9-in diameter

area, whereas at 20 yards (25% loss in velocity), pellets will spread out over an 18-in diameter area. SGWs are categorized based on distance and pattern of injury. Type I wounds are >7 yards from the victim and typically cause minor to moderate tissue damage. Type II wounds occur at a distance of 3 to 7 yards, have a pellet spread of 10 to 25 cm, and create deeper wounds, frequently into the thoracic or abdominal cavities. Finally, type III wounds (<3 yards) create massive destruction of tissue and organs due to their close range.

Differential Diagnosis

Although there may be an obvious penetrating abdominal injury, additional wounds to the head, neck, and extremities should also be sought. Hemodynamic instability may be caused by intra-abdominal hemorrhage, but other etiologies, such as tension pneumothorax, pericardial tamponade, hemothorax and massive arterial or venous bleeding, should also be pursued. For these reasons, a prompt assessment, including history, PE, US, x-ray, and CT are crucial to the care of the trauma patient with penetrating abdominal injury.

ED Evaluation

All patients with suspected trauma must be completely undressed and carefully examined as the scalp, axilla, and perineum can hide seemingly innocuous but deep and life-threatening wounds. History in these cases may at times be confusing or even misleading and therefore reports of a single wound should not be accepted until a thorough pursuit for additional wounds has been undertaken.

Determining the presence of organ injury necessitating immediate laparotomy is the primary initial decision point in the care of the patient with penetrating abdominal injury. For patients without clinical indications to proceed to the operating room (OR), additional testing including focused assessment with sonography for trauma (FAST) scan, laboratory data, CT, and serial PE are typically utilized.

KEY TESTING

- Complete blood count
- Basic metabolic panel
- PT/INR
- Point of care glucose
- Lactate
- Urinalysis
- Urine pregnancy test
- Type and screen, type and cross
- Blood alcohol level
- Bedside x-ray studies, including CXR and pelvis x-ray
- FAST U/S
- DPL as indicated
- CT if hemodynamically stable

ED MANAGEMENT

Ideally, all patients with an SW or a GSW to the abdomen are triaged from the point of injury directly to the nearest appropriate trauma center. When this does not occur, transfer to such a center at the earliest opportunity is advisable. Only life-saving maneuvers such as endotracheal intubation, tube thoracostomy, pericardial aspiration, fluid resuscitation and emergent surgical stabilization are indicated before initiating transfer.

When possible, prehospital personnel should attempt to notify the trauma center of their arrival. Information gleaned from prehospital communication is usually sufficient to activate the appropriate resources, including ED staff, the trauma team, OR staff, radiology staff, and blood bank.

Stab Wounds

While peritoneal violation occurs in 50% to 70% of anterior abdominal SWs, laparotomy is required in only 25% to 30% of patients who sustain SWs to their abdomen. Not surprisingly, management (conservative versus operative) depends on the type of

injury, severity of injury, and hemodynamic stability of the patient (4). Three sequential questions form the basis for an algorithm for patients with SWs to the abdomen (Fig. 34.1).

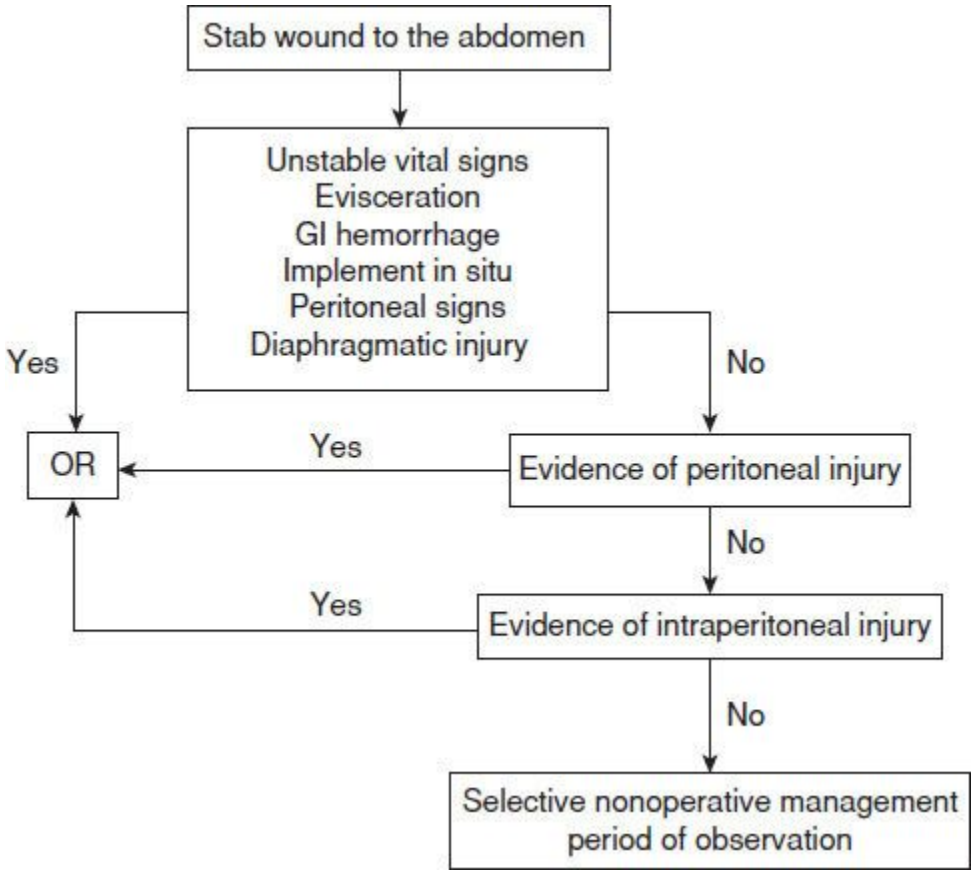

FIGURE 34.1 Algorithm for the management of patients with stab wounds to the abdomen.

Are There Indications for Immediate Laparotomy?

There are six clinical scenarios that suggest a high likelihood of intraperitoneal injury requiring laparotomy after an anterior abdominal SW. If one or more of these is present, then immediate surgical consultation should ensue with likely operative management to follow.

Unstable Vital Signs

Any patient with unstable vital signs has a potential major visceral or vascular injury that requires immediate surgical consultation.

While other causes of hemodynamic instability, such as tension pneumothorax or cardiac tamponade should also be considered and ruled out, preparation for laparotomy should begin immediately.

Evisceration

In patients with evisceration of abdominal contents, approximately 75% have concomitant intraperitoneal injuries that require operative intervention (5). With the high likelihood of significant injury, many surgeons proceed to the OR; however, others will reduce the bowel at the bedside and perform other diagnostic studies to determine the need for laparotomy. This practice is supported by a recent study that found in hemodynamically stable patients with evisceration, admission and serial examinations were associated with shorter lengths of stay than in patients managed with laparotomy (6).

Peritoneal Signs

Peritoneal signs on PE may indicate the need for exploratory laparotomy (7). However, as these signs are neither sensitive nor specific, it is important that the most seasoned physician or surgeon available perform a PE that determines the need to proceed to the OR.

Diaphragmatic Injury

Diaphragmatic injuries due to SWs are often small and thus difficult to discern using routine chest x-ray and PE. These may lead to significant morbidity or mortality due to herniation of abdominal contents into the chest, which can occur months or even decades following the initial injury. With these reports, some centers conduct mandatory laparotomy or thoracotomy for SWs to the left lower chest or left upper quadrant of the abdomen to avoid missing diaphragmatic tears, whereas other centers use diagnostic laparoscopy (DL) or DPL to evaluate for diaphragmatic injury instead of mandatory laparotomy (7). Of note, the presence of the

liver on the right side of the abdomen makes right diaphragmatic injury far less common.

Gastrointestinal Hemorrhage

Evidence of upper gastrointestinal (GI) hemorrhage after SW suggests hollow visceral injury, particularly to the stomach or duodenum, and the need for operative intervention.

Implement In Situ

To limit hemorrhage and remove an impaled foreign object in a controlled fashion, most surgeons proceed to the OR for implement in situ. There are exceptions to this axiom. Patients with severe comorbid illness or pregnant women may sustain greater harm from general anesthesia and therefore their foreign body removal may be safer at the bedside. Furthermore, in rare instances, it is necessary to remove the implement to provide adequate prehospital or ED resuscitation.

Is There Evidence of Peritoneal Violation?

If there is no indication for immediate laparotomy, the practitioner should next assess the wound tract to determine presence of peritoneal penetration. Caution should be used when determining whether to proceed to the OR when managing wounds that affect the upper abdomen as injury to structures in this area may not manifest with clinical peritonitis (8).

Plain Radiographs

The presence of free air on an upright chest or left lateral decubitus radiograph establishes the stabbing implement penetrated the peritoneal cavity which caused a track that brought air inside the peritoneal cavity. It does not, however, identify that a hollow viscus injury has necessarily occurred. Upright chest radiographs, while often the first test of choice, are neither sensitive nor specific and therefore must be weighed against the overall clinical picture of the patient.

Local Wound Exploration

With proper anesthesia, LWE can be safely performed on the anterior abdomen, flank, or back. A negative LWE establishes that the end of an SW tract is anterior to the rectus fascia. Such patients may be safely discharged from the ED after appropriate wound care and period of observation (9). Patients with multiple wounds, significant muscle mass, or morbid obesity may not be suitable candidates for LWE.

Computed Tomography

CT scans for SWs of the abdomen can be helpful in excluding peritoneal violation, predicting the need for laparotomy with a sensitivity of 96% and specificity of 97% (10). However, its exquisite sensitivity for diagnosing free intraperitoneal air may lead to unnecessary operations.

Ultrasound

US is helpful in evaluating the intraperitoneal, pleural, and pericardial spaces in wounds that may have violated the mediastinum or diaphragm. A positive FAST examination may mandate laparotomy or thoracotomy depending on whether intraperitoneal or intrapericardial hemorrhage is discovered and the clinical status of the patient. However, a negative FAST examination does not rule out injury, particularly to hollow viscera and the diaphragm, as these tend to bleed minimally.

There is an evolving role for US in the detection of peritoneal violation in penetrating abdominal trauma. A recent study evaluating the use of US to identify fascial violation deep to the SW found excellent specificity in identifying peritoneal penetration (11).

Diagnostic Laparoscopy

DL can be used to evaluate the depth of a wound tract, and although it compares favorably with LWE, it is more invasive and can only be performed by a surgeon trained in its use. Therefore, DL is primarily relegated for inspecting the diaphragm in left low chest and upper

abdominal wounds. In addition, it may allow immediate repair of diaphragmatic and certain organ injuries, often decreasing the cost and length of stay of patients who would otherwise have gone for an exploratory laparotomy (12). Although in some medical centers DL is used as a screening tool for patients with abdominal SWs, for most it represents a novel approach and remains controversial (13).

Is There Evidence of Intraperitoneal Injury?

If there are equivocal findings of peritoneal violation, further diagnostic evaluation with DPL, CT, or DL is indicated to determine whether injury requiring operative intervention is present.

Diagnostic Peritoneal Lavage

DPL, although invasive, is a rapid, reliable indicator of intra-abdominal injury and need for operative management (14). It is also effective in determining hollow viscus or diaphragmatic injury. The presence of 10 cc of gross blood or lavage fluid with 10,000 red blood cells (RBC) per high power field (HPF) indicates the presence of visceral injury. When low chest wounds are also present, the cutoff is dropped to 5,000 to 10,000 RBC/HBF to pick up potential isolated diaphragmatic or small bowel injury. Of note, bleeding from torso muscles and subcutaneous tissues at the SW site can cause false-positive DPL results.

Computed Tomography

CT is an important diagnostic modality following blunt trauma, as it is excellent for detecting solid visceral injury and hemoperitoneum. Its role in hemodynamically stable patients with penetrating abdominal trauma is expanding, and it can help facilitate nonoperative management for selected injuries. Many centers are now using CT with only intravenous (IV) contrast for hemodynamically stable patients with penetrating abdominal trauma, a protocol that appears to be safe for patients and effective in determining free air, free fluid, hematoma, and other injuries. Nonetheless, most practitioners recommend those patients at high risk for diaphragmatic, bowel, or pancreatic injury with a negative

abdominal CT should have further testing, observation, and serial examinations, because even new high-resolution CT lacks adequate sensitivity in detecting these injuries (15). Triple-contrast CT (IV, oral, and rectal) is generally reserved for low abdominal, flank, and back wounds to detect colorectal injury.

Diagnostic Laparoscopy

DL has been used for direct inspection of the diaphragm, detection of peritoneal violation, and evaluation of solid viscera. However, it remains inadequate for identifying hollow viscus and retroperitoneal injury. In centers experienced with DL, it is usually used for low chest, upper flank, and upper back penetration on the left side where the diaphragm is far more vulnerable to herniation of abdominal contents into the chest.

Selective Nonoperative Management

While many centers proceed to laparotomy for patients found to have peritoneal injury, others employ selective nonoperative management (SNOM) of hemodynamically stable patients with SWs to the abdomen. With this approach, patients typically have serial clinical examinations over 12 to 24 hours along with other diagnostic modalities such as CT, US, or DPL. Although safely employed in selected trauma centers, SNOM requires careful and frequent observation, which may prove to be impractical for some systems. Nevertheless, for patients with stable hemoglobin levels, stable or declining white blood cell counts and nonconcerning PEs, SNOM remains a viable option. In fact, one study which used SNOM managed 18 cases with grade III to V solid organ injuries without a laparotomy (15). This practice has been confirmed by others that found for selected patients with penetrating abdominal injury and a negative ED workup they may be discharged safely from the ED after a period of observation (16).

Stab Wounds to the Flank and Back

The risk of retroperitoneal injury is significantly greater after an SW to the flank and back than to the anterior abdomen. Not surprisingly, the risk of intraperitoneal injury resulting from an SW to the flank or back ranges from just 15% to 40%, markedly lower than the risk from SW to the anterior abdomen. LWE can be very difficult to perform in the flank and back because of the lack of a definite fascial plane of demarcation with the peritoneal cavity and therefore CT in hemodynamically stable patients with flank and back wounds is commonly used to triage patients.

Stab Wounds in Proximity to the Diaphragm

Because missed injuries to the diaphragm can cause substantial morbidity and mortality, some centers recommend mandatory exploration for SWs in close proximity to the diaphragm. Although this protocol is the most sensitive technique to determine injury, it also carries the risk of a high negative laparotomy rate.

As CT can miss diaphragmatic injury from penetrating abdominal trauma, laparoscopy, thoracoscopy, and DPL are commonly employed as adjuncts to diagnose injury. There is evidence showing in asymptomatic hemodynamically stable patients with penetrating thoracoabdominal injury, laparoscopy is sufficient to exclude diaphragmatic injury (17).

Gunshot Wounds

In most institutions, the knowledge or strong suspicion of peritoneal violation is enough to prompt laparotomy. As compared to SWs, GSWs are more frequently associated with multiorgan injury and have a 10-fold higher mortality rate. However, studies have found GSW to the anterior abdomen incur peritoneal violation and resultant intra-abdominal organ injury in only 30% to 74% of patients, far lower than the nearly 90% reported in other papers citing mostly military experience (18). An algorithm for patients with abdominal GSWs can be predicated on three sequential questions (Fig. 34.2).

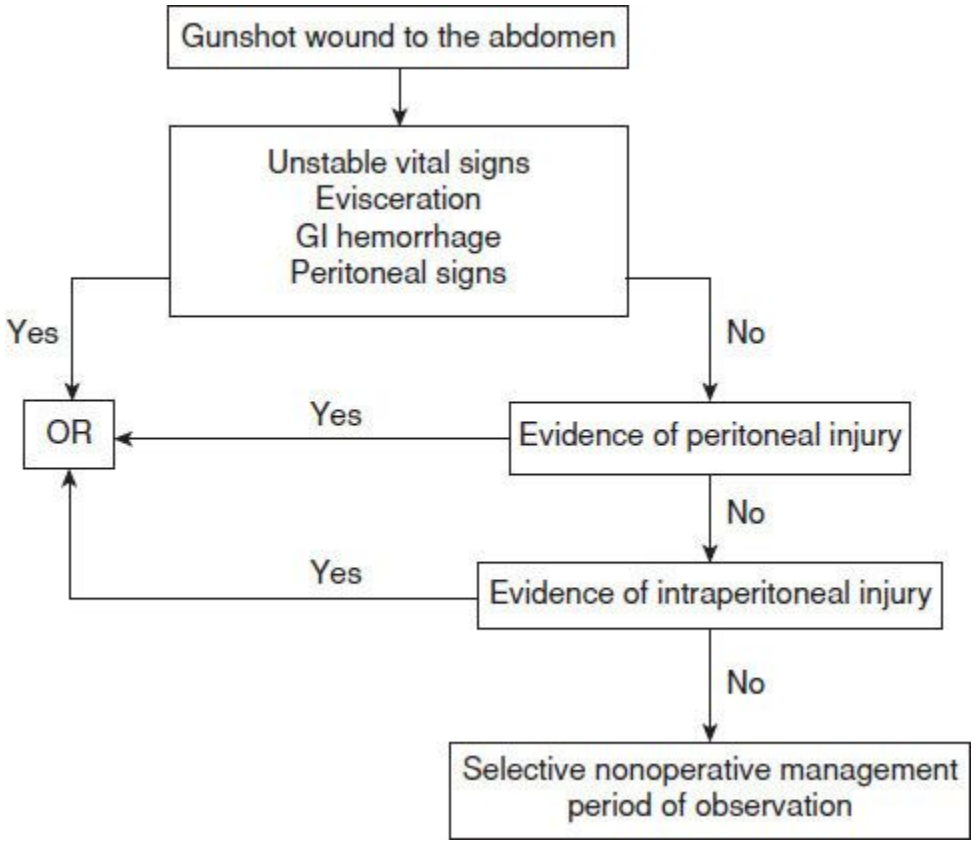

FIGURE 34.2 Algorithm for the management of patients with gunshot wounds to the abdomen.

Are There Indications for Immediate Laparotomy?

As with abdominal SWs, GSWs to the abdomen have accepted criteria for immediate surgical consultation and operation. In a recent study, 74.3% of US trauma surgeons practice SNOM of abdominal GSWs, regarding peritonitis, bowel evisceration, and hemodynamic instability after resuscitation as indications to proceed to the OR (19), but there are marked differences in the acceptance of this practice, ranging from 30% of Canadian trauma surgeons to 100% of South African trauma surgeons (20). One study delineated acidosis (base deficit ≥ 8), blood loss $>1{,}500$ mL, temperature $<35^{\circ}$C, and New Injury Severity Score $>$ 35 as indications for early damage-control resuscitation (21).

Unstable Vital Signs

Any victim of a GSW with unstable vital signs requires immediate surgical consultation as it may be presumed that an injury to a major vessel or solid organ is present. Hemopneumothorax, hemopericardium, or both may be causal or contributory to the clinical situation and should be ruled out.

Peritoneal Signs

As with SWs, there is a well-documented lack of specificity of peritoneal signs with GSWs, but patients with initial diffuse abdominal tenderness or exhibiting signs of peritonitis after a GSW to the abdomen often require surgical exploration (18).

Gastrointestinal Hemorrhage

As is true for patients with SWs, GI bleeding in association with a GSW to the abdomen, flank, or back mandates surgical exploration for potential intestinal injury.

Evisceration

Because of the great amount of energy transference and cavitation that occurs with GSWs to the abdomen, evisceration warrants surgical exploration.

Is There Evidence of Peritoneal Penetration by the Missile?

The following methods can determine if the missile has penetrated the peritoneum. In many centers, this is enough to prompt laparotomy.

Plain Films

If performed in two planes, radiographs can help determine the trajectory of the missile. However, plain films are not helpful when the missile has already left the body. Furthermore, multiple missiles and a ricocheting effect of bones make interpretation of plain films more difficult.

Local Wound Exploration

LWE is more difficult for GSWs than SWs because there is more tissue destruction and difficulty in visualizing the entire tract. It is best used for low-velocity missiles with superficial wounds.

Ultrasound

As with SWs, US may be used to detect the presence of hemoperitoneum and pericardial fluid in patients with GSWs to the abdomen. However, a negative FAST does not rule out the presence of intra-abdominal injury, particularly to hollow viscera and the diaphragm.

Diagnostic Laparoscopy

DL may help identify the presence of peritoneal violation and diaphragmatic injury, but it is inadequate to evaluate for hollow viscus injury. However, DL is an invasive procedure that can increase risk and cost to the patient and therefore its role in the evaluation of patients with abdominal GSWs is still evolving.

High-velocity GSWs transmit tremendous energy and oftentimes cause serious intraperitoneal damage. If no peritoneal violation is initially determined, these patients should be observed for 12 to 24 hours unless their injury was of low velocity with a superficial missile path. If peritoneal penetration is discovered or if it is suspected, then most centers proceed with laparotomy. However, a SNOM approach in a setting that employs the opportunity for close serial PE and additional diagnostic testing, such as DPL, CT, and DL, is now being adopted by some trauma centers (18).

Is There Evidence of Intraperitoneal Injury?

In those centers not proceeding to laparotomy when peritoneal violation is found or strongly indicated, several diagnostic techniques have been utilized to include or exclude intraperitoneal injury following GSWs to the abdomen. Of these, DPL and CT have received the most attention, with a smaller number of studies evaluating DL.

Diagnostic Peritoneal Lavage

DPL, with a RBC threshold lowered to 5,000 to 10,000 RBC/HPF, coupled with clinical examination, can help guide the need for laparotomy. One study found DPL had a sensitivity of 87.5% and specificity of 95.8% in predicting intra-abdominal injuries from SGWs (22).

Computed Tomography Scan

In patients with torso injuries, CT has been used to determine peritoneal violation and avoid nontherapeutic invasive procedures, including laparotomy, in selected hemodynamically stable patients with penetrating trauma to the abdomen, flank, or pelvis (23). In patients with wounds concerning for colon or rectal injury based on location or other associated PE findings such as rectal bleeding, triple-contrast CT (oral, IV, and rectal) should be performed. In a study of 75 consecutive patients with penetrating torso trauma, triple-contrast CT accurately predicted whether laparotomy was necessary in 96% of patients (24). In another study of 200 patients, triple-contrast CT was 97% sensitive and 98% specific in determining peritoneal violation for hemodynamically stable patients with penetrating torso trauma (25). With the advent of high-resolution CT, some centers utilize CT with only IV contrast in stable patients with nontangential abdominal GSWs and a reliable PE.

Diagnostic Laparoscopy

DL is best used in those patients with tangential GSWs to the abdomen who do not have a clear indication for laparotomy or in those with GSWs to the left low chest without indication for thoracotomy or laparotomy.

CRITICAL INTERVENTIONS

- Completely undress and carefully examine all patients with suspected penetrating trauma to the abdomen.
- Obtain early surgical consultation for patients with penetrating abdominal trauma.

- Perform LWE as an initial screening test in stable patients with anterior abdominal SWs to determine the potential for peritoneal penetration.
- For patients with left low chest or upper abdominal SWs, perform a workup for diaphragmatic injury (laparoscopy, thoracoscopy, or DPL).

DISPOSITION

In most centers, patients who undergo a negative DPL, CT, or DL are observed for 12 to 24 hours to ensure absence of injury, an approach that has been shown to have a wide margin of safety.

Ideally, all patients with an SW or a GSW to the torso are triaged from the point of injury directly to a level I or level II trauma center. When this does not occur, transfer to such a center at the earliest opportunity is recommended. Only lifesaving maneuvers such as endotracheal intubation, tube thoracostomy, pericardial aspiration, fluid resuscitation, and emergent surgical stabilization are indicated before initiating transfer.

Common Pitfalls

- Failure to recognize an SW or GSW.
- Minimizing the injury. The presence of peritoneal injury should be assumed.
- Delaying transport to the OR for patients with indications for laparotomy.
- Blind probing of wound tracts with digits or instruments; this is inaccurate and potentially dangerous.
- Relying on a negative PE or abdominal US to rule out injury after penetrating abdominal trauma.
- Failure to observe and admit the patient with penetrating abdominal trauma for repeat examinations after a negative DPL or CT.
- Failure to obtain early consultation with the trauma team.
- Failure to observe and properly monitor trauma patients who are undergoing diagnostic procedures outside of the ED (e.g., CT

scan in the radiology suite).

ACKNOWLEDGMENTS

This chapter is dedicated to the memory of John A. Marx. The author gratefully acknowledges the contributions of Jennifer L. Isenhour and John A. Marx to the content of this chapter.

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CHAPTER 35

Genitourinary Trauma

Carrie D. Tibbles

The genitourinary (GU) system is involved in approximately 10% of acutely injured patients (1). The presentation of GU trauma may be occult and is often overshadowed by more dramatic and immediate life-threatening injuries. However, if these injuries are not identified and properly treated, the patient may experience delayed complications and significant long-term morbidity. Clues to suggest the possibility of GU trauma lie in the mechanism of injury, a constellation of associated injuries, and physical examination findings identified during the secondary survey. For diagnosis and management, GU trauma is generally divided into upper tract injuries (kidney and ureter) and lower tract injuries (bladder, urethra, and external genitalia). A systematic approach and thorough understanding of the appropriate diagnostic modalities are necessary for emergency physicians to effectively manage these injuries.

CLINICAL PRESENTATION

Upper Tract Injury

The kidneys and ureters lie securely in the retroperitoneum, beneath the lower ribs and musculature of the back. Therefore, injuries to the upper urinary tract typically occur in the setting of high-energy, multisystem trauma. Blunt force to the back, flank, or abdomen; falls from height; or, less commonly, rapid deceleration may result in injuries to the kidneys or ureters (2). Upper tract injuries may occur in isolation. However, more commonly, trauma that results in renal injuries produces associated bony, vascular, and visceral injuries that

directly contribute to the observed morbidity and mortality (1). Penetrating injury, which accounts for 6% to 11% of renal injuries, is suggested by transaxial wounds or wounds in anatomic proximity to the kidneys and ureter. Although nearly all significant blunt renal injuries will present with either gross or microscopic hematuria, about 25% to 30% of ureteral injuries will not have associated hematuria. The presence of hematuria is a less reliable indicator of upper tract injury with penetrating trauma and the location of the wound is used to guide subsequent management decisions (3). A vascular pedicle injury may present as refractory hypotension following severe blunt trauma; this injury usually results from a deceleration mechanism.

The American Association for the Surgery of Trauma (AAST) has established a classification system for renal injuries based on anatomic location and severity (Table 35.1; Fig. 35.1) (4). Grade I and grade II injuries consist of contusions and lacerations confined to the cortex respectively and are considered minor injuries. Eighty-five percent of renal injuries are classified as minor injuries. Grade III injuries are deeper lacerations that extend into the corticomedullary junction. Lacerations into the collecting system or those involving segmental arteries are grade IV injuries. The most severe injuries are classified as grade V and include a shattered kidney, thrombosis of the main renal artery, or avulsion of the renal hilum. A review of the National Trauma Data Bank found that the AAST injury scale predicts the need for nephrectomy in both blunt and penetrating trauma and mortality in blunt trauma patients (5). Recently investigators from Parkland recommended a substratification of grade IV injuries into high risk and low risk based on three predictors of needing operative intervention, specifically, intravascular contrast extravasation, hematoma size greater than 3.5 cm, and a medial renal laceration site (6,7).

TABLE 35.1
Grading System for Renal Injuries

Minor Injuries

Grade I: Contusions and contained subcapsular hematomas

Grade II: Nonexpanding perirenal hematomas and cortical lacerations

Major Injuries

Grade III: Parenchymal lacerations into the corticomedullary junction and thrombosis of a segmental artery without an associated parenchymal laceration

Grade IV: Renal lacerations involving segmental renal vessels, lacerations violating the collecting system, and contained injuries to the renal vessels

Grade V: Avulsion of the renal hilum, thrombosis of the main renal artery, shattered kidney

American Association for the Surgery of Trauma grading system.

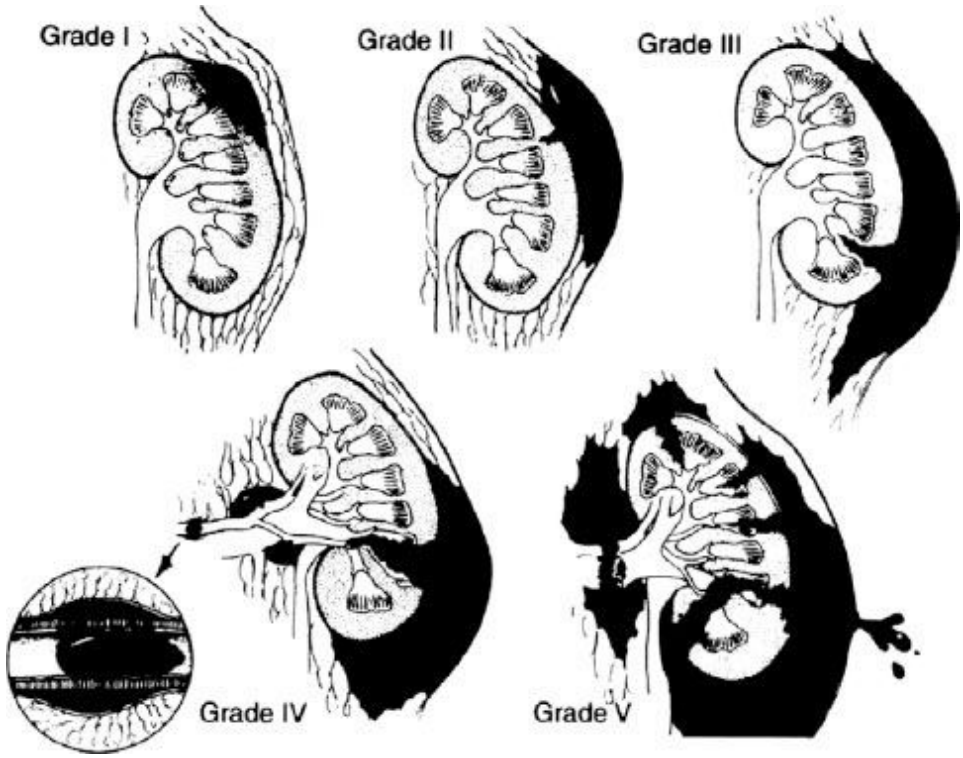

FIGURE 35.1 Grading system of renal injuries. (From Santucci RA, McAninch JW, Safir M, et al. Validation of the American Association for the Surgery of Trauma organ injury severity scale for the kidney. J Trauma. 2001;50:195–200, with permission.)

Lower Tract Injuries

Blunt trauma to the lower urinary tract (bladder and urethra) is usually associated with pelvic rami fractures and symphyseal

diastasis. *Anterior urethral injuries* (penile and bulbous urethra, below the urogenital diaphragm) are associated with self-instrumentation, falls, and straddle injuries. *Posterior urethral injuries* (membranous and prostatic urethra, above the urogenital diaphragm) commonly accompany pelvic fractures (Fig. 35.2). As the urinary continence mechanism and autonomic innervation responsible for erection are contained in the posterior urethra, posterior urethral injuries may result in permanent incontinence and erectile dysfunction. Signs of anterior urethral injury depend on the integrity of Buck fascia. If this fascial layer is torn, blood and urine may pass into the penis, scrotum, and abdominal wall. Clinical signs of urethral injury are blood at the urethral meatus, high-riding prostate, scrotal or perineal hematoma, and difficulty voiding. However, these signs can be absent in some patients with urethral injury.

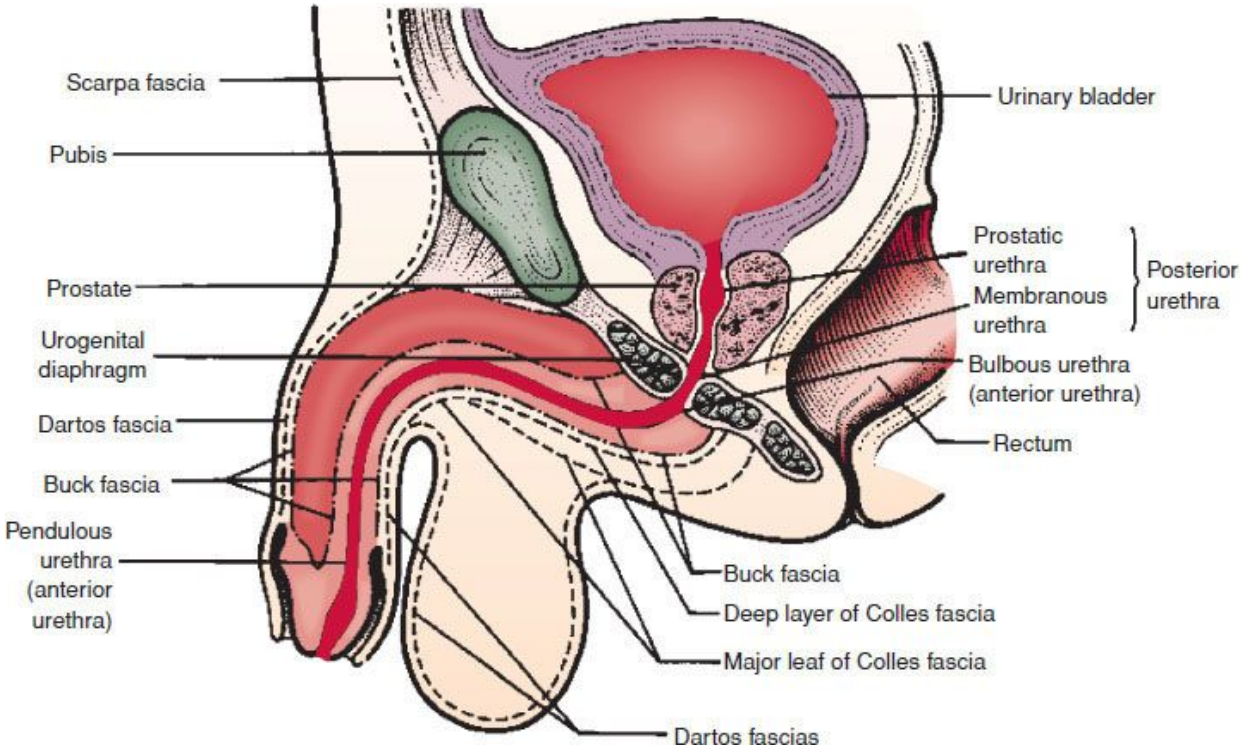

FIGURE 35.2 Normal anatomy of the male urethra. (From Schneider RE. Genitourinary system. In: Marx JA, Hockberger RS, Walls RM, eds. Rosen's Emergency Medicine Concepts and Clinical Practice. 5th ed. St. Louis, MO: Mosby; 2002:438, with permission.)

Bladder rupture is classified as *extraperitoneal* or *intraperitoneal*. *Extraperitoneal* bladder injuries are most commonly associated with pelvic fractures and bladder laceration by bony fragments. There is leakage of urine into the perivesicular space. *Intraperitoneal* bladder injuries result from compressive forces in the presence of a full bladder, and rupture occurs at the dome of the bladder through the peritoneum into the abdominal cavity. The presence of a pelvic fracture and gross hematuria is virtually diagnostic of bladder rupture. Bladder injury is more likely in pelvic fractures with a widened pubic symphysis and sacroiliac disruption (8). Ninety-eight percent of patients with bladder rupture will have gross hematuria. Other signs of bladder injury are suprapubic or lower abdominal pain and tenderness, inability to void, and blood at the urethral meatus.

As with penetrating trauma to the upper GU tract, penetrating injuries to the lower tract are suggested by location of wounds. Any penetration of the lower abdominal wall in the region of the pelvis raises the possibility of urinary tract injury. Given the variability of the projectile tract, any gunshot wound in the region should include consideration of GU tract injury.

External Genitalia Trauma

Testicular injuries are often the result of a fall or direct trauma. They include lacerations, contusions, dislocations, or fractures. Symptoms include pain, nausea, lightheadedness, and acute urinary retention. A swollen, tender testicle or a hematoma may be seen on physical examination. Penile injuries range from small lacerations and contusions to complete amputations. Penile fracture, which involves rupture of the tunica albuginea, most commonly occurs during overzealous vaginal intercourse, although several other mechanisms have been reported (9). Any constricting object placed around the penis can result in marked edema and eventual incarceration and necrosis distal to the constriction. Entrapment of the penis in a zipper occurs most often in uncircumcised young boys.

Vaginal injuries are frequently complications of pelvic fractures but may also be seen following sexual assault or other penetrating injuries. The majority of patients present with vaginal bleeding. A

careful vaginal examination is required in any female patient suspected of having a pelvic fracture. According to one series, up to one-third of patients with vaginal trauma unrelated to childbirth will have concurrent urethral injuries (10).

ED EVALUATION

Upper Tract Injury

The emergency department (ED) evaluation of a multitrauma patient begins with the standard advanced trauma life support assessment and resuscitation. In this manner, immediately life-threatening injuries are identified and treated. In the unstable patient requiring emergency laparotomy for other reasons, gross hematuria and signs of a pelvic fracture should be noted during the secondary survey. Definitive evaluation of the GU tract can be performed once the patient has been stabilized. In the stable patient, the emergency physician determines the necessity of further evaluation and diagnostic imaging.

The first task is to identify those patients at risk for significant renal injuries. Mee et al. published the classic article establishing criteria for the evaluation of blunt renal trauma. This 10-year prospective study of 1,007 consecutive blunt trauma patients established markers associated with increased risk of major renal lacerations. Gross hematuria, microscopic hematuria (>5 red blood cells [RBCs]/high power field [HPF]) with shock either in the prehospital setting or in the ED, or, less commonly, a history of significant deceleration, are associated with renal injuries. The authors concluded that if radiographic evaluation were limited to those patients, no significant renal injuries would be missed (11). These guidelines have been supported by subsequent studies and have become the criteria defining the population of patients who require further radiographic evaluation (2,3,12). While children are more prone to renal injuries than adults because the pediatric kidney is proportionally larger and has less protection from surrounding tissues, the same criteria screening used to image adult patients may be appropriately applied to pediatric patients (13,14). Most authors

advocate radiologic imaging in the setting of penetrating trauma to evaluate for upper urinary tract injuries, as a substantial percentage of patients may have significant injury in the absence of hematuria (2,3).

Computed tomography (CT) scanning is the preferred diagnostic modality for evaluating the hemodynamically stable patient with blunt or penetrating trauma. CT clearly defines parenchymal lacerations, hematomas, and the presence of urinary extravasation; may identify renal vascular injuries; and can identify associated injuries (Fig. 35.3). Significant findings on CT scan include a devitalized renal segment, a nonfunctioning kidney, actively expanding hematoma, or extravasation of urine. Nonfunction suggests extensive trauma to the kidney, renal artery thrombosis, or a severely shattered kidney. Extravasation of contrast material implies trauma involving the capsule, parenchyma, or collecting system.

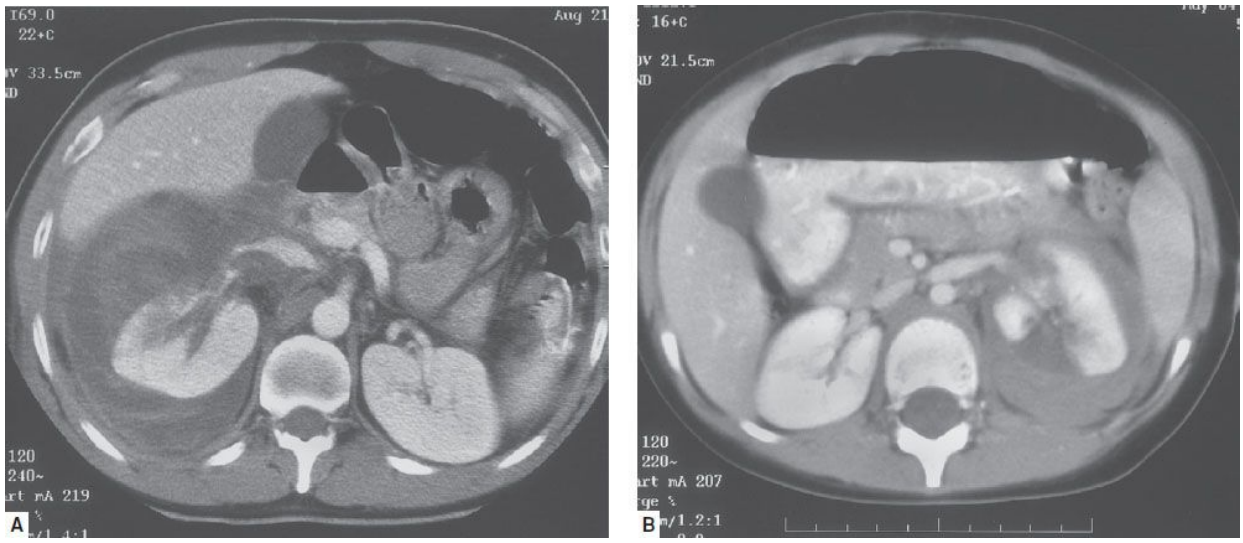

FIGURE 35.3 Renal lacerations with perirenal hematoma.

Arteriography has a very limited role in the evaluation of renal injuries and is reserved for stable patients requiring further clarification of pedicle injuries. Arteriography may demonstrate intimal tears and complete or partial disruption of the renal vasculature. CT findings requiring further evaluation by

arteriography include large perirenal hematomas, major renal fractures, or segmental areas of nonenhancement. Nonenhancement of the kidney on CT scan is diagnostic of renal artery thrombosis and is sufficient indication for surgery without additional studies (15).

Ureteral injury remains a diagnostic challenge. Approximately one-third of ureteral injuries are not identified on initial evaluation. If a ureteral injury is suspected, a contrast enhanced helical CT with delayed images should be obtained. Extravasation of contrast visualized on the delayed images may be the only sign of ureteral injury (Fig. 35.4).

FIGURE 35.4 Delayed CT image demonstrating extravasation of contrast diagnostic of ureteral disruption following blunt trauma.

Lower Tract Injury and External Genitalia Injury

Lower tract GU injuries should be evaluated in a retrograde fashion. Once the potential for injury has been identified based on mechanism of injury, physical findings (i.e., scrotal hematoma, blood at the urethral meatus, or a high-riding prostate), or radiographic

evidence of associated high-risk injuries (i.e., pelvic fracture), the urethra should be evaluated first. The presence of urethral injury should be ruled out prior to Foley catheter placement, because catheter placement may potentially convert a partial urethral tear to a complete urethral disruption. A retrograde urethrogram (RUG) is the diagnostic modality for evaluating the urethra. However, many trauma patients may require urgent CT scan for the evaluation of multiple injuries. The performance of the RUG and subsequent Foley catheter placement can often be delayed until after more urgent CT scans are performed. High resolution CT scan may demonstrate signs of urethral trauma, typically extravasation of urinary contrast material, but is not adequately sensitive to rule out a urethral injury or to fully evaluate or characterize specific injuries.

A RUG is performed with the patient supine. An initial KUB (kidneys, urethers, bladder) is obtained for comparison. A Foley catheter is then passed approximately 1 to 2 cm to the fossa navicularis, and the balloon is inflated with 1 to 2 mL of saline. Alternatively a 60-cc Toomey syringe with a Christmas tree or Cooke adapter may be gently inserted until snug. Lateral traction is applied to the penis, and 60 mL of water-soluble contrast material is injected over 30 to 60 seconds. The radiograph is exposed as the last 10 mL of contrast material is injected. Extravasation of contrast material or failure of contrast material to reach the bladder is diagnostic of urethral injury, mandates urologic consultation, and precludes the passage of a urethral catheter by the emergency physician (Fig. 35.5).

FIGURE 35.5 Retrograde urethrogram with partial tear of membranous urethra.

If a team member inadvertently places a urinary catheter prior to adequate evaluation for urethral injury, *it should not be removed.* It is not necessary to remove the catheter to perform a RUG. Instead, the presence or absence of urethral injury should be determined by passing a small feeding tube beside the catheter and performing a modified RUG.

A diagnostic workup for bladder injury is indicated for patients with gross hematuria, inability to void, or a pelvic ring fracture in association with microscopic hematuria. After exclusion of urethral injury and placement of catheter, a CT cystogram may be performed. Importantly, while a routine CT scan of the abdomen and pelvis may demonstrate evidence of a bladder injury, it is not sufficient to fully exclude these injuries. A CT cystogram is performed after retrograde instillation of 400 mL of dye through a Foley catheter into the bladder to cause bladder distension. CT cystogram is 95% sensitive and 100% specific for the detection of bladder rupture (16).

Clinical examination of the scrotum after blunt trauma is often difficult because of severe pain and swelling. If there is a clinical suspicion of a testicular injury, further evaluation with a CT scan should be performed. Any patient with significant external genitalia trauma with hematuria, urinary retention, or pain with urination should have a RUG to evaluate for a urethral tear.

KEY TESTING

- Hemodynamically stable patients with any of the following require a contrast enhanced CT scan for upper tract injury:
  - Penetrating trauma
  - Blunt trauma with gross hematuria
  - Blunt trauma with microscopic hematuria and hemodynamic instability (hypotension or tachycardia)
  - High-energy deceleration mechanism or suspected associated intra-abdominal injuries
- Patients with any of the following signs require imaging to assess for a lower tract injury:
  - Indications for a RUG:
    - High-riding prostate
    - Gross hematuria
    - Blood at the meatus
    - Trauma to the external genitalia
  - Indications for a CT cystogram:
    - Gross hematuria
    - Inability to void

Pelvic ring fracture
Lower abdominal pain following significant trauma

ED MANAGEMENT

Upper Tract Injury

The principles of care for the patient with multisystem trauma apply to the patient with trauma to the upper GU tract. Hemodynamic stabilization with crystalloid and blood products is the initial priority. Once immediately life-threatening injuries are addressed, evaluation of the GU tract and associated injuries can occur as outlined in the previous section.

In a review of more than 2,500 trauma patients, Santucci et al. (17) demonstrated a very strong correlation between AAST renal injury grade and the subsequent need for surgical intervention. In general, the majority of blunt renal trauma may be successfully managed nonoperatively. Expectant management of grade I, II, and III renal injuries is widespread. In many centers, hemodynamically stable patients with grade IV and potentially grade V injuries are also initially managed with a trial of expectant management. Overall injury severity, renal grade, hemodynamic instability, and transfusion requirements are predictors of subsequent nephrectomy (18). CT scan findings that predict need for operative intervention include extravasation of contract, a perirenal hematoma greater than 3.5 cm, and a medial location of the renal laceration (6). Delayed interventions may be necessary in a subset of patients managed nonoperatively who develop complications, including persistent bleeding, formation of urinoma, or persistent urine leak. As expected, these complications are more common in patients with higher grade injuries. Patients with the combination of a devitalized renal segment and extravasation of urine on the initial CT scan are particularly at risk. Most complications can be managed by either endoscopic or percutaneous techniques (19). Following traumatic nephrectomy or conservative management of high grade lesions, the majority of patients will have full recovery of their renal function and a normalization of their creatinine (20).

The management of penetrating upper tract trauma has evolved in recent years. There is a lower threshold for operative exploration and intervention after penetrating trauma, but many of these injuries are now managed nonoperatively as well. According to the EAST Practice Guidelines, nonoperative treatment of penetrating renal lacerations is appropriate in hemodynamically stable patients without associated injuries who have been staged completely with CT scan (12). Expectant management of stab wounds is more widely accepted, although small series of successful nonoperative management of renal gunshot wounds have also been published. Delayed bleeding can be seen in up to 20% of patients following nonoperative management of renal stab wounds, particularly when the patient increases activity. This bleeding may be managed by therapeutic angiography and rarely requires intervention (19). Figure 35.6 outlines a potential algorithm for the conservative management of renal injuries. Ureteral injuries and injuries to the renal pelvis are repaired surgically or stented. Renovascular injuries are typically managed with an immediate nephrectomy or they are repaired primarily.

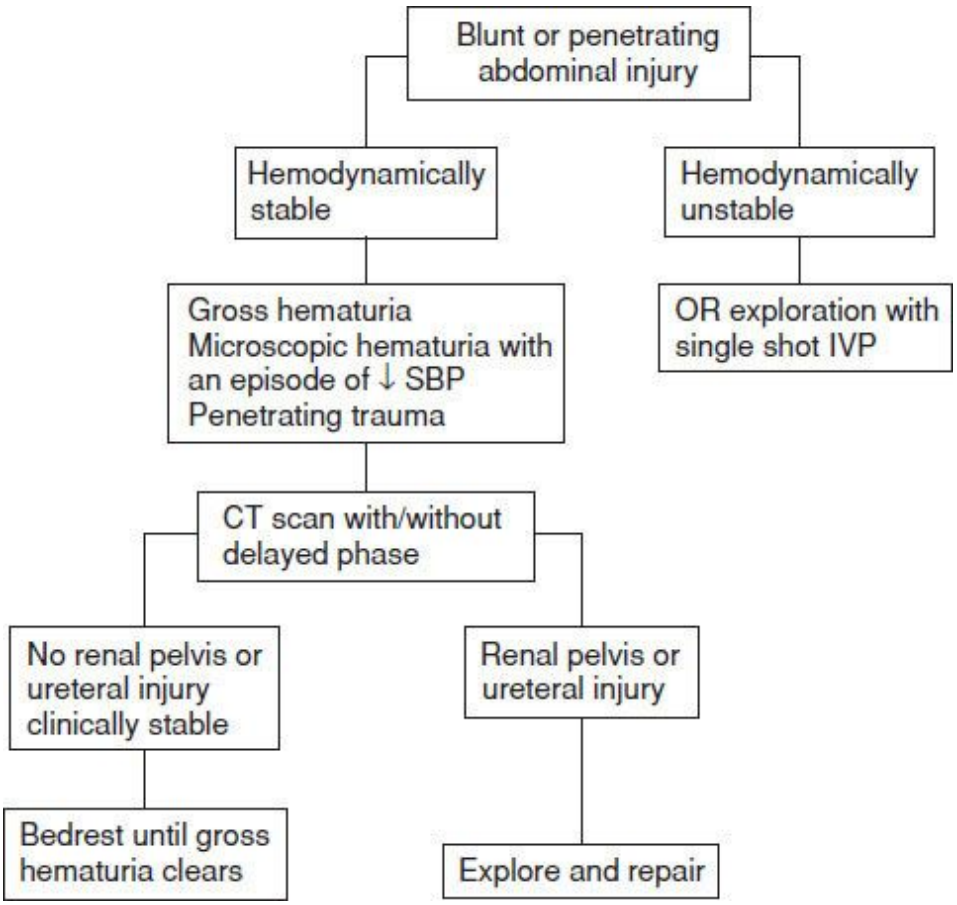

FIGURE 35.6 Algorithm for the management of renal parenchymal injuries. (Adapted from Santucci RA, Fisher MB. The literature increasingly supports expectant (conservative) management of renal trauma—a systematic review. J Trauma. 2005;59: 493–503.)

Lower Tract Injuries

If a urethral disruption is identified, urologic consultation should be obtained and a suprapubic tube should be placed to allow drainage of the bladder. This may be performed in the resuscitation bay if the patient is stable. If the patient is unstable and requires operative intervention for associated injuries, it can be performed in the operating room. If a catheter was placed prior to identifying the injury, it should be left in place. Occasionally, a catheter may be placed through a partial urethral tear. Once the partial disruption is

identified, however, any gentle and limited attempts at urethral catheterization should be done by a urologist.

The acute management of bladder rupture is bladder drainage via Foley catheter. Patients with intraperitoneal bladder rupture undergo primary surgical repair. Those patients with extraperitoneal bladder rupture are typically managed nonoperatively, with simple urinary drainage by Foley catheter or a suprapubic catheter. In general, in the absence of urethral injury, a transurethral catheter is preferred over a suprapubic catheter as it is associated with fewer complications and days of catheterization (12).

External Genitalia Injury

Diagnosis of testicular rupture or dislocation should prompt urgent urologic consultation, as surgical repair within 72 hours dramatically improves the salvage rate.

There have been several reported cases of microvascular reimplantation following amputation of the penis. Successful repair depends on the condition of the severed part and the ischemia time. In the prehospital and emergency setting, the amputated penis should be preserved in a manner similar to that for other amputated parts. Prompt urologic and microvascular consultation is imperative for successful reimplantation (21). Penetrating trauma to the external genitalia mandates early surgical exploration and conservative debridement; this is followed by primary repair in most cases (22). Some authors have also advocated operative repair of penile fractures, proposing that it decreases the incidence of erectile deformity and may speed recovery (9). For patients with penile zipper entrapment, Nolan and associates described the successful atraumatic removal by cutting the median bar of the zipper with bone cutters. The upper and lower shields of the zipper device separate, releasing the skin with minimal injury (23). Penile incarceration may be managed by the string technique, similar to that described for removal of rings from fingers.

CRITICAL INTERVENTIONS

- Address immediately life-threatening injuries first. If the patient is hemodynamically unstable, evaluation of the GU system can be performed after operative intervention for other injuries (e.g., intraperitoneal injuries).
- Rule out a urethral injury by clinical examination, and RUG if necessary, before placement of a Foley catheter.
- Obtain an urgent urology consultation if testicular disruption is diagnosed.

DISPOSITION

The majority of patients with blunt renal injuries require admission to the hospital. Selected patients with microscopic hematuria in the absence of any hemodynamic instability, and no associated injuries, may be discharged with a follow-up repeat urinalysis in 1 week to ensure resolution. All patients with penetrating renal or ureteral trauma require admission or transfer to a facility capable of providing definitive diagnostic and therapeutic care. Disposition following trauma to the external genitalia depends on the complexity and severity of the injury as well as any associated injuries. Many of these patients will require a urology consultation in the ED or close outpatient urology follow-up.

Common Pitfalls

- Failing to consider upper tract injury in the absence of hematuria. Patients with renal pedicle injury resulting from a deceleration mechanism, or ureteral injury resulting from penetrating trauma, may not have hematuria.
- Delaying an urgent laparotomy to perform further diagnostic imaging of the GU tract.
- Ruling out significant injury following penetrating trauma to the flank based on a suboptimal local wound exploration. If the wound is in anatomic proximity to the GU tract, the patient requires further diagnostic evaluation.
- Failure to obtain a RUG prior to attempting to place a Foley catheter in the presence of a potential urethral injury.

- Attempting to rule out bladder injury with routine abdominal CT without adequate distension of the bladder (i.e., instillation of 400 mL of contrast).

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CHAPTER 36

Peripheral Vascular Injuries

Maria E. Moreira and Peter T. Pons

Prompt recognition and management of peripheral vascular injuries is crucial to limb salvage and preservation of function. A vascular injury should be suspected in any patient with a penetrating injury or a major fracture or dislocation secondary to blunt trauma. Penetrating trauma accounts for approximately 85% of vascular injuries in the United States; blunt trauma and iatrogenic causes are responsible for the rest.

Blunt trauma can cause spasm, external compression, mural contusion, intimal tear, thrombosis, or aneurysm formation. A high index of suspicion is necessary in these cases as injury can be very subtle in presentation. Stretching, tearing, or shearing forces can damage a vessel while leaving very little external injuries. The classic example is dislocation of the knee with associated popliteal artery injury in which there are very few visual clues to indicate vascular injury.

In penetrating trauma, the penetrating object can directly injure vascular structures when traversing the path of a vessel. Injuries can include partial or complete vessel transection, contusion, laceration, or arteriovenous fistula. The most commonly involved vessels are the brachial and axillary arteries in the upper extremity and the femoral and popliteal arteries in the lower extremity.

The emergency physician must obtain a complete history, perform a careful physical examination, and be aware of the mechanics that

produce vascular injury, even if there are minimal or absent physical findings that suggest vessel damage.

CLINICAL PRESENTATION

Evaluation of extremity pulses distal to the injury is essential to the identification of vascular injuries. The following pulse findings are indicative of a vascular injury: diminished or absent pulses, thrill or bruit suggestive of an arteriovenous fistula, a pulsatile mass or rapidly expanding hematoma. Other etiologies for the pulse difference, such as shock should also be considered. Pulse differences due to shock should correct with resuscitation. The examiner must consider that the presence of a pulse does not completely exclude a vascular injury. Collateral circulation or transmitted pressure waves through a small clot or intimal flap can produce a distal pulse.

A Doppler can be used to further assess quality of pulses. The three levels of Doppler signal are monophasic, biphasic, and triphasic. Triphasic is the normal signal in an intact vessel. Changes in the signal can provide an indication of vascular compromise. When a triphasic signal changes to a monophasic signal the provider needs to consider loss of flow. This signal is evaluated in conjunction with other physical examination evidence of perfusion (1).

Determining the arterial pressure index (API) is an important adjunct to the physical examination. A Doppler is used to determine the systolic blood pressure distal to the penetrating injury. The systolic pressure is then measured in the same location in the contralateral uninjured extremity. The ratio of the injured to the uninjured extremity is the API. A normal API is greater than or equal to 0.9. A ratio of less than 0.9 is indicative of a vascular injury and necessitates further evaluation (1–3). The sensitivity and specificity of API of less than 0.9 is 87% and 97%, respectively. In one study when insignificant injuries were excluded the sensitivity of API less than 0.9 increased to 95% (4).

Ankle-brachial index (ABI) is often considered synonymous with API. The ABI is calculated as follows: systolic blood pressure at dorsalis pedis or posterior tibialis divided by the brachial systolic blood pressure. An ABI less than 0.9 is considered abnormal.

Typically, ABI has been used in the diagnosis of peripheral vascular disease, although it is not uncommonly used for trauma patients as well. In a patient with underlying peripheral vascular disease obtaining both an ABI and an API may be useful in identifying a new injury due to trauma.

The other "P"s of arterial compromise leading to ischemia include pallor, pain, poikilothermia, paresthesias, and paralysis. Additional findings may include tenseness of the extremity, coolness to touch, and delayed capillary refill (>3 seconds). Unfortunately, some of these signs require a patient who can relate these complaints, and many multiply injured patients cannot. In addition, concomitant neurologic injury of the extremity may present with similar findings. Careful examination is necessary to differentiate the paresthesias of vascular insufficiency from those of neurologic injury. As many as 70% of upper- and 30% of lower-extremity vascular injuries have associated nerve damage, of which 40% to 45% result in permanent deficit.

Many vascular injuries appear relatively innocuous at first glance. Penetrating wounds of an extremity can present with a small entrance site that harbors significant underlying vascular damage. Blunt injury may be quite misleading because of minimal obvious external signs. Thus, repeat examination of the patient is important to look for evolving signs of vascular injury.

Finally, the structural integrity of the skeletal system must be evaluated. About 18% of patients with peripheral vascular injuries have an associated fracture from either blunt or penetrating trauma.

ED EVALUATION

Initial physical examination findings will dictate further evaluation. Patients with hard signs of vascular injury (Fig. 36.1) require immediate intervention. Hard signs include absent pulses, active hemorrhage, rapidly expanding hematoma, and palpable thrill/bruit. In such cases, operative intervention should not be delayed for other diagnostic studies or radiographic imaging, unless the location of the vessel injury cannot be determined clinically (5). In the absence of hard signs in a hemodynamically stable patient, further evaluation

can be undertaken. Patients with an API <0.9 require further testing. Those with soft signs of injury (diminished pulses, large nonexpanding hematoma, peripheral nerve injury, or delayed capillary refill) and proximity wounds can be followed with serial physical examinations, tracking the API (3,6–9). Color-flow duplex Doppler ultrasonography can also be used to assess patients with soft signs (10–12). Color-flow duplex Doppler ultrasonography interprets the sound of blood flow and shows it as red and blue colors based on the speed and direction of the flow relative to the ultrasound probe. This sonographic technique will easily demonstrate absence of arterial flow but is less valuable for more subtle injuries such as intimal flaps or pseudoaneurysms that may not interrupt blood flow in the damaged vessel (10).

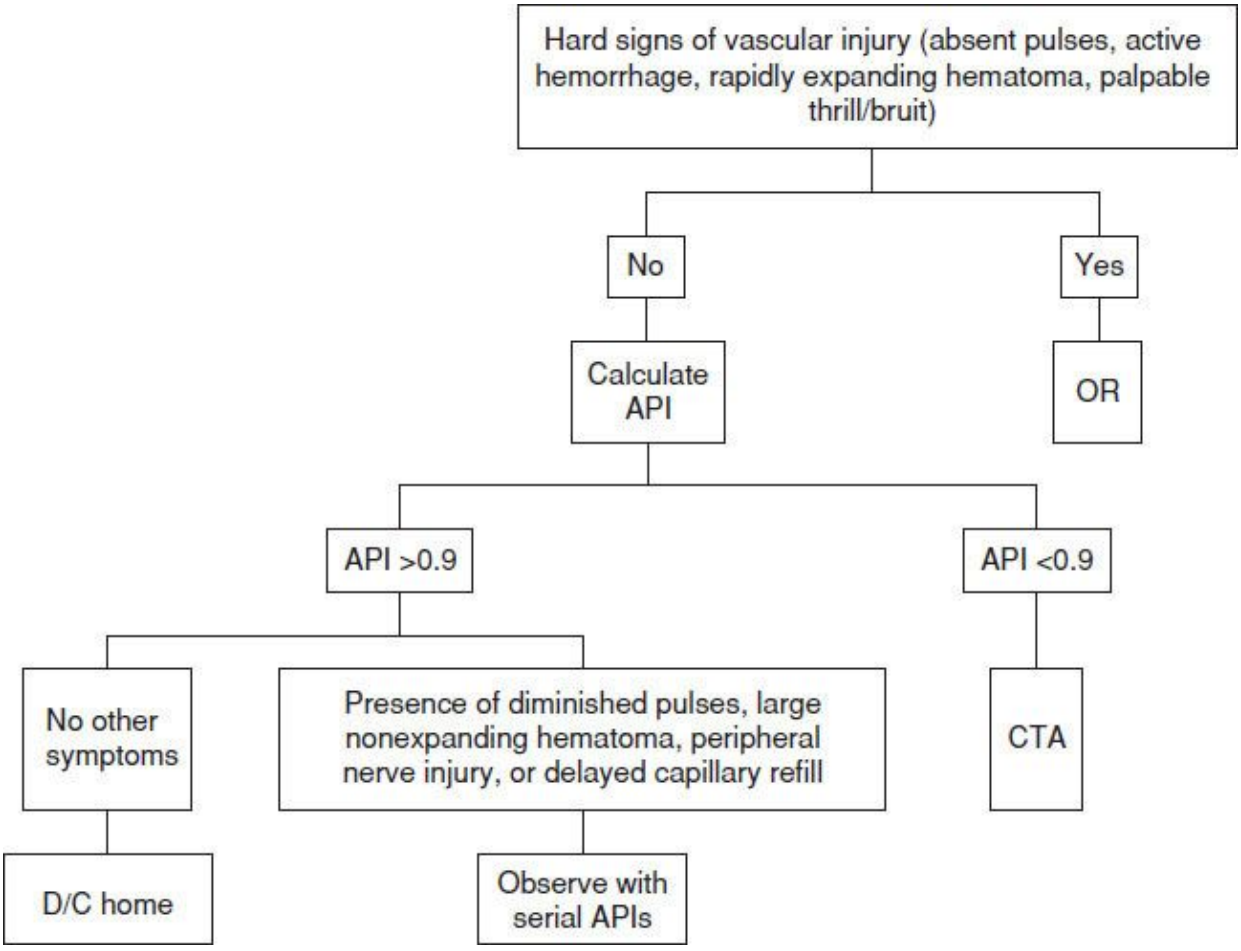

FIGURE 36.1 Peripheral vascular injury clinical algorithm.

The mainstay of evaluation and diagnosis has been contrast arteriography, with a sensitivity of 97% to 99% for detecting arterial injury. Magnetic resonance angiography (MRA) and spiral computed tomographic angiography are other options for evaluating vascular injuries (13–18). CTA is currently the preferred study for initial evaluation of the vasculature due to its ready availability and use of only intravenous contrast. Several studies demonstrated CTA to have a 100% sensitivity and specificity for detecting clinically significant arterial injuries (4,19,20).

Shotgun wounds to an extremity have a much higher incidence of vascular injury owing to the nature of the weapon (i.e., multiple missiles and multiple trajectories) (12). In addition, victims of blast injury, high-velocity weapons, and military munitions have a higher incidence of vascular injury (21). Therefore, angiography is indicated in these patients unless the physical examination, including API, suggests that the potential for vascular injury is remote. If angiography is not performed, a period of observation is warranted.

Each institution should determine in advance how it plans to evaluate patients with potential peripheral vascular trauma by having protocols in place agreed upon by the emergency medicine, surgery, and radiology departments.

KEY TESTING

- Determine the arterial pressure index (API)
- CTA should be performed in patients with API <0.9
- Patients with soft signs can be followed by serial examinations monitoring the API

ED MANAGEMENT

Prehospital and emergency department (ED) management priorities include control of hemorrhage, fluid resuscitation, and assessment and management of other life threats (9).

Hemorrhage should be controlled by direct pressure over the bleeding site. Blind clamping of bleeding vessels deep in a wound is to be condemned, as adjacent structures such as nerves and tendons

may be crushed in the attempt to stop hemorrhage. If a bleeding vessel can be identified and isolated, it may be clamped using a noncrushing vascular clamp. Recent work in animals and experience in the conflicts in Iraq and Afghanistan suggest that hemostatic agents may be of benefit in controlling exsanguinating hemorrhage secondary to proximal vascular injury such as femoral artery or vein injury in the groin (22). If compression or hemostatic agents are unsuccessful at stopping the bleeding, tourniquets can be used as a temporizing method (3). The key is to minimize the tourniquet time.

Fluid restoration is accomplished by initiating one or more intravenous lines (as the trauma mechanism and vital signs dictate) and infusing crystalloid. After bleeding is controlled and resuscitation started, a careful examination for other life-threatening injuries is performed. As with all trauma patients, a patent airway and adequate ventilation must be ensured while circulation is being addressed. Vascular injuries are treated after other potential life threats have been assessed and managed.

Angulated fractures associated with pulse deficits should be anatomically repositioned and splinted. This may restore perfusion to an ischemic extremity by alleviating kinking of the blood vessel.

Blood for type and crossmatch should be sent to the laboratory and appropriate preparations made for transfusion if blood loss or anticipated surgical needs indicate. Unless indications for immediate surgery are present, complete evaluation for possible vascular injury should follow.

Tetanus immunization status should be ascertained and the patient immunized, if necessary. Prophylactic antibiotics are indicated when operative repair or vascular grafts are to be undertaken and if there is an open fracture. Anticoagulants should generally not be given until surgical consultation has been obtained, the absence of other major injuries has been determined, and the patient is ready to undergo arterial repair.

CRITICAL INTERVENTIONS

- Control hemorrhage by using direct pressure over the bleeding site.

- Resuscitate with crystalloid infusion and blood when indicated.
- After bleeding is controlled, perform a general examination for other life-threatening injuries.
- Measure the arterial pressure index in all patients with penetrating extremity trauma.
- Reduce angulated fractures associated with pulse deficits immediately.

DISPOSITION

Surgical consultation must be obtained as early as possible, as the amount of time elapsed from injury until operative repair is a crucial determinant of successful repair and decreased morbidity in the ischemic extremity. Endovascular embolization may be an option for treatment of nonessential vessels in select situations. Endovascular stent placement is an alternative to surgery for the treatment of vascular injuries and is gaining increasing acceptance and use (23). Observation for a period of 12 to 24 hours is appropriate for vascular proximity wounds in patients without obvious signs of vessel injury and a normal API. In fact, one study suggests that asymptomatic patients with an API ≥ 1 may be safely discharged from the ED (24). In addition, clinically occult arterial injuries have been shown to have a benign course. Therefore, patients meeting the following criteria are candidates for observation: <5-mm intimal disruption, adherent intimal flaps, intact distal circulation, and no active hemorrhage (6,9). The medical team taking care of the patient will need to make the assessment of whether operative repair versus amputation is the optimum treatment for the patient given other potential injuries (25).

Common Pitfalls

- Failure to realize that vascular injuries may be subtle in origin and misleading on physical examination.
- Failure to appreciate injury mechanics or vessel proximity to a penetrating wound.

- Failure to recognize that delays in diagnosis of vascular compromise may lead to permanent deficit or loss of the limb.
- Blind clamping of bleeding vessels deep in a wound.

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PART 3 • ORTHOPAEDIC TRAUMA

CHAPTER 37

Approach to Musculoskeletal Injuries

Andrew D. Perron and Carl A. Germann

Musculoskeletal injury has been cited as the second most common reason for emergency department (ED) visits in the United States (1). In addition, missed fracture has been cited as a common reason for medical malpractice lawsuits against emergency physicians (2). A coherent and systematic approach to the assessment and management of patients with orthopedic injuries and other musculoskeletal complaints is essential (3). Musculoskeletal injuries range from minor (tendinosis, sprains, strains, and contusions) to potentially life- and limb-threatening trauma (pelvis fracture, femur fracture, knee dislocation). Most of the time, acute trauma is responsible for the presenting complaints, and usually the primary impairment is an inability to move a part of the body owing to pain or discomfort. The mechanisms of trauma include sports injuries, assaults, motor vehicle collisions, falls in the home, and industrial catastrophes. When acute trauma is absent, overuse syndromes or repetitive movements are often the culprits.

The immediate tasks of the emergency physician evaluating a patient with a musculoskeletal complaint include the following:

- Accurately determining those injuries that need only symptomatic care and distinguishing them from ones that require more complex, timely specialist intervention.
- Differentiating injuries that can be handled solely by an emergency physician (the vast majority of musculoskeletal injuries) from those that require emergent consultation or

timely referral to an orthopedic surgeon (e.g., open fractures, compartment syndrome, growth plate injuries, and flexor tendon injuries).

- Formulating a logical, cost-effective algorithm for the diagnosis and management of each patient.
- Realizing the limitations of diagnostic modalities and the potential for "missed" injuries.
- Aggressively managing the pain associated with these injuries early and effectively, recognizing that "a mere sprain or contusion" can be the source of exquisite pain. Also paying particular attention to analgesia in those patients at the extremes of age (very young and very old), where it has been shown that oligoanalgesia is the rule, rather than the exception.
- Recognizing that care for many musculoskeletal injuries is not complete when emergency care has been delivered. Successful management of the patient is complete only when appropriate follow-up has been arranged, as a large percentage of acute musculoskeletal injuries require reevaluation and ongoing care (e.g., physical therapy and rehabilitation) for optimal recovery.

CLINICAL PRESENTATION

Sprains

A sprain is a ligamentous injury. Ligaments link bone to bone. Damage to the fibers of the ligament ranges from microscopic damage to complete disruption. A sprain can result from an abnormal (nonbiomechanical) force vector applied to a joint, an excessive force applied along a normal vector, or a combination of the two mechanisms. It is possible to sustain a sprain that is significantly more severe than an analogous fracture. For example, a complete lateral ankle ligament rupture and a transverse avulsion fracture of the distal fibula cause the same pattern of instability. However, because bone regenerates without scarring, the outcome for the latter injury can be significantly better.

The grading of sprains is based on the severity of the damage, recognizing that with an acute injury there may be too much pain

and spasm to accurately determine the grade of the sprain.

Grade I Sprain

A grade I sprain (in older terminology, “first-degree”) represents microscopic tears of the ligament, which lead to localized hemorrhage and inflammation as the healing process evolves. Active range of motion is usually preserved but painful. Abnormal movement of the joint stabilized by the sprained ligament is not elicited by stress maneuvers, but these maneuvers may produce focal pain, and the area overlying the sprained ligament is tender to palpation.

Grade II Sprain

In a grade II sprain (“second-degree”) or partial tear, the overall macroarchitecture of the ligament is preserved, with the majority of fibers still in continuity, but clearly some of them have been completely ruptured. Hemorrhage is more extensive, and swelling is often pronounced. Loss of function secondary to decreased and painful range of motion is the hallmark. When the joint that the ligament stabilizes is stressed, there may be some gapping of the joint or abnormal motion. However, with a grade II sprain, any abnormal laxity is limited, and frank instability does not occur.

Grade III Sprain

A grade III sprain (“third-degree”) denotes a complete tear of the ligament and is synonymous with a complete rupture. Hemorrhage is more extensive, and healing involves the formation of scar tissue in the area between the torn fragments of the ligament. Stressing the joint reveals greater gapping than in the case of a grade II sprain, and frank instability without a well-defined end point may be elicited. This frank instability can be summed up by the examiner’s thought, “I should stop stressing this joint, as it isn’t going to resist my efforts.” This is tempered by the knowledge that with acute injury, the physical examination may be severely limited owing to acute pain and muscular spasm.

Common ligament sprains seen in the ED include lateral ankle sprains, injuries to the anterior cruciate and collateral ligaments of

the knee, and ligamentous injuries of the shoulder, associated with either glenohumeral dislocations or acromioclavicular separations.

The clinical signs of a sprain typically include point tenderness to palpation, swelling, painful or decreased range of motion, and ecchymosis. With a complete (grade III) sprain, with no fibers in continuity, the joint may be completely pain free when stressed. Often, athletes will continue to play after a grade III sprain of the medial collateral ligament of the knee, but it is rare that they continue activities after a grade II sprain. In fact, pain may be inversely proportional to the severity of the injury. A grade I sprain is extremely painful when stressed, as there are many intact but damaged and inflamed fibers that will be stretched, triggering the discharge of pain fibers as the ligament is loaded with force. With a grade III sprain, the same maneuver does not cause any stretching of the ligament, as it cannot be loaded by force, and the only pain fibers triggered by the stress maneuver will lie in surrounding soft tissue. Bone can be injured at the same time as a ligament is damaged. For example, grade III sprains of the medial, deltoid ligament of the ankle are often accompanied by fibula fractures. Bony evidence of sprains on x-ray may include small avulsion fractures at the point of insertion of the ligament into the bone, impaction injuries, or joint space widening.

Strains

Tendons connect muscles to bone. A strain is an injury to this musculotendinous unit, which can range from mild “pulled muscles” to complete tendon ruptures. The mechanisms of injury are twofold: (a) Stretching a muscle beyond its normal range of motion by forced extension (“overstretching injury”) and (b) tearing of muscle or tendon fibers by a violent, uncontrolled contraction or repetitive, prolonged contractions, often in attempted compensation for an unexpected change in direction of movement, unanticipated variations in terrain, or a sudden force applied to the antagonist muscle group.

Strains are graded from first-degree to third-degree, reflecting the severity of damage:

- In a first-degree strain, microscopic damage occurs to the musculotendinous unit, with associated localized hemorrhage, inflammation, and tenderness to palpation. Active range of motion is often unrestricted, but pain can be elicited by resisted contraction or forced extension of the muscle group.
- A second-degree strain involves more severe damage, with rupture of some fibers of the muscle or tendon. Hemorrhage is usually visible, swelling more severe, and range of motion limited by pain.
- In a third-degree strain, the muscle or tendon is completely ruptured. The rupture can occur in the muscle belly, at the musculotendinous junction, within the tendon itself, or at the point of insertion of the tendon into bone.

Common strains seen in the ED include those to the quadriceps, hamstring, rotator cuff, thigh adductor (groin), and Achilles tendons.

The clinical signs of a strain include pain, ecchymosis, edema, and decreased or painful range of motion. With complete disruption of the muscle or tendon, a palpable defect is often present. Physical examination should include inspection of the injured area, observation of active and passive range of motion, palpation of the affected area, and provocative maneuvers (either resisted contraction or passive stretching) to elicit the location and extent of injury. In addition, with certain suspected injuries, specific tests should be performed. For example, if an Achilles tendon rupture is suspected, then a Thompson test is performed. While the patient lies prone with the knee flexed at 90 degrees, the examiner squeezes the calf on the affected side and observes whether the foot plantar flexes. The presence of plantar flexion indicates an Achilles tendon that is at least partially intact. Absent plantar flexion often represents complete Achilles tendon rupture.

Contusions

A contusion is a bruise caused by a direct blow to a body part. Contusions can occur to bone, with significant pain from periosteal bruising and bone edema, or, more commonly, to soft tissue, especially fat and muscle. In these crush injuries, the degree of injury is proportional to the force of the blow and the surface area of impact. Tissue damage occurs as the energy transmitted by the impact dissipates into or is absorbed by surrounding structures.

The diagnosis of contusion is one of exclusion, with fracture, dislocation, sprain, and strain being the most important diagnoses that must be ruled out. Common contusions seen in the ED include bruised quadriceps muscles, rib cage contusions, contusions of the ulnar aspect of the forearm in "defensive maneuvers" during an assault, and direct blows to the anterior tibia.

Either the blow itself or the body's reaction to it causes signs and symptoms that prompt the patient to seek emergency care. Typically, they include pain, swelling, ecchymosis, and decreased range of motion of the affected part.

Usually, the entities that are ruled out (e.g., fracture, dislocation, sprain, and strain) are potentially more serious than the diagnosis of contusion itself. However, the clinician must remember that contusions can lead to serious complications, including severe pain, rhabdomyolysis, compartment syndrome, and *myositis ossificans.*

One of the most common reasons that patients seek reevaluation in an emergency room is inadequate analgesia following a soft tissue injury. Initial attention to adequate analgesia ensures patient comfort and decreases the need for reevaluation. A number of studies have confirmed that physicians notoriously undertreat painful conditions (4–6). This is particularly true in both the pediatric and geriatric patient populations.

Severe muscle breakdown can occur after strenuous exercise without an acute, isolated injury or after a significant contusion to a muscle body. *Rhabdomyolysis* results from the destruction of myocyte cell membrane integrity. The subsequent release of intracellular contents, including potassium, myoglobin, uric acid, phosphate, and the enzyme creatine kinase, into the bloodstream can result in a number of systemic complications, including

metabolic abnormalities and acute renal failure. The emergency physician must assess the extent of tissue involvement, the degree of tissue destruction, and the potential for systemic complications. If rhabdomyolysis is suspected, urinalysis should be performed to look for evidence of myoglobinuria (dipstick positive for blood without microscopic evidence of erythrocytes), and the serum creatine kinase level should be checked (see Chapter 213, "Rhabdomyolysis" for details).

Compartment syndrome occurs when pressure within soft tissues in a fixed body compartment increases to the point at which it compromises venous blood flow and limits capillary perfusion. This leads to muscle ischemia and necrosis. Most commonly associated with long bone fractures, it can occur in the setting of severe contusion, crush injury, or excessive exertion and must be considered in any patient with pain out of proportion to physical findings or with swelling causing obvious tautness in a nonexpansible compartment, such as the anterior tibial compartment. When this diagnosis is considered, it must be objectively ruled out by manometry (see Chapter 48, "Acute Compartment Syndrome," for details).

Severe hemorrhage into a muscle can initiate a cascade of "healing," which can lead to the formation of ectopic bone within the muscle, or *myositis ossificans.* A large number of these cases have occurred in athletes treated with early, aggressive nonsteroidal anti-inflammatory drugs (NSAIDs), heat, massage, and physical therapy in the hope of facilitating early return to athletic competition.

This is of concern to the emergency physician for a number of reasons. If severe quadriceps tear and resultant hemorrhage and ecchymosis are suspected, the initial management should include ice, a brief period (24 hours) of immobilization in a stretched position (knee flexed to 120 degrees for severe quadriceps contusion), and acetaminophen, instead of NSAIDs, for pain control (7). This regimen limits the ongoing bleeding and inflammation in the area. These patients must be referred for appropriate long-term follow-up care. In addition, a decreased range of motion, ongoing pain, and a mass or firmness in soft tissue weeks to months after

sustaining a contusion should suggest the possibility of *myositis ossificans,* as noted above. A soft tissue x-ray is the best way to evaluate for heterotopic bony formation. If heterotopic bone is present, the patient should be referred to an orthopedic surgeon for close follow-up care and potential resection of the bone when it has matured (usually at 9 to 12 months).

Fractures

Most fractures require urgent medical attention. Without appropriate emergency care, many will not heal properly or healing will be accompanied by unnecessary complications. A *fracture* is defined as a partial or complete break in a bone. Bone is unique in that it is the only tissue in the human body, other than the liver, that heals by regeneration, not by scarring (8–10). For regeneration to occur, however, the bone must be immobilized to allow uninterrupted formation of new bone. Ensuring appropriate immobilization is one of the fundamental tasks of the emergency physician when dealing with musculoskeletal problems.

The process of new bone formation begins with hematoma bridging the realigned fracture fragments. Hematopoietic cells in the hematoma secrete growth factors, which stimulate the formation of granulation tissue at the fracture ends, resulting in slow resorption of the hematoma. Over the next several weeks, a primary callus is formed, beginning as a soft callus and progressing to a hard callus. The final phase of healing is remodeling, during which the bone reassumes its original architecture as it is exposed to the normal stresses of weight bearing and movement (9,10).

Fractures also require immediate attention for several other reasons. Virtually all fractures are painful. The vast majority of fractures result from high-energy trauma (relative to sprains, strains, and contusions) and, because of force vectors, are accompanied by well-known associated injuries (e.g., 15% of calcaneal fractures sustained in a fall from height have associated lumbar vertebral fractures). In addition, many fractures place the patient at risk for specific complications (e.g., compartment syndrome in long bone

fractures, blood loss in pelvic fractures, avascular necrosis [AVN] in scaphoid fractures of the hand, fat embolism with femur fracture).

A working knowledge of the nomenclature of fractures is essential to the successful management of fractures in the ED and to ensure clear communication with radiologists and consulting orthopedic surgeons. Adequate description of a fracture includes the bone(s) involved, whether it is open or closed, the location and direction of the fracture within the bone, the number of fragments, the alignment of the fracture fragments, the displacement of the fragments, and notation of associated complications (e.g., compartment syndrome, neurologic or vascular deficits).

The description of the injury should include the side of the body, the specific bone, and the location within the bone. By convention, long bones are divided into proximal, middle, and distal thirds, and these divisions are used to describe the fracture location. Alternatively, long bone injuries can be described as diaphyseal (shaft), metaphyseal (flared ends), or epiphyseal (rounded ends). If the fracture lies at the junction of any two-thirds of the bone, it should be described as such. Fractures in children deserve special mention. In this group, fractures occur frequently through the physis (growth plate), as this is the weakest point in the bone or investing soft tissue. Fractures to the physis can disrupt future bone growth if not recognized and adequately treated. These injuries are described with the Salter–Harris classification system (Fig. 37.1).

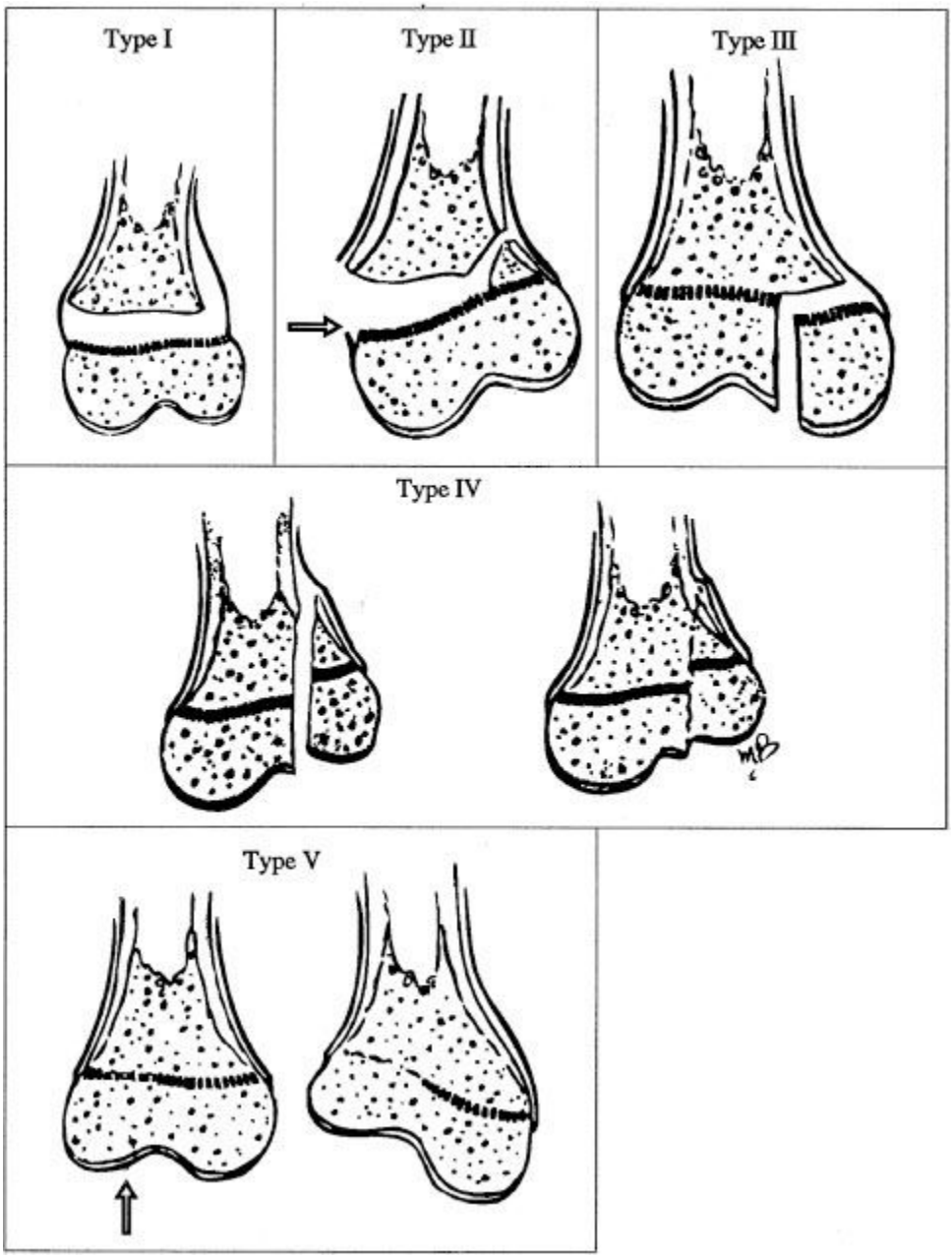


FIGURE 37.1 Salter–Harris fracture classification. (From Rang M. The growth plate and its diseases. In: Rockwood CA Jr, Wilkins KE, King RE, eds. Fractures in Children. 3rd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1991:128, with permission.)

Closed Versus Open Fractures

The old terminology of *simple* (closed) and *compound* (open) fractures should be abandoned, as "simple" linear fractures may be open, and comminuted fractures may be closed. In a closed fracture,

the skin and soft tissue overlying the fracture have not been violated. Therefore, no communication exists between the outside environment and the fracture fragments. Any break in the skin overlying a fracture must be considered an open fracture until proven otherwise. It is frequently difficult to tell whether there has been actual communication between the bone and the environment or whether the patient has simply sustained an abrasion to the skin overlying the fracture.

Open fractures are traditionally classified into three types based on the size of the wound and the amount of soft tissue injury. *Type I* wounds are <1 cm long, the energy dissipated by the mechanism of injury is low, and there is minimal soft tissue trauma. *Type II* wounds are <10 cm long, the mechanism of injury has dissipated a low or moderate amount of energy, and there is moderate soft tissue trauma but no gross contamination of the wound, major crush injury, or soft tissue defects or flaps. *Type III* wounds are >10 cm long. These include high-velocity gunshot wounds, close-range shotgun wounds, open fractures with major vascular injuries, fractures more than 8 hours old, or open fractures sustained in environments where exposure to fecal contents is a concern (e.g., open pelvic fractures with perineal exposure), or extensive soft tissue or periosteal stripping of bone, or evidence of gross contamination or significant crush injury (11).

Open fractures are orthopedic emergencies. These injuries frequently require immediate control of hemorrhage, which can usually be accomplished with appropriate splinting. In addition, open fractures may require emergent reduction if neurovascular compromise exists. Principles of care include irrigation, early administration of sufficient analgesia and appropriate antibiotics, tetanus prophylaxis, and emergent consultation with orthopedic surgery for definitive irrigation, debridement, reduction, and fracture repair in the operating room. Appropriate early intervention is the best way to prevent future complications, as the incidence of infection following open fracture is directly proportional to the time from injury to definitive irrigation and debridement.

Direction and Description of Fractures

The *direction* of a fracture refers to the configuration of the fracture—the way the fracture disrupts the bone. By convention, this descriptive modifier communicates the direction of the fracture in relation to the long axis of the involved bone (Fig. 37.2). A *transverse* fracture disrupts the bone perpendicular to its long axis; an *oblique* fracture lies at an angle to the long axis of the bone; a *spiral* fracture results from a rotational force and spirals around the center of the long axis of the bone. Given the relative flexibility of their bones, children may present with a *greenstick* fracture, or a partial fracture of the cortex with deformity of the intact bone.

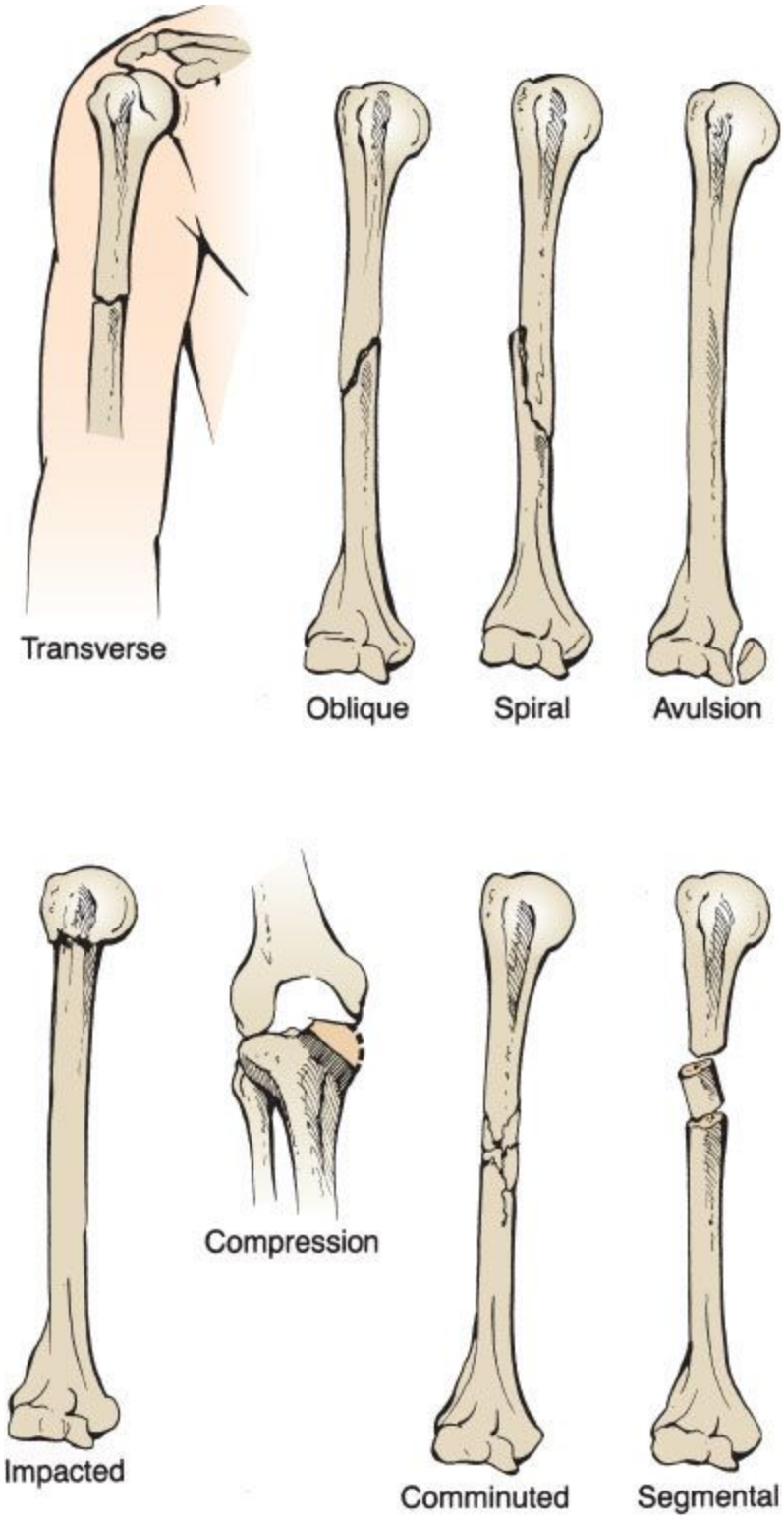


FIGURE 37.2 Fracture configuration.

Additional terms are used to describe the configuration of a fracture. A c*omminuted* fracture has three or more fragments. *Segmental* refers to the presence of two or more fractures in a bone, creating at least one segment of bone that is not connected to either end of the bone. An *avulsion fracture* occurs when a piece of bone is pulled off at the site of insertion of a tendon or ligament. Avulsion fractures are usually the result of traction injuries. Their presence indicates potential instability at the joint, which is caused by the loss of stabilization normally provided by the avulsed ligament or tendon. An *impacted* fracture occurs when the fractured surfaces of the bone are forced into each other, foreshortening the bone. On computed tomography (CT) scan, impacted fractures are often comminuted with numerous small fragments wedging across the main fracture line. *Compression* refers to a fracture in which the trabeculae of the bone are compressed, decreasing the overall volume of the affected part of the bone.

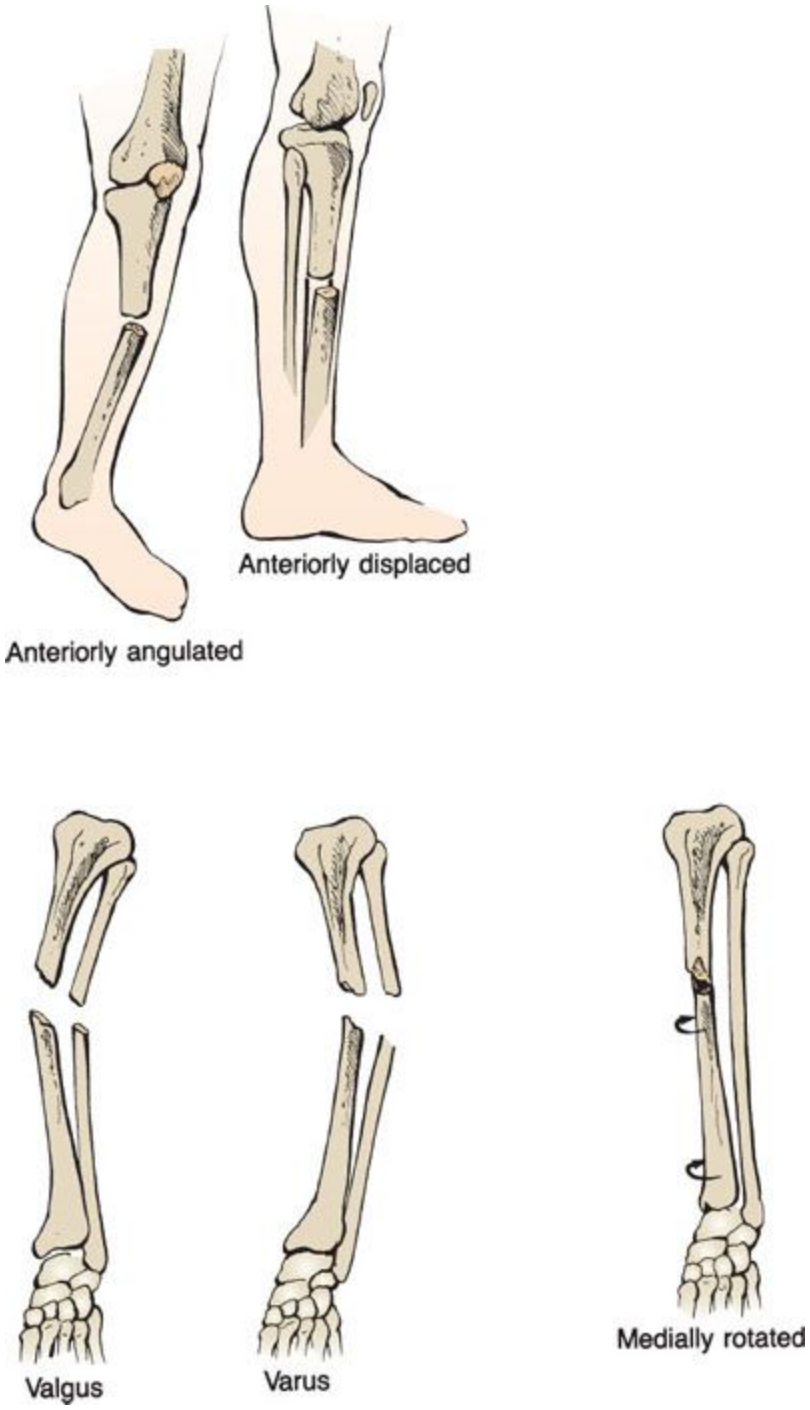
Fracture Alignment

A fracture is also described in terms of its alignment—the relationship of the fracture fragments to each other. The fracture may be *displaced, angulated,* or *rotated.*

A fracture is *displaced* if the fragments are offset in a transverse or longitudinal plane. The position of the distal fragment in relation to the proximal fragment is described. The distal fragment may be displaced in an anterior, posterior, medial, lateral, radial, ulnar, proximal, or distal direction. The amount of displacement is commonly measured in terms of the width of the fractured shaft, using fractions of the width in the description.

A fracture is *angulated* if there is a deviation from the normal relationship of the bony fragments along the longitudinal axis of the bone (eFig. 37.1). The direction of angulation may be expressed in two ways. It may be described in terms of the direction of the apex of the angle formed at the fracture site by the two main fracture fragments. The apex may point in an anterior, posterior, lateral, or medial direction. The direction of the apex may also be described by other adjectives, including ulnar, radial, dorsal, or volar, depending

on the involved bones. A second way to describe the angulation of the fracture is in terms of the relation of the distal fragment to the proximal fragment. If the distal fragment is angled away from the midline of the body, there is *valgus* angulation (the fracture is in valgus). If the distal fragment angles toward the midline, there is *varus* angulation to the distal fragment (the fracture is in varus).



eFIGURE 37.1 Fracture alignment.

Rotation refers to twisting of the distal fragment in relation to the proximal fragment around the center of the long axis of the fractured bone. When viewed along the long axis of the bone from the most distal point on the bone, if the distal fracture fragment has

rotated toward the midline in relation to the proximal fragment, it is *medially rotated;* if it has rotated away from the midline, it is *laterally rotated.*

Other Descriptive Modifiers

An *incomplete* fracture involves only one cortex of the bone; a *complete* fracture disrupts both cortices. A *pathologic* fracture occurs in an area of abnormal bone, weakened by disease or prior trauma, and is often the result of apparently trivial trauma or a biomechanically routine force applied along a natural vector. Pathologic fractures may occur at sites of old fractures, through primary osteosarcomas, at sites of tumor metastases, near cysts, and in bone weakened by Paget disease, rickets, osteomalacia, tuberculosis, osteomyelitis, chronic steroid therapy, obesity, anorexia, and many other disease processes. A *stress* fracture is the result of the bony cortex becoming fatigued by repeated low-level loading rather than disrupted by one acute episode of trauma. The repeated stress to the cortex causes bone resorption and may result in overt fracture if adequate healing is not allowed. Clinically, patients have pain with activity and tenderness to palpation over the affected bone. Eating disorders and amenorrhea predispose to stress fractures in female athletes. Stress fractures are most common in the proximal tibia but have also been described in the spine, pelvis, femur, ribs, tarsal navicular, and metatarsal bones, among other sites (12).

COMPLICATIONS OF FRACTURES

No assessment and description of a fracture is complete without a thorough assessment for, and identification of, possible associated complications (eTable 37.1). Well-recognized complications of fractures are suggested by the site of the fracture and the mechanism of injury.

TABLE 37.1
Orthopedic Emergencies

Vascular injuries
Compartment syndrome
Open fractures
Open joints
Dislocated hip
Dislocated joint with vascular compromise or threat to skin integrity

eTABLE 37.1
Complication of Fractures and Dislocations

Vascular injuries ischemic necrosis
Nerve injuries delayed union
Compartment syndrome nonunion
Infection malunion
Shock joint stiffness
Cast-induced injuries posttraumatic arthritis
DVT
Fat embolism
Complex regional pain syndrome

DVT, deep vein thrombosis.

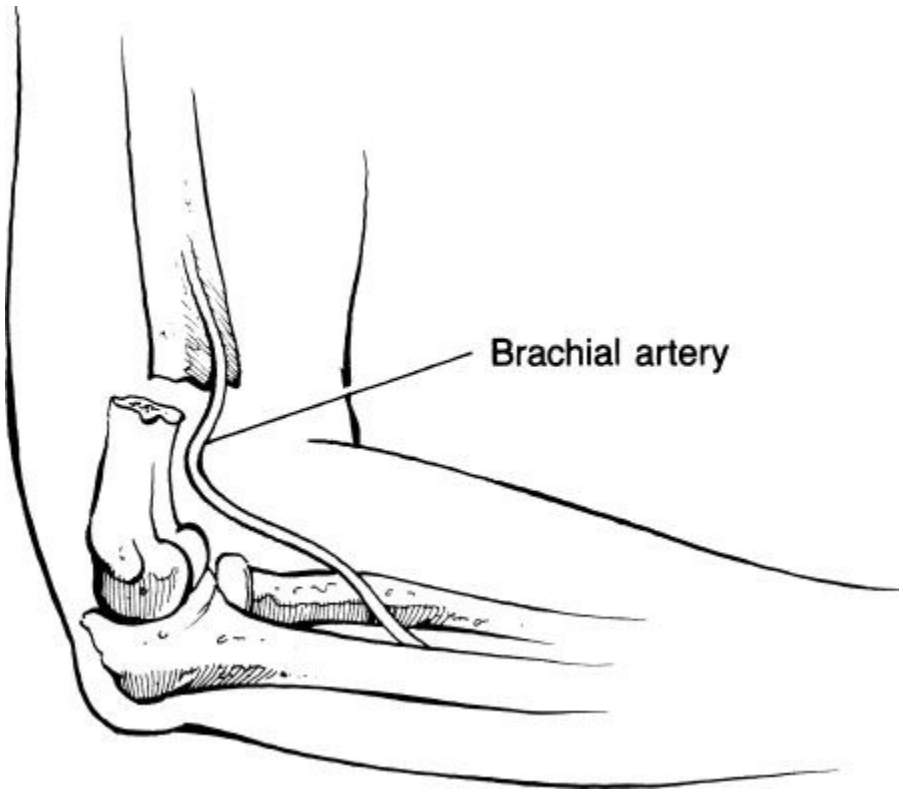
Blood Loss and Shock

Bone has a generous blood supply, and fractures can disrupt the blood vessels, causing localized bleeding. If this bleeding results in the loss of a significant percentage of the patient's blood volume, hypovolemic shock can result. Rarely, exsanguination occurs. An isolated long bone fracture is rarely the cause of shock, with a unilateral tibia and fibula fracture typically resulting in loss of approximately 500 mL of blood. Certain femur fractures can result in the loss of 3 or 4 units of blood into the thigh, with subsequent development of shock. Hemorrhagic shock can occur with pelvic fractures, in which typical blood loss is between 1,500 and 3,000 mL (10). If a bleeding disorder such as hemophilia A, thrombocytopenia, or marked anemia is present, a fracture that typically results in modest blood loss may be the source of life-

threatening hemorrhage. This is also true in patients on anticoagulation therapy. In these patients, isolated long bone fractures may require administration of vitamin K, fresh frozen plasma, and transfusion of packed red blood cells.

Vascular Injuries

Vascular injuries occur most commonly in open fractures, widely displaced fractures, or fracture-dislocations and at sites where the vessels lie close to the bone or are held in a relatively fixed position. Vulnerable sites include the popliteal artery at the knee, which may be injured in supracondylar fractures of the distal femur or in fracture-dislocations of the knee; the axillary artery at the shoulder, injured in fractures of the proximal humerus and humeral head; and the brachial artery at the elbow, which is at risk in supracondylar fractures of the distal humerus (eFig. 37.2). Even at the most vulnerable sites, these injuries are rare, but if they are not diagnosed in a timely fashion, the consequences can be devastating.



eFIGURE 37.2 Fracture-associated vascular injury.

The classic signs of vascular injury are the "Five *P*s": Pain, pallor, pulselessness (or diminished pulse), paresthesia, and paralysis. The Five *P*s are present only in a complete injury to the vessel. A partial injury can have subtle clinical signs and symptoms or be completely asymptomatic. In addition, collateral circulation may maintain distal flow around a vascular injury. Vascular compromise may also be delayed, as in the case of an initial vascular intimal injury leading to progressive thrombosis. Therefore, the location of the fracture and the mechanism of injury determine the need to assess for a potential vascular injury in the asymptomatic patient. Initial evaluation should involve assessment of pulses, evaluation with a Doppler stethoscope if palpable pulses are diminished or absent, observation of the color of the distal extremity, and assessment of capillary refill. With extremity injuries, this assessment should be compared to that of the opposite limb. The ankle-brachial index may be assessed to help evaluate patients where there is concern after the foregoing examination. The systolic pulse is assessed in the brachial artery and in the dorsalis pedis artery in the foot with a Doppler stethoscope. The ratio of the pressure in the ankle is then compared to that in the arm. A ratio of >0.9 is reassuring, although it does not completely rule out partial arterial injury (13,14).

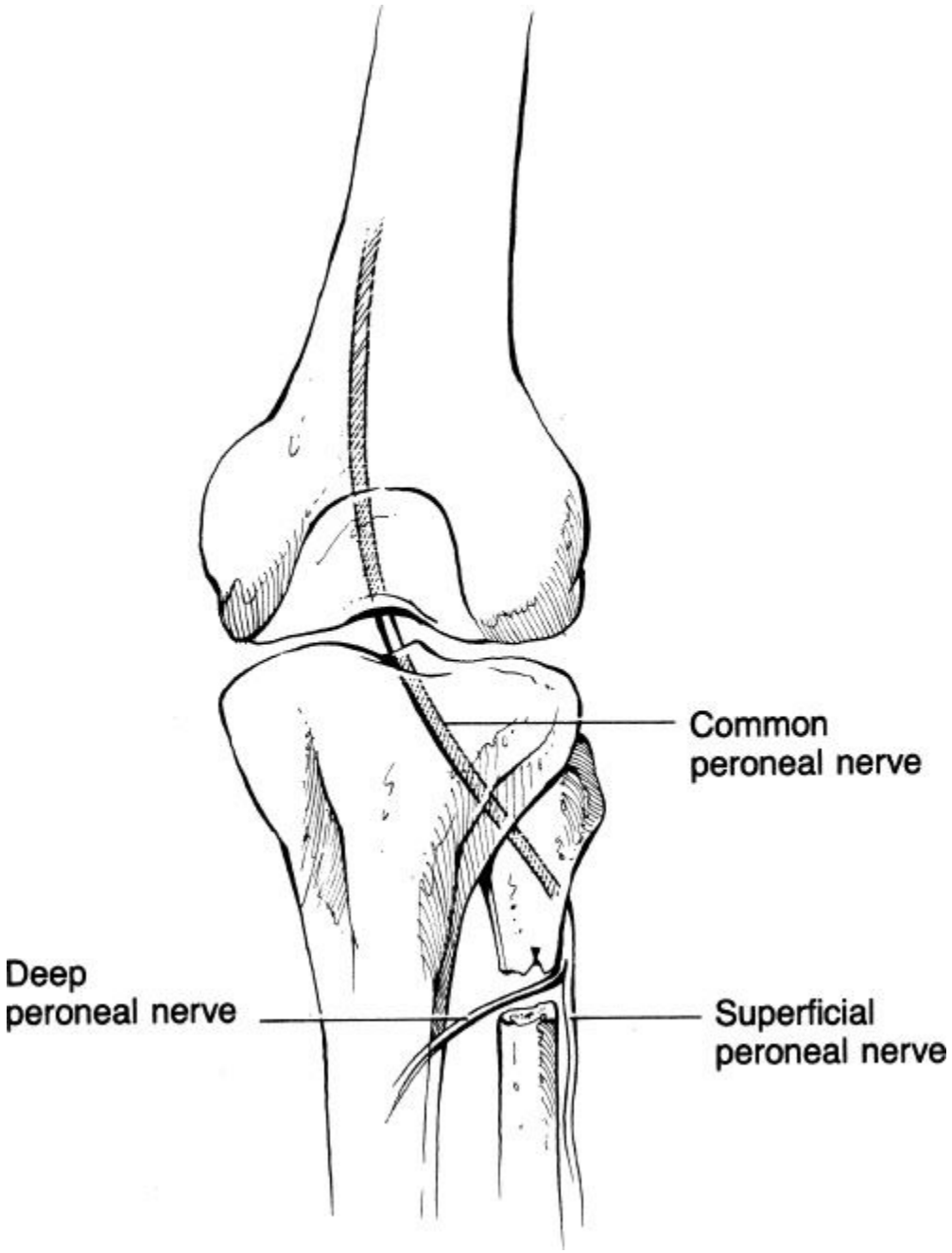
If vascular injury is suspected, further evaluation with angiogram, CT angiogram, color-flow Doppler ultrasound, magnetic resonance angiography, or surgical exploration is usually warranted. Complications of fracture-associated vascular injuries include in situ thrombosis, false aneurysms, true aneurysms, compartment syndrome, arteriovenous fistulas, and distal limb ischemia with mechanical dysfunction.

Nerve Injuries

Nerves are more frequently injured than vessels in association with fractures. They can be damaged by blunt trauma, along the trajectory of penetrating trauma causing an associated fracture, or by the fracture fragments themselves. Nerves are at increased risk of

injury when they are superficial, lie close to the bone, or span the joint, making them susceptible to stretch injury.

The most frequently injured nerves in association with specific fractures include the axillary and musculocutaneous nerves in shoulder fracture-dislocations; the radial nerve in fractures of the distal third of the humerus; the radial, median, and ulnar nerves in supracondylar elbow fractures; the median nerve in fracture-dislocations about the wrist; the peroneal and tibial nerves in knee fracture-dislocations; and the peroneal nerve in fractures of the fibular head or proximal fibula (eFig. 37.3).



eFIGURE 37.3 Peroneal injury associated with a knee fracture.

Nerve injuries are classified based on the amount of damage to the nerve according to Seddon staging system:

- *Neuropraxia:* The least severe injury, neuropraxia involves a contusion to the nerve, with minor injury to the myelin sheath. Sensory loss and transient paralysis may occur, but spontaneous

and complete recovery occurs over a period of several days to weeks (occasionally, a few months).

- *Axonotmesis:* In axonotmesis, more severe crush injury to the nerve occurs with axonal breakdown followed by distal wallerian degeneration. The epineurium and the continuity of Schwann tubes are maintained. Prolonged paresthesias and muscle weakness are the clinical hallmarks. Recovery can be complete but takes months to years. The axon has to regenerate proximally to distally and, for functional conduction to occur, the myelin sheath must be fully repaired. Recovery is often incomplete.
- *Neurotmesis:* The most severe form of nerve damage is neurotmesis disruption of the axon, epineurium, and Schwann cell sheath (complete severance of the nerve). When complete disruption occurs, all functions controlled by the injured nerve are interrupted.

The emergency evaluation of a nerve injury should involve assessment of motor strength, deep tendon reflexes, light touch, and two-point discrimination. Formal testing can be performed using electromyogram; however, this is not necessary in the ED.

Compartment Syndrome

Compartment syndrome (fully discussed in Chapter 48) should be suspected in long bone fractures and fractures associated with significant vascular injuries or pronounced swelling, especially when the patient has pain out of proportion to physical examination findings or paresthesias. Manometry should be performed if compartment syndrome is suspected, as the clinical signs are variable and may be delayed. Compartment syndrome is a surgical emergency and requires prompt decompression to prevent or minimize the associated morbidity.

Infection

Infections occur primarily in open fractures, especially in those in which there is a delay in treatment. The general rule in open

fractures is that they need “urgent” irrigation and debridement in the OR. Though 6 hours was historically cited as the cutoff time for this urgent procedure, recent literature has questioned this time frame. Although the exact amount of time is debated, most authors agree that “sooner is better” for this procedure (15). Infection can also occur with extensive hematoma or after open reduction internal fixation repair. It may also occur without a fracture in cases of osteomyelitis, septic arthritis, and abscesses eroding to bone. Septic arthritis should be suspected in the patient with monoarticular arthritis and ruled out in those who present with a swollen, erythematous, hot joint. If the diagnosis is in question, aspiration for crystal analysis, Gram stain, cell count, and culture should be performed. Most orthopedic surgeons recommend aggressive arthroscopic lavage to prevent destruction of the joint space by bacteria and inflammatory-mediated damage.

Casts and Splints

Immobilization devices have the potential to cause postinjury problems. They may become too tight as swelling increases during the first 24 to 48 hours after injury and cause pain and impair circulation. Pressure sores may occur on the skin in areas where a cast or external fixation device exerts localized excessive pressure (e.g., over the heel in a patient with a bimalleolar fracture). Immediate steps should be taken to correct the problem. A cast that is too tight can be split lengthwise; the underlying padding can then be cut and the cast spread open. A cast that is pressing on a particular site can have a window cutout. The window may be replaced more loosely with plaster or covered with soft dressing. An ill-fitting splint can be trimmed. The clinician should take great care in the selection of the appropriate splint (type and material), its placement (to make sure that it has adequate padding and effectively immobilizes the intended joint), and perform a postsplinting examination to ensure neurovascular integrity.

Fat Emboli Syndrome

Single or multiple long bone fractures in the young and hip fractures in the elderly predispose to fat emboli. Twenty percent of patients with pelvic or long bone fractures have detectable fat droplets in their blood. However, the clinical significance of this is not clear, as the vast majority of these patients remain asymptomatic. Fat emboli syndrome is the most common form of nonthrombotic embolism and has a characteristic clinical course. Its etiology is unclear, but three main hypotheses have been postulated: (a) After fat droplets enter the bloodstream, the liberation of free fatty acids from marrow fat by circulating lipase causes a toxic vasculitis and capillary leak syndrome; (b) it is the end result of extensive platelet–fibrin thrombosis; and (c) it results from direct obstruction of distal vascular lumen by fat emboli. After the injury, the patient often remains asymptomatic for 12 to 36 hours before suddenly and unexpectedly developing a life-threatening syndrome that is characterized by rapid cardiopulmonary and neurologic deterioration. Patients develop agitation, hallucinations, delirium, coma, hypoxia, dyspnea, tachypnea, tachycardia, and a petechial rash. If this deterioration is not quickly reversed, refractory hypotension, anemia, thrombocytopenia, disseminated intravascular coagulopathy, and adult respiratory distress syndrome often ensue, with an associated high morbidity and mortality.

Ischemic or Avascular Necrosis

Ischemic or AVN is characterized by bone death that occurs following the interruption of blood supply to bone. AVN is most frequently associated with carpal scaphoid fractures, lunate dislocations, hip dislocations, femoral neck fractures, and complex fractures of the talus. The time required for an injury to result in AVN is extremely variable and is location and patient specific.

Delayed Complications

Other complications of fractures may occur some time after the initial injury. Many fractures require reduction of the displaced fracture fragments in the ED or the operating room. The goal in

reduction is always to reestablish anatomic position; eliminate displacement, angulation, and other forms of malalignment; and immobilize the broken bone in the reestablished anatomic position to promote healing. Sometimes, this ideal condition is not achieved, and the systematic progression from hematoma to callus formation to bony union is delayed or interrupted. *Delayed unions* are fractures that take longer than usual to heal; *malunions* are fractures that heal in a faulty position; and *nonunions* occur when the process of fracture healing stops before the fracture is united.

Joint stiffness, posttraumatic arthritis, and *complex regional pain syndrome* (CRPS)—type I (formerly known as reflex sympathetic dystrophy [RSD])—may also occur as delayed complications of extremity trauma. Any intra-articular fracture of a weight-bearing joint predisposes the patient to early degenerative changes. The patient may present to the ED years after a fracture, complaining of *perceived* sudden onset of joint pain and decreased range of motion. Radiographs typically demonstrate extensive *osteoarthritis.*

CRPS is a three-stage, posttraumatic syndrome of unclear etiology, the development of which has no known correlation to the severity of the initial injury (16). CRPS remains a clinical diagnosis with symptoms that are often difficult to differentiate from normal posttraumatic characteristics. The first, or early, stage characterized by continuous burning and aching in the posttraumatic extremity, is exacerbated by weightbearing and by movement. After a variable period of time, the middle, or dystrophic, stage ensues, characterized by the development of shiny, cool skin over the affected extremity and a progressively decreased range of motion. In the final, or atrophic, stage, the skin atrophies, the muscles atrophy, and flexion contractures develop.

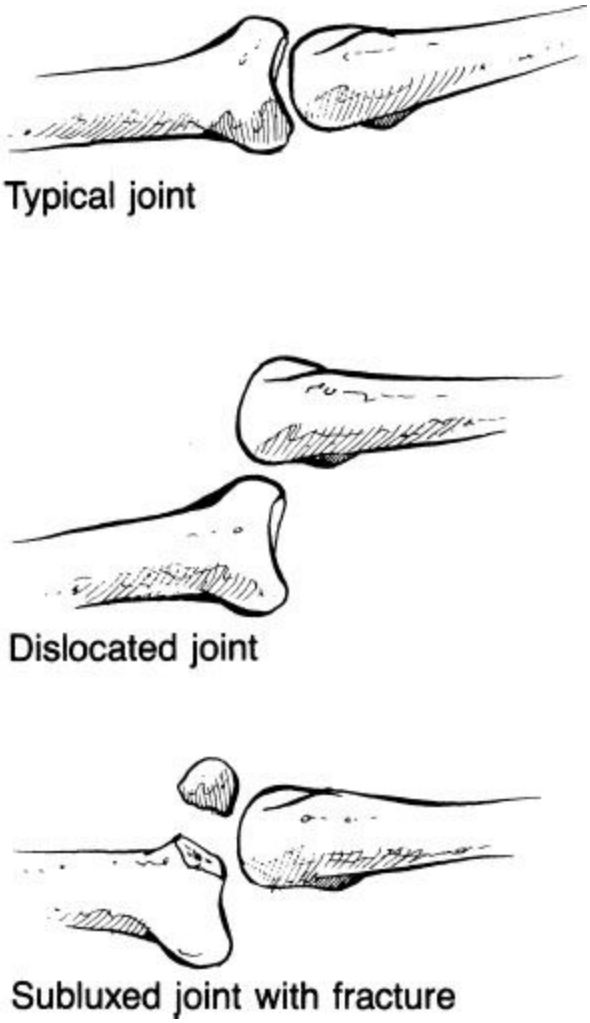
In 1992, Gibbons and Wilson, in the *Clinical Journal of Pain,* developed an RSD score that was proposed as a strict system for the clinical diagnosis of RSD. The scoring system consists of nine criteria and has more than academic interest. Early diagnosis and subsequent early treatment may potentially improve outcome, interrupting the progression from burning to dystrophy to atrophy. The nine criteria are (a) allodynia—the phenomenon whereby pain

is increased by stimuli that activate the involved nerve, such as a breeze blowing on the area, temperature changes, or emotional outbursts (hyperpathia); (b) burning pain; (c) edema; (d) change in color or hair growth in the affected area; (e) change in sweating; (f) change in temperature; (g) demineralization of bone in the involved limb, as documented in radiographs; (h) quantitative measurements of vasomotor disturbances; and (i) a triple-phase bone scan consistent with RSD. A score of five points qualifies as a clinical diagnosis of RSD; one point is given for each positive criterion, zero points for each negative criterion, and one-half point for each equivocal criterion. Application of heat or cold, exercises, early sympathetic blockade, or sympathectomy to the affected limb can halt the progression to atrophy. A minority of patients have been helped by a short course of high-dose prednisone (a 3-week taper) in conjunction with heat, cold, and exercise therapy (17).

Subluxations and Dislocations

Acute or chronic ligamentous laxity or tearing can result in subluxation or dislocation of a joint. Chronic ligamentous laxity is usually the result of an overuse syndrome, in which repetitive microtrauma leads to an attenuation of the static restraints of the joint. Acute ligamentous tears are the result of excessive or abnormal forces applied to the joint. The classic example is subluxation or dislocation of the glenohumeral joint. *Subluxation* occurs when one bone becomes partially disarticulated from the other bone that forms the joint. The articular surfaces forming the joint remain partially intact. *Dislocation* occurs when the bones are completely disarticulated and no parts of their articular surfaces are in contact. Dislocations can occur in isolation or with an associated fracture (eFig. 37.4). Often, the fracture is anatomic evidence of the direction of the pathologic force vector resulting in the dislocation. For example, 90% to 95% of shoulder dislocations occur anteriorly, disrupting the continuity of the anterior capsule and the labrum. Sometimes, these structures resist the forces producing dislocation

to the point that a fracture occurs, avulsing a piece of bone from the anterior glenoid rim, known as a *Bankart lesion.*



eFIGURE 37.4 Joint subluxation and dislocation.

The nomenclature of subluxations and dislocations is straightforward. Most subluxations and dislocations occur at a joint formed by two bones, and the subluxation or dislocation is named after the affected joint (e.g., posterior dislocation of the distal interphalangeal [DIP] joint of the fourth finger of the right hand). If a joint is formed by three bones, and the two major bones are disarticulated, the subluxation or dislocation is named after the joint involved (e.g., posterior dislocation of the knee). If the joint is formed by three bones, and the minor bone is subluxed or

dislocated, the abnormality is named after the minor bone (e.g., lateral dislocation of the patella). As for fractures, direction is assigned with reference to the distal segment.

Specific subluxations and dislocations are frequently seen in the ED and should be skillfully and efficiently reduced, with restoration of anatomic position, by the emergency physician. These include anterior and posterior dislocations of the shoulder joint; anterior and posterior dislocations of the sternoclavicular joint; posterior dislocations of the elbow joint; posterior dislocations of the proximal interphalangeal and DIP joints, often with accompanying avulsion fractures; posterior dislocations of the hip joint; posterior dislocations of the knee joint; lateral dislocations of the patella; and fracture-dislocations of the ankle.

The hallmarks of subluxations and dislocations are pain, deformity, and decreased range of motion. Certain dislocations are associated with specific complications, and these must be ruled out in the evaluation and treatment of the injury. For example, the aorta and trachea are at risk in posterior dislocations of the sternoclavicular joint, and injury to them can lead to rapid respiratory compromise or intrathoracic hemorrhage. The axillary nerve and, less commonly, the musculocutaneous nerve are at risk in anterior shoulder dislocations. Their function must be clearly assessed prior to any attempted reduction and then reassessed after the reduction is complete. The popliteal artery can be stretched, torn, or completely disrupted in a posterior dislocation of the knee. Radiographs are often obtained prior to attempts at reduction and after the reduction has been achieved to document the position of the bones, restoration of anatomic position, and the presence of associated fractures. The need for pre- and postreduction radiographs for all types of dislocations, however, has been challenged in the literature (18,19).

Techniques for the reduction of specific joints are discussed in the chapters dedicated to those joints, but certain principles hold true for all subluxations and dislocations. The length of time between injury and relocation corresponds proportionally to the severity of spasm and swelling that will occur and the difficulty involved in

reducing the joint. Adequate pain control and muscle relaxation can facilitate smooth reduction; excess force applied during the reduction may result in fractures, nerve damage, and vascular injury. The technique used to reduce the dislocation should initially replicate the mechanism of injury to release the dislocated bone from the anatomic structure that is keeping it dislocated. In certain dislocations, the incidence of delayed complications is directly proportional to the time from injury to relocation. For example, AVN of the femoral head occurs in 10% to 20% of hip dislocations. The rate is directly proportional to the total time from injury to successful reduction. Similarly, myositis ossificans is a well-recognized complication of posterior dislocation of the elbow. The incidence of myositis ossificans is directly related to three variables: The number of attempts at reduction, the length of time from injury to successful reduction, and whether the joint is adequately immobilized after reduction.

Tendinosis

Tendinosis is a subset of strain since it is an injury to the musculotendinous unit, but it is more appropriately considered a separate entity. In the past, tendinosis was felt to represent inflammation to the musculotendinous unit, and was hence termed "*tendinitis.*" Recent work has indicated that a more correct term is *tendinosis,* as there is no significant inflammatory response by the body in these conditions (20). Instead, there is a degeneration of the collagen portion of the tendon in the absence of inflammatory cells. Tendinosis differs from strain in that the pathologic changes are *isolated* to the tendon and *involve the insertion of the tendon into the bone,* which occurs via a transitional, calcified fibrocartilage known as Sharpey fibers. Tendinopathy can result from chronic use or from one acute episode of overuse. In acute tendinopathy, the tendon is irritated, and an acute response occurs. Microscopically, there is loss of collagen continuity with an associated increase in ground substance, vascularity, and cellularity. The cellularity results from the presence of fibroblasts and myofibroblasts, not inflammatory

cells. If this cycle is not interrupted, permanent changes in the architecture of Sharpey fibers and atrophy of the tendon fibers occur.

Common tendons involved in acute or chronic tendinosis presenting to the ED include patellar, quadriceps, rotator cuff, and the Achilles tendons.

Clinically, tendinosis presents with pain during active range of motion, loss of function, point tenderness over the affected tendon near its insertion into bone and, often, localized edema and erythema. Forced contraction of the affected muscle against resistance elicits pain, which is exacerbated by pressure over the point of insertion. Pain may also be elicited by forced extension of the tendon, stretching the injured fibers.

Calcific tendinitis is an entirely different entity, representing a truly inflammatory response by the body. It is usually associated with chronic inflammation and consists of calcium deposition within the body of the tendon. It is often an indication of tendinous degeneration altering the macrostructure of the tendon. Calcific tendinitis has a characteristic radiographic appearance, revealing the calcium depositions within the tendon. For example, a band of calcification can be seen passing over the bicipital groove in calcific biceps tendinitis at the shoulder.

Muscle Spasms

Muscle spasms are a poorly understood phenomenon in which a voluntary muscle undergoes sustained involuntary contraction, leading to depletion of stored glycogen, localized buildup of lactic acid, and severe pain. The causes of muscle spasm are not known, but hypotheses include localized alterations in blood flow, regional or systemic electrolyte imbalances (especially sodium and calcium; less often, potassium), and postural abnormalities that place a bone in a nonanatomically neutral position, causing attached musculature to fire continuously. For example, overdevelopment of the muscles on one side of the body in a racquet sports athlete can cause latissimus dorsi spasm, as the proprioceptors present in the

latissimus sense that the arm is out of the neutral position, resulting in repetitive muscle contraction in attempted compensation.

Muscle spasms typically seen in the ED include spasms of the gastrocnemius, levator scapulae, trapezii, rhomboids, and latissimus dorsi. Rectus abdominus muscle spasm can mimic an acute abdomen.

Treatment may be frustrating for both the patient and the clinician, as complete relief is difficult to achieve. The treatments are not perfect, and many are controversial. Treatment options include freezing the muscle belly with fluoromethane spray, followed by passive, gentle, forced range of motion to "break the spasm"; massage; treatment with muscle relaxants, including diazepam and other benzodiazepines; and pain control with acetaminophen, NSAIDs, or opioid analgesics. Recent research indicates that treatment with muscle relaxants for these conditions may not be as good as basic analgesia (21).

ED EVALUATION

The ED evaluation of any injured patient begins with the basic ABCs: Airway, breathing, and circulation. If the patient is reliable, not intoxicated, and has an isolated injury and the mechanism of injury does not suggest other possible injuries, then evaluation and treatment are limited to the injured joint along with the joints immediately proximal and distal to the injury. The contralateral side of the injured joint or limb should be examined for comparison of range of motion, anatomy, laxity, and neurovascular findings.

In patients with multiple injuries, head trauma, amnesia, intoxication, or medical illnesses resulting in their musculoskeletal injury (e.g., a distal radial fracture after syncope), a complete physical evaluation is mandatory and should follow basic trauma guidelines. This should begin with a primary survey and assessment of the ABCs; evaluation of neurologic disability and Glasgow Coma Scale; then continue with complete exposure of the patient and a search for any accompanying injuries. Once this is complete, the emergency physician should systematically evaluate the underlying

medical problem that could have produced the trauma. If a problem is identified, it should be addressed before moving on to the next step in the systematic evaluation. For example, the motorcyclist thrown from the cycle, who presents with an open fracture of the tibia and fibula and flail chest, needs breathing stabilized before the leg is further evaluated. In extremity wounds, hemorrhage can often be rapidly but temporarily controlled with a direct-pressure dressing, ensuring continued circulatory stability until the source of bleeding can be systematically evaluated. After the primary survey, each joint should be palpated and ranged systematically, and the integrity of long bones assessed by inspection, palpation, and range of motion.

As alluded to previously, certain extremity injuries are true orthopedic emergencies, meriting expeditious evaluation and management. These include vascular injuries, compartment syndromes, open fractures and dislocations, and certain dislocated joints (Table 37.1). They should be addressed immediately after the ABCs have been evaluated, stabilized, and recorded on a trauma flow sheet. If vascular compromise is suspected, immediate consultation with an orthopedic or vascular surgeon is advised. When vascular insufficiency is caused by stretching of the vessel across the site of a dislocation or displaced fracture, reduction of the fracture or dislocation may correct the problem. Pulses should be documented after the reduction. If an injury to the vessel itself is suspected, arteriography, color Doppler ultrasound, magnetic resonance angiography, or surgical exploration may be indicated. Color Doppler ultrasound evaluation, followed by close observation with serial neurovascular examinations, is a relatively newer option and is still being validated as a modality. These decisions are usually made in consultation with a surgeon. Blood flow to an ischemic extremity should, ideally, be reestablished within 6 to 8 hours to prevent permanent injuries, including ischemia and necrosis.

Similarly, if compartment syndrome is suspected, it should be ruled out by manometry. This is usually accomplished through emergent consultation with an orthopedic surgeon. If compartment pressures are elevated, emergent fasciotomy is mandatory.

After all life- and limb-threatening injuries have been addressed, attention can be directed toward the identification of individual injuries—fractures, dislocations, sprains, strains, tendinosis, and spasm. This evaluation begins with a *thorough history* to ascertain the mechanism of injury, timing of the injury, previous injury to the limb, handedness where applicable, and medical problems potentially contributory to current disability. The history should include questions about associated symptoms of pain, paresthesia, weakness, signs of pallor, or deformity.

On physical examination, the emergency physician should note the appearance of the injury, looking for deformity, swelling, erythema, ecchymosis, and exposed bone. Other physical findings include the presence of purulent fluid drainage from the wound, abrasions, or lacerations over the injured area.

The emergency physician should palpate for deformity, local or diffuse tenderness, edema, warmth, and induration. Palpation should include a careful assessment of neurovascular integrity. Patients with vascular compromise will have dusky or mottled skin, diminished distal pulses, and delayed capillary refill. Sensation to light touch may be decreased, and hypesthesia often occurs over an area of acute injury. Active range of motion should be tested. In the majority of acute injuries, the patient is not enthusiastic about actively ranging the joint and passive range of motion, and provocative maneuvers are of limited utility due to pain.

Radiographs are the cornerstone of further evaluation and management of most musculoskeletal complaints. Many fractures can be diagnosed clinically. However, in the vast majority of cases, the diagnosis should be supported radiographically. Radiographs frequently determine the need for operative reduction, the length of time the fracture needs to be immobilized, and potential complications during the rehabilitation process. Criteria for obtaining radiographs of specific injuries are formalized but constantly evolving and are beyond the scope of this chapter. They are addressed in the chapters on injuries to specific joints. The goals of objective criteria for obtaining radiographs include reduction in unnecessary imaging, increased efficiency of patient flow in the ED,

decreased exposure to radiation, and containment of healthcare costs. For example, the Ottawa Ankle Rules are objective criteria for obtaining an ankle series after an ankle injury. They state that ankle films are required in patients older than 18 years if pain in the malleolar area is accompanied by inability to bear weight (defined as walking four steps) immediately after the injury and in the ED or by bony tenderness over the posterior aspect of the distal 6 cm of the medial or lateral malleolus. Strict implementation of the Ottawa Ankle Rules has been shown to reduce the number of ankle films ordered by 28%, increase ED efficiency, and decrease ED costs without increasing the percentage of missed fractures (22).

When the decision is made to obtain roentgenograms, the correct views must be obtained, they need to be of sufficient quality to competently evaluate for fracture, and they need to be read thoroughly, in a systematic fashion. Poor-quality films should not be accepted. Many fractures have been missed because of technically inadequate films. In addition, thorough examination of the soft tissue and every bone in the x-ray is essential to avoid missing subtle findings that may indicate fracture or dislocation. For example, the fat pad sign on an elbow x-ray may be the sole indication of a radial head fracture.

Other pitfalls in radiographic interpretation include the following:

- A nutrient foramen, housing a nutrient artery, may be misinterpreted as a fracture. A nutrient foramen will appear less radiolucent than a fracture (very smooth-edged) and will angle obliquely from the edge of the bone through the cortex, and then terminate without involving the cortex on the other side of the marrow.
- Sesamoid bones or accessory ossicles may be confused with fractures. These anatomic variants usually have smooth edges and are well corticated, and no defect in the adjacent bone will be noted. In some instances, a comparison view of the unaffected side can help clarify the structure in question. For example, the patient with pain over the patella following a dashboard injury, who is found to have a two-part patella on x-

ray, may have bipartite patella, which is confirmed by its presence on an x-ray of the unaffected knee.

- Fat and clothing folds, casts, or splints may be misinterpreted as fractures, and jewelry or body piercings may be misinterpreted as foreign bodies.

Every x-ray series should include a minimum of two views that are *taken at right angles to each other.* If the plane of the fracture is at 90 degrees (perpendicular) to the plane of the x-ray beam, the fracture may not be evident on that view but would be readily visible on an x-ray taken in a plane parallel to the plane of the fracture line.

Fractures in the shaft of long bones are often accompanied by additional fractures in that bone proximal or distal to the main fracture site or by dislocations at the joints at either end of the bone. Therefore, all long bone shaft fractures require imaging of the entire length of the bone, including adequate views of its joints. For example, a midshaft femur fracture requires x-rays of the entire shaft, a two-plane knee series, and a two-plane hip series.

Fractures to paired long bones, such as the radius and ulna or the tibia and fibula, may present with different associated fractures. In other words, a fracture to one bone is sometimes accompanied by a distant fracture to the other bone in the pair. For example, medial malleolar ankle fractures resulting from a lateral twisting mechanism sometimes have an associated proximal fibular or fibular head fracture or dislocation. The mechanism of injury explains this association: The twisting force that breaks the medial malleolus is transmitted up the shafts of the tibia and fibula and is dissipated at the weakest point, the proximal fibula, resulting in either fracture or dislocation. Thus, more complex ankle fractures require imaging of the entire shafts of the fibula and tibia and a two-way series of the knee. Certain forearm fractures are commonly associated with a fracture-dislocation of the other bone of the forearm, such as a radial shaft fracture and distal radioulnar joint dislocation, known as a Galeazzi fracture (eFig. 37.5).

eFIGURE 37.5 Galeazzi fracture dislocation.

Additional views are sometimes helpful. A dedicated scaphoid view can aid in the detection of a subtle scaphoid fracture. An axial view of the calcaneus can reveal a fracture missed on standard ankle and foot series. Many posterior dislocations of the shoulder are not evident, except on an axillary view of the glenohumeral joint, clearly depicting the relationship between the humeral head and the glenoid fossa. In certain instances, comparison views to the patient's

other side are helpful. For example, in *distal clavicle osteolysis,* characterized by pain and osteolysis of the distal clavicle, bilateral clavicle views help confirm the diagnosis when a larger separation is seen at the affected acromioclavicular joint compared with the unaffected side. Distal clavicle osteolysis occurs in power lifters and in contact with sports who suffer significant blunt trauma to the point (acromion) of the shoulder.

Adequate films, correctly interpreted, are not 100% sensitive for fractures. Growth plate injuries (also known as Salter–Harris injuries) may appear entirely normal on plain radiographs. The diagnosis may not become evident until there has been new bone deposition or resorption at the site of injury. Similarly, nondisplaced, hairline fractures often become visible, or radiolucent, only on radiographs 7 to 10 days after injury, as bone resorption widens the fracture line, hematoma develops, and new bone formation proceeds. If there is potential morbidity associated with a missed fracture on plain x-rays, a clinically fractured bone should be treated as a fracture, or more sophisticated imaging studies should be obtained. A patient with a story and examination consistent with a femoral neck fracture, which has normal plain radiographs and remains nonweight bearing in the ED, should be treated as having a nondisplaced hip fracture. Assessment of a patient's ability to ambulate is essential prior to discharge, and the inability to ambulate can further confirm the presence of an occult lower extremity fracture. These patients should be kept nonweight bearing, and magnetic resonance imaging should be performed to demonstrate the fracture; a bone scan may also be diagnostic.

Similarly, tenderness in the snuff box (the space on the radial side of the wrist between the extensor pollicis longus tendon and the paired extensor pollicis brevis and adductor pollicis longus tendons) after a *fall on an outstretched hand* should be treated as a scaphoid fracture, *even if the radiographs are normal.* If the radiographs show no fracture, immobilization in a thumb spica with follow-up examination and repeat radiographs in 10 days is mandatory (23).

KEY TESTING

Plain radiographs for skeletal injuries must

- Include the appropriate bone/joint injured.
- Have at least two views at right angles to each other.
- For long bone injuries, include the whole length of the bone and the joint above and below

CT Imaging

- Provides greater osseous detail and can do so in multiple planes (axial, coronal, sagittal)
- Consider when the relationship of fracture fragments is complex or will impact down-stream care (e.g., calcaneal fractures, tibial plateau fractures)
- Can be combined with angiographic contrast (CT-A) to identify injuries to major blood vessels

MR Imaging

- Provides greatest soft tissue detail (tendons, ligaments, disc)
- Can also provide imaging in multiple planes (axial, coronal)
- Consider when there is a potential soft tissue injury that will impact care (e.g., spinous ligaments)
- Can be combined with angiographic contrast (MR-A) to identify injuries to major blood vessels

Ultrasound

- An imaging modality being used by some practitioners in the bedside diagnosis of musculoskeletal injuries.
- In trained hands can identify fractures, dislocations, and some soft tissue injuries (e.g., tendon tears).

ED MANAGEMENT

In general, the initial management of musculoskeletal injuries includes immobilization of the affected extremity and administration of pain medication. As previously mentioned, pain related to musculoskeletal injuries is often undertreated in the ED. Once a fracture or dislocation is identified, appropriate analgesia should be provided, and reduction should be performed as needed; this is determined by the location of the injury and the amount of

distraction or angulation. The management of specific injuries is discussed in subsequent chapters.

The initial management of open fractures and joints should be directed toward reducing the chances of infection. Gross particulate debris in the wound should be removed. Exposed bone *should not be replaced in the wound,* because this may further introduce contamination. A sterile dressing should be applied. The extremity is splinted to prevent further tissue and neurovascular injury. Intravenous antibiotic therapy, usually with a first- or second-generation cephalosporin, is instituted (if not contraindicated by drug allergies), and tetanus prophylaxis (sometimes including tetanus immune globulin) is given when indicated. A macrolide antibiotic or trimethoprim–sulfamethoxazole is a good choice for the penicillin-allergic patient. An aminoglycoside such as gentamicin is frequently added to the cephalosporin when there is heavy contamination of the wound. After these initial management steps have been taken, orthopedic consultation should be obtained. Most open fractures and dislocations require formal debridement in the operating room, which should be performed as soon as patient stability will allow (15). The incidence of infection is directly proportional to the length of time from injury until irrigation and formal debridement occurs.

Certain dislocations require expeditious reduction. Dislocated hips are at risk for development of ischemic necrosis, and dislocated elbows are at risk for development of Volkmann ischemic contracture (compartment syndrome, decreased blood flow, necrosis, and contracture after a dislocation). AVN of the hip is thought to be caused by damage to the vessels supplying the femoral head. In general, these vessels are not completely torn in the dislocation; rather, they are stretched, and blood flow through them is compromised. Therefore, the incidence of AVN is directly related to the length of time from injury to adequate relocation of the hip. Similar principles apply to the development of Volkmann ischemic contracture after elbow dislocation. Therefore, reduction should be accomplished as soon as is feasible.

CRITICAL INTERVENTIONS

- Once the patient has stabilized, palpate every bone and put every joint through a range of motion to search for occult injury.
- Relocate or realign any fractures or dislocations that result in neurovascular compromise in an attempt to alleviate the neurovascular deficit as expeditiously as possible.
- Splint fractures as quickly as is possible to minimize pain, prevent injury to adjacent structures, and reduce blood loss associated with these injuries.
- Perform manometry and obtain early consultation for patients with suspected compartment syndrome.
- Administer intravenous antibiotics (first- or second-generation cephalosporin and gentamicin) early for patients with open fractures.

DISPOSITION

ED care is not complete when the diagnosis is made. Appropriate immobilization should be instituted and instructions for immediate care and follow-up given. These should be tailored to the specific injury but, in general, involve rest, ice, and elevation. These simple, cost-effective steps are often overlooked in the rush to discharge patients from the ED and can, in some cases, affect more than the patient's comfort. For example, the simple application of ice to a lateral ankle sprain during the first 24 hours after injury has been shown to decrease time to return of full function by 50% (24). Conversely, inadequate treatment can lead to decreased mobility, chronic pain, and joint instability.

Depending on the injury, the patient may be instructed to remain nonweight bearing or keep the injured joint immobilized. In other cases, activity as tolerated is appropriate and may speed recovery (e.g., low-back strain). Pain control must be achieved in the ED, and the pain medications given for the outpatient setting should be commensurate with the injury. For example, the patient who requires morphine in the ED for a rib cage contusion should not be discharged with instructions to take acetaminophen as needed for

pain. Adequate postinjury pain control improves outcome and decreases repeat visits to the ED.

Patients should be instructed to return to the ED if they experience any signs or symptoms of neurovascular compromise, excessive pain, coldness, erythema, fevers, chills, cough, pleuritic chest pain, or a cast or splint that feels too tight or causes pain. Appropriate follow-up depends on the nature and extent of the injury and can range from a visit to the patient's primary care doctor in 2 weeks, to orthopedic referral in 10 days' time, to being seen by a hand surgeon in the next few days for operative repair of a flexor tendon laceration.

Patient with CRPS should be referred early to a physician with expertise in this area, which is usually in the realm of pain management. Frequently, multimodality treatment is required, and a great deal of care coordination must occur.

Common Pitfalls

- Ordering the wrong x-ray because of an inadequate physical examination
- Not recognizing all injuries because the physician's attention is focused on one specific injury. For example, the patient who falls off a ladder and presents with a grade II lateral ankle sprain may have a calcaneal fracture from the initial impact.
- Relying on poor-quality x-rays or on a single view without obtaining an additional view at 90 degrees to the initial one
- For patients with long bone fractures, failure to include the length of the bone, the joint above and below in adequately exposed radiographs
- Failure to rule out infection or similar condition (olecranon bursitis) in a patient presenting with a swollen joint. It may be a mistake to assume that the swollen joint in the patient with a history of gouty arthritis is another flare of gout if the presentation is atypical or there are other concerning signs.
- Failure to realize that drops of blood or small abrasions on the skin in the area of a fracture are signs of an open fracture

- Failure to access or document a focused neurovascular examination on initial presentation and after reduction of a fracture or dislocation
- Attributing pain to the fracture itself, rather than thoroughly investigating other potential sources of pain, such as a cast problem, neurovascular compromise, or compartment syndrome
- Not evaluating a patient for compartment syndrome with manometry after considering the diagnosis
- Not pursuing additional studies when the plain radiographs are normal in patients with a suspected fracture, especially if they are unable to bear weight
- Undertreating the pain associated with musculoskeletal injuries.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of David F. Gaieski and Joseph Bernstein to the content of this chapter.

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CHAPTER 38

Shoulder Injuries

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The shoulder joint is composed of three bones (humerus, clavicle, and scapula) and three joints (sternoclavicular [SC], acromioclavicular [AC], and glenohumeral). Figure 38.1 demonstrates the essential osseous and ligamentous anatomy of the shoulder. The rotator cuff surrounds the glenohumeral joint and is composed of the teres minor, infraspinatus, and supraspinatus muscles, which insert on the greater tuberosity of the humerus; and the subscapularis muscle, which inserts on the lesser tuberosity of the humerus. Superficial to these muscles is the deltoid muscle.

The proximal humerus articulates with the glenoid, forming the glenohumeral joint. Because the articular surface ends at the anatomic neck, fractures located proximal to this location are considered articular surface fractures. The surgical neck is the narrow portion of the proximal humerus distal to the greater and lesser tuberosities.

The clavicle is anchored to the scapula by the AC and coracoclavicular ligaments. The SC and costoclavicular ligaments anchor the clavicle medially. The scapula lies over ribs 2 through 7 posteriorly. It is covered with thick muscles over its entire body and spine. The scapula is connected to the axial skeleton solely by the AC joint.

The glenohumeral joint and scapulothoracic articulation function as a unit in abducting the humerus. The ratio of scapular to glenohumeral movement is 1:2; therefore, for every 30 degrees of abduction of the arm, the scapula moves 10 degrees and the glenohumeral joint moves 20 degrees. If the glenohumeral joint is

completely immobilized, the scapulothoracic articulation can provide 65 degrees of abduction.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of shoulder injuries includes tendonitis, rotator cuff tears, bursitis, fractures of the clavicle, proximal humerus and scapula, shoulder dislocations, and injuries to the AC and SC joints.

ED EVALUATION

The clinician should ask the patient about the mechanism of injury, as this frequently aids in diagnosis. In atraumatic conditions, inquire about overuse and activities that worsen pain. A history of prior shoulder injury or surgery is also useful. Finally, the clinician should consider the possibility that the source of pain is not due to shoulder pathology and may represent referred pain from a more severe underlying condition (e.g., myocardial ischemia, perforated viscus).

The examination of the shoulder should be systematic to avoid missing injuries. The examiner starts by inspecting and noting how the patient holds the shoulder and also the presence of any gross deformities or ecchymosis. Palpation begins at the SC joint immediately lateral to the suprasternal notch. The examiner then moves laterally along the clavicle, noting any areas of deformity or tenderness. The AC joint is palpated by pushing in a medial direction against the distal end of the clavicle as it protrudes above the flattened acromion process.

Next, the examiner palpates the proximal humerus. The greater tuberosity of the humerus lies lateral to the acromion process and can easily be felt by following the acromion process to its lateral edge and then sliding the fingers inferiorly. Absence of the proximal humerus in its typical location and a squared-off appearance of the shoulder are consistent with an anterior shoulder dislocation. The bicipital groove, which contains the biceps tendon, is located anterior and medial to the greater tuberosity and is bordered laterally by the greater tuberosity and medially by the lesser tuberosity. Tenderness in this location is consistent with bicipital

tendonitis. External rotation places the groove in a more exposed position for palpation and permits the examiner to palpate the greater tuberosity first, then the bicipital groove, and finally the lesser tuberosity by moving from a lateral to a medial position. Lastly, the attachment of the supraspinatus tendon on the greater tuberosity is palpated. Tenderness in this location is seen in patients with supraspinatus tendonitis and subacromial bursitis.

As with any extremity injury, the clinician must consider injury to nerves and blood vessels and perform a thorough neurovascular examination. The subclavian vessels and the brachial plexus lie in close proximity to the clavicle, so displaced clavicle fractures can be associated with injuries to these structures, but this is rare. The brachial plexus, axillary nerve, and axillary artery lie in close proximity to the proximal humerus, and injuries to these structures may accompany proximal humerus fractures.

The examiner should test function of the associated muscles and range of motion of the shoulder joint. Inability to initiate abduction *or* hold the arm in a 90-degree position despite a slight pressure on the distal forearm suggests a significant tear to the rotator cuff muscles. Strength of abduction is proportional to the size of the tear. Inability to externally or internally rotate the shoulder suggests the possibility of a shoulder dislocation.

Radiographs are indicated in most traumatic situations. Routine shoulder radiographs consist of an anteroposterior (AP) view in internal and external rotation as well as a scapular “Y” view. The scapular “Y” view is obtained by placing the radiographic film along the lateral side of the humerus, with the beam projected along the length of the scapula. The “Y” consists of the scapular spine, body, and coracoid process, with the humeral head positioned at the junction of the “Y.” This radiograph is useful to identify dislocations of the glenohumeral joint and scapular fractures. When the location of the humeral head is in question, it is important to obtain an axillary view. The axillary view requires abduction of the shoulder and the beam is projected superiorly through the axilla with the plate on top of the shoulder.

Clavicle radiographs include an AP view of the upper thorax to define the structures. An AP view with the tube directed 45-degree cephalad (apical lordotic) is useful to detect medial-third fractures or SC joint dislocation (1). Multidetector CT will aid in diagnosing occult fractures or better delineate complex proximal humerus fractures, but is not routinely indicated in the ED (2).

KEY TESTING

- Routine shoulder radiographs that include AP views in internal and external rotation and a scapular "Y" view.
- An axillary view should be obtained when a dislocation is suspected on routine views.
- SC joint dislocation will be occult on routine views of the clavicle. Computed tomography (CT) scan or apical lordotic view should be ordered when clinically suspected.

ED MANAGEMENT

Clavicle Fractures

Clavicle fractures account for 5% of all fractures. They are the most common childhood fracture and may be encountered in newborns secondary to birth trauma. Two mechanisms are responsible: (i) Force applied directly to the clavicle and (ii) force applied to the outer end of the clavicle, which can push the shoulder inward toward the chest, causing a shearing force that fractures the clavicle. Most patients have swelling and tenderness over the fracture site. Frequently, the shoulder is held in downward and inward positions due to loss of support.

Middle-third clavicle fractures are most common, occurring in 80% of all clavicle fractures (eFig. 38.1). Nondisplaced middle-third fractures in adults have an intact periosteum. These heal well and require only a sling for support and ice to reduce swelling. For displaced fractures, a figure-of-eight harness can be used for reduction and maintenance of position, but it provides no more benefit in pain control or fracture reduction than a simple sling. Surgical fixation is frequently recommended in adults with displaced

clavicle fractures, necessitating referral to an orthopedist. Complications of middle-third clavicle fractures include malunion; excess callus formation, resulting in cosmetic defect; and neurovascular compromise.

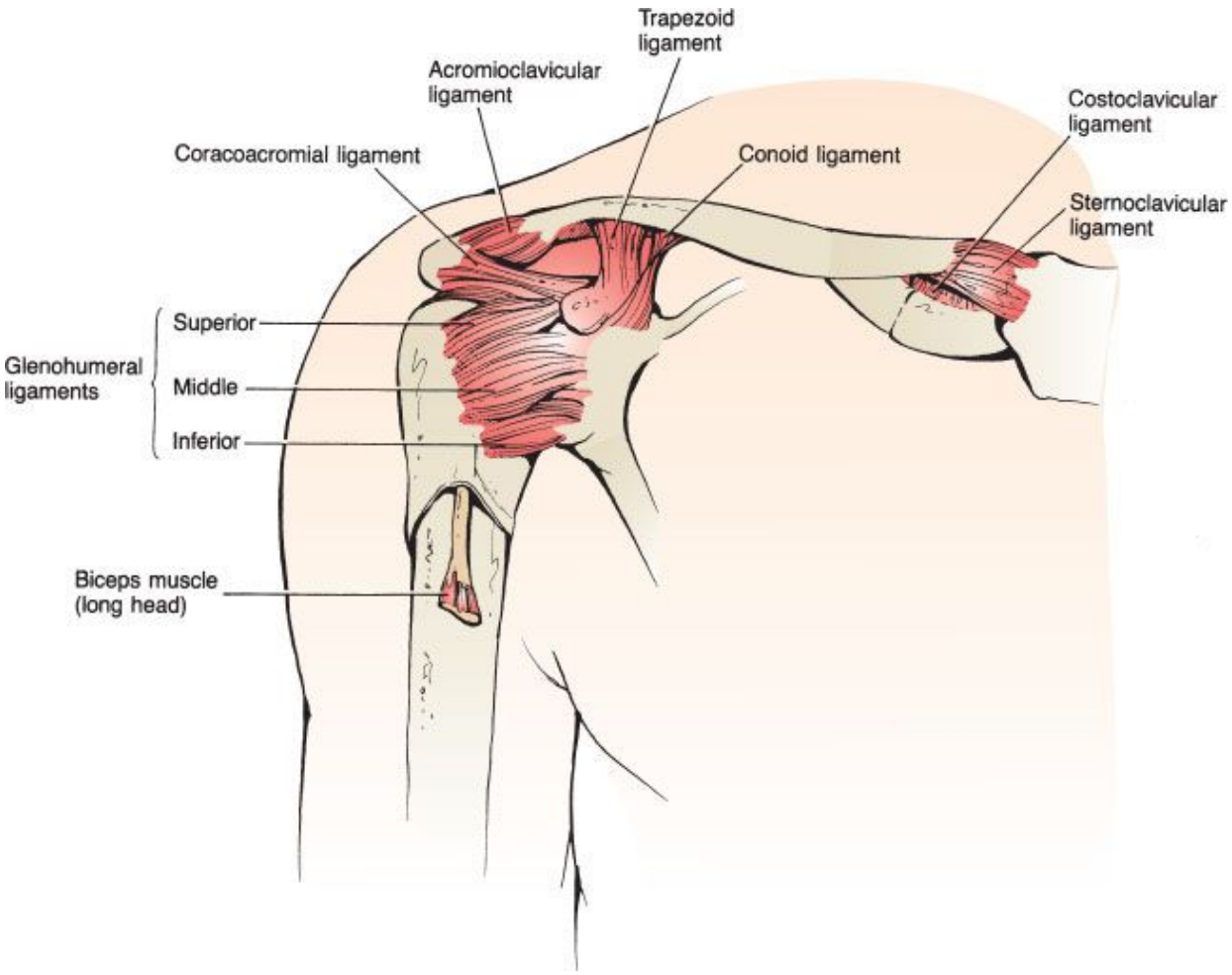


FIGURE 38.1 The ligamentous and bony anatomy of the shoulder.

eFIGURE 38.1 Clavicle fracture. The attachment of the sternocleidomastoid muscles pulls the medial segment superiorly.

Distal-third clavicle fractures account for 15% of all clavicle fractures. Nondisplaced fractures of the distal clavicle are splinted by the surrounding intact ligaments and muscles. They are usually treated symptomatically with ice, analgesics, a sling, and early motion. Displaced fractures of the distal clavicle may require surgical intervention because of rupture of the coracoclavicular ligament (3). Complications of displaced fractures treated conservatively include nonunion. Degenerative arthritis may occur when there is intra-articular involvement.

Medial-third clavicle fractures represent only 5% of all clavicle fractures. Considerable force is required to fracture the medial clavicle, so associated intrathoracic injuries should be considered. Management includes ice, analgesics, and a sling for support. Displaced fractures require orthopedic referral for reduction. Degenerative arthritis frequently complicates these fractures.

Proximal Humerus Fractures

Proximal humeral fractures account for approximately 2% to 3% of upper extremity fractures. They are most common in elderly osteoporotic women. Anatomically, proximal humeral fractures

include all humeral fractures proximal to the surgical neck. Two mechanisms of injury are commonly responsible: (i) a direct blow on the lateral aspect of the arm and (ii) a fall on an outstretched arm. Patients present with pain and swelling over the upper arm and shoulder. Most commonly, the arm is held adducted.

The Neer classification system for proximal humerus fractures is widely used and has both prognostic and therapeutic implications. In this system, the proximal humerus is divided into four segments: greater tuberosity, lesser tuberosity, humeral head, and humeral shaft (4). Depending on the displacement and angulation of fractures of these four components, the injury is divided into one-, two-, three-, and four-part fractures (eFig. 38.2).

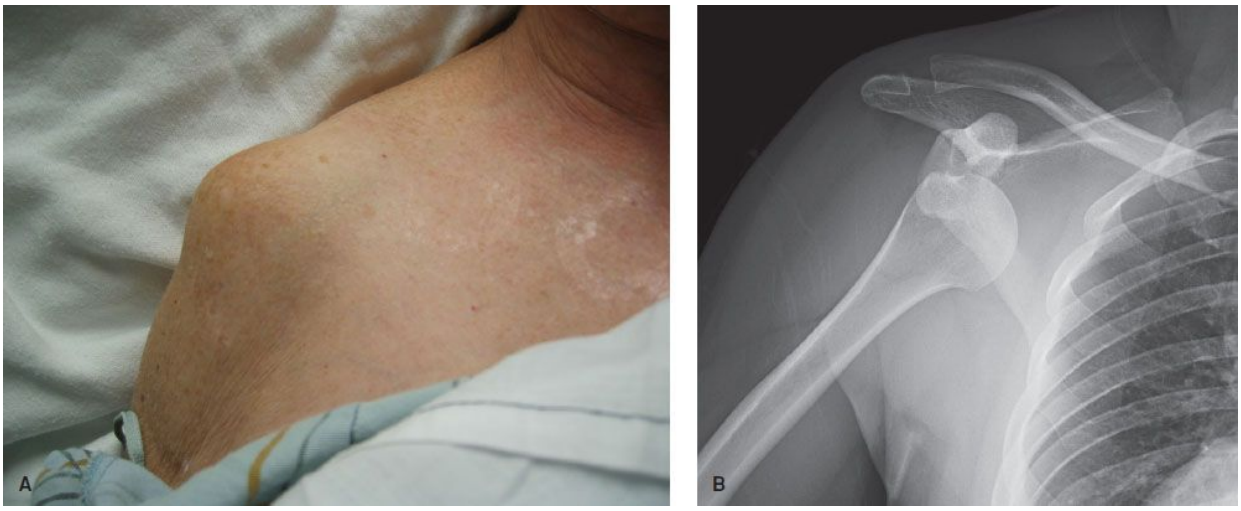
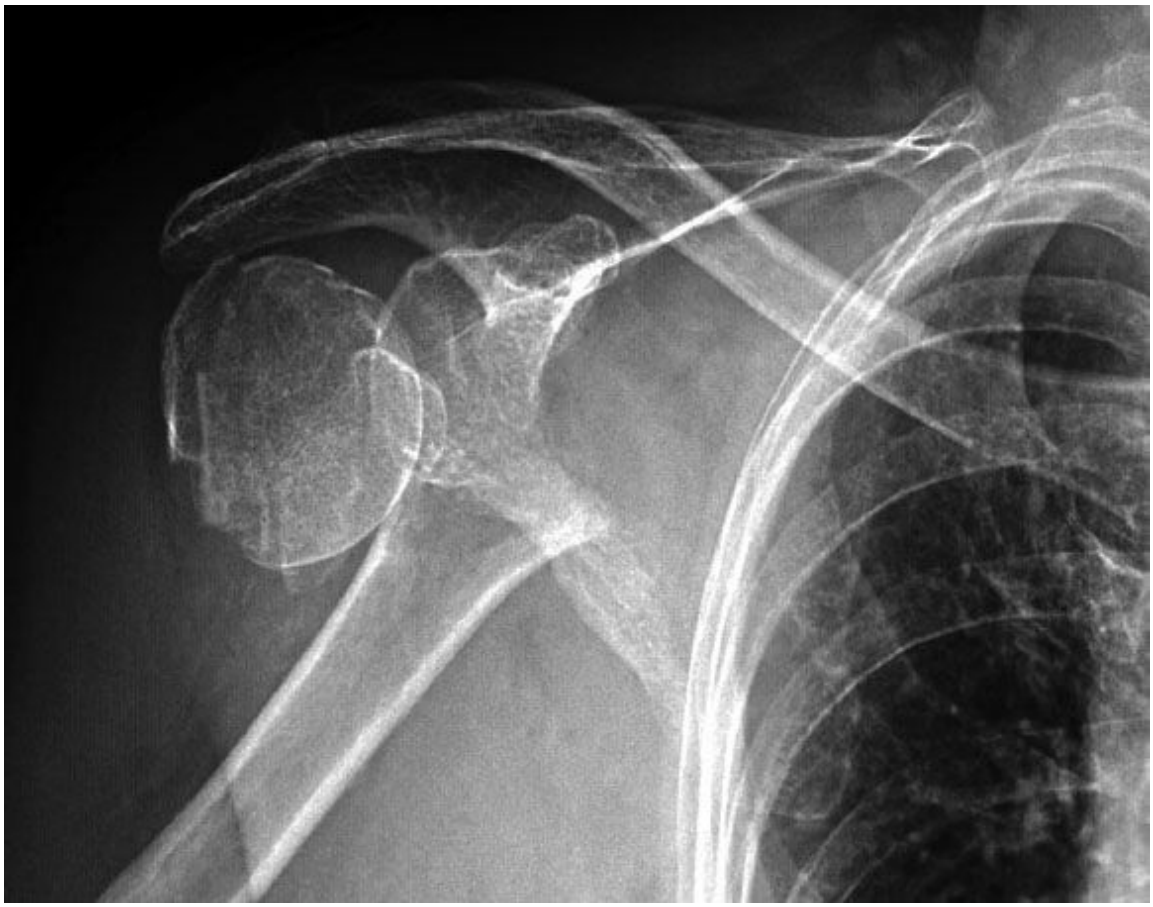


FIGURE 38.2 Anterior shoulder dislocation. A: A “rounded off” appearance of the affected shoulder is typical clinically. B: Characteristic radiographic appearance of a subcoracoid dislocation.



eFIGURE 38.2 Proximal humerus fracture. This image is of a surgical neck fracture with complete displacement. This is an example of a two-part fracture.

One-part fractures are nondisplaced (<1 cm) fractures without significant angulation (<45 degrees). These fractures are the most common type of proximal humerus fracture and represent more than 85% of cases. The humeral fragments are held in place by the periosteum, rotator cuff, and joint capsule. Therapy for one-part fractures includes immobilization in a sling and swathe and orthopedic referral within 4 to 5 days. Circumduction exercises should begin as soon as tolerated, and should be followed by passive exercise of the elbow and shoulder at 2 to 3 weeks. Shoulder motion exercises can usually be started within 3 to 4 weeks.

Two-part fractures have a fragment with more than 1 cm of displacement or over 45 degrees of angulation. These fractures require immobilization with a sling and swathe and orthopedic

referral. Surgery is recommended for two-part fractures of the greater and lesser tuberosity, angulated surgical neck fractures, and in unstable surgical neck fractures in which there is disengagement of the shaft from the humeral head.

Three- and four-part fractures result from severe forces. Three-part fractures involve two fragments that are individually displaced from the humeral head. Four-part fractures involve three fragments individually displaced from the remaining humeral head. These fractures are associated with shoulder dislocations, rotator cuff injuries, and neurovascular compromise. Therapy includes sling immobilization and emergent orthopedic referral or admission. Virtually all of these fractures require surgical repair.

Scapular Fractures

Scapular fractures are rare and represent only 1% of all fractures and 5% of fractures involving the shoulder. Treatment, associated injuries, and complications depend on the portion of the scapula that is fractured.

Body or spine fractures are significant because a great deal of force is usually required to cause these fractures; therefore, they are sometimes associated with other more serious injuries to thoracic structures. Typically, there is little displacement, due to the support of the investing muscles and periosteum. Treatment includes sling and swathe immobilization, early limited exercise, and orthopedic referral.

Acromion fractures result from a direct downward blow to the shoulder. Due to the large amount of force required to produce these fractures, they are often accompanied by brachial plexus injuries, rotator cuff tears, and shoulder dislocations. Nondisplaced fractures are treated with sling immobilization in conjunction with an elastic circular dressing that pushes the elbow up and the lateral clavicle down. Displaced fractures require internal fixation.

Glenoid rim fractures are associated with two mechanisms of injury. A direct blow may result in a stellate fracture. An upward force, secondary to a fall on the flexed elbow, may cause a displaced glenoid rim fracture. Glenoid rim fractures also occur with shoulder

dislocations and are referred to as Bankart lesions. Therapy for fractures with small fragments consists of sling immobilization, ice, and analgesia. Large or widely displaced fragments and stellate fractures require surgical fixation.

Coracoid process fractures occur from a direct blow to the superior part of the shoulder, or from violent contraction of one of the inserting muscles. The patient presents with tenderness to palpation over the coracoid process. Radiographs should include an axillary view for delineation of any displacement of the fragment. Coracoid fractures are usually treated symptomatically with a sling, ice, and analgesics.

Anterior Shoulder Dislocation

Anterior shoulder dislocation is one of the most common dislocations, accounting for half of all dislocations presenting to the ED. This injury occurs when a blow to an abducted, externally rotated arm disrupts the anterior capsule and the glenohumeral ligaments (5). Less commonly, a force to the posterior humerus or a fall on an outstretched arm is the cause.

The patient presents with the affected arm held to the side and resistant to all movements. The patient will be unable to touch the uninjured shoulder with the hand of the dislocated shoulder. In thin individuals, the acromion is prominent, and there is loss of the normal rounded contour of the shoulder (Fig. 38.2A). Upon palpation lateral to the acromion, there is a noticeable gap where the humeral head used to be positioned.

Axillary nerve injury is the most common associated neurologic injury in anterior shoulder dislocations. The axillary nerve is assessed by testing pinprick sensation over the lateral aspect of the deltoid in the “shoulder badge” distribution or deltoid muscle weakness. Unfortunately, sensory loss is not reliably present and an accurate motor examination is impractical in a patient with an acute dislocation. While nerve dysfunction is common, it is seen in up to 42% of patients, most patients recover without intervention.

On AP radiographs, the humeral head is in one of three locations: subclavicular, subcoracoid, or subglenoid (Fig. 38.2B). The physician

should determine the position of the humeral head to ascertain if there are associated injuries. The typical position is subcoracoid. If the humeral head is in a subglenoid or subclavicular position, the patient has either a greater tuberosity fracture or a rotator cuff tear. The scapular Y view, true AP (Grashey view—beam directed at a 45-degree angle from a medial to lateral direction with the plate parallel to the scapular body), and axillary view are used in equivocal cases.

Clinically important fractures are seen in approximately 25% of cases and are more common in patients over age 40, first-time dislocations, and after a traumatic mechanism. In patients with none of these three factors present, a prereduction radiograph is unlikely to be beneficial when the diagnosis is obvious clinically (6,7). The most common associated fracture is an impaction fracture on the posterior lateral portion of the humeral head known as the Hill–Sachs deformity. It is present in 40% of dislocations. Other fractures include Bankart fractures of the anterior glenoid rim (5%) and greater tuberosity fractures (10%). A nondisplaced fracture of the surgical neck is a rare associated injury, but important to note, as attempts at closed reduction of the shoulder dislocation are contraindicated. Attempts at reduction may displace the fracture and worsen the prognosis.

Reduction should begin after obtaining informed consent. Procedural sedation is not necessary in all cases, especially in recurrent dislocators who present promptly. Patient preference should be considered. Reduction without procedural sedation is unlikely to be successful in a patient who is anxious, in pain, and unable to assist in the reduction by relaxing their musculature. Some have used intra-articular lidocaine with good results (8).

There are numerous reduction techniques described, but most techniques use or combine scapular movement, external rotation, shoulder abduction, and traction of the arm. The best technique is one that is quick, simple, associated with few complications, and requires the smallest amount of force. One method that meets these requirements is scapular manipulation with downward traction on the arm by an assistant. Success rates with this maneuver range from 80% to 100% (9–11). This technique is attempted without

procedural sedation in most cases. If this is unsuccessful, the external rotation technique can be used, followed by traction–countertraction, if necessary. Other acceptable alternative techniques include the Milch, Stimson, Spaso, Fares, and Cunningham methods.

Scapular Manipulation Technique

The head of the stretcher is placed at 90 degrees. The patient sits upright with the unaffected shoulder leaning against the head of the stretcher and the legs hanging off the edge (no procedural sedation). The physician stands behind the patient and pushes the tip of the scapula medially and the superior aspect of the scapula laterally (11). This scapular rotation allows the humeral head to disengage from the glenoid. An assistant, standing in front of the patient, gently applies a downward force (Fig. 38.3A) (18).

FIGURE 38.3 Methods of reducing an anterior shoulder dislocation. **A:** Scapular manipulation with downward traction on the arm for

anterior shoulder dislocation. **B:** External rotation technique for anterior shoulder dislocation. **C:** Traction–countertraction technique for reducing anterior shoulder dislocations.

External Rotation Technique

This technique is also simple and may permit the shoulder muscles to reduce the dislocation with minimal analgesia (13). The patient lies supine with the shoulder adducted and elbow flexed to 90 degrees. The patient is encouraged to allow their arm to fall to the side. One of the physician's hands supports the elbow, and the other hand slowly guides the patient's arm (Fig. 38.3B). When pain or spasm is experienced, movement is stopped and the muscles are allowed to relax. Over the course of 5 to 10 minutes, the arm is externally rotated to 90 degrees. The rotation must be performed gradually, and the patient must remain relaxed. After reaching 90 degrees, the shoulder reduces spontaneously with success rates ranging from 80% to 90% (14).

If the shoulder is not reduced, an additional maneuver (Milch technique) can be added. The externally rotated arm is slowly elevated above the patient's head, and slight traction is applied. If the patient is unable to tolerate the external rotation technique because of pain and anxiety, procedural sedation will frequently allow the necessary muscle relaxation to reduce the shoulder.

Traction–Countertraction

With the patient lying in the supine position, an assistant applies countertraction with a folded sheet in the axilla while the examiner applies traction to the arm (Fig. 38.3C). Additional lateral traction may be added with a second sheet applied around the proximal portion of the humerus. To prevent avulsion injuries when using this maneuver, the patient must have good muscle relaxation.

Reduction in the ED is unsuccessful in 5% to 10% of cases. If the dislocation cannot be reduced, general anesthesia should be considered and reduction attempted in the operating room. Irreducible dislocations are usually due to soft tissue interposition.

Upon successful reduction, the arm is immobilized and the patient is sent for radiographs. Postreduction radiographs are not necessary if the prereduction radiographs did not reveal a fracture, the reduction was performed smoothly, and the postreduction physical examination is not suspicious for an unsuccessful reduction.

There is controversy regarding whether the shoulder should be immobilized in internal (sling and swathe or commercially available shoulder immobilizer) or external rotation (15–17). Immobilization in external rotation has been postulated to put the detached labrum in a better position to heal and consequently reduce the rate of recurrent dislocation. Study results are mixed, but immobilization of these patients in internal rotation is recommended until more conclusive evidence becomes available.

The patient is referred to an orthopedic surgeon within 1 week. The older the patient, the earlier mobilization should be instituted to avoid stiffness. For patients younger than 30 years of age, the shoulder is immobilized for 3 weeks, followed by gentle active range-of-motion exercises. The patient should avoid abduction and external rotation for an additional 3 weeks. For patients older than age 30, the shoulder is immobilized for 1 week, followed by active range-of-motion exercises, avoiding abduction and external rotation.

Complications of anterior shoulder dislocations include tears of the rotator cuff, avulsion of the greater tuberosity, axillary nerve injury, and fracture of the humeral head. The most common complication is recurrent dislocation due to labral and ligamentous injury. This complication occurs in 50% to 90% of patients younger than age 20. Prevention of recurrent dislocation is achieved by internal rotation exercises that strengthen the subscapularis muscle. Operative repair is indicated in patients with recurrent dislocations and occasionally in young, first-time dislocators engaged in highly demanding physical activities.

Posterior Shoulder Dislocation

Posterior dislocations are less common and more subtle on examination and radiographs than their anterior counterpart, making delayed and misdiagnosis more likely. The common mechanisms

involved in this injury include violent internal rotational force occurring during a fall on the forward-flexed, internally rotated arm or a violent muscle contraction following a generalized tonic–clonic seizure or electrocution.

On physical examination, the arm is held in adduction and internal rotation, with abduction severely limited. External rotation of the shoulder is blocked, a critical feature of the examination that should raise clinical suspicion. Additional physical examination findings include prominence in the posterior aspect of the shoulder accompanied by flattening of the normal anterior shoulder contour. Neurovascular compromise is uncommon.

Evidence of a posterior shoulder dislocation on a standard AP view is subtle and may be undiagnosed in 50% of cases (18). Some clues to the radiographic diagnosis include the *light bulb, trough line,* and *rim signs* (Fig. 38.4A). The light bulb sign refers to the circular appearance of the humeral head caused by internal rotation that changes the projection of the tuberosities. The trough line sign is a linear appearance within the humeral head that represents the "trough" of the reverse Hill–Sachs impaction fracture. The rim sign is present when the distance between the medial aspect of the humeral head and the anterior glenoid rim is abnormal, usually with additional overlap between the two. Whenever there is a question of a posterior shoulder dislocation on AP views, an axillary view should be obtained (Fig. 38.4B). Isolated fractures of the lesser tuberosity are commonly associated.

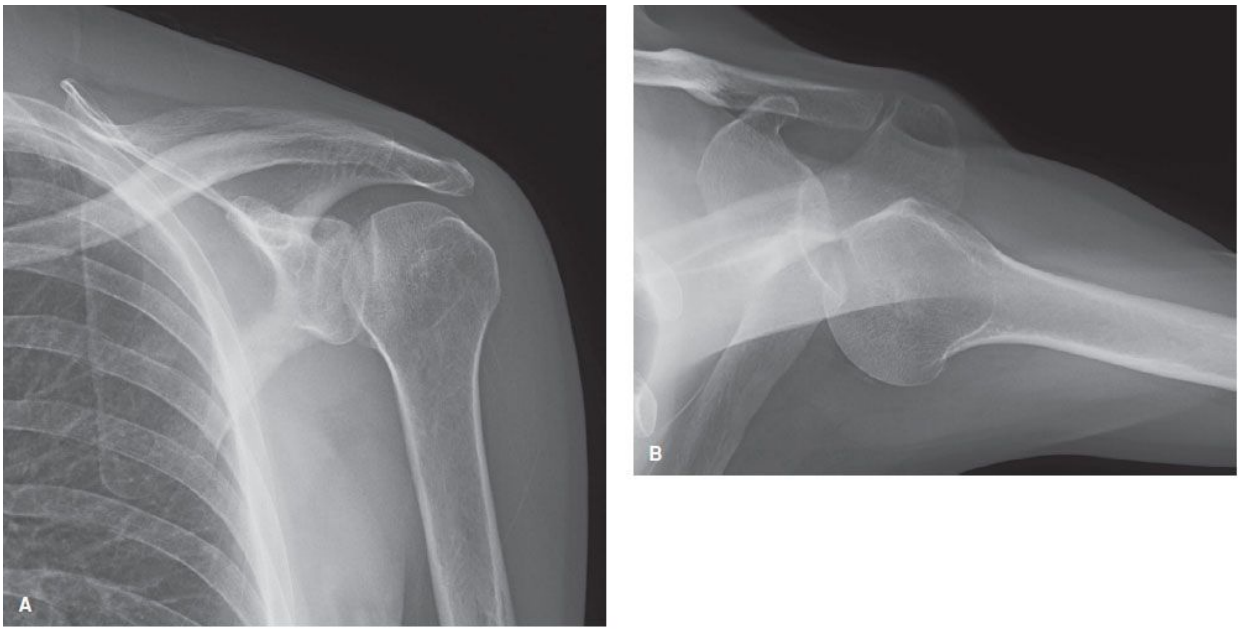


FIGURE 38.4 Posterior shoulder dislocation. A: AP view. Notice there is additional overlap of the glenoid and humeral head (rim sign), a rounded appearance of the humeral head (light bulb sign), and a linear opacity medial within the humeral head (trough line sign). B: Axillary view.

Consultation with an orthopedic surgeon is recommended for posterior shoulder dislocations. Closed reduction is attempted only if the anterior surface defect ("reverse Hill–Sachs deformity") is $<20\%$ of the total humeral head surface and the duration of dislocation is <3 weeks (19). Posterior shoulder dislocations may be reduced by hanging the arm with weights (Stimson method), or other techniques that push the posteriorly displaced humeral head forward. If there is severe pain or muscle spasm, general anesthesia may be necessary. Surgical intervention is needed when the articular surface defect is $>20\%$ of its surface area, when the dislocation is irreducible using closed techniques, or when a lesser tuberosity fracture remains displaced after joint reduction.

Inferior Shoulder Dislocation (Luxatio Erecta)

Inferior dislocations of the shoulder are uncommon, representing approximately 0.5% of all shoulder dislocations. The mechanism of

injury is forceful hyperabduction. Because of its dramatic presentation, this dislocation is rarely missed.

On physical examination, the patient is in severe pain and holds the arm upright, as if asking a question. The humeral head can be palpated along the lateral chest wall. Compression of the axillary artery and brachial plexus may occur as the humeral head tears through the inferior capsule. Vascular injury occurs in approximately 3% of patients, but it is more common with inferior dislocations than with any other form of shoulder dislocation (11,20).

Radiographically, the humeral head is seen beneath the coracoid or glenoid with the humerus abducted. Associated fractures of the acromion, inferior glenoid rim, and greater tuberosity may be present (20).

To reduce the dislocation, the physician applies traction in the longitudinal axis of the humerus while an assistant applies countertraction with a folded sheet wrapped around the supraclavicular region. With traction maintained, the arm is rotated inferiorly in an arc toward a position of complete adduction. Closed reduction is successful in most cases. After reduction, the shoulder is immobilized for 2 to 4 weeks. Rotator cuff tears are frequently present. Occasionally, general anesthesia may be required to reduce the dislocation and repair the torn rotator cuff.

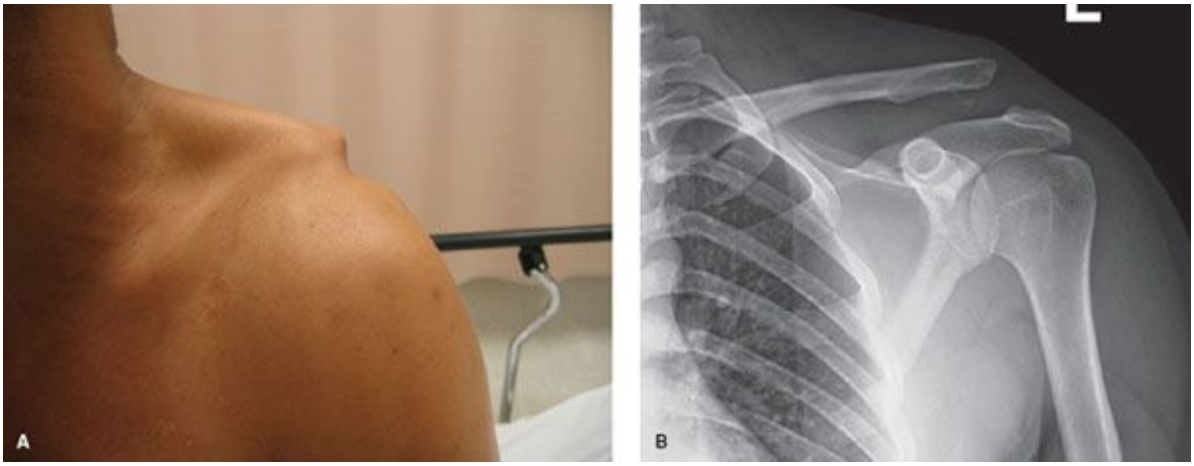
AC Joint Injury

The AC joint functions to elevate and abduct the arm. Stability is provided by two ligaments—the AC and the coracoclavicular. Injury to these ligaments, commonly referred to as a “shoulder separation,” accounts for 10% of all dislocations. Most injuries of the AC joint are caused by a direct force applied to the point of the shoulder. The therapy for AC joint injuries depends on the amount of ligamentous injury—first-, second-, or third-degree injuries (21).

First-degree injuries are a simple sprain of the AC ligament and involve an incomplete tear of that structure. The patient complains of pain and has tenderness over the AC joint. Swelling is minimal, no subluxation is present, and radiographs are normal. Therapy includes rest, ice, and a sling, with early range of motion.

Second-degree injuries involve disruption of the AC ligament, with sprain of the coracoclavicular ligament. There is a partial subluxation of the distal end of the clavicle from the acromion. The patient experiences tenderness to mild palpation and moderate swelling is present. Radiographic findings are subtle and include an increased width of the AC joint of 3 mm or more or greater than a 50% increase compared to the opposite side. The distal clavicle is elevated no more than half its diameter from the acromion. Stress films, previously recommended to help distinguish between second- and third-degree injuries, are no longer routinely recommended because they do not affect treatment decisions (22). Second-degree injuries are treated conservatively with ice, rest, and immobilization in a sling. Commercially available clavicle braces (Kenny-Howard sling) may be used but have not been shown to produce superior long-term function over a sling.

Third-degree injuries result in complete dislocation at the AC joint, with disruption of both the AC and coracoclavicular ligaments. The diagnosis of an AC joint injury is made by examining the patient in the upright position and looking for a deformity at the tip of the shoulder (eFig. 38.3A). On radiographs, the inferior border of the distal clavicle is above the midpoint of the acromion (eFig. 38.3B). Treatment is controversial. In the past, third-degree injuries were treated surgically in young patients. However, conservative treatment has been shown to be equivalent to surgery. Patients with these injuries should be immobilized in a sling and referred to an orthopedist within 1 week (23,24).



eFIGURE 38.3 Acromioclavicular separation—Third degree. A: Clinical picture. B: Radiograph of the same injury.

SC Joint Injuries

The SC joint is stabilized by the SC ligament and the costoclavicular ligament. The most common mechanism of injury to this joint is a force that thrusts the shoulder forward. In the absence of trauma, an infectious process within the joint should be considered. Traumatic injuries are divided into mild and moderate sprains and SC joint dislocation.

Mild SC joint sprain involves incomplete tears of the SC and costoclavicular ligaments. The patient experiences minimal swelling and has tenderness at the joint. Therapy includes ice, analgesics, and a sling for 3 to 4 days.

Moderate SC joint sprain involves subluxation of the clavicle from its manubrial attachment. Complete rupture of the SC ligament and partial rupture of the costoclavicular ligament occur. There is pain on abduction of the arm, and swelling is noted over the joint. Treatment includes 6 weeks of immobilization with a figure-of-eight clavicle strap and a sling to permit ligamentous healing.

SC joint dislocation involves complete rupture of the SC and costoclavicular ligaments, permitting the clavicle to dislocate from its manubrial attachment. Anterior dislocations are much more common, but posterior dislocations have the potential to result in much more serious injuries. Patients experience severe pain, which is

increased by any motion of the shoulder. Posterior dislocations may constitute a true emergency because respiratory embarrassment can occur secondary to tracheal compression, pneumothorax, or venous congestion. These associated injuries may necessitate emergency reduction by the emergency physician, whereas reduction in the operating room is recommended in all other cases (1). Reduction is accomplished by placing a folded sheet between the shoulders, with the patient supine. This serves to separate the clavicle from the manubrium. The arm is abducted and traction is applied. For posterior dislocations, following the instillation of local anesthesia, the clavicle should be grasped near its medial border with a towel clip and pulled out of its posterior position. Unstable SC joint dislocations may require surgical intervention (3).

Complications of anterior SC dislocation are cosmetic, with chronic swelling around the joint. Although it has been reported that up to 25% of posterior dislocations are associated with complications—including pneumothorax, laceration of the superior vena cava, occlusion of the subclavian artery or vein, and rupture or compression of the trachea—this may be an overestimate (1).

Rotator Cuff Injury

Tears of the rotator cuff are more common in the elderly and may occur after minimal trauma. The mechanism of injury following an acute injury, which is more common in younger patients, is typically a sudden forceful elevation of the arm against resistance. The most common area of cuff injury is at the anterosuperior portion, at the attachment of the supraspinatus muscle. The tendon at this point is worn down by the compressive forces between the humeral head and the coracoacromial arch.

Patients complain of pain that radiates to the anterior aspect of the arm and is aggravated by activity. Abduction and external rotation of the arm are painful and weak. Tenderness is present over the insertion at the greater tuberosity. Thirty percent or more of the tendon must be ruptured to produce a significant reduction of strength. The extent of the tear is directly related to the limitation of shoulder abduction.

The *drop arm test* is positive in patients with significant tears. This is performed by horizontally elevating the arm to the 90-degree position and asking the patient to continue to hold the arm in this position. Slight pressure on the distal forearm will cause the patient to drop the arm suddenly. In addition, the patient cannot bring the arm from the abducted position to the side in a slow fashion, but drops it precipitously.

Emergency treatment includes ice, immobilization, and orthopedic referral within 4 to 5 days. Passive range-of-motion exercises should be instituted as soon as possible in elderly patients. Magnetic resonance imaging is diagnostic of full-thickness tears with 100% sensitivity, but is not indicated in the ED (25). Conservative therapy results in a good outcome in 50% of patients. In the young, early surgical repair is indicated for complete tears of the rotator cuff. Anterior tears have the best outcome, while patients with posterior tears are poor candidates for arthroscopy (26). In the elderly patient with a more sedentary life, repair may not be indicated.

CRITICAL INTERVENTIONS

- Evaluate patients with scapular fractures for associated thoracic injuries, with careful physical examination, radiographs, and further testing when indicated.
- In patients who have had a grand mal seizure, check external rotation of both shoulders to evaluate for posterior shoulder dislocation.
- Use the towel clip method to reduce posterior SC dislocations when they are associated with respiratory distress due to tracheal compression.

Common Pitfalls

- Failure to obtain an axillary view when assessing the shoulder for dislocation.
- Failure to remember that lesser tuberosity fractures are often associated with posterior shoulder dislocations.

- Attempting to reduce an anterior shoulder dislocation in a patient with a concomitant surgical neck fracture.

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CHAPTER 39

Elbow Injuries

Andrew D. Perron and Carl A. Germann

The elbow is a complex synovial hinge joint consisting of three articulations between the distal humerus, radius, and ulna. Because of the need for a wide variety of articular motions (flexion–extension and pronation–supination), the joint is at risk for instability with injury. The humerus widens distally to form the lateral and medial condyles. The capitellum is a spheroidal cartilaginous structure of the lateral condyle that articulates with the radial head, permitting pronation and supination. The trochlea is a spoon-shaped cartilaginous projection of the medial condyle that articulates with the deep trochlear notch of the ulna, permitting flexion and extension at the elbow. The articulating surfaces of the head of the radius and ulna are held together by the annular ligament. The associated musculature and the anterior capsule combined with the radial and ulnar collateral ligaments provide stability at the elbow joint.

A number of important structures traverse or are located within the elbow. The wrist flexor and pronator muscle groups originate from the medial epicondyle. The wrist extensor and supinator muscles attach to the lateral epicondyle. The brachial artery traverses the elbow and is palpable medial to the biceps tendon in the antecubital space. The median nerve traverses deep in the antecubital fossa medial to the brachial artery. The ulnar nerve courses posteriorly in the cubital tunnel between the medial epicondyle and olecranon process. The radial nerve passes between the heads of the triceps in the posterior humerus and is at risk for injury in humeral shaft fractures.

There are several bursal structures in and around the elbow that help facilitate the wide range of motion possible in the joint. The superficial olecranon bursa lies beneath the skin over the olecranon process and is particularly vulnerable to traumatic and infectious processes. Figure 39.1 illustrates the anatomy of the elbow.

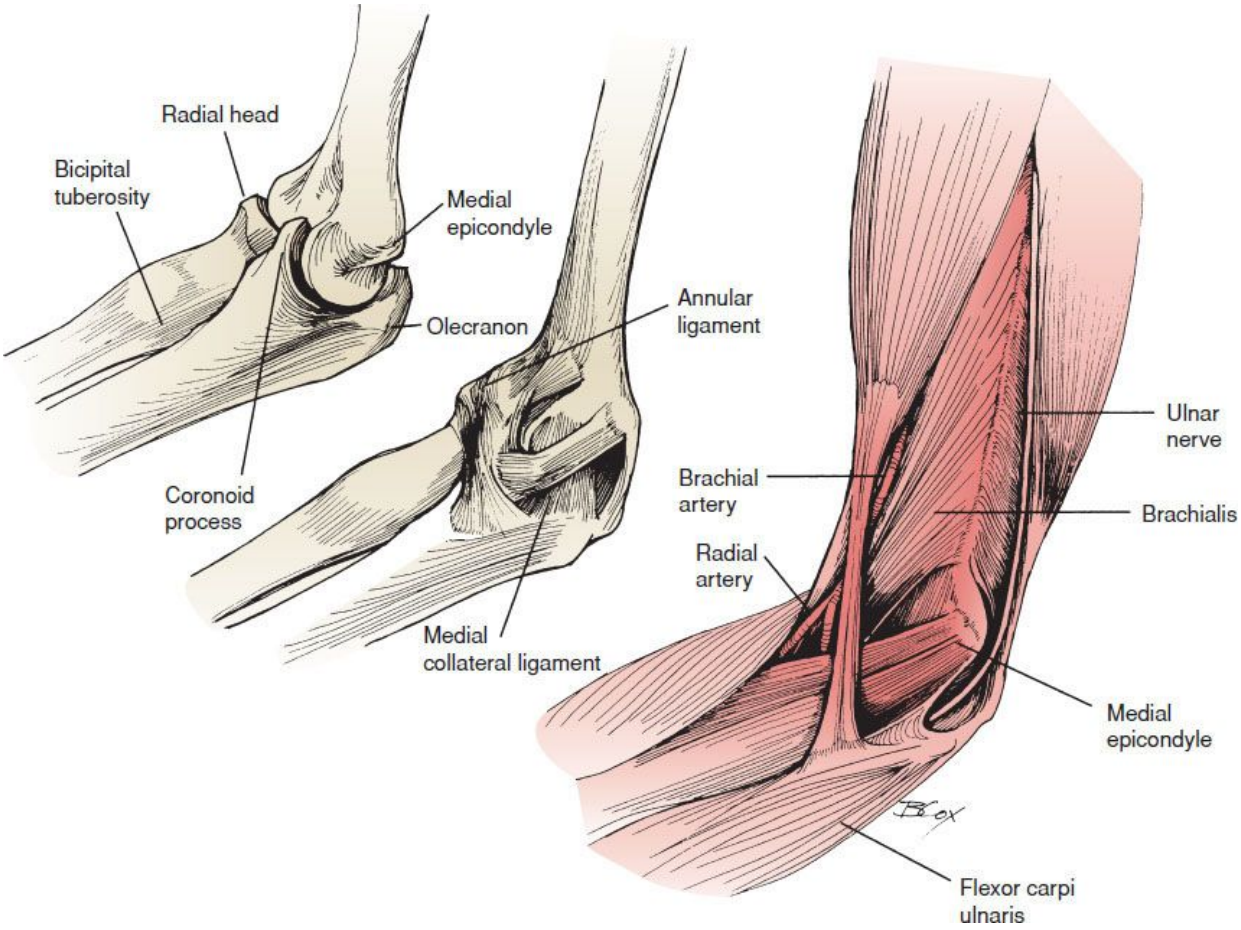


FIGURE 39.1 Elbow anatomy. (From McCue FC III, Sweeney T, Urch S. The elbow, wrist, and hand. In: Perrin DH, ed. The Injured Athlete. 3rd ed. Philadelphia, PA: Lippincott-Raven; 1999, with permission.)

ED EVALUATION

The emergency department (ED) assessment of elbow injuries should include a focused history of the mechanism of injury. The most common complaints are pain, restriction of movement, and swelling. A description of the location and duration of pain, aggravating factors, and presence of paresthesias or loss of movement is

important. Elbow pain may also be referred from injuries to the shoulder, forearm, or wrist. Conversely, injuries to the elbow may refer pain to the wrist. Identification of one injury should not preclude the search for other injuries. An occupational history may provide a clue to the diagnosis in patients presenting with chronic pain.

Inspection of the involved extremity for swelling, open wounds, deformities, effusions, and discoloration is the first step in the physical examination of the patient with elbow pain. In most cases, the involved joint should not be extensively manipulated until radiographs have been obtained to exclude fracture and dislocation. The shoulder, forearm, wrist, and hand should also be carefully examined to look for associated injuries. Laceration over the medial epicondyle should raise suspicion of an ulnar nerve injury, whereas laceration over the antecubital fossa should raise suspicion for injury to the brachial artery or median nerve. Any abnormality noted in the involved extremity should be compared with the contralateral extremity.

An effusion is best palpated over the soft tissue area lateral to the radial head. The bony prominences of the medial and lateral condyles, olecranon, and radial head should be palpated for tenderness. The radial head is best palpated with the thumb of one hand while pronating and supinating the forearm with the examiner's other hand. Limitation of motion, crepitance, or pain should all be noted. With the elbow flexed to 90 degrees, the medial and lateral condyles and the olecranon should form a triangle. In an elbow dislocation, this triangle is disrupted with displacement of the olecranon. A posterior dislocation or extension-type fracture is suggested by a prominent olecranon. Loss of the olecranon prominence suggests an anterior dislocation or supracondylar fracture. The triangular relationship is maintained in supracondylar fracture. Each of the muscle groups should be tested against resistance and the muscle belly palpated during contraction.

Careful neurovascular examination of the structures distal to the elbow is of critical importance. Brachial, radial, and ulnar pulses should be palpated and capillary refill assessed. The brachioradialis,

biceps, and triceps reflexes should be elicited. The radial nerve is best tested by evaluating wrist and finger extension. Wrist drop results from radial nerve injury. Flexion of the wrist and digits and pronation of the forearm are the functions of the median nerve. Inability to flex and abduct the thumb is diagnostic of median nerve injury. Loss of strength of the interossei muscles and adduction of the thumb suggests ulnar nerve injury. The sensory component of the radial nerve innervates the dorsum of the hand and is best tested in the web space between the thumb and index finger. Median nerve sensation is tested over the palmar aspect of the thumb and the digits to the radial one-half of the ring finger; at the volar tip of the index finger, there is no overlap from the radial or median nerves. The ulnar nerve is tested at the volar tip of the small finger. The neurovascular examination of the extremity should be repeated after manipulation and at regular intervals as edema from a fracture may result in neurovascular compromise.

The radiographic examination of the elbow should consist of a minimum of two views at right angles to each other (anteroposterior [AP] and true lateral). Radiographs are most commonly misread because a true lateral view of the elbow is not obtained. In one university ED setting, the incidence of missed elbow fractures was 12% (1). Oblique views may be obtained to provide additional information. Specialized views, such as the radial head–capitellum view, are indicated when a suspicion for particular injury exists.

On the lateral radiograph, a line parallel to the anterior border of the humerus should intersect the anterior portion of the middle third of the capitellum (Fig. 39.2) (2). If this intersection is displaced, usually anterior to the capitellum, a supracondylar fracture should be suspected.

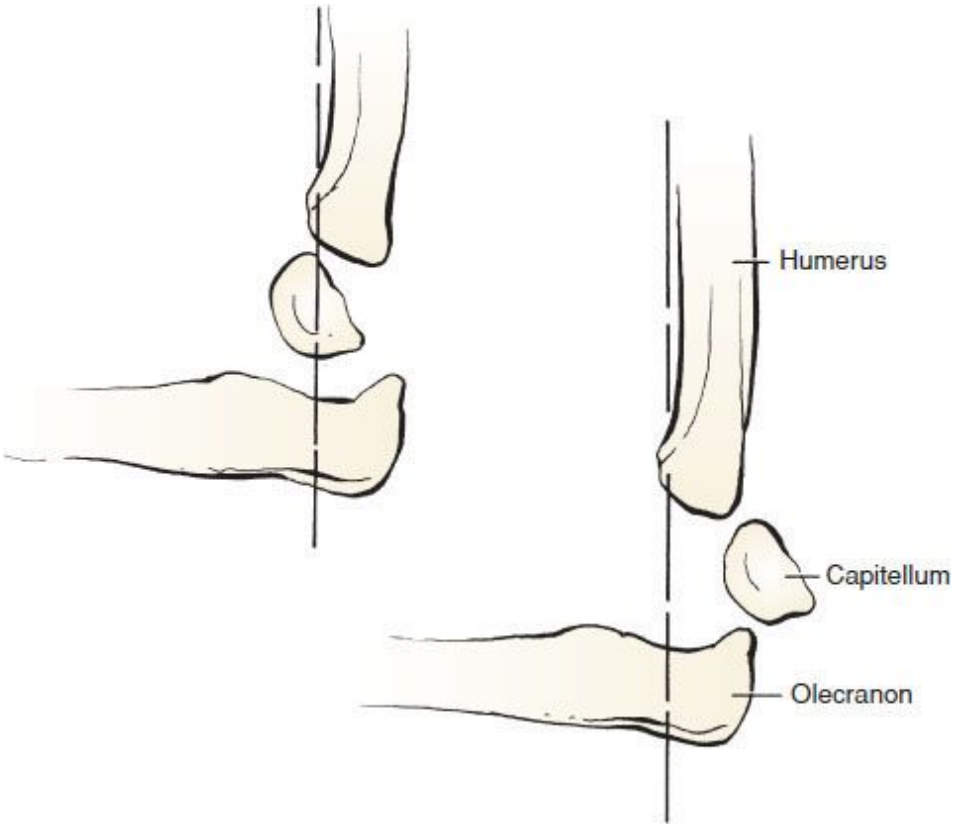


FIGURE 39.2 Anterior humeral line. The anterior humeral line is drawn on the lateral radiograph along the anterior surface of the humerus through the elbow. Normally this line transects the middle of the capitellum (left). With an extension fracture of the supracondylar region, this line will either transect the anterior third of the capitellum or pass entirely anterior to it (right). (Adapted from Simon RR, Koenigsknecht SJ. Emergency Orthopaedics: The Extremities. 2nd ed. Norwalk, CT: Appleton & Lange; 1987, with permission.)

The radiocapitellar line extends from the center of the radius and should intersect the middle third of the capitellum on the lateral view (2). Disruption of this line suggests radial head dislocation or fracture and is most useful in evaluating subtle fractures in children.

Fat pad signs are helpful in diagnosing occult fractures within the joint capsule. The *anterior fat pad* consists of fat in the coronoid and radial fossa. This radiolucent fat overlaps and normally appears as a triangular area anteriorly over the distal humerus on a lateral

radiograph of the elbow. The *posterior fat pad* is located in the olecranon fossa and is normally hidden by the overlying humeral condyles on a lateral radiograph.

When an effusion is present, it distends the joint capsule and displaces the fat pads (Fig. 39.3). The *anterior fat pad* displaces anteriorly and superiorly and appears bowed out as a "ship's sail." The *posterior fat pad* becomes visible on radiography with elbow injury and is highly indicative of intra-articular disease. In the setting of elbow trauma, a visible posterior fat pad or a prominent anterior fat pad in the absence of visible fracture should prompt consideration of occult fracture, most commonly of the radial head.

FIGURE 39.3 Anterior and posterior fat pad signs are indicated by the large white arrows. Small black arrows indicate the radial head fracture that produced the effusion displacing the fat pads.

Positive fat pad signs can also be present with any intra-articular disease process and thus are not strictly pathognomonic for fracture. Fat pad signs may be seen with arthritis, gout, pseudogout, infection, neoplasia, or other disease process causing an intra-articular fluid collection (3). A fat pad sign may not be present with severe injury causing disruption of the joint capsule.

Though usually not necessary in the ED evaluation of these patients, computed tomography (CT) scanning may be useful in delineating complex fractures in adults. Magnetic resonance imaging (MRI) has become the procedure of choice for evaluating soft tissues, cartilaginous surfaces, joint space, and trabecular bone (4).

KEY TESTING

Plain radiographs for skeletal injuries must:

- Include the appropriate bone/joint injured
- Have at least two views at right angles to each other
- Be adequate for diagnosing most elbow fracture and dislocation injuries

CT Imaging:

- Particularly useful to better characterize elbow injury and assist in preoperative planning
- Consider when the relationship of fracture fragments is complex or will impact downstream care (e.g., multifragment radial head fractures, fracture/dislocation injuries)
- Can be combined with angiographic contrast (CT-A) to identify injuries to major blood vessels)

MR Imaging:

- Provides greatest soft tissue detail (tendons, ligaments, disc)
- Can also provide imaging in multiple planes (axial, coronal)
- Consider when there is a potential soft tissue injury that will impact care (e.g., degree of tendon injury)

Ultrasound:

- An imaging modality being used by some practitioners in the bedside diagnosis of musculoskeletal injuries
- Trained hands can identify fractures, dislocations, and some soft tissue injuries (e.g., tendon tears)

ED MANAGEMENT

Supracondylar Fractures

Supracondylar fractures occur in the distal humerus proximal to the epicondyles and are most commonly seen in children. In adults, because of their stronger bones, elbow dislocations from ligamentous disruption are more common. These fractures most commonly result from a fall on the outstretched hand with the elbow in extension.

Twenty-five percent of supracondylar fractures are nondisplaced. Treatment of a *nondisplaced* fracture is a posterior splint from axilla to palm, with the elbow flexed to 90 degrees. These patients should be urgently referred to an orthopedic surgeon for follow-up within 24 to 48 hours. The patient and parents should be carefully counseled regarding warning signs of compartment syndrome. A child with elbow tenderness and swelling should be splinted, even without a demonstrable radiographic fracture, because of the possibility of occult fracture (5).

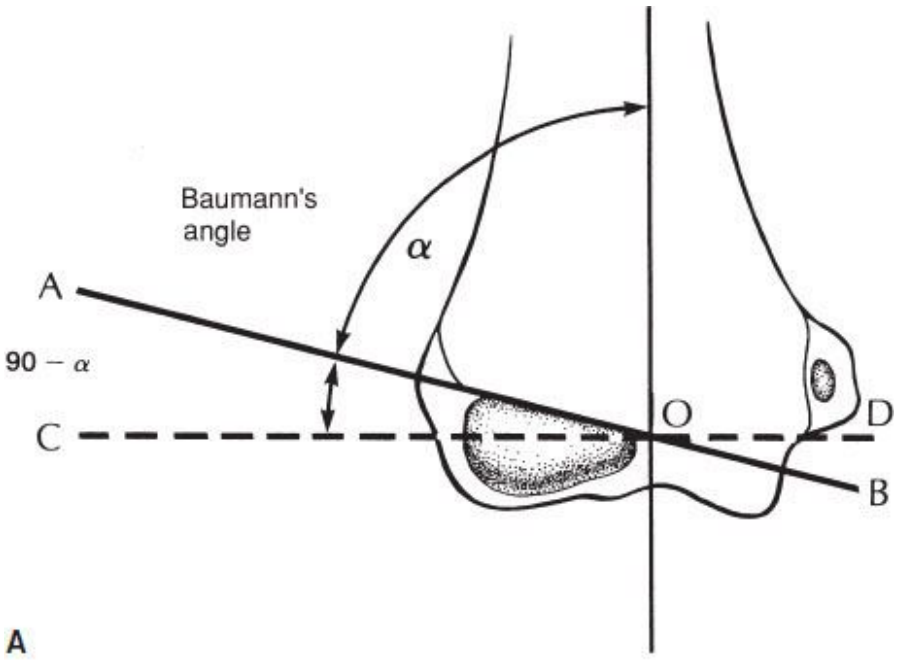
In displaced fractures, the distal fragment is usually displaced posteriorly (extension injury), and an abnormal anterior humeral line will be visualized on the lateral radiograph. Anterior displacement of the distal fragment (flexion injury) occurs less frequently and is caused by a direct blow to the posterior aspect of the flexed elbow.

Assessment of neurovascular function is essential, especially with extension injuries, because occult injury to the brachial artery may occur. A strong pulse does not completely rule out arterial injury, and a vascular study should be performed if injury is clinically suspected. The reported rate of nerve injury in displaced supracondylar fractures is up to 20% (6). Injury to the median and radial nerve can occur from stretching or entrapment on the proximal humeral fragment. The ulnar nerve may also be disrupted and is more frequently damaged in a flexion-type fracture (6). Closed reduction of displaced fractures should be attempted as soon as possible if neurovascular compromise is present.

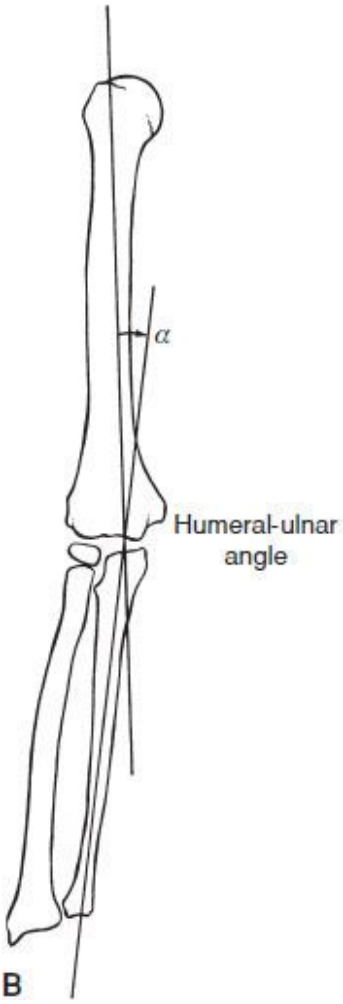
Displaced fractures require internal fixation or percutaneous pinning if good alignment is not maintained with closed reduction.

Patients with displaced fractures should be admitted because of the risk of delayed swelling and neurovascular compromise, including compartment syndrome, and the potential for Volkmann ischemic contracture. Flexion fractures may also require internal fixation and should be splinted in extension.

A common complication of supracondylar fracture is an abnormal carrying angle. The normal carrying angle is 10 to 15 degrees of valgus. Measurement of Baumann's angle, formed by a line perpendicular to the humeral shaft and a line through the lateral humeral condyle, is predictive of an acceptable carrying angle (7). This angle normally measures about 75 degrees. A discrepancy of >5 to 10 degrees, compared with the uninjured extremity, is an unacceptable reduction, as it may impair useful function of the arm (Fig. 39.4).



A



B

FIGURE 39.4 A: Baumann's angle. B: Humeral–ulnar angle. (From O'Brien WR, Eilert RE, Chang FM, et al. The metaphyseal-diaphyseal angle as a guide to treating supracondylar fractures of the humerus in children. Unpublished data, with permission.)

Intercondylar Fractures

Intercondylar fractures usually occur in older patients as a result of direct trauma to the flexed elbow. They usually occur in "T" and "Y" configurations, and treatment is based on the amount of displacement of the humeral condyles from each other and from the proximal humerus. Neurovascular complications are uncommon, and these fractures rarely require manipulation by the emergency physician.

Nondisplaced fractures are treated in a posterior splint for 3 weeks, and then active range of motion is begun. Displaced fractures are treated with internal fixation and early range of motion beginning after 1 week. Severely comminuted fractures may be treated with olecranon traction for 3 to 4 weeks if operative repair is not possible.

Humeral Condyle Fractures

Isolated humeral condyle fractures are caused by a fall on the outstretched hand, by direct trauma, or by avulsion of bone from the pull of the flexor or extensor muscles from the medial and lateral condyles, respectively. Lateral condyle fractures are more common than medial condyle fractures and frequently involve the joint surface.

Nondisplaced lateral condyle fractures are immobilized in a posterior splint, with the elbow flexed to 90 degrees and the forearm in supination with the wrist extended. The forearm should be in pronation and the wrist flexed for medial condyle fractures. Active range of motion is begun as early as 2 to 3 weeks after injury. Operative fixation is required for displaced fractures, owing to instability caused by the pull of the forearm muscles. All of these

patients should be treated in consultation with an orthopedic surgeon.

Epicondyle Fractures

Epicondyle fractures in adults are usually caused by a direct blow. The medial epicondyle is involved more commonly than the lateral epicondyle, and ulnar nerve function should be evaluated, as it is in close proximity to the medial epicondyle at the elbow (Fig. 39.5). There is up to a 50% incidence of associated elbow dislocation with medial epicondyle fracture (8).

FIGURE 39.5 Avulsion fracture of the medial epicondyle. (From Yochum TR, Rowe LJ. Yochum and Rowe's Essentials of Skeletal

Radiology. 3rd ed. Philadephia, PA: Lippincott Williams & Wilkins; 2004.)

Nondisplaced fractures may be treated with immobilization and early range of motion. If more than 10 mm of displacement is present, then surgical fixation may be required. Intra-articular fragments may impede joint mobility and are difficult to visualize radiographically. Entrapment of the ulnar nerve is a possible complication.

Articular Surface Fractures

Fractures of the capitellum and trochlea usually occur as a result of a posterior elbow dislocation. Isolated fractures are rare, and joint stability is maintained because the condyles remain intact, but motion may be impeded.

Nondisplaced fractures with normal anatomic alignment can be treated with immobilization for 2 to 3 weeks. Displaced small fragments may ultimately need excision, whereas larger fragments may require internal fixation with early range of motion. Common complications of capitellar fractures include restriction of motion and, rarely, nonunion and avascular necrosis.

Proximal Ulna Fractures

Olecranon fractures are usually intra-articular and may result from a direct blow or an avulsion injury from the pull of the triceps muscle (Fig. 39.6). On examination, the patient is unable to extend the elbow against resistance. Because of its proximity, the ulnar nerve may be injured, and its function should be assessed.

FIGURE 39.6 Olecranon fracture. (From Chambers H, Jose Fernando DLG, O'Brien E, et al. Fractures of the radius and ulna. In: Rockwood CA, Wilkins KE, Beaty JH, eds. Fractures in Children. 4th ed. Philadelphia, PA: Lippincott-Raven; 1996. Fig 9.217 C, p.633, with permission.)

Treatment of these injuries varies with the amount of displacement and usually requires orthopedic consultation. Nondisplaced fractures may be splinted with the elbow in a semiflexed position and with early range of motion begun at 2 to 3 weeks after injury. Complete healing generally occurs in 6 to 8 weeks. If more than 2 mm of displacement is present, then operative intervention is usually indicated. Treatment options include tension band wiring, olecranon screws, or plates (9). Range-of-motion exercises may be started in 1 week. Management of severely comminuted fractures is controversial and may require removal of the loose fragments.

Fractures of the coronoid process usually occur in combination with a radial head fracture, a dislocation of the elbow, or both. Large

coronoid fractures are often associated with persistent elbow instability even after reduction of the dislocation. Nondisplaced coronoid fractures may be missed on AP and lateral radiographs; thus, CT or MRI should be considered to rule out small fractures (10).

Fractures involving $<50\%$ of the coronoid process are often treated with closed reduction and splinting with flexion. Complicated coronoid fractures or fractures involving $>50\%$ of the coronoid may require internal fixation or a hinged external fixator. Treatment of these injuries should be performed in conjunction with an orthopedic surgeon.

Radial Head Fractures

Radial head fractures are the most common elbow injuries in adults. They usually occur as a result of a fall on the outstretched hand, which drives the radial head into the capitellum. On examination, patients have tenderness to palpation over the radial head and pain with pronation and supination of the forearm.

Fractures are classified as nondisplaced, displaced, or comminuted. Nondisplaced fractures may be difficult to visualize on standard radiographs. Any disruption of the normally smooth, concave cortical contour of the radial head suggests fracture. A positive fat pad sign on a lateral radiograph without evidence of fracture should raise suspicion for an occult radial head fracture. This fracture may be better visualized radiographically with a radial head–capitellum view.

Nondisplaced fractures are treated with a posterior splint or sling, followed by early range of motion after a few days. Aspiration of the hemarthrosis in the ED may provide pain relief and expedite mobilization. Minimally displaced fractures may be treated in a similar manner. Fractures displaced >3 mm or involving more than one-third of the joint surface are often treated with operative fixation (Fig. 39.7). However, the amount of displacement that favors open reduction with internal fixation (ORIF) rather than nonsurgical treatment has not been elucidated (11). These patients should begin early range of motion postoperatively.

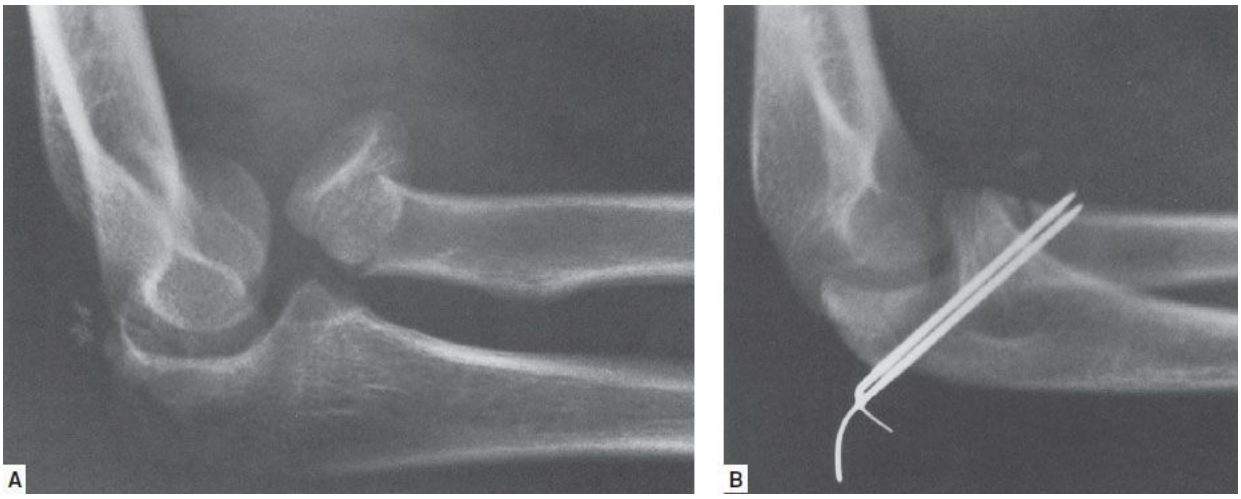


FIGURE 39.7 Displaced radial head fracture. (From Wilkins KE, ed. Operative Management of Upper Extremity Fractures in Children. American Academy of Orthopaedic Surgeons Monograph Series. Rosemont, IL: AAOS; 1994:57.)

Comminuted fractures may be treated with a sling and early range of motion in 1 to 2 weeks. Joint aspiration and injection of a local anesthetic can aid in assessing joint mobility. The treatment of severely comminuted and displaced fractures is controversial and may include excision of fragments or complete radial head excision, with or without prosthetic implants.

Any patient with a radial head fracture should also be examined for wrist tenderness. The *Essex-Lopresti lesion,* a radial head fracture with disruption of the distal radioulnar joint ligaments and forearm interosseous membrane, must be recognized early because internal fixation produces the best results (12).

Aspiration of the radiohumeral joint should be considered to relieve pain, promote early range of motion, and assess joint mobility with radial head fractures. This can be performed in the acute setting, to the great relief of the patient. Elbow joint aspiration is also indicated to diagnose a septic joint. The aspiration should be performed over the lateral elbow in the center of the triangle that connects the radial head, lateral epicondyle, and olecranon process (Fig. 39.8) (13). No neurovascular structures are located in this area, and the joint capsule is present beneath the skin and the thin

anconeus muscle. Using sterile technique, the skin over this area is anesthetized with a local anesthetic. An 18-gauge needle on a 10- to 20-mL syringe is directed into the center of the triangle and perpendicular to the skin. Aspiration of up to 5 mL of blood from the joint and injection of 1 to 2 mL of a long-acting anesthetic provide relief of pain and allow assessment of joint mobility.

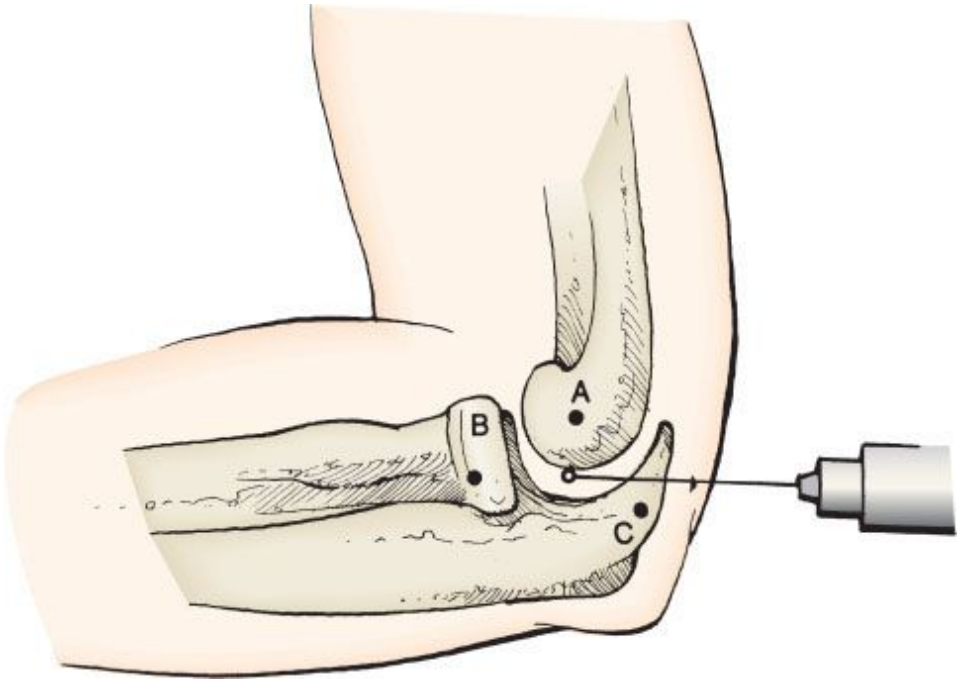


FIGURE 39.8 Elbow aspiration. The safest place to aspirate the elbow is in the center of a triangle produced by connecting (A) the lateral epicondyle of the humerus, (B) the radial head, and (C) the olecranon. (Adapted from Simon RR, Koenigsknecht SJ. Emergency Orthopaedics: The Extremities. 2nd ed. Norwalk, CT: Appleton & Lange; 1987, with permission.)

Nursemaid's Elbow

Subluxation of the radial head is most commonly seen in children 1 to 3 years of age but has been described even into the early teen years. The mechanism of injury is usually a sudden longitudinal pull of the forearm, causing fibers of the annular ligament to become stuck between the capitellum and the radial head. The child is

unwilling to move the arm, and the elbow is held in slight flexion with pronation of the forearm.

When a child presents with the characteristic history for radial head subluxation, radiographs are not necessary. However, the presence of swelling or deformity, or the child's refusal to resume normal use of the arm after reduction, is an indication for a radiograph.

Treatment usually consists of supination and flexion of the forearm in one continuous motion. The examiner's thumb can be used to apply pressure over the radial head. If this reduction maneuver is unsuccessful, pronation with extension is also described as an option (14). With successful reduction of a nursemaid's elbow, the child will resume using the arm normally within several minutes, and no further treatment is necessary.

Monteggia Fracture

Fracture of the proximal one-third of the ulna with dislocation of the radial head is a Monteggia fracture (Fig. 39.9). Based on the position of the radial head, there are four types of Monteggia fractures. The radial head dislocates anteriorly in 60% of cases, with posterolateral, lateral, and posterior dislocations being less common. The mechanism of injury involves direct trauma, forced hyperpronation, or hyperextension. The most commonly associated injury is paralysis of the radial nerve. The usual treatment is ORIF. Any patient found to have an ulnar fracture should be carefully examined for elbow pain or limitation of range of motion. The radiocapitellar line should be closely examined on the lateral elbow radiograph to ensure a normal relationship (15).

FIGURE 39.9 Monteggia fracture. The first component is fracture of the proximal one-third of the ulna; the second component is dislocation of the radial head.

Elbow Dislocation

Dislocation of the elbow accounts for 20% of all joint dislocations and is described by the direction in which the forearm is displaced in relationship to the distal humerus. Posterior and posterolateral dislocations account for 90% of all elbow dislocations. Dislocation may also occur between the radius and ulna. Posterior dislocations are caused by a fall on an extended and abducted arm. Patients present with significant swelling, tenderness, and deformity, with the elbow held in flexion and prominence of the olecranon. Anterior dislocation is the result of a blow to the olecranon while the elbow is held in extension with the forearm supinated and is associated with loss of the olecranon prominence.

Radiographs should be obtained before reduction to exclude associated fractures, which occur in up to 60% of patients with elbow dislocation. Avulsion fractures of the medial or lateral epicondyle, radial head and neck fractures, coronoid fractures, and supracondylar fractures in the younger patient may occur (16). A complete neurovascular examination must be performed on presentation. Neuropraxia is present in 20% of patients, most commonly involving the ulnar and median nerves. As with most nerve injuries associated with dislocations and fractures, these deficits are usually transient (17). Brachial artery injury is most commonly associated with open dislocations and those with concomitant fractures. The incidence of vascular injury is greater with anterior dislocations. Closed dislocations are rarely associated with vascular injury, especially in the absence of accompanying fracture (18).

Analgesia and muscle relaxation are required for closed reduction. Posterior, medial, and lateral dislocations are reduced using the same technique. With the patient lying supine, the area of the wrist and forearm is grasped, and traction is applied along the long axis of the forearm. An assistant provides countertraction to the upper arm. Any medial or lateral displacement is corrected. While forearm traction is continued, the elbow is flexed, and a palpable “clunk” should be felt as the elbow is reduced. Downward pressure over the proximal forearm may aid in disengaging the coronoid from the olecranon fossa (Fig. 39.10). After reduction, the neurovascular examination should be repeated and postreduction films obtained. The elbow should be flexed to 90 degrees as long as good pulses are maintained and then immobilized in a posterior splint. Patients should be assessed serially over 2 to 4 hours after reduction for vascular injury to the brachial artery. Any concern for vascular compromise should prompt consultation with an orthopedic or vascular surgeon. All patients should follow up with an orthopedic surgeon within 1 week to begin early range-of-motion exercises and help prevent contractures.

FIGURE 39.10 Technique for reduction of posterior dislocation of the elbow.

Indications for open reduction include an associated fracture, open dislocation, neurovascular injury, or inability to accomplish a closed reduction. Long-term complications include stiffness, contractures, neurovascular injury, heterotopic bone formation, and ankylosis. Recurrent elbow dislocations are rare.

Epicondylitis

Tennis elbow, or *lateral epicondylitis,* is an "overuse syndrome" characterized by inflammation at the radiohumeral joint or the lateral epicondyle. It is believed to represent a failure (microtearing of the ligament) of the extensor carpi radialis brevis attachment to bone in this region (19). It is most commonly seen in athletes or adults with occupations requiring repeated rotary motion, as in twisting or grasping (e.g., tennis players, pipefitters, and carpenters) (20). The gradual onset of a dull ache appears over the lateral epicondyle and radiates into the forearm. Dorsiflexion of the wrist and supination of the forearm against resistance with the elbow extended will reproduce the pain. Radiographs should be obtained to exclude an associated fracture. In chronic conditions, calcification may be seen over the lateral epicondyle.

The mainstay of treatment is avoidance of the offending activity and immobilization. A posterior splint is applied with the elbow flexed 90 degrees, the forearm supinated, and the wrist slightly dorsiflexed. Moist heat, nonsteroidal anti-inflammatory agents (NSAIDs), and physical therapy may be helpful. Local infiltration of the affected area with 1 to 2 mL of a corticosteroid and anesthetic mixture will give dramatic relief. Although corticosteroid injection is effective in the short term, it does not provide a clear long-term therapeutic benefit. All patients should have an orthopedic or sports medicine referral.

Medial epicondylitis, or "*golfer's elbow,*" is similar to tennis elbow and involves the common flexor origin at the medial epicondyle of the humerus. It is seen in golfers but occurs more frequently in people who routinely perform household chores, manual labor, and other tasks involving repetitive movements. Maximal tenderness is localized over the medial aspect of the elbow and medial epicondyle. Treatment is similar to that for lateral epicondylitis, and routine orthopedic follow-up (in 7 to 10 days) should be arranged. Surgery is often performed if there is no response after 3 to 6 months of conservative treatment (21).

Olecranon Bursitis

Olecranon bursitis is inflammation of the bursa overlying the olecranon process at the proximal aspect of the ulna. The bursa functions to provide a mechanism for the skin to glide freely over the olecranon process, preventing tissue tears. Inflammation of the bursa can be caused by a variety of mechanisms, including acute trauma; chronic friction (due to overuse, also known as "draftsman's bursitis"); crystal deposition (e.g., gout, pseudogout); local infection; and systemic diseases such as rheumatoid arthritis, scleroderma, uremia, and oxalosis. Regardless of the etiology, patients usually present with focal swelling and pain exacerbated by pressure over the posterior aspect of the elbow. Flexion of the elbow may be slightly restricted, due to tightening of the skin over the inflamed bursa. Regardless of etiology, the area may be warm and tender, so this is not a reliable determinant of infectious versus other etiologies. Repetitive trauma can result in a chronic inflammatory process and a thickened, rubbery, and usually painless bursa.

Aspiration of the bursa is essential for both diagnostic and therapeutic purposes if infection is suspected. The aspirated fluid should be analyzed for crystals, Gram stain, cell count, and cultures. The cell count should be interpreted in light of the clinical picture and other synovial fluid results, as there is considerable overlap between expected counts in noninflammatory, inflammatory, and infectious conditions. Cell counts $>$50,000 to 100,000 white blood cells (WBCs) per mm^3 and cell counts with polymorphonuclear cells (PMN) predominance are strongly suspicious for infectious etiologies. However, cell counts can be as low as 5,000 WBC per mm^3 in cases of early infection. In these situations, the Gram stain and culture become critical in the evaluation of the fluid results. The bursa is aspirated utilizing an 18-guage needle from a posterolateral approach so that the ulnar nerve is not inadvertently injured. Care should be taken to avoid aspiration of the bursa through an area of superficial cellulitis, to avoid seeding of a noninfected bursa. Patients suspected of having septic bursitis should be treated with antibiotics while awaiting culture results. *Staphylococcus aureus* is the most commonly identified organism in septic olecranon bursitis, and high resistance to penicillin has been reported (22). Antistaphylococcal

coverage should be provided. Besides antibiotics in cases of suspected infectious bursitis, other measures that can be utilized include analgesia (NSAID and narcotic), moist heat, and splinting for comfort. Occasionally, cases of septic bursitis will require serial aspiration (every 1 to 3 days) to resolve. Rarely, in cases that progress despite drainage and antibiotics, open incision and drainage will be required by an orthopedic or general surgeon.

In simple noninfectious olecranon bursitis, drainage of the bursa should be considered with subsequent compression dressing, NSAIDs, and protective measures to prevent recurrence. Symptoms may be recurrent, and serial drainage may be required. In refractory cases, bursal excision by a surgeon may be performed.

Rupture of the Distal Biceps or Triceps Tendon

Distal rupture of the biceps tendon may be the result of degenerative changes or sudden, forceful flexion of the elbow against resistance. Patients present with a history of a painful snap at the elbow. Flexion of the elbow and supination of the forearm are weakened. On flexion, the belly of the biceps retracts, producing a bulbous swelling in the upper arm. The treatment is surgical if significant motor weakness is present and should occur within 2 weeks after injury (23).

Avulsion of the triceps tendon should be considered in patients with pain, swelling, and weakness with arm extension. A defect is often palpable just proximal to the olecranon. Associated injuries include radial head and neck fractures and wrist fractures. The diagnosis is confirmed radiographically when a bony avulsion is seen on the lateral view of the elbow. Orthopedic consultation in the ED within 24 to 48 hours should be assured, and early surgical treatment is usually recommended.

Osteochondritis Dissecans

Osteochondritis dissecans (OCD) is a process of avascular necrosis of the subchondral bone and the overlying articular cartilage and is most common in males and adolescents. There is usually a history of

trauma or sports-related activities. Repetitive trauma or overuse is thought to lead to microfracture and compromised circulation on the subchondral bone, followed by separation of the articular surface and formation of loose bodies (24). Patients may complain of the gradual onset of dull, aching pain; limited extension; intermittent swelling; and catching, locking, or clicking of the affected elbow (25). The capitellum is the most common site of involvement, and joint effusion may be present. Diagnosis is made in the ED using plain x-rays of the involved joint. The clinician may either see the lucency of the fracture or an osteochondral fragment free in the joint. MRI is useful for distinguishing normal cartilage and bone formation from edema and OCD irregularities (26). Treatment consists of immobilization with a sling or cast, avoidance of all throwing activities, and NSAIDs. Loose bodies within the joint may restrict movement of the elbow and should be surgically removed. Prognosis is usually good.

CRITICAL INTERVENTIONS

- Assess the radial head for dislocation in patients with a fracture of the proximal ulna. Monteggia fractures require internal fixation, whereas isolated ulna fractures are treated with immobilization.
- In patients with radial head fractures, examine the wrist for the Essex-Lopresti lesion. These patients require internal fixation, whereas radial head fractures are usually treated conservatively.
- Obtain radiographs before reducing an elbow dislocation to exclude associated fractures, except with nursemaid's elbow. Postreduction films should always be obtained (except with nursemaid's elbow).
- Measure the anterior humeral line to aid in diagnosing supracondylar fractures in children. Splint the arm if a significant mechanism of injury or swelling exists, and refer for orthopedic consultation.

DISPOSITION

Disposition of patients with elbow injuries is important, as deformity or loss of motion at the elbow can affect proper function of the forearm, wrist, and hand. Clearly, any patient with an open fracture or neurovascular compromise after elbow injury needs urgent ED consultation. Compartment syndrome, due to the location of the brachial artery, and neurologic entrapment may occur after injuries to this region. All pediatric supracondylar fractures are concerning for complications and future disability, and orthopedic consultation in the ED may be necessary. Occasionally, patients in this group with nondisplaced supracondylar fractures can be splinted and discharged but only if urgent orthopedic follow-up is assured (24 to 48 hours), and the patient and parents are fully cognizant of warning signs that would require return to the ED. Most nondisplaced elbow fractures in adults seen in the ED will require urgent orthopedic follow-up (24 to 48 hours), but this decision should be made in phone consultation with the orthopedist who will be seeing them subsequently.

Common Pitfalls

- Failure to diagnose an occult radial head fracture. This injury should be suspected when a positive fat pad sign is present on radiography without demonstrable fracture. Oblique views of the radial head may demonstrate the fracture.
- Making the assumption that a negative radiograph rules out elbow injury. Injuries to cartilaginous and ligamentous structures, as well as soft tissues, may be present. Splinting of the elbow and orthopedic referral should be considered for patients with a significant mechanism of injury.
- Failure to diagnose neurovascular injury. A careful neurovascular examination should be documented, in addition to interval reexamination.
- Failure to diagnose avulsion of the biceps muscle from the bicipital tuberosity of the radius. The patient will still be able to flex the elbow with the brachialis muscle.

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CHAPTER 40 Wrist and Forearm Injuries

James R. Gardner and Carl R. Chudnofsky

Wrist injuries are among the most common emergency department (ED) complaints, are often difficult to accurately diagnose, and may result in decreased use of the associated hand if left undiscovered and untreated. Outcome depends on accurate assessment of the injury, appropriate initial management, and prompt recognition of those injuries that require immediate specialty consultation or outpatient referral.

To adequately diagnosis and treat wrist injuries a basic understanding of the underlying anatomy is crucial. The central portion of the wrist is composed of eight carpal bones connected by over 20 ligaments. With the exception of the pisiform (which is actually a sesamoid bone in the tendon of the flexor carpi ulnaris), the carpal bones lack direct muscular attachments. Instead, they function as a passive "intercalated" joint, whose movement is governed by muscles that originate on the radius and ulna and insert on the metacarpals.

To reduce this anatomic complexity, the wrist may be thought of in a simpler, more functionally oriented fashion. Specifically, the eight carpal bones may be grouped into four primary working units —the *scaphoid,* the *lunate,* the *triquetrum,* and the *distal row* (Fig. 40.1). Though it has important stabilizing functions, the pisiform may be neglected in this model, since it lies outside the plane of the other bones and is less important in defining wrist motion. The four bones of the distal row—the *trapezium, trapezoid, capitate,* and *hamate* —are tightly bound and for conceptual purposes, may be viewed as a single unit with the capitate at the center. The articulations of these

four functional units, with each other and with the forearm, allow the bulk of wrist movement (1,2).

FIGURE 40.1 Key conceptual components of carpal anatomy. T, triquetrum; L, lunate; S, scaphoid; DR, distal row; *, space of Poirier. (Graphic overlay by Dr. Gardner J.R. X-ray from Moore KL and Agur A. Essential Clinical Anatomy. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002. Courtesy of Dr. E.L. Lansdown, Professor of Medical Imaging, University of Toronto, Toronto, Ontario, Canada.)

The lunate and scaphoid bones attach to the radius, whereas the distal row attaches firmly to the metacarpals. The intracarpal ligamentous connections are arranged in an "oval" fashion; the distal row attaches to the scaphoid and triquetrum, which then attach to either side of the lunate. The central junction between the distal row and the lunate has no direct ligamentous attachments. This "space of Poirier" enhances mobility, but also provides a locus of anatomic instability when the wrist is injured (3).

While both the triquetrum and the scaphoid provide connection and rotation between the proximal lunate and the distal row, the scaphoid deserves particular attention. Unlike the relatively compact

triquetrum, the scaphoid is an elongated bone that rotates through a wide arc during wrist movement. In addition, the scaphoid attaches directly to the radius, assuming significant load-bearing responsibilities. The scaphoid's elongated shape and load-bearing function enhance its susceptibility to injury, making it the most frequently fractured carpal bone (4).

The *forearm* consists of the radius and ulna, although only the radius directly articulates with the carpal bones (the lunate and the scaphoid). The distal radius has three articular surfaces: the *radiocarpal joint* (RCJ), the *distal radioulnar joint (DRUJ),* and the *triangular fibrocartilage complex (TFCC)*.

The RCJ is formed by a concavity in the distal radius where the scaphoid and lunate bones are seated. Radiocarpal ligaments originating on the radial styloid and on the edges of the RCJ concavity stabilize the radiocarpal connection. Fractures to these segments of the radius may destabilize the carpal bone complex.

The DRUJ is formed by a shallow concavity on the side of the radius where the ulna rests. The radius rotates about the ulna at this point.

The TFCC is a soft tissue complex located on the distal end of the ulna. It is composed of an articular disc that interposes between the ulna and the carpal bones, as well as ligamentous attachments that tether to the lunate and triquetrum distally and to the radius proximally. The proximal attachments serve to stabilize the DRUJ.

The *interosseous membrane* is a collection of fibrous bands that join the radius and ulna along their entire length. This membrane translates mechanical load from the radius onto the ulna, which in turn translates the load to the upper arm. Because of this tight membranous connection, injury to either forearm bone often results in a fracture of the other or causes a dislocation of either the distal or proximal joints (see Forearm Fracture–Dislocations below) (5).

The *ulnar nerve* and *ulnar artery* enter the *volar* aspect of the wrist next to the pisiform bone, running under the *palmar carpal and pisohamate ligaments* in a tissue space known as *Guyon canal.* The *flexor retinaculum,* which lies beneath the Guyon canal, forms the roof of the *carpal tunnel.* The carpal tunnel is the deepest volar space

of the wrist and contains the *median nerve,* flexor pollicis longus, and all of the digital flexors. On the *dorsal* aspect of the wrist, the *radial artery* dives from its volar position in the forearm to run across the dorsal surface of the scaphoid and trapezium. It then circles back over the first metacarpal to form the *deep palmar arch.* The *superficial branch of the radial nerve* also crosses the dorsoradial aspect of the wrist, but unlike the radial artery it runs much nearer the surface, superficial to the fascial plane.

CLINICAL PRESENTATION

Patients with wrist injuries complain of varying degrees of pain, swelling, and limited range of motion in the wrist or forearm. Fractures of the distal radius or ulna may be confused with, or accompanied by, a carpal injury. The carpal bones in children are primarily cartilaginous; as such, carpal injuries are rare. Children are more likely to injure the weakest part of the wrist complex—the immature radial metaphysis or its epiphyseal growth plate. In contrast, the elderly more commonly injure the distal radius because of osteoporosis.

ED EVALUATION

Important historic information includes hand dominance; occupation and avocation; prior hand injuries and preinjury hand function; past medical history (e.g., diabetes mellitus, immunosuppression), including previous tetanus immunizations; and time, mechanism, and circumstances of injury. Mechanism of injury is particularly important, as the precise position of the hand and wrist during the injury help guide investigation and treatment.

On physical examination, surface anatomy should be used to identify and examine specific structures. The volar wrist crease marks the location of the proximal carpal bones and the flexor retinaculum. The EP should palpate the pisiform bone at the base of the hypothenar muscles just distal to the volar crease and the hook of the hamate in the soft tissue of the palm 1 cm distal and radial to the pisiform. On the dorsal side of the wrist the *anatomic snuff box* (*ASB*) is formed by the *radial styloid* proximally, the extensor pollicis

brevis tendon radially, and the abductor pollicis longus tendon along the ulnar aspect. The scaphoid is palpated in the floor of this space. Moving in an ulnar direction from the radial styloid, a small bony prominence (the *Lister tubercle*), can be palpated on the dorsal radial surface. The *scapholunate joint* lies immediately distal to this prominence. With the hand in the neutral position, a small depression can be palpated midway between the base of the third metacarpal and the Lister tubercle. The capitate lies just distal to this depression. With wrist flexion, the depression disappears, and the lunate can be palpated proximally. The ulnar styloid is the largest bony prominence on the ulnar aspect of the wrist—the TFCC and triquetrum are located just distally (6).

It is important to note that damage to important underlying structures may occur despite innocuous-appearing surface wounds. Consequently, it is essential to explore lacerations and evaluate tendon function through a full range of motion. Neurovascular testing is best performed in the hand and is described in Chapter 41. The EP should always test neurovascular integrity before the instillation of local anesthetics.

Radiographs of the wrist and forearm should be obtained in all but the most trivial of injuries. On an adequately positioned posterior–anterior (PA) view (Fig. 40.2), the distal radius and ulna should not overlap, and the third metacarpal axis should be in line with that of the radius. The radial styloid should project between 9 and 15 mm beyond the DRUJ and should create an ulnar inclination of 15 to 30 degrees. A normal PA radiograph should also demonstrate three arcs outlining the carpal bones. The proximal and distal surfaces of the scaphoid, lunate, and triquetrum make up the two proximal arcs, whereas the distal third is formed by the proximal surfaces of the capitate and hamate in the midcarpal area. The carpal bones should be separated from one another by no more than 2 mm; increased intercarpal spaces imply ligamentous disruption and potential instability.

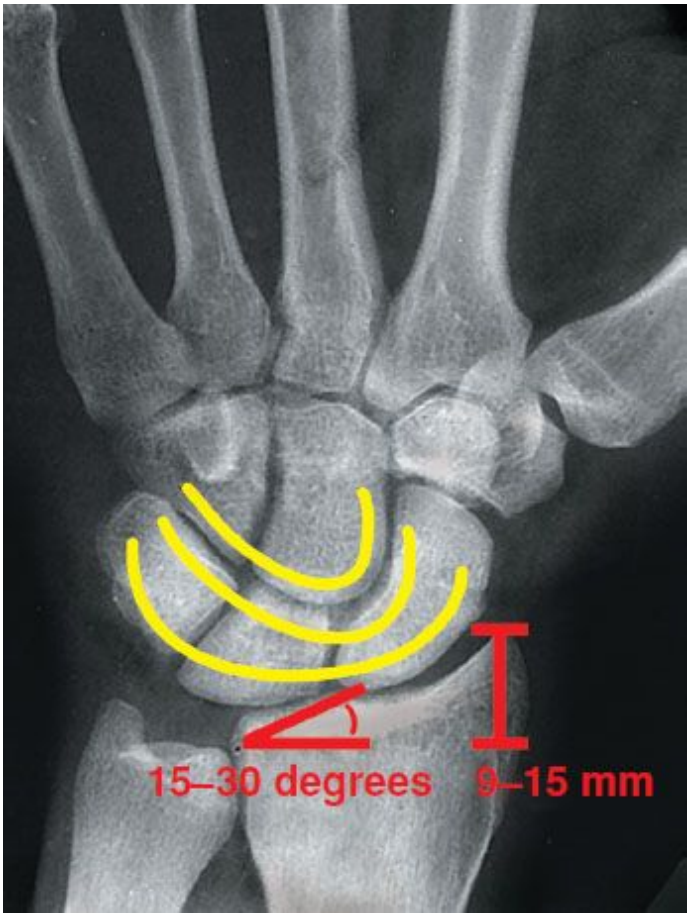

FIGURE 40.2 PA radiograph of wrist. Note 9 to 15 mm of radial styloid projection past the DRUJ, 15 to 30 degrees of ulnar inclination of the distal radius, three smooth arcs outlining the carpal bones, and no more than 2 mm of separation between carpal bones. (Graphic overlay by Dr. J.R. Gardner. X-ray from Moore KL and Agur A. Essential Clinical Anatomy. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002. Courtesy of Dr. E.L. Lansdown, Professor of Medical Imaging, University of Toronto, Toronto, Ontario, Canada.)

On an adequately positioned lateral projection (Fig. 40.3), the palmar edge of the pisiform should lie between the scaphoid and capitate. The normal volar tilt of the radius is between 10 and 15 degrees and the radius, lunate, and capitate are arranged in a straight line (their axes should not vary by more than 10 to 20 degrees). The lunate appears as a “cup in a saucer” articulating with

the distal radius, and the articular surfaces of the three bones create neatly overlapping "C"s. The scaphoid and lunate axes should form an angle of 30 to 60 degrees (the scapholunate angle); an angle of more than 70 degrees is abnormal and suggests scapholunate dissociation (7).

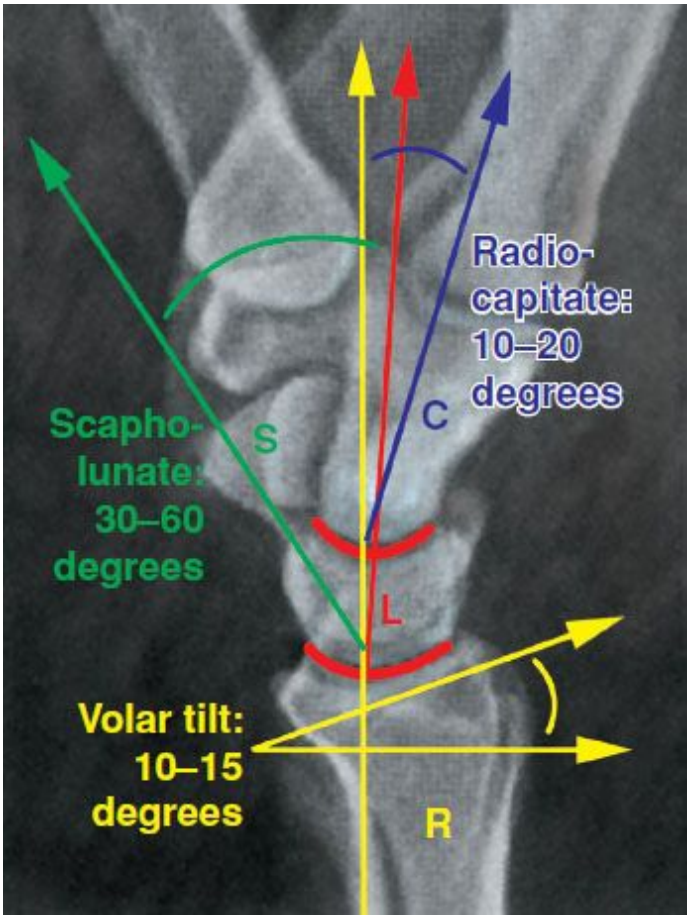

FIGURE 40.3 Lateral radiograph of wrist. Note 10 to 15 degrees of volar tilt of the distal radius (R); smooth "C"-shaped articulations between the radius, lunate (L), and capitate (C); 10 to 20 degrees of axial variance between the radius and capitate; and 30 to 60 degrees of axial variance between the scaphoid (S) and lunate. (Graphic overlay by Dr. Gardner JR. X-ray courtesy of Dr. E. Becker, University of Toronto, Toronto, Ontario, Canada.)

Oblique radiographs project the pisiform and triquetrum away from the other carpal bones making identification of fractures to

these bones easier. Additional radiographic views (e.g., scaphoid view, carpal tunnel view) may be helpful in certain cases; however, CT imaging is increasingly being utilized to evaluate more subtle or complex injuries.

KEY TESTING

- Wrist x-rays (PA and lateral views; other views as needed)
- Forearm and elbow x-rays, if indicated
- Evaluate for ligamentous instability
- Evaluate for tendon disruption
- Evaluate for associated neurovascular compromise

ED MANAGEMENT

During evaluation, the EP should temporarily immobilize, elevate, and apply ice packs to the injured wrist. Analgesics should be administered to control pain and intravenous antibiotics administered for open fractures and dislocations and for severely contaminated or infected wounds. The EP should provide tetanus immunization as needed (see Chapter 21) and cover open wounds with sterile, moist gauze pending radiographs, surgical consultation, or wound closure.

Carpal Fractures

Carpal fractures account for 8% to 19% of all hand and wrist injuries. They are far more common in adults than in pediatric patients in whom the carpal bones remain largely cartilaginous. If not recognized and properly treated, carpal fractures may lead to significant disability, including arthritis, nonunion, loss of function, and *avascular necrosis* (*AVN*).

As noted previously, *scaphoid fractures* are the most common carpal bone fractures (60% to 80%). The injury is most often caused by an axial load or "*fall-on-an-outstretched-hand*" *(FOOSH),* with the main impact on the thenar eminence. Patients usually complain of pain in the radial wrist, particularly with pressure or movement. Tenderness on palpation of the ASB is a common feature. Examining

the wrist in ulnar deviation brings the scaphoid up from the floor of the ASB, making it easier to assess. Scaphoid loading (applying axial pressure on the thumb) elicits pain in many patients (eFig. 40.1).

The blood supply to the scaphoid is notoriously fragile, entering the bone distally via small branches off the radial artery. As a result, scaphoid fractures have an increased risk of proximal AVN, nonunion, and pseudoarthrosis (4).

Isolated *lunate fractures* are relatively rare; they occur more commonly in association with other wrist injuries. Given the anatomic location of the lunate in the space of Poirier, the application of significant force to the lunate is more likely to produce a perilunate or lunate dislocation (see Carpal Ligamentous Injury below). Patients will complain of pain in the middle of the wrist and axial loading of the third metacarpal causes pain. Examination reveals tenderness over the lunate.

Like the scaphoid, the blood supply to the lunate enters distally, giving these injuries a high incidence of AVN (known as *Kienböck disease*), nonunion, and subsequent carpal instability. Patients with Kienböck disease present with pain localized in the area of the lunate, stiffness, occasional swelling, and marked loss of grip strength; a history of significant wrist trauma is often lacking. Plain radiographs demonstrate sclerosis and collapse of the lunate.

Trapezium fractures are often due to a direct blow to the thumb or forced dorsiflexion. There is tenderness at the ASB and thenar eminence; decreased thumb pinch strength secondary to pain is another diagnostic clue. These fractures are often intra-articular and can extend distally, where they are analogous to a *Bennett* or *Rolando* fracture of the thumb metacarpal (see Chapter 41, “Hand Injuries”).

Nondisplaced scaphoid, lunate, or trapezium fractures are treated with immobilization in a thumb spica splint and timely follow up with a hand surgeon. Immediate consultation should be obtained for open and/or unstable fractures, fractures with displacement of ≥ 1 mm, and those associated with other wrist fractures or dislocations.

On the ulnar side of the wrist, *triquetrum fractures* are most often dorsal avulsion fractures due to a FOOSH, or they occur when rotation of the hand is suddenly resisted, causing the hamate or ulnar

styloid to forcefully impact the triquetrum. Patients complain of dorsal wrist pain and are maximally tender just distal to the ulnar styloid. Dorsal triquetrum fractures are best seen on lateral or oblique radiographs of the wrist with the hand in slight pronation (a "triquetral view") where the fractured fragment appears as a small piece of bone dorsal to the triquetrum. Triquetrum body fractures are less common and imply significant force. They are frequently accompanied by other fractures and/or ligamentous injuries.

Though rare, *hamate fractures* usually present with sudden pain to the ulnar wrist when a swinging motion (i.e., golf club, bat) has been abruptly interrupted. Pain is maximal over the hamate, which is located 1 cm distal and just radial to the pisiform. Pain is also often noted in the fourth and fifth fingers with active grasp or when flexion is resisted. The hook is fractured much more frequently than the body of the hamate; hook fractures are best demonstrated on a "carpal tunnel" view.

For both triquetrum and hamate fractures, the EP should carefully assess the integrity of the ulnar nerve and artery. Fractures of the hamate hook in particular may be associated with compression of Guyon's canal. Treat uncomplicated fractures of the triquetrum or hamate with volar splinting in the neutral position and close hand surgery follow-up. Fractures that are unstable, displaced, open, or associated with other wrist injuries or neurovascular compromise require immediate specialty consultation.

Fractures of the pisiform, capitate, and trapezoid are extremely rare. *Capitate fractures* bear mention for two reasons: The capitate has a distal blood supply, placing it at risk for AVN, and the fracture is often missed owing to the more obvious surrounding bony and ligamentous injuries that frequently accompany it. The EP should splint these injuries in a short-arm thumb spica with the wrist in slight dorsiflexion and the thumb immobilized to the IP joint and be sure to consult with a hand specialist prior to discharge (8,9).

Occult Carpal Fractures

Studies have shown that 23% to 36% of patients with concerning examination findings after wrist trauma (e.g., ASB tenderness,

significant wrist pain, or swelling) will have fractures that are not appreciated on initial x-rays (10,11). Consequently, the diagnosis of "wrist sprain" should be made with trepidation. About one-third of occult fractures involve the scaphoid; less-common sites include the distal radius, other carpal bones, and proximal metacarpals. MRI has been touted as the gold standard for diagnosis in such cases. Nevertheless, in the hands of an experienced radiologist, CT has also been found to have excellent sensitivity (95% to 100%) and negative-predictive value (12,13).

Traditional therapy for suspected occult fractures has been immobilization and close outpatient follow-up for repeat examination and plain radiographs. Recently, advanced imaging (e.g., MRI, CT) in the ED has been advocated as a more accurate and possibly more cost effective treatment option (14). Until definitive studies are performed, therapy for occult fractures is best guided by institutional policies, local practice, or personal preference.

Carpal Ligamentous Injury

Injuries to the carpal ligaments range from partial tears ("sprains") to complete disruption accompanied by carpal dissociation or dislocation. As with carpal fractures, most ligamentous injuries are caused by a FOOSH mechanism. In 1980, Mayfield et al. (15) observed that such ligamentous injuries tend to develop in a predictable pattern that begins radially and proceeds in a circular fashion around Poirier's space as more force is applied.

In Mayfield's model, the proximal scaphoid ligaments are the first to be damaged, causing scapholunate dissociation. This leads to forward flexion and radial displacement of the scaphoid. Because of the resulting unopposed action of the triquetrum, the lunate and distal row rotate dorsally. This pattern is known as *dorsal intercalary segment instability* (DISI) (eFig. 40.2).

Clinically, patients complain of wrist pain, dorsal swelling, and wrist weakness. They may also note an unpleasant snapping sensation with wrist movement. However, overall range of motion may be preserved and the injury may appear relatively minor.

The PA wrist x-ray demonstrates widening of the scapholunate joint to >2 mm ("Terry Thomas sign") (Fig. 40.4), as well as foreshortening of the scaphoid as it rotates into forward flexion causing the appearance of the "scaphoid ring" sign. On the lateral view, the scapholunate angle increases to >60 degrees, while the axis of the lunate becomes angled dorsally to the axis of the radius. Of note, isolated rupture of the scapholunate ligament may occur without causing these radiographic findings—the presence of such changes means that secondary supporting ligaments have been torn as well (16).

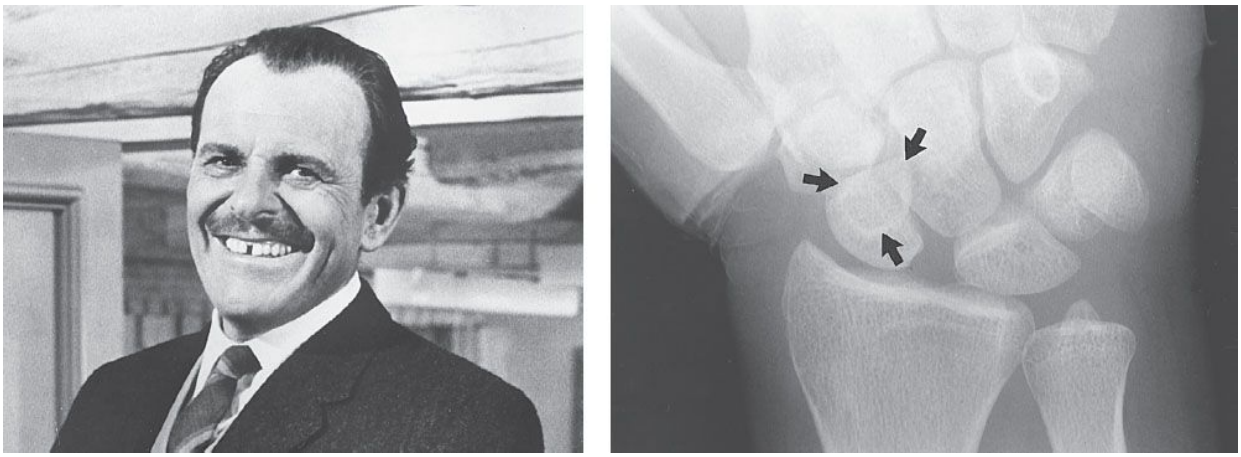

FIGURE 40.4 Scapholunate dissociation. Note the widened scapholunate space ("Terry Thomas" sign) and the foreshortened scaphoid with a "scaphoid ring" sign (arrows). Adjacent is British comedian Terry Thomas and his famous teeth. (Courtesy of the Bettmann Archive.)

If further stress is applied to the wrist, the path of ligamentous disruption travels to the distal carpal ligaments, leading to dorsal dislocation of the distal row, particularly the capitate. When this occurs, the capitate may be palpated dorsally and there is usually significant wrist pain and swelling. On a PA view the capitate and lunate overlap, whereas on the lateral view the capitate now lies dorsal to the lunate.

With continued stress, the pattern of ligamentous damage circles back around to the triquetrolunate ligament. When this ligament

ruptures, the triquetrum dislocates dorsally as well, leaving the lunate attached only to the radius, thus completing a full *perilunate dislocation.* On lateral view the axis of the lunate now angles forward.

In the final stage, the dorsal radiolunate ligaments rupture, and the lunate, now tethered only by its volar attachments, flips forward out of its RCJ socket, while the capitate falls into the space that the lunate had previously occupied. This is a *lunate dislocation.* On PA view the lunate will appear triangular (the "Piece of Pie" sign) and there may be substantial overlap of the capitate and lunate (Fig. 40.5A). On lateral view the lunate is pushed forward off the radius, creating the "spilled teacup" sign (Fig. 40.5B). It should be noted that the lunate dislocates into the space of the carpal tunnel, causing median nerve impingement in 16% to 46% of cases (3,16).

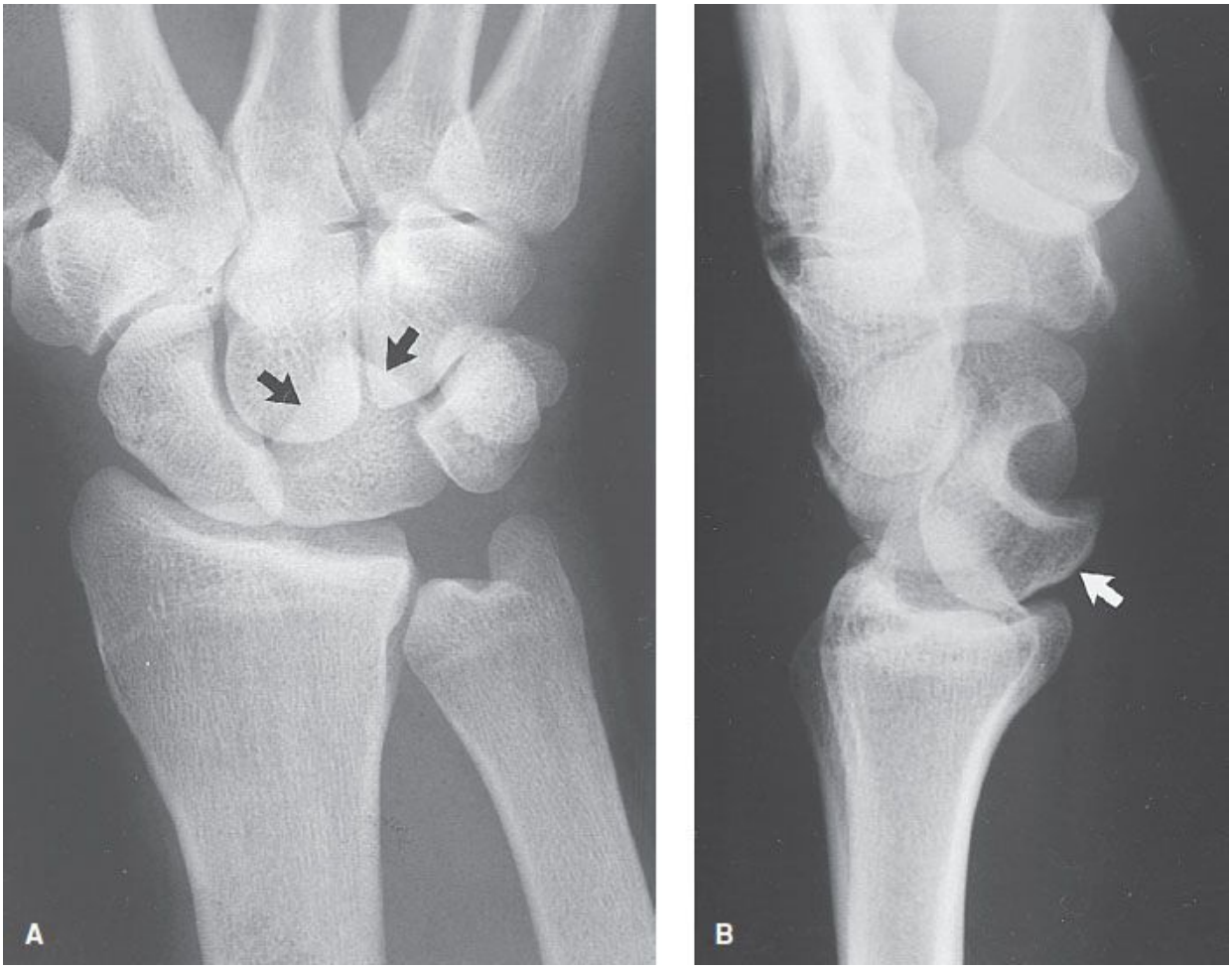

FIGURE 40.5 Lunate dislocation. On PA view (A), note the triangular shape of the lunate ("piece of pie" sign, black arrows) and the overlap of the lunate and other carpals. On lateral view (B), note how the lunate has rotated forward almost 90 degrees ("spilled teacup" sign, white arrow). (From Terry R. Yochum, Lindsay J. Rowe. Yochum and Rowe's Essentials of Skeletal Radiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

Mayfield's progression may also occur in the reverse order, starting with triquetrolunate disruption and proceeding radially around Poirier's space. In this scenario, the initial injury is an isolated triquetrolunate rupture, which in many respects is the ulnar equivalent of a scapholunate rupture. When this occurs, the lunate will be subjected to unopposed forward flexion by the scaphoid. Thus, on lateral radiographs the lunate axis will be angled volarly, but the scapholunate angle will be unchanged. This pattern is known as *volar intercalary segment instability* (VISI).

Isolated scapholunate or triquetrolunate ligamentous ruptures should be treated with radial or ulnar gutter splints, respectively, and referral for timely hand surgery follow-up. However, perilunate dislocations, perilunate fracture–dislocations, and lunate dislocations all require immediate specialty consultation. These injuries represent the end point of extensive ligamentous and bony disruption, and as such may be accompanied by significant neural compromise and serious long-term disability. Many hand surgeons will attempt closed reduction in the ED, but definitive treatment requires ORIF.

Distal Radial Fractures

Distal radius fractures are common, accounting for about one-sixth of all adult fractures seen in the ED. They are even more common in children, accounting for 20% to 35% of all pediatric fractures and 25% to 50% of pediatric physeal fractures. Radiographically occult Salter–Harris type 1 fractures are common in this population. Therefore, as with adults, the diagnosis of a simple wrist "sprain" in children should be made with great caution (17).

A *Colles* fracture is a dorsally displaced radial metaphyseal fracture, usually caused by a FOOSH, and is the most common of all wrist fractures. Dorsal bone comminution is often seen, and extension into the RCJ or DRUJ can occur. A fracture of the ulnar styloid is seen in up to 60% of cases suggesting associated injury to the TFCC. On examination, the wrist will have the classic "dinner fork" or dorsiflexion deformity. Associated pressure on the median nerve may produce palmar paresthesias. On PA radiograph, the distal radius may appear shortened. The lateral radiograph provides the best view of the angulation and comminution (eFig. 40.3).

Uncomplicated Colles fractures may be reduced in the ED, but fractures associated with postreduction instability, intra-articular involvement, marked comminution, >20 degrees of angulation, or >5 mm of radial shortening usually require surgical intervention. Hence, these injuries require emergent consultation. In addition, any neurovascular compromise or an open fracture requires immediate surgical evaluation (18).

A *Smith* fracture, also known as a *reverse Colles,* is a fracture of the distal radius with volar angulation of the distal fracture fragment. This injury is produced by a blow to the dorsum of the wrist or a FOOSH in supination. The hand is palmarly displaced, creating the so-called *garden spade* deformity. PA and lateral radiographs are diagnostic. The complications and treatment are similar to those for a Colles fracture (eFig. 40.4).

A *Barton* fracture is an oblique intra-articular fracture of the volar or dorsal rim of the distal radius. The more common dorsal rim fracture results from forced pronation and dorsiflexion of the wrist, whereas the volar rim fracture results from a fall on the supinated outstretched hand. Associated ligamentous injuries may produce radiocarpal instability. Treat nondisplaced fractures with immobilization in a short-arm volar splint. Fractures involving more than 50% of the articular surface, fractures associated with carpal subluxation, and displaced fractures require emergent consultation as they frequently require ORIF (eFig. 40.5).

A direct blow along the radial side of the wrist can produce an oblique or transverse fracture of the radial styloid. Intra-articular

radial styloid fractures are also known as *Hutchinson* or *Chauffeur's* fractures. These are most easily seen on a PA radiograph and appear as a thin, lucent line proximal to the radial styloid. Because the major carpal ligaments of the radial wrist insert on the radial styloid, these fractures can produce carpal instability. ORIF is often required for even minimal displacement. Posttraumatic arthritis may be worsened if associated intercarpal ligament tears go unrecognized and untreated.

Distal radius fractures are associated with a number of potential complications. Acute carpal tunnel syndrome with median nerve impingement may develop in 5% to 8% of patients. Symptoms include pain, paresthesias and numbness in the median nerve distribution, and weakness of thumb opposition. More generalized *forearm compartment syndromes* are rare, but can be potentially devastating if not promptly recognized and treated. A compartment syndrome will primarily produce severe pain, but examination may also reveal tense compartments on palpation, pain with passive finger flexion and extension, and diffuse paresthesias or numbness distally. These symptoms necessitate emergent specialty consultation to prevent permanent disability (19).

Up to 10% of adults with distal radius fractures will go on to develop some degree of *complex regional pain syndrome*. This disabling condition is characterized by persistent pain and hyperalgesia accompanied by vasomotor and sudomotor changes in the affected extremity. The etiology is not well understood, though abnormal distal nerve regeneration is thought to play a role. Women in their 50s to 70s are particularly at risk. Several studies have demonstrated that the prophylactic administration of Vitamin C, 500 mg PO daily for up to 2 months (a dose commonly found in over-the-counter supplements) helps to reduce the incidence of this syndrome, possibly through its antioxidant effects. Consider this treatment for at-risk patients (20,21).

Distal Ulnar Fractures

Ulnar shaft fractures (also known as *nightstick fractures*) most often result from direct blows to the forearm. Nondisplaced nonangulated

fractures are immobilized in a sugar tong splint with the elbow in 90 degrees of flexion and the forearm neutral. Close follow-up should be arranged and the patient instructed to watch closely for further swelling. Fractures with >10 degrees of angulation or with displacement >50% of the width of the bone usually require ORIF.

Ulnar styloid fractures are produced by forced radial dorsiflexion, radial deviation, and rotary stress. These fractures may be isolated or accompany other injuries, such as a Colles fracture. Patients often complain of a painful clicking or locking sensation in the wrist. Delineation of an accompanying TFCC injury may require wrist arthroscopy or magnetic resonance imaging. Ulnar styloid fractures should be immobilized with a volar or ulnar gutter splint in the neutral position with slight ulnar deviation and timely outpatient follow-up should be arranged.

Ligamentous Injuries

Disruption of the DRUJ ligaments frequently accompanies forearm fractures, but may also act as an isolated injury (eFig. 40.6). Because attention is usually given to the more obvious fracture, DRUJ disruption is missed in almost half the cases. The diagnosis is often not made until chronic pain and decreased wrist mobility are noted. Localized tenderness is present over the wrist and distal radius. Examination reveals weak grip strength and decreased pronation and supination; subtle prominence of the ulnar head may also be noted. The more commonly seen dorsal dislocation is usually produced by falls on a hyperpronated wrist, whereas volar dislocation is produced by forced hypersupination. Dorsal or volar displacement of the ulna can be seen on lateral films. PA radiography demonstrates narrowing of the distal radioulnar joint, which may be subtle. ED management includes immobilization (in supination to reduce dorsal ulnar dislocation; in pronation to reduce volar ulnar dislocation) and orthopedic follow-up within 7 to 10 days.

Forearm Fracture–Dislocations

As noted above, the radius and ulna have tight ligamentous connections at the DRUJ, the proximal radial ulnar joint, and the interosseous membrane. Thus, when a forearm bone fractures, a concomitant dislocation may also occur at one or more of these ligamentous attachments. Such fracture–dislocation injuries carry the potential for significant morbidity, and accurate ED diagnosis is critical for a positive outcome. The usual mechanism for all of these fracture–dislocations is an axial load or FOOSH-type injury.

A fracture of the middle or distal radius, coupled with an associated DRUJ dislocation or subluxation, is called a *Galeazzi fracture* (eFig. 40.7). Similar DRUJ disruptions can also occur when both the radius and ulna are fractured. Approximately 20% to 25% of diaphyseal radius fractures will in fact be Galeazzi fractures. Clinically, there is often angulation of the radial forearm, along with prominence and mobility of the ulnar head. On PA films there is narrowing of the DRUJ, whereas the lateral view demonstrates dorsal or volar displacement of the ulna (which is normally overlapping the radius) (22).

A fracture of the ulnar shaft with associated radial head dislocation is referred to as a *Monteggia fracture–dislocation* (eFig. 40.8). This is usually a diaphyseal fracture in the proximal one-third of the ulna, with an associated anterior dislocation of the radial head. Clinically, the forearm may appear angulated and shortened. Although less obvious than the ulnar findings, there is usually pain and swelling at the elbow, and the radial head may be palpated in a posterior or anterior location. On plain radiography, the apex of the ulnar fracture points toward the radial head dislocation, and the radial head will not line up with the capitellum on all views. Monteggia fracture–dislocations may be associated with other injuries, including radial head fractures, coronoid fractures, lateral collateral ligament instability, and posterior interosseous nerve palsies (23).

A third injury pattern that combines features of both Galeazzia and Monteggia injuries is the *Essex-Lopresti lesion.* This is a rare and often underdiagnosed entity that can lead to significant long-term disability. It is characterized by a radial head fracture at the elbow

along with DRUJ disruption at the wrist and interosseous membrane disruption throughout the forearm. Elbow pain due to the radial head fracture usually predominates clinically, but tenderness is also present throughout the forearm and DRUJ, and excessive mobility between the radius and ulna may be noted distally. DRUJ disruption in these cases may be detected radiographically in the same manner as with a Galeazzi injury (24).

Galeazzi, Monteggia, and Essex-Lopresti fracture–dislocations all require specialist consultation in the ED. These injuries can be subtle, and therefore must be actively sought by the emergency physician. It is critical to obtain true lateral distal forearm views to detect DRUJ dislocation in radius fractures and true lateral elbow views to detect radial head dislocation in ulna fractures. In addition, pediatric patients may sustain Monteggia-variant injuries with only plastic deformation (e.g., buckle fracture, greenstick fracture) of the ulna—these may be mistaken for simple radial head dislocations if not properly evaluated (25).

Tendon Lacerations

Detailed examination and careful wound exploration are essential for detecting tendon injuries in the wrist. It is important to note that partial tendon lacerations may have entirely normal function passively. Frequently, the only clue to their presence is pain with active motion. Only meticulous wound exploration that includes evaluating tendon integrity through the entire range of motion will prevent complications associated with a missed partial tendon laceration (e.g., adhesions, delayed rupture, triggering, and bow-stringing). Once identified, management depends on the type and location of injury. Consultation with an appropriate surgeon is recommended for almost all tendon lacerations, although emergency physicians experienced and comfortable with these injuries can perform simple extensor tendon repairs.

Multiple tendon lacerations, those associated with underlying fractures, those requiring extension of the wound to locate the retracted ends, and all flexor tendon lacerations require repair in the operating suite. The repair does not have to be performed at the time

of injury but should be accomplished within 72 hours whenever possible.

Patients whose tendon lacerations are not repaired at initial presentation should be seen by the hand specialist within 24 hours. Prior to discharge, thoroughly clean and irrigate the wound, approximate the skin edges, and immobilize the wrist and hand in a well-padded splint. Many emergency physicians will also administer an intravenous dose of an antistaphylococcal antibiotic (e.g., cephazolin), followed by a short course of an oral antibiotic with similar coverage. However, there is no evidence that this practice improves outcome. Patients who undergo tendon repair in the ED require similar immobilization and should be referred to a hand specialist within 48 hours for a wound check.

Nerve Injuries

The emergency physician should be proficient in the diagnosis of hand and wrist injuries complicated by nerve injury, because outcome is improved with early diagnosis. Nerve injuries may occur secondary to bony impingement, compartment syndrome, or direct laceration. It is imperative that a careful examination of the hand and wrist be performed before the instillation of any local anesthetics. If there is suspicion of a peripheral nerve injury, anesthetics should be withheld until consultation with the hand surgeon. Immediate operative intervention may be required, depending on the etiology of the nerve injury.

Arterial Injuries

Arterial injuries may complicate either blunt or penetrating trauma and are frequently associated with nerve injuries owing to their close proximity to peripheral nerves. Though most cases are obvious (i.e., a history or observation of pulsating hemorrhage), others require recognition of more subtle signs of impaired perfusion (e.g., capillary refill, Allen test). Careful wound exploration is essential as even complete arterial lacerations may spasm, and the bleeding will have stopped by the time the patient is evaluated.

Management of arterial injuries depends on the structures involved and the extent and location of the injury. Because the hand has a dual blood supply, ischemia is uncommon with a single artery injury. Consequently, isolated injury to the radial or ulnar arteries without distal ischemia or sensory impairment is often managed by simple ligation. In contrast, arterial injuries with distal ischemia or associated nerve injury usually require surgical repair. If a severed digital artery is not repaired, ligate both the proximal and distal ends to avoid rebleeding. Consultation with a specialist is strongly recommended prior to repair or discharge.

CRITICAL INTERVENTIONS

- For patients with clinical signs of a wrist fracture but negative radiographs, immobilize the wrist and refer the patient for follow-up in 7–10 days or obtain advanced imaging in the ED.
- Obtain immediate orthopedic consultation in the ED for lunate and perilunate dislocations, and fractures at risk for carpal instability.
- Arrange timely (i.e., within 1 week) follow-up for forearm fractures to minimize long-term complications.
- Screen for associated neurovascular compromise with all fractures or dislocations.

DISPOSITION

The disposition of patients with wrist or forearm injuries depends on the nature and severity of the injury. Institutional and regional protocols may influence the indications and timing of consultation as well as the specialty background of surgical consultants (e.g., orthopedic surgeon, plastic surgeon). However, certain injuries (discussed earlier) require immediate specialty evaluation and treatment; consultation in these cases should occur in the ED before the patient is discharged.

For discharged patients, emphasize elevation and intermittent ice application for the initial 24 to 48 hours. As appropriate, discharge instructions should address splint and wound care; the timing of

return visits for wound checks or specialty follow-up; and indications for immediate return to the ED, such as symptoms of infection or compartment syndrome. Timely follow-up arrangements should be provided for all patients treated in the ED.

Common Pitfalls

- Failure to immobilize the wrist and arrange close follow-up or order advanced imaging studies when plain films are negative and there is clinical suspicion for a fracture.
- Failure to diagnose and immobilize a scapholunate or triquetrolunate dissociation.
- Failure to identify a lunate or perilunate dislocation and obtain immediate consultation.
- Failure to identify a forearm fracture–dislocation and obtain immediate consultation.
- Failure to appreciate a Salter–Harris I or plastic deformation fracture in pediatric patients.
- Failure to diagnose compartment syndrome.
- Failure to perform a thorough neurologic evaluation prior to the use of local anesthesia.

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CHAPTER 41

Hand Injuries

David Q. Bell and Douglas Doehrman

Hand injuries account for 5% to 20% of emergency department (ED) visits (1). The outcome depends on accurate assessment of the injury, appropriate initial management, and prompt recognition of those injuries that require immediate specialty consultation or outpatient referral.

An understanding of the anatomy and terminology of the hand is crucial for the evaluation and treatment of hand injuries. The surfaces of the hand and digits are referred to as dorsal, palmar, ulnar, and radial. The palmar surface anatomy is shown in Figure 41.1. Finger motion is described as extension, flexion, abduction, and adduction. Motion is related to the midline of the long finger. The thumb can perform opposition to touch the pads of all the fingers.

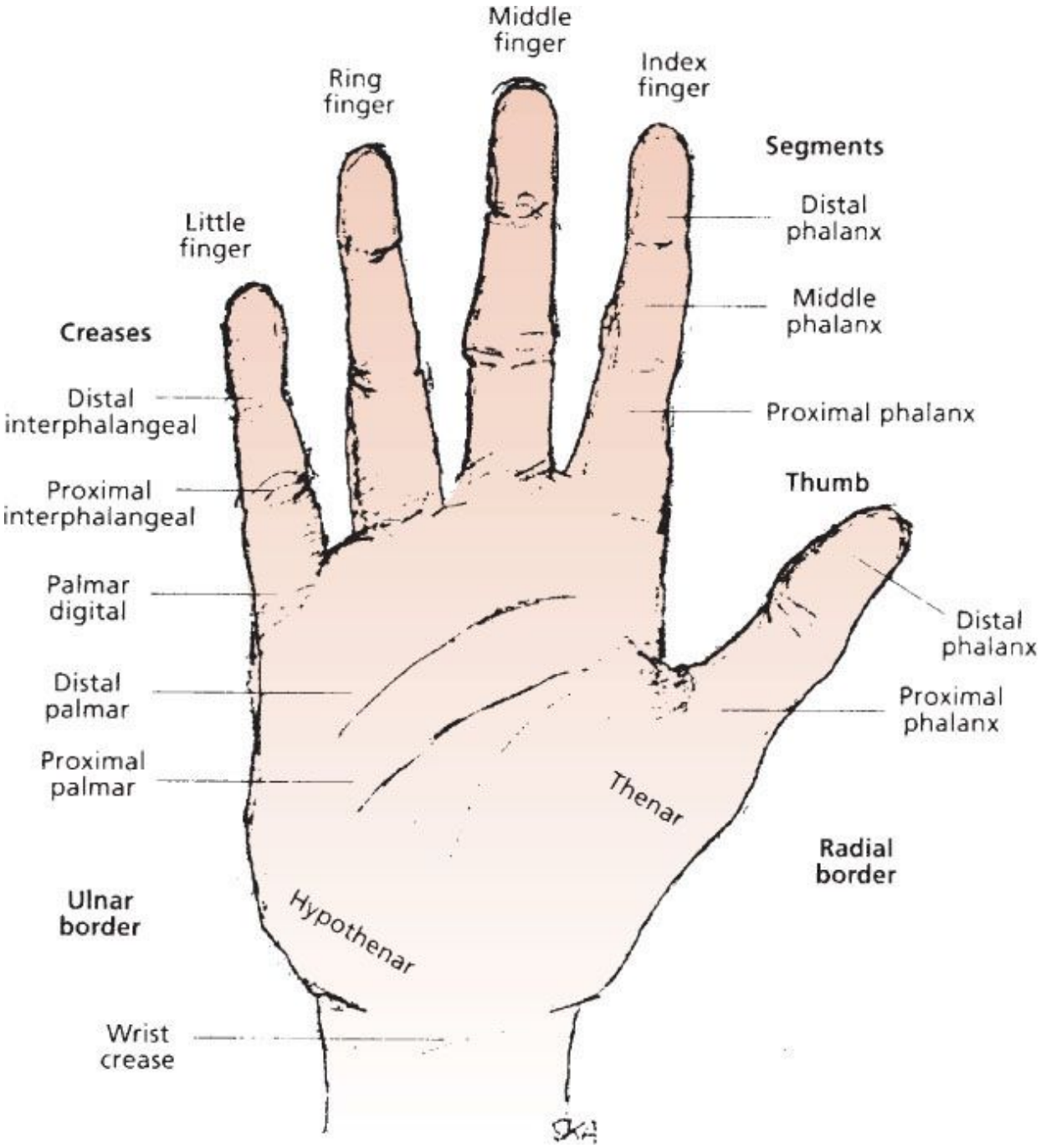


FIGURE 41.1 Palmar (volar) surface anatomy.

Muscles that control hand motions are divided into flexors and extensors, each of which may be intrinsic or extrinsic to the hand. The intrinsic muscles have their origins and insertions within the hand. The thenar muscles and adductor pollicis are tested by flexing, adducting, and abducting the thumb. The four dorsal and three

palmar interossei originate from the lateral metacarpals and insert on the base of the proximal phalanges and extensor expansion (Fig. 41.2). Motor function of the lumbricals and interossei is tested by placing the hand on a flat surface and moving each finger from side to side. The hypothenar muscles are tested by adducting the little finger.

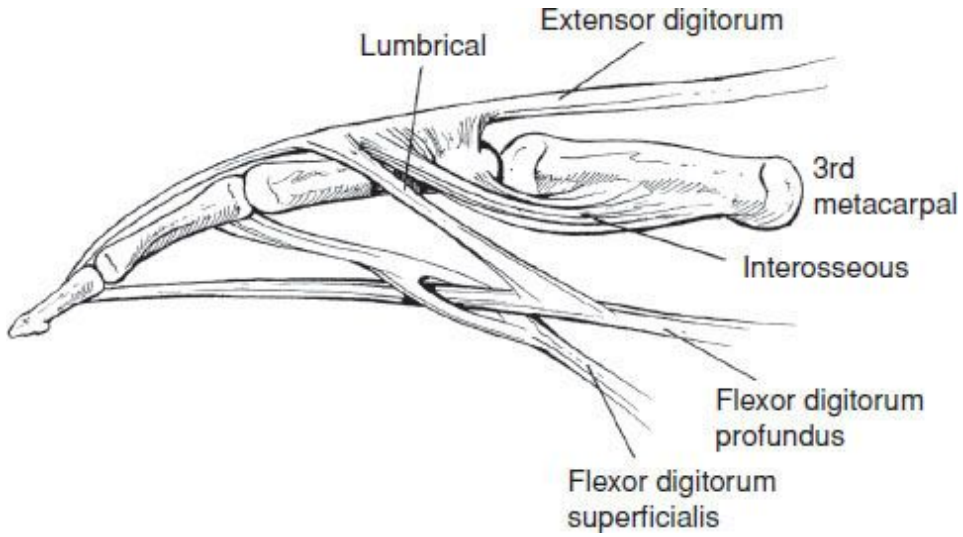


FIGURE 41.2 Musculotendinous anatomy of the finger.

The extrinsic muscles have their origins in the forearm. The extensor tendons pass under the extensor retinaculum at the wrist. The extensor tendons produce extension of the fingers by their dorsal attachments on the metacarpals and phalanges. Because there are many interconnections between the extensors, care must be taken in evaluating suspected extensor tendon injuries. Normal movement may be preserved via these interconnecting bands. The extrinsic finger flexors enter the hand via the carpal tunnel. The flexor pollicis longus of the thumb is tested by flexing the thumb against resistance. All four fingers have two flexors. The flexor digitorum superficialis (FDS) attaches to the base of the middle phalanx. The flexor digitorum profundus (FDP) attaches at the base of the distal phalanx. The FDS and FDP tendons of each finger are tested individually by flexing the distal interphalangeal (DIP) joint and the proximal interphalangeal (PIP) joint against resistance with the other fingers

held in extension. It is important to test both FDS and FDP function in each finger individually to avoid missing an isolated injury.

The median, radial, and ulnar nerves provide the sensory and motor innervation to the hand. The sensory innervation of the hand is detailed in Figure 41.3. The median nerve supplies motor function to the extrinsic flexors of the hand, the intrinsic thenar muscles, and the first and second lumbricals. The ulnar nerve innervates the flexor carpi ulnaris, the ulnar portion of the FDP, and all the remaining intrinsic muscles of the hand. The radial nerve innervates those muscles of the forearm that provide extension of the wrist and digits, as well as extension and abduction of the thumb.

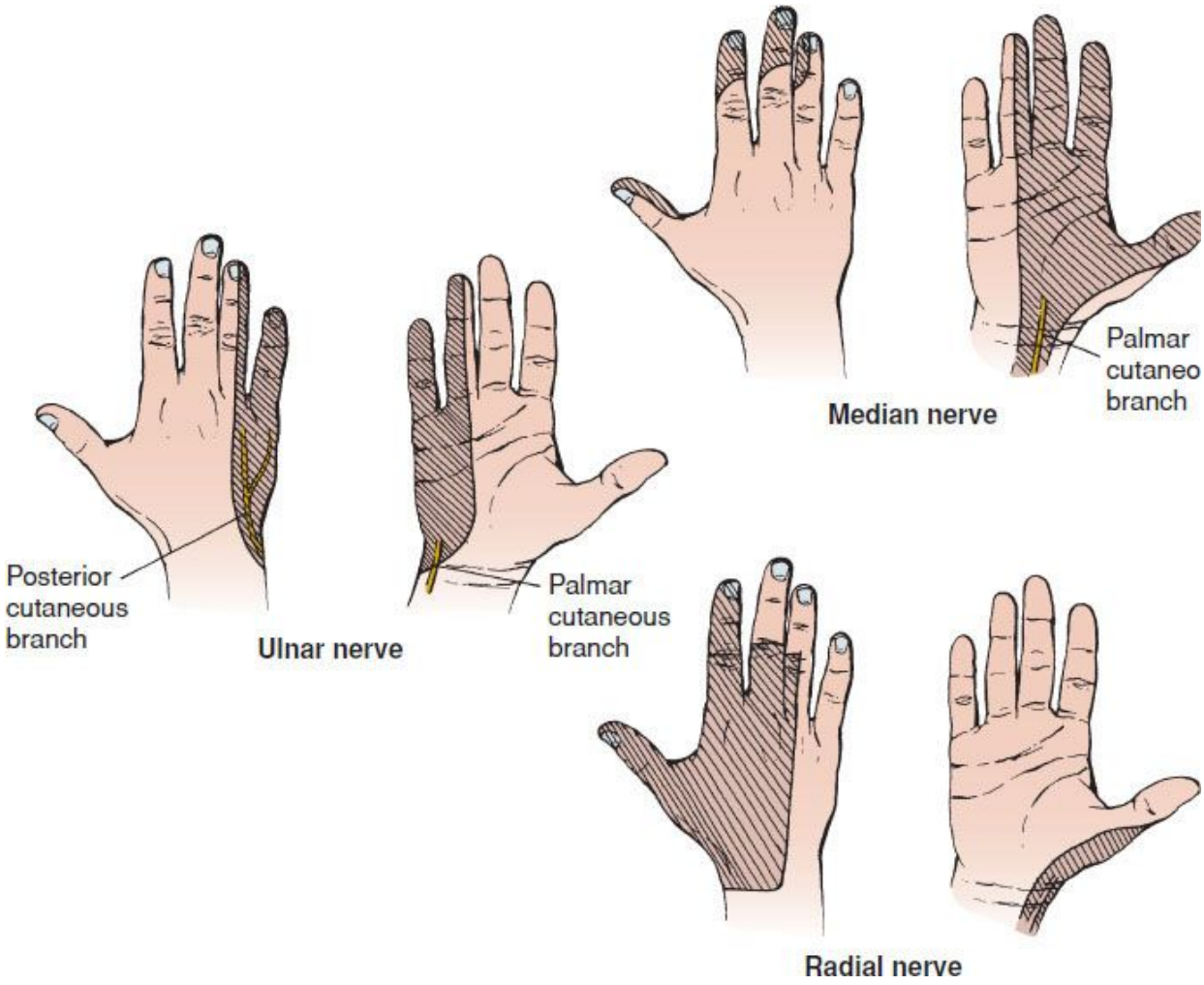
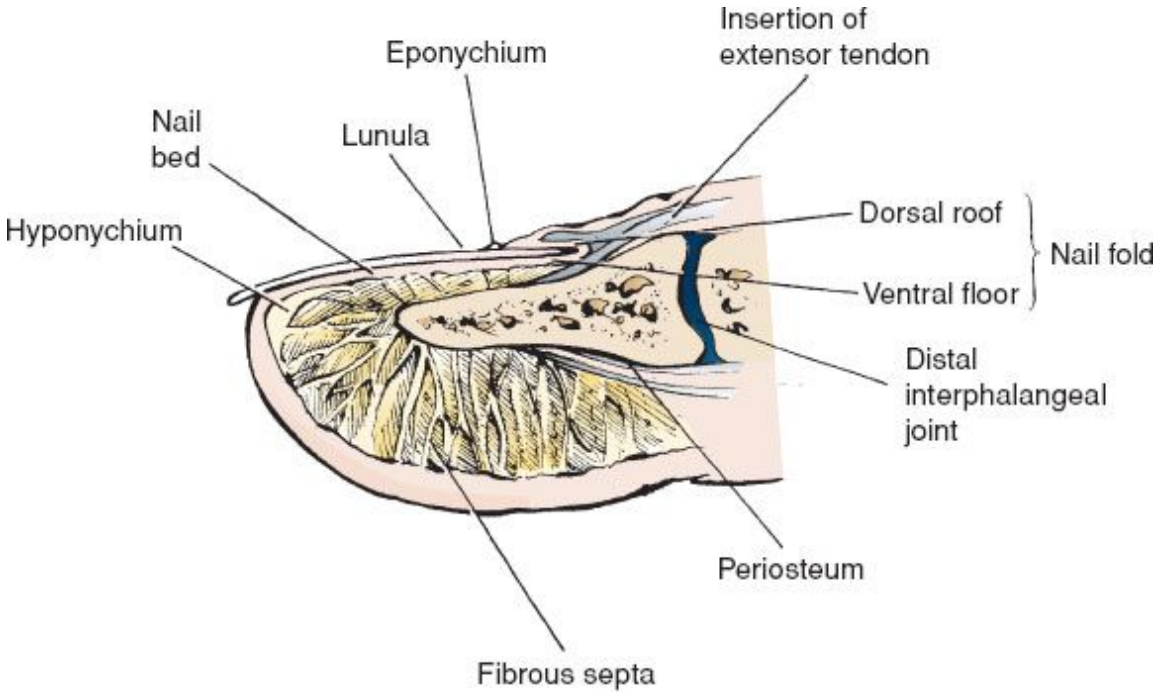


FIGURE 41.3 Sensory innervation of the hand.

The arterial supply to the hand is provided by the radial and ulnar arteries. The radial artery terminates where the deep palmar arch and the ulnar artery forms the superficial palmar arch. Extensive collateralization occurs between the two vessels. The four common digital arteries arise from the superficial palmar arch where they divide to form the proper digital arteries.

The thick palmar skin is tightly adherent to the deep fascia of the palm. The dorsal skin of the hand is thin and supple with little underlying adipose or fibrous tissue. These qualities cause edema from hand injuries to be more pronounced on the dorsal surface.

Knowledge of fingertip and nail bed anatomy is essential when evaluating distal finger injuries **(eFig. 41.1)**.



eFIGURE 41.1 Fingertip and nail bed anatomy.

CLINICAL PRESENTATION

Patients with acute hand injuries present with varying degrees of pain, swelling, and loss of function. Injuries resulting from repetitive motions and systemic or bone diseases usually present more insidiously with chronic waxing and waning symptoms (see Chapter 145).

Patients with metacarpal injuries generally present with pain, swelling, and limitation of movement. Finding the place of maximal tenderness or deformity will help localize the area of injury. In patients with a metacarpal head fracture, axial compression of the extended digit causes severe discomfort. In patients with a metacarpal base fracture, movement of the wrist or longitudinal compression exacerbates the pain. Metacarpal fractures 2 through 5 are classified together. They are divided into head, neck, shaft, and base fractures. First metacarpal fractures are classified separately as shaft fractures and extra-articular or intra-articular base fractures.

Patients with phalangeal injuries present with varying degrees of pain, limited mobility, and deformity of the involved digit.

Hand lacerations range from clean, superficial wounds to severely contaminated crush injuries or amputations. Associated tendon injuries may cause a partial or complete loss of motor function, and injury to surrounding nerves may result in loss of both motor and sensory function.

Patients with fingertip injuries may present with a minor laceration or a severe injury with significant tissue loss or destruction.

DIFFERENTIAL DIAGNOSIS

Metacarpal injuries include fractures, dislocations, or combinations of the two. If an injury is associated with an open wound, the possibility of infection of the underlying structures should be considered (see Chapter 147). The differential diagnosis of acute phalangeal injuries includes fractures, fracture–dislocations, and ligamentous injuries.

The diagnostic challenge of hand lacerations lies in the detection of underlying injuries that may threaten the function of the hand. Tendon lacerations and injuries to bones, joints, nerves, and arteries must be excluded by examination, radiography, and direct exploration of the wound. Older wounds must be evaluated for the possibility of a developing deep space infection. Wounds that do not heal or have persistent pain with movement should be evaluated for an occult foreign body.

ED EVALUATION

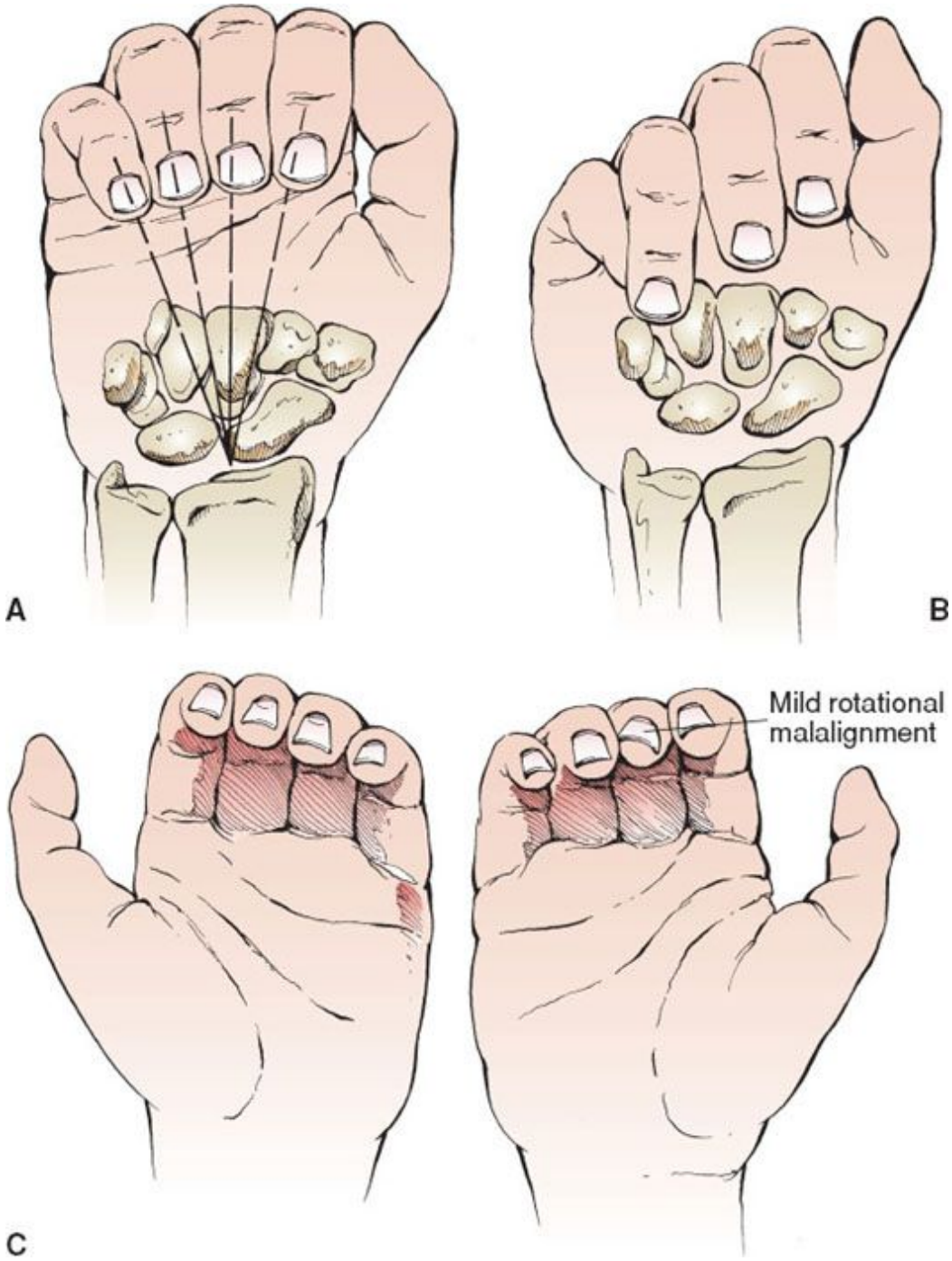
Evaluation and treatment of potentially life-threatening injuries should precede any evaluation of the hand. Once evaluation and treatment have been accomplished, assessment of the hand can begin. Direct pressure should be used to control bleeding. In rare instances when direct pressure is not sufficient, careful and intermittent use of a tourniquet will usually gain control of the bleeding and allow adequate visualization of the wound. Blind clamping of bleeding vessels should be avoided, because adjacent nerves and tendons may be injured.

A focused history is essential. Important historical information includes the patient's age, dominant hand, occupation, prior hand injuries, previous tetanus immunization, and past medical history. Details of the traumatic event should include time and mechanism of the injury, position of the hand during the accident, and treatment administered before arrival.

All dressings should be removed to completely expose the hand. Rings should be removed, because swelling may create a tourniquet effect. The location and type of wounds, skin loss, ecchymosis, pallor, swelling, and the resting attitude of the digits should be noted. The normal resting cascade of the fingers reveals progressive flexion of the digits from the index to the little finger. The normal resting cascade is generally symmetric.

Alterations in the resting cascade may indicate an underlying tendon injury. For example, a flexor tendon injury may appear as an extended digit because of unopposed extensor tone, and an extensor tendon injury may reveal a flexion deformity. The hand should also be observed during passive flexion and extension of the wrist. With wrist extension, the fingers naturally assume a flexed posture. With wrist flexion, the fingers will passively extend (2). This method may be particularly helpful in evaluating children or uncooperative patients. Emergency physicians may misdiagnose up to 35% of tendon injuries based on clinical examination alone (3). Bedside ultrasound has been shown to aid in the detection of tendon injuries (4).

The hand should be carefully palpated to identify areas of tenderness, deformity, and crepitus. In patients with phalangeal or metacarpal fractures, the presence of rotational malalignment must be sought. Rotational deformity may be diagnosed by having the patient make a fist. Normally, all of the fingers point to a single spot on the scaphoid **(eFig. 41.2)**.



eFIGURE 41.2 Clinical signs of rotational malalignment. A: Normally, all fingers point to the same spot on the scaphoid when making a fist. B: With rotational malalignment, the affected finger does not point to the scaphoid. C: Loss of the usual parallel relationship of the finger nails with rotational malalignment. (Redrawn from Simon RR, Koenigsknecht SJ. Emergency Orthopedics: The Extremities. 3rd ed. Norwalk, CT: Appleton and Lange; 1995:64.)

Nerve integrity is assessed by testing both sensory and motor functions. Sensation should always be evaluated and documented before the administration of any anesthetic agent. Digital nerve sensory function is best assessed by two-point tactile discrimination. The volar lateral aspects of the digits are lightly stroked in a longitudinal direction at the two points. Comparison with the opposite hand may be helpful. Motor function of the median nerve is tested by touching the thumb to the little finger and elevating the thumb of the pronated hand as the hand is lying on a flat surface. Radial nerve function is checked by extending the wrist and fingers. Ulnar function is tested by spreading the fingers apart against resistance. Emergency physicians may fail to identify up to 55% of nerve injuries (3).

In young children or uncooperative patients, it can be difficult to accurately perform two-point tactile discrimination. In these circumstances, nerve integrity can be assessed by testing for the presence of sympathetically mediated skin wrinkling and skin sweating. Soaking the hand in warm water for 30 minutes should cause wrinkling of the normally innervated skin. Skin sweating can be assessed by stroking the digit with a smooth object (such as the barrel of a pen). Less resistance (shown by loss of sweating) should be noted over the denervated area.

Vascular integrity of the hand is evaluated by looking for pallor, noting skin temperature, assessing capillary refill, and palpating the ulnar and radial arteries at the wrist (2). The Allen test is utilized to evaluate the patency of the radial and ulnar arteries and the palmar arches. The test is performed by having the patient clench the fist to

exsanguinate the hand while the examiner occludes the radial and ulnar arteries. When the hand is blanched, pressure over one of the arteries is released. Normal hand color should return in 3 to 5 seconds. The test is repeated, releasing the other artery.

Testing for tendon integrity is another important aspect of the hand examination. When evaluating finger lacerations, the digit should be moved through a full range of motion against light resistance. A tendon laceration may be proximal or distal to the skin wound depending on the position of the hand when the injury occurred. Partial tendon lacerations may have full function, so these lacerations are easily missed. If there is any concern about the possibility of a foreign body or injury to a deep structure, the wound should be evaluated under bright lighting with a dry field. A bloodless field is obtained by first emptying the veins. The veins are emptied by elevating the extremity and inflating a proximally placed blood pressure cuff above systolic pressure. The blood pressure cuff may be left in place for up to 20 minutes as the wound is explored. A dry field can be obtained in individual digits by placing a sterile glove on the injured hand, cutting off the tip of the glove on the injured finger, and rolling the end of the cut glove proximally to simultaneously exsanguinate and tourniquet the finger.

Radiographs of the hand should be obtained whenever the mechanism might result in fracture, joint instability, or a retained foreign body. If a thumb injury is suspected, posteroanterior (PA) and lateral views of the thumb should be obtained, because the thumb is not adequately visualized on standard hand radiographs. If there is suspicion of a foreign body despite negative plain radiographs, ultrasonography, computed tomography, or magnetic resonance imaging may be required to visualize the object (5).

KEY TESTING

- Assess sensation and motor function in the distribution of the medial, ulnar, and radial nerves. Document two-point discrimination when possible.
- Examine wounds in a clean bloodless field through passive range of motion to evaluate for tendon injury.

- Assess both flexor digitorum superficialis and flexor digitorum profundus integrity.
- Evaluate and document vascular integrity of hands and digits.
- Evaluate for rotational deformity.

ED MANAGEMENT

ED management of hand injuries includes application of ice and elevation of the extremity to reduce swelling. The liberal use of analgesics is also recommended. IV antibiotics are indicated for tendon lacerations, open fractures, dislocations, and severely contaminated or infected wounds. Tetanus immunization should be updated appropriately. Open wounds should be covered with a sterile, moist gauze dressing pending radiographs, surgical consultation, or wound closure. Suspected fractures should be temporarily immobilized with a bulky hand dressing or a splint while awaiting radiographs, reduction, or surgical consultation.

The patient's disposition depends on the nature and severity of the injury. A hand surgeon should evaluate the patient in the ED when there is an irreducible dislocation, any vascular injury with ischemia, or grossly contaminated open wounds. The remainder of most fractures, tendon, nerve, and soft tissue injuries can be splinted and seen on a prioritized basis. There are regional variations in the aggressiveness with which hand surgery consultants perform primary repair of injuries in the ED.

Anesthetic Techniques

Anesthesia for the evaluation and repair of hand injuries can be provided by a local infiltration digital nerve block or a regional nerve block at the wrist. A hematoma block is useful for the reduction of metacarpal fractures (6). Lidocaine without epinephrine should be used in 2% concentration for nerve blocks and in 1% or 2% concentration for infiltration. Lidocaine with epinephrine can be safely used for digital blocks. Lidocaine with epinephrine has the advantages of providing improved hemostasis and a longer duration of anesthesia than lidocaine alone (7).

A digital block is performed by injecting 2 to 3 mL of local anesthetic at the medial and lateral aspects of the base of the proximal phalanx. Infiltration of the proximal dorsal surface of the digit is also required to anesthetize the dorsal digital nerve. Complete anesthesia usually requires 5 to 10 minutes. Bupivacaine may be a more appropriate agent for digital nerve blocks. It can provide anesthesia for up to 8 hours and is ideal for situations where prolonged anesthesia is preferred (8). Circumferential infiltration of the digit is not recommended, because circumferential infiltration may result in distal necrosis. Small randomized controlled studies have demonstrated that a single volar injection method achieves similar anesthesia with less patient discomfort. A 25-gauge needle should be injected at the volar metacarpophalangeal (MCP) skin crease while the physician is slightly pinching the proximal aspect of the proximal phalanx. The needle should be advanced until it hits the bone then retracted 1 to 2 mm; 2 to 3 cc of anesthetic should be injected (9).

Regional nerve blocks at the wrist can anesthetize the median, ulnar, and radial nerves. A median nerve block is performed by injecting 5 mL of local anesthetic 1 cm proximal to the distal wrist flexion crease, radial and deep to the palmaris longus tendon, or deep to the ulnar aspect of the flexor carpi radialis tendon in those individuals lacking a palmaris longus tendon. An ulnar nerve block is accomplished by injecting 5 mL of local anesthetic 1 cm proximal to the distal wrist flexion crease just radial and deep to the flexor carpi ulnaris tendon. The ulnar artery at this level lies in close proximity to the ulnar nerve. Aspiration before injection is important to avoid intravascular injection of the anesthetic. The dorsal sensory branch of the ulnar nerve is blocked by subcutaneous infiltration of anesthetic just distal to the ulnar styloid. A radial nerve block is performed by subcutaneous infiltration of 5 mL of anesthetic agent just distal to the radial styloid. Ultrasound is a useful adjunct to performing forearm nerve blocks and is within the scope of practice for an appropriately trained emergency physician to perform (9). A hematoma block is performed by injecting a local anesthetic into the hematoma surrounding a fracture. A 27-gauge needle is inserted over

the fracture site. When blood is aspirated into the syringe, indicating correct needle placement, 5 to 10 mL of anesthetic is injected. Ten minutes are often required before complete anesthesia is obtained with regional and hematoma nerve blocks.

Metacarpal Neck Fractures

Most commonly seen in the fifth metacarpal (i.e., boxer fracture), neck fractures are usually the result of striking an object with a closed fist. Metacarpal neck fractures are easily reduced, but reduction may be difficult to maintain. Because metacarpals 2 and 3 are relatively fixed and immobile, reduction of these fractures must be nearly anatomic. Any volar angulation will project the metacarpal head into the palm and impair grip strength. Greater angulation is acceptable in metacarpals 4 and 5. These digits have greater mobility, and they can move dorsally without impairment of grip strength. Most hand surgeons will allow up to 40 degrees of angulation in fractures of the fifth metacarpal neck and 20 degrees of angulation in fractures of the fourth metacarpal neck. In contrast, as little as 10 degrees of angulation is unacceptable for metacarpals 2 and 3. Even minor rotational deformity can lead to impaired grip strength and requires referral to hand surgery for possible surgical correction.

The technique for reduction of metacarpal neck fractures is the same regardless of which metacarpal is fractured. Surgical consultation is recommended before reduction of metacarpals 2 and 3, because some surgeons prefer operative fixation. After adequate anesthesia has been obtained, the MCP and PIP joints are flexed to 90 degrees. Pressure is applied to the PIP joint in a dorsal direction to force the metacarpal head into its normal position. Stabilizing volar pressure should be applied with the physician's other thumb just proximal to the fracture site (Fig. 41.4). If reduction is difficult, longitudinal distraction may be needed to disimpact the fracture before successful reduction can be accomplished.

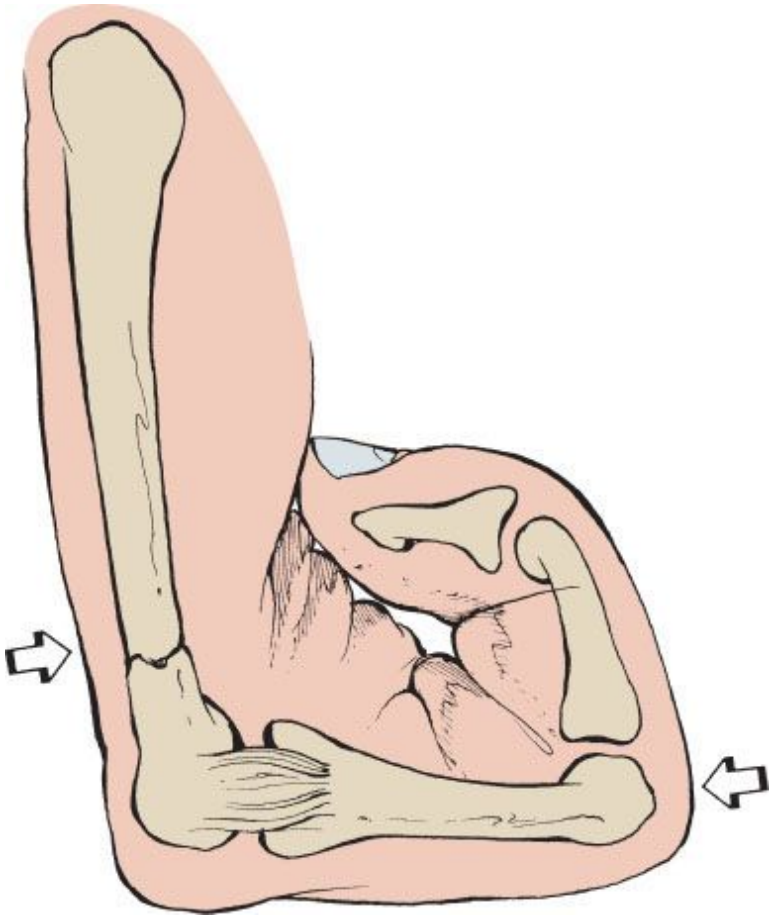


FIGURE 41.4 The 90–90 method of reduction for metacarpal neck fractures.

After reduction, a gutter splint incorporating the adjacent finger should be placed while keeping the MCP joint flexed to maintain reduction. The wrist should be splinted in 20 degrees of extension, the MCP at 90 degrees of flexion, and the interphalangeal (IP) joints in extension. It is important to immobilize the MCP joint as close to 90 degrees as possible, so contraction of the collateral ligaments does not occur. This contraction would permanently limit flexion of the MCP joint. Follow-up should be arranged within 7 days. If loss of reduction occurs, operative fixation may be needed.

Metacarpal Head Fractures

Metacarpal head fractures are rare injuries that are usually the result of a direct blow or crush injury. Management consists of temporary

immobilization in a well-padded volar splint. Evaluation by a hand surgeon is indicated for most metacarpal head fractures, because anatomic reduction frequently requires operative intervention. Even with optimal management, severe metacarpal head fractures may have a poor functional outcome.

Metacarpal Shaft Fractures

Metacarpal shaft fractures may be transverse, comminuted, oblique, or spiral. Nondisplaced transverse fractures are treated by immobilization in a gutter splint with the wrist in 20 degrees of extension, the MCP joint in 60 degrees of flexion, the PIP joint in 20 degrees of flexion, and the DIP joint in 15 degrees of flexion (10). Displaced transverse metacarpal shaft fractures should, whenever possible, be reduced by a hand surgeon. If consultation is not available, the emergency physician may attempt reduction by applying volar force over the dorsal apex of the fracture and dorsal pressure on the flexed MCP joint. If reduction is successful, the hand is splinted as described earlier, and the patient is referred for follow-up within 7 days. If a transverse fracture cannot be reduced, or if an oblique, spiral, or comminuted fracture is present, refer the patient to a hand surgeon for operative repair.

Metacarpal Base Fractures

Fractures of the base of the metacarpals are generally stable, but slight rotational deformity will be greatly amplified at the fingertip (11). Nondisplaced fractures without rotational deformity may be treated by immobilization in a gutter or volar splint and by surgical referral. Displaced or intra-articular base fractures require hand surgery consultation for open reduction and internal fixation.

First Metacarpal Fractures

First metacarpal fractures are uncommon. These fractures most often occur at or near the base of the thumb. Extra-articular fractures are more common, and the fractures may be transverse or oblique. Transverse fractures with <30 degrees of angulation are treated with

immobilization in a short-arm thumb spica splint and prompt follow-up. A transverse fracture with >30 degrees of angulation requires reduction. After reduction, the thumb is splinted, and the patient is referred for follow-up. Oblique fractures are often unstable, and they frequently require percutaneous pinning for adequate immobilization. Consultation is advised before manipulation or discharge.

There are two types of intra-articular fractures: the Bennett fracture and the Rolando fracture. A Bennett fracture is a two-part intra-articular fracture of the metacarpal base with subluxation or dislocation at the carpometacarpal (CMC) joint. A Rolando fracture is a comminuted, often T- or Y-shaped intra-articular fracture of the base of the first metacarpal. Both fractures result from an axial blow to the metacarpal, commonly sustained by striking an object with a closed fist. Management includes immobilization in a thumb spica splint and expeditious follow-up with a hand surgeon. Bennett fractures frequently require pinning for a stable anatomic reduction. Rolando fractures often require open reduction. Rolando fractures have a poor prognosis, even with optimal management (11,12).

Metacarpal Dislocations

Dislocations involving the metacarpals are either CMC or MCP. CMC dislocations are uncommon, and they require a significant force. These dislocations are generally dorsal, and they are often associated with metacarpal or carpal fractures and significant soft tissue trauma. The presence of a displaced proximal metacarpal fracture should prompt a careful search for an associated CMC dislocation. The lateral view is the most helpful standard view for diagnosing CMC dislocations. However, overlapping densities on standard wrist radiographs may make the detection of CMC dislocations difficult, so special views may be needed to detect CMC dislocations. CMC dislocations are easily reduced, but operative fixation is usually required to maintain reduction. Complications of CMC dislocations are ulnar and median nerve injuries, extensor tendon injuries, and circulatory compromise.

MCP joint dislocations usually occur dorsally. These dislocations are generally well visualized on standard radiographs of the hand. Reducible dorsal dislocations are the most common, and this injury can usually be treated by the emergency physician. Irreducible dorsal dislocations occur when the volar plate is interposed between the metacarpal head and the proximal phalanx. This dislocation traps the metacarpal head between the flexor tendons and the lumbricals, making the injury irreducible by closed techniques. Radiographically, the presence of a sesamoid bone within the MCP joint space is pathognomonic of a complex dislocation (11). Simple dorsal MCP dislocations are reduced by slight flexion of the wrist to relax the extrinsic flexors, followed by gentle hyperextension of the MCP joint and firm pressure on the dorsal aspect of the proximal phalanx. Longitudinal traction and extreme hyperextension should be avoided because this may entrap the volar plate, thus converting a simple dislocation into a complex one. After reduction, the hand is immobilized, with the wrist in 20 degrees of extension, the MCP joint in 60 degrees of flexion, the PIP joint in 20 degrees of flexion, and the DIP joint in 15 degrees of flexion. One attempt at reduction of a complex MCP dislocation may be warranted, but multiple attempts should be avoided. These patients usually require open reduction and repair of the volar plate injury.

Collateral MCP ligament injuries occur infrequently, and are often missed. The presence of an avulsion fracture from the metacarpal head or corner fracture of the base of the proximal phalanx suggests an MCP collateral ligament injury. Consultation with a hand surgeon is recommended for patients with a collateral ligament injury (11). ED care involves immobilization in a gutter splint, with the MCP in 60 degrees of flexion, and appropriate referral.

Ulnar Collateral Ligament Injury (Gamekeeper's Thumb, Skier's Thumb)

Ulnar collateral ligament injury is an acute rupture of the ulnar collateral ligament caused by sudden forced abduction of the thumb.

Plain radiographs may be normal or may reveal an avulsion fracture from the ulnar aspect of the base of the proximal phalanx. If plain radiographs do not reveal a fracture, stressing the ligament may help determine if a complete tear has occurred.

ED management includes immobilization in a thumb spica splint and early referral to a hand surgeon. A frequent complication of ulnar collateral ligament rupture is chronic laxity of the MCP joint because of interposition of the adductor aponeurosis between the ends of the torn ligament. This injury is referred to as a Stener lesion (13). Because of this complication, many surgeons prefer routine operative repair of ulnar collateral ligament tears.

Proximal and Middle Phalangeal Fractures

Stable, nondisplaced middle and proximal phalangeal fractures without angulation or rotational deformity can be managed with dynamic splinting (i.e., "buddy taping") to an adjacent normal digit. Padding should be placed between the digits to prevent maceration of the skin. The patient should bend the fingers normally and use the hand as comfort allows. Radiographs are obtained in 7 to 14 days to assess angulation and healing. Unstable fractures of the proximal and middle phalanges (e.g., oblique, condylar, displaced, or angulated transverse fractures) and displaced intra-articular fractures generally require operative reduction or fixation. ED management of these fractures includes immobilization in a gutter splint and consultation.

Avulsion fractures off the dorsal aspect of the base of the middle phalanx are of special concern. If not recognized and treated appropriately, these fractures can result in a *boutonnière* deformity (i.e., fixed flexion of the PIP joint and fixed hyperextension of the DIP joint). This deformity is caused by avulsion of the central slip of the extensor tendon with loss of extensor function at the PIP joint and unopposed force from the FDS (Fig. 41.2). With time, the lateral bands of the extensor expansion sublux laterally and volarly, and the lateral bands will become PIP joint flexors and DIP joint extensors. Contractures make this injury a fixed deformity. These fractures should be immobilized in a volar splint with the PIP joint in extension, and the patient should be promptly referred to a hand

surgeon for evaluation. If more than 40% of the articular surface is involved then the fracture may require surgical stabilization (14).

Avulsion fractures from the volar aspect of the base of the middle phalanx may be indicative of a volar plate injury. These injuries should be immobilized in a volar splint in 15 degrees of flexion. Immobilization should be followed by appropriate referral.

Volar plate avulsion fractures are of special concern. The volar plate is a strong fibrous structure joining and stabilizing the middle and proximal phalanges. It primarily acts by limiting hyperextension. Injury typically occurs with forced hyperextension. The diagnosis is made by obtaining plain x-rays of the digit. The lateral view is the most useful for making this diagnosis that is characterized by an avulsion fracture at the base of the middle phalanx. Absence of this fracture, however, does not rule out volar plate injury. In the absence of a fracture, signs such as subtle subluxation or an abnormal crescent-shaped gap at the dorsal aspect of the PIP joint (V sign) may indicate injury. These injuries should be immobilized in a volar splint in 15 degrees of flexion and referred to a specialist (14).

Distal Phalanx Fractures

Distal phalanx fractures are divided into intra- and extra-articular fractures. Extra-articular fractures usually result from a direct blow to the distal phalanx. These injuries are often associated with injury to the fingernail or nail bed. Extra-articular fractures are managed with oral analgesics and placement in a protective splint for 3 to 4 weeks. A U-shaped splint can be constructed using an aluminum and foam splint.

Intra-articular fractures often involve the dorsal surface of the joint and may result in loss of extension of the DIP, an injury commonly referred to as a mallet finger. This injury may occur when an object strikes the tip of an extended finger resulting in forced flexion of the distal phalanx with the finger in taut extension. The extensor tendon ruptures, or the dorsal aspect of the distal phalanx snaps. Patients typically present with tenderness over the dorsal aspect of the DIP joint and loss of extension at the DIP joint. Management includes immobilization using a padded dorsal aluminum splint with the DIP

joint in extension. If the fracture involves <25% of the articular surface, immobilization is maintained for 8 weeks to coapt the tendon or fracture segments. If the fracture involves >25% of the articular surface, the patient should be referred for surgical fixation. Untreated mallet finger may result in a swan-neck deformity characterized by hyperextension of the PIP joint and flexion at the DIP joint (15). Open distal phalanx fractures are treated by copious irrigation and wound closure, ensuring complete soft tissue coverage of exposed bone. If the nail bed has been injured it must be repaired.

FDP avulsion (jersey finger) requires urgent hand surgery referral. FDP function must be checked in all patients with DIP injuries. FDP avulsion may occur with forced sudden extension of a flexed DIP joint. Patients will be unable to flex their DIP when their PIP is locked in extension. Avulsion fractures on the palmar aspect of the DIP are often seen on plain films; however, this injury may have no radiographic abnormality. Early surgical intervention is necessary to restore normal DIP function. Primary repair is often impossible after 7 days (14).

Proximal Interphalangeal Joint Dislocations

Dislocations at the PIP joint are the most common dislocations of the hand. Dorsal dislocations result from hyperextension forces, such as those that occur when the outstretched finger is struck by a ball. Dorsal PIP dislocations are accompanied by partial or complete rupture of the volar plate or collateral ligaments. Volar dislocations occur less often, but they are associated with complete rupture of the volar plate and collateral ligaments, as well as the central slip of the extensor mechanism. Patients usually present with pain and deformity of the PIP joint. The presence of pain and a locking sensation with flexion suggests a volar plate injury. Radiographs are diagnostic for acute dislocations, but small avulsions of the volar plate may not be visible. Most dorsal dislocations are easily reduced, but the volar plate may become interposed in the joint space, which prevents reduction by closed techniques. If this complication occurs, open reduction is required. For closed reduction, a digital nerve block provides adequate anesthesia. The distal portion of the digit is

firmly grasped and slightly hyperextended. With gentle traction parallel to the middle phalanx, the base of the middle phalanx is pressed back into position and the PIP joint is flexed. The PIP joint should be immobilized using a volar splint, in 20 degrees of flexion for 2 to 5 weeks. If there is instability after reduction, the patient should be immobilized in a gutter splint and expeditiously referred to a hand surgeon.

Volar PIP dislocations can be problematic. They can be reduced by traction with both the MCP and PIP joints flexed. Consultation with a hand surgeon before reduction is recommended, because some surgeons prefer to treat these dislocations operatively. Joint stiffness is a common complication after both volar and dorsal dislocations.

Distal Interphalangeal Joint Dislocations

Dislocations of the DIP joint are relatively uncommon injuries. These injuries are almost exclusively dorsal, and they are often associated with an open wound. DIP joint dislocations can usually be reduced with digital block anesthesia and simple traction. After reduction, the DIP joint should be immobilized in extension using a dorsal splint, and the patient should be referred to a hand surgeon.

Hand Lacerations

The objectives of ED care of hand lacerations are to preserve function, prevent infection, minimize scar formation, and provide the optimal wound environment for rapid healing. Simple lacerations (clean, <6 hours old, and not involving tendons, joints, or neurovascular structures) are managed in the same manner as lacerations elsewhere. In many areas of the hand, vital structures are extremely superficial, and injuries to these structures are not always readily apparent.

Evaluation of a hand laceration begins with a pertinent history and meticulous examination. Adequate exploration of the wound requires a clean, bloodless, well-illuminated field and adequate anesthesia. A proximal blood pressure cuff (for hand wounds) or finger tourniquet (for digit wounds) provides optimal visualization of the wound.

Anesthesia may be obtained by direct infiltration of a local anesthetic or regional nerve block but should not be attempted until a sensory examination has been performed. Radiographs are indicated in cases in which the mechanism of injury could produce a fracture, dislocation, joint capsule injury, or retained foreign body. Exploration should be carried out through a full range of motion, otherwise injury to underlying structures, particularly tendon lacerations, may be missed. Simple lacerations are cleaned, irrigated, and repaired in the same fashion as in other areas of the body. Deep sutures should be avoided. After repair, lacerations over areas of motion should be splinted until the skin edges are well adherent. Antibiotics are not required for simple hand lacerations in otherwise healthy patients, for there is no convincing evidence for their use in this setting (16).

Clenched Fist Injuries (Fight Bites)

Lacerations over the MCP joints are often a result of striking an object with a clenched fist. Lacerations may be associated with extensor tendon injury, joint capsule violation, or metacarpal neck fracture. Because infection or septic arthritis may occur with any laceration over the MCP joints, these lacerations must be approached with suspicion. The laceration should be assumed to be a human bite wound until proven otherwise. Human bites are particularly prone to infection, usually with *Staphylococcus aureus* and *Streptococcus* sp or anaerobes such as *Eikenella corrodens* (12,17). Patients with an uncomplicated wound (i.e., no tendon or joint capsule damage) who present within 24 hours with uninfected wounds may be treated with copious irrigation, immobilization, and follow-up within 24 hours. Antibiotics should be prescribed. One option for outpatient treatment is amoxicillin–clavulanic acid (500/125 mg/tid). All other patients with clenched fist injuries are copiously irrigated, splinted in the ED, and admitted for possible debridement in the operating room by a hand surgeon. Admitted patients receive parenteral antibiotics. One option for inpatient therapy is ampicillin–sulbactam IV (1.5 g/q6h).

Tendon Lacerations

Tendon injuries are frequently associated with hand lacerations. A detailed examination and careful wound exploration are essential for detecting these injuries, for a partially cut tendon may demonstrate normal function. Once identified, management of a tendon laceration depends on the type of tendon injured, the cross-sectional area of tendon involved, and the location of the laceration.

Because of their complex structure, deep location, and high complication rate after injury, all suspected flexor tendon lacerations require consultation and repair by a hand surgeon. When a hand surgeon is not immediately available, the wound can be copiously irrigated and the skin closed primarily without tendon repair. The hand is then immobilized in a volar splint with the wrist in 20 degrees of flexion, the MCP joint in 60 degrees of flexion, and the IP joints in 15 degrees of flexion. The patient is referred for delayed repair within 5 days. Broad-spectrum antibiotic coverage is generally recommended for tendon lacerations.

In contrast to flexor tendons, extensor tendons are anatomically less complex, have a more superficial location, and are associated with fewer complications after repair. Tendon lacerations not involving the PIP joint are amenable to ED repair. Once a lacerated extensor tendon is identified, a holding stitch can be placed through the proximal tendon for traction during repair. The tendon can then be repaired with 4-0 or 5-0 nonabsorbable sutures using simple, interrupted sutures or a horizontal mattress suture with the knot "buried" between the ends of the tendon. Sutures should be placed 5 to 10 mm from the cut edge of the tendon to avoid the suture tearing through the end of the tendon. Lacerations over the PIP joint may involve the lateral bands or the central slip of the extensor mechanism. If this laceration is not repaired meticulously and followed closely, the injury can result in a *boutonnière* deformity. Patients with extensor tendon injuries over the PIP joint should be referred to a hand surgeon for repair.

The patient with a lacerated extensor tendon should be splinted in a position with the extensor mechanism relaxed. Tendon repairs at

the DIP joint can be treated with a mallet finger splint while leaving the PIP joint mobile. Injuries at, or proximal to, the PIP joint should be splinted with the wrist in 30 degrees of extension, the MCP joint in 20 degrees of flexion, and the IP joints in slight flexion.

Nerve Injuries

A careful examination of the hand is performed before the instillation of any local anesthetics. If there is a suspected peripheral nerve injury, anesthetics should be withheld until consultation with the hand surgeon to decide if microsurgical repair is needed and to determine the timing of the repair of the injury.

Arterial Injuries

Because of the extensive collateral flow of the palmar arches, ischemic injuries to the hand are rare. Arterial lacerations may spasm and stop bleeding by the time the patient is evaluated, so careful wound exploration is important. Arterial injuries with distal ischemia or associated nerve injury usually require surgical repair. Isolated injuries to the radial or ulnar artery without distal ischemia or sensory impairment require hand surgery consultation for possible repair or ligation.

Fingertip Lacerations, Avulsions, and Amputations

Fingertip injuries are classified by the extent and level of injury. Simple lacerations and small avulsion injuries are easily managed by the emergency physician. Injuries that involve significant tissue loss or bony exposure should be referred to a hand surgeon for repair. Partial or complete amputations should also be managed by a hand surgeon (see Chapter 47).

These injuries frequently necessitate skin grafts or skin flaps for adequate coverage. Pending consultation, ED care includes administration of a parenteral antistaphylcoccal antibiotic, appropriate analgesia, and wound cleansing. Avulsion injuries with minimal soft tissue loss (wound area <10 mm^2) and no bone loss or exposure may be allowed to heal by secondary intention with

excellent cosmetic and functional results. This method works particularly well in children, who have excellent regenerative capacity. The digit is debrided of dead and devitalized tissue, and it is copiously irrigated. The digit is then bandaged with a nonadherent dressing (e.g., Xeroform) and splinted. The patient performs daily dressing changes.

Subungual Hematoma

A subungual hematoma is a collection of blood under the nail plate. This hematoma commonly occurs after a direct blow to the fingertip, and it may be associated with a nail bed laceration or distal phalanx fracture. Patients may complain of severe throbbing pain and a variable amount of blood will be visible beneath the nail plate. There may also be associated injury to the nail bed and surrounding nail folds. When distal phalanx pain and swelling are not related to a recent traumatic event, the possibility of an infection such as a felon or paronychia should be considered (see Chapter 147).

Most subungual hematomas may be treated conservatively. More extensive subungual hematomas may be treated by simple nail trephination as long as the nail plate and surrounding nail folds are intact (18). The use of a battery-operated microcautery device is one effective and painless method to drain a subungual hematoma. After trephination, the digit should be dressed with absorbent gauze. If a distal phalanx fracture is present, it should be splinted. If there is extensive disruption of the nail plate or surrounding nail folds, the nail plate should be removed, and proper alignment of the nail bed should be restored by careful wound repair.

Nail Bed Lacerations

Crush and avulsion injuries that result in nail plate avulsion or deformity to the nail bed should be repaired. Failure to properly repair these lacerations can result in a split nail deformity, irregular nail surface, or failure of the nail to adhere to the nail bed. These deformities may be significant from both a cosmetic and a functional standpoint.

Complex lacerations may require repair by a hand surgeon. Management of simple and stellate lacerations may be performed in the ED under digital block anesthesia and tourniquet hemostasis. The broken nail can be removed with a small hemostat or iris scissors by gently opening and closing the instrument beneath the distal free edge of the nail until the nail plate is loose. The distal end of the nail is then grasped with a hemostat and gently removed. The lacerations should be explored carefully for foreign bodies and irrigated copiously. Debridement of the wound margins should be avoided, because removal of small amounts of tissue can lead to increased scar formation. Lacerations should be closed with interrupted 6–0 absorbable sutures. The sutures should be tied with only three to four knots, so they do not interfere with nail replacement.

After repair, the involved nail (if available) should be used as a protective covering for the injured nail bed. The nail should be inspected for debris or foreign matter, and the nail should be rinsed in normal saline before replacement. No tissue should be removed from the undersurface of the nail, because replacing the nail in its normal position often replaces avulsed tissue as well. A hole should be placed in the center of the nail to permit blood drainage. The proximal end of the nail is inserted under the eponychium until the nail is in its normal position on the nail bed. A 5-0 monofilament nylon suture placed through the fingertip and the distal free border of the nail secures the nail plate. The suture is cut in 2 to 3 weeks, allowing growth of the new nail to push out the old one. If the nail is missing or damaged, metal foil or a nonadherent sterile dressing can be used to cover the injured nail bed. It is important to insert foil or other material into the proximal nail fold between the eponychium and the nail, so adhesions do not impair normal nail regrowth. An absorbent gauze dressing and application of a splint for comfort and protection are important adjunctive measures.

High-Pressure Injection Injuries

A high-pressure injection injury of the hand may at first appear innocuous, but clinical sequelae are devastating, if the initial recognition or management is inadequate or delayed. Three types of

industrial equipment (grease guns, spray guns, and diesel injectors) account for most injection injuries (19). Injection often occurs as the operator uses a finger to wipe the plugged nozzle. At the time of the injury, the patient may feel temporary stinging or no pain at all, which may result in delay in seeking treatment (20).

Several factors determine the type and degree of high-pressure injection injury (21). The type of material is the most important element in determining the subsequent morbidity. Paint and paint thinner create the greatest tissue inflammatory response, and high-pressure injection injuries involving them result in a high rate of amputation.

At the time of injury, the patient may only feel a stinging sensation at the site of penetration, and a small puncture wound will be present at the site. Within several hours, increased discoloration and swelling occur, accompanied by severe pain. Patients usually present to the ED in significant pain. The amount and location of swelling, tendon function, and joint range of motion are evaluated. Plain radiographs of the involved extremity are useful in determining the extent of the dispersed material, and the radiographs may help guide the extent of surgical debridement. Material can be dispersed at a considerable distance from the site of penetration. Imaging to the elbow is mandatory (19).

The time from injury to proper treatment is the prime determinant of prognosis (22). ED care includes elevation of the extremity, administration of broad-spectrum antibiotics, tetanus prophylaxis, and preparation for surgery. Pain control is provided through opiates or proximal extremity nerve blocks. Digital nerve blocks are absolutely contraindicated because of the additional fluid volume and tissue and vascular compression added to the already compromised digit (19,21). Warm soaks are contraindicated since they increase blood flow to the compromised extremity, and they cause increased tissue compression. Immediate surgical consultation is mandatory.

Compartment Syndrome of the Hand

Compartment syndrome in the hand is rare, but should be considered in patients with high-risk mechanisms such as crush injuries, high-pressure injection injuries, or IV extravasation injuries. Signs and symptoms include pain, tightness of the skin, paresthesias, palor, and vascular compromise as a late finding. The classic presentation of compartment syndrome of the hand may be complicated by nerve injuries or regional anesthesia. There are 10 separate compartments of the hand: thenar, hypothenar, and adductor pollicis in addition to 4 dorsal and 3 volar interossei compartments. If there is concern for compartment syndrome, consultation with a hand specialist should occur immediately. Measurement of the thenar and hypothenar compartments should occur by inserting the needle of a measurement device perpendicular to the skin at the site of maximal swelling. Measurement of the adductor pollicis compartment is taken on the radial side of the second metacarpal in the muscle belly of the thumb-index webspace. To measure the dorsal interosseous compartments the needle is placed 1 cm proximal to the metacarpal head and advanced until the needle rests in the muscle belly. The needle is advanced approximately 0.5 cm further to obtain volar interossei compartment pressures. Compartment pressures greater than 30 are generally considered to be diagnostic of compartment syndrome. If one compartment pressure is found to be elevated all compartments of the hand should be released (23).

CRITICAL INTERVENTIONS

- Perform a systematic examination including a careful neurovascular assessment in all patients with hand injuries, and document the results.
- Carefully explore all wounds for tendon lacerations and foreign bodies using a tourniquet to obtain a bloodless field, and document the results.
- For patients with a fight bite, copiously irrigate and splint in the ED, obtain hand surgery consultation, and admit for intravenous antibiotics and possible operative debridement.
- For most injuries, splint the hand with the wrist in 20 degrees of extension, the MCP joint in 60 degrees of flexion, and the IP

joints in 15 degrees of flexion.

DISPOSITION

Most patients with metacarpal injuries can be discharged from the ED with appropriate immobilization and instructions. Those patients with open fractures, irreducible fractures or dislocations, or circulatory compromise should be evaluated by a hand surgeon. Patients with stable fractures, anatomically reduced dislocations, or ligamentous injuries can be discharged with early follow-up.

Patients with stable, anatomically reduced phalangeal injuries can be discharged from the ED with appropriate follow-up. Patients with open fractures, nonreducible or unstable fractures, or dislocations require consultation with a hand surgeon.

Patients with simple hand or extensor tendon lacerations repaired in the ED can be discharged. Reevaluation in 48 hours for signs of wound infection is advisable for all but minor lacerations. Surgical referral should be made for any complex injury. Discharge instructions should include strict hand elevation, intermittent application of ice for the first 24 hours, and splint precautions. Patients should receive written instructions on specific signs or symptoms which should prompt a return to the ED.

Patients with simple fingertip lacerations and minor avulsion injuries may be discharged from the ED. A follow-up visit at 48 hours to check for infection is advised. Patients with more significant injuries require surgical consultation.

Patients with a subungual hematoma may be discharged from the ED. If a fracture was detected on radiographs, the digit should be immobilized. The patient should be informed about the possibility of nail loss or deformity. Patients with a significantly avulsed nail matrix should be referred to a hand surgeon. Follow-up in 48 hours is recommended for patients with a distal phalanx fracture and those with nail bed lacerations who required nail removal and suturing. Antibiotics are unnecessary in immunocompetent patients with clean, fresh wounds. For high-risk patients, prophylactic use of an antibiotic, such as cephalexin 250 mg, given every 6 hours for 3 days is recommended.

The patient with a high-pressure injection injury should receive immediate surgical consultation with expectation of wide debridement and copious irrigation of all involved areas.

Discharge instructions for all patients with hand injuries should include elevation of the extremity and the use of ice for the initial 24 hours. Instructions regarding signs of infection, the timing of return visits for complications, wound checks, and suture removal are mandatory. Patients with injuries who are splinted should also receive instructions regarding splint care and problems that should prompt an immediate return to the ED. Appropriate and timely follow-up arrangements should be provided for all patients treated in the ED.

Common Pitfalls

- Failure to appreciate the extent of a PIP joint injury, which may lead to a *boutonnière* deformity, or failure to appreciate the extent of a DIP injury which may lead to a swan-neck deformity.
- Failure to perform a detailed neurologic assessment prior to regional anesthesia.
- Failure to recognize and treat MCP lacerations as potential human bite injury.
- Failure to recognize a partial tendon laceration due to inadequate wound exploration.
- Failure to identify a foreign body in a wound as a result of inadequate exploration or omission of a radiograph.
- Failure to appreciate the significance of a high-pressure injection injury.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Kenneth Jackimczyk, Suzanne Moore Shephard, and Paul Blackburn to the content of this chapter.

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CHAPTER 42 Pelvic Fractures

Carrie D. Tibbles and Michael Gibbs

Pelvic fractures are a common and often life-threatening consequence of major trauma. A pelvic fracture suggests a significant force of injury, mandating a careful evaluation for multisystem involvement. Many of these patients are hemodynamically unstable, requiring aggressive volume resuscitation. These patients are at increased risk for associated injuries and significant morbidity and mortality (1). Motor vehicle collisions and automobile–pedestrian trauma are responsible for 60% to 70% of pelvic fractures. Falls from a height account for 10% to 20% of pelvic fractures, and the rest are made up of athletic and direct crush injuries (2). Early resuscitation, accurate fracture classification, stabilization of the pelvis, diagnosis of associated injuries, and coordination of key specialists are the priorities in the emergency department (ED) management of these complex injuries.

CLINICAL PRESENTATION

An understanding of both the anatomy of the pelvis and the mechanism of injury is necessary to manage patients with significant pelvic trauma. It is useful to visualize the pelvis as a ring with anterior and posterior components (Fig. 42.1). The posterior pelvic ring, which is critical for stability, is strengthened by several ligaments: the anterior and posterior sacroiliac (SI) ligaments, sacrospinous ligament, and sacrotuberous ligament (Fig. 42.2A,B). Disruption of this powerful ligamentous complex is a marker of tremendous energy transfer. Major blood vessels traversing the posterior pelvic ring are vulnerable when fractures occur here.

Anteriorly, the pubic symphysis is the weakest link in the pelvic ring. Disruption of the symphysis alone does not lead to instability, provided the posterior ligamentous structures remain intact. Because the pelvis is a ring structure, if one fracture is identified, there is almost always a second disruption of the ring.

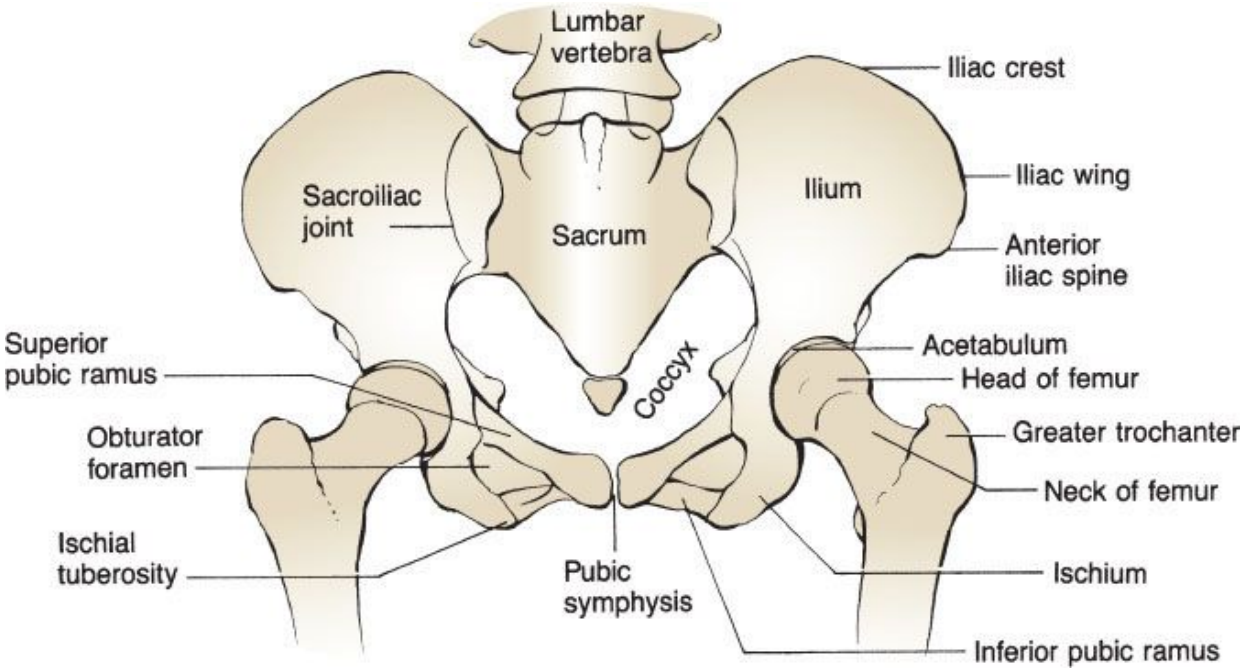

FIGURE 42.1 The pelvis.

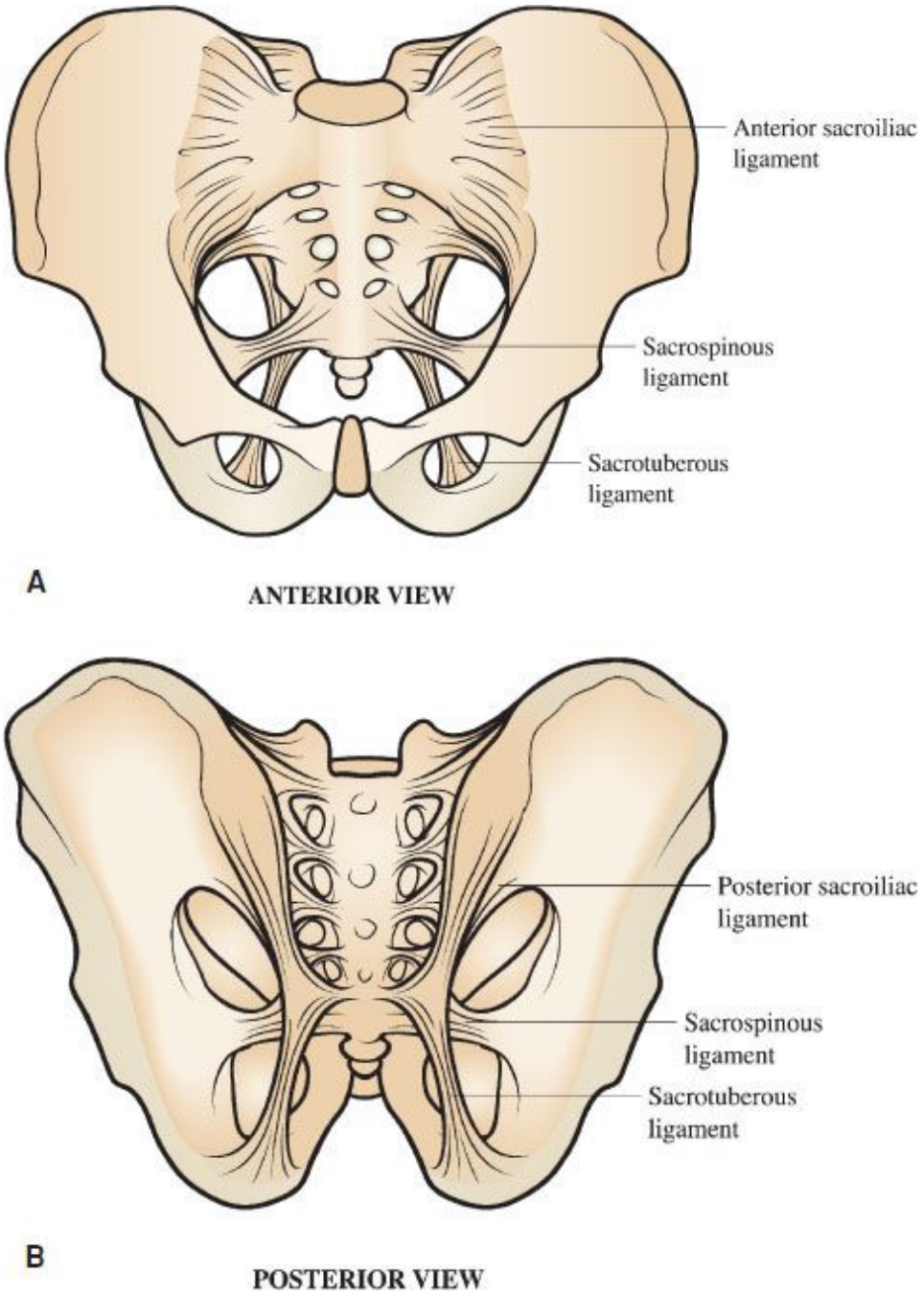

FIGURE 42.2 Ligamentous support of the bony pelvis, (A) anterior, and (B) posterior views. The posterior pelvic ring is stabilized by several strong ligaments. Disruption in this region implies major energy transfer and the potential for significant multisystem injury.

Several different pelvic fracture classification systems have been developed. The most widely used system was developed by Young

and Burgess and is based on the mechanism of injury (3). Three force vectors are described: lateral compression (LC), anteroposterior (AP) compression, and vertical shear (VS). "Complex patterns" describe injuries that are the result of more than one force vector. Each of these vectors breaks or dislocates the pelvic ring in a predictable pattern and is associated with varying degrees of mechanical instability (Table 42.1) and potential for hemorrhage. Each injury force vector has a unique effect on "pelvic volume": that is, the potential space created after injury that may accommodate pelvic hemorrhage. Injury vectors that increase pelvic volume (e.g., AP compression, VS) are much more likely to be associated with brisk pelvic bleeding and hemodynamic instability than injury vectors that decrease pelvic volume (e.g., LC).

TABLE 42.1
Young–Burgess Classification of Pelvic Fractures

Lateral Compression (LC)
Anterior injury—rami fractures
(a) LC I: Sacral fracture on side of impact
(b) LC II: Crescent fracture on side of impact
(c) LC III: Type I or type II injury on side of impact with contralateral open-book injury
anteroposterior compression (APC)
Anterior injury—symphysis diastasis/rami fractures
(a) APC I: Minor opening of the symphysis and sacroiliac (SI) joint anteriorly
(b) APC II: Opening of anterior SI, intact posterior SI ligaments
(c) APC III: Complete disruption of the SI joint
Vertical Shear (VS type)
Vertical displacement of the hemipelvis with symphysis, diastasis or rami fractures anteriorly, iliac wing, sacral fracture, or SI dislocation posteriorly
Combination (CM type)
Any combination of above injuries

Lateral Compression

LC fractures account for almost 50% of pelvic fractures. The force is delivered to the pelvis from the side. LC fractures are common after a

"T-bone" motor vehicle collision or when a pedestrian is struck from the side. The affected hemipelvis is crushed inward (Fig. 42.3). Stability is usually maintained, and therefore, LC injuries are less likely than other pelvic fractures to have associated major hemorrhage. Morbidity is secondary to coincident blunt force trauma to the head and torso, rather than the pelvic fracture itself.

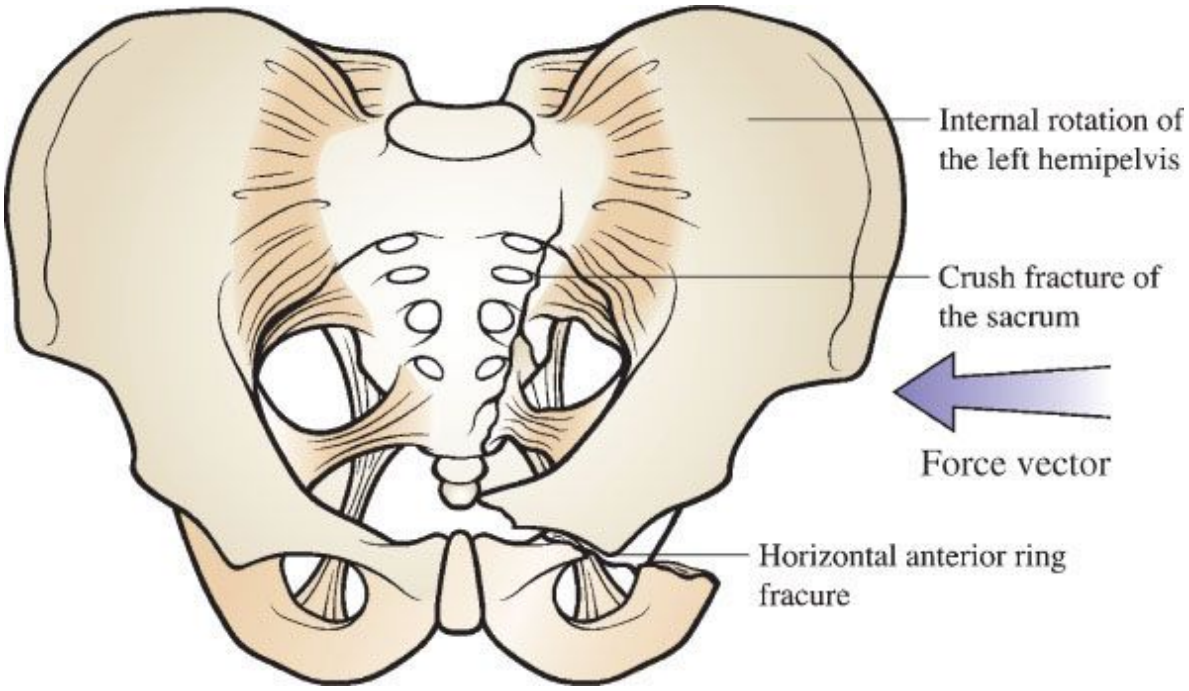

FIGURE 42.3 Lateral compression injury. The causative force vector is delivered from the side, crushing the affected hemipelvis inward. Lateral compression injuries typically reduce pelvic volume. Instability is variable.

Essential radiographic features of LC fractures include horizontal pubic rami fractures. These fractures are visible 80% of time on the AP view, and this feature alone is highly suggestive of LC injury. Crush fractures of the sacrum are seen in 88% of cases. This fracture may only be visible as a disruption of the arcuate lines. The combination of a crush fracture of the sacrum and a horizontal pubic ramus fracture is diagnostic for a LC injury. Fractures of the acetabulum or hip dislocations can also be seen. SI joint diastasis in combination with any of the other findings also suggests a LC injury.

Another type of fracture that results from LC is the “stove-in” or pelvic wing fracture that was first described by Duverney in 1751 (Fig. 42.4). This fracture may produce an unstable fragment off the iliac crest, but the load-bearing stability of the pelvic ring is not jeopardized.

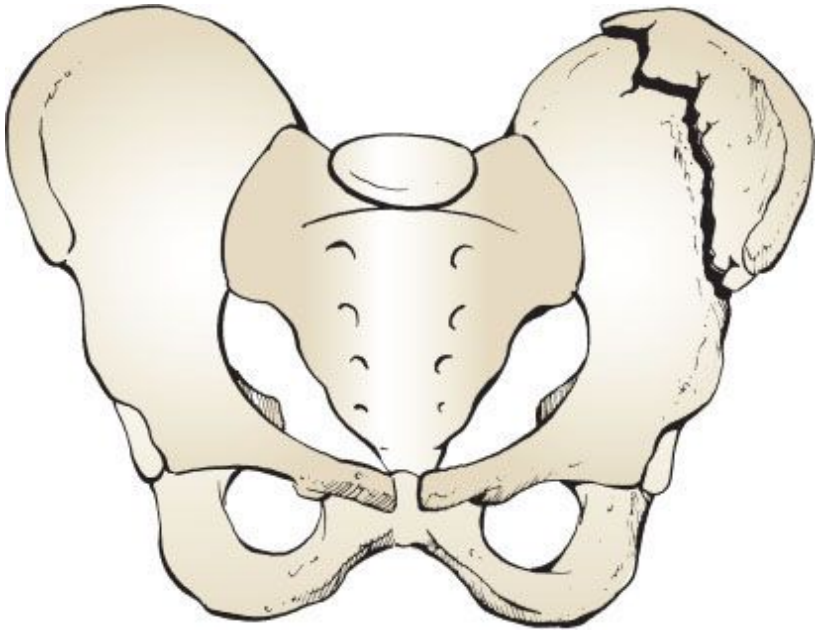

FIGURE 42.4 Duverney fracture. Pelvic wing or “stove-in” fracture.

Anteroposterior Compression

Nearly one-third of pelvic fractures are AP compression injuries. An anterior compressive force causes rupture of the symphyseal ligament and diastasis of the anterior pelvic ring. The posterior ligaments will tolerate up to 2.5 cm of symphyseal diastasis. Progressive widening of the symphysis beyond this point results in disruption of the anterior SI and sacrospinous ligaments. This injury is commonly referred to as an “open-book” pelvic fracture. Severe trauma will disrupt the posterior SI ligaments as well. In these circumstances, the SI joint is shown widely displaced on radiographs.

AP compression fractures are seen following head-on motor vehicle collisions or as a pedestrian is struck head-on by an oncoming vehicle. Forces may also be delivered in a posterior–anterior direction. Both iliac wings are forced outward (Fig. 42.5).

AP compression injuries are unstable, and are often associated with brisk pelvic and retroperitoneal hemorrhage. Coincident injuries of the thorax and abdomen are the rule.

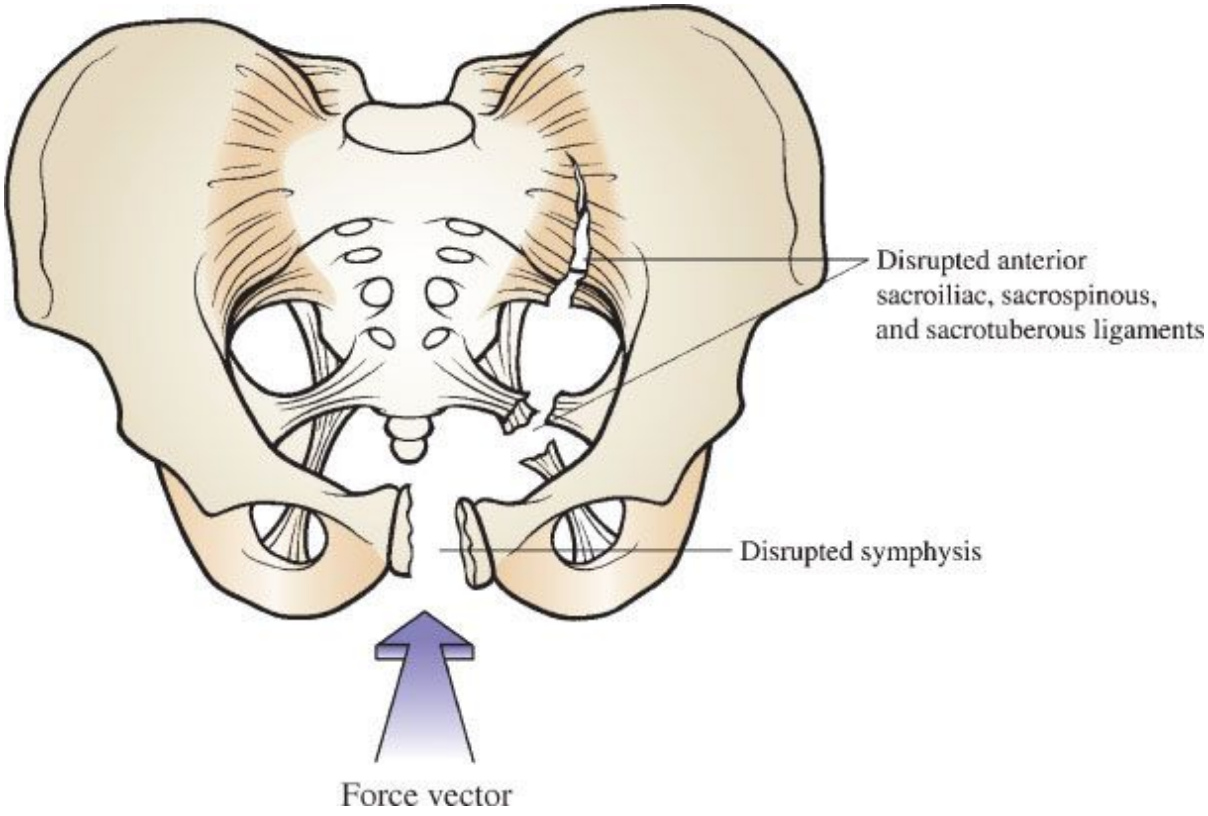

FIGURE 42.5 AP compression injury. The causative force vector is delivered from the front (or back), causing the pelvic ring to "open like a book." These injuries are mechanically unstable, and associated with increases in pelvic volume.

Radiographs of anterior compression injuries will demonstrate vertically oriented pubic rami fractures, symphyseal diastasis, or both, and a variable degree of SI joint disruption. An acetabular fracture is seen in up to one half of patients.

Vertical Shear Fractures

VS injuries occur when a vertically oriented force is delivered to the pelvis via the extended femurs. These rare injuries are usually the result of a fall from a height or follow a head-on motor vehicle

collision in which the occupant had the legs fully extended. VS injuries can also result from a downward force delivered to the pelvis via the spine, which may occur when a heavy object falls on the back or shoulders. Because one hemipelvis is driven up (or down) compared to the other (Fig. 42.6), these injuries produce major instability. The hemodynamic consequences are similar to those associated with AP compression injuries. Radiographs of a VS fracture demonstrate severe posterior disruption. This injury appears as either complete SI joint disruption, a vertical sacral fracture, or a medial iliac wing fracture with associated symphyseal disruption or pubic rami fractures.

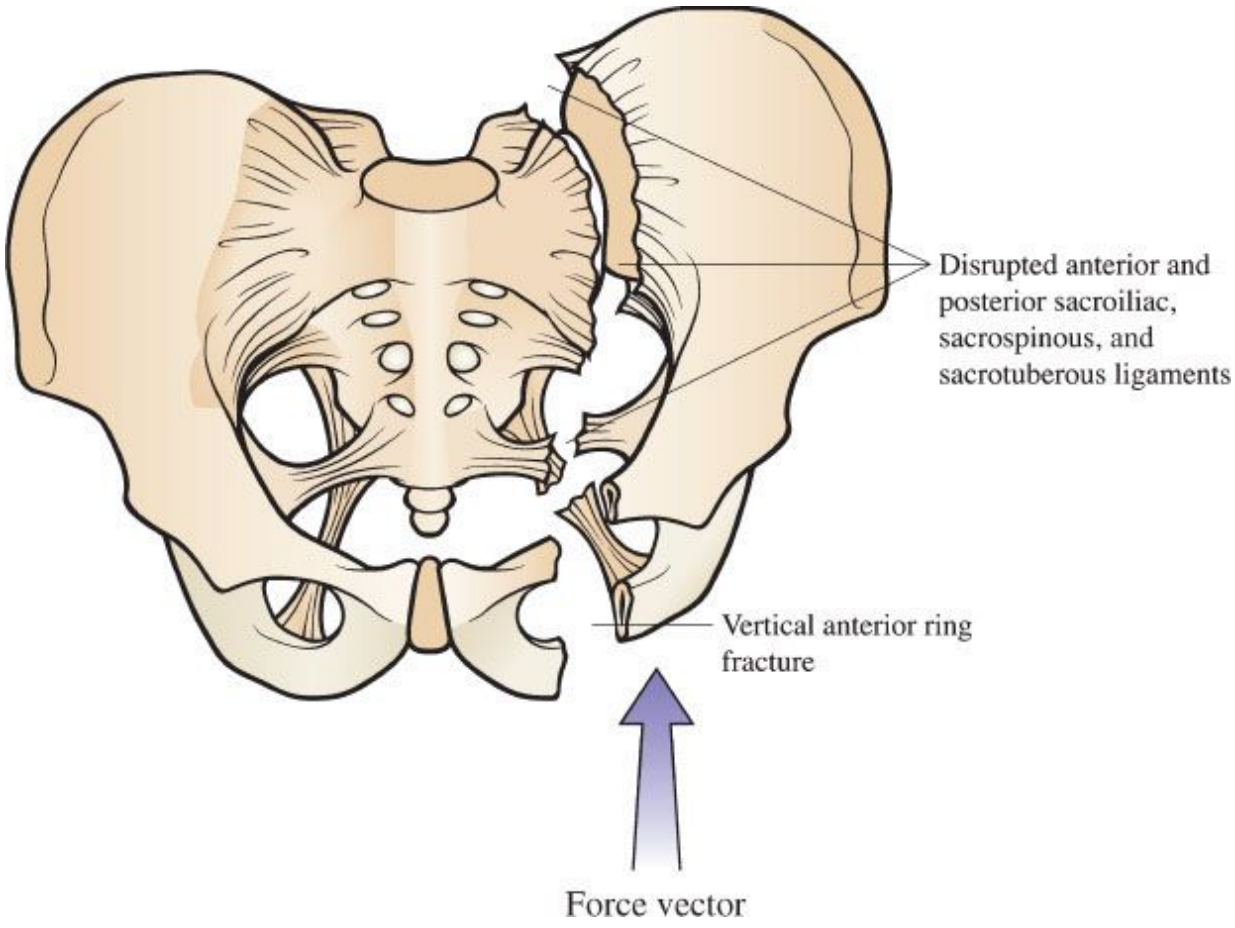

FIGURE 42.6 Vertical shear injury. The causative force is transmitted up the ipsilateral femur, driving the affected hemipelvis upward. Vertical shear injuries are extremely unstable and associated with increases in pelvic volume.

The Malgaigne fracture, first described in 1859, is characterized by anterior disruption of the pubic symphysis or two to four pubic rami fractures and ipsilateral SI joint disruption. Because of involvement of the posterior arch, these injuries can be complicated by significant neurologic and vascular injury. These patients are often hypotensive, and the mortality rate approaches 20%.

Other Types of Pelvic Fractures

Straddle Injuries

A straddle injury is an unstable injury characterized by bilateral double pubic rami fractures. Classically, this fracture results from falling while straddling a solid object between the legs. Both lateral and AP compressive forces can cause straddle injuries as well. The lower genitourinary tract is particularly susceptible to injury by this mechanism. These injuries are usually closed fractures. Patients will have perineal tenderness, ecchymosis, and gross hematuria. Male patients may be unable to void. The incidence of hemorrhage and bowel injury is high.

Avulsion Fractures

These injuries are among the most trivial of pelvic fractures and are often sustained by athletes who stress the muscular or ligamentous insertions onto the bony pelvis (Fig. 42.7). Avulsions of the anterior superior iliac spine generally occur in adolescent hurdlers and long jumpers. These injuries reflect forceful contraction of the sartorius muscle or abdominal musculature transmitted to the iliac epiphysis. Less commonly, the anterior inferior iliac spine may be avulsed by intense contraction of the straight head of the rectus femoris muscle. This injury may occur in athletes playing sports that involve kicking (e.g., soccer and rugby). Avulsion fractures of the ischial tuberosity are even less common. This injury usually results from strenuous stretching of the pelvic ring, as in hurdling or pole vaulting. Patients with avulsion fractures generally present with a characteristic history and local tenderness. In isolated trauma, there are usually no associated complaints or injuries. These are stable fractures, because the integrity of the pelvic ring remains intact.

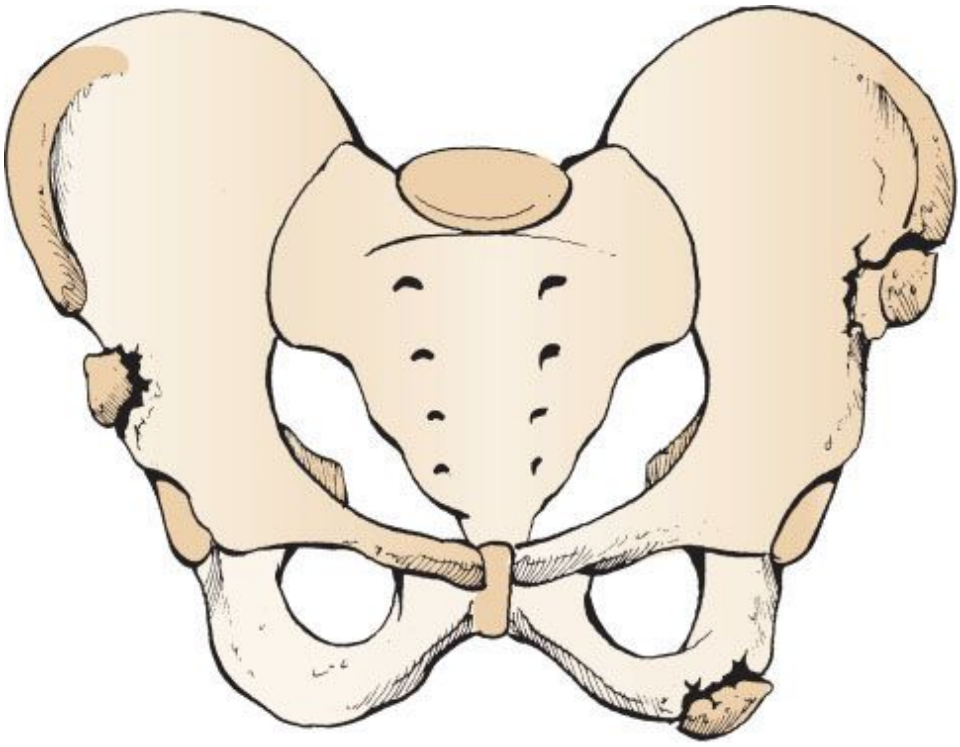

FIGURE 42.7 Fractures due to stress on muscular or ligamentous insertions onto the bony pelvis.

Sacral Fractures

Sacral fractures are defined by the orientation of the fracture line and occur in transverse upper, transverse lower, and vertical planes. Upper sacral fractures are frequently difficult to recognize both radiographically and clinically. These fractures often present only as buttock and perianal pain. These fractures may injure sacral nerve roots resulting in decreased anal sphincter tone and loss of perineal sensation. Lower sacral fractures are equally painful but are rarely complicated by neurologic injury. A careful physical examination to exclude rectal tears is important. Vertical sacral fractures occur as a result of VS injury.

Patients who fall from a standing height frequently present with pelvic pain localized to the bony prominences. Areas such as the iliac spine, ischial tuberosities, superior pubic rami, and coccyx are particularly susceptible to direct trauma. These fractures are stable injuries and are particularly common in elderly osteopenic patients.

Presentation involves localized pain, swelling, and ecchymosis. There are usually no associated injuries.

Associated Injuries

Significant force is required to disrupt the pelvic ring. Consequently, associated injuries, both to adjacent viscera as well as organs distant to the pelvis, are common following major pelvic trauma. The Injury Severity Score, as a surrogate marker of organ injury, is an important predictor of mortality in patients with pelvic fractures (4).

Approximately one-fourth of pelvic fractures are complicated by injuries to the urethra or bladder (5). More than 95% of patients with an injury to the posterior urethra and 70% to 95% of patients with a bladder injury following blunt trauma have a pelvic fracture. Bladder injury is usually the result of perforation by fracture fragments and is found in patients with symphyseal diastasis and those with multiple pubic rami fractures. The posterior urethra is also prone to injury following anterior pelvic fractures because it is firmly attached to the pubis by the puboprostatic ligament.

Upper sacral fractures, VS fractures, fractures of the sciatic notch, and SI joint injuries are frequently complicated by injuries to the lumbosacral plexus. The overall incidence of neurologic injury in patients with pelvic fractures is reported to be 10% to 21%. The incidence of neurologic injury is as high as 50% in fractures with posterior disruption (4). Such patients may present with distal motor weakness (impaired dorsiflexion or plantar flexion of the great toe), numbness on the dorsal and lateral aspect of the foot, a diminished Achilles tendon reflex, or evidence of cauda equina syndrome, including perianal anesthesia and loss of sphincter tone.

Open pelvic fractures are defined as a fracture with direct communication with a vaginal, rectal, or skin wound. These fractures are invariably associated with severe injuries of the pelvic viscera. Early mortality is attributed to severe blood loss or associated chest or intracranial injuries. Historically, mortality may be as high as 30% to 50% (6). Following the initial resuscitation phase, heavy contamination of perineal wounds resulting from damage of the rectum and genitourinary tract increases the risk of delayed

complications, including abscess formation, sepsis, and multiorgan failure.

ED EVALUATION

Physical Examination

During the initial resuscitation of the severely injured trauma patient, the priorities are to rapidly identify immediate life-threatening injuries and to initiate resuscitation. In the patient with a pelvic fracture, hypotension is an ominous sign, and a search for the cause should be rapidly initiated.

The objectives of the physical examination of the pelvis are to estimate the likelihood of a pelvic fracture and to identify any complications and associated injuries. The physician should inspect and palpate the front and back of the pelvis noting any abrasions, contusions, lacerations, tenderness, or crepitus. Although the identification of an unstable pelvic ring is important, overzealous rocking of the disrupted pelvis may cause additional retroperitoneal bleeding. It is preferable to apply gentle steady downward and lateral pressure on the iliac wings to detect or exclude tenderness. If tenderness is present, appropriate imaging should follow. In the obtunded blunt trauma patient with a possible pelvis injury, imaging should be performed.

Signs of urethral injury include blood at the urethral meatus, penile or scrotal hematoma, and a high-riding prostate. Patients with these findings should have a retrograde urethrogram before insertion of a Foley catheter to avoid worsening of an incomplete urethral tear. A careful vaginal examination should be performed in female patients. Perineal lacerations may have associated intravaginal mucosal tears. Bleeding is the hallmark of vaginal trauma, although it may not be immediately apparent because of muscle spasm. Vaginal injury should also be suspected if hematuria is present, or it is difficult to pass a Foley catheter.

The lumbosacral plexus is prone to injury in pelvic fractures, and a neurologic examination of the lower extremity should be performed with particular attention to the L5 and S1 nerve roots. In the patient

who is awake, motor function of the L5 nerve root is assessed by dorsiflexion of the great toe against resistance. The S1 nerve root is tested by having the patient plantar flex the great toe. L5 supplies sensation to the dorsum of the foot, and S1 supplies sensation to the lateral aspect of the foot. The Achilles tendon reflex, perianal sensation, and sphincter tone should also be assessed.

Indications for Pelvic Imaging

The severely injured blunt trauma patient who is either hemodynamically unstable or obtunded or who has clinical evidence of lower abdominal or pelvic injury requires pelvic imaging. For less severely injured patients, a thorough physical examination can be used to identify the patient at low risk for pelvic fracture who can be managed safely without imaging. In a prospective trial of 2,176 alert blunt trauma patients, Gonzalez et al. (7) demonstrated that the physical examination was 93% sensitive for detecting pelvic fractures and 100% sensitive for detecting those requiring operative repair. Pelvic imaging in blunt trauma patients is recommended for patients who:

1. Are clinically unstable.
2. Have lower abdominal or pelvic tenderness.
3. Have other signs of pelvic trauma (perineal hematoma, blood at the urethral meatus, gross hematuria).

Pelvic x-Rays

A single AP radiograph will identify the large majority of pelvic fractures and can provide sufficient information to guide early management. The AP radiograph provides specific clues that will help identify the various injury patterns and fractures described in the previous section (Figs. 42.8–42.12). The film should visualize the iliac crests, each hip joint, the fifth lumbar vertebrae, and the proximal portion of each femur. Important landmarks include the pubic symphysis, superior and inferior rami, anterior superior and anterior inferior iliac spines, SI joints, sacral ala, sacral foramen, and L5 transverse processes.

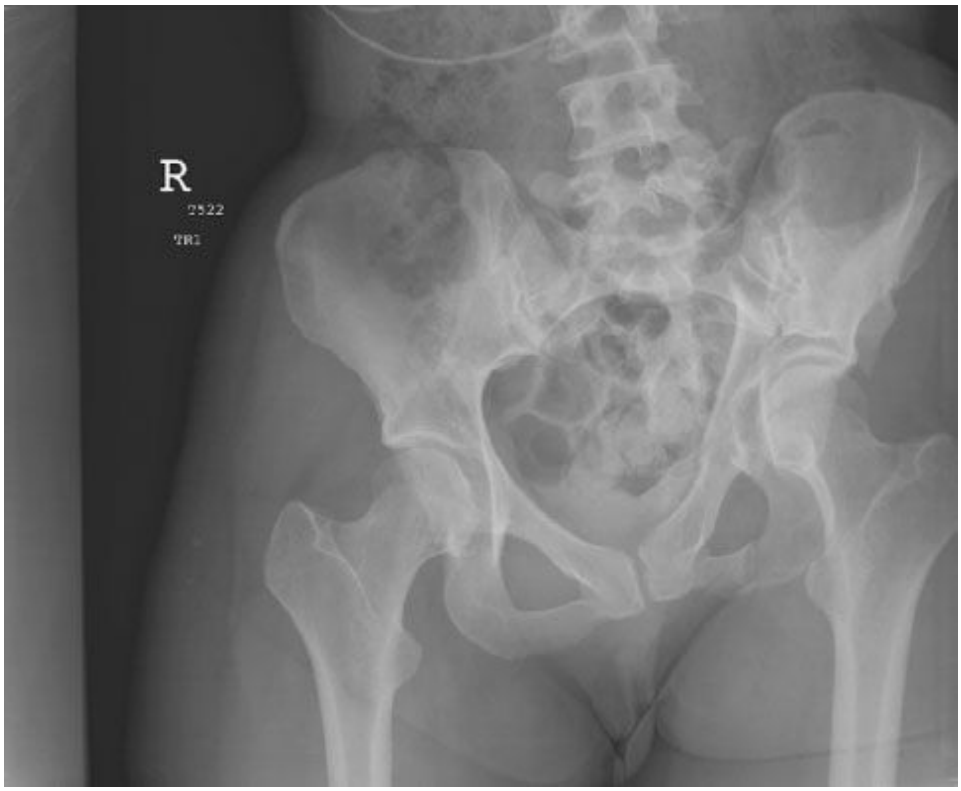

FIGURE 42.8 AP plain film of a severe lateral compression injury. The left hemipelvis is crushed inward.

FIGURE 42.9 CT scan of a left lateral compression injury with a crush fracture of the affected sacrum.

FIGURE 42.10 AP plain film of a severe AP compression injury with symphysis diastasis and left posterior SI joint disruption.

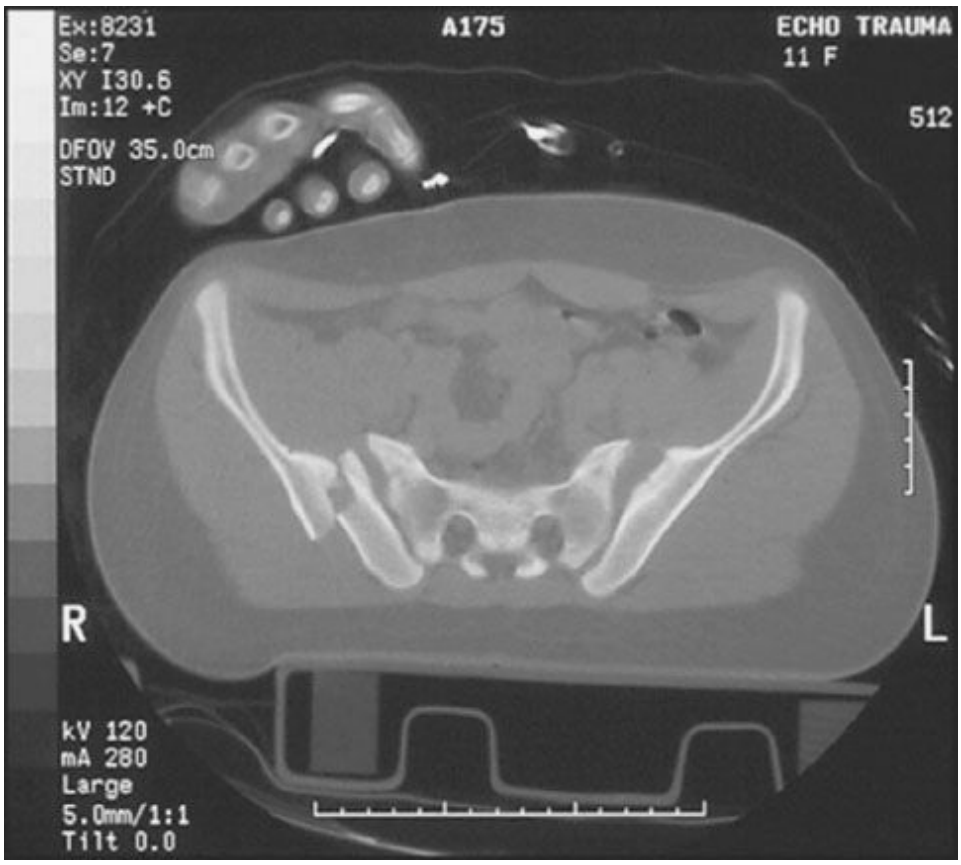

FIGURE 42.11 CT scan of an AP compression injury with major disruption of the posterior pelvic ring.

FIGURE 42.12 AP plain film of vertical shear injury with symphysis diastasis and upward migration of the left hemipelvis.

The increased use of abdominopelvic computed tomography (CT) scan in trauma patients has diminished the role of pelvic x-rays. A pelvic x-ray may be omitted in the hemodynamically stable patient who will have an abdominopelvic CT scan. An x-ray of the pelvis plays an important role in the hemodynamically unstable patient; as it may reveal the presence of an unstable pelvic fracture, suggesting a likely source of hemorrhage (8,9).

Computed Tomography

The use of CT has revolutionized the assessment of injured patients, and pelvic trauma is no exception. When compared to plain films, CT has a higher sensitivity for the detection of fracture in both adults and children. Other advantages include a more accurate assessment of pelvic instability, the ability to provide reconstructed three-dimensional images, and visualization of adjacent pelvic and abdominal viscera. Contrast extravasation seen on abdominopelvic

CT is useful for the detection of arterial bleeding and accurately predicts the need for therapeutic angiography (10,11). Blackmore et al. (12) demonstrated that visualization on CT of pelvic hematoma volume greater that 500 mL was predictive of the need for angiography compared to patients with volumes less than 200 mL.

ED MANAGEMENT

Initial ED management of the severely injured patient with a pelvic fracture can be challenging and requires a multidisciplinary approach with trauma surgery, emergency medicine, orthopedics, and interventional radiology (13). Aggressive resuscitation, pelvic fracture stabilization, and determination of the most likely source of hemorrhage to guide subsequent management are the immediate priorities in the ED. In the unstable trauma patient with a pelvic injury, the critical decision is summarized as follows: Does this patient have ongoing arterial bleeding related to the pelvic fracture, therefore, warranting angiography and therapeutic embolization, or is there intra-abdominal hemorrhage where urgent laparotomy is indicated? Rapid detection of intraperitoneal hemorrhage, an understanding of fracture patterns and stability, and local protocols and available resources guide decision making.

Resuscitation

During the initial resuscitation of the patient with significant pelvic injury, the physician should anticipate hypotension and initiate early aggressive resuscitation. Adequate intravenous access and careful monitoring are crucial. A blood sample should be sent for a cross match for type-specific blood. Hemoglobin, serum lactate, and the base deficit are also used to guide resuscitation. The critically ill patient requires vigorous resuscitation with warmed crystalloid and early transfusion, as well as precautions to prevent hypothermia.

Pelvic Stabilization

Vascular injuries and substantial blood loss often complicate displaced pelvic fractures. Venous bleeding accounts for the majority

of blood loss associated with pelvic fractures. Mechanically unstable injuries and those that increase pelvic volume create a potential space for ongoing hemorrhage. Pelvic stabilization can reduce pelvic volume. This practice can stabilize displaced fracture segments, which can also decrease fracture-related bleeding. Pelvic stabilization can be accomplished by several simple measures in the ED. Wrapping a sheet tightly around the pelvis will close the pelvic ring to some degree. Commercial pelvic binders are also available, and they are recommended with fractures amenable to compression, such as fractures with a widened symphysis (14).

With the advent of effective, noninvasive pelvic stabilization techniques and rapid angiography and embolization, external fixators are no longer routinely placed in the ED. External fixators may be used in the operating room in patients requiring laparotomy. When transfer to a regional trauma center is imminent, time should not be wasted waiting for an orthopedic surgeon to apply a fixator. Instead, a temporary device should be applied, and transport should proceed without delay.

Detection of Intraperitoneal Hemorrhage

During the initial assessment of the unstable patient with pelvic trauma, it is essential to quickly identify the predominant site of hemorrhage. Immediate angiography and pelvic stabilization is indicated if pelvic bleeding poses the primary life threat. An exploratory laparotomy should be performed first, however, if there is evidence of intra-abdominal hemorrhage.

Focused abdominal sonography for trauma (FAST) is routinely used in trauma centers for the rapid detection of hemoperitoneum following blunt abdominal injury. However investigators have found that the FAST examination is not sufficiently sensitive in patients with pelvic fractures to rule out intraperitoneal hemorrhage. Friese et al. reported a sensitivity of 26% for hemoperitoneum in patients with a pelvic fracture. Thirty-one of 96 patients had a false-negative study. The authors concluded that a patient with a negative FAST examination still requires a confirmatory test, such as CT or diagnostic peritoneal lavage (DPL) (15). Tayal et al. (16) also

reported a lower sensitivity of the FAST examination in the presence of a pelvic fracture (80.8%) compared to patients with blunt abdominal injury without a pelvic fracture. While not sensitive in these patients, the FAST examination does have sufficient specificity in patients with unstable vital signs and a pelvic fracture to recommend laparotomy for control of intra-abdominal hemorrhage.

The following approach based on the Ultrasound (US) findings and hemodynamic status of the patient is recommended.

1. US (+), patient stable: Perform abdominal CT.
2. US (+), patient unstable: Perform DPL aspirate or laparotomy.
3. US (–), patient stable: Perform abdominal CT or close observation.
4. US (–), patient unstable: Perform DPL aspirate (17).

When using a DPL in patients with pelvic fractures, the supraumbilical technique is preferred and has higher specificity. Classically, it has been recommended that the DPL be performed using a semi-open technique, but some authors are now reporting success using a percutaneous technique. Because the lavage can be falsely positive in patients with a pelvic fracture, the DPL aspirate should be used to guide decision making. An aspirate of 10 mL of gross blood is suggestive of intra-abdominal hemorrhage (17). An algorithm for the detection of intraperitoneal hemorrhage is presented in Figure 42.13.

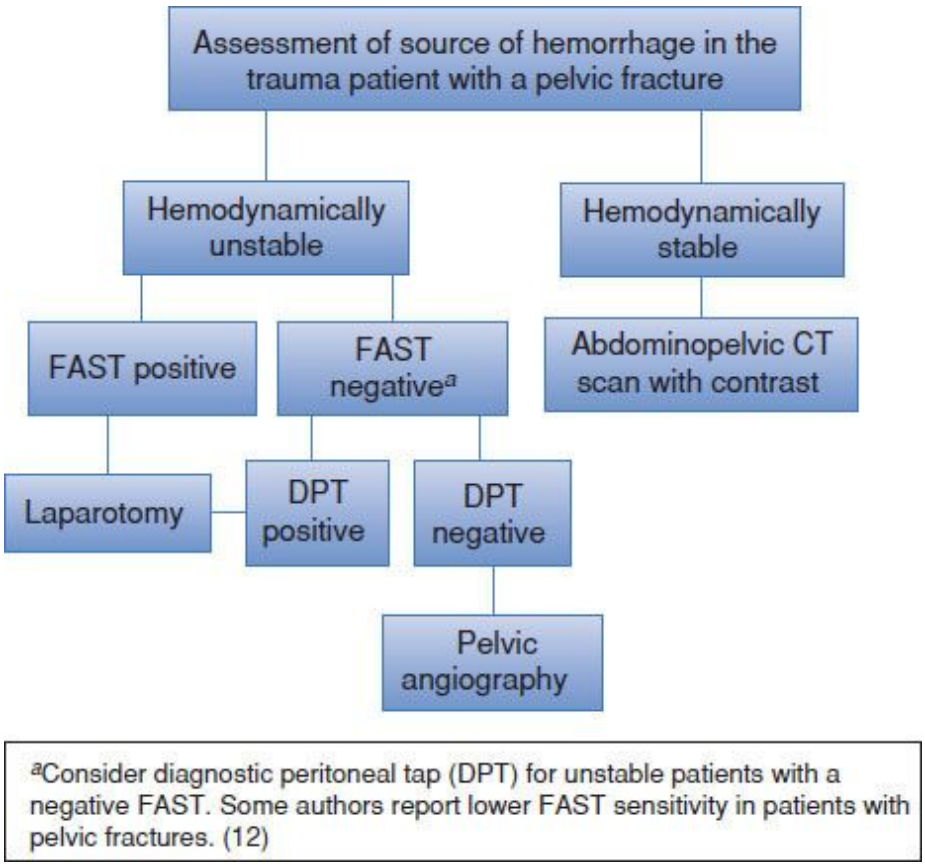

FIGURE 42.13 Evaluation of hemorrhage in patients with pelvic fractures.

CT imaging in the patient with pelvic trauma is straightforward, and the study of choice in the hemodynamically stable patient. Clinicians should be wary of potential delays in the unstable patient in need of immediate laparotomy or pelvic angiography.

KEY TESTING

- Plain films for hemodynamically unstable patients.
- FAST examination to assess for intraperitoneal bleeding.
- Abdominal/pelvic CT for hemodynamically stable patients.

Definitive Management

Although venous bleeding accounts for the majority of bleeding in the pelvis, injury to pelvic arteries results in brisk hemorrhage that is not controlled by pelvic stabilization alone. Arterial injury is found

in up to 20% of patients with AP compression and VS injuries, but it is uncommon in LC injury (18). The most commonly injured vessels include the superior gluteal, internal pudendal, obturator, and lateral sacral arteries. In the presence of arterial injury, vascular embolization is effective in 86% to 100% of cases and improves outcome (19,20). Early mobilization of the angiography team is essential because the length of time before embolization impacts survival.

Recently, investigators have attempted to determine factors that predict which patients would benefit from early angiography and embolization. As mentioned previously, contrast extravasation and increased pelvic hemorrhage volume on CT scan are predictive of associated arterial bleeding. Blackmore et al. (21) reported that a hematocrit <30, a pulse >130, or a displaced obturator ring fracture and pubic symphyseal wide diastasis predict major hemorrhage from a pelvic fracture. Miller et al. (22) found that patients with repeated episodes of hypotension despite adequate fluid resuscitation have a high likelihood of arterial injury. Pelvic fracture patterns may be predictive of the most important source of bleeding in the unstable patient, but should not be used in isolation, but in combination with other clinical signs (18). Eastridge et al. described the injury patterns in 231 hypotensive patients with pelvic trauma. In persistently hypotensive patients with “stable” fractures (i.e., LC and AP compression injuries with minor displacement), abdominal hemorrhage was the culprit in 85% of cases. Conversely, in patients with “unstable” fracture patterns (i.e., LC and AP compression injuries with major displacement and all VS injuries), hemorrhage was predominantly from a pelvic source. Pelvic angiography was positive in 59% of cases (23). Of note, anterior acetabular fractures were recently shown to have similar rates of arterial bleeding as pelvic ring fractures (18).

Intraoperative packing of the pelvis, in an effort to tamponade venous bleeding, has become an important adjunct in the management of these patients in some trauma centers. In general, peritoneal packing is used in the unstable patient also requiring an emergent laparotomy, as a temporizing measure if angiography is

not available, or as first-line procedure, with angiography following evidence of ongoing hemorrhage. Evidence suggests this technique reduces the need for transfusions and subsequent angiography (24,25).

CRITICAL INTERVENTIONS

- Aggressively resuscitate with crystalloid and early blood transfusion
- Activate a multidisciplinary team including emergency medicine, trauma surgery, interventional radiology, and orthopedics
- Rapidly detect or exclude hemoperitoneum at the bedside using US, CT scan, or diagnostic peritoneal aspirate
- Evaluate for associated visceral injuries (torso, genitourinary, and neurologic)
- Immobilize fractures that open the pelvic ring using a pelvic binder or wrapped sheet
- Initiate timely transfer to a level I trauma center

DISPOSITION

Patients with complex pelvic fractures require the resources of a level I trauma center. Rapid transport to a hospital capable of handling such injuries is essential, for these patients may deteriorate quickly. Preparation of the pelvic fracture patient for interfacility transport includes appropriate clinical stabilization, temporary pelvic stabilization, and communication with the accepting physician.

A small minority of patients with pelvic fractures can be discharged from the ED and managed as outpatients. The mechanism of injury, the age, and social supports of the patient should be factored into this decision. An example might be an isolated pubic ramus fracture in an otherwise healthy person. Consulting with an orthopedic surgeon, careful discharge instructions, and close outpatient follow-up are essential.

Common Pitfalls

- Failure to order pelvic imaging in all unconscious blunt trauma patients.
- Delays in immobilizing interventional radiology for definitive arterial embolization.
- Underresuscitation of a patient with an unstable pelvic fracture.
- Failure to diagnose associated intraperitoneal, retroperitoneal, and neurovascular injuries.
- Delaying transfer to a level 1 trauma center.

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CHAPTER 43 Hip and Femur Injuries

Carl A. Germann and Megan L. Fix

Hip injuries are common and associated with notable morbidity and mortality, especially in older patient populations. It is predicted that by the year 2050, 6.3 million hip fractures will occur yearly worldwide (1). Causes of hip fracture are primarily pathologic (from osteopenia) and falls, whereas motor vehicle collisions account for the majority of hip dislocations.

Anatomically, the hip is an articulation between the femoral head and the acetabulum. The femoral head is firmly seated in the acetabulum, which is reinforced by labral cartilage, capsule, overlying ligaments, and proximal musculature of the lower extremity (Fig. 43.1). It is a very stable articulation, requiring violent injury to fracture or dislocate. The femur is the longest and strongest bone in the human body and is often subjected to substantial forces produced during powerful muscle contraction, weight transmission, or trauma. The length, angle, and narrow circumference of the femoral neck allow substantial range of motion at the hip, but these same characteristics subject the neck to incredible shearing forces.

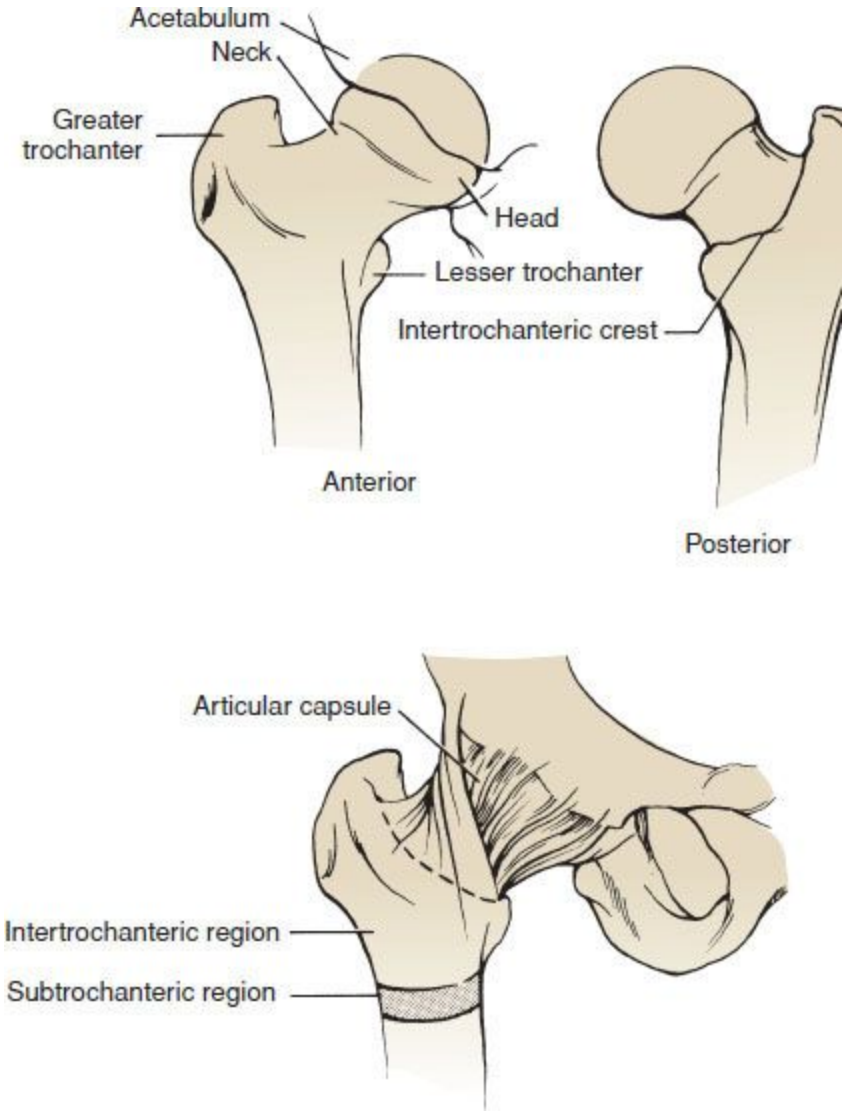


FIGURE 43.1 Anatomy of the hip. Anterior and posterior views of the femur (top) and division of the proximal femur (bottom).

Primary sources of blood flow for the femoral head are the retinacular branches of the circumflex femoral artery. These arteries enter the femur in the region of the femoral neck; fractures proximal to their entry can result in disruption of blood flow and cause avascular necrosis (AVN) of the femoral head.

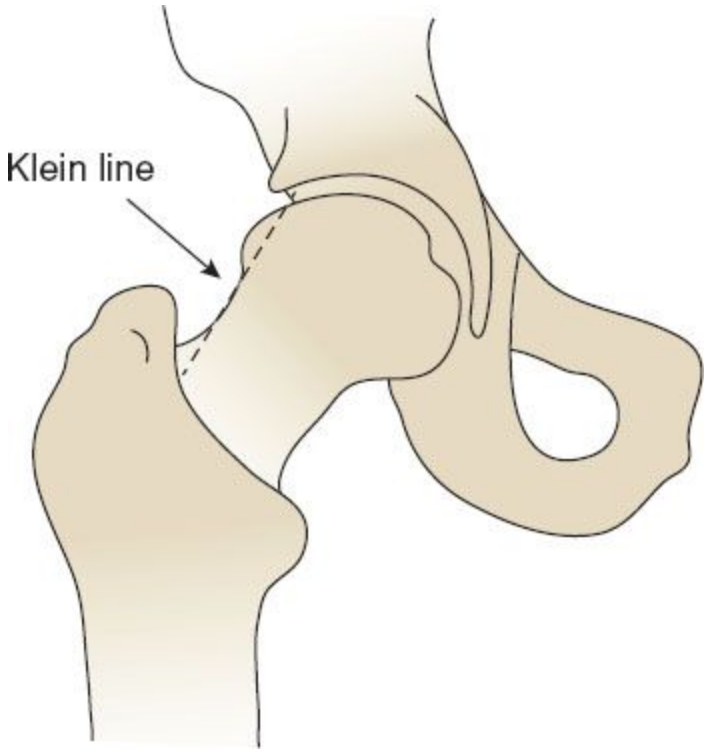
ED EVALUATION

During the initial evaluation, details of the mechanism of injury as well as a thorough physical examination and search for associated

neurovascular injuries are imperative. The initial radiographic studies in patients with suspected hip and femur injuries are the anteroposterior (AP) and lateral views. When analyzing the AP view of the hip, there are two important radiographic lines that help identify femur fractures and slipped capital femoral epiphysis (SCFE): Shenton and Klein lines. The Shenton line is a gentle arc seen on the AP view that runs along the inferior border of the femoral neck and extends to the inferior border of the superior pubic ramus (eFig. 43.1). The Shenton line will have a step or discontinuity in subtle cases of femoral neck and head fractures. The line may also appear disrupted in the radiograph of a normal hip, if it is not a true AP view. Klein line runs along the superior border of the femoral neck and intersects the superior portion of the femoral head (eFig. 43.2). The Klein line will project superior to a subtle fracture of the femoral head. The Klein line will also project superior to the epiphysis in a subtle case of SCFE.

FIGURE 43.2 Posterior hip dislocation.

eFIGURE 43.1 The Shenton line. (From Gruber JE, Gibbs MA, Ferrera PC, et al. Trauma Management: An Emergency Medicine Approach. St. Louis, MO: Mosby; 2001:398 (Figure 26–2), with permission.)



eFIGURE 43.2 The Klein line. (From Gruber JE, Gibbs MA, Ferrara PC, et al. Trauma Management: An Emergency Medicine Approach. St. Louis, MO: Mosby; 2001:398 (Figure 26–3), with permission.)

Approximately 2% to 10% of all hip fractures are radiographically "occult" on plain films (2). Therefore, if clinical suspicion remains and plain radiographs are negative, magnetic resonance imaging (MRI) is indicated. Although computed tomography (CT) scan can be used, small studies suggest that it is inferior to MRI (2,3). CT does seem to have merit when the patient does not have significant osteoporosis or in the setting of significant trauma (3). MRI is the imaging modality of choice with a sensitivity and specificity approaching 100%. In studies of patients with suspicion of hip fracture and normal plain radiographs, MRI showed occult fracture in 37% to 55% of patients (4).

KEY TESTING

- The initial radiographic studies in patients with suspected hip and femur injuries are the AP and lateral views.

- If clinical suspicion remains high and plain radiographs are negative, MRI is recommended to evaluate for occult fracture.
- Failure to detect these injuries results in increased mortality, risk of subsequent displacement, and a higher incidence of complications such as AVN.

ED MANAGEMENT

Hip Dislocations

The relationship of the femoral head to the acetabulum is used to classify dislocations into posterior, anterior, inferior, and central. Posterior dislocations account for 80% to 90% of cases. Anterior dislocations are seen in 10% to 15% of patients. Inferior dislocation (luxatio erecta) of the hip is very rare and occurs almost exclusively in children younger than 7 years of age. Central dislocation is often used to describe the translocation of the hip joint causing a comminuted fracture of the acetabulum.

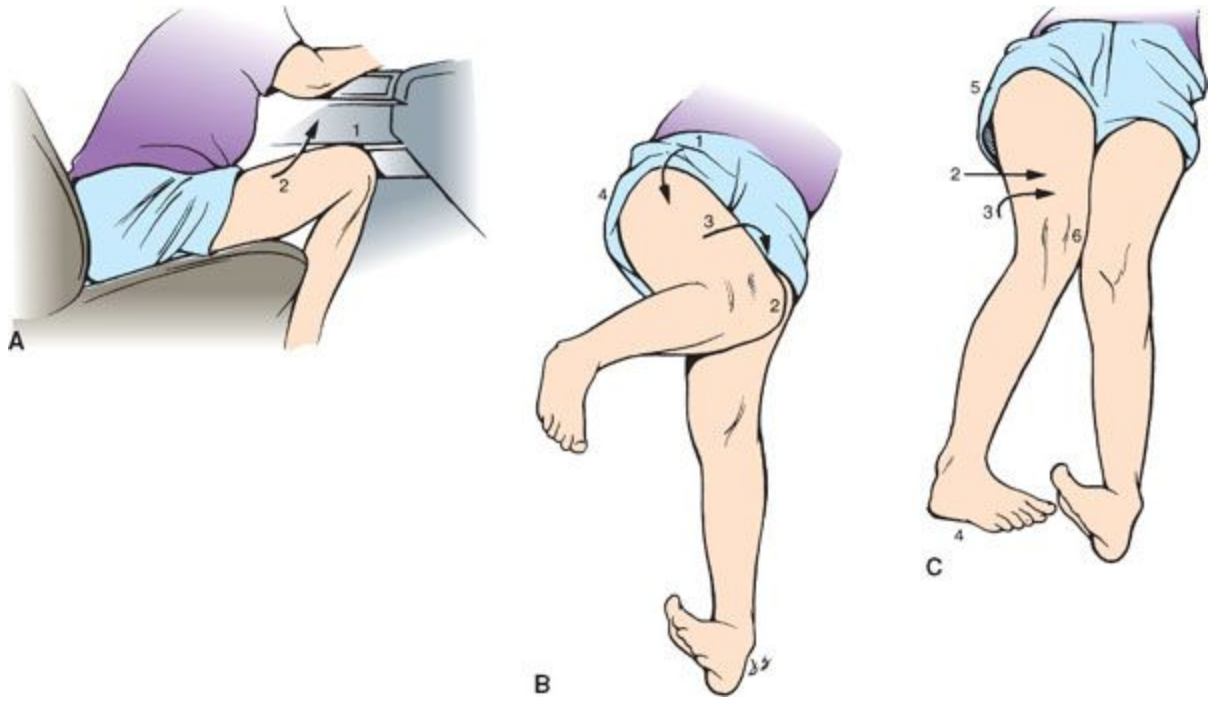
The neurovascular examination after a hip dislocation should focus on the sciatic nerve and femoral nerve and vessels. Sciatic nerve palsy is more likely to occur in conditions such as traumatic dislocation of a nonprosthetic hip or during the total hip arthroplasty (THA) procedure itself. Sciatic palsies may be present in approximately 10% of patients who experience traumatic hip dislocation. The sciatic neuropathy may produce paralysis of the peroneal muscles. The femoral artery and its branches are the most likely vessels to be injured, particularly after an anterior dislocation. The development of AVN of the femoral head caused by arterial injury has been reported in 1% to 17% of dislocations (5). Risk factors for the development of AVN include the total dislocation time, severity of the injury, number of reduction attempts, and presence of comorbid conditions. The incidence of AVN, traumatic arthritis, permanent sciatic nerve palsy, and joint instability logarithmically increases with the length of time for which the hip remains dislocated (6). Of course, prosthetic femoral heads are not at risk for developing AVN.

Posterior Hip Dislocations

Posterior hip dislocations are the most common type of hip dislocation and result from force applied to a flexed knee and hip. These injuries usually occur as a result of motor vehicle crashes where a seated occupant typically has the hip adducted, flexed, and internally rotated at the time of impact. This injury may be prevented by the use of a lap belt.

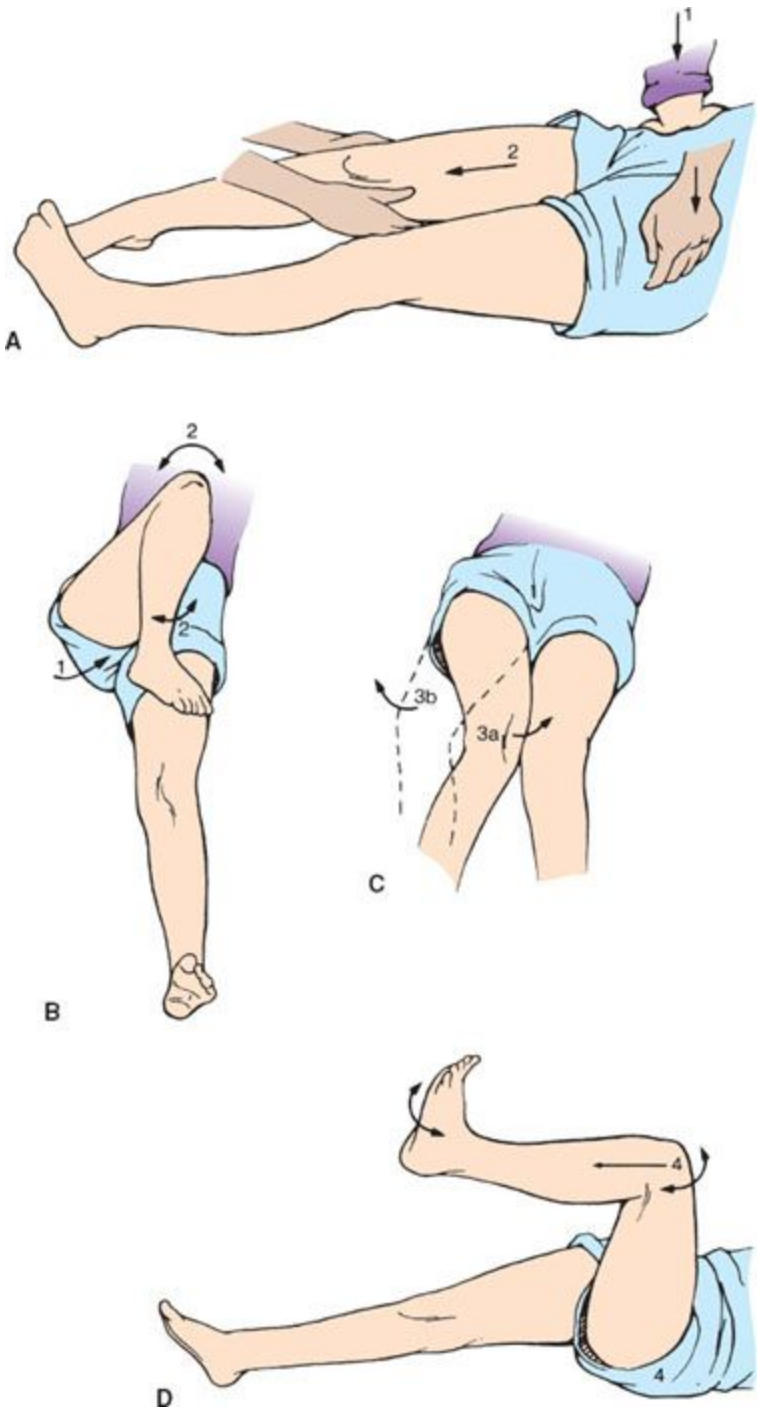
In posterior hip dislocations, the limb is often found flexed, adducted, internally rotated, and shortened. The knee of the affected extremity often rests on the opposite thigh. The greater trochanter may be unusually prominent. Likewise, the femoral head can often be palpated in the buttocks region (Fig. 43.2 and eFig. 43.3). Examination of the leg should ensure vascular function (rarely compromised) and include neurologic evaluation for possible sciatic nerve injury. Up to 50% of dislocations are associated with acetabular or femoral head fractures.

FIGURE 43.3 Slipped capital femoral epiphysis. A 13-year-old boy with a severe left-sided SCFE. (From Swiontkowski MF, Stovitz SD. Manual of Orthopaedics. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)



eFIGURE 43.3 Posterior dislocation of the hip. A: Mechanism of injury: The knee (1) strikes the dashboard. The thigh (2) is forced into flexion and adduction, and the femoral head is driven backward out of the acetabulum. B: Ischial dislocation: The hip (1) is flexed. The hip is markedly adducted, so that the knee (2) of the affected limb lies on the opposite thigh. The limb (3) is in extreme internal rotation. The greater trochanter and buttock (4) on the affected side are unusually prominent. C: Iliac dislocation: As in (B), the hip is flexed and is adducted (2).

Optimally, posterior dislocations should be reduced within 6 hours to minimize the risk for AVN (7). Therefore, this procedure should be attempted in the emergency department (ED) (eFig. 43.4). Adequate analgesia and muscle relaxation must be obtained using appropriate agents (e.g., a short-acting opioid and a short-acting benzodiazepine or propofol) and monitoring.



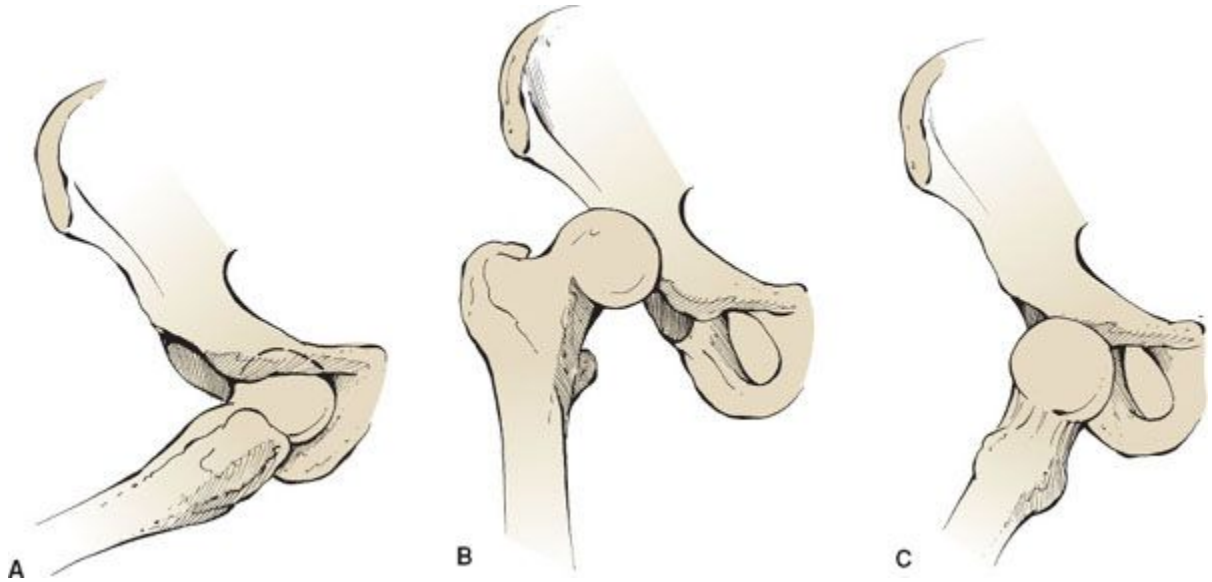
eFIGURE 43.4 Posterior dislocation of the hip: method of manipulative reduction. A: The assistant holds downward pressure (1) on the anterior superior iliac spine. With the knee flexed (2), the operator pulls on the limb in the line of deformity. B: The assistant slowly brings the thigh (1) to 90 degrees of flexion. The assistant gently rotates the thigh internally and externally and rocks the thigh

(2) backward and forward to disengage the head from the external rotator muscles and the posterior capsule. C: The assistant relocates the femoral head by further internal rotation and extension of the thigh (3a) or external rotation and extension of the thigh (3b). D: The assistant pushes firmly on the trochanter to direct the femoral head into the acetabulum while the limb is rotated and extended (4). Forceful rotation should be avoided, because it can fracture the femoral neck. If the reduction is not accomplished with two adequate attempts, open reduction is indicated.

Among the several techniques described in the literature, the Allis technique is commonly used to relocate posterior hip dislocations. After the patient is adequately sedated, the hip is flexed and an upward traction is applied to the supine patient. An assistant may apply pressure to the iliac crests, stabilizing the pelvis from lifting off the bed. To apply constant traction to the leg, it is often necessary to stand on the bed and straddle the patient. Upward traction and continued longitudinal force is applied with gentle internal and external rotation. Successful reduction is often felt by a dull click. After reduction, the extremity should be placed in extension and neurovascular function of the extremity should be reassessed. Postreduction radiographs should be obtained to identify the proper location of the femoral head. General anesthesia is occasionally necessary if procedural sedation is unsuccessful.

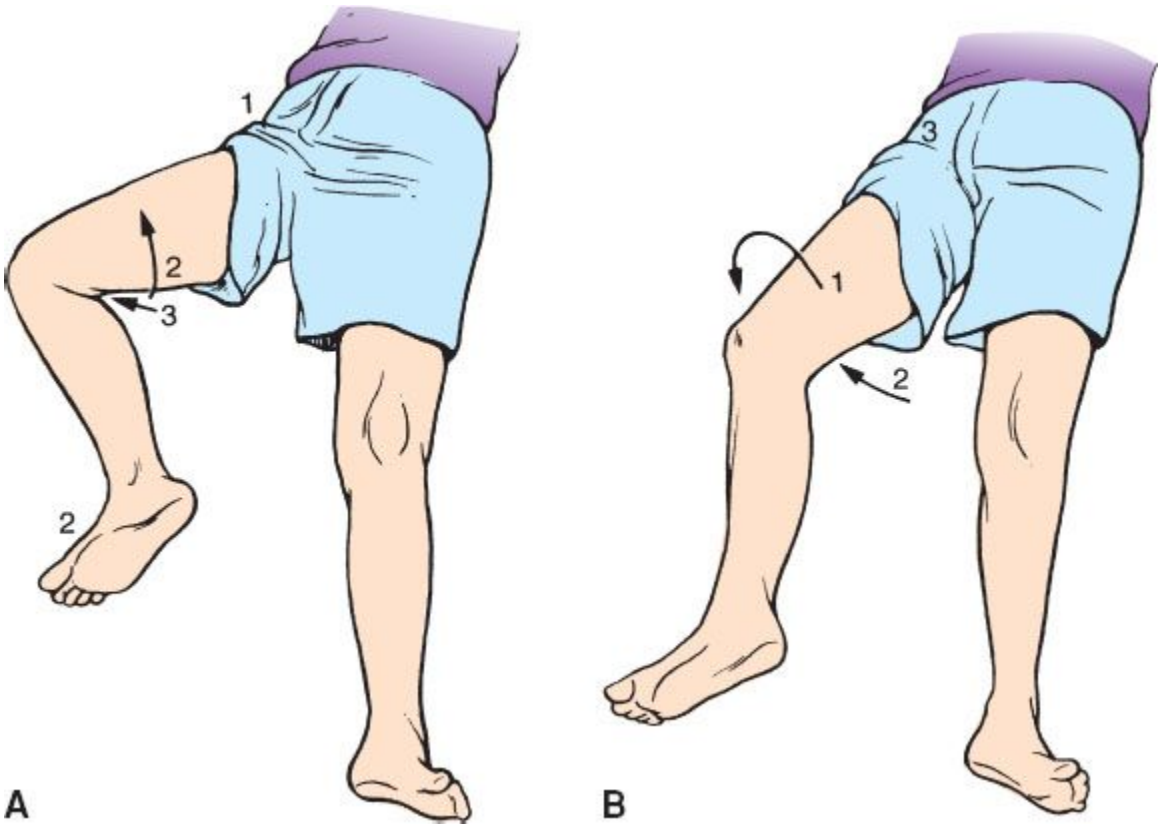
Anterior Hip Dislocations

Anterior hip dislocations occur most commonly from a direct blow to the abducted hip. A distally applied force causes the femoral head to tear through the anterior capsule and lever out of the acetabular cup. The mechanism of injury is most often an MVC during which the occupant has the hip abducted and externally rotated at the time of impact or a fall or sports injury causing forced hyperextension. Anterior dislocations are classified as obturator, iliac, and pubic (eFig. 43.5).



eFIGURE 43.5 Anterior hip dislocations. Anterior obturator hip dislocation (A), anterior iliac hip dislocation (B), and anterior pubic hip dislocation (C).

On physical examination, patients with anterior obturator dislocations present with abduction, external rotation, and flexion of the involved extremity. Patients with anterior iliac and pubic dislocations present with slight abduction, external rotation, and extension of the involved extremity (eFig. 43.6). Following anterior dislocation, a careful neurovascular examination is mandatory as the femoral artery, vein, or nerve are prone to injury.



eFIGURE 43.6 Anterior dislocations of the hip. A: Obturator dislocation. The hip (1) is slightly flexed. The limb (2) is externally rotated. The thigh (3) is abducted. B: Pubic dislocation. The extremity (1) is in severe external rotation (90 degrees). The extremity (2) is abducted only slightly (15 to 20 degrees), and it is slightly flexed. The femoral head (3) can readily be palpated in the inguinal region.

Early reduction is recommended to minimize neurovascular complications, such as AVN. A modified Allis maneuver is a commonly used reduction technique for anterior dislocations. Like the Allis technique, the patient is placed supine and an assistant stabilizes the pelvis. Traction is applied along the long axis of the femur with slight hip flexion. Gentle adduction and internal rotation may encourage reduction. If reduction is unsuccessful using common procedural sedation techniques, closed reduction under general anesthesia may be required.

Prosthetic Hip Dislocations

More than one million hip arthroplasties are done every year worldwide, and the number is projected to double within the next two decades given the ageing population and obesity epidemic (8). After THA, instability in the form of dislocation is second in frequency to joint loosening as a major complication of this procedure. Dislocation of the prosthesis occurs in 1% to 3% of patients with primary THA and in 5% to 20% of patients with a revised THA (9). Dislocations after THA can occur in a posterior or anterior direction. Posterior dislocation is the most common and accounts for 75% to 90% of THA dislocations (10). Dislocations often occur in the first 3 months postoperatively and are generally caused by relaxed soft tissues and immature scar formation (11). Over time, stretching of the pseudocapsule caused by extremes of motion may lessen soft tissue constraints and allow for dislocation.

Reduction techniques for prosthetic hip dislocations are identical to those described earlier. While a dislocated prosthetic hip carries no risk of AVN, injury to the sciatic nerve can occur.

Hip Fractures

Given the increasing elderly population and number of patients with osteoarthritis of the hip, the number of hip fractures may double over the next 20 years, reaching half a million a year by 2050 (12). A third of those over age 65 who live at home and half of institutionalized individuals are estimated to fall yearly. Morbidity in this age group is staggering, with a third dying within 1 year (13). Thirty percent of those who were independently ambulatory prefracture require permanent postinjury crutches or a walker, and 7% of them become permanently bedridden (14).

The term hip fracture refers to a fracture of the femur proximal to the subtrochanteric region. Hip fractures are generally classified into six anatomic groups: femoral head and neck fractures, intertrochanteric fractures, subtrochanteric fractures, and isolated fractures of greater or lesser trochanters. The terms intracapsular (femoral head and neck) and extracapsular (intertrochanteric,

subtrochanteric, and greater and lesser trochanter) are also commonly used.

Currently, treatment of these fractures is hemiarthroplasty or open reduction and internal fixation (ORIF) for femoral neck fractures.

Femoral Head Fractures

Isolated fractures of the femoral head are relatively uncommon and most often due to motor vehicle collisions. They are more common in younger patients as the force required often causes femoral *neck* fractures in older patients. As with dislocations of the hip, acetabular fractures may also be seen. These fractures usually occur in conjunction with hip dislocations caused by severe shearing forces. Femoral head fractures occur in 6% to 16% of hip dislocations (15).

Femoral head fractures may not be visualized on routine radiographs and CT or MRI may be required to confirm the diagnosis. Early recognition and reduction is important to maximize future joint function and minimize complications such as arthritis, AVN of the femoral head, or myositis ossificans. Urgent orthopedic consultation is mandatory. In most cases, satisfactory results can be obtained with closed reduction. However, if the hip cannot be reduced by manipulation or if reduction of the femoral head fragment is unsatisfactory, open reduction will be required. Unfortunately, complications may occur regardless of proper intervention and result in the need for prosthetic replacement.

Femoral Neck Fractures

It is estimated that 5% to 10% of people reaching their 80s will have a femoral neck fracture. These fractures occur below the femoral head and above the greater trochanter and are much more common than femoral head fractures. In the elderly, these fractures may be pathologic, occurring with a fall or minimal trauma. In younger patients, they are usually associated with high-energy mechanisms such as motor vehicle trauma. Osteoporosis is a major

risk factor, making the injury four times more common in women than in men.

Several classifications systems have been described but are not consistently used because of poor interrater reliability and limited clinical utility. More commonly, femoral neck fractures are classified as either nondisplaced or displaced. Most femoral neck fractures are displaced and present with the limb externally rotated, abducted, and slightly shortened. Fifteen percent to 20% of all femoral neck fractures are nondisplaced. The prognosis for nondisplaced fractures is excellent; functional outcome is favorable and the majority of patients heal without complication. However, a nondisplaced femoral neck fracture possesses no inherent stability and may become displaced without surgical fixation.

Stress fractures represent a unique type of femoral neck fracture. These fractures most commonly occur in young, athletic individuals, but they also occur in those with pathologic bones, (rheumatoid arthritis, renal osteodystrophy, and chronic steroid use). Stress fractures may be bilateral and are usually the result of repetitive abnormal stress on normal bone or repetitive normal stress on abnormal bone. The pain is often gradual in onset. Ambulation is common, and patients complain of pain with weight bearing. The usual signs of fracture are missing, both clinically and radiographically. Bone scan or MRI is indicated in any high-risk individual who cannot bear weight. Treatment is based upon the degree of injury and the state of the underlying bone. Treatment ranges from resting the affected hip to prosthetic hip replacement.

AVN and nonunion are the two major complications of femoral neck fractures. AVN of the femoral head is most common and may occur despite optimal treatment. It is identified on x-ray as an increase in density in the region of the femoral head thought to be new bone deposition.

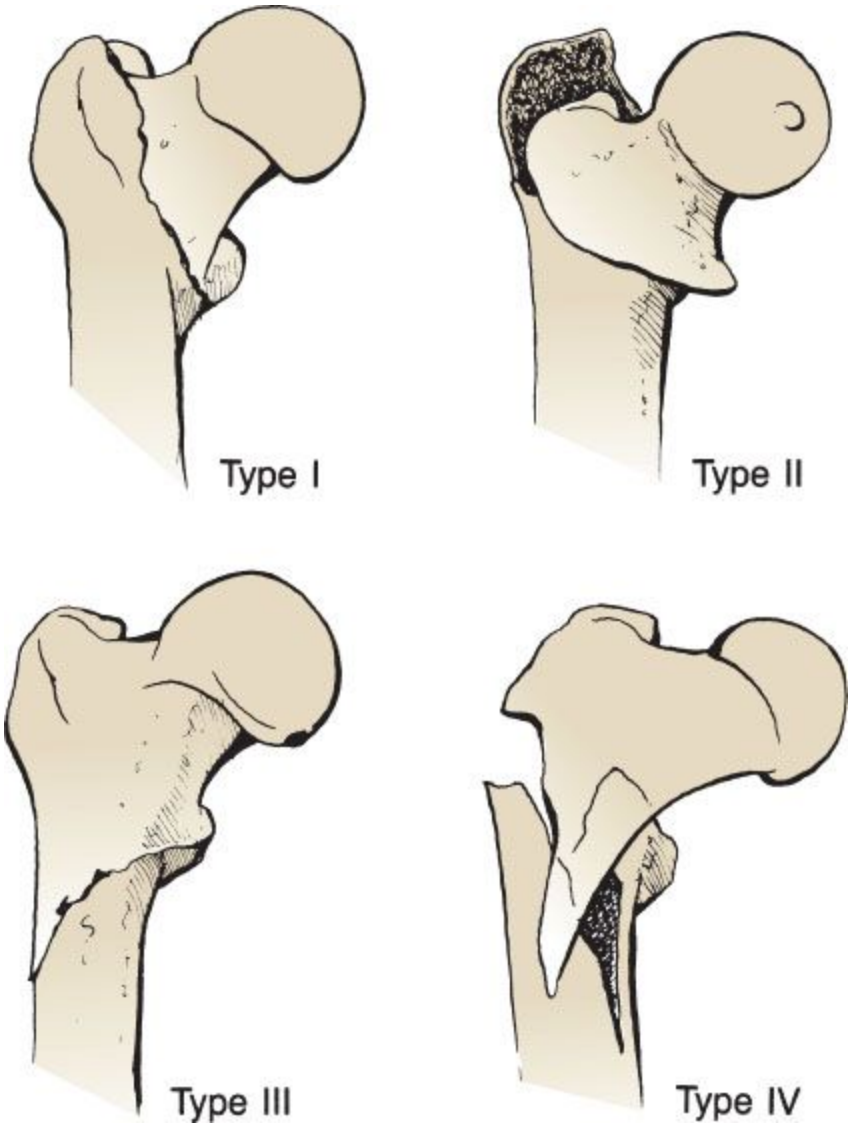
Early and precise anatomic reduction reduces the risk of AVN. Prompt recognition and orthopedic consultation in the ED may help minimize AVN and other sequelae. Treatment of displaced fractures often consists of ORIF, hemiarthroplasty, or THA.

Intertrochanteric Fractures

These are the most common types of hip fractures with the majority being caused by falls in the elderly. Intertrochanteric fractures are often considered pathologic, most commonly secondary to osteoporosis. Other causes include cancer and, less commonly, Paget disease. X-ray findings usually show comminution, the majority with three, four, or more fragments (16).

Emergency diagnosis is usually straightforward. Any movement causes extreme pain, and the hip may be tender to palpation. The affected leg is shortened and externally rotated, and weight bearing is not possible. The diagnosis is usually confirmed with a single AP view of the hip. A lateral or groin view may be necessary to evaluate the degree of comminution.

The intertrochanteric fracture is extra-articular and typically extends in a relatively straight line between the greater and lesser trochanters (eFig. 43.7). A variety of classifications are used to describe these fractures with no universal agreement. The Boyd and Griffin classification uses four categories (eFig. 43.7). When obtaining orthopedic consultation, precise anatomic description may be more useful than a specific classification type.



eFIGURE 43.7 Boyd and Griffin classification of intertrochanteric hip fractures. (Adapted from Rockwood CA Jr, Green DP, Bucholz RW. Rockwood and Green's Fractures in Adults. 3rd ed. Philadelphia, PA: Lippincott Co.; 1991.)

Initial management consists of immobilization with sandbags or Buck traction (2 to 4 kg) which helps decrease blood loss. Intravenous volume replacement, with crystalloid or blood, may be necessary because patients can lose 1 to 2 L of blood with these fractures. Many of these patients have chronic medical problems that should be addressed (including the cause of the fall), and this history will help to establish whether the patient is an operative

candidate. Laboratory evaluation should include the standard preoperative labs, as well as analysis necessary to ascertain cause of the fall (may include neurologic and cardiovascular evaluations).

Operative repair has historically been considered safer than conservative therapy. This opinion is a result of the morbidity and mortality associated with extended immobilization. Surgical reduction and fixation should be considered urgently rather than emergently, and all patients should have a thorough preoperative evaluation. Selected fractures may be managed by splinting, traction, or spica immobilization as determined by the consulting orthopedist and the patient's underlying medical conditions. Complications are common and reflect the frail status of most of these patients. Mortality rates are up to 15% (17).

Greater and Lesser Trochanteric Fractures

Greater trochanteric fractures are rare and occur as a result of direct trauma in adults or secondary to apophyseal avulsion as a result of forceful muscular contraction in young patients (ages 7 to 17). Tenderness to palpation is usually present over the greater trochanter. Patients are usually ambulatory with a limp. When caused by direct trauma, these fractures are rarely displaced and can be difficult to see on routine radiographs, so comparison views of the other leg are recommended. The direct blow (adult) fracture is usually comminuted without significant displacement whereas the epiphyseal avulsion (youth) type is usually displaced but not comminuted. Management varies from adduction splint and bed rest, to ORIF. In most instances, the prognosis is good, regardless of the method used.

Lesser trochanteric fractures usually occur in the young: 85% occur before age 20. These fractures usually occur from forceful contraction of the iliopsoas muscle during strenuous activities. The lesser trochanter can be displaced up to 1 cm. This injury in an adult mandates a search for pathologic bone. Patients have pain and tenderness in the femoral triangle. In a complete avulsion, they are unable to lift the affected extremity in the sitting position (Ludloff

sign). Radiographic imaging frequently requires comparison views. Treatment is usually conservative, unless there is significant displacement and outcomes are uniformly good (18).

Subtrochanteric Fractures

Subtrochanteric fractures are defined as fractures occurring between the lesser trochanter and a point 5 cm distally. These fractures account for 10% of hip fractures and are associated with more severe trauma or pathologic bone (such as osteoporosis, Paget disease, or bony metastasis).

Clinical presentation is similar to that of intertrochanteric fractures. The forces of the muscles extending across this region frequently result in abduction, flexion, and external rotation. Young patients with these fractures are subject to violent forces, and associated injuries or other associated hip fractures are common. Blood loss can be substantial in fractures of the midshaft femur. Classification is varied and complex. Anatomic description is best used when describing these fractures.

Treatment involves immobilization, analgesia, volume replacement (if indicated), and timely orthopedic intervention. Examination for associated neurovascular injury should be performed. The presence of a tense, swollen upper thigh should be evaluated with angiography or Doppler for an acute vascular injury. Prompt vascular surgery consultation should be obtained if this is suspected. Operative reduction and fixation (usually intramedullary nail) is used based on specific patient and fracture characteristics.

Acetabular Fractures

Acetabular fractures should be considered in patients with femoral head dislocations and, more commonly, pelvic fractures. The force of injury applied to the femur from impact onto the dashboard is transmitted to the acetabulum.

There are four types of acetabular fractures: posterior lip fracture (most commonly associated with posterior hip dislocations), transverse acetabulum fracture, anterior fracture, and ilioischial (or

posterior) fracture. In the ilioischial fracture, the entire posterior column (the bone extending from the ilium to the ischium) becomes separated from the pelvis. An occult acetabular fracture should be suspected when the patient gives a history of a recent fall, but the pelvic radiograph is normal. Oblique views, CT scan, MRI, and bone scan are often necessary for diagnosis, as initial films generally do not visualize the injury. MRI is the gold standard for diagnosis of clinically suspected occult injury (3).

Acetabular fractures are managed in consultation with an orthopedic surgeon. ED management involves immobilization, analgesia, volume replacement (if necessary), and identification of associated injuries.

Slipped Capital Femoral Epiphysis

SCFE is the most common hip disorder in adolescents. If this injury is untreated, it can result in profound lifelong morbidity due to AVN. The diagnosis is initially frequently missed. SCFE is a Salter–Harris type 1 fracture of the femoral capital epiphysis where the head of the femur slips posteriorly and inferiorly. This fracture occurs in boys twice as often as in girls. SCFE prior to age 8 mandates a metabolic workup for endocrine disorders, although ED treatment remains the same. Most affected children are obese, suggesting a primary mechanical problem. However, the disease is considered multifactorial. Up to half of SCFEs present bilaterally and hips are usually affected within 18 months of each other (19).

The most common presentation is a limping obese adolescent, complaining of hip pain. Because of referred pain from the hip, a common presentation is knee pain (15%). The average onset is 13.5 years for boys and 12 years for girls. The hip is externally rotated with an antalgic gait. Bilateral hip radiographs are mandatory and need to include AP and frog-leg lateral views. Klein line will not project through the femoral head if SCFE is present (Fig. 43.3).

All patients with SCFE should be nonweight bearing, and need operative percutaneous fixation of the femoral head. There is controversy as to specifics including timing or surgery and value of

reduction, thus immediate consultation with orthopedics is indicated. The most common complication of SCFE is AVN, which ultimately requires hip replacement. Chondrolysis is another potential complication that has decreased with improved surgical techniques, and now occurs in about 1% to 2% of SCFE cases (19).

CRITICAL INTERVENTIONS

- Evaluate patients with hip dislocations for associated acetabular, femur, or knee injuries.
- Perform early closed reduction of hip dislocations (<6 hours is ideal). This treatment lowers the risk of AVN and posttraumatic osteoarthritis.
- Perform a CT or MRI in patients with persistent hip pain in the absence of radiographic findings to identify an occult hip fracture.

DISPOSITION

Orthopedic consultation is recommended for all hip dislocations and fractures. Hip dislocations require careful observation with frequent neurovascular checks. Young healthy patients with nondisplaced femoral neck fractures are typically managed by keeping weight off the joint. Occasionally they will require surgical fixation. Both elderly and young patients with intertrochanteric and subtrochanteric fractures require surgical fixation. Hospital admission for all elderly patients with acute hip fractures is recommended. These patients generally require evaluation and consultation for preoperative medical clearance, as well as frequent neurovascular checks. If there is a strong clinical suspicion of occult disease, then further imaging (bone scanning or MRI) is appropriate, either in the ED or as an inpatient.

Common Pitfalls

- Failure to consider SCFE in adolescent patients with knee or hip pain.

- Failure to image the hip in an elderly patient with a history of a recent fall and a complaint of knee pain.
- Failure to realize that hip pain and inability to walk, even in the absence of trauma, may be due to a hip fracture and advanced imaging should be considered (MRI).
- Failure to look for acetabular fractures in patients with hip dislocations and inferior pubic ramus fractures.

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CHAPTER 44
Knee Injuries

Christine B. Irish and Christopher T. Bowe

Knee trauma accounts for more than one million emergency department (ED) visits each year (1). The knee joint is made up of bones, ligaments, muscles, and cartilage (Fig. 44.1). The three bones that make up the knee are the distal femur, patella, and proximal tibia. The femoral condyles articulate with the proximal tibia (tibial plateau) to form the weight-bearing portion of the knee joint. The patella does not function in weight bearing, but rather provides protection to the distal femur, in addition to improving stability and strength of the extensor mechanism.

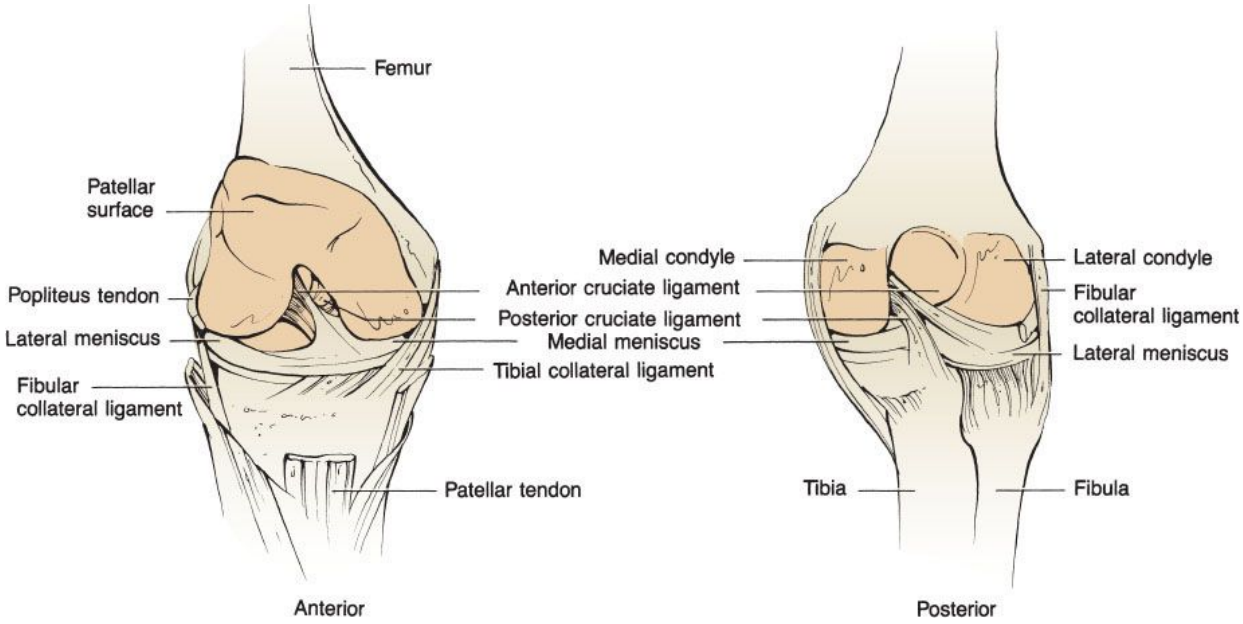


FIGURE 44.1 Anatomy of the knee.

The knee relies on four major ligaments: the medial collateral ligament (MCL), the lateral collateral ligament (LCL), the anterior cruciate ligament (ACL), and the posterior cruciate ligament (PCL) for stability and proper function (2). The MCL provides most of the resistance to valgus stress, while the LCL protects from varus stress. The cruciate ligaments are located within the intercondylar notch. The ACL prevents anterior displacement of the tibia relative to the femur while the PCL prevents posterior displacement (2). The anatomy of the posterior lateral corner of the knee is complex; its major structures consist of the LCL, the arcuate complex, the popliteal tendon, and the popliteal-fibular ligament (3). The posterolateral corner primarily resists posterior lateral rotation of the tibia relative to the femur but also contributes to resisting posterior tibial translation. The posteromedial corner of the knee consists primarily of the posterior oblique portion of the MCL and the associated joint capsule. These structures provide resistance to valgus stress and posterior medial tibial translation. The menisci are cartilage positioned on the articulating surface of the tibia. The menisci function to provide a contact surface between the tibia and femur and distribute and dissipate forces within the knee (4).

The muscles involved with normal knee function are divided into extensors and flexors. Extension is primarily provided by the quadriceps muscles, composed of the vastus medialis, vastus intermedius, vastus lateralis, and rectus femoris. The tendons of these muscles combine to form the quadriceps tendon, which inserts into the superior patella and the medial and lateral retinaculum of the joint capsule. This tendon then becomes the patellar tendon, which connects to the tibial tubercle (5). The primary flexors of the knee are the hamstring muscles, consisting of the semimembranosus, semitendinosus, and the two heads of the biceps femoris of the posterior thigh.

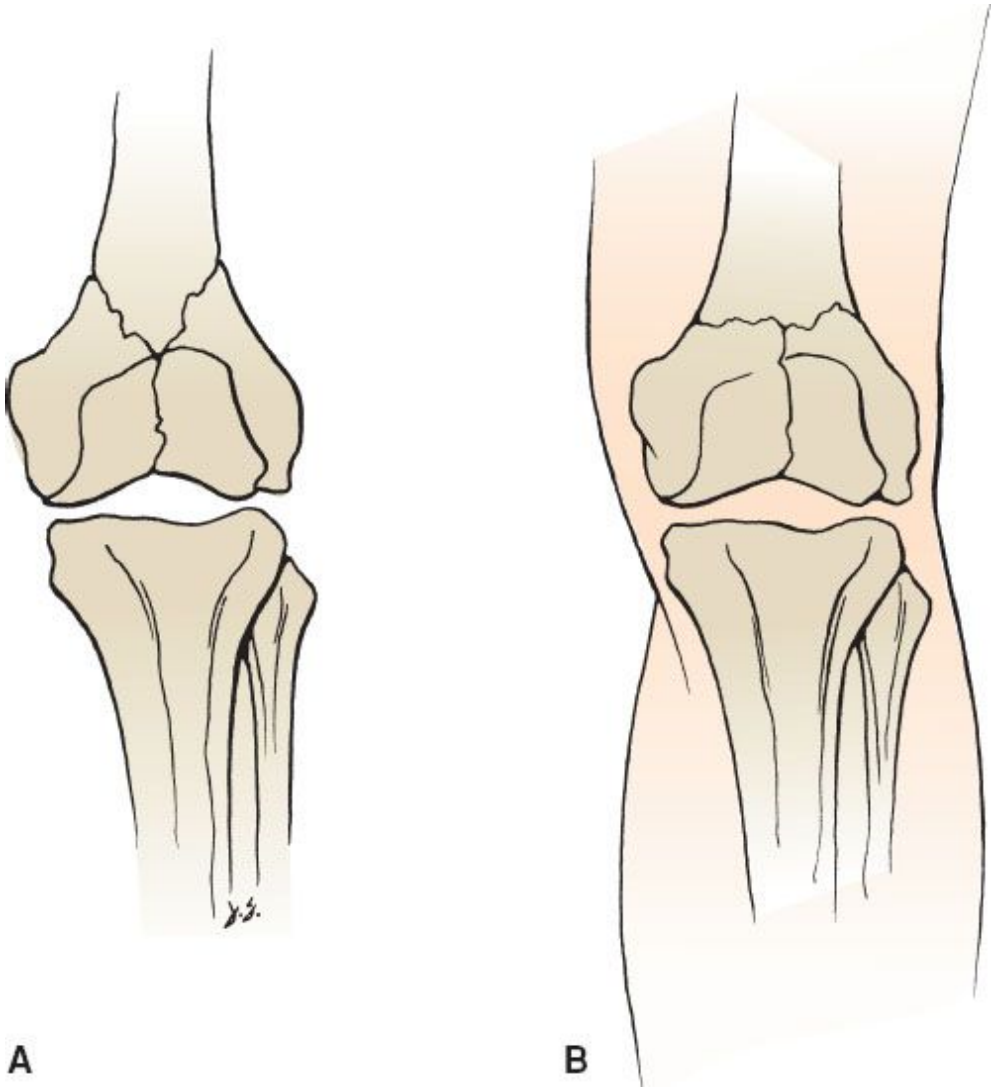
The major vascular structures around the knee are located posteriorly. The popliteal artery is fixed proximally. This tethering makes the popliteal artery susceptible to injury by traction forces, as seen with dislocations. The popliteal artery is also at risk of disruption by fractures or penetrating wounds (6). There is limited

collateral circulation, so damage to the popliteal artery places the viability of the lower limb in jeopardy. The sciatic nerve separates into the tibial and peroneal nerves proximal to the knee. The tibial nerve passes posteriorly and is therefore susceptible to the same mechanisms of injury as the popliteal artery, while the peroneal nerve courses superficially around the lateral aspect of the knee to the proximal fibula (6).

CLINICAL PRESENTATION

Fractures

Distal femoral fractures are typically described relative to the femoral condyles and are separated into supracondylar or intercondylar **(eFig. 44.1)** (7). The proximity of the femoral artery and peroneal nerves to the bone requires that the neurovascular status of the extremity be evaluated and documented in the setting of a fracture.



eFIGURE 44.1 Distal femur fractures. A: Y-shaped intercondylar and B: T-shaped intercondylar.

Tibial plateau fractures occur as a result of varus–valgus forces, axial loads, or both. Fractures of the tibial plateau may cause a major impairment in stability and function of the knee (8). The potential for neurovascular injuries is much higher in patients with proximal tibial fractures than in distal femoral fractures. The potential for the development of a compartment syndrome is also significant. Paresthesias and paralysis from compartment syndromes may be mistaken for a primary nerve injury. Injuries to the menisci, as well as to the collateral and cruciate ligaments, should be suspected as well.

A fracture of the tibial tuberosity often represents an avulsion injury caused by the patellar tendon. This is an uncommon fracture. It occurs with either strong flexion or extension against resistance. Fractures of the tibial tuberosity most commonly occur before closure of the epiphysis. The differential diagnosis of pain over the tibial tuberosity should also include Osgood–Schlatter disease, which is a traction injury to the apophysis of the tibial tuberosity. Although it is most common in boys aged 10 to 13 years, it may be seen in girls, usually aged 8 to 13 years. It is thought that repetitive trauma to the epiphysis results in incomplete separation of parts of the cartilaginous and osseous portions of the tibial tuberosity. Diagnosis is based on the history and physical examination. The tubercle is painful, tender, and usually enlarged. Pain is exacerbated by extension of the knee, particularly against resistance.

Patellar fractures result most commonly from direct forces. Less common are fractures resulting from severe tension placed on the patella by strong contraction of the quadriceps; the usual result is a transverse fracture, which may disrupt the extensor mechanism (5).

Knee Dislocation

Knee dislocations are orthopedic emergencies and require immediate attention. Knee dislocations are generally associated with high-energy trauma. The dislocation is described as anterior, posterior, medial, lateral, or rotary based on the position of the tibia relative to the femur. For a dislocation to occur, significant trauma to the surrounding soft tissue is generally seen, including the collateral ligaments, cruciate ligaments, menisci, joint capsule, and neurovascular structures. Physical examination may be difficult, and a dislocation may spontaneously reduce before the patient arrives at the ED. The patient may describe a history of abnormal position of the joint before reduction. Because of the concern for peroneal nerve and popliteal artery injury, specific attention should be devoted to this aspect of the physical examination. The absence of distal pulses is highly correlated with significant vascular injury; the presence of pulses, however, does not eliminate the possibility of vascular damage (9). Considering the significant mechanisms of injury and

the potential for vascular damage, compartment syndrome is also a potential complication.

Patellar Dislocation

The patella may be completely dislocated or subluxed from the intercondylar groove as a result of a direct blow or by hyperflexion of the knee joint. The patella almost always displaces laterally. Diagnosis is usually made by careful physical examination. If the patella has spontaneously reduced, plain films will confirm proper placement and identify any bony injury (9).

Ligamentous Injuries

LCL injuries are more commonly seen after falls and motor vehicle collisions (MVCs). MCL and LCL tears are associated with cruciate ligament injuries, with the LCL injury less likely to occur as an isolated event (2). The patient generally presents with tenderness along the distribution of the ligament. There may be a history of "popping" and abnormal bending of the knee. The physical examination should include the diagnostic tests discussed below, with varus and valgus forces applied to the knee at extension and 30 degrees of flexion.

Injuries to the cruciate ligaments are common with low-velocity trauma as well as with high-energy forces. The ACL is weaker than the PCL and is more commonly injured. Tests for ACL injuries include the Lachman, anterior drawer, and pivot shift tests. The Lachman test is the most sensitive. PCL stability is evaluated by the posterior drawer and posterior sag tests (2).

Meniscal Tears

Meniscal injuries generally occur with a twisting force applied to the knee. Patients frequently complain of hearing a "pop," which is common but not specific to meniscal injuries. Often, the patient reports locking of the knee, usually a result of a "bucket-handle" tear, with a free central portion of the cartilage becoming lodged in

the intercondylar notch. The medial meniscus is most commonly affected. The patient usually presents with a joint effusion.

Tendon Injuries

The extensor mechanism includes the quadriceps tendon, the patella, and the patellar tendon. Injuries to these structures, or avulsion of the tibial tubercle, can disrupt the extension of the knee. Disruption may result from high-energy or penetrating trauma but is also seen with low-energy forces (9). The quadriceps tendon is more commonly ruptured and usually ruptures just proximal to the patella (10). The patellar tendon frequently ruptures at the insertion into the patella. The physical examination generally reveals a swollen, tender knee, and a palpable deficit may be present. Tenderness is usually identified at the site of injury. To evaluate the tendons properly, the patient's ability to extend the knee fully against resistance must be tested. The diagnosis is usually suspected clinically. Partial injuries may be difficult, if not impossible, to detect in the ED.

DIFFERENTIAL DIAGNOSIS

Common important bony injuries to the knee include fractures, dislocations, and subluxations. Of further concern are tendon and cartilage injuries, as well as injury to the vasculature and nerves surrounding the knee.

ED EVALUATION

The history is extremely useful in guiding the evaluation of the injured knee. The chief complaint, mechanism of injury, and the exact nature and timing of symptoms will help to differentiate acute trauma from chronic injuries. The traumatic mechanism should be fully explored, as well as the position of the knee at the time of injury. The history should also assess for additional injuries, particularly to the hip and ankle.

The physical examination begins with visual inspection of the knee, followed by the remainder of the lower extremity. The examiner should note any obvious deformity, ecchymosis, erythema,

edema, or cutaneous lesions. Often, comparison with the uninjured knee will be helpful in assessing for joint effusion and local edema. Following gross inspection, palpation will elicit specific areas of tenderness, crepitus, abnormal skin temperature, or the presence of an effusion. Finally, the examiner should assess active and passive range of motion, alignment, and neurovascular status (2). The comprehensive examination will include evaluation of the knee in the standing, sitting, and supine positions, when not limited by pain or swelling.

After completion of a thorough physical examination, appropriate radiographic studies may be ordered when clinically indicated. Several clinical decision rules regarding the use of radiographs in the acutely injured knee have been proposed (Table 44.1). Prospective validation has shown excellent sensitivity of these rules (1). Adherence to these clinical decision rules can substantially reduce the incidence of unnecessary radiographs (11). Standard imaging includes the anteroposterior and lateral views and can be supplemented with sunrise (skyline) and tunnel views to evaluate the patellofemoral joint and intercondylar notch.

TABLE 44.1
Decision Rules for the Use of Radiographs in the Acutely Injured Knee

Pittsburgh	Ottawa
Mechanism of injury (blunt trauma, falls)	Age (>55 yrs)
Age (<12, >55 yrs)	Tenderness at fibula head
Inability to walk (four weight-bearing steps)	Isolated tenderness of the patella
	Inability to flex to 90 degrees
	Inability to transfer weight for four steps (either immediately following injury or in the emergency department)

If radiographs are not indicated or are negative, the assessment of potential injuries should continue with a systematic examination of the soft tissues, as well as testing of weight bearing and gait. As

previously noted, the unaffected knee should also be examined for comparison. Any obvious discrepancies between the patient's joints should be noted and are more important than absolute laxity. During examination of the uninjured knee, the physician should demonstrate the specific maneuvers that will be performed on the affected joint. This can diminish the patient's fears and improve cooperation during examination of the affected knee. Often, the presence of excessive tenderness or large joint effusions will make the examination difficult. In these cases, tensing of the musculature secondary to pain may give the impression of more joint stability than is actually present (2). To facilitate a more accurate examination and appropriate treatment recommendations, it is often necessary to immobilize the injured knee in the ED and arrange for a follow-up examination within 5 to 7 days (12).

Specific Tests for Soft Tissue Injuries

Collateral Ligaments

To assess for integrity of the LCLs and MCLs, the knee should be examined in both full extension (0 degree) and at 30 degrees of flexion. The tibia and femur should be stabilized by the examiner's hands while applying varus and valgus force across the joint line. Varus force tests for LCL laxity and is noted by lateral joint line opening, whereas valgus force assesses MCL stability and is noted by medial joint line opening. In both tests, the endpoint should be compared to the uninjured knee (Fig. 44.2A,B) (2).

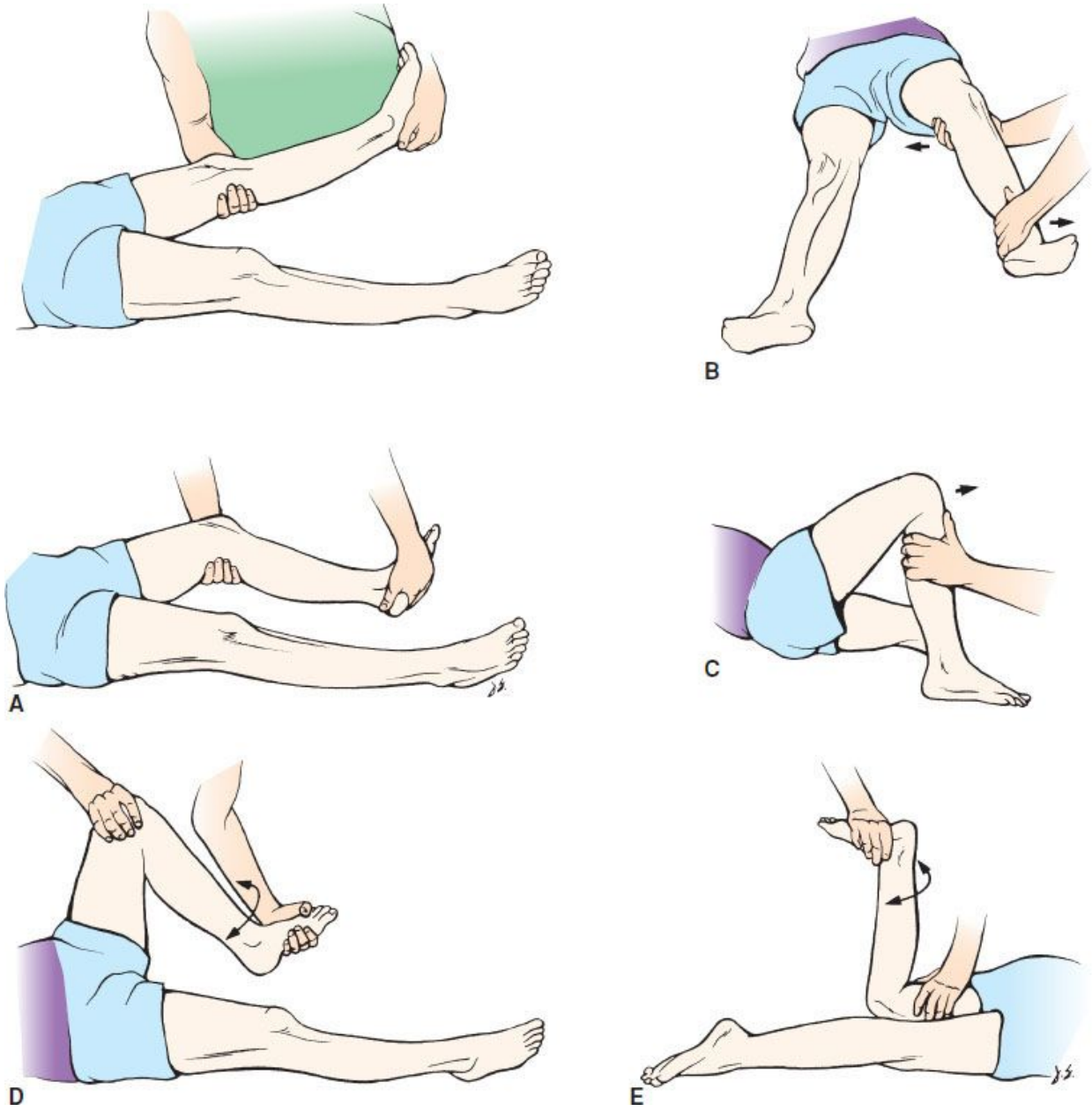


FIGURE 44.2 Examination of the knee. A: valgus stress at 0- and 30-degree flexion, as viewed from the side; B: valgus stress at 0-degree flexion, as viewed from above; C: anterior drawer test; D: McMurray test; and E: Apley test.

Cruciate Ligaments

Given that the primary function of the ACL is to prevent excessive anterior movement of the tibia relative to the femur, the focused physical examination should assess for abnormal anterior tibial

translation. The Lachman test is the test of choice to detect ACL injury (2). The patient should be supine with the knee flexed at 30 degrees. The examiner's hands are placed on the anterolateral femur and posterior proximal tibia. Anterior force is then directed on the posterior tibia, with a positive result noted when there is excessive anterior displacement of the tibia relative to the femur and lack of a distinct endpoint. A positive result indicates an ACL laxity or rupture (13). The Lachman test has a high sensitivity and specificity for ACL injury (approaching 85% and 95%, respectively) (12); False negatives most often result from surrounding muscular contraction in the presence of hemarthrosis, pain, and guarding. False positives may be noted in cases of PCL rupture where the knee is initially subluxed posteriorly (2).

The anterior drawer test may also be utilized to evaluate for ACL injury but it is noted that the accuracy is limited due to hamstring spasm and difficulty achieving appropriate positioning in the acutely injured patient. The knee should be flexed to 90 degrees and stabilized, with the foot flat on the stretcher in a neutral position (Fig. 44.2C). The examiner holds the proximal tibia with both hands and exerts anterior force. Significant displacement of the tibia anteriorly (compared with the unaffected knee) suggests rupture (2).

A third test for ACL injury is the pivot shift, which has a good positive predictive value but poor specificity (12). The examiner should lift the leg by the distal tibia with the knee fully extended. With an ACL rupture, the tibia is subluxed anteriorly in this position. The examiner then applies a mild valgus force while the knee is carefully flexed through 20 to 40 degrees. At this point, the tibia jumps into a reduced position and the examiner and the patient may appreciate a sudden clunk (2). Pain may hinder the performance of this test in the acutely injured knee.

The posterior drawer test is the reverse of the anterior drawer test and is the most accurate test of isolated PCL injury, with sensitivity and specificity of 90% and 99% respectively (2). The posterior Lachman test may be selected as an alternative to the posterior drawer test if flexion to 90 degrees is limited, as the posterior Lachman test is performed in only 30 degrees of flexion. A third

technique for detection of PCL injury is the posterior sag test. The examiner holds the knee in 90 degrees of flexion with the thigh supported by a pillow and the foot secured. In this position, the tibia will displace posteriorly or “sag” if the PCL is ruptured (2).

Meniscus

The McMurray test is commonly used to identify meniscal injury (Fig. 44.2D). While the patient is supine, the examiner holds the knee (flexed at 90 degrees) with one hand and holds the lower leg or foot in the other hand. Then the examiner applies internal and external rotation to the lower leg while flexing and extending the knee which is palpated for catching or clicking sensations. A medial meniscal tear should be suspected if clicking occurs as the leg is extended and externally rotated after being completely flexed. Clicking with internal rotation during extension is used to help identify a lateral meniscal injury. A positive test does not guarantee a meniscal injury but indicates the need for further evaluation (14).

Another test used to identify meniscal injury is the Apley test (Fig. 44.2E). The patient is placed in the prone position, and the knee is flexed to 90 degrees. The examiner applies upward force to the tibia while it is rotated, and the knee is extended (14). A positive test is noted with pain and clicking in the joint and suggests a meniscal injury.

Patellar Subluxation

The apprehension sign is seen with patellar subluxation during manual translation maneuvers. The knee is positioned in extension and the examiner exerts lateral force on the patella. In patients with patellar subluxation, this manipulation is painful and induces apprehension. A positive test is noted when the patient contracts the quadriceps and attempts to flex the knee to resist subluxation (2).

Extensor Mechanism

The extensor mechanism of the knee includes the quadriceps muscle, quadriceps tendon, patella, patellar tendon, and surrounding retinacula. As expected, injuries to the extensor mechanism may lead to the inability to extend the leg. Physical examination of the knee

should include an evaluation of active leg extension; decreased ability to extend indicates an injury to the extensor mechanism (15).

Diagnostic Studies

As previously mentioned, several excellent clinical decision rules exist to help in the decision to order plain films (Table 44.1). Radiographs help diagnose fractures, effusions, dislocations, foreign bodies, and calcified loose bodies. Additional findings include fluid–fluid levels that may represent lipohemarthrosis (fat floating on synovial fluid and an indication of an occult fracture) in the appropriate clinical setting. The presence of such a finding warrants further evaluation utilizing computed tomography (CT) scanning, or magnetic resonance imaging (MRI).

CT scanning may be used to better define bony injuries, particularly tibial plateau fractures. Ultrasound and MRI are indicated to evaluate the soft tissues of the knee. Angiography can be used after knee dislocation to rule out an occult injury to the popliteal artery, and should be considered even in the presence of symmetric pedal pulses (1). Angiography is also indicated in the presence of penetrating trauma in proximity to vascular structures and (16).

Occasionally, it may be difficult to clinically distinguish hemarthrosis from an infective or inflammatory joint effusion. Arthrocentesis and joint-fluid analysis may be helpful in these cases to determine the etiology of an effusion, particularly when the traumatic mechanism is unclear. An acute hemarthrosis may suggest a significant injury, such as an ACL or PCL tear, and the presence of lipid droplets in a bloody effusion can signify an occult fracture. Arthrocentesis of acute hemarthrosis can be quite therapeutic in providing pain relief, however this practice is controversial given the rate of reaccumulation and the small risk of introducing infection associated with the procedure.

For patients with deep lacerations of the knee, it is important to evaluate the integrity of the joint capsule. Methylene blue should be injected into the joint, and simultaneous inspection of the wound will reveal dye extravasation in cases of joint capsule disruption.

KEY TESTING

- Use of the Ottawa Knee Rules is recommended to reduce unnecessary radiographs in acute trauma setting.
- Remember to examine the ipsilateral hip and ankle for associated injury.
- CT scanning may be particularly useful in patients with tibial plateau fractures.
- Methylene blue injection is useful to assess joint space involvement in deep lacerations.

ED MANAGEMENT

Fractures

The initial management of patients with distal femur fractures includes immobilization, pain management, and evaluation for associated injuries. Early orthopedic consultation is indicated for development of definitive care plans (skeletal traction or surgical repair).

For tibial plateau fractures, diagnostic tests include plain radiographs and CT scans. CT scanning has demonstrated improved accuracy over plain radiography as it is more sensitive for detecting subtle nondisplaced fractures as well as occult lesions. With severely comminuted fractures, CT scanning can quantify the extent of the articular surface involved and the amount of displacement or depression of the fracture line. The additional information gained by CT scanning is useful for planning operative repair, and will often modify the surgical plan (1).

Complications of tibial plateau fractures include vascular injury, deep venous thrombosis (DVT), and compartment syndrome. Any indication of distal ischemia, including paresthesias, diminished distal pulses, or a diminished ankle-brachial index should immediately alert the physician to the possibility of a vascular injury, and an arteriogram should be promptly obtained. Although not generally a concern in the acute setting, DVT is a recognized sequelae of this injury and is most easily diagnosed by lower extremity ultrasound. If significant swelling and tenderness are

present, the physician should suspect a developing compartment syndrome. The diagnosis of compartment syndrome is suggested by the presence of the five Ps (pain, pallor, paresthesias, paralysis, pulselessness); however, these findings are not universally present initially and early diagnosis is critical. Compartment pressures should be measured to definitively rule out the diagnosis.

Standard management of tibial plateau fractures includes immobilization, evaluation for other injuries, and timely orthopedic consultation. Depressed fractures require surgical reduction. Because of the risk of compartment syndrome and the possibility of delayed onset, patients with tibial plateau fractures are often admitted for observation.

Tibial tuberosity fractures are generally diagnosed on plain radiographs. In cases of suspected Osgood–Schlatter disease, plain radiographs may be difficult to interpret, as fragments of the tuberosity may be a normal variant. Tibial tuberosity fractures can require open reduction but are usually treated with immobilization. Osgood–Schlatter disease is treated with rest, occasionally plaster cast immobilization, and rarely surgical excision of loose ossicles to relieve symptoms.

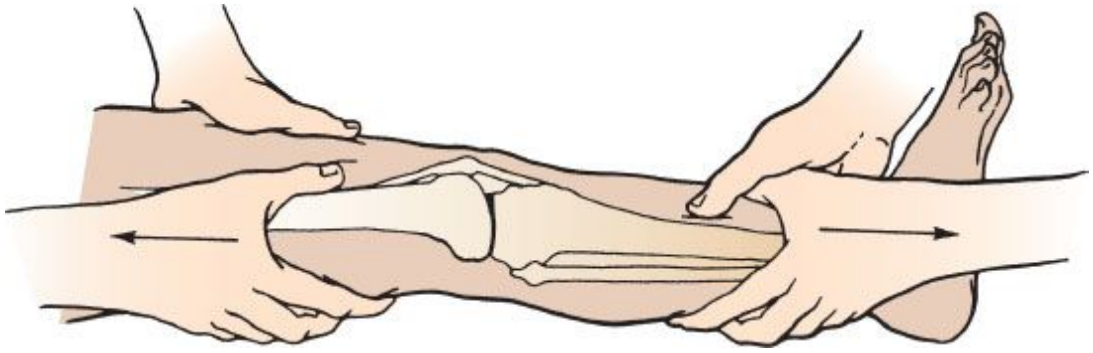
Diagnosis of patellar fractures is generally made with plain radiographs. A bipartite patella may be confused with a fracture. Often, the margins of a bipartite patella are rounded and well corticated but, in the setting of acute trauma, it may be difficult to differentiate from an acute fracture. Management is based on the type of fracture, degree of separation, and integrity of the extensor mechanism. Orthopedic referral is indicated. Simple nondisplaced fractures are treated with immobilization and outpatient orthopedic referral. Fractures that disrupt the extensor mechanism, typically displaced transverse or severely comminuted fractures, will require open reduction and internal fixation for optimal results.

Knee Dislocation

Arteriography has been used in the evaluation of knee dislocations to identify injuries to the popliteal artery. If there are signs of vascular injury (absent/decreased pulses, a diminished ankle-brachial index

[< 0.90], expanding hematoma, hemorrhage, ischemia, or bruit), the patient requires an arteriogram (6). Patients without hard signs may be admitted for serial examinations although some authors have advocated the use of routine arteriography in all patients with posterior knee dislocations, even in patients with intact distal pulses. There is disagreement about mandatory arteriography in patients with intact distal pulses, as the majority of these patients will have nonsurgical lesions, such as intimal tears. Therefore, others advise a more selective approach to arterial imaging, combined with admission and frequent neurovascular examinations (17). CT angiography (CTA) is being used with increasing frequency in place of traditional arteriography to assess for vascular injury, given the reduced radiation dose and less invasive nature of CTA (6).

Emergency management involves rapid reduction of the dislocation, particularly in cases with vascular compromise. Reduction can be accomplished by longitudinal traction (eFig. 44.2). If the clinical status permits, intravenous sedation and analgesia may facilitate the reduction. The limb's neurovascular status must be reassessed periodically, particularly after manipulation. Orthopedic and vascular surgery consultations should be obtained (6).



eFIGURE 44.2 Technique for reduction of knee dislocation.

Patellar Dislocation

Emergency management of patellar subluxations involves acute reduction. Reduction is typically performed by applying medial force to the patella while the knee is passively extended. Once reduced,

the knee is immobilized, and the patient is treated with elevation, ice, crutches, and outpatient orthopedic follow-up.

Ligamentous Injuries

Treatment of patients with collateral ligament injuries is based on the severity of the injury. These patients should be initially treated with immobilization, ice, and crutches. The patient should be referred for timely orthopedic follow-up.

For patients with cruciate ligament injuries, plain radiographs are often nonspecific. Sonography and MRI scanning are used to evaluate the cruciate ligaments and arthroscopy is useful for both diagnosis and treatment (13). Initially, immobilization and orthopedic consultation are necessary.

Meniscal Tears

MRI scanning is very helpful in identifying meniscal injuries. Arthroscopy is generally reserved for treatment, as the accuracy of the MRI is well documented (1). Initial treatment consists of immobilization, analgesia, and outpatient orthopedic referral within 1 week.

Tendon Injuries

X-ray findings may include a high-riding patella (*patella alta*) with a patellar tendon rupture or low-riding patella (*patella baja*) with quadriceps tendon rupture (15). CT or MRI may be necessary but can be deferred to outpatient follow-up. A complete rupture requires surgical repair. Incomplete ruptures usually will heal in 6 to 8 weeks with immobilization. Complete ruptures necessitate outpatient orthopedic referral within 5 to 7 days for further evaluation and definitive management.

Bursitis

If bursitis is suspected, rest, ice, and nonsteroidal anti-inflammatory medications are prescribed. The patient may be referred to an orthopedist for follow-up.

CRITICAL INTERVENTIONS

- Rapidly reduce knee dislocations utilizing longitudinal traction after intravenous sedation and analgesia, especially when vascular compromise is present.
- Perform arteriography in patients with knee dislocations, if there are hard signs of vascular injury (absent pulses, expanding hematoma, hemorrhage, ischemia, or bruit).
- Administer appropriate intravenous antibiotics in patients with open fractures.

DISPOSITION

Many of the knee injuries described may be evaluated in the ED and safely referred for orthopedic follow-up as an outpatient. The emergency physician should ensure that the knee is properly immobilized and provide the patient with appropriate analgesia and clear activity restrictions (weight bearing, crutches, etc). Follow-up appointments should generally take place within 1 week.

More severe injuries often require hospital admission. Significantly displaced fractures, open fractures, fractures with associated vascular or nerve damage, and injuries with the potential to develop compartment syndrome should all be admitted for further evaluation and treatment. Such injuries include distal femur fractures, tibial plateau fractures, patellar fractures (with disruption of the extensor mechanism), and knee dislocations.

Common Pitfalls

- Performing a physical examination while the patient remains in the wheelchair.
- Failure to examine the hip carefully. Knee pain is often referred from the hip, and knee trauma may precipitate hip injuries.
- Misinterpreting a bipartite patella as a patellar fracture on plain films.
- Failure to examine the knee in full extension against resistance when evaluating the extensor mechanism.

• Failure to diagnose a proximal fibula fracture or dislocation resulting from an ankle injury.

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CHAPTER 45

Ankle and Foot Injuries

Kaushal Shah and Natasha Desai

Ankle injuries are among the most common sports-related and extremity injuries presenting to the emergency department (ED) accounting for approximately 20 million injuries per year and up to 20% of all sports injuries (1,2,3). Although the vast majority are benign injuries, there are instances when immediate action and emergent consultation are necessary.

The ankle and foot are relatively simple structures. The ankle is formed by (a) the tibia, which forms the medial malleolus, the posterior malleolus, and the plafond (ceiling); (b) the fibula, which forms the lateral malleolus; and (c) the talus (Fig. 45.1). The ankle is held together by (a) the medial ligaments collectively termed *deltoid ligament;* (b) the lateral ligaments–-anterior talofibular ligament (ATFL), calcaneofibular ligament (CFL), and posterior talofibular ligament (PTFL); and (c) the syndesmosis between the distal tibia and fibula (Fig. 45.2). The foot has three general parts: the hindfoot (calcaneus and talus), the midfoot (navicular, cuboid, and cuneiforms), and the forefoot (metatarsals and phalanges) (Fig. 45.1).

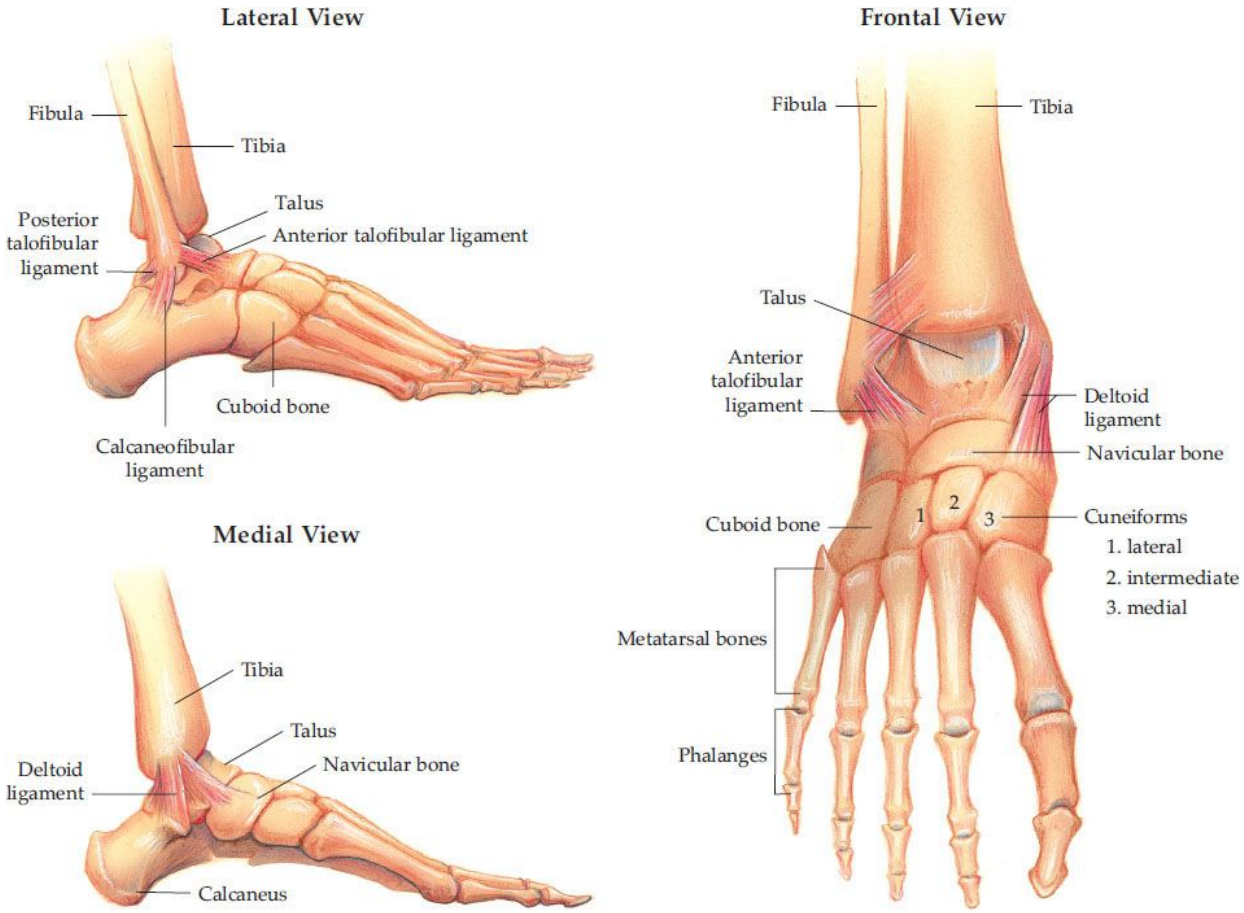


FIGURE 45.1 Anatomy of ankle and foot.

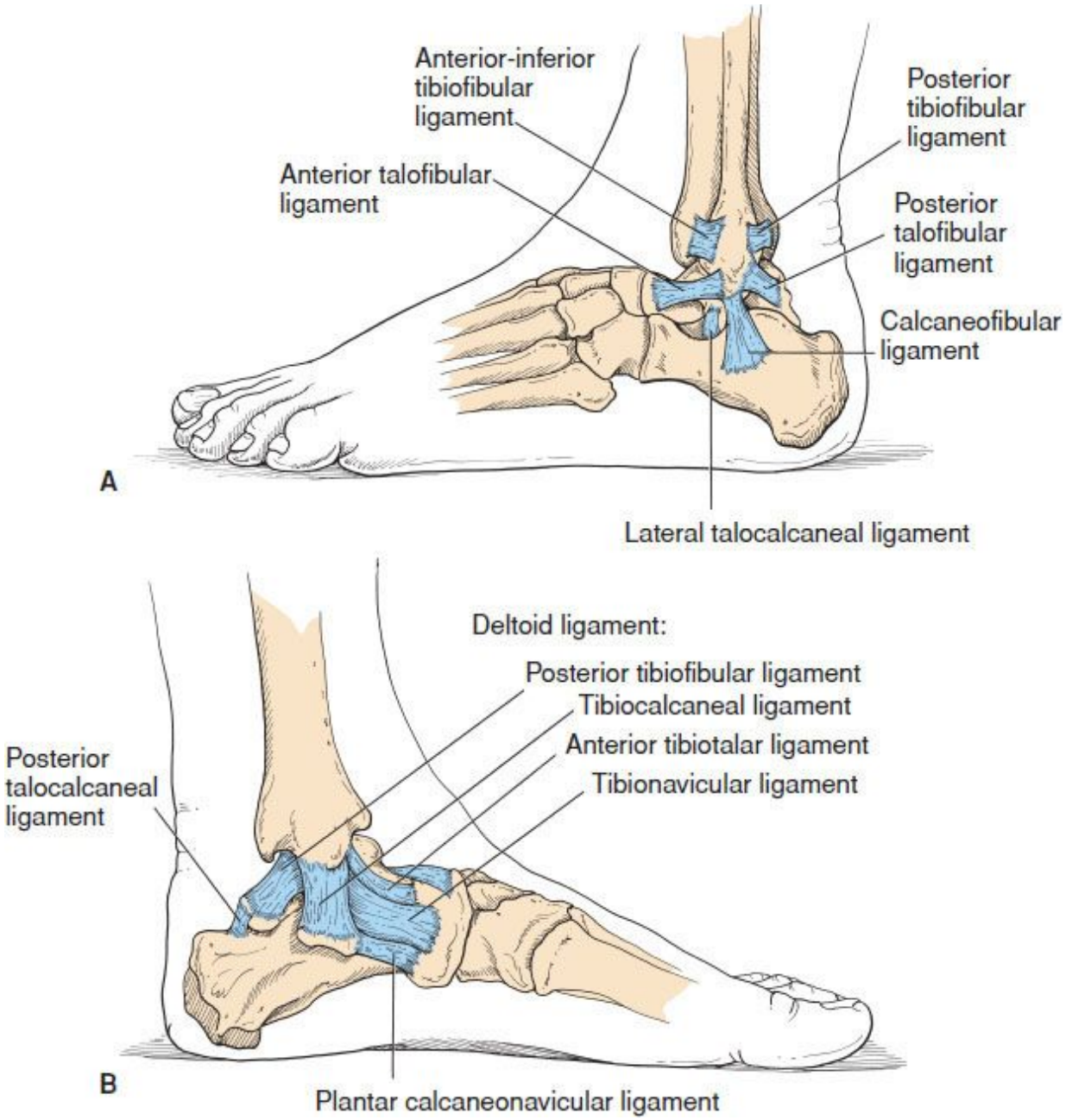


FIGURE 45.2 Ankle and foot – ligaments (A) lateral view; (B) medial view. (From Cipriano J. Photographic Manual of Regional Orthopaedic and Neurological Tests, 2nd ed. Baltimore, MD: Lippincott Williams & Wilkins; 1991.)

CLINICAL PRESENTATION

Ankle injuries can be anticipated by the position of the foot and direction of the force at the time of injury. Other key factors include

the ability to ambulate after injury and a history of previous injuries (1). Most common “red flags” suggestive of a fracture rather than a sprain are inability to bear weight, significant swelling, or tenderness. The ankle should be considered as a closed ring with the tibia, fibula, and talus as the main parts held together by ligaments. A break in two or more places results in instability.

ED EVALUATION AND MANAGEMENT

Ankle Ligamentous Injuries

Approximately 90% of ankle ligamentous injuries are due to inversion of the ankle, resulting in sprain of the lateral ligaments, most commonly the ATFL (1). Significant injuries from an eversion mechanism are far less common because the broad deltoid ligament is strong and resistant to tears. The clinical findings associated with ankle sprains range from mild pain and swelling to severe pain with edema and ecchymosis. Neurovascular status should be checked by palpating the posterior tibial and dorsalis pedis pulses, checking capillary refill, and assessing distal sensation. However, without gross deformity, it is extremely unlikely that the neurovascular status will be compromised. Palpation of the medial and lateral malleoli and the base of the fifth metatarsal for focal tenderness are critical to evaluate for associated fracture. The Ottawa Ankle Rules (OAR) are useful in determining which patients do not need radiographic evaluation for an ankle injury; the sensitivities range from 97% to 100% (Table 45.1) (4–6). In the pediatric population, the OAR have been shown to be 98.5% sensitive for predicting significant ankle and midfoot fractures in a meta-analysis of 12 studies which included 3,130 children older than 5 years (B). If x-rays are obtained, the physician should inspect the AP view for talar shift and malleolar fractures, the mortise view for widening of the tibiotalar joint, and the lateral view for posterior malleolar fracture and general alignment.

TABLE 45.1
Ottawa Criteria for Ankle Radiographs

An ankle radiographic series is required in patients aged 18–55 only if there is any malleolar pain and any of the following findings:

1. Bone tenderness at the posterior edge or tip of the medial malleolus
2. Bone tenderness at the posterior edge or tip of the lateral malleolus
3. Inability to bear weight for four steps both immediately and in the emergency department

From Ankel F. The Ankle. In: Hart RG, Rittenberry TJ, Uehara DT, eds. *Handbook of orthopedic emergencies.* Philadelphia, PA: Lippincott-Raven Publishers; 1999, with permission.

Provocative tests for ankle stability are necessary to determine the grade of injury. eTable 45.1 describes the grading of ankle sprains. The *anterior drawer test* assesses the integrity of the ATFL (Fig. 45.3). The test is positive if greater subluxation is noted on the injured ankle than the opposite one. The *talar tilt test* can be used to assess the lateral and medial ligaments (Fig. 45.3). If there is significant subluxation with inversion, tears of the ATFL or CFL should be suspected. Significant subluxation with eversion raises suspicion for a tear of the deltoid ligament. Integrity of the tibiofibular syndesmosis can be tested via the *squeeze test,* which involves squeezing the proximal tibia and fibula together. If pain is elicited, the test is positive (eFig. 45.1).

eTABLE 45.1
Classification of Ankle Sprains

Severity	Symptoms	Signs	Examination	Treatment
Grade I	Mild pain and swelling, able to bear weight	Slight edema	Negative anterior drawer and talar tilt	RICE[a] and referral to primary care physician in 1 wk
Grade II	Moderate pain and swelling, difficulty bearing weight	Moderate edema and ecchymosis	Positive anterior drawer (4–14 mm) and talar tilt test (5–15 degrees)	Rigid splint and referral to orthopedist in a week
Grade III	Severe pain and swelling, inability to bear weight	Severe edema and ecchymosis	Positive anterior (>15 mm) and tilt test (>15 degrees)	Rigid splint and referral to orthopedist within a week

[a]Rest, ice, compressive dressing, and elevation.
From Ankel F. The Ankle. In: Hart RG, Rittenberry TJ, Uehara DT. (eds). *Handbook of orthopedic emergencies.* Philadelphia, PA: Lippincott–Raven Publishers; 1999, with permission.

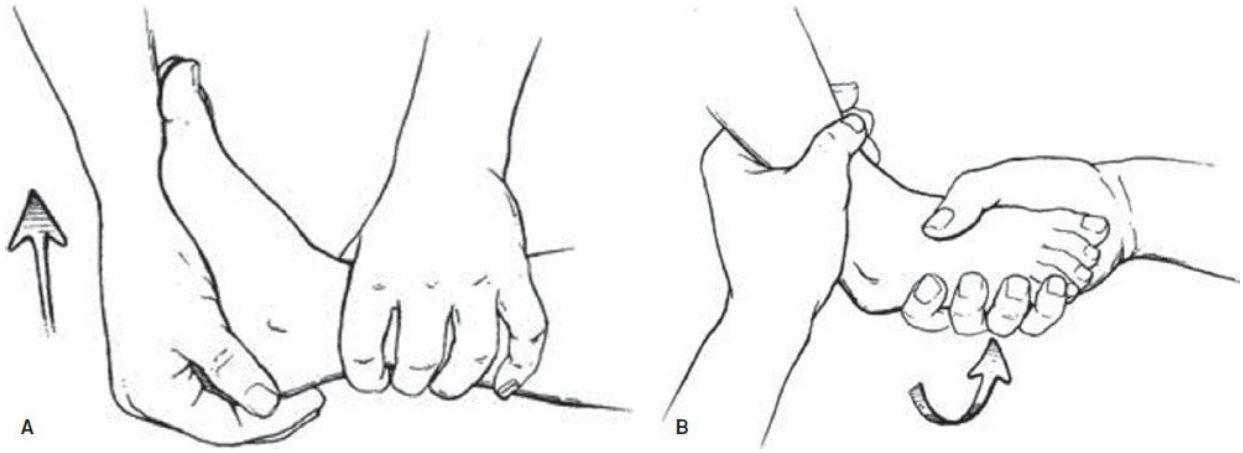
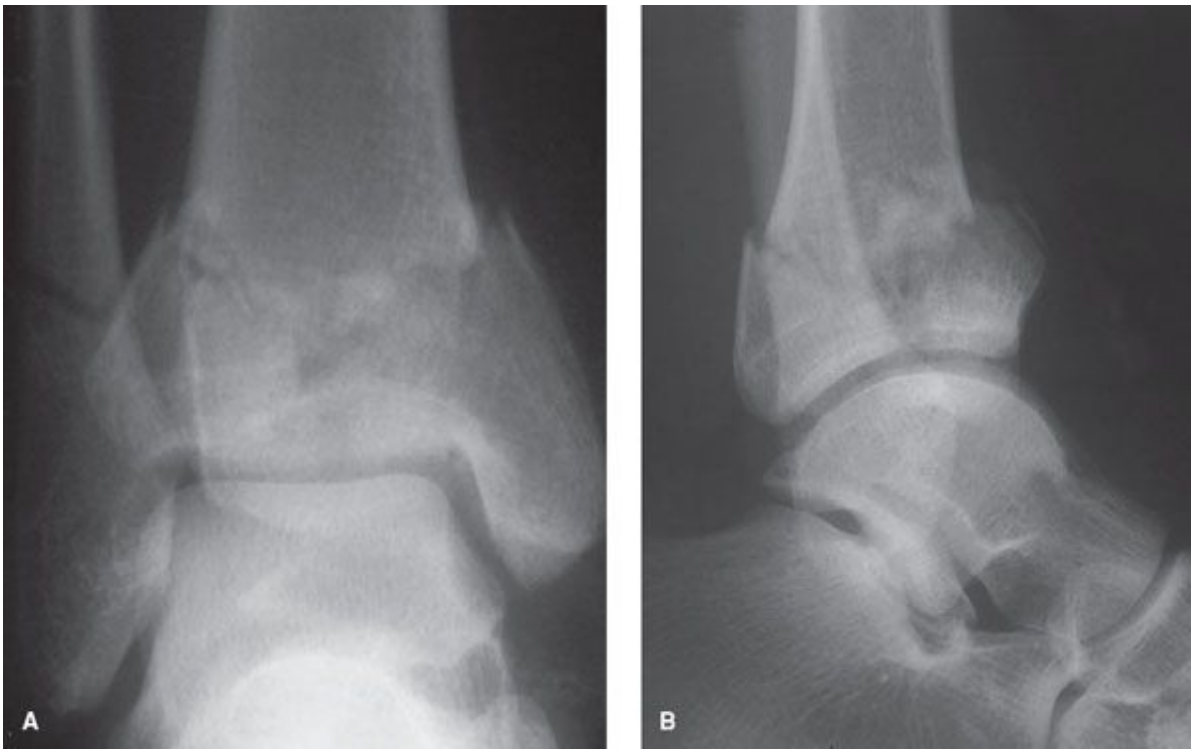


FIGURE 45.3 A: The anterior drawer test is performed by placing the patient's heel in the palm of the examiner's hand with the ankle at a 90-degree angle to the long axis of the leg. The examiner gently, but firmly, moves the heel and foot forward (arrow). B: In the talar tilt maneuver, the heel is firmly adducted (arrow) and assessed for increased laxity or instability compared with the noninjured side. (Adapted from Fleisher GR, Ludwig S, Henretig FM, et al. Textbook of Pediatric Emergency Medicine. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.)

eFIGURE 45.1 The squeeze test—practitioner squeezes the tibia and the fibula together. If pain is elicited, it suggests a tibiofibular syndesmosis injury. (From Dale Berg, Katherine Worzala. Atlas of Adult Physical Diagnosis. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)



eFIGURE 45.2 X-ray of a pilon fracture in a 46-year-old man, resulting from an axial load in a motorcycle accident. A: AP view. B: Lateral view.

Acutely, ibuprofen 10 mg/kg (not to exceed 800 mg) PO or acetaminophen 15 mg/kg (not to exceed 1,000 mg) PO should be administered for pain. Ketorolac 30 to 60 mg IM or IV, in an adult, is also effective. General management guidelines follow the "*RICE*" mnemonic: *r*est ankle and avoid reinjury which may entail use of crutches; *i*ce the ankle for 20 minutes three to four times per day for the first day to reduce swelling; *c*ompress with an elastic ACE wrap or ankle brace to reduce swelling and pain; *e*levate the extremity as often as possible to reduce swelling. eTable 45.1 describes the management based on the grade of the injury. If serious ligamentous injury is suspected, resulting in joint laxity (i.e., grade II and higher sprains), more rigid splinting methods should be considered. An air stirrup splint is moderately effective in preventing inversion and eversion of the ankle and is appropriate for grades I and II ankle sprains. For grade III injuries, a short-leg posterior rigid splint (e.g., plaster) that runs from midcalf to the toes should be used to further

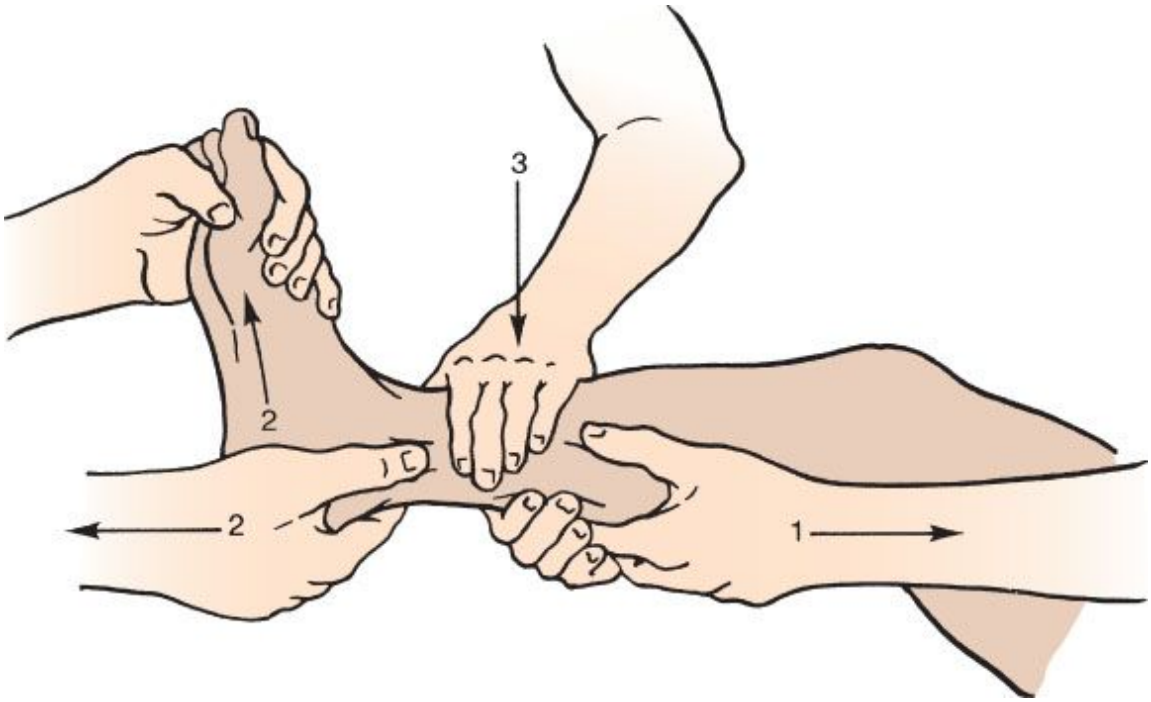
immobilize the ankle to prevent worsening of the injury and promote healing.

All patients with ankle sprains can be discharged home but should have appropriate follow-up within 1 week. Although pain and swelling should abate and the ability to ambulate should improve with time, occult fractures and high-grade sprains may require further orthopedic or sports medicine care. Other indications for orthopedic referral include (a) a "pop" that is heard or felt, (b) a history of several previous injuries, (c) medial ankle tenderness, (d) a positive squeeze test or other stress test, and (e) grade II and higher sprains in children with open growth plates (7). In children, less force is required to sustain a Salter–Harris I fracture than is required to tear a ligament (see Chapter in Pediatric Section, "Extremity fractures"). Thus, any patient who is suspected of having a significant ankle sprain and no clear fracture on x-ray should be splinted and referred to an orthopedic surgeon for follow-up.

Ankle Fractures

Ankle fractures can present after a significant traumatic mechanism or after a simple ankle inversion or eversion twisting injury. There are several types of ankle fractures that should be considered in the differential diagnosis. A *lateral malleolus* fracture is the most common type of ankle fracture resulting from inversion of the ankle. Isolated *medial malleolus* fractures are less common because the injury requires more force than a lateral malleolus fracture. Therefore, other associated fractures and joint instability should be suspected. Patients with *bi-* or *trimalleolar fractures* present with significant pain, swelling, and ecchymosis, and associated dislocations are common. A distal tibial fracture through the articular surface is called a *plafond fracture.* Although commonly used interchangeably with the term plafond fracture, a *pilon fracture* is specifically a comminuted plafond fracture that results from an axial compression force to the tibial plafond (eFig. 45.3). The *Maisonneuve fracture* is an oblique fracture of the proximal fibula associated with a medial malleolus fracture or deltoid ligament tear. It can easily be missed if the proximal fibula is

not routinely palpated in patients with ankle-twisting injuries. These last two fractures require radiographs of the entire tibia and fibula.



eFIGURE 45.3 Technique for posterior dislocation reduction.

As with ankle sprains, neurovascular status should be checked immediately. The history and physical examination are identical to that of ankle sprains. If there is gross deformity, a dislocation should be considered and should be reduced emergently if there is neurovascular compromise. Lacerations and wounds should be examined closely to ensure that an open fracture is not present.

Suspected ankle fractures require x-rays in three views as described above. The two most common classification systems for ankle fractures are the *Lauge-Hansen* and *Danis–Weber*. The Danis–Weber classification system is simpler and is based on the location of the fibular fracture (Fig. 45.4). A fibular avulsion fracture below the tibiotalar joint line is called a *Weber type A* fracture. If the fibular fracture is in the joint line, it is a *Weber type B* fracture. Fractures above the joint line disrupting the syndesmosis ligament are termed *Weber type C* fractures.

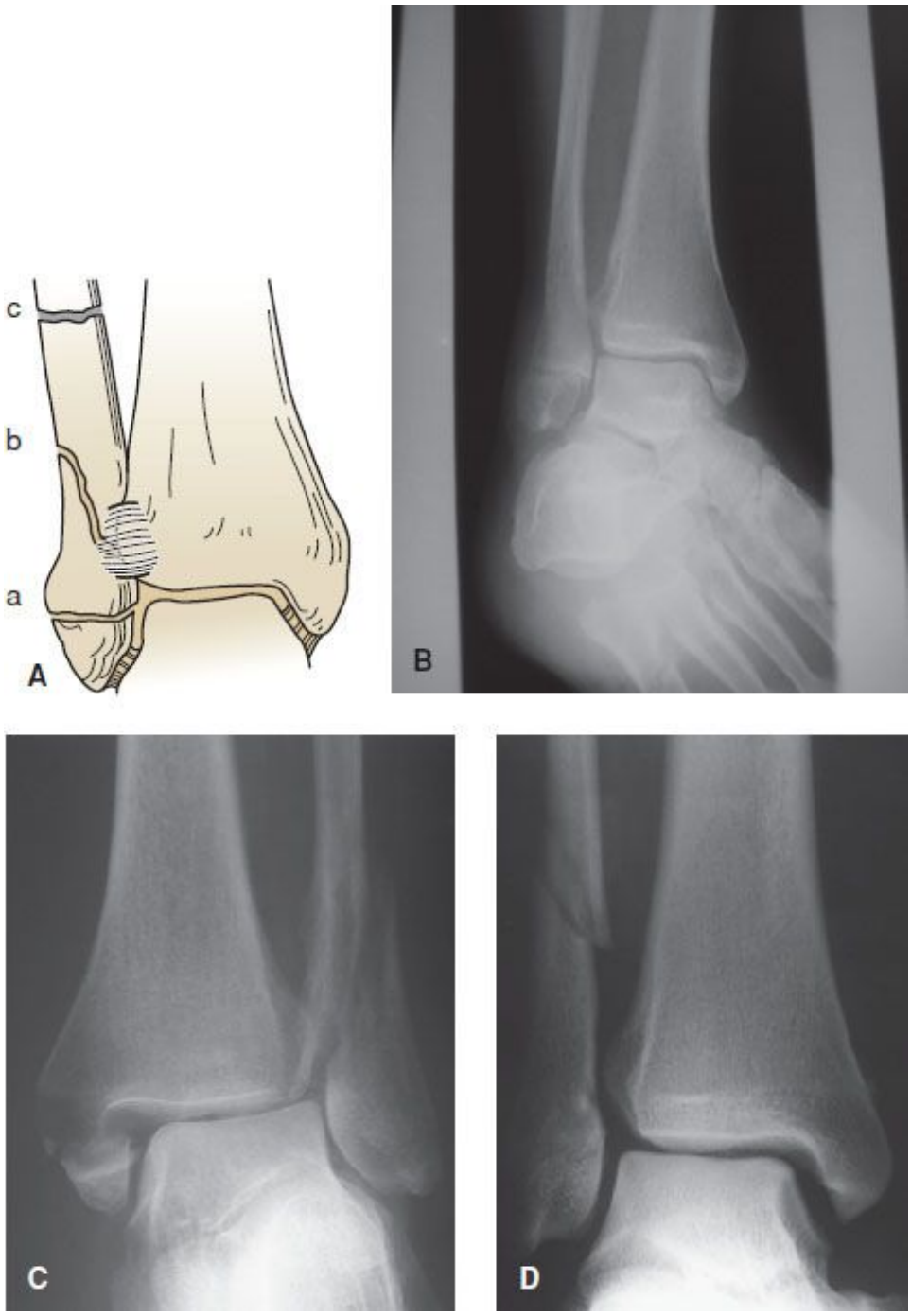


FIGURE 45.4 A: Schematic diagram of the Danis–Weber classification of ankle fractures. B: A type A fracture where the anterior tibiofibular ligament remains intact. C: A type B fracture with the fracture extending through the ligament. D: A type C fracture where the fracture is above the joint line. (From Bucholz RW, Heckman JD, Court-Brown C, et al., eds. Rockwood and Green's

Fractures in Adults. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)

Patients should receive adequate analgesia. Intravenous, intramuscular, and subcutaneous injections are preferred (rather than oral administration) until it is certain the patient will not require an operative procedure. Isolated lateral or medial malleolar fractures without instability can be safely discharged home without orthopedic consultation in the ED. The emergency physician should first place the ankle in a posterior splint, provide crutches for nonweight bearing, provide adequate analgesia, and ensure close orthopedic follow-up. All other ankle fractures will require orthopedic consultation in the ED.

Isolated fractures of the distal tibia and fibula should be immobilized in a short-leg posterior splint. A *sugar tong* splint (U-splint) can also be used; it wraps along both the medial and lateral sides of the leg with the base of the "U" under the foot (similar to an air stirrup) and is more effective in stabilizing the medial and lateral ligaments. Patients with severe injuries to the ankle, such as bi- and trimalleolar fractures, should be placed in both a posterior splint and a sugar tong splint ("AO" splint). This provides immobilization similar to that of casting but allows for the expected ankle swelling.

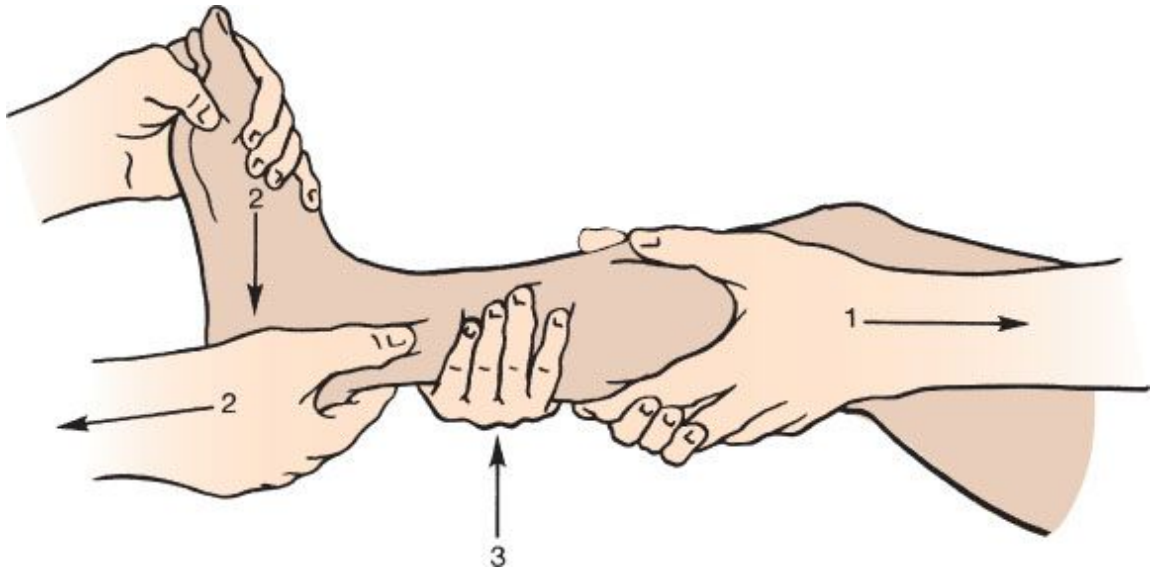
Ankle Dislocations

For the talus to dislocate from the distal tibia, multiple ligaments are torn, and there are often associated malleolar fractures. Significant force is required, and there is always gross deformity and inability to bear weight.

The emergency physician should perform immediate reduction if there is neurovascular compromise or significant skin tenting with concern for conversion into an open fracture–dislocation. In cases of uncomplicated dislocations, x-ray evaluation should precede reduction.

Reduction of the ankle requires conscious sedation and two assistants. For posterior dislocations, the first assistant flexes the

knee to 45 degrees and applies counter-traction over the calf while the second assistant pushes down on the front of the lower leg. The physician applies traction to the heel and forefoot after first plantar flexing the foot and then lifting the heel (eFig. 45.3). For anterior dislocations, the first assistant flexes the knee to 45 degrees and applies counter-traction over the calf while the second assistant lifts up on the lower leg. The physician should dorsiflex the foot initially to disengage the talus and then push downward on the foot (eFig. 45.4). For lateral dislocations, the physician applies longitudinal and medial traction whereas an assistant applies counter-traction.



eFIGURE 45.4 Technique for anterior dislocation reduction.

Orthopedic consultation is necessary for all fracture–dislocations of the ankle. If a patient needs to be transferred, the emergency physician should reduce the ankle and place the ankle in a short-leg posterior splint (with or without a sugar tong splint). For open dislocations, IV antibiotics should be administered prior to transfer. Cefazolin 1 to 2 gm IV in adults is usually adequate, but patients with contaminated wounds should also receive gentamicin 2 mg/kg IV.

Achilles Tendon Rupture

The classic presentation is a middle-aged man complaining of ankle pain and inability to bear weight after hearing a “pop” while playing sports. Risk factors for rupture include steroid injections and tendonitis. The Achilles tendon usually ruptures at the narrowest segment, approximately 5 cm above its attachment to the calcaneus.

Occasionally an obvious defect in the Achilles tendon can be palpated. However, the most useful signs of this injury are weakness of plantar flexion and a positive *Thompson test* (the foot does not plantar flex when the calf is squeezed) (eFig. 45.5). The test is performed with the patient prone and the knee flexed to 90 degrees.

eFIGURE 45.5 The Thompson test for continuity of the gastrocnemius-soleus complex. Without rupture of the Achilles tendon, squeezing the calf causes active plantar flexion of the foot. With rupture, squeezing the superficial posterior compartment of the leg does not induce plantar flexion of the foot. (Adapted from Browner B, Jupiter J, Levine A. Skeletal Trauma: Fractures, Dislocations, and Ligamentous Injuries, 2nd ed. Philadelphia, PA: WB Saunders; 1997.)

Orthopedic consultation should be obtained. Operative versus conservative management is currently under debate; surgical repair has been shown to decrease rate of rerupture; however, complication rates increase (8). It is also appropriate to place a posterior splint

with the foot in plantar flexion and refer to an orthopedist within 48 to 72 hours.

Peroneal Tendon Subluxation

These patients present very similar to those with a simple ankle sprain. However, the mechanism is different. The injury is caused by dorsiflexion and eversion of the ankle resulting in contraction of the peroneal muscle and disruption of the peroneal retinaculum. Because the peroneal tendon subluxes out of its groove along the posterior lateral malleolus, the ankle is swollen, tender, and ecchymotic around the lateral malleolus.

Although x-rays are usually negative for bony disruptions, these patients should be placed in a sugar tong splint with extra lateral malleolar padding. Patients should be referred to an orthopedist within a week for casting and should remain nonweight bearing for 4 to 6 weeks. Occasionally, surgery is recommended for athletes, those who fail nonoperative management, and those with chronic subluxations (9).

Calcaneal Fractures

A vertical compression force, such as jumping or falling from a height and landing directly on the feet, is the most common etiology of calcaneal fractures. They occur more commonly in men who are 30 to 50 years old. Patients complain of heel pain and have difficulty bearing weight.

Three radiographic views (AP, lateral, and axial) of the heel should be obtained. Fractures are often not clearly visible owing to a predominantly compressive force. A helpful measurement to make the diagnosis is determination of *Boehler angle* on the lateral view (Fig. 45.5). A normal angle is 20 to 40 degrees, and an angle less than 20 degrees indicates a calcaneal fracture.

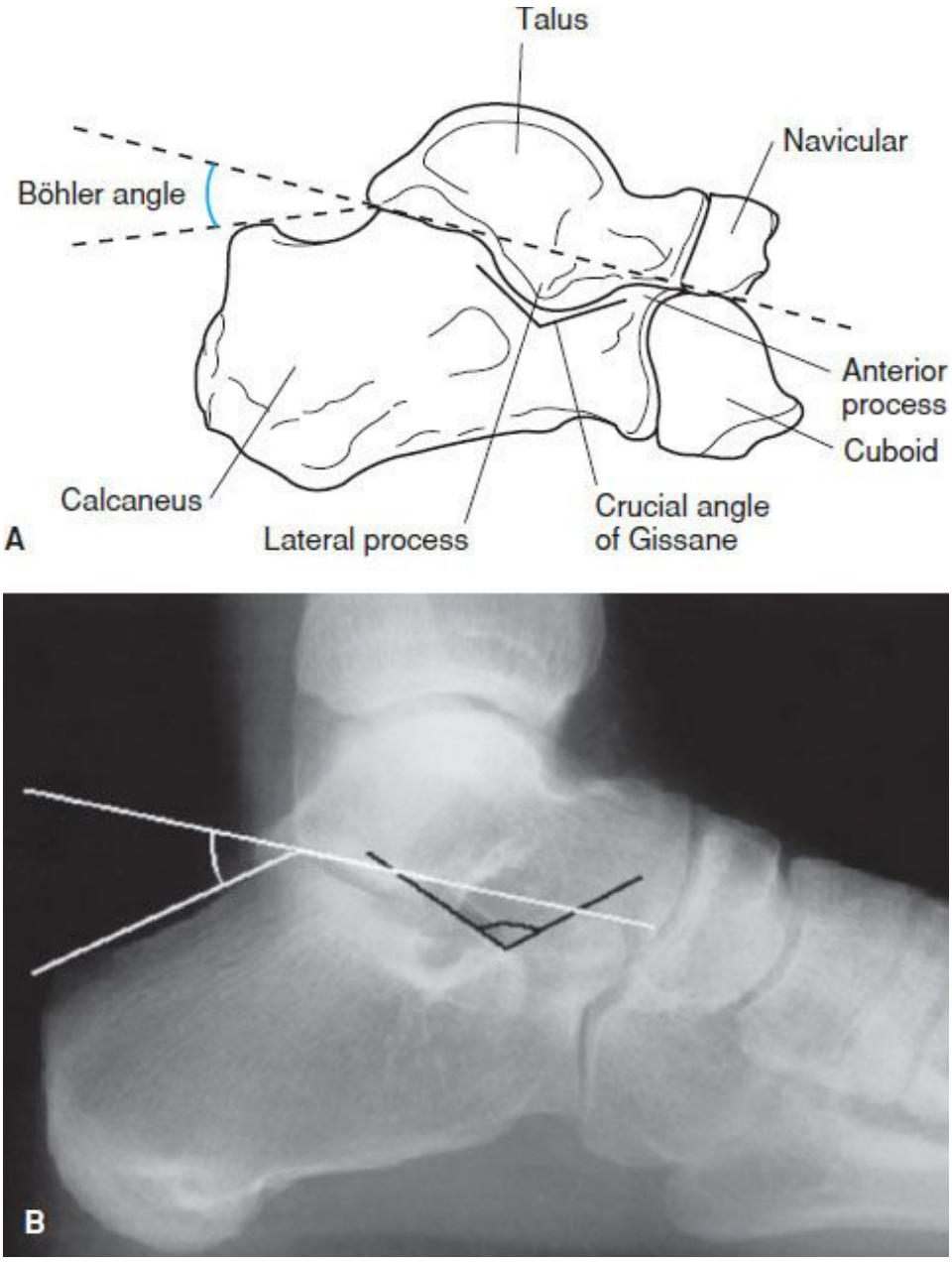


FIGURE 45.5 Lateral view of the calcaneous. A: A schematic outlining Boehler (also known as Böhler) angle and the crucial angle of Gissane. B: Lateral radiograph showing both anatomical angles. (From Bucholz RW, Heckman JD. *Rockwood & Green's Fractures in Adults*. 5th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2001.)

Owing to the mechanism and force required, a thorough trauma evaluation is important. Calcaneal fractures are specifically

associated with lumbar spine injuries in 10% of patients.

Patients with calcaneal fractures require emergent orthopedic evaluation. It is likely that the specialist will request a computed tomography (CT) scan or magnetic resonance imaging (MRI) to better delineate the fracture pattern. Operative verses nonoperative management is controversial. However, both are associated with a high incidence of chronic pain and loss of joint mobility and function. If orthopedic consultation is not immediately available and the patient has no associated injuries warranting admission, the physician should provide analgesia and place the patient in a short-leg posterior splint. The patient should be nonweight bearing. Orthopedic follow-up should occur within 24 to 48 hours (10).

Talus Fractures

A high-impact mechanism is required to fracture the talus. A hyperdorsiflexion injury from a motor vehicle collision or fall from a height is necessary to compress the talus between the tibia and calcaneus. Osteochondral fractures of the talar dome (also termed *osteochondritis dessicans*) occur after an inversion mechanism. Patients usually present with chronic pain after the diagnosis is missed on the initial visit because physical findings are nonspecific and plain radiographs may be normal. Suspected talar dome fractures may benefit from bone scan, CT, or MRI for further evaluation and classification.

Unlike talar dome fractures, fractures through the body and neck are usually visible on plain radiographs. It is particularly important to evaluate for the commonly associated *subtalar dislocation.* In addition, the *os trigonum* (accessory bone) can occasionally be mistaken for a posterior process fracture.

Recently, there has been increased attention to fractures of the lateral process of the talus (LPT). This fracture is closely associated with snowboarding and was relatively rare prior to the advent of the sport. It now accounts for less than 1% of all ankle injuries and for 15% of snowboarders' ankle injuries (11,12), leading to the name snowboarder's fracture. The LPT is a wedge-shaped prominence which articulates with the fibula and the calcaneus. Although the

incidence is increasing because of the growing popularity of the sport, this fracture is frequently misdiagnosed as an ATFL sprain, leading to inadequate immobilization and less orthopedic intervention. Misdiagnosis can lead to significant morbidity, such as nonunion and degenerative arthritis (13,14). The mechanism of injury is still under investigation. It is most commonly believed to be a high impact injury on an axially loaded and dorsiflexed ankle, combined with foot inversion (13). Like other talus fractures, it can be difficult to identify an LPT fracture on plain radiographs, with a miss rate of approximately 40%. CT or MRI is often required to make the diagnosis, and thus a high index of suspicion is necessary (15). These fractures often present to the ED as chronic pain after an ankle sprain. All LPT fractures should be immobilized, and require nonweight bearing and close orthopedic evaluation. Operative management is dependent on severity (11,12).

Talus fractures require evaluation and continued care by an orthopedic surgeon because the bone has a tenuous blood supply and, as a result, there is a high rate of avascular necrosis. Most talar fractures require short-leg casting for 6 to 8 weeks, but some require open reduction and internal fixation. Patients should be nonweight bearing. Disposition is based on recommendations by the orthopedist. Patients can be referred for an outpatient CT or MRI for suspected talar dome fractures (10).

Subtalar Dislocation

A subtalar dislocation involves the talocalcaneal and talonavicular joints (without disruption of the tibiotalar joint). This injury results from a significant torsional force usually causing a medial or lateral dislocation. There is usually an obvious deformity of the foot, but swelling can occasionally mask the deformity.

As with any dislocation, assessing the neurovascular status is important. Although uncommon, compromised neurovascular status is an indication for immediate reduction. Plain films of the foot are diagnostic; the AP view is most likely to reveal the subtalar dislocation.

Subtalar dislocations require urgent closed reduction either under conscious sedation or general anesthesia. Reduction is performed by flexing the knee and applying longitudinal traction on the foot with initial reproduction of the injury followed by reversal of the deformity. If closed reduction in the ED is unsuccessful, orthopedic consultation is essential. Successfully reduced subtalar dislocations should be immobilized with a short-leg posterior splint and sugar tongs (U-splint). After reduction, if orthopedic consultation is not available in the ED, follow-up should occur within 24 to 48 hours.

Lisfranc Fracture–Dislocation

The Lisfranc joint is the joint between the midfoot and forefoot (metatarsals and phalanges). Direct trauma or hyperdorsiflexion of the Lisfranc joint (e.g., in a motor vehicle collision) can result in a Lisfranc fracture–dislocation, defined as a fracture at the base of the second metatarsal or second cuneiform with dislocation of the lateral four metatarsals. The occurrence is rare but results in significant morbidity when there is a delay in treatment. This particular fracture has a high misdiagnosis rate of approximately 20%.

The foot is usually very swollen and tender over the tarsometatarsal joint. Plantar ecchymosis has been described as a relatively common finding in patients with Lisfranc fracture–dislocations (17).

When examining an AP foot x-ray, the physician should look for a fracture at the base of the second metatarsal and assess alignment of the cuneiform bones with the metatarsals. The space between the bases of the metatarsal bones is widened (Fig. 45.6). The standard foot x-ray series can miss up to 50% of Lisfranc fractures. If there is suspicion and standard plain films are normal, then stress- or weight-bearing AP and lateral views can be obtained to reveal the widening (17).

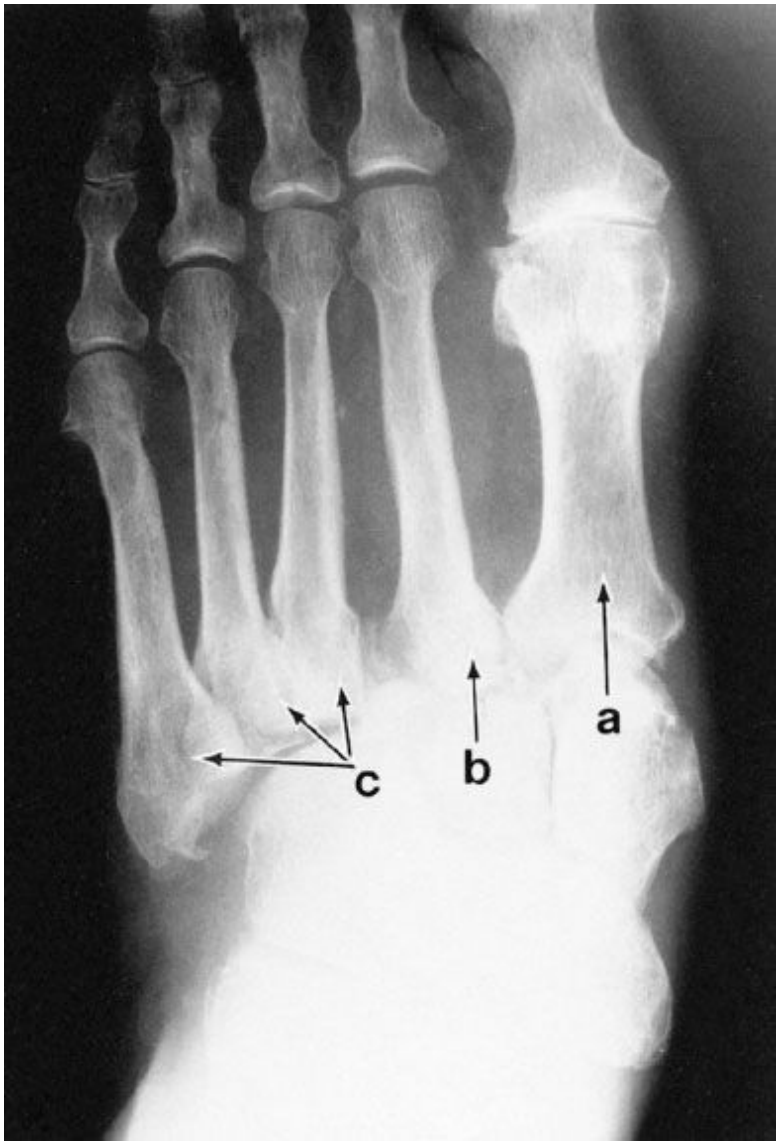


FIGURE 45.6 Radiograph of a Lisfranc dislocation: (a) first metatarsal; (b) second metatarsal; (c) third, fourth, and fifth metatarsals, which have been dislocated laterally.

Lisfranc fracture–dislocations require orthopedic consultation in the ED. These injuries require open reduction and internal fixation to improve outcome and reduce complications. If an orthopedic consultant is not immediately available, the physician should provide analgesia and place the patient in a short-leg posterior splint, preferably with a sugar tong splint. The patient should be nonweight bearing. Orthopedic follow-up should occur within 24 to 48 hours,

and the timing of definitive treatment and the degree of reduction are critical to the outcome.

Midfoot Fractures

Fractures of the midfoot (cuboid, navicular, and cuneiforms) are rare and usually occur from direct blunt trauma. Most midfoot injuries involve a combination of fractures, isolated bone fractures are the exception. There is typically focal tenderness and swelling over the fractured bones.

Midfoot fractures are usually visible on plain radiographs. Nondisplaced fractures can be immobilized and nonweight bearing with a posterior splint. They can be discharged with prompt orthopedic follow-up for evaluation and a short-leg cast for 6 to 8 weeks.

Proximal Fifth Metatarsal Fractures

Fractures of the fifth metatarsal usually result from an ankle inversion mechanism. The *Jones* and *pseudo-Jones* fractures present with pain over the base of the fifth metatarsal. A *Jones fracture* is a transverse fracture at the proximal diaphysis of the fifth metatarsal. A *pseudo-Jones* or *Dancer's fracture* is an avulsion fracture of the proximal end of the fifth metatarsal by the peroneus brevis tendon resulting from plantar flexion and inversion of the foot.

Palpation of the fifth metatarsal is essential in any patient with an ankle-twisting injury to determine the need for foot films in addition to ankle films to make the diagnosis of Jones or pseudo-Jones fractures (eFig. 45.6). The Ottawa criteria are useful to determine the need for foot x-rays (Table 45.2).

eFIGURE 45.6 Proximal fifth metatarsal injuries. A: Avulsion or pseudo-Jones fracture. B: Jones fracture.

TABLE 45.2
Ottawa Criteria for Foot Radiographs

A foot radiographic series is required in patients aged 18–55 only if there is pain in the midfoot and any of the following findings:

1. Bone tenderness at the base of the fifth metatarsal
2. Bone tenderness at the navicular bone
3. Inability to bear weight for four steps both immediately and in the emergency department

From Ankel F. The Ankle. In: Hart RG, Rittenberry TJ, Uehara DT, eds. *Handbook of orthopedic emergencies*. Philadelphia, PA: Lippincott-Raven Publishers; 1999, with permission.

Jones fractures have a high incidence of delayed healing or nonunion. Orthopedic evaluation in the ED is recommended. If immediate consultation is not available, the foot should be immobilized with a posterior splint with or without a sugar tong splint, and the patient should have an orthopedic referral in 24 to 48 hours. Athletes are usually treated operatively, and nonathletes are treated with a walking cast for 4 to 6 weeks (17).

Pseudo-Jones fractures are stable and can be treated with a hard-sole shoe or a *Jones dressing* with weight bearing as tolerated. A *Jones dressing* is a bulky dressing used for injuries that require moderate immobilization when swelling is expected. The dressing consists of multiple layers: a thick layer of Webril (cotton roll), followed by an ACE wrap (elastic bandage), then another layer of Webril and another layer of ACE wrap.

Forefoot Injuries

The most common metatarsal and phalangeal fractures result from direct trauma and present with swelling, tenderness, and ecchymosis. Dislocations of the metatarsophalangeal (MP) and interphalangeal (IP) joints are caused by dorsiflexion and compression of the phalanges. In addition to swelling and tenderness, there is usually visible deformity.

More subtle stress fractures can occur to the second and third metatarsal bones. During push off, the maximum load is placed on the forefoot. As a result, these bones are prone to stress fractures. Patients usually have a history of increased walking, jogging, or marching activity, and they complain of poorly localized pain in the foot with minimal swelling (17).

The neurovascular status of the foot should be documented, especially the presence of the dorsalis pedis pulse. Dislocations with neurovascular compromise should be reduced immediately; otherwise it is prudent to assess the plain films for fractures before manipulation.

Plain films are adequate to evaluate for acute traumatic fractures and dislocations. However, initial radiographs will often not reveal stress fractures. Stress fractures are usually apparent 2 to 3 weeks later as callus formation or periosteal reaction, but they can also be detected earlier by bone scan.

In patients with MP joint dislocations, the phalanx is usually dorsally displaced. Reduction is performed by hyperextension, followed by longitudinal traction and dorsal pressure. Patients can be discharged with a dorsal toe splint, crutches, and orthopedic follow-up. IP joint dislocations can occur in a dorsal or volar direction. The reduction technique is similar for both types. Patients can be discharged after the injured toe is buddy taped to the adjacent toe. Patients should follow up with an orthopedist in a week because of the possibility of unstable dislocations.

Nondisplaced fractures should be placed in a short-leg splint and follow-up should be arranged. Displaced fractures require reduction by an orthopedist. Stress fractures or suspected stress fractures require close orthopedic follow-up and discontinuation of any pain-producing activity.

Turf Toe

Turf toe is a sprain of the MP joint of the great toe that results from pushing off of a hyperdorsiflexed toe. The toe is tender and swollen. An x-ray should be obtained to rule out fracture. Like most sprains, the treatment is joint rest with a hard-soled shoe limiting dorsiflexion, ice and analgesia, and ibuprofen or acetaminophen for pain. Orthopedic consultation is necessary only for patients with persistent pain beyond 1 to 2 weeks.

Plantar Fasciitis

Patients with plantar fasciitis complain of pain in the arch and heel of the foot that is worse in the morning or when climbing stairs. There is usually a history of overuse (hill running or sprinting) or poor arch support. Evaluation reveals tenderness over the plantar fascia and reproduction of the pain with dorsiflexion of the toes. If there is focal tenderness or a stress fracture is suspected, plain films of the foot are indicated. Treatment involves rest, ice, analgesia, and splinting for comfort. Follow-up with an orthopedist, sports medicine specialist, or physical therapist is recommended. These patients may require evaluation for an orthotic device or exercise program.

Puncture Wounds

Plantar puncture wounds have the potential for serious complications (e.g., soft tissue infection and osteomyelitis). Wounds should be inspected, cleansed, irrigated, and explored, especially if a foreign body is suspected. Deep probing, extensive coring, or debridement of vital tissue does not improve outcome. Radiographic studies are warranted if the history suggests a foreign body and exploration is inconclusive. Puncture through tennis shoes have been implicated in pseudomonal infections, but most soft tissue infections are due to *streptococcus* and *staphylococcus* species. Most cases of osteomyelitis are due to *pseudomonas* (18,19). The use of prophylactic antibiotic for puncture wounds to the foot is controversial. Given the risk of complications such as osteomyelitis, its use should be considered. If the decision is made to use antibiotics, a first-generation cephalosporin should be given. For clean, superficial wounds with no concern for retained foreign body, local wound care is the sufficient treatment. A wound check in 48 hours is recommended for contaminated wounds and those with possible retained foreign bodies.

Patients presenting with infection after a puncture wound should be treated with broad-spectrum antibiotics, and the physician should search for a foreign body via exploration, radiographs, or CT scan. Surgical consultation may be needed.

KEY TESTING

- Perform a complete neurovascular examination distal to injury
- Assess for ankle instability with provocative testing
- Obtain three-view ankle x-rays or three-view foot x-rays according to Ottawa Ankle Rule
- Obtain stress- or weight-bearing views to assess for Lisfranc injury if there is a high suspicion

CRITICAL INTERVENTIONS

- In a patient with neurovascular compromise and a visibly deformed extremity, reduce the fracture emergently to restore sensation and blood flow.
- Obtain radiographic confirmation in patients with dislocated joints without neurovascular compromise and then reduce the joint.
- In patients with open fractures, administer antibiotics and obtain emergent orthopedic consultation for wash-out and admission.
- Provide appropriate follow-up care for all patients with ankle and foot injuries.

DISPOSITION

Most patients with ankle or foot injuries should have close follow-up in the event that symptoms do not improve and further investigation and treatment are required. Exceptions are minor ankle sprains and turf toe. Patients who are sent home in a posterior short-leg or sugar tong splint should have orthopedic follow-up within 24 to 48 hours for reassessment and definitive immobilization with a cast.

Orthopedic consultation should be obtained in the ED for the following fractures and dislocations: plafond, bi-, or trimalleolar fractures; calcaneal, talar, or Jones fractures; Lisfanc fracture/dislocation; and ankle and subtalar dislocations. If orthopedic consultation is not immediately available, appropriate reduction or splinting should be performed, and arrangements should be made for orthopedic evaluation within 24 to 48 hours. Open fractures will require immediate orthopedic consultation.

Common Pitfalls

- Failure to palpate the base of the fifth metatarsal to evaluate for a Jones fracture.
- Treating a Jones fracture as a pseudo-Jones fracture.
- Failure to squeeze the proximal tibia–fibula area to evaluate for a Maisonneuve fracture in patients with presumed ankle sprains.
- Applying the Ottawa Ankle Rules to patients younger than 5 and older than 55 years.
- Failure to recognize a Lisfranc fracture.
- Treating grade I and II ankle sprains with prolonged immobilization rather than early mobilization and exercise.

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of Daniel R. Martin and Wenzel Tirheimer to the content of this chapter.

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PART 4 • SPECIAL CONSIDERATIONS

CHAPTER 46

Burns

Adam J. Singer and Steven Sandoval

The incidence of burn injuries requiring medical attention in the United States has declined from 2 million annually in the 1960s to an estimated 450,000 per year in 2012 (1). Approximately 40,000 burn injuries require hospitalization, and 3,400 of these people die. In the United States, in 2004, someone died in a fire on average every 135 minutes, and someone was injured every 30 minutes (2). Approximately 6% have a related inhalation injury, which raises mortality from about 5% to >25% (3). More than 60% of burns are <10% total body surface area (TBSA), so the emergency department (ED) may be the only location where many are treated. Seventy-six percent of burn or fire deaths in 2002 resulted from residential fires (4). Many of these deaths were related to smoke inhalation. Children younger than 5 years and adults older than 65 have higher mortality rates (5). Burns remain the third leading cause of unintentional death in children, surpassed only by motor vehicle collisions and drownings. In the general population, the most frequent source of burns is flames (40%) (6). Approximately 70% of pediatric burns are scalds from hot liquids associated with cooking or bathing, and nearly 20% of hot liquid burns involve neglect or abuse, particularly water immersion.

CLINICAL PRESENTATION

The severity of thermal trauma is determined mainly by the depth and size of injury, but it is also influenced by the presence of inhalation injury, circumferential burns, or specific locations of the burn injury, such as hands, feet, major joints, face, or genitalia (7).

Other factors that contribute to the severity of the injury include the causative factors, age of the patient, toxic exposures, concomitant traumatic injuries, and comorbidities.

The skin is a laminar structure with the outermost layer being the epidermis, composed of keratinocytes that arise from the stratum germinativum, migrate upward, and finally desquamate. Beneath the epidermis lies the dermis, which contains the epidermal appendages: hair follicles, sweat glands, and sebaceous glands that give rise to the new epidermis after injury. The dermis also contains blood vessels, nerve endings, immunocytes, fibroblasts, and elastin and collagen fibers. Under these two layers is the subcutaneous tissue.

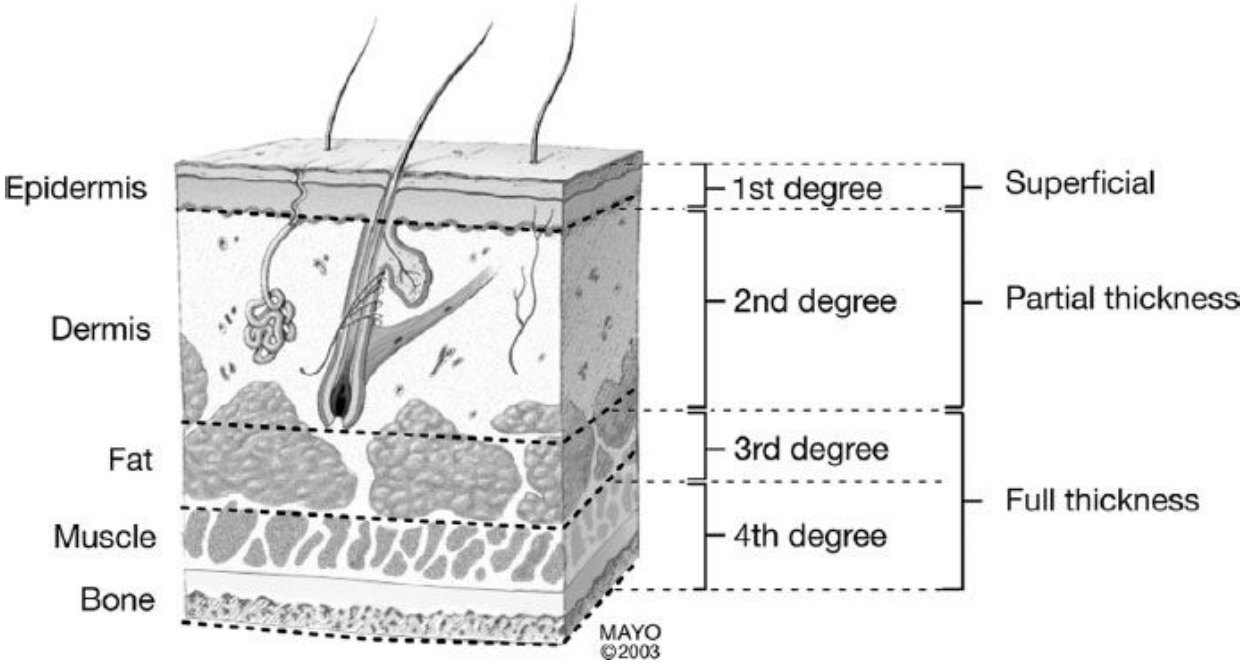
The depth of injury depends on the source type, the source temperature, the length of exposure, and the skin thickness. A scald injury usually results in partial-thickness burns, whereas a flame injury typically results in full-thickness burns. Infants, young children, and the elderly have a thinner dermal layer of skin, which gives them a greater propensity for deep burns. Certain causative agents, such as grease, chemicals, and electricity, have the potential to cause a deeper, more severe injury because of their higher temperature, greater heat-transferring ability, and sustained effect. The systemic response to burn injuries is driven by the loss of the skin's barrier functions, the release of vasoactive mediators from the wound, and the subsequent infections that are commonly encountered (8).

Burns are traditionally classified based on depth of injury (eFig. 46.1), summarized in eTable 46.1.

TABLE 46.1
Criteria for Transfer of a Burn Patient to a Burn Center

Second-degree burns >10% total body surface area
Third-degree burns
Burns that involve the face, hands, feet, genitalia, perineum, and major joints
Chemical burns
Electrical burns including lightning injuries
Any burn with concomitant trauma in which the burn injuries pose the greatest risk to the patient
Inhalation injury
Patients with pre-existing medical disorders that could complicate management, prolong recovery, or affect mortality
Hospitals without qualified personnel or equipment for the care of the critically burned children

From American Burn Association. Practice guidelines for burn care. *J Burn Care Rehabil*. 2001; 22:S1–S69.



eFIGURE 46.1 Cross section of skin demonstrating various depths of burn.

eTABLE 46.1
Classification of Burns

Degree	Thickness	Structures Comprised	Description	Time to Heal	Excision/ Grafting	Common Source
First	Superficial	Superficial epidermis	Red, painful, no blisters	Few days, no scar	No	Sun, hot liquids
Second	Partial thickness, superficial	Full epidermis, partial dermis	Red, painful, blistered, weeping	Up to 3 wks, no scar	No	Scalds, short flashes
	Partial thickness, deep	Full epidermis, deep dermis with epidermal appendages compromised	Red and blistered combined with waxy and dry areas; usually painful	Weeks to months, with scars	May need	Scalds, flames, oil, grease
Third	Full thickness	Full epidermis and dermis	Dry, leathery, pale or brown, inelastic, and painless	Months, heals by contraction	Yes	Flames, oil, grease, electricity, chemicals
Fourth	Full thickness	Full epidermis, dermis and underlying muscle, tendons, or bone	Dry, leathery, pale or brown, inelastic, and painless	Months, heals by contraction	Yes	Flames, oil, grease, electricity, chemicals

Superficial burns (first degree), such as those from sunlight or very short flash, are limited to the superficial epidermal layers. They are erythematous and painful, do not form blisters, are sensate, and heal within 1 week without scars. These burns are not included in calculations of TBSA.

Second-degree burns are divided into superficial and deep partial-thickness burns based on the depth of injury to the dermis. Superficial partial-thickness burns, from scalds or short flashes, involve the entire epidermis and the uppermost dermis. Since they spare important structures, and leave epidermal appendages in the dermis, they generally heal without scarring in 2 weeks as epidermal cells migrate from these surrounding normal skin and the remaining appendages. They are erythematous, blistered, weeping, blanch, and very painful. Deep partial-thickness burns are usually caused by flames, oil, or grease. They involve deeper layers of the dermis with fewer remaining dermal structures and epidermal appendages. Such burns may have areas that are waxy and dry, may not blanch, and can be difficult to distinguish from full-thickness burns. Deep partial-thickness burns often take at least 2 to 3 weeks to heal resulting in scar formation. As a result, many deep partial-thickness wounds require excision and skin grafting for an optimal functional result (9).

Full-thickness burns can be caused by flames, scalds, and chemical and electrical contact. They destroy dermal structures (third-degree) or underlying tendons, muscle, and bone (fourth-degree). The skin appears dry, stiff, and leathery with a pale-to-brown color, does not blanch with pressure, and may exhibit underlying thrombosed vessels. The patient will generally not have pain on palpation and the

burn will be insensate. While third-degree burns may not be painful, it is important to remember that many patients have mixed burns and experience considerable pain. These injuries require at least 3 weeks to heal resulting in significant scarring and contractures.

Differentiating between deep partial-thickness and full-thickness burns may be difficult in the ED. In addition, burns are often dynamic in nature progressing in depth and extent over the first few days after injury. Despite various advances in technology, serial examinations by an experienced clinician is still the most common method for determining the depth of a burn (10). As a result close follow-up, preferably by a burn specialist, is required.

DIFFERENTIAL DIAGNOSIS

Although burn-injured patients usually present with a straightforward history, this situation is not universal. Some presentations may be the result of self-inflicted or nonaccidental injury. Children with unreported hot liquid ingestion or steam inhalation have been initially managed as having croup, laryngomalacia, and tracheobronchitis (11). Several dermatologic conditions such as toxic epidermal necrolysis, Stevens–Johnson syndrome, staphylococcal scalded skin syndrome, and purpura fulminans may present with bullae and skin sloughing much like burn patients. These patients are often referred to burn centers for definitive management of the large wounds.

Burn injuries to the skin do not occur in isolation. The emergency physician must consider associated injuries. Internal injuries may be sustained as burn victims attempt to escape the fire. Furthermore, patients may have been thrown during an explosion. Inhalation injuries may be present. Because burn victims often require immediate airway management, they may not be able to provide an appropriate history. In patients with central nervous system (CNS) or cardiopulmonary depression, carbon monoxide poisoning and cyanide toxicity should be considered, particularly in industrial settings.

Because up to 20% of pediatric burns are a result of abuse or neglect, the emergency physician must consider the possibility of

abuse when evaluating burn-injured children (12). Intentional burn injuries are suggested by a history inconsistent with injuries or the child's developmental stage, conflicting histories from caregivers and child, a delay in seeking treatment, and a history of previous injury. Immersion injuries are common intentional burns, and key physical examination findings include uniformity of burn depth, absence of splash marks, sharply defined circumferential wound margins, flexor surface sparing, and stocking glove patterns. Suspected abuse must be reported, and the child may need to be admitted for further evaluation and protection.

Another consideration in children is household cleaners that often cause chemical burns. Ingestion should also be suspected in any young child with a chemical burn. Any dry chemicals should be gently brushed away and the burn should be copiously irrigated with room temperature water or normal saline for at least 20 to 30 minutes after removal of the child's clothing. Then the extent and depth of the burn can be assessed and treated (see Chapter 312).

ED EVALUATION

All burn-injured patients should be evaluated first as trauma patients using a systematic approach following the Advanced Trauma Life Support guidelines. Adhering to an organized approach improves patient outcomes.

Airway evaluation in the burn patient primarily centers on the concern for inhalation injury. A history of closed-space exposure to hot gases, steam, or products of combustion supports inhalation injury, as do physical examination findings of carbonaceous sputum, singed facial hairs, tachypnea, stridor, wheezing, cough, dysphonia, loss of consciousness, and altered mental status. Although elevated carboxyhemoglobin or cyanide levels also raise suspicion of inhalation injury, reliance on laboratory tests or radiographs cannot be utilized to determine the need for intubation. Patients with suspected inhalation injury may require early prophylactic intubation because progressive airway edema may preclude successful intubation once the patient is in respiratory distress (see Chapter 320). Direct visualization of the airway under topical

anesthesia, with or without dissociative anesthesia with ketamine, using fiberoptic, video, or standard laryngoscopy is helpful in questionable cases. While extreme vigilance is required, overzealous endotracheal intubation should also be avoided.

All burn patients with suspected inhalation injury should receive 100% humidified oxygen via nonrebreather mask during the evaluation of their respiratory status. Patients with inhalation injury, comorbidities, or circumferential burns of the neck and chest may develop respiratory compromise and may require intubation. Serial chest x-rays are of value, but the initial ED chest x-ray is often normal. Arterial blood gas (ABG) or venous blood gas measurements of carboxyhemoglobin should be obtained in patients with headache, syncope, nausea, or altered mental status. Noninvasive point-of-care devices that measure carboxyhemoglobin are also available (13). Although of limited utility in the ED, other tests to evaluate for inhalation injury include Pa_{O_2}/Fi_{O_2} ratio and xenon and technetium scanning. Bronchoscopy is considered the gold standard when diagnosing inhalation injury. These tests guide ventilatory management and decision making regarding transferring patients to specialized burn centers, although clinical impression suffices for the majority of situations in the ED.

Evaluation of the circulatory system is often difficult in the severely burned patient. Level of consciousness may be altered because of inhaled toxins, blood loss from coexisting trauma, or "burn shock." *Burn shock* refers to hypovolemic shock caused by increased blood flow to the wound, capillary leak, decreased cardiac output, and "third spacing" (extracellular and extravascular fluid shifts). Blood pressure measurement and peripheral pulses may be difficult to obtain and unreliable secondary to pain and catecholamine response. Capillary refill and skin color may also be difficult to assess in severely burned patients. Circulation distal to circumferential burns should be evaluated repeatedly. Emergent escharotomy is indicated if distal perfusion remains poor despite adequate intravenous (IV) volume resuscitation.

The physician should quickly determine the neurologic status of the patient. Any alteration of mental status should prompt immediate

reevaluation of oxygenation, ventilation, and perfusion. Concern for CNS trauma warrants head computed tomography (CT) scanning.

The patient should be completely undressed to facilitate a thorough examination and halt ongoing injury. Usually the burning process has ceased prior to the ED evaluation, but certain fabrics can ignite and melt into residues that continue to burn the patient. Chemicals or other substances may be embedded in the clothing. Any substance should be safely removed, and the involved skin surface should be copiously irrigated with water. Dry chemicals should be carefully brushed off before irrigation.

The secondary survey includes a systematic head-to-toe thorough examination. Key components of the history should now be obtained. These components include documentation of the mechanism and time of injury, closed-space exposure, substances consumed by flames, and prehospital interventions.

After the initial stabilization of the burn patient, the physician should determine the extent of the burn injury by calculating the percentage of TBSA that is burned. The TBSA burn should be subdivided into partial-thickness and full-thickness percentages. This analysis will facilitate further patient management and categorization of the injury severity. There are various methods for calculating the TBSA of burn injury. Superficial burns (first-degree) are not included in calculations of TBSA.

Classically, the “rule of nines” has been used in adult patients (Fig. 46.1). The head, each arm, and each half of each leg approximates 9% TBSA. The torso is assigned 18% each for the anterior and posterior aspects. The genitals are 1% TBSA. The “rule of nines” is not applicable in the pediatric population as the head compromises a larger TBSA (18%) and the legs a smaller TBSA (14%). This evaluation is a good rough estimate, but it can lead to overestimation and inappropriate patient transfer to burn centers. Lund and Browder charts are more accurate in all age groups and should be used after the initial resuscitation is complete (eFigs. 46.2 and 46.3). Another method for small burns is using the patient’s hand to estimate the TBSA. The palmar surface of the hand (excluding fingers) represents approximately 0.5% TBSA (14).

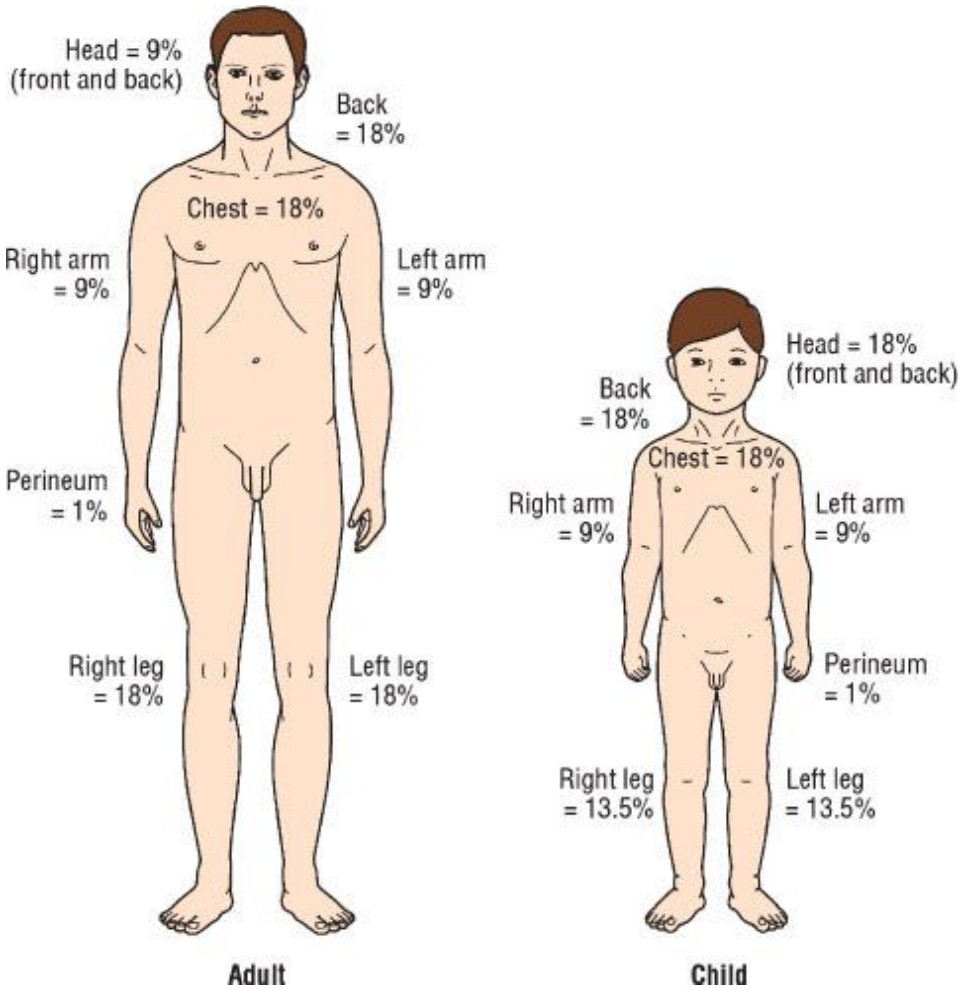
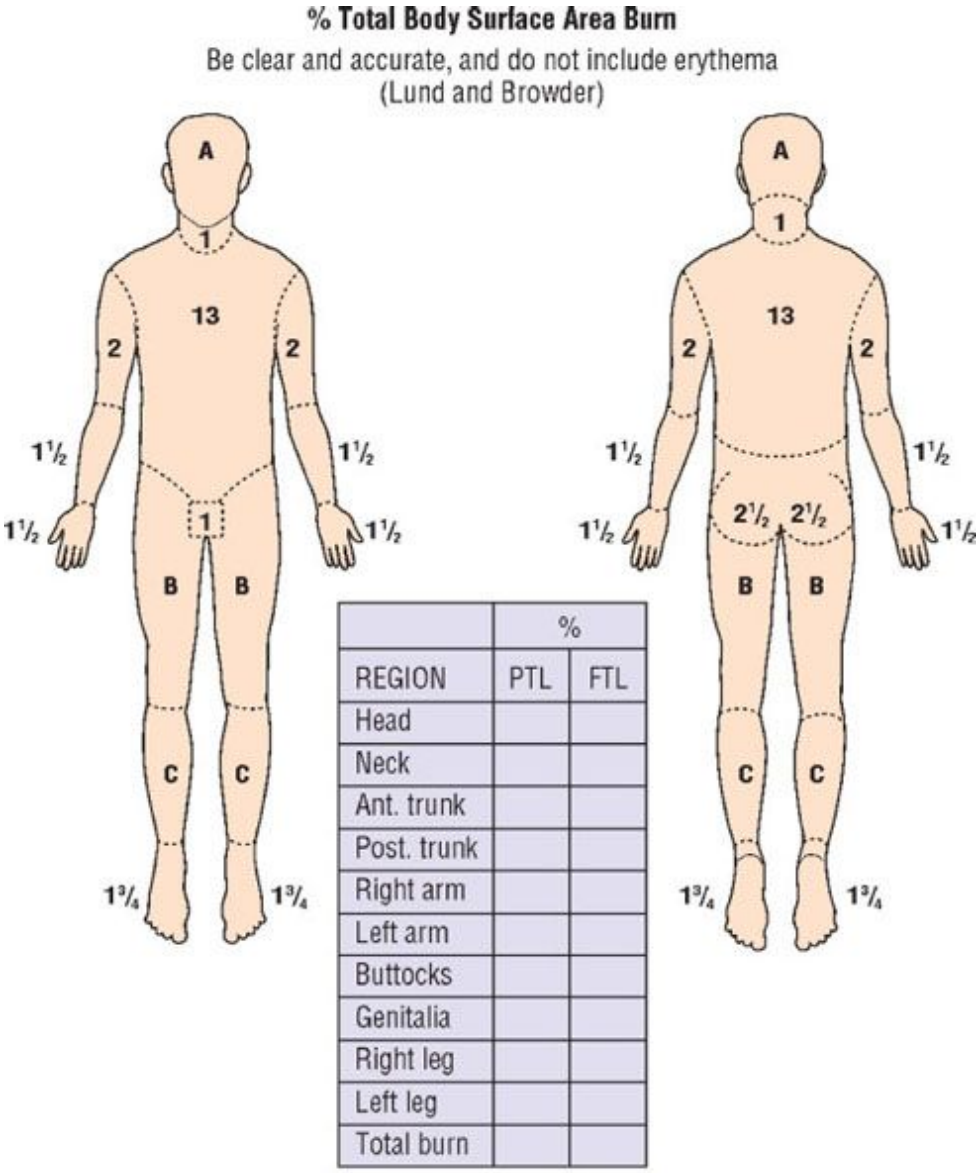


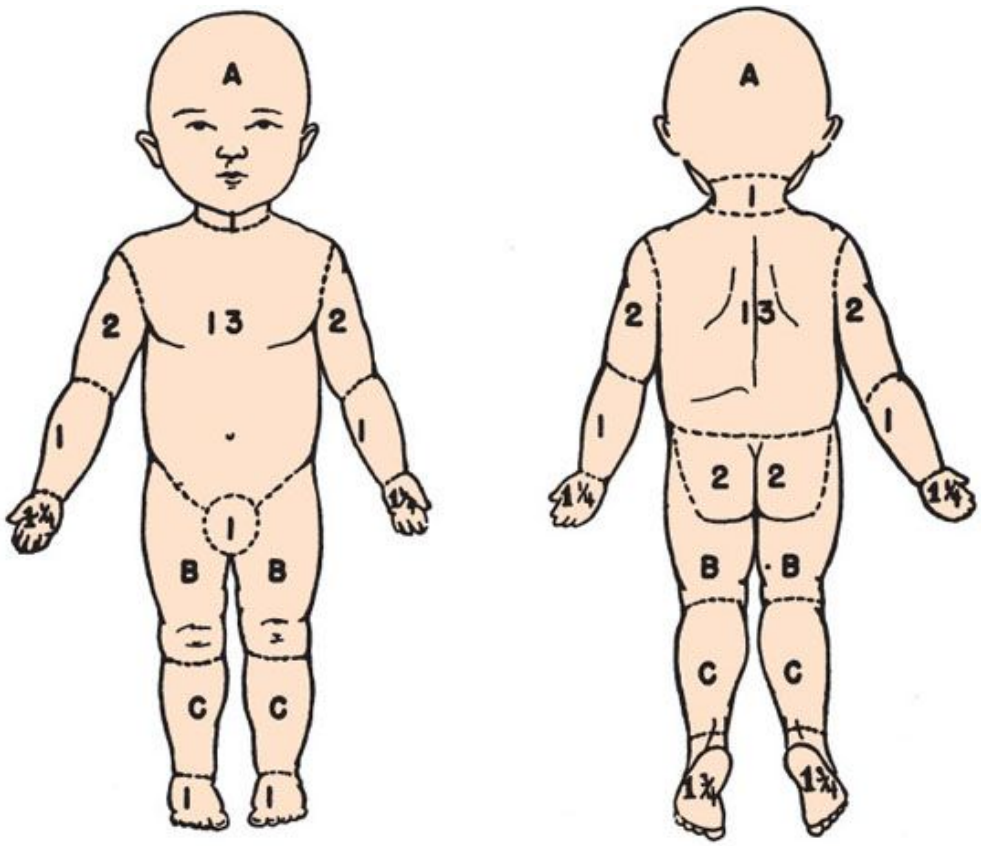
FIGURE 46.1 Methods to evaluate the percentage of body surface area burned. Rule of nines.



	%	
REGION	PTL	FTL
Head		
Neck		
Ant. trunk		
Post. trunk		
Right arm		
Left arm		
Buttocks		
Genitalia		
Right leg		
Left leg		
Total burn		

AREA	Age 0	1	5	10	15	Adult
A = ½ OF HEAD	9½	8½	6½	5½	4½	3½
B = ½ OF ONE THIGH	2¾	3¼	4	4½	4½	4¾
C = ½ OF ONE LOWER LEG	2½	2½	2¾	3	3¼	3½

eFIGURE 46.2 Lund and Browder chart.



RELATIVE PERCENTAGES OF AREAS AFFECTED BY GROWTH

Area	Age 0	1	5
A = ½ of Head	9½	8½	6½
B = ½ of One Thigh	2¾	3¼	4
C = ½ of One Leg	2½	2½	2¾

% BURN BY AREAS

Probable 3rd° Burn { Head____ Neck____ Body____ Up. Arm____ Forearm____ Hands____ / Genitals____ Buttocks____ Thighs____ Legs____ Feet____

Total Burn { Head____ Neck____ Body____ Up. Arm____ Forearm____ Hands____ / Genitals____ Buttocks____ Thighs____ Legs____ Feet____

Sum of All Areas____ Probably 3rd° ____ Total Burn____

eFIGURE 46.3 Modified Lund and Browder chart for estimation of body surface area burn involvement in infants and children.

Further radiographic evaluation including x-rays and CT scans should be performed based on the mechanism of injury. In addition to ABG determination, baseline hematocrit, electrolytes, and glucose, a pregnancy test should be obtained in females of childbearing age. Cardiac monitoring and an electrocardiogram may be necessary for

burns associated with electrical injuries (see Chapter 349). Human studies in critically ill patients have demonstrated that blood lactate levels are highly accurate as a guide to the efficacy of resuscitation. Although admission lactate values have been shown to be higher in nonsurvivors, no cutoff value has been consistently associated with mortality (15).

KEY TESTING

- If inhalation injury is suspected, a CXR and ABG with CO levels may be required.
- For inhalation injury, bronchoscopy may also be required.
- With burn shock a CBC and metabolic panel may be required.

ED MANAGEMENT

The ED management of burn patients is focused on four main aspects of care: (a) airway management, (b) fluid resuscitation, (c) pain control, and (d) appropriate management of associated injuries.

As with all emergency patients, the physician should consider the ABCs (airway, breathing, and circulation) as part of the initial assessment. All clothing should be removed as soon as possible. If there has been associated trauma, the neck should be immobilized until a cervical spine injury has been ruled out. Until a good history of the circumstances of the injuries is obtained, significantly burned patients should be given humidified 100% oxygen by a nonrebreathing mask.

Airway Management

In severely burned patients, an expeditious decision must be made regarding potential airway damage. Intubation should be performed before the airway is lost. Intubation should be performed in unconscious patients with a history of prolonged smoke or fire exposure in a confined space and in patients with a high suspicion for airway edema (stridor, voice changes, increasing respiratory distress, hypoxia despite 100% oxygen, and poor peak flow). While airway management can be performed using rapid-sequence

orotracheal intubation technique, awake intubation with topical anesthesia with or without dissociative anesthesia with ketamine should be strongly considered if a difficult airway is likely with immediate availability of a surgical airway setup. If rapid-sequence intubation is used, succinylcholine can be safely administered within 12 to 24 hours of a burn injury. Succinylcholine should be avoided in patients 24 to 48 hours following a thermal injury and for at least 1 year after the burned skin has healed due to the risk of fatal hyperkalemia (16).

Many patients require positive end-expiratory pressure (PEEP) to keep the distal airways open. PEEP should begin at 5 cm H_2O. Bronchodilators may be effective if secretions or particulate inhalation leads to bronchospasm. Recent studies have shown improved outcomes and reduced risk of acute lung injury with low tidal volume (6 mL/kg) ventilation (17). High peak pressures (>35 cm H_2O) should be avoided, which may require some degree of permissive hypercapnea where CO_2 levels are allowed to rise above normal. Since bronchoscopy and pulmonary toilette are often required, endotracheal intubation should be performed with the largest-sized endotracheal tube possible.

Fluid Resuscitation

With large burns massive fluid shifts can occur even though total body water remains unchanged. IV fluids should be administered to adults and children with burns covering 20% of their TBSA or greater. A large number of fluid resuscitation formulas are available. With all formulas, calculation of fluid requirements should only serve as an initial estimate with frequent adjustments based on patient response. Overzealous hydration termed “fluid creep” is all too common and may result in worse outcomes due to compartment syndromes in the abdomen and extremities (18).

The most commonly used resuscitation formula is the Parkland formula that requires 4 mL/kg of lactated Ringers solution for every 1% TBSA of second- and third-degree burns over the first 24 hours, half of which is given within the first 8 hours after injury. The

modified Brooke formula that calls for 2 mL/kg/% TBSA burned is also recommended by the American Burn Association (19). The US Army Institute of Surgical Research has recently proposed a simplified formula termed “the rule of tens” in which 10 mL is given per hour for every 1% TBSA burn (20). With all formulas, careful attention to the patient’s condition is necessary to avoid over- and under-resuscitation. A good method to monitor the adequacy of fluid resuscitation is to maintain a urine output between 0.5 and 1 mL/kg/hour in adults and between 1 and 1.5 mL/kg/hour in children. While colloids (such as albumin or plasma) may be advantageous after the first 12 to 24 hours, their use in the first 12 hours after injury is not recommended. Hypertonic saline may be considered, but should only be used by specialists experienced in its use. The volume of fluid necessary to resuscitate burn patients depends on the severity of injury, physiologic status, age, and associated injuries. Two large-bore IV lines should be placed through unburned skin if possible. The patient should be placed on a cardiac monitor, and a urinary catheter should be placed to monitor output. The amount of fluid needed to treat the burn shock should be calculated keeping in mind the additional fluid loss from other sources (i.e., trauma and inhalation injury). Patients with special fluid management problems such as heart failure, renal insufficiency, or on dialysis may require more aggressive central monitoring of hemodynamic parameters.

The burned child presents a special challenge, because resuscitation therapy must be more precise than for an adult with a similar burn. Children require more fluid for burn shock resuscitation than adults with similar thermal injury; fluid requirements for children average 5.8 mL/kg/% burn over 24 hours (7). In addition, children commonly require IV resuscitation for even relatively small burns (10% to 20% TBSA). The use of hypertonic saline and albumin is better accepted in children than in adults. There are two formulas used for fluid resuscitation in pediatrics (eTable 46.2) (21). Both formulas are relatively easy to use, and both appear to result in similar outcomes. The presence of inhalation injury increases fluid requirements for resuscitation from burn shock after thermal injury.

Several authors have documented that patients with inhalation injury require crystalloid at a rate of 5.7 mL/kg/% burn over the first 24 hours (7). Fluid resuscitation utilizing a calculation of 6 mL/kg/% burn (over the first 24 hours) should work well in the ED. The first half should be given in the first 8 hours and the rest in the next 16 hours.

eTABLE 46.2
Formulas for Estimating Pediatric Resuscitation Needs

	Calculation	Time	Fluid and Mixture
Cincinnati Shriners Burns Hospital (modified Parkland)	4 mL/kg/% TBSA burn + 1,500 mL/m^2 BSA	1/2 total volume over first 8 hrs 1/4 total volume over 8 hrs 1/4 total volume over 8 hrs	LR + 50 mEg $NaHCO_3$/L LR LR + 12.5 g albumin
Galveston Shriners Burns Hospital[a]	5,000 mL/m^2 BSA burn + 2,000 mL/m^2 BSA	1/2 volume over first 8 hrs 50 mL of 25% human	LR + 12.5 g albumin Serum albumin (12.5 g)

[a]The Galveston resuscitation solution is prepared by mixing with 950 mL of LR.
TBSA, total body surface area; LR, lactated Ringer solution.

Pain Management

Pain can be severe, particularly in patients with partial-thickness burns and analgesia is often neglected (22). While full-thickness burns tend to be painless because nerve endings have been destroyed, many patients have mixed burns of varying depths, some of which can be extremely painful. All pain medications should be given via IV in small, frequent aliquots, titrated to pain relief to avoid adverse events such as hypotension or respiratory depression. Morphine remains the narcotic of choice; doses of 0.1 mg/kg in the young patient and 0.05 mg/kg in the elderly are usually well

tolerated. Fentanyl in doses of 1 to 2 μg/kg IV over 1 to 3 minutes is also a safe option. Because of its shorter duration (45 to 90 minutes) and potential for hypotension with rapid administration, this medication should be used as an alternative for patients intolerant to morphine. If the patient is extremely anxious and is not hypoxic or hypotensive, small doses of IV lorazepam (1 to 2 mg) may be used. In stable patients with severe pain that require procedures, such as hand escharotomies, major debridement, or fracture reductions, moderate or deep sedation is warranted. Small aliquots of ketamine (10 to 20 mg IV) should be considered in patients that appear tolerant to opioids.

Management of Associated Injuries

The standard treatment for burn patients with concomitant carbon monoxide exposure is to administer 100% oxygen. Hyperbaric oxygen therapy should be considered for those with documented serious exposure to carbon monoxide (carboxyhemoglobin level >25% with depressed mental status). Patients must be hemodynamically stable and not require ongoing burn resuscitation (see Chapter 311).

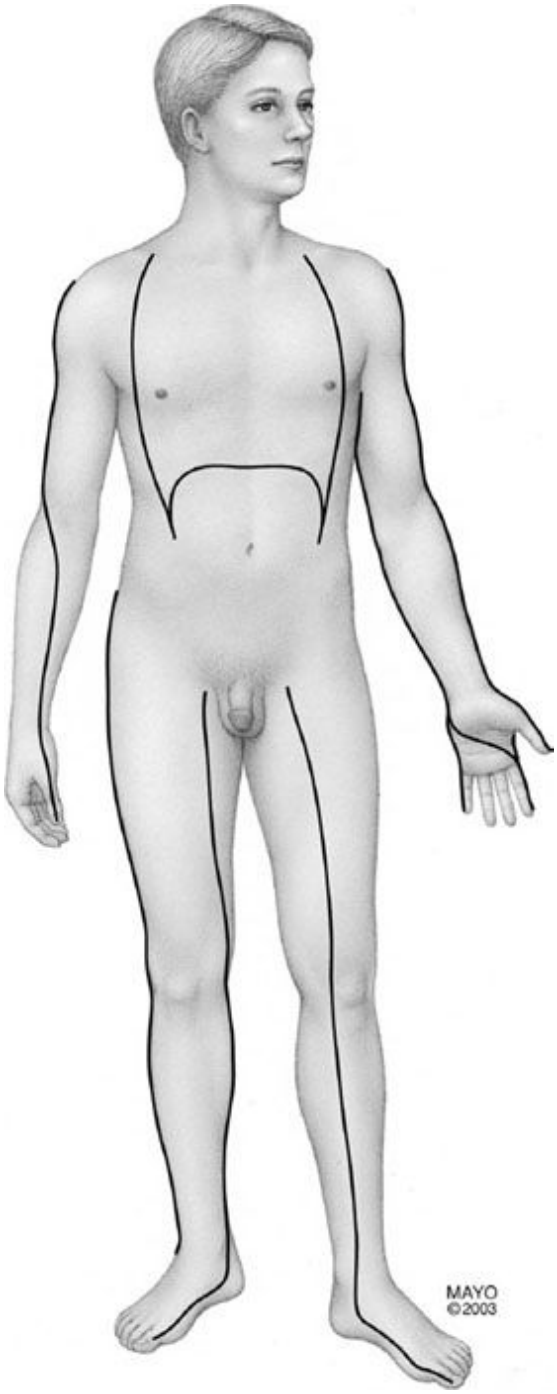
Cyanide is another product of incomplete combustion that may be inhaled by house fire victims. Isolated cyanide-related fatalities are rare and tend to be associated with high carboxyhemoglobin levels. Furthermore, laboratory confirmation of cyanide poisoning is always a retrospective event. The diagnosis must be considered and treatment administered long before definitive laboratory tests are available. Burn victims with inhalational exposures do not require specific antidotal therapy, if significant recovery has occurred before reaching medical attention. Many patients have survived cyanide poisoning with supportive care alone. Patients who exhibit persistent metabolic acidosis despite adequate fluid resuscitation, normal carbon monoxide levels, and the absence of other major injuries should be treated for cyanide toxicity (23) (see Chapters 313 and 320).

Hypothermia can contribute to coagulopathy and can result in decreased circulation to the wound and extension of a partial-

thickness burn. Hypothermia should be prevented during resuscitation. Patients who have sustained a burn >25% TBSA should have a nasogastric tube placed because they may develop gastric atony and distension that may compromise ventilation as well as an ileus. The emergency physician should update tetanus prophylaxis for all burn patients as needed.

Deep venous thrombosis has been found to occur in up to 23% of patients suffering from thermal injuries, so prophylaxis should be considered for those who are going to be immobilized (24).

Full-thickness burns create a leathery coagulum of necrotic tissues known as the eschar. If the full-thickness burn on an extremity is circumferential, the inflexible eschar and progressive edema beneath the eschar can lead to increased compartment pressures that impede venous return initially and arterial inflow ultimately. If the circumferential burn involves the chest and upper abdomen, the restriction of chest expansion and diaphragm excursion can result in respiratory compromise. If the patient is in severe respiratory distress and has sustained circumferential burns to the chest, an immediate escharotomy may be necessary. If a surgeon is not available or is delayed, emergent escharotomy may be necessary to preserve a limb or a life. Incisions should be made in the anterior axillary line connected by a third incision in the form of an inverted "V" (eFig. 46.4). An incision through the burn eschar to the underlying subcutaneous fat can be accomplished by using a scalpel or electrocautery. Bulging of the subcutaneous fat with "splitting" of the stiff eschar indicates adequate depth of incision. The escharotomy generally should be extended slightly beyond the eschar both proximally and distally to ensure adequate release. Because the eschar and underlying tissue are insensate, analgesia is not required, but sedation should be considered. Bleeding should be minimal and can be treated effectively with gentle pressure.



eFIGURE 46.4 Escharotomy sites.

Escharotomy is indicated in limbs with distal cyanosis, decreased capillary refill, decreased pulses, or progressive neurologic changes. Serial Doppler flow measurements of vessels distal to the burn are useful in deciding whether an escharotomy is adequate. Poor or

absent pulse oximetry signals from the limb may also indicate diminished or inadequate perfusion. Incisions should be made on the radial and ulnar borders of the arm and forearm and along the midaxial lines of the digits. Incisions are made on the medial and lateral borders of the lower extremities, including involved joints, with care to avoid superficial blood vessels and nerves (eFig. 46.3).

Wound Care

Patients with major wounds that require admission to a burn unit should have sterile dressings or sterile sheets placed over their wounds to decrease exposure to in-hospital multiresistant organisms. If the patient's burns are such that hospitalization is not necessary, the burns should be cleaned with water and a mild soap. Any loose or nonadherent necrotic skin should be gently removed and any large (>2 cm) or tense blisters should be aseptically aspirated with a large-bore needle. First-degree burns do not require any dressing or topical therapy. However, topical aloe vera or an NSAID my help relieve pain and inflammation (25). Second-degree burns can be treated either with once- or twice-daily applications of a topical antibacterial ointment and outer bulky dressing or one of many advanced occlusive dressings (26). Use of occlusive dressings reduces painful dressing changes and speeds healing (9). Since occlusive dressings can be left on the wound for prolonged periods (approximately 1 week) they are also cost effective. Saturated or foul smelling dressings require more frequent changes. Ideally, the dressing should absorb exudate, adhere to the wound bed, and allow easy nontraumatic removal. A silicone-based foam dressing that slowly releases small amounts of silver (which inhibits gram-positive and gram-negative bacteria as well as fungi) meets many of these requirements. When compared with the more traditional topical antimicrobial agent silver sulfadiazine (SSD), this dressing was associated with faster healing and less pain (27). Other commercial occlusive dressings are also available. While still widely used, SSD delays re-epithelialization and is not recommended (28). Full-thickness burns can be covered with a topical antimicrobial ointment and referred to a burn specialist for excision and skin grafting.

Burns to the hand represent a particular challenge. Separate dressings should be used for each finger, and the hand should be immobilized in the position of function (wrist extension, metaphalangeal flexion, interphalangeal extension) that is opposite the position assumed by the burned hand. The extremity should be elevated and joints must be exercised, particularly in the case of burns that cross joints.

Finally, patients should be cautioned that burned skin is sun sensitive for up to a year (29). Therefore, patients should limit sun exposure and when necessary use sunblock agents.

CRITICAL INTERVENTIONS

- Manage the airway immediately in unconscious patients and in those with suspected inhalation injury (stridor, increasing respiratory distress, hypoxia, or poor peak flow).
- Completely undress the burn patient to facilitate a thorough examination and halt ongoing injury.
- Administer 100% oxygen by face mask to patients with suspected carbon monoxide exposure.
- Calculate the amount of fluid needed to treat the burn shock, keeping in mind the additional fluid loss from other sources, for example, trauma and inhalation injury.
- Administer pain medication IV in small frequent aliquots, titrated to pain relief.
- As soon as the patient is stabilized, initiate transfer to a burn center when indicated.

DISPOSITION

Burns should be rechecked in 24 to 48 hours. Some EDs manage their own follow-up burn care for superficial partial-thickness burns. Patients with small deep partial-thickness or full-thickness burns should be referred to a burn-care specialist in 2 to 4 days for consideration of skin grafting and physical therapy. Hospitalization should be considered, even for minor burns, for patients who are immunocompromised, very young, elderly, or patients with poor

home situations or possible abuse. Published criteria for admission or transfer to a burn center are outlined in Table 46.1.

Common Pitfalls

- Delay in intubating a patient with a compromised airway.
- Failure to detect child abuse in suspected immersion burns.
- Failure to diagnose compartment syndrome, especially in the hand.
- Failure to calculate fluid requirements from the time of the burn injury.
- Overestimating or underestimating the size of the burn.
- Failure to assess and treat pain appropriately.

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CHAPTER 47
Replantation

James L. Larson, Jr

Advances in microsurgery have enabled surgeons to perform replantation procedures on almost all parts of the body. Viability is the only one consideration when evaluating for replantation. The most important factor is the ultimate function of the replantation. Decisions by the emergency physician can significantly impact the viability and function of the replantation.

CLINICAL PRESENTATION

The majority of replantations involve digits injured in industrial accidents (1). Cutting machines, press machines, and belts are the leaders in producing amputations. Significant causes of injury and amputation in children are bicycle chain rings and spokes, including those on stationary exercise bikes (2).

DIFFERENTIAL DIAGNOSIS

An amputated part is a completely severed part of the body, and replantation is the reattachment of an amputated part. An incomplete amputation is partially attached, but the part has lost arterial circulation. The repair of an incomplete amputation is a revascularization. Revascularization is more successful than replantation, because the venous outflow system may be intact.

ED EVALUATION

Identification and treatment of life-threatening injuries takes precedence over the evaluation for potential replantation. A

systematic approach to patients with traumatic injuries is necessary to avoid distraction from amputations (see Chapter 18, General Principles of Trauma). Serious undetected concomitant injuries have been found in patients after transfer to a tertiary care facility for replantation (3).

Indications and Contraindications for Replantation

The evaluation of a patient with an amputation or near-amputation should be expeditious. The key considerations are identifying the injuries and the potential for replantation. Amputations that are considered for replantation are listed in Table 47.1. The decision to proceed with replantation is based on potential viability and long-term function. Success rates have been reported to be 66% to 91% for digital replantations (4). A working knowledge of factors that impact success will facilitate patient care and case discussion with the surgeon.

TABLE 47.1
Replantation Candidates

Upper Extremity
Indications
Any part in a child
Thumb
Multiple digits
Palm
Wrist
Forearm
Elbow and above (sharp mechanism of injury)
Finger distal to flexor digitorum superficialis insertion
Relative Contraindications
Single digits proximal to flexor digitorum superficialis insertion
Crushed or mangled parts
Multiple level amputations
Other Replantation Candidates
Lower extremity amputation (sharp mechanism of injury)
Ear
Scalp
Lip
Nose
Penis

From Pederson WC. Replantation. *Plast Reconstr Surg.* 2001;103:823–841.

The mechanism of the amputation and resulting condition of the anatomic structures are most significant. Guillotine-like "sharp" amputations are more amenable to surgical repair than crush and avulsion mechanisms. Injuries at one level are easier to replant than multiple insults along an extremity. Children are more likely to have a good result from a replantation, and surgeons are more likely to proceed in pediatric cases (6).

There are several relative contraindications to replantation. Multiply-injured patients who require surgery or prolonged resuscitation for traumatic injuries are not candidates for a prolonged replantation procedure. Patients with complex medical problems that affect vascular integrity, immune function, and healing may be poor candidates for replantation. Patients without sufficient mental capacity or judgment to comply with postoperative

rehabilitation are unlikely to have success with replantation (5). Ultimately the decision to proceed with replantation is made by the consulting surgeon. All potential replantation cases, even those with relative contraindications, should be discussed with a replantation surgeon.

KEY TESTING

- Radiographs of the amputation
- Radiographs of the involved extremity
- These should not delay transfer

Replantation Sites

The digits of the hand are the most frequent sites of replantation. Replantation of the thumb is considered even when function of the replanted thumb is potentially limited. Even a nonfunctioning thumb is important because of its role in opposition. Single-finger replantation proximal to the insertion of the flexor digitorum superficialis (the center portion of the middle phalanx) is usually not performed because of poor functional outcomes. These patients have almost no return of flexion. In contrast, replantation of amputations at the level of the distal interphalangeal joint usually results in a good functional outcome. Fingertip replantations are now considered more frequently, because they consist of an ideal flap repair requiring only the anastomosis of an artery and a vein (7). Multiple-finger amputations are usually considered for replantation. Replantation of hand and wrist amputations results in more function than a prosthesis. Replantation of forearm, elbow, and proximal arm injuries are more successful after a sharp mechanism of injury in young healthy patients.

Replantation of lower extremity amputations is less common. Injuries to the lower extremity often result from a crushing mechanism. The large muscle mass of the lower extremity is less tolerant of ischemia (5). Children and younger adults with noncrushing injuries are the best candidates for repair. Other

amputations in which replantation should be considered include ears, lips, nose, scalp, and penis.

ED MANAGEMENT

The priorities in management of an amputation are decreasing the ongoing ischemia in the amputated part and expediting the time to the operating room for definitive repair. Hemorrhage is a frequent complication in amputations. Direct pressure is the preferred method to control bleeding. Tourniquets may be used to control hemorrhage temporarily and to facilitate evaluation of the wound. Tourniquets should not be used as the primary means of hemostasis. Prolonged use of a tourniquet can produce increased loss of function. Blind clamping or ligation should not be performed to avoid damage to vessels and nerves that may be needed for the definitive repair.

Care of the amputated part can prolong its viability and improve the success of the surgical repair. All tissues that are available should be kept. Smaller portions of skin can be used for wound coverage. The amputated part should be cleaned with normal saline solution to remove gross contaminants. Alcohol, iodine, formaldehyde, or other cleaning solutions should not be used. The amputated part should be wrapped in saline-moistened gauze and placed in a sealed plastic bag or container. The sealed bag or container with the amputated part is then placed in a water and ice bath (Figure 47.1). To avoid freezing the tissue, the amputated part should not be placed directly on ice. “Dry” ice should not be used. An amputated limb can survive 6 hours of warm ischemia and 12 hours of cold ischemia. Amputated digits can tolerate ischemia for longer periods of time (8). Incomplete amputations should be splinted to minimize further trauma and to maintain vascular integrity. Tetanus prophylaxis (0.5 mL tetanus toxoid) should be administered to patients who are more than 5 years from their last booster. Tetanus immune globulin should be given to those who have not been primarily immunized. Patients with open fractures or

contaminated wounds should receive a first-generation cephalosporin and an aminoglycoside as prophylactic antibiotics (9).

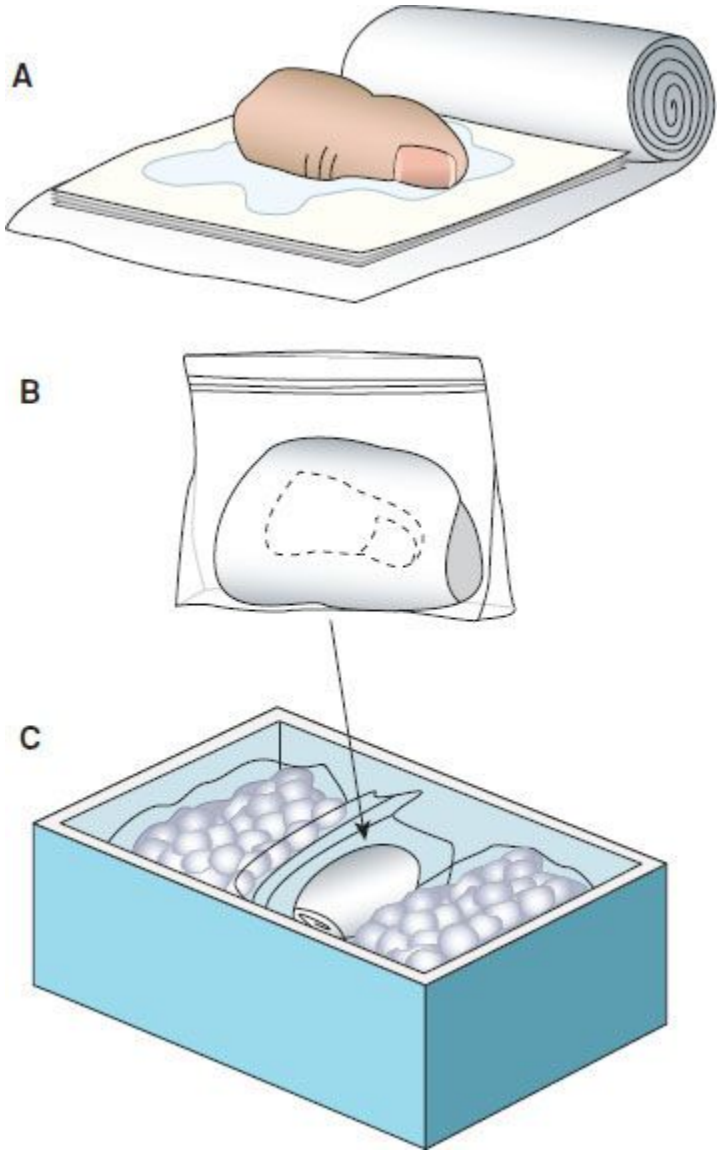

FIGURE 47.1 Replantation. The wound should be rinsed with saline solution. Do not scrub or apply antiseptic solution to the wound. The amputated part should be rinsed in saline. Do not scrub or apply antiseptic solution to the amputated part. A: Wrap the part in a saline-moistened sterile gauze or a towel, depending on the size. B: Set the wrapped part in a waterproof plastic bag or plastic container. C: Place the bagged part in an insulated container cooled by separate plastic bags containing ice or an ice water bath.

CRITICAL INTERVENTIONS

- Contact replantation surgeon early
- Control hemorrhage only with direct pressure
- Place the amputated part in a waterproof container after wrapping it in saline-soaked gauze. Place the waterproof container in an ice and water bath
- Administer tetanus toxoid and antibiotics
- Provide protection by splinting incomplete amputations

DISPOSITION

Early communication with a replantation surgeon is critical because replantation is a time-sensitive process. Having protocols in place that identify specialists and medical centers capable of performing replantations is important to expedite definitive care. One group has used mobile phones with cameras to evaluate potential replantation candidates prior to transfer (10). To avoid disappointment, the patient and family should not be told a replantation will occur. They should be told a replantation surgeon will evaluate the patient for possible replantation.

Common Pitfalls

- Failure to recognize concomitant serious injury.
- Failure to notify replantation surgeon early.
- Indiscriminant use of clamps or prolonged tourniquets to control hemorrhage.
- Failure to properly cool the amputated part.

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CHAPTER 48

Acute Compartment Syndrome

Andrew D. Perron, Christopher T. Bowe, and Christine Irish

Acute compartment syndrome is a serious life- and limb-threate-ning complication of extremity trauma. Fractures, crush injuries, burns, and arterial injuries all can result in an acute compartment syndrome. Compartment syndrome is defined as the presence of pathologically elevated intramuscular pressures within confined osseofascial compartments resulting first in tissue ischemia and ultimately infarction and subsequent contractures if not treated in a timely and appropriate manner (1). Dr. Richard Von Volkmann first described this entity in 1881; he noted the complication of muscle ischemia, paralysis, and ultimate contracture in a child with a supracondylar fracture (2,3). The various compartments in the extremities are composed of muscle groups bound by dense fascial tissue planes that result in limited ability to accommodate increased pressure. In addition to muscle, these compartments contain various nerves and blood vessels. Elevated pressure in these spaces, above normal physiologic ranges, can compromise capillary blood flow and produce predictable clinical signs and symptoms. Delays in diagnosis and treatment can result in myonecrosis, permanent nerve damage, distal ischemic injury, and muscle contracture. The exact incidence of compartment syndrome is unknown, although it is thought to be relatively rare. Three-quarters of cases are associated with fractures. Fractures of the tibia are the most likely to result in compartment syndrome; the incidence in patients with tibial fractures is reported to range from 1% to 29% (2). The most frequently involved

compartments are the anterior compartment of the lower leg and the flexor compartment in the forearm (2). Table 48.1 lists the common locations of compartment syndromes.

TABLE 48.1
Common Locations of Compartment Syndromes

Upper Limb Compartments	Lower Limb Compartments	Miscellaneous Compartments
Arm	**Buttock**	**Pelvic**
Deltoid	Gluteal	Iliacus
Biceps	**Thigh**	
Forearm	Quadriceps	
Dorsal	**Leg**	
Volar	Anterior	
Hand	Lateral	
Interosseous	Superficial posterior	
	Deep posterior	

Modified from Matsen FA. *Compartmental Syndromes*. New York, NY: Grune & Stratton; 1980.

The pathophysiology of compartment syndrome involves local hydrostatic and osmotic pressure conditions within the myofascial compartment. When the intracompartmental pressure increases above a specific level due to the above factors, perfusion to the compartment is impaired, resulting in disruption of skeletal muscle metabolic processes. Cell wall membrane integrity is compromised, leading to cytolysis with the release of osmotically active cellular contents into the extracellular compartment. This draws additional fluid from plasma into the interstitial space. The net effect is increased intracompartmental pressure and further impairment of perfusion to the closed space of the myofascial compartment as well as to distal structures in that vascular distribution. This progressively leads to compromise of circulation and nerve conduction and ultimately to irreversible damage to the contents of the compartment (4).

Normal compartment pressure is below 10 to 12 mm Hg (2). Capillary blood flow depends on the pressure gradient between the

arterial and venous systems. With elevated compartmental pressures, this gradient is interrupted, compromising the blood flow across the capillary bed. When the pressure within a compartment rises sufficiently to interrupt this arteriovenous gradient, blood flow will be reduced to the point at which the metabolic demands cannot be met. Then functional abnormalities and compartment syndrome occur (2). Two general mechanisms can result in elevated compartment pressures: Either an *extrinsic* compressive force constricts the compartment (e.g., a cast) or there is an *intrinsic* increase in the size of the fascia-bound compartment owing to edema or hemorrhage.

Clinically significant reduction of blood flow and blood oxygenation can occur at tissue pressures above 20 mm Hg (5,6). Cellular metabolic derangements are closely associated with the difference between mean arterial blood pressure and compartment pressure. This difference is known as the *delta P*. In one study, the lowest delta P that was compatible with a normal metabolic state was 30 mm Hg in normal muscle (7). The length of time that tissue can tolerate elevated pressures before pathologic changes occur is less clear. Sensory changes including paresthesias and hypesthesia can develop within 30 minutes of ischemia, whereas irreversible nerve damage begins as soon as 6 hours and almost universally after 12 to 24 hours (2).

Other factors should also be considered when assessing potential compartment syndrome. Externally applied pressure (i.e., casting) tends to produce less elevation in compartment pressures as compared to similar levels of internally developed pressures (i.e., edema or hemorrhage) (8). Postischemic compartment syndrome is caused by revascularization after a prolonged period of ischemia (2), leading to the release of vasoactive factors that result in fluid extravasation and elevated pressures. Concurrent hypotension, hypoxia, and associated premorbid conditions such as peripheral vascular disease adversely affect the ability of ischemic tissue to tolerate even mildly elevated tissue pressures.

CLINICAL PRESENTATION

Pain out of proportion to examination findings is the classically described clinical finding in acute compartment syndrome. This assumes an awake, neurologically intact patient. Unfortunately, many patients at risk for compartment syndrome are severely injured or impaired and cannot relate the degree of pain they are experiencing. When reported, the pain is often described as deep, aching, and poorly localized and does not typically respond to immobilization or analgesic medications alone. Increasing analgesic requirements may be the only clue to a developing compartment syndrome. Classically, passive stretching of involved muscles produces intense pain, as does compression of an affected compartment. Weakness or paresis of muscle function is a late finding. Distal hypesthesias or paresthesias may be noted in the distributions of nerves passing through the compartment. Two-point discrimination and light touch are considered more sensitive than pinprick when assessing sensation. Tenseness of externally palpable compartments is the earliest and most objective finding, although tenseness of compartments such as the deep posterior compartment of the lower leg and the iliacus compartment can be difficult to assess due to anatomic location. Findings of compartment syndrome can present within 2 hours of injury but may first appear up to 6 days later (2). Progressive worsening over time helps to distinguish compartment syndrome from other injuries that cause primary nerve and muscle damage.

Griffith's mnemonic, the *five Ps* (*p*ain, *p*allor, *p*ulselessness, *p*aresthesias/*p*aresis, and poikolothermia), is traditionally used for this clinical entity. However, pulses are most often maintained, and the skin does not typically develop pallor (1). The presence of all five of these signs more accurately reflects the *late* findings of acute arterial obstruction or insufficiency. As noted previously, the reliance on the clinical examination makes it difficult to assess emergency department (ED) patients with altered sensorium, acute intoxication, spinal cord injuries, or overlying extensive burns, as well as children. Moreover, obtunded patients are often at risk for compartment syndrome by compression, entrapment, or unknown mechanisms of trauma. Overdose-related compartment syndromes tend to affect the

lower extremities (9,10). Critically ill pediatric and adult patients may experience iatrogenic causes of compartment syndrome produced by intravenous and intraosseous infiltrations, transfusions under pressure, or tourniquet malfunction. Table 48.2 lists common etiologies of compartment syndrome. Owing to dense eschar, severely burned patients lose most, if not all, clinical signs of compartment syndrome. In these more complex cases, the clinician should have a lower threshold for using invasive monitoring.

TABLE 48.2
Common Etiologies of Compartment Syndromes Seen in Emergency Medicine

Increased compartment content
Infiltrated infusion
Bleeding
Vascular injury
Coagulation defect
Increased capillary permeability
Reperfusion after ischemia
Trauma
Fracture
Contusion
Intensive use of muscles
Exercise
Seizures
Eclampsia
Tetany
Burns
Cold
Snakebite
Increased capillary pressure
Venous obstruction
Diminished serum osmolarity
Nephrotic syndrome
Externally Applied Pressure
Casts, dressings, splints, pneumatic garment
Lying on limb

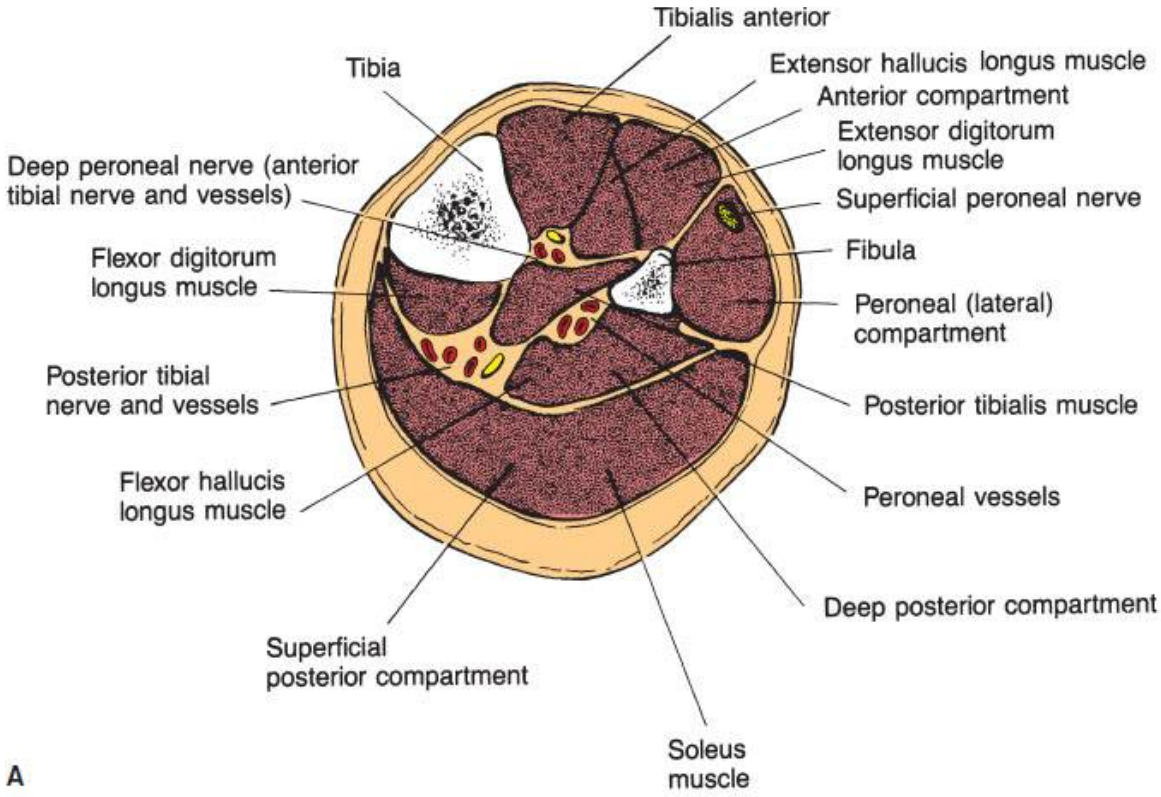
From Matsen FA. *Compartmental Syndromes*. New York, NY: Grune & Stratton; 1980, with permission.

The clinical findings for specific anatomic compartments are summarized in Table 48.3. Figure 48.1 illustrates the anatomy for the two most common sites. The three most common etiologies of an acute compartment syndrome are fractures, crush injury, and reperfusion of an ischemic limb. The lower leg and forearm have relatively "tight" compartments and are the most common sites for developing compartment syndrome. In the pediatric population, fractures are the most common cause, specifically supracondylar fractures. Open fractures are *not* protective against compartment syndrome, as the tear in the fascia is usually quite small and does not allow decompression of the compartment when pressure is elevated. Overall, the most common fracture etiologies for compartment syndrome include tibial shaft, supracondylar, and forearm fractures (7).

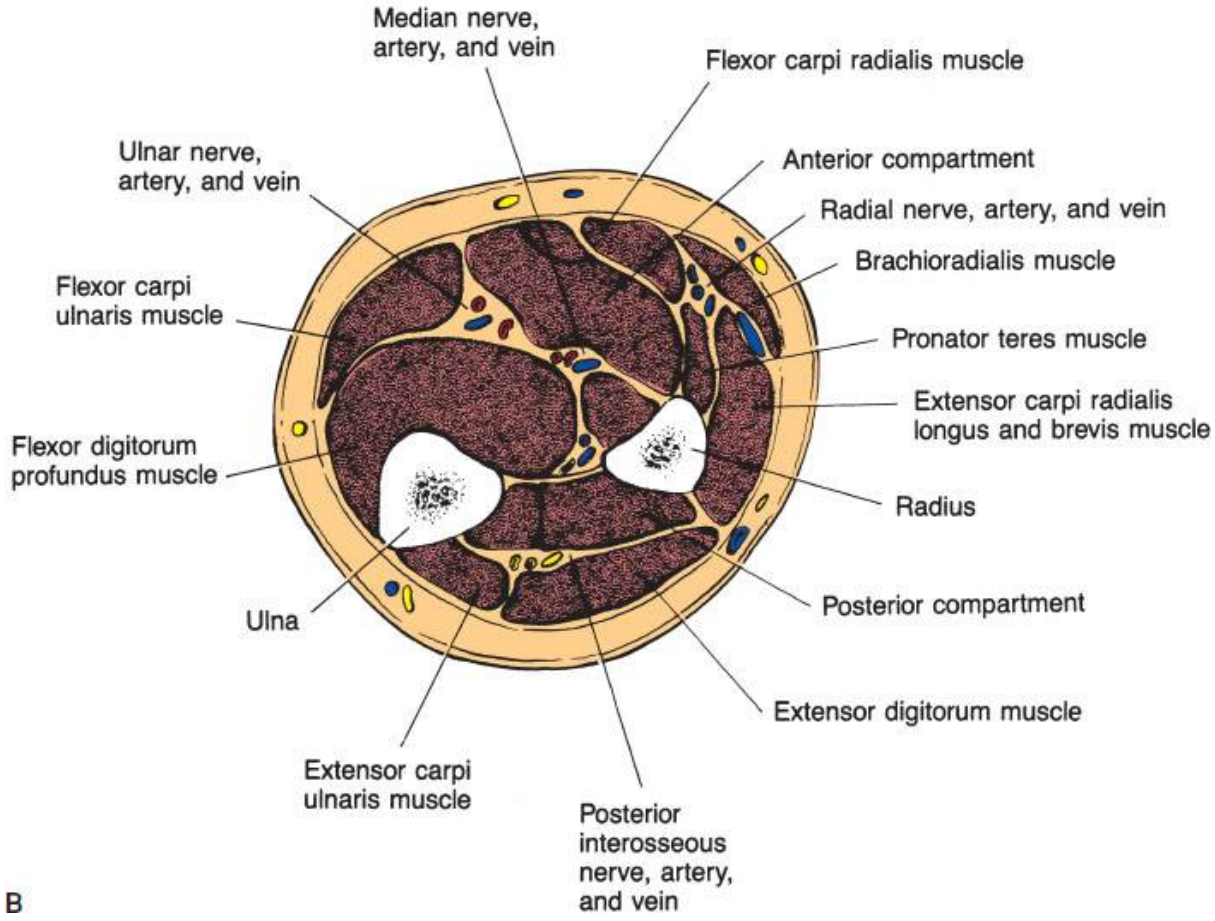
TABLE 48.3
Compartment Syndromes and Associated Physical Signs

Compartment	Painful Passive Movement	Location of Tenseness	Muscles Weakened	Sensory Loss
Forearm				
Dorsal	Thumb and finger flexion	Dorsal forearm	Thumb and finger extensors	—
	Thumb and finger extension	Volar forearm	Thumb and finger flexors	Ulnar and median nerves
Hand				
Interosseous	Adduction, abduction of metacarpophalangeal joints	Dorsum of hand between metacarpals	Interosseous	—
Leg				
Anterior	Toe flexion	Anterior aspect of leg	Toe extensors and tibialis anterior	Deep peroneal nerve
Lateral	Foot inversion	Lateral aspect of leg over fibula	Peroneal muscles	Superficial and deep peroneal nerves
Superficial posterior	Foot dorsiflexion	Calf	Soleus and gastrocnemius	—
Deep posterior	Toe extension	Distal medial leg between Achilles tendon and tibia	Toe flexors and tibialis posterior	Posterior tibial nerve
Pelvic				
Iliacus	Hip extension	Not palpable	Iliacus, psoas major and psoas minor	Femoral nerve

Modified from Matsen FA. Compartmental syndromes. *Clin Orthop*. 1975;113:8.


Tibialis anterior
Tibia
Extensor hallucis longus muscle
Anterior compartment
Extensor digitorum longus muscle
Deep peroneal nerve (anterior tibial nerve and vessels)
Superficial peroneal nerve
Fibula
Flexor digitorum longus muscle
Peroneal (lateral) compartment
Posterior tibial nerve and vessels
Posterior tibialis muscle
Flexor hallucis longus muscle
Peroneal vessels
Deep posterior compartment
Superficial posterior compartment
Soleus muscle

A


Median nerve, artery, and vein
Flexor carpi radialis muscle
Ulnar nerve, artery, and vein
Anterior compartment
Radial nerve, artery, and vein
Brachioradialis muscle
Flexor carpi ulnaris muscle
Pronator teres muscle
Extensor carpi radialis longus and brevis muscle
Flexor digitorum profundus muscle
Radius
Posterior compartment
Ulna
Extensor digitorum muscle
Extensor carpi ulnaris muscle
Posterior interosseous nerve, artery, and vein

B

FIGURE 48.1 Compartments of the leg (A) and forearm (B).

DIFFERENTIAL DIAGNOSIS

Differential diagnostic considerations include deep vein thrombosis, necrotizing fasciitis, arterial embolus or insufficiency, gas gangrene, myositis, and rhabdomyolysis.

ED EVALUATION

Laboratory and radiologic studies cannot confirm or rule out the diagnosis of compartment syndrome but may help in assessing for other etiologies and secondary complications such as rhabdomyolysis. Significant elevation of serum creatinine phosphokinase may indicate severe muscle damage or ischemia but is not helpful for early diagnosis (2). The critical diagnostic test for compartment syndrome is the direct measurement of intracompartmental pressures. This is especially important in those patients who are unreliable because of distracting injury or altered sensorium. These direct tissue measurements can also be used to provide ongoing monitoring in patients who are at high risk for development of a compartment syndrome, as in the case of a crush injury. Various pressure measurement techniques have been described, such as the central venous pressure manometer, the wick catheter, the slit catheter, and the portable Stryker handheld monitor. Experimental noninvasive methods of compartment pressure measurement have been described but are not in widespread clinical use currently. These include near-infrared spectroscopy, which measures the levels of muscle hemoglobin and myoglobin; laser Doppler flowmetry; and 99Tcm-methoxyisobutyl scintigraphy (2). The direct measurement techniques all provide acceptable accuracy, although the self-assembled needle manometer has been shown to be the least accurate and least reproducible (2). Most compartments are superficial, but access to deeper ones such as the gluteal and deep posterior compartments may require a spinal needle.

Whatever the method employed, once the compartment pressure has been obtained, there is ongoing debate over which pressure levels warrant a fasciotomy. Absolute pressures of >30 mm Hg have been suggested as an indication for fasciotomy. Alternatively, a "delta P" (the difference between the diastolic pressure and the compartment pressure) of <30 mm Hg has been suggested as being more specific for the requirement of a fasciotomy (2,7). These pressure measurements must be assessed in the context of hypotension, anemia, hypoxia, or other factors that would increase the tissue sensitivity for ischemia at less elevated pressures. Nerve conduction studies and arteriography are used primarily to distinguish primary nerve and arterial injuries and not useful in the acute diagnosis of compartment syndrome.

It should be noted that pulse oximetry has been advocated as a simple, noninvasive indicator of vascular compromise. This is *not* true. Clinical studies using pulse oximetry have shown a sensitivity of 40% for vascular compromise at clinically significant elevated compartment pressures (11). With a >50% risk of a false-negative result, pulse oximetry is not recommended in the evaluation of this disease process.

KEY TESTING

Compartment pressure measurement:

- If elevated compartment pressure is suspected, pressure testing is strongly suggested (unless there is clear evidence of compromise, in which case operative fasciotomy may occur by the surgeon without taking the time to assess intracompartmental pressures).
- Many techniques are described (wick, slit catheter, Stryker). The Stryker pressure manometer is a self-contained unit that assesses intracompartmental pressure using a needle and a calibrated digital readout. Knowledge of both the anatomic layout of the fascial compartments as well as the mechanics of the manometer itself is required for accurate use.
- Absolute compartment pressures >30 mm Hg/delta-P <30 mm Hg are generally used cutoffs as indications for fasciotomy. Normal compartment pressure is <10 mm Hg.

ED MANAGEMENT

The key to management of ED patients with compartment syndrome is early consideration and diagnosis. Surgical fasciotomy is the definitive treatment and surgical consultation should be initiated early. Surgical decompression should ideally be performed emergently, as soon as possible after the diagnosis is made (2,7). Supportive care is aimed at resuscitation and stabilization of the patient and preparation for appropriate operative intervention.

In patients who are suspected of having compartment syndrome owing to casts, bivalving and spreading of the cast may be necessary and can produce an almost 65% reduction in applied external pressures while maintaining alignment (12). Complete removal of the cast can further reduce pressure by up to 85% (4). Elevation of an extremity at risk to the level of the heart is recommended, as this promotes venous drainage without compromising arterial inflow (4). Ice should be avoided, as it can further compromise microvascular blood flow. The emergency physician should remove aggravating factors specific to the involved extremity, such as MAST suits or pneumatic splints, and treat systemic factors such as hypotension, anemia, and hypoxia.

CRITICAL INTERVENTIONS

- Measure intracompartmental pressures.
- Initiate surgical consultation early.
- Elevate the involved extremity to the level of the heart in the least restrictive dressing possible.

DISPOSITION

Patients with suspected compartment syndrome require emergent surgical or orthopedic consultation. Patients are typically admitted for observation and repeated clinical examinations and pressure measurements if they do not undergo immediate surgical intervention. Patients with multiple trauma may require intensive care unit admission for management of other associated injuries.

Common Pitfalls

- Failure to consider the diagnosis of compartment syndrome.
- Failure to recognize early signs and symptoms of compartment syndrome.
- Attributing the signs and symptoms of compartment syndrome to other types of injuries.
- Failure to do a thorough extremity and neurologic examination, especially in patients who are intoxicated or unreliable.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of John A. Siefert to the content of this chapter.

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CHAPTER 49

Ballistics

Jason Imperato and Leon D. Sanchez

Ballistics is the scientific study of the characteristics of projectiles, how they move in flight, and how they impart tissue damage. The majority of projectiles that cause significant injury in the United States are in the form of firearm injuries. According to 2011 data, there were 32,163 deaths involving firearms with even higher numbers involving serious injury (1). These injuries can be classified as violence related, accidental, or self-inflicted.

Ballistic science is typically divided into three stages: internal, external, and terminal (or wound) ballistics. *Internal* ballistics describes the forces that apply to a projectile from the time the propellant is ignited to the time the projectile leaves the barrel. *External* ballistics refers to the forces that act on the bullet in flight. *Terminal* ballistics is the behavior of the bullet once it impacts the target (2).

A firearm is a weapon designed to expel a projectile by the action of highly combustible, gas-generating gunpowder. Firearms are generally classified as handguns (i.e., pistols and revolvers), rifles, and shotguns. Most rifled firearms (i.e., handgun or rifle) have barrels with internal grooves, referred to as *rifling,* that impart spin to the bullet, enhancing inflight stability and accuracy. When the cartridge is fired, the burning of the powder generates gas in a contained space and the pressure generated by the gas propels the bullet forward. The bullet accelerates while inside the barrel and reaches its maximum speed, or muzzle velocity, upon exit.

Bullets are rotated around their long axes by the rifling of the barrel, which, once in the air, gives them sufficient gyroscopic

stability to maintain the point-forward position while in flight. Without gyroscopic stabilization, bullets would preferentially travel in the more stable *base-forward* orientation where the greater mass of the bullet is. Bullets fired from a properly designed rifled barrel *yaw* no more than a few degrees during flight. The yaw angle is the angle between the long axis of the bullet and the line of flight. This angle is greatest as the bullet exits the barrel and is reduced as the gyroscopic spin stabilizes the bullet's flight through the air.

Once a bullet enters a denser medium, the gyroscopic spin is insufficient to stabilize the bullet. As a result, when a bullet enters tissue, it will begin to tumble and deform. Depending on the makeup of the bullet and the properties of the tissue through which it travels, it may expand, fragment, or remain in one piece (3–13).

Bullet mass, which is related to the diameter and length of the bullet, is a major determinant of how deeply the bullet will penetrate the tissue. Bullet construction, such as whether the bullet is solid lead with no bullet jacket, is partially jacketed, or has a full metal jacket, is a primary determinant of how the bullet will deform or fragment once in tissue. The majority of bullets in use today are at least partially jacketed. The jacket is a layer of hard metal that surrounds what is typically a lead core. Without a jacket, lead bullets fired at speeds of >600 m/s would have some of the lead stripped by the rifling of the barrel (5). Jacketing allows bullets to reach greater muzzle velocities. Though military bullets are fully jacketed (14), civilian bullets usually have the lead core exposed at the tip (soft point). The tip is often further modified into different varieties of hollow-point bullets. The exposure of lead at the tip will cause the softer lead to deform much more than a fully jacketed bullet upon entry into tissue. These hollow-point bullets are designed to expand and deform as they penetrate tissue. A soft- or hollow-point bullet will deform earlier in its travel through tissue than a comparable fully jacketed projectile. As a result, the injury patterns will be different, although the claims that soft- or hollow-point bullets cause more tissue destruction are not consistently borne out.

Shotguns differ from rifles and pistols in that they have a smooth barrel that discharges hot gases, wad, and either multiple projectiles or a single projectile (rifled slug). Shot charges containing multiple projectiles spread out from the muzzle in a cone-like pattern. The distance from the muzzle of the shotgun to the point of impact of the projectiles is a key determinant of the magnitude of injury. At short range (<6 m), the shot charge containing multiple projectiles results predominantly in a single-hole wound (diameter ≤ 6 cm) that communicates with a deep underlying wound with massive tissue destruction. At this short range, soft tissue impact deforms the individual pellets, increasing their original cross section with a concomitant increase in tissue crush or hole size. The multiple pellets result in severe disruption between the multiple wound channels. A gradual decrease in the amount of pellet deformation and tissue destruction occurs as the distance of the impact range increases. When the impact range exceeds 7 m, the multiple projectiles result in numerous discrete wounds that are not associated with underlying massive tissue destruction (5).

Shotguns also can discharge rifled slugs that are designed for killing larger animals. The muzzle velocity of rifled slugs (487 m/s) is approximately half that of nonexpanding, fully jacketed rifle projectiles. The rifled slug does not hold the point orientation that it has as it is propelled from the muzzle of the gun but drifts toward a sideways orientation as it moves toward the target. The rifled slugs experience a 25% decrease in velocity as the impact range increases from 5 to 45 m. At short range (≤ 45 m), the slug deforms on striking the tissue, thereby enhancing the size of the cavity.

CLINICAL PRESENTATION

The nature of a projectile wound is dependent on both missile and tissue characteristics. As discussed earlier, missile characteristics are partly inherent and partly conferred by the weapon firing the projectile. Tissue characteristics also strongly affect the nature of the wound.

Tissue is injured by a bullet via two mechanisms: tissue crush and tissue stretch. These two mechanisms correspond to the permanent and temporary cavities created by the passage of the projectile through the tissue (6–9). As the bullet travels through tissue, it will crush tissue that is directly in its path. This is the primary method of injury from gunshot wounds. The most important determinant of injury is the properties of the tissue that the bullet crushes. The tissue that is crushed corresponds to the permanent cavity formed by the bullet. If the bullet is traveling with its pointed end forward and its long axis parallel to the longitudinal axis of flight (0 degrees of yaw), it crushes a tube of tissue approximately equal to its diameter. When the bullet yaws to 90 degrees, the entire long axis of the bullet strikes the tissue, amplifying the amount of tissue crushed.

Passage of the projectile at a high rate of speed also displaces other tissue away from the path of the projectile. As the tissue stretches away from the path of the projectile, a temporary cavity that exists for a brief time (measured in milliseconds) is formed. The temporary cavity is comparable to the splash formed by throwing a stone into a pool of water. By definition, no tissue is present in the temporary cavity. The stretch of tissue away from the temporary cavity can injure tissue to different degrees depending on the tissue elasticity defined as the resistance of tissue to stretch. The same stretch that causes moderate contusion and functional changes in the relatively elastic muscle, skin, lung, and bowel wall can cause catastrophic disruption of the inelastic liver, heart, and brain. Muscle, skin, and lung are flexible and elastic, having the physical characteristics of good energy absorbers. Though temporary cavitation stretches these tissues, their elastic properties allow them to maintain their structure and function. For example, muscle, when disrupted, will have an area of devitalized nonfunctioning tissue surrounding the permanent cavity whereas tissue farther away, which was stretched by the temporary cavity, is still structurally sound and maintains its contractile function. In comparison, the inelastic liver is fractured and rendered nonviable to a much greater degree by the temporary cavity (15). The brain is a special case of

inelastic tissue. Not only is brain tissue very sensitive to structural disruption but this is magnified by the fact that the brain is encased in a solid container (the skull) that prevents tissue displacement. As a bullet penetrates the skull, temporary cavitation will increase pressure within the skull, and this pressure will be relieved either through the entrance or exit wound.

The size of the temporary cavity depends on the energy of the projectile, the surface area the projectile presents to the tissue as it moves through it, and the mass of tissue displaced. As the bullet tumbles through tissue from the point-forward orientation to the final base-forward orientation, it will present its greatest surface area at 90 degrees of rotation. It is at this point where maximal tissue displacement will occur and the size of the temporary cavity is greatest.

These permanent and temporary cavities are the sole wounding mechanisms of missiles. The sonic shock wave generated by supersonic missiles does not cause either tissue displacement or detectable damage. Projectile fragmentation can greatly enhance the effects of the temporary cavity by providing points of weakness on which the stretching effects of cavitation are focused, rather than being absorbed evenly by the tissue mass. Fragmentation can refer to the projectile's forming multiple parts or to secondary fragments such as clothing, bone, or teeth that develop from being struck by the projectile.

ED EVALUATION

Gunshot injuries frequently do not occur in isolation. As a result, the emergency physician must evaluate the patient for not only the penetrating injury resulting from the gunshot wound but the blunt injury that may result from the victim's falling to the ground after being struck by the projectile.

The initial evaluation of the gunshot victim is similar to that of any multiple trauma patient and should focus on rapidly identifying life-threatening conditions. Patients should be evaluated by the Advanced Trauma Life Support (ATLS) Guidelines (14). This

includes an assessment of the primary survey (airway, breathing, circulation, disability) with rapid attention to immediately life-threatening injuries, followed by the secondary survey, ongoing monitoring of vital signs and pulse oximetry, and initial stabilizing interventions as indicated.

A careful history is important in obtaining useful information about the number and types of injuries sustained. Patients who are awake should be asked how many shots they heard and any other information they have relating to the event such as their distance from the weapon and the type of weapon utilized.

The physical examination should focus on the detection of penetrating or perforating injuries. A careful examination of the patient including the back, under the hair, axillae, and gluteal folds will help identify injuries. The location of the external wounds may suggest a track for the projectile, but the physical examination is generally not sufficient to determine the direction and extent of the penetrating projectiles due to the cavitation effects of the projectile through body tissues. Penetrating projectiles may ricochet off of bony structures altering the trajectory of the permanent cavity produced. A small external wound may belie massive internal injuries that are not immediately evident on examination (4). The identification of an initial wound should not negate the need for a complete survey of the patient to avoid missing other injuries.

Radiographs of the areas the bullet is thought to have traversed are indicated to identify the position of the projectiles. It is best to obtain at least two radiographs in planes separated by 90 degrees to determine a more accurate position. If the patient is clinically stable, a computed tomography (CT) scan may aid in the assessment. Laboratory studies should be ordered as clinically indicated and guided by ATLS Guidelines. The evaluation and management of injuries is best conducted in conjunction with a trauma surgeon and should follow the algorithms presented in previous chapters. (See Chapters 18, 32, 34, and 36.)

Gunshot wounds must be reported to the appropriate authorities. In most cases, shootings become the subject of a criminal investigation by law enforcement authorities. Therefore, the medical

record and patient property should be preserved as evidence. If a patient's clothing is cut, care should be taken to avoid cutting through the portions a bullet might have traversed. Any material that needs to be saved for law enforcement should be placed in paper bags, as plastic bags will trap moisture and thereby degrade evidence.

The location of all wounds identified should be recorded in the medical record, including comments on the presence of any powder residue observed surrounding the wound. It is often difficult to differentiate entrance from exit wounds. Although it is often thought that the smaller wound must be the entrance wound, this is not always true. It is best to record the size and location of the wounds, rather than using the terms *entrance* and *exit*. If a bullet is recovered, the emergency physician should avoid making any markings on the sides of the bullet because this will interfere with the forensic evaluation of rifling patterns (5). Any marking of recovered bullets that may be necessary for the preservation of chain of custody should therefore be done at the nose or base.

KEY TESTING

- Complete blood count, blood gas, serum electrolytes, renal function, liver function tests, lactic acid, and urinalysis
- Type and crossmatch for blood products
- FAST scan
- Radiographs to identify path and position of projectile
- CT—as indicated

ED MANAGEMENT

The evaluation, resuscitation, and ongoing management of the patient with a gunshot wound should proceed as it would for any other victim of multiple trauma in both the prehospital setting and the emergency department (ED). For prehospital personnel, it is important that the scene be secured and declared safe before approaching the victims (11). The treatment of gunshot wounds is best conducted in consultation with a trauma surgeon. If resources

are unavailable, the decision to transfer the patient should be made early in the course of treatment.

Wounds that may have crossed the mediastinum require a thorough evaluation, even in stable patients. Potential injury to the aorta, heart, pericardium, lungs, great vessels, tracheobronchial tree, and esophagus must be ruled out. Rapid reversal of hypoxia is often necessary, with supplemental oxygen and airway control, if the patient is unable to protect their own airway or respiratory distress is present. Patients who present with unstable vital signs or who become unstable during evaluation should receive bilateral chest tubes to treat pneumothorax, hemothorax, or hemopneumothorax. Bedside ultrasound should be used to identify the presence of pericardial tamponade. If present, pericardiocentesis and ED thoracotomy may be necessary. Surgical exploration is often indicated in these patients (1,10). See Chapter 32.

Patients with penetrating gunshot wounds to the abdomen usually require an exploratory laparotomy, even in the presence of stable vital signs. A focused assessment with sonography in trauma (FAST) examination may be helpful in the early detection of hemoperitoneum. Patients with back or flank wounds can be evaluated by CT and observation, as long as they maintain stable vital signs. These patients may also benefit from surgical exploration. This decision must be made in conjunction with the trauma surgeon. See Chapter 34.

Injuries to the extremities require evaluation of the distal neurovascular status. A bullet does not need to transect a vessel to cause injury. The development of compartment syndrome as swelling of the injured area develops should be considered. If arterial injury is suspected, angiography is indicated. Fractures from a gunshot wound should be treated as open fracture, and early antibiotics should be administered. Debridement of devitalized soft tissue is often necessary (12,13).

Gunshot wounds to the head are often not survivable. For patients with this type of injury who arrive at the hospital alive, consultation with a neurosurgeon is indicated. Injuries to the spine can occur even when the bullet does not actually pass through the vertebral

canal, as temporary cavitation can damage the cord without the presence of crushed tissue. The use of steroids is not indicated for penetrating cord injuries. The presence of a CNS injury should not delay the assessment for thoracoabdominal injuries, which can be rapidly fatal.

CRITICAL INTERVENTIONS

- Carefully examine the back, scalp, axillae, and gluteal folds for wounds in patients with penetrating trauma.
- Obtain trauma surgery consultation early in the management of patients with gunshot wounds.
- Report gunshot wounds to the appropriate authorities.

All penetrating injuries should be considered highly contaminated. As a result, adequate wound irrigation, prophylactic antibiotics and tetanus vaccination should be addressed. See Chapter 21.

DISPOSITION

Gunshot victims are ideally managed in conjunction with a trauma surgeon. Those patients with significant suspected injury generally require emergent operative intervention and close inpatient monitoring often in the critical care setting. Those patients who do not need immediate operative intervention can be managed more conservatively. Because it is often difficult to assess the full extent of injury from a gunshot wound, a prolonged observation of 12 to 24 hours is often required.

If a trauma surgeon is not available at the receiving hospital, transfer to a regional trauma center must be considered early in the course of treatment. Prior to transfer, stabilizing interventions may be necessary and can include endotracheal intubation, mechanical ventilation, tube thoracostomy, and volume resuscitation.

Common Pitfalls

- Failure to identify all wounds. All patients with suspected gunshot wounds must be completely undressed and carefully examined, as small skin wounds can be difficult to identify
- Failure to transfer gunshot victims to another facility promptly when a qualified trauma surgeon is not available
- Delaying the evaluation for thoracoabdominal injuries in stable patients with gunshot wounds
- Failure to notify the proper law enforcement authorities after a gunshot injury

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CHAPTER 50 Blast Injuries

David W. Callaway and Leon D. Sanchez

During the period from 1996 to 2006 global terrorism-related bombings have increased fourfold with associated injuries increasing nearly eightfold (1). In the United States alone, there were over 36,000 explosion-related events and greater than 5,900 injuries from 1983 to 2002 (2). The extent of blast-related trauma is determined by a complex interaction of the physical components of the explosive device (e.g., size, explosive choice, delivery system, and adulterants), the environment (e.g., open versus confined space, distance from blast, reflecting surfaces, structural collapse, or medium in which the blast is transmitted), and intrinsic host factors such as age and comorbidities (3).

Conventional explosives are categorized as either *high-order* or *low-order*. High-order explosives (HE), such as TNT, Semtex, and dynamite produce a supersonic overpressure shock wave that results in rapid transient increases in ambient pressure (peak overpressure). This shock wave causes rapid external loading on the body, especially at points of air–tissue interface and is responsible for primary blast injuries (PBIs). High-order explosive detonations also result in secondary, tertiary, and quaternary blast injuries (Table 50.1). In contrast, low-order explosives (LE), such as pipe bombs and petroleum-based bombs result in subsonic explosions without resulting peak overpressure.

In HE detonations, the blast wave is composed of three components: the positive phase, the negative phase, and subsequent blast wind. During the *positive* phase, the blast wave expands radially at the speed of sound, causing a sudden increase in the ambient

pressure (peak overpressure). This peak overpressure is responsible for PBIs. The biologic effect of the PBI depends directly on the level of peak overpressure and the duration of this positive phase. In the following *negative* phase, pressure drops below ambient levels, creating a vacuum and subsequent blast wind. The *blast wind* generates projectiles and can throw victims, resulting in secondary and tertiary blast injuries.

Blast wave propagation depends on the medium in which the explosion is detonated. As the shock wave expands, the overpressure decreases, and the velocity of propagation diminishes. In open air, the peak pressure of the shock wave falls off as the inverse of the distance from the explosion to the third power. In denser media, such as water, explosions produce shock waves that have a much higher peak overpressure and a faster rate of propagation than comparable explosions in air (1). The compressive shock wave results in greater blast loading on the victim and more severe injuries. The shock waves reflect off the surface of the water, creating tension waves that interact with the blast wave and diminish wave propagation. As a result, the overpressure effects increase with depth of submersion. Explosions within confined spaces are subject to reflection and magnification of the blast wave, leading to greater overpressure, longer positive phase duration, and an increased incidence of PBIs and death (Fig. 50.1).

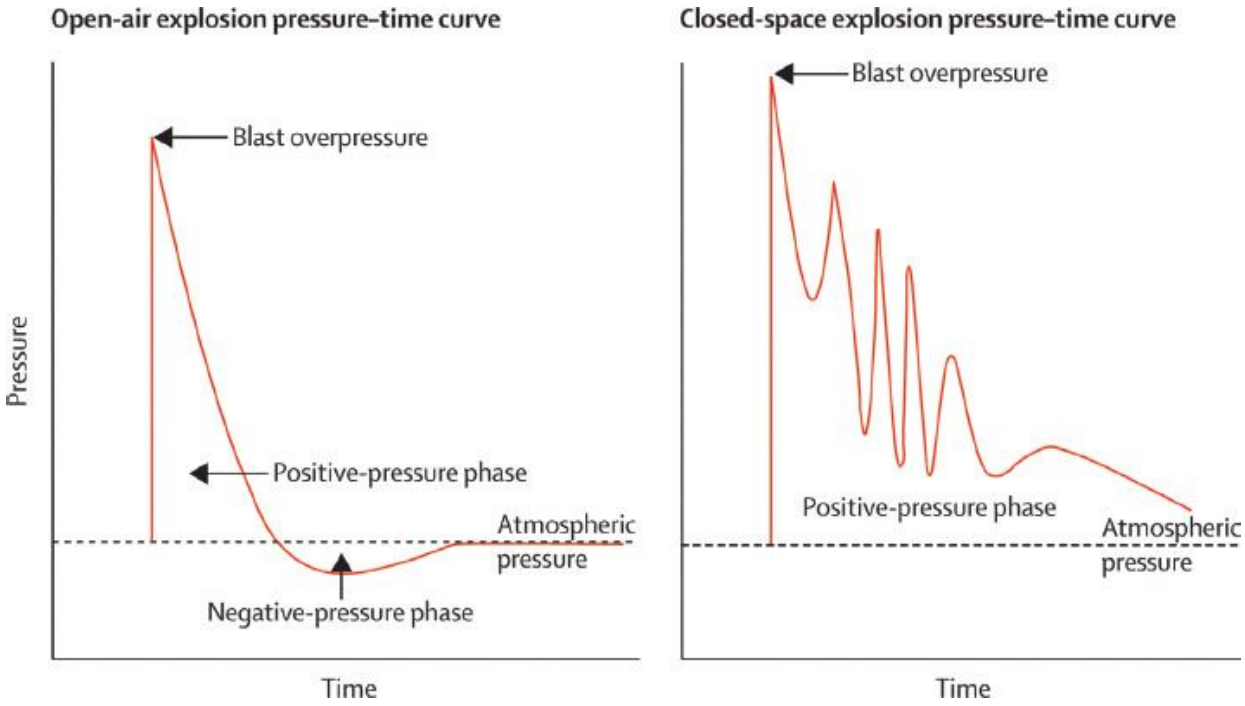

FIGURE 50.1 Difference in pressure curves between open- and closed spaces. (From Wolf SJ, Bebarta VS, Bonnett CJ, et al. Blast injuries. Lancet. 2009;374(9687):405–415.)

CLINICAL PRESENTATION

Blast injuries are classified into four categories: primary, secondary, tertiary, and quaternary (Table 50.1). PBI is unique to HE explosions. As the shock wave passes through biologic tissue, the injury is greatest at the interface between tissues of different densities, such as the lungs, the tympanic membrane (TM), and the bowel. The organ most vulnerable to PBI is the TM, followed by the lungs (4–8). The incidence of PBI in open space explosions is 10%, as compared to 38% in confined spaces (9). PBI is relatively uncommon in *survivors* of major explosive attacks. Many victims with PBI are very close to the source of the explosion and succumb to secondary and tertiary injuries prior to receiving medical care.

TABLE 50.1
Mechanisms of High-Order Explosive Blast Injury

Category	Characteristics	Affected Body Region	Types of Injuries
Primary (high-order explosives)	Impact of blast wave (overpressure) with body surface	Gas-filled structures and areas of air–fluid interface (e.g., lungs, middle ear, and intestines)	• Blast lung injury • TM rupture • Middle ear damage • Abdominal perforation/hemorrhage • Globe rupture • Concussion
Secondary	Result of flying debris/bomb fragments	Any body region	• Penetrating or blunt injuries (may be occult)
Tertiary	Result of individual being thrown by blast wind or structural collapse	Any body region, especially extremities	• Fractures • Traumatic amputations • Crush injuries • Closed- and open-head injuries
Quaternary	All other explosion-related injuries or illnesses (including exacerbation of pre-existing conditions)	Any body region	• Burns (chemical, electric, scalds) • Crush injuries • Angina/AMI • COPD, asthma • Asphyxiation (carbon monoxide or cyanide)

Modified from Almogy G, Mintz Y, Zamir G, et al. Suicide bombing attacks: Can external signs predict internal injuries? *Ann Surg.* 2006; 243(4):541–546.

Secondary blast injury (SBI) predominates in victims presenting to emergency departments (EDs) (10). In SBI, the blast wave can propel objects, either intrinsic (e.g., shrapnel) or extrinsic (e.g., components of the target such as metal from a bus door) to the device that result in both blunt and penetrating trauma. The effective range of injury in SBI is greater than for PBI. *Tertiary blast injuries* are a result of the victims being thrown by the blast wind or by subsequent structural collapse. *Quaternary blast injuries* comprise a broad range of blast-related injuries that include burns, toxic inhalations (e.g., cyanide or carbon monoxide), asphyxiation, particulate inhalation, and exacerbation of pre-existing conditions. Quaternary blast injuries are common in industrial explosions.

An overwhelming majority (80% to 90%) of blast survivors present to the ED with non–life-threatening secondary, tertiary, and quaternary injuries (11,12). Soft tissue injuries (burns, abrasions, and embedded foreign bodies) are by far the most common injuries from terrorist bombings. Nine percent to 22% of victims will present with critical injuries (13). Studies of terrorist bombing incidents reveal

that 50% of surviving casualties present to treatment facilities within the first hour (8,10). In general, there is a biphasic presentation, with more critically ill patients presenting in the “second wave” (8,11).

The TM is the structure most sensitive to peak overpressure and most commonly injured in blast victims, seen in up to 9% to 47% of blast survivors with significant injuries (14,15). Depending upon the orientation of the victim to the blast, increases in ambient pressure of 2 to 5 psi can result in rupture of the TM. The most common PBI is a linear tear in the inferior portion (pars tensa) of the TM. With increases in overpressure, the blast wave may also result in damage to the cochlea or ossicle dislocation (resulting in sensorineural hearing loss and tinnitus) (16). There is debate about the correlation between TM rupture and more life-threatening PBI. Isolated TM rupture does not appear to predict serious PBI reliably and with sufficient sensitivity (17,18,19). There is increasing evidence that suggests TM rupture as a predictor of significant concussive closed head injury.

The lung is the second most commonly affected organ in PBI. The threshold for lung damage is approximately 15 psi of peak overpressure, with moderate to severe lung damage observed with 50 psi (4). The advancing blast wave creates a pressure differential across the alveolar–capillary interface that results in damage to the lung parenchyma. Blast lung injury (BLI) is a unique injury defined by diffuse lung contusions, pulmonary edema, and occasionally pneumothorax or hemothorax. BLI is the most common fatal PBI among initial survivors.

The blast wave can also cause diffused parenchymal lacerations and can create fistulas between the alveolar spaces and the pulmonary veins. Venoalveolar fistulas allow air into the pulmonary venous system, which can then travel to the left side of the heart and enter the systemic circulation. Arterial air embolisms can result in sudden death, neurologic syndromes (e.g., cerebral or spinal infarction), and myocardial ischemia seen in some victims in the immediate postblast period.

Blast injury to the bowel requires higher peak overpressure and is more frequent in confined space or underwater blasts than in open-

air explosions. The blast wave can cause serosal tears, intramural hemorrhages, or bowel perforation. Shear injuries to mesenteric vessels can cause ischemia or infarction that leads to delayed intestinal rupture. The colon (primarily the ileocecal region) is the visceral organ most frequently injured in PBIs. Solid organ damage is rare and directly related to proximity to the blast.

DIFFERENTIAL DIAGNOSIS

An accurate history of the timing, location, and proximity to the explosion is critical to the diagnosis and initial management of blast injuries. In patients with signs of respiratory distress, BLI should be suspected. The clinician should also consider cardiac contusions, reactive airway disease, acute myocardial infarction, toxic exposure (e.g., carbon monoxide or cyanide), or exacerbation of other underlying diseases. The differential diagnosis of shock in the blast victim must include BLI, hemorrhagic shock, spinal shock, ammonia nitrate exposure (explosive adulterant), acute myocardial infarction, and acute arterial embolism.

The etiology of altered mental status in the blast victim ranges from physiologic shock (e.g., hypovolemic, cardiogenic, or neurogenic) to closed head injury to psychogenic shock. Hearing loss may be from TM rupture, ossicle dislocation, foreign body impaction, or temporary stunning of the vestibular–cochlear system.

ED EVALUATION

Blast trauma does not occur in isolation. Emergency physicians must evaluate blast victims for blunt and penetrating trauma, blast-specific injuries, and exacerbations of chronic disease. The initial evaluation of the blast victim focuses on rapidly identifying life-threatening conditions and risk stratifying multiple patients.

One approach is to segregate patients based on the presence or absence of external signs of trauma. Patients in apparent distress or with signs of external trauma should be evaluated based on the ATLS Guidelines with secondary and tertiary examination focusing on ENT, ocular, and neurologic examination. Of note, the Injury Severity Score grossly underestimates the complexity of injury and

the necessary resource utilization (9). In patients without apparent life-threatening injury, the main goal of initial evaluation is to identify PBI that may be obscured by secondary or tertiary wounds. The provider should obtain a *focused history* including location of blast (confined space or open air), distance of victim from blast, status of additional casualties, any details regarding the explosion (e.g., single suicide bomber, vehicle borne improvised explosive device, or presence of industrial chemicals, etc.). History should focus on *symptoms* concerning for PBI including chest pain, shortness of breath, cough, abdominal pain, tinnitus, or focal neurologic deficits. Concerning *physical examination* findings include tachypnea, hypoxia, decreased breath sounds, oropharyngeal pettechiae, chest wall crepitance, or abdominal tenderness. While absence of TM rupture does not preclude serious PBI, TM rupture should raise suspicion for more serious PBI and possible closed head injury (8,10). Any patient with a ruptured TM or with cardiopulmonary symptoms requires a chest radiograph to evaluate for BLI.

Routine laboratory testing is rarely useful in the management of PBIs. The arterial blood gas (ABG) is one exception. The ABG is particularly useful in the symptomatic patient, and oxygen desaturation may be the earliest sign of decompensation in the patient with BLI. The ABG may also assist with the diagnosis and management of toxic exposures to chemicals such as cyanide or carbon monoxide.

KEY TESTING

- Chest x-ray for suspected BLI
- ABG for suspected BLI

ED MANAGEMENT

Upon notification of an explosion and potential mass casualty incident (MCI), a triage area should be established at the entrance to the ED. The triage area may be needed for decontamination procedures and should be physically separate from treatment areas. Unlike traditional trauma triage where overtriage rates of 50% are

accepted as the standard, in MCI blast scenarios, overtriage can actually result in increased overall mortality for initial survivors by taxing the emergency response system and delaying care for the critically ill (5).

Initial stabilization, resuscitation, and ongoing management should proceed in a similar fashion to other victims of multiple trauma. The focus is on identifying patients with moderate-to-severe, yet correctable, blast trauma. Immediate attention should be paid to signs of significant BLI (i.e., tachypnea, shortness of breath, altered mental status), controllable extremity hemorrhage, and abdominal trauma.

Otoscopic examination of the TM should be conducted early in the patient assessment. Asymptomatic patients with intact TMs rarely have significant PBI (19). TM perforation has a high rate of spontaneous healing, especially if the tear is small and marginal in location (20). For large and central perforations, an otolaryngologist should be consulted, and immediate paper patching has been advocated (18). Treatment in the ED is generally expectant. The external auditory canal should be kept clean and dry; there is no need for routine irrigation or use of topical solutions. Some literature suggests the use of antibiotic suspensions for traumatic TM rupture (16). Otolaryngology follow-up is appropriate for patients that do not need evaluation in the ED.

Primary BLI has a reported mortality of nearly 70% (21). Initially, chest radiography should be performed and supplemental oxygen administered via nasal cannula or nonrebreather. Complications such as pneumothorax and hemothorax should be treated aggressively with early tube thoracostomy. Positive pressure ventilation in patients with BLI may cause or exacerbate pneumothorax, increase the alveolar-to-pulmonary vein pressure gradient, and potentiate systemic air embolization. Some studies suggest that a Pa_{O_2}/Fi_{O_2} ratio of <200 can be used as an indication for mechanical ventilation. For patients with severe pulmonary blast injuries, lung protective ventilation strategies are important. A regimen of volume-controlled, synchronized, intermittent, mandatory ventilation with small tidal volumes (5 to 7 mL/kg), limited peak inspiratory

pressure, and permissive hypercapnia ($PaCO_2 \leq 57$ mm Hg) appears beneficial (22,23).

General anesthesia is poorly tolerated in patients with PBI during the first 24 to 48 hours. If not contraindicated, regional or spinal anesthesia should be considered for patients who require surgery. Intravenous fluid management should be carefully monitored and fluid overload avoided. There exists significant debate regarding the role of permissive hypotension in blast and polytrauma resuscitation (24). Pulmonary artery and arterial catheters may be required to manage fluids appropriately. No definitive evidence supports the routine use of antibiotics or corticosteroids.

The blast victim presenting in shock should be evaluated and treated based on standard ATLS Guidelines. The clinician should also be aware that blast load focused on the thorax can produce a unique, vagally mediated cardiogenic shock without compensatory vasoconstriction (13). Patients may present with the triad of hypotension, bradycardia, and apnea (12,25).

For victims with systemic air emboli, hyperbaric oxygen (HBO) therapy is indicated. HBO therapy can be effective for cerebral air emboli, even up to 12 hours after the acute event. The Trendelenburg and the left lateral decubitus positions are sometimes advocated to reduce embolization to the brain and coronary circulation but there is no conclusive evidence of benefit in the literature.

Intestinal PBI is rare except in submersion blast injuries. Clinical symptoms may not manifest for 6 to 72 hours, and computed tomography or serial examination is indicated in patients with significant abdominal pain, tenderness, tenesmus, or penetrating injuries. Abdominal blast injury is managed in the same manner as any other blunt force trauma to the abdomen.

Secondary and tertiary injuries predominate in explosive MCI events. Extremity injuries are particularly common. From 1% to 7% of victims will present with traumatic amputations (1). Early tourniquet application should be considered for potentially life-threatening extremity injuries. Lacerations, abrasions, fractures, and burns resulting from secondary and tertiary blast injury can be

managed as in other trauma patients. Fragments generated by small explosions tend to produce wounds with little damage and can usually be managed without extensive wound exploration for removal of fragments (18). Generally, shrapnel wounds should be treated as low-velocity gunshot wounds. With high-velocity fragment wounds, as many fragments as possible should be excised and the wound left open for delayed primary closure. All penetrating secondary and tertiary injuries should be considered highly contaminated, and proper wound care and tetanus prophylaxis are therefore important. Ocular injuries occur in 10% of blast victims and are often occult. Penetrating ocular injuries require prompt ophthalmology consultation. Patients with crush injuries, compartment syndrome, burns, or soft tissue injuries should be managed in the standard fashion.

CRITICAL INTERVENTIONS

- Triage blast victims rapidly and accurately.
- Consider early activation of the hospital mass casualty system.
- Obtain detailed history regarding the explosive event to risk stratify victims.
- Perform a careful primary and secondary survey, examining the back, scalp, axillae, and gluteal folds for penetrating wounds.
- Perform a thorough pulmonary examination and early evaluation for ruptured TM in all blast victims.

DISPOSITION

Blast victims with significant injuries or signs of polytrauma require evaluation by a trauma surgeon or referral to a trauma center. Survivors with significant BLI, hemorrhagic shock, or intestinal damage generally manifest symptoms within the first hours after the blast; they often require emergent operative intervention, ICU admission, and close monitoring. Patients with suspected arterial air embolism require stabilization and urgent hyperbaric treatment. If transfer is required and air transport is employed, pressurized aircraft or low-altitude flights are important to limit the likelihood of

exacerbation of arterial air embolism or the development of clinical pneumothorax.

The majority of blast victims are not critically ill (8,13). Asymptomatic patients with isolated TM rupture should receive a chest radiograph and, if it is negative, they can be discharged after a brief period (6 to 8 hours) of observation. Most TM ruptures, especially if they involve $<80\%$ of the surface, heal spontaneously without long-term sequelae. Patients with middle- or inner ear symptoms should be referred to an otolaryngologist. Patients with ongoing abdominal symptoms should be admitted for observation and serial examinations. Patients with loss of consciousness or ongoing neurologic complaints should be admitted and observed.

Common Pitfalls

- Failure to appreciate that triage both at the scene and in the emergency department is an important determinant of survival for critically injured victims of explosions
- Failure to appreciate the importance of scene history, especially structural collapse, time of extraction, distance from explosion potential chemical contaminants, and number of victims
- Failure to recognize symptoms suggestive of cerebral, spinal, or myocardial ischemia resulting from arterial air embolism
- Failure to appreciate that positive pressure ventilation poses a significant risk for pneumothorax and for producing systemic air embolization in patients with blast lung

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CHAPTER 51

Hanging and Strangulation Injuries

Leon D. Sanchez and Richard E. Wolfe

Strangulation occurs when pressure is applied to the neck. This common injury accounts for 2.5% of traumatic deaths worldwide. Men are three to five times more likely to be victims than women, and those injured are most often between the ages of 21 to 40 (1). Causes of death from strangulation have been attributed to asphyxia, arterial occlusion, spinal cord injuries, and cardiac arrest due to pressure on the vasoactive centers of the great vessels. The specific role played by each of these causes as well as the types of injuries depend on the method used to apply pressure, the force, and the duration of the strangulation. To better manage this injury, it is helpful to subdivide strangulation by the methods used to apply the pressure: hanging, garroting, or throttling.

Hanging occurs when the ligature pressure is applied by the weight of the individual's body as part of a judicial, homicidal, suicidal, or accidental event. Although judicial hangings are rarely performed today, hanging is the third most common form of suicide after firearms and ingestions. Men attempt hanging three times more often than women do. Newly jailed prisoners are at particular risk. Complete hanging refers to the body being suspended, and incomplete hanging describes situations where the body exerts pressure but is not suspended. Accidental hangings are most commonly incomplete. Children and individuals who practice autoerotic asphyxiation are the most common victims of accidental hanging (1).

Garroting or ligature strangulation involves pressure being applied to the neck by a ligature just as in hanging. The difference is that the force used to exert this pressure is something other than the individual's body weight. Throttling can be considered a type of garroting where the ligature is the assailant's hands, which exert the pressure directly.

CLINICAL PRESENTATION

Hanging or strangulation may result in injury to vascular structures in the neck. Venous obstruction results from forces applied to the jugular system (2,3). This leads to vascular congestion and cerebral hypoxia. As a result of the hypoxia, the neck musculature is thought to relax, leading to further compression that can lead to arterial and airway occlusion (2). Injury to the arteries is caused by hyperextension and rotation of the head. The carotid artery can be stretched over the transverse process of C2 or compressed by direct pressure over the transverse process of C6 (2,4). This can result in an intimal tear (4,5). Vertebral artery flow is not affected by direct pressure except at the extremes of rotation and lateral flexion (2).

Neurologic injury after hanging results from decreases in ventilation and cerebral perfusion. Autonomic stimulation from pressure on the carotid bodies or vagal sheath can lead to cardiac arrest (3,6). Hypoxia secondary to upper-airway obstruction plays a role in the development of neurologic injury or death but is thought to be second in importance to ischemia. Ischemic injury is caused by venous vascular congestion and arterial compression, both of which result in decreased cerebral flow (3,7–9). Increased intracranial pressure (ICP) secondary to cerebral edema is common in patients with altered mental status (10,11). Nevertheless, delayed neurologic sequelae are rare, and even patients who present with a low Glasgow Coma Scale (GCS) often recover fully (3,8,9).

Injury to the laryngotracheal apparatus may be caused by compression or traction of the involved structures. Manifestations of these injuries may not be evident at presentation (12). Most airway injuries by themselves are not life threatening (3). In one study that

looked at 112 deaths and 59 survivors of strangulation, only one case required emergent operative management (13). None of the deaths could be attributed to airway injury (13). Fractures of the hyoid bone and thyroid cartilage are seen with some regularity, whereas cricoid fractures are less common (13,14). The incidence of these fractures increases with greater age of the patient, probably due to calcification of the structures (14). Throttling victims have a much higher incidence of fractures as compared to hanging victims. The incidence of thyroid and hyoid fractures in hanging victims ranges from 10% to 15%; cricoid fractures are rare. Throttling victims have an incidence of fractures ranging from 30% to 40% (3,13,14). Even with the higher rates of injury in throttling victims, injuries to the laryngotracheal apparatus are rarely life threatening. Asphyxia from upper-airway obstruction due to the ligature itself is also rare, although pressure from the ligature can displace the tongue upward and obstruct the airway (6,9).

In the late 19th and early 20th centuries, British postmortem studies of judicial hangings demonstrated that a minimum drop force (patient weight multiplied by the length of the drop) was needed to cause a cervical spine fracture. The required drop height varies depending on factors such as the weight of the subject, the neck musculature, and the strength of the bone itself. Although generally a drop height greater than the patient's height is required to cause a spinal fracture, in rare circumstances shorter drop heights can produce these injuries. The minimum reported drop height is 3 ft (15,16). The most common spinal injury with long drops is disjointing of the second from the third cervical vertebra and bilateral fractures of the second cervical vertebra, the classic hangman's fracture (Figs. 51.1 and 51.2). The position of the knot is important.

FIGURE 51.1 Lateral radiograph of cervical spine. Fracture of the posterior elements of C2 is indicated by the arrow. (Image courtesy of Marc Camacho, MD.)

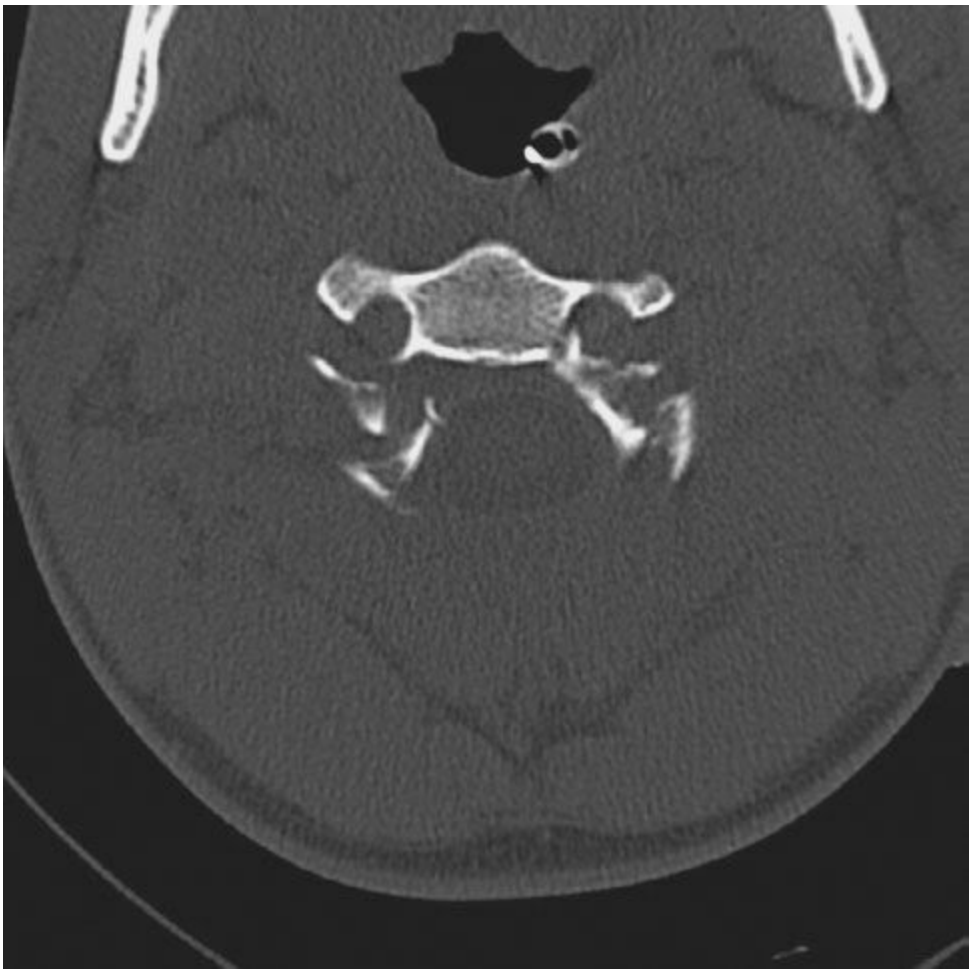

FIGURE 51.2 Axial image of computed tomogram of C2 showing bilateral pedicle fractures. (Image courtesy of Marc Camacho, MD.)

In typical (nonjudicial) hangings, the knot is placed under the occiput and has the greatest ability to cause arterial occlusion rather than a spinal fracture. A hangman's fracture will most likely occur when the knot is placed under the chin (submental) to ensure hyperextension, yet many judicial hangings were performed with the knot on the side of the jaw (subaural) which was less likely to result in a spine fracture and cord transection (17,18). Despite drops from body height and knot placement under the chin, even "proper" judicial hangings do not always cause cervical spine fractures (14,17,19). In complete suicidal and accidental hangings, most victims have negligible drop distances, and few sustain cervical spine fractures (7,9,16,20).

Pulmonary complications from strangulation injury include pulmonary edema, aspiration pneumonia, and the adult respiratory distress syndrome (ARDS). Pulmonary edema is thought to be caused by markedly increased pulmonary transvenous pressures from forced inspiratory efforts against an occluded upper airway (21). Aspiration pneumonia in patients with a depressed mental status is reported in case series of strangulation victims (3,9,10). The ARDS in strangulation victims is secondary to brain hypoxia (22). Brain hypoxia leads to autonomic mediated vasoconstriction of the pulmonary venules, leading to ARDS and possibly contributing to pulmonary edema (22,23).

The clinical presentation of a patient with a strangulation injury can vary widely. The presenting mental status and GCS are related to the duration of hanging. The GCS is a poor predictor of the patient's final outcome, and patients presenting with very low scores have a strong likelihood of surviving the injury with a normal mental status. Ligature marks are often, but not always, present (9). Subconjunctival, gingival, and oral petechial hemorrhages may be observed. These are thought to be caused by vascular congestion (13). Patients may also present with hoarseness or voice change (6), both of which may represent injury to the laryngotracheal apparatus. Subcutaneous emphysema can also be present (13). Occasionally, patients will present with frank stridor. Tachypnea can be an early sign of aspiration pneumonia or pulmonary edema (6,21).

Mental status changes may be secondary to brain anoxia, preexisting mental illness, or posttraumatic response to the event (6,9). In many of these patients, the evaluation may be more difficult owing to the presence of alcohol or other substances (6). One study found that 70% of hanging patients had concomitant drug or alcohol ingestion (16). Throttling victims often present after a domestic abuse incident and frequently will not volunteer the fact that they were throttled unless specifically asked (24).

ED EVALUATION

After immediate life-threats have been addressed, a more extensive history and physical examination should be performed. The presence of alcohol and other substances in these patients is common and may complicate the examination. In alert patients, attention should be paid to the evaluation of the laryngotracheal apparatus and to the pulmonary status. The presence of hoarseness, difficulty in swallowing, or other complaints that raise suspicion for laryngotracheal injury should prompt a more extensive workup. Although relatively rare, studies have shown an incidence of cervical spine fractures after suicidal near-hanging that may be as high as 7% (11,25). Imaging of the cervical spine may thus be indicated in the emergency evaluation of these patients and may reveal soft tissue swelling or a hyoid bone fracture. Evidence of laryngeal edema should be followed by prompt otolaryngology consultation. Computed tomography (CT) of the neck can be very helpful in delineating an injury to the laryngeal skeleton. Early control of the airway should be considered in these patients.

Pulmonary complications are the leading cause of death in patients who survive to hospital admission. Pulse oximetry and chest radiographs should be routinely performed in these patients. Manifestations of pulmonary edema and ARDS may be delayed by several hours. Aspiration pneumonia is also common and more likely in those patients with a depressed mental status.

Vascular injuries that are clinically significant are essentially restricted to the arterial tree. Although extremely rare, clinical signs of arterial dissection should prompt further workup. The most common signs that should raise suspicion for dissection are neurologic abnormalities consistent with a transient ischemic attack or cerebrovascular accident, Horner syndrome, amaurosis fugax, unexplained nausea or vomiting, and vertigo. Headache and neck pain are also common presenting complaints, although they are nonspecific.

The gold standard for detection of vascular injuries is four-vessel angiography. Magnetic resonance angiography and CT angiography are reasonable alternatives if angiography is unavailable or if they are available faster than angiography, as they may help delineate

the injury and expedite the workup. However, these "techniques" may miss injuries, and a negative MRI or CT result does not completely rule out the diagnosis. Doppler ultrasonography is not useful for the evaluation of the vertebral arteries but can provide useful information about the carotid arteries; however, the sensitivity of duplex ultrasound is not high enough to completely rule out carotid injury. In patients in whom there is a high suspicion for arterial injury, four-vessel angiography remains the test of choice. If unavailable, transfer of the patient to another institution should be considered.

KEY TESTING

- CXR to evaluate for pulmonary edema, ARDS, and aspiration pneumonia
- Cervical spine CT or plain films to evaluate for fracture. As angiography (CTA) may often be done CT/CTA may obviate need for plain films
- Angiography for vascular injuries (CTA, MRA, angiography)

ED MANAGEMENT

The initial presentation of the patient will dictate the need for early management of the airway owing to respiratory distress or poor neurologic status. Cervical spine injury is extraordinarily rare in strangulation victims, and excessive cervical spine precautions need not be taken. Airway injuries severe enough to interfere with airway management are uncommon, and intubation using rapid sequence intubation is recommended. When possible, ICP blunting techniques should be used during the intubation. Positive end-expiratory pressure should be instituted early, as these patients are at high risk for the development of pulmonary edema and ARDS.

Once the life-threats have been addressed, special attention should be paid to psychosocial issues. Throttling and ligature strangulation victims are often victims of domestic abuse. It may not be safe for these patients to be discharged even in the absence of medically important injuries. In the adult population, hangings are

predominantly a result of suicide attempts. Ingestion of toxic substances in these patients is common and should be ruled out. These patients should be separated from their property and placed under direct observation to avoid further attempts at harming themselves. Psychiatric consultation is indicated.

CRITICAL INTERVENTIONS

- Ensure a patent airway. Monitor the respiratory status closely and manage the airway if needed.
- Obtain early otolaryngology consultation for suspected laryngotracheal injuries.
- Consider the possibility of increased ICP in patients with a depressed sensorium.
- If there is evidence of increased ICP, obtain neurosurgical consultation and initiate measures to decrease ICP.
- Consider toxic ingestions.
- Address the psychiatric or social issues that are at the root of the strangulation once immediate life-threats have been managed.

DISPOSITION

Owing to the presence of delayed neurologic and pulmonary complications in strangling victims, observation for at least a 24-hour period is recommended. Otolaryngology and neurosurgical consultation should be considered when warranted. Psychiatric consultation as well as social work involvement may be necessary.

Common Pitfalls

- Failure to consider early airway management.
- Failure to diagnose vascular dissections.
- Failure to involve otolaryngology and neurosurgery when needed.
- Failure to consider interpersonal violence.
- Failure to consider toxic ingestions.
- Failure to involve psychiatry.
- Early discharge of the patient.

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CHAPTER 52

Trauma in Pregnancy

Bonnie Lau and Susan B. Promes

Significant trauma affects approximately 7% of pregnant women (1). In fact, trauma was reported to be the leading cause of death during pregnancy in at least one series (2). Statistically, pregnant women sustain approximately 4.1 trauma-related hospitalizations per 1,000 deliveries (3). The pregnant trauma patient presents a unique challenge to the emergency department (ED) team caring for her. Not only is the physician caring for two patients, but both of the patients have their own unique needs. In general, when faced with a pregnant trauma patient, the emergency physician should resuscitate the mother first. The well-being of the unborn fetus is dependent upon the hemodynamic stability of the mother.

It is imperative that the physician caring for the gravid woman be aware of the physiologic changes that occur during pregnancy and the impact these changes may have on the resuscitation of the pregnant woman and her unborn fetus (eTable 52.1). This knowledge will be critical to the evaluation and treatment of the woman and her unborn child.

eTABLE 52.1
Changes in Maternal Physiology During Pregnancy

Cardiovascular system	↑ cardiac output
	↑ pulse to 80–95 bpm
	↓ BP in second trimester
	↓ central venous pressure left axis deviation on electrocardiogram
	↓ venous return when patient supine
Respiratory system	↑ respiratory rate
	↑ tidal volume
	↑ minute ventilation
	↓ functional residual capacity
	+ respiratory alkalosis
	↑ oxygen consumption
Hematologic system	↑ blood volume producing a dilutional anemia
	↑ white blood cell count
	↓ platelet count
	↑ erythrocyte sedimentation rate
	↑ fibrinogen, factors VII, VIII, IX and X
	↑ risk thromboembolic disease
Urinary system	↓ motility in collecting system
	↑ glomerular filtration rate
	↓ BUN and creatinine levels
	↑ glucose excretion
Gastrointestinal system	↓ motility
	↓ tone in lower esophageal sphincter
	↑ dilation of hemorrhoidal veins
	↑ risk of gallstone formation
	↑ spider angiomas & palmar erythema
	↓ albumin & total protein levels
	↑ serum alkaline phosphatase
Musculoskeletal system	↓ total calcium levels
	↑ ligamentous laxity
Endocrine system	↑ aldosterone & cortisol levels
	↑ peripheral resistance to insulin
Central nervous system	↓ coordination in late gestation
	↑ emotional lability

Adapted from Gordon MC. Maternal physiology in pregnancy. In: Gabbe SG, Niebly JR, Simpson JL, eds. *Obstetrics: normal and problem pregnancies*. New York: Churchill Livingstone, 2002: 63–91.

Airway. Although airway anatomy does not change significantly, progesterone causes smooth muscle relaxation, affecting the lower esophageal sphincter and increasing the risk of aspiration.

Breathing. The diaphragm is gradually pushed up 3 to 4 cm during pregnancy, causing a 25% decrease in functional residual capacity

and resulting in decreased maternal oxygen reserve. Pulmonary function is further compromised by increased oxygen consumption. Starting in the first trimester, stimulation of the medullary respiratory center by progesterone increases minute ventilation by up to 50% (a result of increased tidal volume). This is accompanied by a 10-mm Hg increase in PO_2, a 10-mm Hg decrease in PCO_2, and a compensatory decrease in bicarbonate to about 19.5 mEq/L. These physiologic changes result in less respiratory reserve in the pregnant trauma patient.

Circulation. Pregnancy is a high-flow, low-resistance state of cardiovascular homeostasis. Heart rate increases until the end of the second trimester, when it plateaus at 10 to 15 beats above baseline. Systolic, and to a greater extent diastolic, blood pressure decrease during the first and second trimesters, returning to prepregnancy baseline levels during the third trimester. Cardiac output increases by 40% by the end of the first trimester and persists at this level, causing a cardiac flow murmur in 90% of pregnant women. By the third trimester, there is increased vascular congestion in the pelvis and a 50% decrease in the velocity of venous flow in the lower limbs (4). These changes predispose the gravid patient to deep venous thrombosis as well as increased bleeding from lower extremity and pelvic trauma.

In addition, several hematologic changes accompany pregnancy. A 50% increase in blood volume and concomitant increase in red blood cell mass by only 20% to 30% results in a 3% to 6% drop in hematocrit. The white blood cell count increases to 12,000 to 18,000/μL by the second trimester and may increase to 25,000/μL with stress. The prothrombin and partial thromboplastin times are somewhat decreased. Coagulation factors rise gradually and exceed fibrinolytic activity by the third trimester.

The fetus has a higher hemoglobin concentration than the mother, and fetal hemoglobin has a higher affinity for oxygen. As a result, fetal oxygen consumption does not decrease until oxygen delivery decreases by 50% (5). This allows the fetus to tolerate brief periods

of maternal hypoxia and hypoperfusion. In late pregnancy, the fetus is capable of redistributing blood to the heart and brain (6).

CLINICAL PRESENTATION

Critically ill pregnant trauma patients may present with normal vital signs due to the physiologic changes that occur in pregnancy; this should not give the emergency physician a false sense of security. Pregnant women have increased blood volume as they near term, so blood loss must be excessive before hypotension occurs. Abdominal pain in the pregnant trauma patient may be due to common intra-abdominal injuries associated with blunt trauma. Other causes of life-threatening problems include uterine rupture, placental abruption, and premature labor.

Pregnant trauma patients tend to have a slightly different injury pattern when compared to the general trauma population, with increased intra-abdominal injuries and decreased traumatic brain injuries (7). In penetrating trauma, this may be due to changes in maternal anatomy with increasing gestational age. The diaphragm and intra-abdominal contents are displaced upward by the enlarging uterus; hence, injury patterns will vary from the general population. For example, someone with a stab wound to the left upper quadrant is at increased risk for intestinal injury because the uterus displaces the intestinal contents superiorly.

Whether the pregnant patient is involved in blunt or penetrating trauma, the fetus in addition to the mother is at risk for injury. Even minor maternal injuries can lead to placental abruption, uterine rupture, fetal–maternal hemorrhage, and premature birth. The emergency physician should look for signs of occult injury that are manifested by uterine irritability, vaginal bleeding, and fetal tachycardia.

DIFFERENTIAL DIAGNOSIS

The emergency physician caring for the pregnant trauma patient should first consider the typical injury patterns that are associated with a given mechanism of injury. The pregnant trauma patient is

not immune to common traumatic injuries. While the emergency physician is evaluating the pregnant patient for common injuries, the physician should also consider the unique role the gravid uterus plays in the traumatic event. As the uterus enlarges during pregnancy, changes in intra-abdominal anatomy alter the injury pattern. For example, the diaphragm moves cephalad into the thoracic cavity. Subsequently, in a pregnant patient who sustains a penetrating injury to the chest, the physician should have a greater suspicion for a diaphragmatic injury. In addition, the large gravid uterus displaces the intra-abdominal contents, making bowel injuries less common and injury to the uterus more common in blunt trauma. A few important injuries associated with pregnancy include placental abruption, uterine rupture, maternal–fetal hemorrhage, and premature labor. The greater the severity of maternal trauma, the more likely a significant fetal insult will occur. Pearlman and Tintinalli (8) reported a fetal loss rate of 41% with life-threatening maternal injuries while the fetal loss rate was 1.6% with nonlife-threatening injuries.

Seizures in trauma patients are generally associated with head injuries. However, in the gravid trauma patient, the emergency physician must also consider eclampsia as the etiology of the seizure and subsequent trauma.

ED EVALUATION

As the survival of the fetus is dependent upon maternal resuscitation, the evaluation of the pregnant trauma patient should proceed in a step-wise fashion. Advanced trauma life support principles should be followed as in the nonpregnant trauma patient. However, during the primary and secondary trauma surveys, the emergency physician must apply a detailed understanding of the physiologic changes that occur in the pregnant state to detect potentially life-threatening conditions. The airway must be managed aggressively. All pregnant trauma patients should be placed on oxygen, since oxygen consumption is increased with pregnancy, and it is important to avoid fetal hypoxia. When evaluating the

circulatory status, the physician should remember that the second-trimester pregnant patient without significant injuries may have an elevated heart rate and lower blood pressure. Conversely, she may also have significant life-threatening hemorrhage without alteration in vital signs due to the physiologic increase in cardiac output and intravascular volume.

After the primary survey, a complete history should be obtained, including last menstrual period, estimated date of delivery, previous pregnancy history, and any problems associated with the pregnancy.

The fetus is evaluated during the secondary survey. The fundal height should be assessed, recognizing that a fundal height at or above the level of the umbilicus may indicate a potentially viable fetus. The distance between the symphysis pubis and the uterine fundus measured in centimeters approximates gestational age in weeks (Fig. 52.1). The threshold for fetal viability is 23 to 24 weeks depending on the resources available at the facility to care for the neonate (9). The presence of fetal heart tones should be documented. In patients at 20 weeks or more gestation, cardiotocographic monitoring should be obtained as soon as possible. This gives the physician information regarding fetal–maternal well-being. A normal fetal heart rate is between 120 and 160 bpm. Fetal tachycardia, fetal bradycardia, contractions, loss of beat-to-beat variability, or late or prolonged decelerations after contractions may be signs of fetal distress heralding such pathologic states as placental abruption or occult maternal shock. If the patient has vaginal bleeding, then a sterile vaginal speculum examination should be performed to identify the source of bleeding, being mindful of potential placenta previa. Aside from evaluation of the pregnancy itself, a speculum examination may reveal signs of genitourinary trauma such as lacerations from pelvic fractures or penetrating trauma.

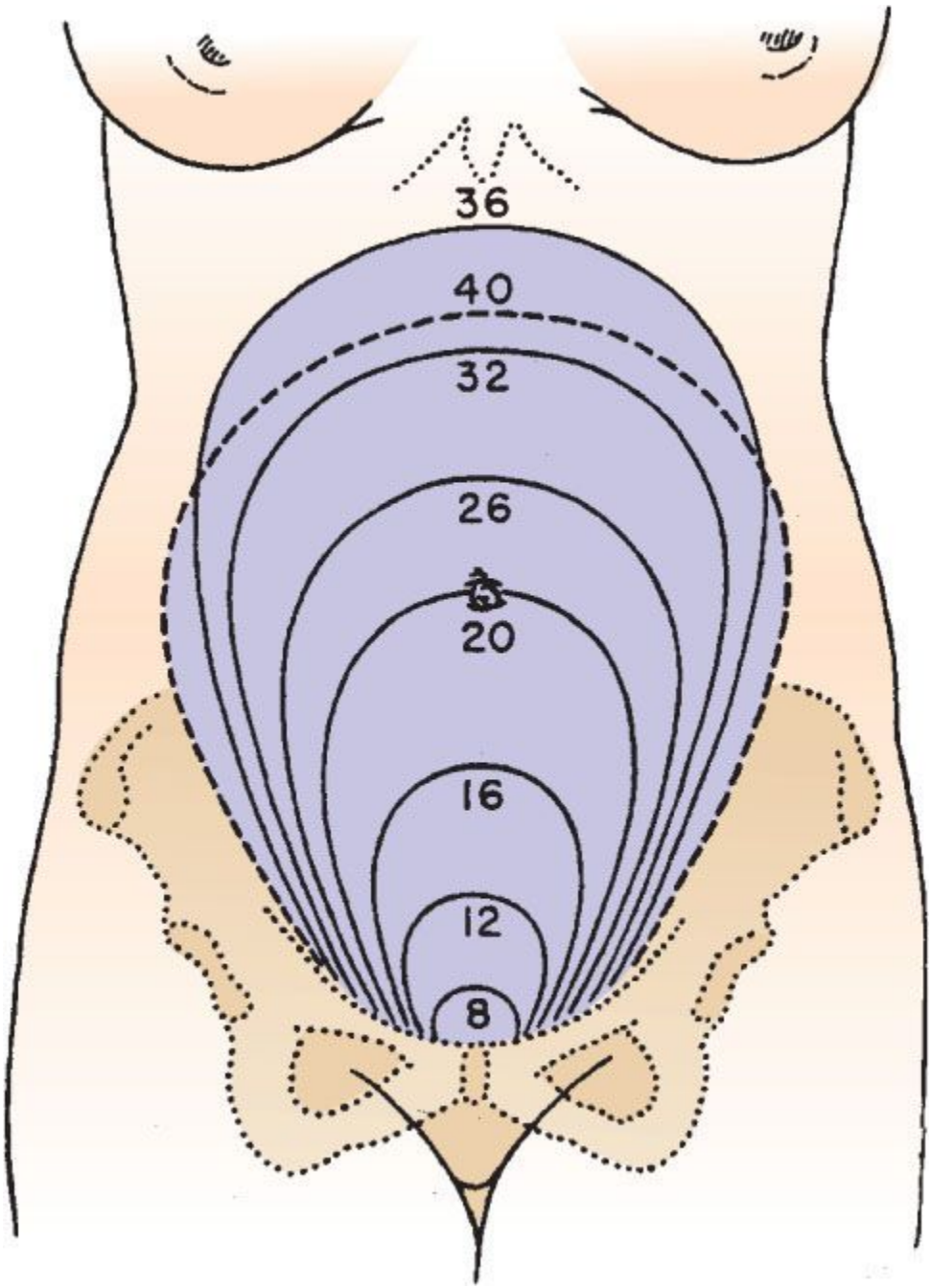

FIGURE 52.1 The height of the uterine fundus at different gestational dates.

Upon completion of the primary and secondary surveys, the clinician should tailor further diagnostic studies to the individual patient. As the fetus is dependent on maternal well-being, diagnostic tests and therapy should be directed primarily at the care of the

mother and should not be delayed because of the pregnancy. As classic signs of shock may present late, a more detailed initial workup may be appropriate in pregnancy. The hematologic changes of pregnancy must be considered when evaluating any laboratory results. It is important to remember that pregnant women have a "dilutional anemia" due to their increased blood volume (eTable 52.2). They also have an elevated white blood cell count and sedimentation rate. Fibrinogen levels are increased, as are coagulation factors. All pregnant trauma patients should have blood type determination as all Rh-negative women require Rho(D) immune globulin (RhoGAM). The recommended dose for all Rh-negative gravidas is 300 μg unless there is risk of massive isoimmunization. Based on the results of a Kleihauer–Betke (KB) test, additional RhoGAM (300 μg per 30 mL of estimated fetomaternal hemorrhage) may be warranted (10,11).

eTABLE 52.2
Hemoglobin Values in Pregnancy

Gestational Age (Weeks)	Mean Hemoglobin (g/dL)	Fifth Percentile (g/dL)
12	12.2	11.0
16	11.8	10.6
20	11.6	10.5
24	11.6	10.5
28	11.8	10.7
32	12.1	11.0
36	12.5	11.4
40	12.9	11.9

Adapted from U.S. Department of Health and Human Services: *MMWR* 1989;38:400–404.

The Eastern Association for the Surgery of Trauma (EAST) recommends a major change in the management of pregnant trauma patients in which physicians would order a KB test for all pregnant patients ≥20 weeks of gestation, regardless of Rh status (10–12).

This recommendation is based on the results of two class II and one class III studies in which investigators found that a positive KB test regardless of Rh status detected *all* cases of preterm labor (5,10,12). Given that the EAST level II recommendation was based on only three studies, no change in ED management can be suggested at this time. Therefore, patients with a potentially viable fetus (i.e., ≥20 weeks of gestation) sustaining a traumatic injury should have cardiotocographic monitoring for a minimum of 6 hours (12).

Ultrasound examination (13) can be used to evaluate for a traumatic pericardial effusion and tamponade or to demonstrate free fluid in the abdomen. In addition, it may help determine fetal age, position, and amniotic fluid volume. However, its limitations must be recognized. Ultrasound may miss placental abruption; the reported sensitivity is only 24% (14). This diagnosis is made by signs of maternal compromise or fetal distress on cardiotocographic monitoring and not generally by ultrasound.

As fetal outcome is dependent upon maternal condition and resuscitation, radiographic studies should not be withheld to prevent fetal radiation exposure. However, knowledge of the underlying principles of fetal radiation exposure must be understood by the practitioner to address patient concerns and guide appropriate evaluation (eTable 52.3). The issues of concern include risk of fetal demise, fetal malformation, childhood cancer, and fetal neurodevelopment versus the risk of missed injury that would require intervention. In the first 10 days of pregnancy, the response to significant radiation exposure is an all-or-none response. From 10 days to 10 weeks, the fetus is at greatest risk for radiation-related malformation. After 20 weeks, the fetus does not appear to be at increased risk of malformation (15). Fortunately, exposure to <5 to 10 rads does not increase the baseline risk of malformation. The increased risk of childhood cancers from prenatal radiation exposure is unclear. However, the associated risk of in utero radiation with childhood cancers has been estimated at 8% increase in childhood cancers per 100 rads. To place this in perspective, this is equivalent to an excess absolute risk of childhood cancer from 0.00006 to 0.00008 for each 100 mrad (16,17). The risk of growth restriction,

microcephaly, and mental retardation are highest at 8 to 15 weeks and appear to be associated with high-dose radiation of at least 20 to 40 rad (10). Most shielded plain film radiographs, brain computed tomography (CT), and chest CT scans are well below these concerning levels. The risk of a significant missed injury is usually higher than the risk of adverse sequelae from radiation in injured patients. However, an abdominal CT scan may deliver 3 to 9 rads to the fetus. The emergency physician may consider shielding the uterus and scanning only the upper abdomen to rule out solid organ injury and subsequently observing the patient and monitoring her clinically for signs of increasing abdominal pain, worsening anemia, fetal distress, or maternal hemodynamic changes.

eTABLE 52.3
Estimated Radiation Dose to Fetus per Radiograph

Cervical spine	<1 mrad
Chest	1–3 mrad
Abdomen	200–500 mrad
Pelvis	200–500 mrad
Lumbar spine	600–1,000 mrad
Hip/femur	100–450 mrad
CT head/chest with shielding	<1 rad
CT abdomen	3 rad
CT pelvis	3–9 rad

Diagnostic peritoneal lavage (DPL) may be performed in pregnancy using the supraumbilical technique. As with ultrasound, DPL cannot be used to evaluate the retroperitoneum. Exploratory laparotomy may be necessary during pregnancy, especially in patients with penetrating trauma to the upper abdomen. Although surgical exploration was previously recommended for all pregnant patients with penetrating trauma, some authors advocate nonoperative management with observation for penetrating wounds directly to the uterus if the patient is hemodynamically stable and

there are no signs of fetal distress (18–20). The determination of whether to perform a cesarean section at the time of exploration is based on evidence of fetal–maternal compromise detected on cardiotocographic monitoring.

KEY TESTING

- Type and screen (especially for Rh status)
- Consider Kleihauer–Betke test
- Any necessary radiographic studies
- Bedside ultrasound (pericardial effusion, free fluid in abdomen, fetal age/position, amniotic fluid volume)
- Cardiotocographic monitoring for at least 6 hours

ED MANAGEMENT

As with all trauma patients, the initial management of the pregnant trauma patient occurs simultaneously with the ED evaluation. Emphasis is placed on maternal resuscitation to maximize both maternal and fetal outcomes. Special care should be taken if the patient requires intubation. The pregnant patient's airway may be edematous. The gravid woman is at increased risk of aspiration secondary to delayed gastric emptying and decreased lower esophageal sphincter tone. In addition, gravidas have decreased oxygen reserves and may require early intubation to maximize oxygenation and ventilation; also, they may desaturate rapidly after paralysis (21). In later pregnancy, if a chest tube is necessary, it should be placed one to two rib spaces higher than usual, as the diaphragm will be elevated. This, along with palpation of the diaphragm with a finger during thoracostomy placement, will prevent inadvertent intra-abdominal placement of the tube.

After the 20th week of pregnancy, the trauma patient is at risk for the *supine hypotensive syndrome,* the result of uterine compression of the inferior vena cava by the gravid uterus, leading to decreased venous return to the heart. All pregnant trauma patients of 20 weeks or greater gestation who are supine should, therefore, be placed in 15 degrees of left lateral tilt to prevent this compression (10,11,20).

Aggressive early resuscitation is particularly important as gravid patients may not develop overt signs of hypovolemia until they are in the late stages of shock. Changes in uterine blood flow, which can lead to fetal distress, occur before maternal vital signs change. Crystalloid fluid replacement should be started, and blood administered as necessary. Vasopressor support should be avoided as pressors significantly decrease uterine blood flow and do not address the likely underlying cause of hypotension, namely hemorrhage. Hemodynamic instability secondary to dysrhythmias that are amenable to defibrillation or cardioversion should be treated as such without concern for fetal injury.

There are several unique situations that the emergency physician must consider in the gravid trauma patient. Pelvic fractures may be particularly dangerous during pregnancy. They may lead to increased blood loss from dilated pelvic veins. They also may lead to direct fetal injury, resulting in a high incidence of fetal morbidity and mortality. Medical antishock trousers have no role in the management of the gravid trauma patient.

Uterine injury is uncommon in the first trimester, as the bony pelvis protects the small gravid uterus. However, later in pregnancy minor uterine injury, such as contusion, is relatively common. This usually presents with uterine contractions, which resolve spontaneously in 90% of cases. Rarely, blunt abdominal trauma can cause uterine rupture, which can present with catastrophic blood loss and fetal demise (5,8). This may be diagnosed on physical examination by palpating a flattened uterus or fetal parts free in the abdominal cavity. Ultrasound can also be used to identify a traumatic uterine rupture.

Placental abruption, a premature separation of the placenta from the uterine wall, is common with blunt abdominal trauma and can cause fetal distress. It occurs in 1% to 3% of pregnant women with minor trauma and in 40% to 50% of pregnant women with major life-threatening trauma (6,8). Abruption may present with vaginal bleeding, abdominal pain and tenderness, uterine contractions, or fetal distress. However, it may be occult and, moreover, may be missed on ultrasound examination. The most sensitive test for the

evaluation of placental abruption is cardiotocographic monitoring to detect uterine irritability and fetal distress. Cesarean section may be necessary to save the fetus in severe cases of placental abruption.

Amniotic fluid embolism can occur with trauma and placental abruption. Debris and amniotic fluid become lodged in the maternal respiratory system, causing sudden dyspnea, hypoxia, and hypotension. These patients are also at risk for developing disseminated intravascular coagulation. Treatment of amniotic fluid embolism in patients is supportive, but the mortality rate unfortunately is high. Cardiopulmonary bypass has been used successfully to treat severe cases.

Fetal outcomes in pregnant patients with burns are directly related to the extent of the burn and the gestational age of the fetus. A burn of $<20\%$ total body surface area usually does not lead to pregnancy complications, but extensive burns may lead to fetal demise or premature labor (22). Conversely, maternal outcomes in the setting of burns are not affected by pregnancy.

The burn patient should also be assessed for carbon monoxide exposure. There is increased binding of carbon monoxide by fetal hemoglobin, resulting in increased carbon monoxide exposure to the fetus. All symptomatic patients or those with a carboxyhemoglobin level greater than 15% should be placed on 100% oxygen by mask and should be considered for hyperbaric oxygen therapy (23).

If the pregnant trauma patient arrests, the clinician should consider a perimortem cesarean section if there is a potentially viable fetus (≥ 23 weeks of gestation). As time is critical to the survival of the fetus, the procedure should be initiated promptly and should be performed by the most experienced physician available. Delivery within 5 minutes of maternal arrest leads to a higher rate of fetal survival with good neurologic outcome. Survival rapidly declines to 5% (usually with neurologic sequelae) if the procedure is not performed until 15 minutes after maternal arrest (24). Using a number 10 blade, a midline vertical incision should be made from the epigastrium to the pubic symphysis. Ideally, the clinician should make one incision that goes from the skin down to the uterus. The uterine incision is then performed vertically from the fundus to the

reflection of the bladder. The placenta is incised if necessary. The child is delivered and the cord clamped and cut. Neonatal resuscitation should be aggressive and should begin immediately. With delivery of the infant, maternal hemodynamics may actually improve because of increased venous return. It is thus important to continue maternal resuscitative efforts (airway management and CPR) during and after perimortem cesarean section.

CRITICAL INTERVENTIONS

- Resuscitate the mother adequately to resuscitate the fetus.
- Identify and treat early shock prior to development of abnormal vital signs.
- Position the patient in a 15-degree leftward tilt to prevent the *supine hypotensive syndrome*.
- Any pregnant trauma patient with a potentially viable fetus should be admitted for cardiotocographic monitoring for at least 6 hours, even when there are only minor injuries.
- Administer RhoGAM 300 μg intramuscularly (IM) to all Rh-negative patients.

DISPOSITION

Routine obstetric (OB) consultation in all pregnant trauma patients has been recommended by various organizations, although the evidence of improved outcomes with this intervention is lacking. Clearly, appropriate consultation is necessary for the best management of the pregnant trauma patient. Trauma surgery, OB and gynecology, and neonatology may be necessary for the multidisciplinary care of the pregnant trauma patient. The need for consultation is determined by the patient's potential injuries and the estimated gestational age of the fetus. At a minimum, pregnant trauma patients with a viable fetus ($\geq$20 weeks) should receive OB consultation and 6 hours of cardiotocographic monitoring (10). This includes gravid trauma patients with little or no evidence of maternal injury. If monitoring detects an abnormality (vaginal bleeding, abdominal pain, contractions, or fetal heart rate

abnormalities) during this initial observation period, the period of monitoring should be extended to 24 to 48 hours (6,10,25). Although the fetus is not viable until 23 weeks at the earliest, some sources recommend monitoring for all patients who are more than 20 weeks pregnant (9). This recommendation is based on the fact that some obstetricians will attempt tocolysis if there is evidence of premature labor in this group.

Prior to disposition, injury prevention issues must be addressed. The possibility of interpersonal violence or intentional injury cannot be overstated. Data suggest that there is a rise in the rate of domestic violence as the pregnancy progresses. The health care provider should also discuss appropriate seatbelt use prior to discharge. The lap belt should be worn low over the iliac crest, and the shoulder restraint should cross above the uterus. When indicated, the emergency physician must remember tetanus prophylaxis. Standard guidelines for tetanus prophylaxis should be followed. No adjustments are needed in pregnancy.

Common Pitfalls

- Inadequate early maternal resuscitation.
- Failure to perform cardiotocographic monitoring.
- Failure to perform necessary radiographs for fear of fetal complications.
- Failure to treat fetal–maternal hemorrhage in Rh-negative trauma patients.
- Delay in performing a perimortem cesarean section with maternal cardiopulmonary arrest.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Charles J. Gerardo, the coauthor of this chapter in the previous edition.

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CHAPTER 53

Trauma in Older Adults

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The increase in the number of active and independent older US adults has led to an unfortunate corresponding increase in the proportion of older trauma patients (1). Common mechanisms of injury in older adults include falls, motor vehicle collisions, and recreational activities (2). Although geriatric patients currently account for 10% to 15% of all trauma in the United States, it has been projected that this will increase to nearly 40% by 2050 (3,4). This is important because injury patterns and physiologic responses to injury differ between older and younger adults. Further, older trauma victims consume more health care resources, account for more health care expenditures, and have worse outcomes after trauma than younger individuals (5).

Approximately 28% of all traumatic deaths in the United States occur in adults of age 65 or older, and trauma is the fifth leading cause of mortality among geriatric patients. The case-fatality rate for adults of age $\geq$65 ranges from 15% to 30% versus 4% to 8% for those $<$65 years of age (4,6). Though there is evidence to suggest that risk of poor outcome from trauma begins to rise as early as age 40, the risk of death clearly increases after age 65 (7). Despite the risk associated with trauma in older adults, it is important to recognize that survival can be improved through early, aggressive management (6).

CLINICAL PRESENTATION

Injury severity is an important factor in the outcome of older trauma patients. The extent of injury is determined in part by the causal mechanism, but, for similar events, the severity of injury tends to be greater for older than for younger individuals. For example, falls from height and pedestrian-struck incidents are three to four times more likely to result in death for older adults than younger adults and account for nearly 50% of trauma deaths in older adults (8,9). The disproportionate increase in severity among older patients is attributable to a combination of age-related anatomic and physiologic changes. Pre-existing medical conditions, present in approximately 40% of those of age 65 to 74; 65% of those of age 75 to 84; and 90% of those of age ≥85, compromise older adults' response to injury, as does polypharmacy (10).

Pathophysiology

Cardiovascular

Myocyte degeneration leads to a progressive loss of cardiac function with aging (decrement in cardiac index ~1% per year), which limits the ability of older individuals to maintain cardiac output in the presence of diminished filling pressure (10). This is further impaired by a decrease in the number and responsiveness of β-adrenergic receptors and fibrosis of the conduction system, which diminish the chronotropic and inotropic response to catecholamine stimulation. Coronary artery disease may exacerbate the situation by limiting oxygen delivery to the remaining functional myocardium, increasing the risk of ischemia and subsequent cardiac decompensation. Concurrent stiffening of peripheral vessels from atherosclerosis and a general increase in systemic vascular resistance (~1% per year) also occur. This works to preserve blood pressure despite a reduction in forward flow but also results in diminished compliance, which increases susceptibility to injury by shearing forces.

These changes and concurrent use of antihypertensive medications create a cardiovascular system that is less responsive to the drop in intravascular volume that can occur with trauma. Older patients often do not develop tachycardia in response to

hypovolemia, and those with hypertension at baseline may experience a substantial drop in blood pressure without meeting usual criteria for hypotension. As a result, abnormal vital signs are an insensitive indicator of life-threatening injury in older trauma patients, and triage systems should not rely solely on vital signs to identify high-risk patients (11).

Pulmonary

A decline in chest wall elasticity and lung compliance occurs with aging, leading to reductions in functional vital capacity and forced expiratory volume and an increase in residual volume (10). By limiting air movement, these alterations enhance the potential for carbon dioxide retention during periods of hypoventilation and barotrauma with positive-pressure ventilation. Because mucociliary clearance is also diminished, there is an increased risk of mucous plugging from secretions and pneumonia from bronchial obstruction. A progressive loss of alveoli is known to occur as well, which causes a decrease in diffusion capacity and arterial oxygen tension, manifesting as an age-dependent decline in the partial pressure of oxygen. Such changes are strongly potentiated by a history of smoking.

Injuries to the chest wall and lung can impair respiratory mechanics and dramatically increase the work of breathing. As such, they are not well tolerated in older adults. Older patients are particularly susceptible to rib fractures (estimated incidence, ~60%), which may occur even with minor force.

Renal

Renal function diminishes with advancing age due to a combination of progressive glomerular loss and decreases in renal blood flow. This results in a steady decline in glomerular filtration rate (GFR) and consequently, creatinine clearance. Serum creatinine concentration, however, does not accurately assess renal function, particularly in older individuals who have significantly reduced muscle mass. Direct measurement of creatinine clearance or estimation of GFR using validated formulae, therefore, is the preferred method for quantification of renal function in the older

trauma patient. In addition, these effects can be exacerbated by chronic diuretic use or suboptimal fluid intake with a resultant chronic hypovolemia.

Older patients are at high risk for deterioration in renal function even from brief periods of hypoperfusion. During the initial care of the injured older adult, the benefits of ensuring adequate renal blood flow by providing additional fluid must be balanced against the negative effects of aggressive fluid resuscitation, which may exacerbate uncontrolled hemorrhage, accelerate coagulopathy, and increase risk of pulmonary edema (12). Although urine output is considered a useful marker of renal perfusion in younger patients, it is less reliable in older individuals (13). This is due to a progressive reduction in urine concentrating ability, which permits ongoing production of seemingly adequate amounts of dilute urine even in the face of significant hypovolemia. Caution should also be exercised when using agents that have known nephrotoxic effects, particularly nonsteroidal anti-inflammatory medications and intravenous contrast agents.

Musculoskeletal

Osteoporosis is present to some degree in most older individuals, making them highly susceptible to fractures, and it is six times more prevalent in women than in men (14). The bones of the hip, wrist, and spine are at greatest risk and may be injured with minimal force. A seemingly straightforward fracture may result in substantial morbidity and risk of death in the older patient. Fractures often require operative fixation, subjecting the older patient to perioperative complications, whereas nonoperative therapy limits mobility and puts the patient at risk for skin breakdown, pulmonary embolus, and pneumonia. Pain medication, difficulty bearing weight, and mobility equipment devices may worsen balance, resulting in a high risk of falls and injury during the recovery period.

Dermatologic

Thinning of the epidermis, loss of dermal blood vessels, flattening of the dermal–epidermal junction, collagen degeneration, and loss of

subcutaneous tissue all occur with aging and increase the likelihood of damage when frictional or compressive forces are applied to the skin (10). These changes also slow wound healing, which increases the potential for infection and reduces the effectiveness of temperature autoregulation.

Neurologic

Progressive brain atrophy and dural adherence to the skull occur with aging. These changes lead to an increase in the subdural space surrounding the brain, and a stretching of the parasagittal bridging veins, making them more prone to rupture. As a result, older adults have a propensity for the development of subdural hematoma after head trauma; the rate is nearly two times that of younger patients (4.4% vs. 2.4%) (15). Because of brain volume loss, a substantial amount of blood can accumulate in the subdural space without producing a mass effect, leading to an increased risk of a delay between the time of injury and onset of symptoms. Cerebral contusions are also slightly more common in older than in younger adults. In contrast, epidural hematomas and depressed skull fractures are rarely seen (estimated prevalence of 0.5% and 0.2%, respectively) (10).

Mechanisms of Injury

Falls

Falls are responsible for the majority (~60%) of trauma in older adults. Falls in older adults often reflect underlying pathology or result from medication side effects. Falls commonly result in hip fractures, and an older adult with hip pain after a fall should be presumed to have a hip fracture. A negative plain radiograph does not exclude hip fracture, and computed tomography (CT) or magnetic resonance imaging (MRI) should be obtained in patients for whom hip fracture is suspected but not seen on plain films.

Vehicle-Related Accidents

Automobile collisions and injuries of pedestrians are the second and third most common causes of trauma in older adults, respectively,

with the former accounting for an estimated 250,000 US ED visits each year (2). Though most older drivers modify their driving habits as they age (i.e., driving at slower speeds, driving shorter distances, and avoiding driving at night and in adverse weather conditions), older drivers have the highest rate of fatal collisions of any age group. Factors that contribute to vehicle crashes in older drivers include slower reaction times, decreased visual fields, sensory or cognitive deficits, distractions, and medications. Though older drivers are less likely to use drugs or alcohol than younger drivers, impaired driving may also be a factor.

Ambulatory limitations, gait disturbances, and sensory deficits (especially visual and auditory) place older adults at particular risk for being struck by an automobile. Older pedestrians who are struck are more likely to suffer injury, particularly of the head, chest, spine, pelvis, and tibia (9). Of those who survive the initial impact, in-hospital mortality exceeds 25%—nearly four times that of younger patients (9).

Burns

Thermal injuries in older adults are responsible for 13% of all burn unit admissions in the United States. Burns in the geriatric population are associated with extensive tissue damage and significant morbidity as many of these individuals do not have the reflexes, muscle strength, or motor coordination to move away from the source of heat until substantial injury has occurred. In addition, wound healing is slowed in older adults, increasing potential exposure to nosocomial infection and prolonging the time to recovery. Increased age is an independent risk factor for mortality after burn, and the sum of age in years and the percentage of body area burned can be used to estimate burn-related mortality (16).

Penetrating Trauma

Penetrating trauma is responsible for 5% to 10% of all traumatic events that occur in older adults versus 25% to 45% in younger adults (17). Though injuries are generally similar in location and severity to other age groups, firearm injuries in older adults are more likely to be self-inflicted, particularly if the individual is a

white male. Penetrating trauma in the geriatric population is associated with prolonged intensive care unit (ICU) and hospital stays.

Neglect or Abuse

Neglect or abuse is a pervasive problem among older adults (18). Risk factors for abuse include a shared living situation, social isolation from friends and relatives, physical impairments, dementia, and exposure to perpetrators with a history of mental illness or substance abuse. Because caretakers and victims may deny or minimize the extent of the problem, cases are often difficult to recognize. Warning signs for abuse and neglect include delays in seeking medical attention, inconsistent history between caregiver and patient, unexplained injuries (fractures or bruising), discrepancy between history and physical examination findings and diagnostic testing, severe malnutrition, and poor hygiene.

Common Injury Patterns

Head

Closed head injuries are common in older adults, and the head is the most common body area to be severely injured. The incidence of traumatic brain injury and intracranial hemorrhage is increased in those of age ≥ 65 who sustain closed head trauma (12.5% vs. 7.9% in the National Emergency X-Radiography Utilization Study [NEXUS] II), and outcomes are worse, particularly for those in whom the presenting Glasgow Coma Scale (GCS) is ≤ 8 (in-hospital mortality 53% to 76%) (19,20). Because $>75\%$ of these events are related to ground level falls, the history and initial examination can be falsely reassuring. Typical “low-risk” criteria (i.e., absence of loss of consciousness or a GCS of 15) do not exclude intracranial injury in older adults. Both of the large validated instruments designed to determine the need for head CT scan after minor trauma identify advanced age as a criterion for obtaining a head CT (21). Thus, liberal use of CT is recommended for older individuals with closed head trauma. This is particularly true for those on antiplatelet or anticoagulant medications. Patients on these medications with

evidence of intracranial hemorrhage require rapid and complete correction of their anticoagulation to prevent progression of brain injury (22).

Spine

The incidence of cervical spine injuries doubles in older adults, with a particular increase in the occurrence of C1 and C2 fractures (23). As with head trauma, the majority of cervical spine trauma in older adults results from ground level falls (23). Although the Canadian C-spine Rule includes age ≥ 65 as an independent "high-risk" criterion that mandates radiographic assessment for all older trauma patients, the NEXUS criteria do not include age and have been validated in a geriatric cohort (13).

Although spinal cord injury itself is rare, older adults are at increased risk for central cord syndrome owing to a high prevalence of underlying spondylosis and a greater likelihood of cervical hyperextension related to a fall. Classic findings of central cord syndrome include upper motor neuron weakness (arms > legs, distal > proximal) and variable sensory deficits. These patients are at risk for progression of symptoms and must be admitted and closely observed.

Fractures of the thoracic and lumbar spines are also relatively common and may be present in 40% of patients with identified injuries of the cervical spine. They often manifest as anterior wedge compression fractures, particularly in older females with underlying osteoporosis (14). Though neurologic complications are infrequent, such fractures can be a source of debilitating pain. Plain film radiographs or CT are usually sufficient for initial evaluation, but subsequent investigation using MRI or bone scanning may be required to identify occult fractures in those with persistent discomfort.

Chest and Abdomen

Pneumothorax, hemothorax, and pulmonary contusion should all be considered early in the evaluation of the older patient with thoracic trauma. Rib fractures in particular are a marker of more severe injury and are associated with a 19% increase in the risk of death.

Initial evaluation with a single-view chest radiograph is appropriate but may not delineate subtle rib injuries, underlying lung contusion, or small pneumothoraces. CT should be considered in those with a nondiagnostic chest x-ray and significant discomfort, physical examination findings, or respiratory difficulty.

Abdominal trauma in older adults results in injury patterns similar to those in younger patients. Prompt recognition of hemoperitoneum is critical as older individuals do not have the physiologic reserve to withstand large-volume blood loss. Though initial screening with ultrasound is reasonable, negative results should be interpreted with caution, particularly for those with significant abdominal pain. Patients with pain or tenderness should be further evaluated using CT.

Pelvis and Extremities

Fractures of the proximal femur and pelvis are common in older individuals and most often result from a ground level fall. Among pelvic fractures, lateral compression fractures predominate, and 75% involve injury to the pubic rami or acetabulum. As compared to younger patients, older patients with pelvic fractures experience complications such as hemorrhage more commonly, require angiography and ICU admission more frequently, and have an increased risk of death. Owing to trabecular bone thinning, falls that impact the hips and pelvis are more likely to result in injury to the femoral neck and greater trochanter than to the pelvic bones themselves. Falls with the upper extremity in extension may result in fracture to the distal radius or the proximal humerus.

DIFFERENTIAL DIAGNOSIS

Though the consequences of trauma in older adults often require immediate attention, it is essential to consider the precipitating event, particularly in patients with unwitnessed or poorly described falls or those involved in single vehicle collisions. Life-threatening medical conditions such as cerebral vascular accidents, transient ischemic attacks, myocardial infarctions, malignant cardiac dysrhythmias, and critical electrolyte abnormalities could have

precipitated the event and should be considered in all older trauma patients. Some individuals, particularly those who reside in assisted living facilities, may have advanced dementia or other neuropsychiatric conditions that preclude verbal communication. For these patients, discussion with primary caregivers and prehospital personnel regarding the circumstances of the event, pre-existing medical conditions, and baseline medications should be pursued. Involvement of a social worker or adult protective services is necessary if abuse or neglect is suspected.

ED EVALUATION

The initial evaluation and resuscitation of the older trauma patient closely parallels usual trauma protocols. Adequacy of airway protection and respiration should be assessed immediately. Older patients are prone to develop hypoxia, and supplemental oxygen should be administered upon presentation. To avoid precipitous decompensation, early intubation should be considered in those with significant thoracic injuries. For patients who require intubation, care must be taken to limit manipulation of the oropharynx and hyperextension of the neck. Broken dentures, if present, should be removed to prevent further injury, but intact dentures may facilitate bag-valve-mask ventilation and should be left in place until definitive airway control is achieved.

Early identification of hypoperfusion in the older trauma patient is also critical and should be assessed simultaneously with the assessment of airway and breathing. As noted earlier, usual indicators (i.e., heart rate >100 beats/min and systolic blood pressure <90 mm Hg) are insensitive markers of hypovolemia in older adults, and significant hypoperfusion may be present in patients without tachycardia and with systolic blood pressures of 90 to 130 mm Hg. Thus, for all patients with suspected intra-abdominal injury, a bedside focused assessment with sonography for trauma (FAST) should be completed to determine the presence of intra-abdominal hemorrhage and laboratories should be obtained to identify occult reductions in tissue oxygen delivery (24). Impaired

perfusion as indicated by a base deficit greater than 6 mEq/L or a lactic acid concentration $\geq$2.4 mmol/L correlates with greater trauma severity and mortality and is more sensitive than vital signs for identifying life-threatening injuries (15). Worsening of the base deficit or failure to clear lactic acid on serial measurement are particularly ominous signs and should be considered indicative of insufficient resuscitation or developing complications (i.e., blood loss or ischemia).

Advanced hemodynamic monitoring has been shown to be particularly beneficial in older trauma patients, reducing complications of hypoperfusion, including multiorgan system failure, and improving survival (6). Parameters such as cardiac output, systemic vascular resistance, and oxygen delivery and consumption can be measured, and targeted resuscitative efforts using crystalloid fluids, vasopressors, and inotropes can be initiated. Although pulmonary artery catheterization is the time-honored method, noninvasive technology such as thoracic bioimpedance and near-infrared spectroscopy can provide equally accurate data with lower risk and cost. Bedside cardiac ultrasound is a useful adjunct in differentiating volume deficiency versus cardiac dysfunction as causes of hypotension. Patients with low output and elevated preload can be rapidly evaluated for pericardial effusion, and a rough quantification of cardiac function can be determined (10).

Radiographic evaluation of the older trauma patient may need to be delayed if the patient is hemodynamically unstable. However, once the airway has been addressed and access obtained, it is usually possible to perform cross-sectional imaging simultaneously with resuscitation and monitoring. Most, if not all, patients with head trauma (regardless of mechanism or degree of injury) should undergo head CT, especially if they are taking anticoagulants or antiplatelet medications. Plain films have been the traditional method of radiographic assessment for potential cervical spine injury, but CT has emerged as the modality of choice for initial evaluation in those with high-risk mechanisms, altered mental status or intoxication, suspicious clinical findings, or anatomic variants likely to limit plain film interpretation. Head CT has the added

advantage that it can be performed concurrently with other CT scans. Patients with abnormalities on CT or a clinical suspicion of spinal cord injury despite a normal CT require MRI. Given the high prevalence of concomitant injuries, x-rays or CT of the entire spine should be obtained in individuals with cervical spine fractures, even in the absence of physical examination findings.

As previously noted, there should also be a low threshold for ordering CT to evaluate for potential thoracoabdominal injuries. Moreover, although plain films may be adequate for the evaluation of most musculoskeletal injury, further imaging with CT or MRI may be required in patients with negative x-rays but persistent pain. This is particularly important for hip fractures, which may be occult in up to 5% of cases. For patients with signs or symptoms suggestive of a life-threatening injury, the initial evaluation and treatment should be coordinated with a trauma surgeon-intensivist, preferably in a trauma center (25).

KEY TESTING

- With the exception of critically ill trauma patients, the ED evaluation of all trauma patients including older adults is focused on the exclusion of fractures and internal bleeding through the use of imaging.
- In contrast to younger adults, there are no validated criteria for identifying a subset of older adults with blunt head trauma who do not need CT scan. In older adults with loss of consciousness or visible signs of blunt trauma to the head, a head CT is appropriate.
- The NEXUS criteria have been validated in older adults and are a reasonable approach to determining the need for cervical spine imaging. A low-energy mechanism (e.g., ground level fall) does not exclude cervical spine fracture in older adults.
- Patients with either abdominal pain or tenderness should be evaluated with cross-sectional imaging.
- Trauma patients with chest pain that is obviously musculoskeletal (i.e., worse with movement and tender to

palpation) do not need an EKG or cardiac enzymes unless other indications for these tests are present.
- As in younger adults, no older adult trauma patients should be discharged until they have ambulated and had repeat vital signs which are similar to their usual vital signs over a reasonable period of observation, generally at least 3 hours.
- Older trauma patients taking anticoagulant therapy (e.g., Coumadin, direct thrombin inhibitors) should be admitted for observation or sent home only in the presence of a responsible party and given strict return precautions, even if all imaging tests are normal.

ED MANAGEMENT

Survival to hospital discharge with intact neurologic function may be achievable in more than half of severely injured older trauma patients. As such, the initial evaluation should proceed immediately with all therapeutic options open regardless of age. Treatment should involve optimization of perfusion using fluids preferentially, pressors and inotropes if necessary, and maximization of oxygen-carrying capacity using packed red cells for those with ongoing blood loss or a hemoglobin <8 g/dL. Other critical interventions include administration of vitamin K (10 mg IV), fresh-frozen plasma (4 units), or prothrombin complex concentrate (PCC) for those on anticoagulation with closed-head injury (12); use of broad-spectrum antibiotics for open fractures; and administration of opioid analgesics (with a low threshold for intubation) for patients with rib fractures. Adequate treatment of pain in older trauma patients reduces suffering and may also reduce both short- and long-term psychological distress associated with the event. Because elderly trauma patients are more than twice as likely to develop nosocomial infections and more than five times as likely to die as a result of trauma-related complications, it is also important to pay attention to preventive measures such as strict sterile technique during invasive procedures (e.g., central venous access or chest tube placement), and prevention of contrast-induced nephropathy by administering

the minimal amount of contrast needed and giving fluids to those receiving contrast.

Certain combinations of injuries and initial findings, such as severe thoracic or abdominal injury *and* moderate-to-severe (abbreviated injury scale ≥ 3) head injury, hypotension *and* evidence of profound shock (base deficit ≤ -12) are highly predictive of death. Under such circumstances, the decision to withdraw care in the ED may be reasonable but should be made in concert with the attending trauma surgeon, family members, and a palliative care or geriatric specialist, if available.

CRITICAL INTERVENTIONS

- Perform a comprehensive evaluation for ongoing bleeding using bedside ultrasound, serum markers (base deficit and lactic acid), and advanced hemodynamic monitoring (either invasive or noninvasive) with aggressive intervention for identified deficits.
- Use CT liberally for closed-head injury and possible cervical spine injury, particularly in patients with a history of anticoagulation.

DISPOSITION

The mechanism of injury, past medical history, and extent of current injuries should be considered when making disposition decisions. Because occult serious injury and subsequent clinical deterioration are well-recognized threats in older patients, most patients should be admitted for observation unless the mechanism is very minor. Patients with multiple comorbid conditions, limited capacity to follow through with important discharge instructions, or poor social support at home should be admitted. Patients with seemingly minor injuries, such as multiple rib fractures, require admission for observation and pain control, as they are at risk for complications. Appropriate social work consultation and home-safety evaluation should be arranged prior to discharge.

Common Pitfalls

- Assuming that a patient with normal vital signs is “stable.”

- Failure to recognize the potential significance of minor head trauma.
- Failure to evaluate for occult fractures (ribs and hip) in patients with persistent pain despite negative plain films.
- Failure to observe or hospitalize high-risk older patients with seemingly minor injuries.
- Failure to recognize abuse and neglect as the cause of injury.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Phillip D. Levy to the content of this chapter.

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SECTION V
Eye Emergencies

Section Editor: GREGORY W. HENDEY

Medical Foramen

CHAPTER 54 The Eye Examination

Matthew R. Babineau and Leon D. Sanchez

Ocular complaints comprise more than 3% of visits to the emergency department (ED) (1). The severity of these complaints vary from minor to vision threatening, and an emergency practitioner (EP) must be able to risk stratify these to ensure timely diagnosis and appropriate treatment. A thorough and accurate physical examination is therefore an essential skill of all emergency physicians.

ED EVALUATION

History

The history often provides enough information to allow the physician to focus on the appropriate segment of the visual system. Key historical points include age, trauma, current symptoms, ocular history, systemic illness, occupation, and allergies. The patient should be asked if they use corrective lenses (glasses or contact lenses). About 5% of nontraumatic eye complaints are the initial manifestation of systemic illness, so a review of systems should be conducted with special attention to cardiovascular and neurologic symptoms.

Pain and Discomfort

Pathology of the ocular surface or lids usually produces burning, itching, tearing, and foreign body sensation. Orbital or periorbital discomfort is usually described as a dull ache, and may be caused by pathology such as uveitis, episcleritis, scleritis, or acute glaucoma.

Peri- or retro-orbital pain may also be due to nonocular causes, such as sinus congestion, vascular or cluster headaches, or intracranial pathology (e.g., aneurysm, arteritis, infection, tumor). It is important to note that, because of sensory overflow from various segments of the fifth cranial nerve, it may be difficult to identify the source of pain by history alone.

Photophobia

Photophobia typically is due to painful contraction of an inflamed iris (as seen in iritis or uveitis), or from inadequate papillary constriction, resulting in excess light reaching the retina. Nonocular causes of photophobia include migraines and inflammation of the meninges (e.g., meningitis, subarachnoid hemorrhage).

Discharge and Tearing

Discharge is typically a by-product of inflammation of the ocular surface due to allergy or infection. Purulent discharge is suggestive of a bacterial infection. Epiphora (excess tearing) is typically due to emotion, irritation of the ocular surface (due to abrasions, infections, foreign bodies or chemical exposures), or abnormal drainage of tears through the lacrimal system (2).

Redness and Swelling

Redness and swelling of the sclera is most often due to inflammation caused by infections or allergies, though it can rarely be a sign of orbital venous congestion, as can be seen with orbital cellulitis, cavernous venous sinus thrombosis, thyroid ophthalmopathy, and fistulae. Intraocular inflammation will typically cause redness (especially in the perilimbal region), but swelling is rare (endophthalmitis, some cases of scleritis).

Visual Disturbances

Visual disturbances can be a symptom of pathology in the visual system anywhere from the cornea to occipital cortex, and are often related to a nonocular cause. “Blurred vision” may be a catchall term

used by patients to describe a number of different visual abnormalities, and the clinician must attempt to specify the exact nature of the disturbance. Glare or halos are caused by light scatter phenomena from unclear ocular media, as in mucinous tear film, corneal edema or epithelial abnormalities, cataract, and/or vitreous haze. Spots or floaters are often due to opacities within the vitreous. Vision loss should be classified as monocular (indicating pathology of the anterior visual pathway and circulation) versus binocular (indicating pathology of the neurovascular system posterior to the optic chiasm).

Diplopia

Diplopia may be caused by serious underlying disease (see Chapter 59). Monocular diplopia is rare and is caused by pathology within the cornea or lens. Binocular diplopia is caused by ocular motility disturbances, such as cranial nerve palsies or extraocular muscle disorders (e.g., entrapment following trauma).

THE OCULAR EXAMINATION

A systemic approach to the ocular examination will facilitate accurate diagnosis and exclusion of vision threatening pathology. The ocular examination can be divided into eight components

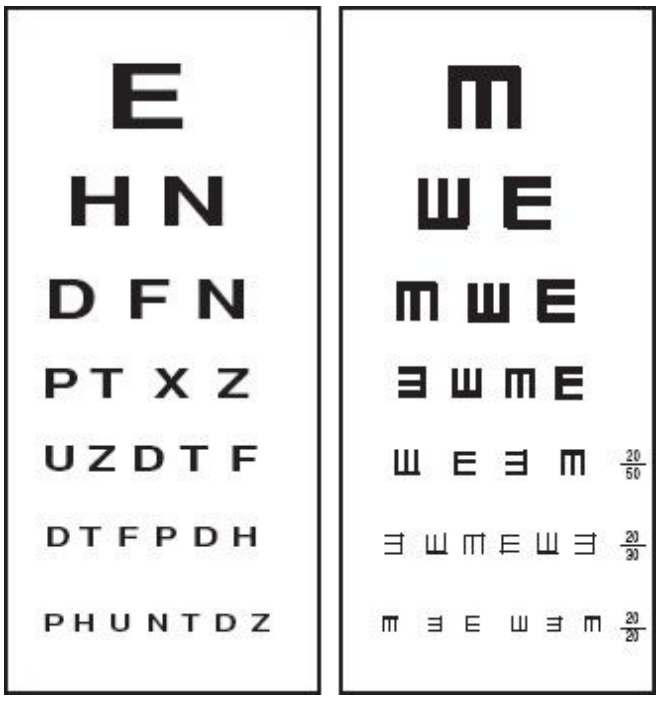
1. Visual acuity
2. Face and external eye
3. Extraocular muscles
4. Visual fields
5. Pupils
6. Anterior segments
7. Posterior segments
8. Intraocular pressure (IOP) measurement

VISUAL ACUITY

Visual acuity is the “vital sign of the eye” (3). There are various methods to measure visual acuity. Regardless of the method chosen, it is essential to measure each eye individually, with the other eye

completely covered, as patients may look around hands or through fingers. If corrective lenses are available, vision should be tested with these. The acuity of each eye should be documented individually (even if they are the same), and the presence or absence of corrective lenses should be documented as well.

The Snellen chart is the standard tool used to measure visual acuity (3) (eFig. 54.1). The patient is asked to read the smallest line that they can see (4). Visual acuity is expressed as a fraction, where the numerator is the distance of the patient from the chart, and the denominator is the distance at which a patient with normal vision can read the line of letters (2). For example, a visual acuity of 20/50 indicates that a patient can see from 20 feet that which someone with normal vision can read at 50 feet. A "near chart" held at 14 in from patient can replace a Snellen chart for patients who are unable to stand, and the visual acuity is recorded in the same fashion (3). The exception is that near-vision abnormalities can also be due to normal age-related presbyopia, or rarely, traumatic mydriasis (4).



eFIGURE 54.1 Snellen and tumbling E charts. The tumbling E chart can be used to test visual acuity in children or illiterate patients, by asking the patient to indicate which direction the E is "pointing."

(From Weber J RN and Kelley J RN. *Health Assessment in Nursing*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

If the visual acuity is not normal, the EP can test the patient using a pinhole card. A pinhole card will correct most refractive errors, so improved vision indicates an optical problem that can be addressed on a nonemergent basis (3). A pinhole card can be easily constructed by punching several holes in the center of a 3- × 5-in index card with an 18-g needle (4). Alternatively, the patient can be asked to view a near chart through the handheld ophthalmoscope, and progressively change the dial until vision is clearest. This will simulate use of corrective lenses (5).

If the patient cannot read the largest letter of the Snellen chart, he should be moved closer to the chart in 5-foot increments, until he can read it. If unable to read the chart at 5 feet, the patient should be asked to count fingers (CF) at 2 feet. If still unable to see, test whether the patient can detect hand motion (HM). If this fails, the patient should be tested for light perception (LP). If they are able to detect light, they should be asked to indicate which direction the light is coming from (this is called “LP with projection”). If there is no light perception (NLP), the patient is considered to be totally blind (6).

If a patient is unable to communicate, or is suspected of factitious blindness or malingering, the practitioner can ensure that the visual pathway is intact by checking for optokinetic nystagmus (4). To perform this test, an object such as newsprint or a tape measure is placed in front of the patient’s eyes, and the patient is asked to fixate on it as it rapidly passes from side to side in front of a patient. If the visual pathway is intact, the EP will note nystagmus-like eye movements which demonstrate that the patient is tracking (4). A variation can be performed using a large mirror held in front of the patient, and slowly moving it to either side of the patient. A patient with intact visual pathway will maintain some degree of eye contact as the mirror moves (4).

Face and External Eye

Obvious abnormalities (trauma, foreign bodies, edema, swelling, erythema) should be noted. The relative positions of the eye within the orbit should be evaluated by gross inspection. Unilateral proptosis may be due to trauma, orbital cellulitis or hemorrhage, cavernous sinus thrombosis, or other causes (6). Bilateral exophthalmos is most often due to hyperthyroidism (2,6). Enophthalmos is often due to an orbital fracture, and may be associated with other findings such as subconjunctival hemorrhage, restriction of upward gaze or hypoesthesia of cheek due to infraorbital nerve injury (2,6). Ex- or enophthalmos may be best appreciated by looking down at the patient's eyes from above their head (3). Proptosis should be differentiated from keratoconus, where the cornea is cone shaped and may give the illusion of exophthalmos (3).

The EP should note the relative positions of the lids, and the size of the palpebral fissure (the space between the upper lid and lower lid). While ptosis can be present from birth, acquired ptosis is often due to Horner syndrome, isolated CN III palsy, or trauma (2,6). It may also be an early sign of myasthenia gravis. In myasthenia, the EP can attempt to provoke the ptosis by asking the patient to look up for several minutes, to fatigue the palpebral muscles (2). Inability to close the lid may be due to a dysfunction of CN VII (i.e., in Bell palsy).

EXTRAOCULAR MOTILITY

Extraocular motility (EOM) should be tested in the six cardinal directions of gaze (right, left, up and right, up and left, down and left, down and right). It is especially important to assess in cases of trauma, suspected infection, or double vision (3). Each eye should be evaluated separately. Extraocular movements require complex coordination between the brain, cranial nerves III, IV, and VI as well as the four extraocular muscles, so abnormalities of gaze may represent pathology in any of these areas. If no deficits are obvious to the EP, the patient should be asked if they experience diplopia

with any movements, and if it is present only when both eyes are open, or only when looking through one eye. Binocular diplopia may be due to orbital infection/tumor/inflammation, nerve compression, or aneurysm in the circle of Willis (3). Monocular diplopia is due to ocular pathology (cornea, iris, lens, or retina) within that individual eye (3).

Nystagmus may be noted during testing of extraocular movements. The two broad types of nystagmus are "jerk nystagmus" (where the eye repetitively drifts slowly in one direction [slow phase], then rapidly returns to normal position [fast phase]) and "pendular nystagmus" (drift occurs slowly and equally in both directions, giving smooth back and forth movement of the eyes) (7). Nystagmus should be described in terms of type (jerk versus pendular), which extraocular motions provoke it (and/or if it is present in primary gaze), the direction of the nystagmus (lateral, vertical, torsional/rotatory), and whether it is extinguishable/fatigable.

Normal individuals may demonstrate a fatigable lateral jerk nystagmus with extremes of gaze (end-point nystagmus), or when fixating on stationary objects while moving (optokinetic nystagmus). Pathologic etiologies of nystagmus are usually due to CNS (thalamic hemorrhage, tumor, stroke, trauma, MS) or toxic/metabolic etiologies (including alcohol, lithium, barbiturates, phenytoin, salicylates, phencyclidine, Wernicke encephalopathy) (7).

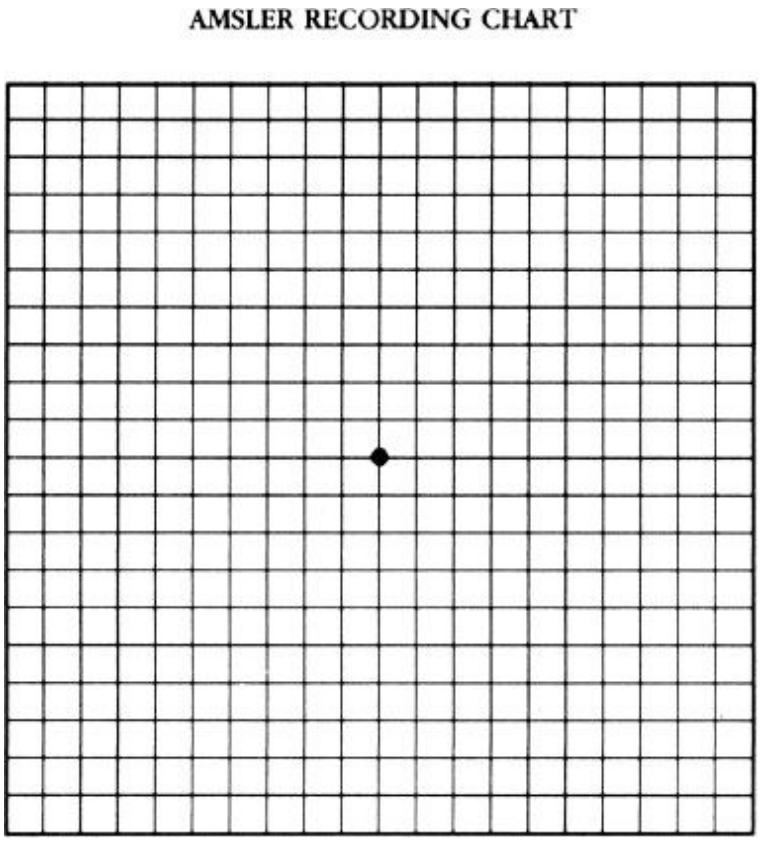
VISUAL FIELDS

The visual fields extend in each eye to 170 degrees horizontally, and 130 degrees vertically (2). Testing of the visual fields is an important test of the global visual path from eyes to occipital cortex. A monocular field deficit suggests ocular pathology, while deficits present in both eyes are often due to an intracerebral process. While formal perimetry is the most accurate way to assess visual fields, it is not practical in the ED, so EPs can test visual fields by confrontation field or the Amsler grid.

To perform confrontation field testing, the examiner faces the patient, and asks the patient to close one eye. The examiner closes the ipsilateral eye, and slowly moves a target (typically fingers) into

the visual field from a 45-degree angle. The object should be seen more or less simultaneously by the patient and the examiner. After testing in several areas, the process is repeated on the other eye. Any field deficit should be noted and documented (2).

To test the central 10 to 20 degrees of vision (the macula), an Amsler grid is used (eFig. 54.2). Using one eye at a time, the patient is asked to fixate on the central dot, and describe any wavy lines (metamorphopsia) or blind spots (scotoma). Abnormalities of Amsler grid testing typically indicate retinal pathology.



eFIGURE 54.2 Amsler grid. (From Harwood-Nuss A, Wolfson AB, et al. *The Clinical Practice of Emergency Medicine*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.)

PUPILS

The clinician should note the size, shape, and symmetry of the pupils. Normal pupils are typically 3 to 5 mm in diameter. Pupillary constriction is mediated by parasympathetic tone, and pupillary

dilation is mediated by sympathetic tone. Myriad disease processes, medications, and toxins can cause pupils to be abnormally small (miosis) or large (mydriasis) (Table 54.1). Unequal pupils (anisocoria) are often thought of as pathologic, however, 20% of normal individuals (2,6,8) may have a physiologic difference of 1 mm or less (essential anisocoria). Pathologic anisocoria can be due to Horner syndrome, uveitis, trauma, uncal herniation, CN III palsy, or due to drugs (including nebulized ipatropium) (6).

TABLE 54.1
Causes of Miosis and Mydriasis

Miotic Pupils		Mydriatic Pupils	
⇑ cholinergic	Pilocarpine drops, opiates	⇓ cholinergic	Atropine, CN III paralysis, Adie's Pupil, Antihistamines
⇓ Sympathetic	Horner syndrome, Aldomet, Reserpine	⇑ sympathetic	Phenylephrine, epinephrine, anxiety, cocaine, decongestants
Irritation to constrictor muscle	Iritis, histamine release from inflammation	Damaged constrictor muscle	High IOP (>40 mm Hg), trauma (especially with hyphema)

Data from Leitman MW. Manual for Eye Examination and Diagnosis. Wiley; 2011: 14 April 2013 <http://lib.myilibrary.com?ID = 345400>.

After noting the pupillary size, the pupillary light reflex should be tested, by shining a bright light into each pupil. The speed and degree of pupillary constriction should be observed in both the pupil receiving the light (direct response), and simultaneously in the other eye (consensual response). The light should then be swung between the two eyes (the swinging flashlight test), allowing the midbrain to sample the intensity of input from each eye, with the direct and consensual response noted. A pupil that dilates as the light is swung to it is referred to as relative afferent pupillary defect (or Marcus Gunn pupil) (6). This indicates a problem in the neuroretinal path of the affected eye, such as occurs in optic neuritis or a large retinal detachment (9). Other pupillary syndromes are found in Table 54.2. It should be noted that neuromuscular blocking agents do not acutely affect the pupillary light reflex, though some induction agents (e.g., ketamine) may depress this reflex (10,11).

TABLE 54.2
Pupillary Syndromes and their Physical Findings

Name	Physical Findings	Comments
Horner syndrome	Miotic pupil on affected side, may be accentuated in dim illumination	Due to lesion in sympathetic pathway (V). Unlike physiologic anisocoria, will not dilate in response to topical cocaine. + Anisocoria
Adie's tonic Pupil	Tonically dilated pupil with reduced direct and consensual light response. Reacts to accommodation, though slowly.	Due to a benign defect in the ciliary ganglion (parasympathetic innervation of eye), often due to infection. + Anisocoria.
Argyll Robertson pupil	Bilateral small pupils that constrict with accommodation but not with light ("light-near dissociation")	Highly specific for neurosyphilis. No anisocoria.
Marcus Gunn pupil	Affected pupil appears to dilate when swinging light shines in it.	In total CN II lesion (affected eye perceives no light), there is no effect. No anisocoria.

Anterior Segments

The anterior segments of the eye (conjunctiva, cornea, anterior chamber, iris, and lens) and the adnexa (eyelids, eyelashes, and lacrimal apparatus) are best evaluated using the slit lamp. While models vary, each slit lamp will have an illumination system and an observation system. The illumination system projects light through a slit aperture onto the patient's eye. The observation system is a binocular stereoscope which can provides 6 to 40× magnification. The observation system is mounted on a chassis that can be moved to allow the examiner to focus on the desired part of the eye.

To perform the examination, the patient's chin is placed on the chin rest, and the forehead against the forehead bar. The chin rest is adjusted so that the patient's eyes are aligned with the black line on the vertical pole next to the patient's face. The light source should be at 45 degrees from the clinician–patient axis, and the light should be set to a low-voltage, wide beam. The microscope should initially be set to the lowest magnification. The chassis is moved with the joystick until the eye comes into focus. Most of the examination can be performed using the low magnification, wide beam setting (4). Only when the cornea and anterior chamber are being examined must the beam be narrowed. The clinician may then begin a systematic evaluation of the anterior chamber. While any system may work, an easy to recall system is "L3C3." (Lids [and lashes], Lacrima, Lens [and iris], Conjunctiva [and sclera], Cornea, and Chamber [anterior]).

Lids and Lashes

Eyelids are evaluated for edema, erythema, trauma, and tenderness. Hordeolum (sty) is acute inflammation or infection of the glands of Zeis or Moll, around the lashes, that will point externally (Fig. 54.1A,B) (2). Chalazion is a chronic (may last for months) obstruction and inflammation of a meibomian gland, appearing as a mildly tender nodule along lid margins or on the palpebral conjunctiva, that will point internally (Fig. 54.1A,B) (12). These may not have typical signs of infection such as redness and swelling, and are often incidentally discovered (12). Diffuse erythema and edema of the lid may indicate a periorbital/preseptal cellulitis, which may be associated with adenopathy and fever (2). Orbital cellulitis may have a similar external appearance, but is often associated with ophthalmoplegia, pain with extraocular movements, and exophthalmos. In a patient who is being treated with antibiotics for lid cellulitis, shriveled skin on the lid may be an indication that the infection is responding to therapy (2).

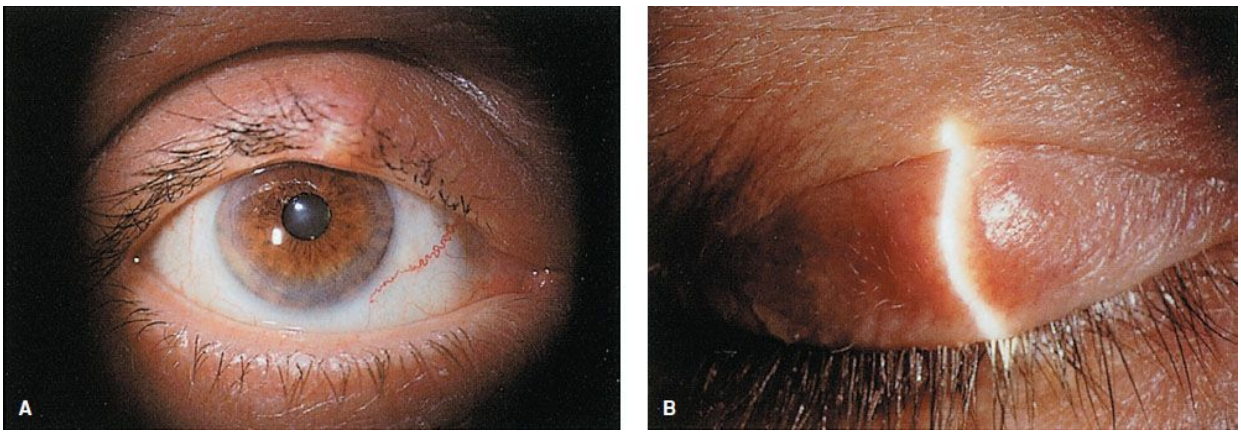


FIGURE 54.1 A: Hordeolum. (From Bickley LS. *Bates' Guide to Physical Examination and History Taking.* 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003:178.) B: Chalazion. (From Bickley LS. *Bates' Guide to Physical Examination and History Taking.* 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003:178.)

Blepharitis (anterior or posterior) is inflammation or infection of the lid margin, and also can manifest as an erythematous, edematous, pruritic eyelid (Fig. 54.2A,B). Anterior blepharitis is

often associated with scalp dandruff, and manifests as crusting, scaling redness, and ulcerative lesions around the eyelashes. Posterior blepharitis is secondary to obstruction and infection of meibomian glands, which are in contact with the surface of the eye. Expressing a white, pasty secretion from the meibomian glands is diagnostic of posterior blepharitis.

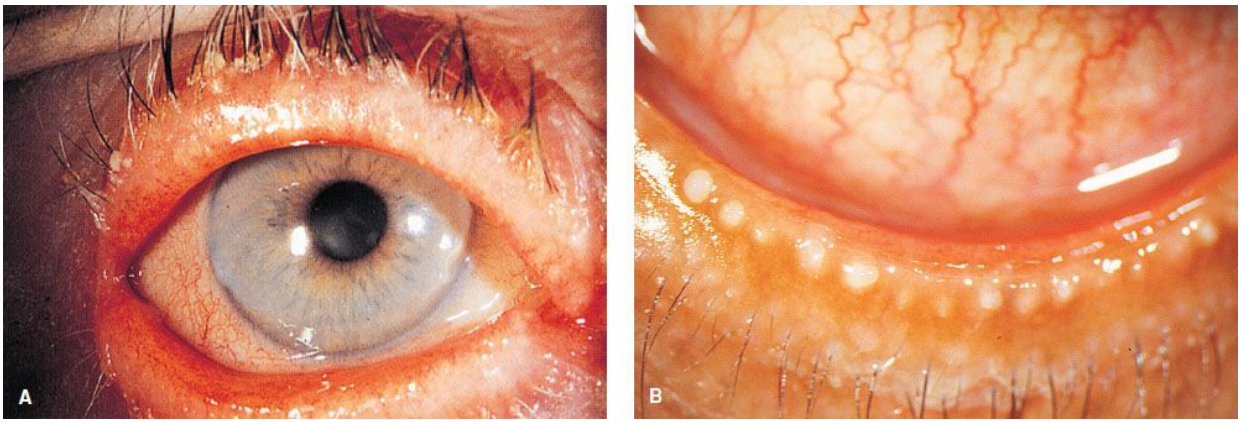


FIGURE 54.2 A: Anterior blepharitis. (From Tasman W, Jaeger E. *The Wills Eye Hospital Atlas of Clinical Ophthalmology*. 2nd ed. Lippincott Williams & Wilkins, 2001.) B: Posterior blepharitis. (From Tasman W, Jaeger E. *The Wills Eye Hospital Atlas of Clinical Ophthalmology*. 2nd ed. Lippincott Williams & Wilkins; 2001.)

Traumatic lacerations that violate the tarsal plate or the lid margin (especially if near the nasal canthus, where there is risk of injury to the lacrimal duct) should be referred emergently to ophthalmology for repair.

To examine the conjunctival surfaces of the superior eyelid, or to look for a foreign body, the lid should be everted. To do this, the patient is asked to look downward. The examiner then grasps the eye lashes at the lid margin, and uses a cotton-tipped applicator applied to the midportion of the upper lid as a fulcrum to evert the eyelid. The patient can look upward to return the eye to a normal position (2,3).

Lacrima

Excess tearing (epiphora) is common and should be noted. Diagnosis of lacrimal obstruction may be made by instilling fluorescein dye into the tear wells of each eye—in the obstructed eye, the fluorescein will dissipate more slowly, or run over the lid onto the cheek.

The lacrimal system can also become infected. Canaliculitis typically involves the lower canaliculi, and a red, "pouting" punctum is visualized (Fig. 54.3A,B) (7). Acute dacryocystitis presents as rapid onset of pain, erythema, edema, and purulent discharge in the medial canthal region (Fig. 54.3A,B). It may coexist with signs of sinusitis, and may progress to orbital or preseptal cellulitis (7). Chronic dacryocystitis typically is less dramatic, and may only be noted by expression of mucopurulent discharge with palpation of the nasolacrimal sac.

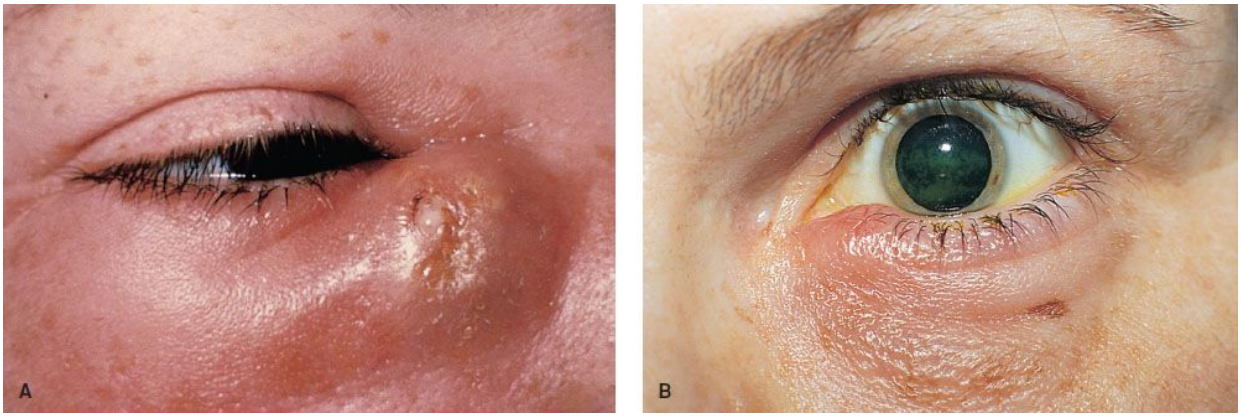


FIGURE 54.3 **A:** Acute dacryocystitis with draining fistula. (From Gold DH, MD, and Weingeist TA, MD, PhD. *Color Atlas of the Eye in Systemic Disease.* Baltimore: Lippincott Williams & Wilkins;2001.) B: Canaliculitis. (From Tasman W, Jaeger E. *The Wills Eye Hospital Atlas of Clinical Ophthalmology.* 2nd ed. Lippincott Williams & Wilkins; 2001.)

Lens (and Iris)

The lens can be rapidly visualized for evidence of cataracts (opacification), as well as traumatic lens displacement. Any potential trauma to the lens capsule must be noted, as the lens may rapidly opacify, necessitating prompt surgical correction. Corneoscleral lacerations can often be noted as the pupil becomes tear shaped as

the iris plugs the laceration (Fig. 54.4). Iridodialysis refers to tearing of the iris from the sclera at its root, and may also result from trauma. Blood vessels growing on the surface of the iris (rubeosis iridis) are abnormal, and associated with proliferative retinopathies.

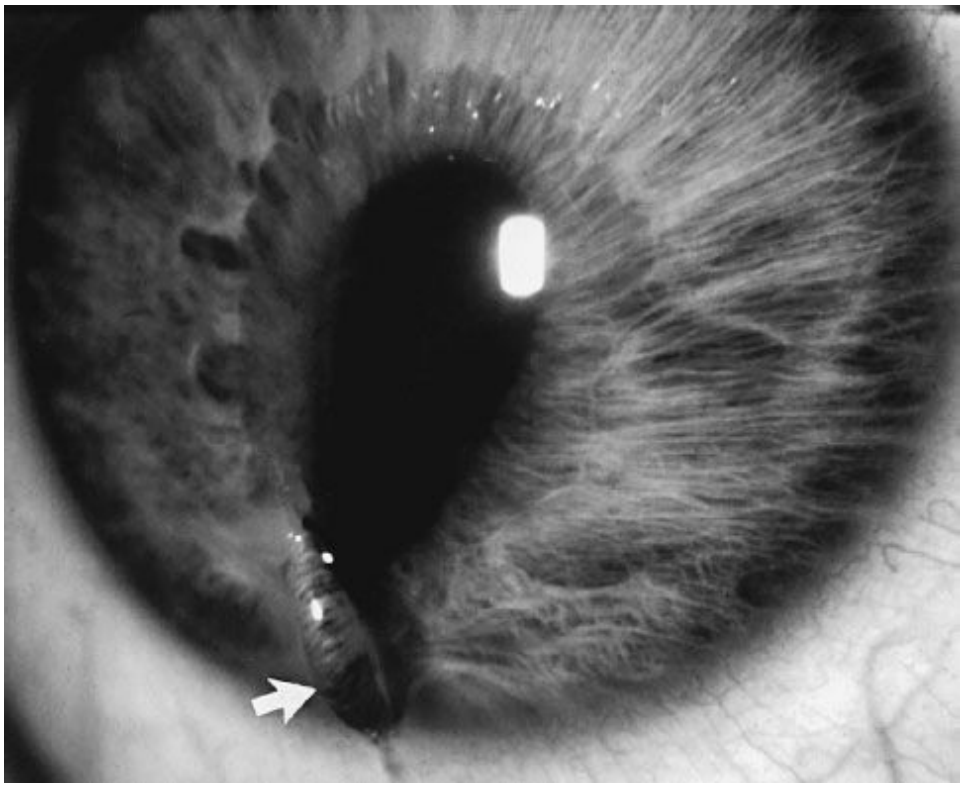


FIGURE 54.4 Tear drop pupil from corneal laceration, with iris protruding through wound (arrow). The pupil points in the direction of the laceration. (From Fleisher GR. *Textbook of Pediatric Emergency Medicine.* 5th Ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.)

Conjunctiva (and Sclera)

The conjunctiva is a mucous membrane that covers the sclera (bulbar conjunctiva) as well as the inner surface of the lids (palpebral conjunctiva) (2). Conjunctivitis typically manifests as diffuse injection of the conjunctiva. Follicles (tiny, white lymphoid elevations of the conjunctiva) and papillae (vascularized elevations of the palpebral conjunctiva which resemble cobblestones) are commonly seen (Fig. 54.5) (13). Allergic conjunctivitis typically

shows bilateral symmetric injection, possibly associated with clear, watery discharge and slight lid swelling (14). Viral conjunctivitis is also typically bilateral, and may be associated with follicles as well as preauricular lymphadenopathy (13). Bacterial conjunctivitis typically has an abrupt onset of initially unilateral injection that is diffuse but may be more pronounced at the fornices (14). It is often associated with mucopurulent discharge with morning crusting, and will often progress to the other eye within 48 hours (14,15).

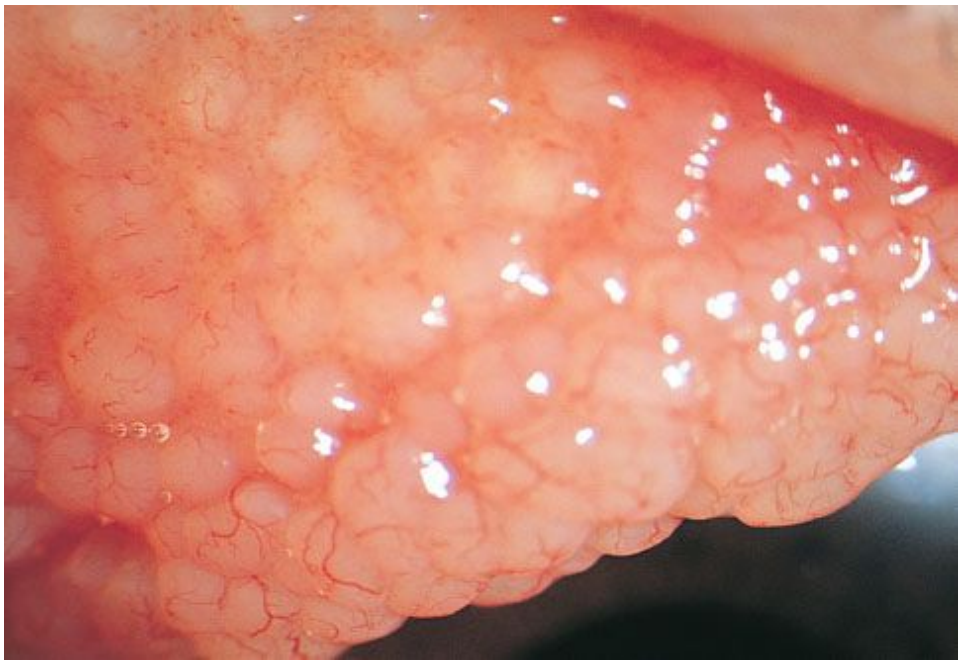


FIGURE 54.5 Follicles = may be seen in conjunctivitis. (From Tasman W, Jaeger E. *The Wills Eye Hospital Atlas of Clinical Ophthalmology*. 2nd ed. Lippincott Williams & Wilkins; 2001.)

The limbus is the area surrounding the iris, where the cornea connects to the sclera. In the patient with complaints of eye pain or redness, this area deserves special attention from the examiner. The presence or absence of injection (prominence of blood vessels) at this site can help differentiate inflammation from the conjunctiva (typically diffuse), to more serious problems such as iritis/uveitis (more prominent in the perilimbal area).

Other conjunctival findings include subconjunctival hemorrhage, which appears as a painless bright red area on the sclera, and is often

spontaneous or after Valsalva maneuvers such as coughing or straining (4). While typically benign and self-limited, severe hemorrhages covering the entire bulbar conjunctiva may signify coagulopathy or ruptured globe. Chemosis refers to edema of the conjunctiva, and is most often due to allergy, but may also be secondary to orbital venous congestion (from infection or tumor). Pterygium is a triangular growth of vascularized conjunctiva that extends to nasal aspect of cornea. It is common in patients who are chronically exposed to wind or ultraviolet light (2). A pinguecula is a common benign elevation of the conjunctiva, which can become red with allergies (2). Both can be referred for excision if they affect vision or are cosmetically bothersome.

Cornea

The cornea is the transparent anterior continuation of the sclera. It contains three layers—a superficial epithelial surface, a central stroma, and a deep endothelial layer. Corneal epithelial cells regenerate rapidly and 40% of the corneal surface can regenerate within 24 hours (2). The central stroma is a connective tissue layer with a dense collection of nerve fibers, thus explaining why corneal pathology may be extremely painful. The deep endothelial layer is responsible for pumping fluid out of the stroma and maintaining clarity of the cornea. It is only one-cell thick and cannot regenerate.

The three layers of the cornea should be visualized under the magnification of the slit lamp. With the lamp offset at 45 degrees, the practitioner should scan back and forth for any abnormalities. Foreign bodies will be obvious. Epithelial edema (translucent) and ulcers (opaque) will appear as irregularities in the contour of the cornea.

Fluorescein examination should be performed in any case of suspected abrasions, foreign bodies, or infections, and it helps to delineate the extent and often, etiology, of corneal injuries (4). The fluorescein should be instilled into the tear well, and the light source changed to cobalt blue. Defects in the corneal surface will appear bright yellow-green (6). The pattern of fluorescein uptake should be noted, as many etiologies of corneal pathology have specific

associated patterns. Circular defects often are due to foreign bodies. Abrasions are typically in the central cornea due to the limited protection from eyelids (4). Multiple vertical defects should prompt close inspection for retained foreign body under the upper lid. Herpetic lesions are classically dendritic in appearance (4). In traumatic ocular injuries, a dark blue-green stream of fluid within a bright yellow-orange area of fluorescein uptake represents leakage of aqueous humor through a corneal defect, and is known as Seidel sign (4,9).

After examining the corneal epithelium, the EP can examine the stromal layer for edema (cloudy appearance), deep ulcerations, and vascularized tissue. An advanced practitioner may also examine the single-cell width endothelial layer, and visualize keratic precipitates (white cells along the endothelium), which is highly specific for uveitis, but may only be seen with chronic inflammation (2).

Chamber (Anterior)

The anterior chamber is the aqueous-filled area between the cornea and the iris. Examination of the anterior chamber should include an evaluation of the depth of the chamber, as well as an assessment for abnormal cells within the aqueous humor.

To assess the depth of the anterior chamber, the slit lamp should be used with low magnification and the narrowest possible beamwidth, and focused on the corneal surface. Two beams will be visible on this view–-a curved beam (reflecting off the cornea) and a straight beam (reflecting off of the iris). The anterior chamber depth is the area between the two. Shallow chambers are pathologic, and may be due to acute–angle-closure glaucoma or corneal perforation (4).

A crude estimate of anterior chamber depth can be approximated with the transillumination test. To perform this test, a penlight is shone across the cornea from the temporal side, perpendicular to the line of vision. If the entire cornea illuminates, this suggests a deep anterior chamber (open angle). Shadowing of the iris on the nasal side implies a shallow anterior chamber (narrow angle) (6). It is

essential to ensure that the light is perpendicular to the line of vision, as oblique angles can give false-negative results (4).

While hyphema and hypopyon can often be seen with the naked eye, more subtle findings such as cells (white blood cells in the aqueous) and flare (cloudy/milky light scatter due to increased proteinaceous material within the aqueous) may only be visualized using the slit lamp magnification (6). These may be seen in uveitis, scleritis, or trauma. First, increase the magnification of the microscope, and make the beam as narrow as possible. Focus the beam on the cornea, and then push forward until it is focused on the lens (4). To illuminate the anterior chamber, move the light backward to a point where the beam is focused on an area midway between the cornea and the lens (4). Visualization will be improved by keeping the light centered on the pupil, to maintain a black background (4). The anterior chamber should be completely clear. Cells are seen as small particles floating within the beam, and flare looks like a "searchlight in the fog" or a "motion projector beam in a smoky room" (3,4). It should be noted that fluorescein can penetrate an abraded cornea and produce a "fluorescein flare" (4). For this reason, some practitioners recommend examining the anterior chamber prior to fluorescein staining.

Posterior Segments

The examination of the retina is another important part of the ocular examination, particularly in cases of vision loss (3). The lights of the examination room should be lowered to facilitate pupil dilation, and the patient asked to fix gaze on a distant object. The dial on the ophthalmoscope should be initially set to zero. The examiner brings the ophthalmoscope as close as possible to the patient's eye (examiner should examine patients right eye with her right eye, and vice versa), and adjusts the dial to bring the retina into focus. Impaired views of the fundus may be due to cloudy media, as can occur with hyphema, vitreous hemorrhage, cataracts, or corneal opacification.

The optic disc should be a pink-orange hue with sharp margins, and size of the cup (the pallid area within the disc) should be noted

(Fig. 54.6A). Conditions such as glaucoma will cause optic disk pallor, and increased cup:disc ratio (normal is less than one-third) (2). Papilledema can be a sign of increased intracranial pressure, and manifests as a swollen, elevated disc with blurred margins (Fig. 54.6B) (16). Absence of normal retinal venous pulsations is also seen with increased intracranial pressures (16).

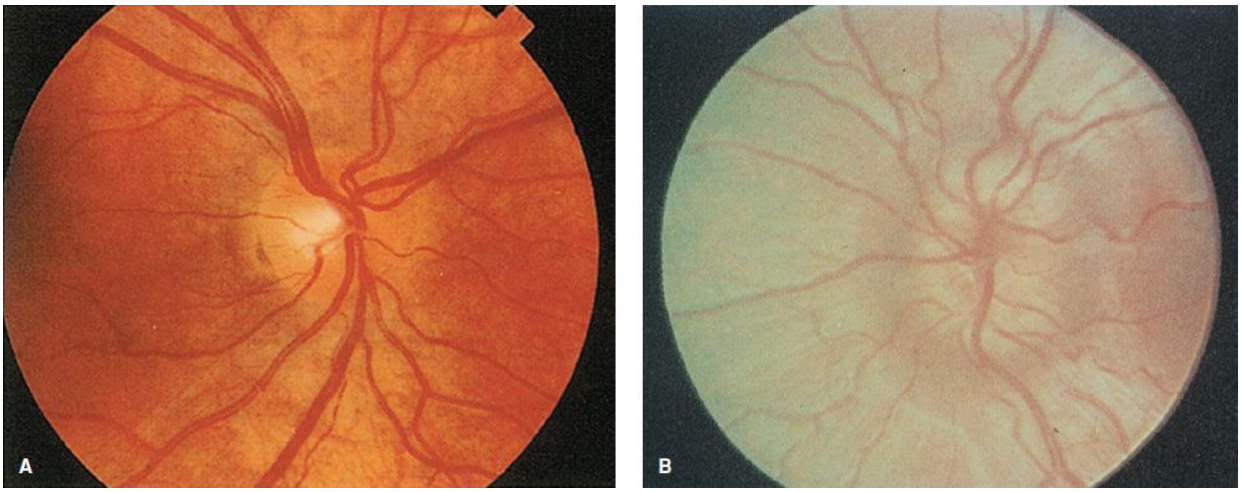


FIGURE 54.6 A: Normal optic disc. (Source of photo: Tasman W, Jaeger E (eds): *The Wills Eye Hospital Atlas of Clinical Ophthalmology*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.) B: Severe papilledema with blurred disc margins. (From Campbell WW (ed.). *DeJong's The Neurological Examination.* 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.)

The remainder of the retina can be evaluated for findings associated with other pathologies. Central retinal artery occlusion can classically be noted as a pale, ischemic retina with a red macula ("cherry red spot"), though this is a late finding (17). Central retinal vein occlusion may have retinal hemorrhages ("blood and thunder"), dilated and tortuous retinal veins, papilledema, and "cotton-wool" spots (small areas of yellow-white discoloration which indicate local retinal ischemia) (17). Retinal detachment often requires indirect ophthalmoscopy to visualize, although a central detachment may be evident by a white billowing retinal separation or an abnormal red reflex (17).

Intraocular Pressure Measurement

Tonometry is the determination of IOP. The main indications are to confirm a clinical diagnosis of acute–angle-closure glaucoma, and to determine a baseline IOP after a blunt eye injury (4). It should be avoided in suspected or confirmed penetrating eye injuries, as the pressure can worsen the defect and lead to extrusion of intraocular contents (18). Relative contraindications include eye infection (unless using a sterile cover) and patients with known corneal defects (4,19). Note that tonometry can rarely cause corneal abrasions (18).

Normal IOP is 10 to 21 mm Hg. IOPs greater than 30 mm Hg, especially in the context of abnormal optic disks or with visual field defects, should mandate immediate initiation of therapy for glaucoma and emergent consultation with ophthalmology (18).

There are many methods of tonometry used in the ED (Table 54.3). A complete discussion of the various modalities is beyond the scope of this chapter, but the practitioner should be familiar with the use of the instruments available to them. A simple, but insensitive, screening method is direct palpation of the globe (20). As the patient looks clinician's index finger is used to gently palpate the globe through the eyelid, with just enough pressure applied to indent the globe slightly. The amount of pressure required to indent the eye is qualitatively compared to the unaffected eye or the examiner's own eye (4).

TABLE 54.3
Methods of Tonometry

Type	Comments
Schiötz tonometer	Cumbersome, can spread infection, may create its own trauma, but is relatively easy to use
Applanation tonometer	Accurate, easy to use, mounted on most slit lamps
Tonometer pen	Electronic devices, easy to use and relatively accurate, but very expensive
Noncontact tonometers	For screening only, may be inaccurate, but does not require eye drops or corneal contact
Pneumotonometer	Effective, relatively easy to use, somewhat expensive to maintain, must be calibrated

DIAGNOSTIC TESTING

If a patient presents with a chemical exposure to the eye, immediate high-volume irrigation should be performed before any other part of the examination, as this has greatest effect on prognosis for vision (21). The pH should be measured by application of litmus paper into the tear well followed by comparison of the color with the scale on the container (18). The eye should be irrigated until the pH is normal (pH 6.8 to 7.4) (19). Once normal, the pH should be rechecked in 5 minutes, to ensure that earlier measurement was not simply sampling the pH of the irrigant fluid. Some authors recommend an additional 30 minutes of irrigation once pH is normal (22).

Bedside ocular ultrasound is a safe, noninvasive tool available to EPs who are familiar with its use. An experienced sonographer can complete an examination within 60 to 90 seconds, and make or confirm many possible diagnoses (Table 54.4) (1). It may be particularly useful in trauma or other situations where periorbital edema limits direct visualization of the eye (1). To perform the examination, ultrasound gel is placed over the closed eye, and the linear, high-frequency (7.5 to 10 Hz, “vascular”) probe is used to scan the globe in sagittal and transverse planes. Visualization may be improved by minimizing power output and gain settings, as this will decrease artifact from the eyelids. Excess pressure should be avoided, and in cases of suspected globe rupture, the transducer should only contact the gel, and not the eyelid itself (23).

TABLE 54.4
Ocular Pathology Visible with Ultrasonography

Pathology	Ultrasonographic Appearance
Retinal detachment	Band of echogenic material within vitreous body
Vitreous detachment	Collection of echogenic material between vitreous body and retina
Vitreous hemorrhage	Echogenic material within vitreous body
Retrobulbar hemorrhage	Hypoechoic lucency deep to retina
Lens dislocation	Lens in abnormal position within globe
Globe rupture	Difference in globe size between eyes; scleral folds
Intraocular foreign body	Echogenic foreign body visualized within globe
Central retinal artery/vein occlusion	Absence of Doppler flow at posterior retina
Increased intracranial pressure	Optic nerve sheath diameter >5.0 mm (adults), >4.5 mm (children 1–15)

Data from Legome E, Pancu D. Future applications for emergency ultrasound. *Emerg Med Clin North Am.* 2004;22:817–827.

Laboratory testing is rarely diagnostic in evaluation of ocular complaints. A complete blood count may be obtained in suspected orbital cellulitis. Erythrocyte sedimentation rate (ESR) may be obtained in suspected temporal arteritis, though 10% of affected patients will have an ESR <30 mm/hr. Advanced radiologic testing may be indicated in select cases. CT scan is useful for evaluation of orbital trauma or cellulitis, intraocular foreign body, or intracranial pathology. MRI may help diagnose optic neuritis, intracranial tumors, cerebrovascular accidents.

DISPOSITION

In general, consultation should be considered with unexplained impairment of vision or unexplained severe ocular pain. Emergent ophthalmologic consultation, with transfer if necessary, is indicated in cases of penetrating globe injury, retinal detachment, retinal artery or vein occlusion, or increased IOP. Most other eye complaints can be referred for urgent ophthalmologic follow-up. Ocular manifestations of neurologic disease should be referred to neurology on an emergent or urgent basis.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of the prior authors, Geoffrey Broocker and Timothy Platts-Mills, to the content of this chapter.

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CHAPTER 55

Common Ophthalmic Medications

Kimberly Schertzer

This chapter provides an overview of medications used to diagnose and treat common ocular conditions.

DIAGNOSTIC MEDICATIONS

Stains

These topical solutions reveal areas of corneal and conjunctival epithelial disruption.

Fluorescein stains are by far the most commonly used stains in the emergency department (ED). These stains highlight defective epithelium within the cornea and conjunctiva, with defective areas enhancing under cobalt blue light after staining. Single-use, sterile paper strips are preferred instead of the 2% solutions for convenience and concern about contamination of multiuse containers. Evaluation must happen quickly, as the ability to see stained areas is limited, usually only 1 to 3 minutes after application.

Other stains such as *rose bengal,* are not commonly used in the ED and may be irritating. *Rose bengal* stains devitalize epithelium and is useful for differentiating a herpetic corneal ulcer from a healing corneal abrasion.

Anesthetics

By providing temporary anesthesia, topical anesthetics facilitate eye examination as well as application of diagnostic drops. Most patients cannot tolerate either the application of ocular stains or testing of intraocular pressure (IOP) without topical anesthesia. Application of a topical anesthetic to the eye of a patient with a presumed corneal epithelial defect can be both therapeutic and diagnostic. The topical anesthetic provides patients immediate pain relief and supports the diagnosis of a corneal injury. Topical anesthetics are not for repetitive use, as they suppress protective ocular blink reflexes, have been linked to delayed corneal healing, and may cause an anesthetic-induced keratitis.

Tetracaine hydrochloride (Pontocaine) (0.5% to 1% solution) may initially sting. Its effect lasts for approximately 15 minutes.

Proparacaine hydrochloride (Ophthetic, Ophthaine) (0.5% solution) is less irritating than other solutions.

Mydriatics and Cycloplegics (Red Cap)

These agents are used diagnostically or therapeutically to dilate the pupil (mydriasis) and/or to paralyze the ciliary body (cycloplegia). This effect facilitates evaluation of the internal ocular structures and blocks accommodation. In addition, these agents prevent formation of synechiae (adhesions of the iris to the lens and cornea) by reducing intraocular inflammation through stabilization of the blood–aqueous barrier and by physically pulling the iris away from greater contact with the anterior lens surface. Mydriatic agents are stored in containers capped in red. The duration of drug effects listed below are for normal, noninflamed eyes.

Phenylephrine hydrochloride (Neo-Synephrine, Mydfrin) constricts the surface vessels and dilates the pupil without causing cycloplegia. The 2.5% solution is recommended because of increased systemic (cardiovascular) side effects with 10% solution. The effect lasts approximately 3 hours.

Tropicamide (Mydriacyl 0.5% and 1%) provides short-term dilation of the pupil, plus cycloplegia (lasting 4 to 6 hours). Tropicamide is relatively easy to reverse if there is a concern about

iatrogenic angle-closure glaucoma. It is commonly used by ophthalmologists.

Cyclopentolate hydrochloride (Cyclogyl 0.5%, 1%, and 2%) is the best short-term cycloplegic for determining refractive error; it may last from 6 to 24 hours.

Homatropine hydrobromide (1%, 2%, and 5%) lasts for several days. It is a useful short-term mydriatic and cycloplegic for low-level inflammation (iritis) caused by trauma or abrasions.

Scopolamine hydrobromide (Hyoscine 0.25%) lasts between 4 and 7 days; it is more effective for long-term inflammation seen postoperatively or in severe uveitis.

Atropine sulfate (0.25% to 2% solution, 0.5% and 1% ointment) lasts for 10 to 14 days; it is most commonly used postoperatively and in severe uveitis. It carries both corneal epithelial and systemic toxicities.

THERAPEUTIC AGENTS

Lubricants

Dry eyes may be the result of decreased tear production, systemic disease, environmental factors, medication effects, or inadequate lid function. Patients with dry eyes may complain of itching, blurred vision, burning, or a foreign-body sensation. Artificial lubricants temporarily restore the precorneal tear film and provide an effective but short-term treatment for dry eye-related symptoms.

Artificial tears are often used. Most of these formulations (Table 55.1) contain "thickening" agents (such as methylcellulose or polyvinyl alcohol), which prolong retention of the tears on the ocular surface. Most formulations contain preservatives to prevent contamination, but patients who find these preservatives irritating may opt for more expensive, single-use packets. Artificial tears are generally recommended for use every 4 to 6 hours but may be used as frequently as hourly if needed.

TABLE 55.1
Artificial Tear Preparations

Agent in Solution	Trade Name (Concentration)	Preservative
Carboxymethylcellulose	Refresh tears (0.5%)	Purite
	Refresh plus (0.5%)	Preservative-free
	Thera tears (0.25%)	Preservative-free
Hydroxypropyl methylcellulose	Bion tears (0.3%)	Preservative-free
	Tears naturale free	Preservative-free
	Visine tears	Benzalkonium chloride
Polyvinyl alcohol	Hypo tears (1%)	Benzalkonium chloride
	Murine (0.5%)	Benzalkonium chloride
Glycerin	Moisture eyes (0.3%)	Benzalkonium chloride
Polycarbophil	AquaSite	Preservative free

Bland lubricating ointments (Lacri-Lube, Refresh P.M.) are more viscous than drops, making these agents useful for maximizing sleep-related lubrication or for patients with incomplete lid closure (e.g., those who have seventh cranial nerve palsy).

Antibiotics (Tan Cap)

The general principles of antibiotic therapy apply to topical antibiotics as well. See Table 55.2 for a detailed description of ocular antimicrobial agents.

TABLE 55.2
Antibiotics for Topical Use (Tan Cap)

General Principles of Administration

Administer topical antibiotics 4–6 times daily for simple infections, more frequently for more serious infections (corneal ulcers, gonorrhea). The most common infectious pathogens vary by age. In adults, they include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus* sp, and *Streptococcus pyogenes*. Children are susceptible to the same bacteria, but unlike adults, they are also at risk for *Moraxella catarrhalis* infection

Antibacterial Agents

Bacitracin. Effective only against gram-positive organisms, diphtheroids, *Haemophilus* sp, and *Actinomyces* sp. Ointment or mixture with polymyxin B (Polysporin, AK-Poly-Bac)

Ciprofloxacin. Second-generation fluoroquinolone, with broad-spectrum activity, including *Pseudomonas aeruginosa*. Allows for ambulatory treatment of most corneal ulcers. Has a lower pH than other fluoroquinolone solutions and causes corneal precipitates in up to 16% of patients. Has higher antimicrobial activity (lower MIC90) than ofloxacin. Low allergy index. Solution, ointment (0.3%) (Ciloxan)

Erythromycin. Effective only against gram-positive organisms, especially *Staphylococcus* sp. Ointment (0.5%) (generic)

Gatifloxacin. Fourth-generation quinolone with enhanced gram-positive coverage. Effective for treating coagulase-negative *Staphylococcus* sp and *Streptococcus viridans* (Zymaxid 0.5%)

Gentamicin. Effective against gram-negative organisms, especially *Pseudomonas* sp, and gram-positive organisms, including *Staphylococcus* sp. Not effective against most *Streptococcus* sp because of resistance patterns. Effective, but fairly high sensitizing and potentially toxic corneal epithelial effects. Solution and ointment (Garamycin 0.3%)

Levofloxacin. Third-generation fluoroquinolone. Approved for treatment of bacterial conjunctivitis with efficacy that parallels ciprofloxacin (Quixin 0.5%)

Moxifloxacin. Fourth-generation quinolone with improved gram-positive coverage. Kills *S. pneumoniae* faster in vitro than other antibiotics. Particular efficacious against coagulase-negative *Staphylococcus* sp and *S. viridans*. Also covers fluoroquinolone-resistant *S. aureus* (Vigamox 0.5%)

Neomycin. Broad spectrum but highly sensitizing and potentially toxic to corneal epithelium. Mixtures in solution or ointment (Neosporin)

Norfloxacin. Approved for treatment of bacterial conjunctivitis with efficacy that parallels ciprofloxacin (Chibroxin 0.3%)

Ofloxacin. Similar indications and coverage as ciprofloxacin. Has a higher solution pH than other second-generation fluoroquinolone solutions and is less likely to cause corneal precipitates (Ocuflox 0.3%)

Polymyxin B sulfate. Fairly effective against most gram-negative organisms (except *Proteus* sp or *Neisseria* sp). Ointment mixtures (Neosporin, Polysporin, others). Solution with trimethoprim (Polytrim)

Sulfacetamide sodium. Broad spectrum. Solution (10%, 15%, and 30%). Ointment (10%) (Bleph-10, Sulf-10, others). Potential for allergy is fairly high and may rarely cause Stevens–Johnson syndrome

Tobramycin sulfate. Similar to gentamicin (Tobrex, AK-Tob, others 0.3%)

Trimethoprim sulfate. Broad spectrum of activity. Is effective against some staphylococcal and streptococcal strains, including methicillin-resistant staphylococci, as well as *Haemophilus* sp. In combination with polymyxin B (Polytrim), it has a wide range of effectiveness. Its safety and effectiveness have not been determined under 2 months of age. Very low allergy index

Antifungal Agents

Natamycin. Effective against many filamentary and yeast forms. Drug of choice for most mycotic corneal injuries (and only ocular formulation commercially available). May be used in conjunction with oral antifungal agents (Natacyn, 5% suspension)

Antivirals

Trifluridine (trifluorothymidine). Drug of choice in the United States for corneal herpetic disease and penetrates the cornea fairly well. Toxic to epithelium, like others. One percent solution (Viroptic) must be initiated at an every-2-hour dosage until ulcer is healing

Anti-Inflammatories

Both steroidal and nonsteroidal anti-inflammatories are available by prescription. These agents suppress ocular inflammation and allergic reactions both inside and outside the eye. Suppression of extraocular inflammation may prevent corneal scarring and permanent abnormalities in tear film. Within the eye, these agents may prevent scarring and the later development of glaucoma.

Steroid anti-inflammatory agents (Table 55.3) (pink cap) decrease inflammation. However, their use may be associated with significant side effects, including worsening of ocular infections and permanent visual loss. Some patients experience an increase in IOP within several weeks of using topical steroids. Topical steroids should be prescribed only after consultation with an ophthalmologist and assurance of reliable follow-up.

TABLE 55.3
Ocular Steroid Preparations (Pink Cap)

Fluorometholone 0.1% (FML, others). Slightly more potent, with fewer side effects than prednisolone and dexamethasone. As fluorometholone acetate 0.1% (Flarex), potency comparable to prednisolone acetate 1% because of better penetration
Rimexolone 1% (Vexol). Similar profile to that of fluorometholone but with a lower propensity to raise IOP
Loteprednol etabonate 0.5% (Lotemax), 0.2% (Alrex). Relatively new preparations with high potency and lower propensity to raise IOP
Prednisolone acetate and phosphate 0.125% and 1% (Pred Mild, Pred Forte, others). Potent and highly effective for anterior segment inflammation. High risk for side effects (IOP and infection, especially herpes simplex facilitation)
Dexamethasone 0.1% (Decadron solution). Potent and highly effective. Very high risk for side effects

Nonsteroidal anti-inflammatory agents (gray cap) have limited systemic effects. These topical agents are useful in the treatment of pain associated with corneal abrasions or following refractive surgery.

Flurbiprofen 0.03% (Ocufen) is often used during surgery.

Diclofenac 0.1% (Voltaren) is used for postoperative inflammation following surgery. It also provides safe and effective analgesia for the initial treatment of traumatic corneal abrasions.

Ketorolac 0.5% (Acular) was developed for allergic conjunctivitis. Ketorolac may also be a useful adjunct in the treatment of corneal abrasions.

Antibiotic–Steroid Combinations

Antibiotic–steroid combinations are useful postoperatively. Multiple formulations are available that combine various concentrations of topical corticosteroids with broad-spectrum antibiotics. Antibiotic–steroid combinations should only be used with ophthalmologic consultation. They are available as both drop and ointment preparations and include these drugs:

TobraDex (Tobramycin 0.3%, Dexamethasone 0.1%)

Cortisporin (Neomycin, Polymyxin B, Hydrocortisone 1%)

Blephamide (Sulfacetamide 10%, Prednisolone acetate 0.2%)

Antiglaucoma Agents

To decrease IOP, most antiglaucoma agents (Table 55.4) either increase aqueous humor outflow or decrease its production, or both. In general, monotherapy with a prostaglandin analog or topical β-blocker is preferred, as each works effectively and results in relatively few side effects. The addition of a carbonic anhydrase inhibitor may be useful in further decreasing IOP.

TABLE 55.4
Antiglaucoma Medications

Topical	
Cholinergic agonists (**green cap**)	Pilocarpine 0.5–10%
Adrenergic agents (**purple cap**)	Epinephrine compounds 0.5–2% (Epifrin, others)
	Dipivalyl epinephrine 0.1% (Propine)
α-2 agonists	Apraclonidine 0.5% and 1% (Iopidine)
	Brimonidine tartrate (generic 0.15% and 0.2%) and 0.15% (Alphagan-P)
β-blockers (**yellow/blue cap**)	Timolol 0.25% and 0.5% (Timoptic, others)
	Betaxolol 0.25% (Betoptic-S)
	Levobunolol 0.5% (Betagan)
	Metipranolol 0.3 % (OptiPranolol)
	Carteolol 1% (generic)
Carbonic anhydrase inhibitors (**orange cap**)	Dorzolamide hydrochloride 2% (Trusopt)
	Brinzolamide 1% (Azopt)
Prostaglandin analogs (**turquoise cap**)	Bimatoprost 0.01% (Lumigan)
	Latanoprost 0.005% (Xalatan)
	Travoprost 0.004% (Travatan Z)
	Oral/parenteral
Other antiglaucoma agents	Acetazolamide (Diamox Sequels, 500-mg extended-release capsules)
	Methazolamide (Neptazane 25 and 50 mg, others)
Osmotic agents	Mannitol (Osmitrol) 20%, 1–2 g/kg IV over 30–45 min

PO, by mouth; IV, Intravenous.

Prostaglandin analogs (turquoise cap) are the preferred initial therapeutic agent. By increasing aqueous humor outflow, these drugs lower IOP by 25% to 30%, although their time to initial efficacy is somewhat longer than with *β-blockers.* Prostaglandin analogs carry some adverse effects, including lash growth, periorbital skin hyperpigmentation, and irreversible iris hyperpigmentation, seen most commonly in patients with light or mixed irides. Tafuprost has recently been approved as a preservative-free prostaglandin analog, with similar efficacy as other drugs in its class.

Topical β-blockers (yellow or blue cap) decrease aqueous humor production and are commonly used in the treatment for glaucoma.

They may cause adverse effects similar to those of systemic β-blockers (affecting the cardiopulmonary and central nervous systems) and should be avoided in patients with asthma, bradycardia, or severe chronic obstructive pulmonary disease. Betaxolol (β-1 cardioselective) is slightly less effective than nonselective β-blockers but exhibits fewer side effects because of its selectivity. As a class, topical β-blockers may have effects on libido and cause cardiac sensitivity.

Carbonic anhydrase inhibitors (orange cap) decrease aqueous humor production, but their use may be limited by potentially adverse effects. They may be oral or topical. Oral forms including acetazolamide and methazolamide decrease IOP nearly twice as much as topical forms but have significantly more adverse events, including renal calculi formation and hypokalemia. While these agents are sulfa-related, they are generally well tolerated by patients with sulfonamide allergies. In general, topical agents are less effective than oral ones, typically reducing IOP by 15% to 20%, but they have fewer adverse effects.

Topical α-2 agonists both decrease aqueous humor production and increase its outflow. Apraclonidine may cause tachyphylaxis and localized allergic reaction. Bromonide may cause respiratory depression in children younger than 2 years and should be avoided in this population. It may also cause systemic hypotension in children and infants. All ocular *α*-agonists are relatively contraindicated in patients taking monoamine oxidase inhibitors.

Adrenergic agents may be used for glaucoma. However, the rapid development of tolerance limits their use, and as a class they are less preferred than selective *α*-agonists.

Cholinergic agonists (green cap) may also be used as antiglaucoma agents. They increase outflow of aqueous humor but have no effect on its production. In general, they have been replaced by newer antiglaucoma drugs and their use is limited by local and systemic adverse effects. Cholinergic agonists may cause transient blurred vision and myopia. Still they are useful in some circumstances, such as the immediate treatment of acute angle-closure glaucoma.

Osmotic agents are not available in a topical form. In oral and parental form, they lower IOP by increasing the osmotic gradient between the blood and the eye. They can cause systemic hyperosmolarity and electrolyte imbalance. In addition, they may produce rebound IOP increases as they are eliminated from the body. The oral form is glycerol, which commonly causes nausea and vomiting, and because glycerin is gluconeogenic, should be used with caution in diabetic patients. The parenteral osmotic agent is mannitol. Both osmotic agents should be reserved for cases where acute, rapid IOP rises are not controlled by topical agents.

Allergy Medications

Environmental irritants including dust and pollen can cause redness, itching, chemosis, and increased tear production. Over-the-counter oral antihistamine–decongestant combinations often provide sufficient relief. If this conservative therapy fails, patients may find more symptomatic relief from topical antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), and mast-cell inhibitors (Table 55.5). Topical steroids may also be considered but should be prescribed only after ophthalmologic consultation.

TABLE 55.5
Allergy Medications

Ocular Decongestants

Naphazoline hydrochloride (Naphcon, others)

Tetrahydrozoline hydrochloride (Murine, Visine, others). Available without a prescription

Antihistamines

Emedastine difumarate 0.05% (Emadine)

Epinastine 0.05% (Elestat). An antihistamine with mast-stabilizing abilities

Azelastine hydrochloride 0.05% (Optivar). Also available for inhaled use

Mast-Cell Stabilizers

Cromolyn sodium 4% (Crolom)

Nedocromil sodium 2% (Alocril)

Lodoxamide tromethamine 0.1% (Alomide)

Olopatadine hydrochloride 0.1% (Patanol)

Ketotifen fumarate 0.025% (Zaditor)

Ocular decongestants whiten eyes and reduce conjunctival congestion and eyelid edema. They do not require a prescription and are very effective. This may cause some patients to delay seeking care for serious causes of red eyes. Chronic use results in tolerance and "rebound" vascular dilation. Some ocular decongestants contain a mild topical antihistamine (antazoline or pheniramine) and are distinguished by the suffix "-A" within the name. Though these antihistamine–decongestant combinations have a short duration of action, they may be more effective than either agent used individually.

Antihistamines are primarily H1-antagonists. They have both antihistaminic and anti-inflammatory effects. Some antihistamines also possess mast-cell–stabilizing effects.

Mast-cell stabilizers may effectively treat seasonal allergies, which are usually attributed to type I (IgE-mediated) hypersensitivity. By blocking the release of histamine and other vasoactive mediators from mast cells these agents may provide relief, although their onset of action is delayed (days to weeks).

Common Pitfalls

- Topical anesthetics are not for outpatient use, as they suppress protective ocular-blink reflexes, have been linked to delayed corneal healing, and may cause a toxic chemical keratitis.
- Topical steroids can lead to worsening of ocular infections and permanent visual loss; they should only be prescribed after consultation with an ophthalmologist.
- Although most topical ocular medications act locally, certain agents (such as β-blockers) may cause serious systemic side effects.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Geoffrey Broocker to the content of this chapter.

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CHAPTER 56 The Red Eye

Megann Young

The red eye is a common emergency department (ED) complaint that may present in isolation or in combination with other ocular or systemic disorders. The differential diagnosis is broad and includes causes ranging from benign to vision threatening.

CLINICAL PRESENTATION

A red eye is produced by dilated, inflamed, superficial ocular vessels and can result from infection, inflammation, allergy, or elevated intraocular pressure. Several ocular components may be involved, most commonly the conjunctiva, but also the uveal tract, episclera, and sclera.

Conjunctivitis

Conjunctivitis is the most common cause of red eye (1,2). The conjunctiva covers the inner aspect of the lids (tarsal or palpebral conjunctiva) and reflects back on itself to cover the sclera (bulbar conjunctiva), stopping at the cornea. Infection, allergy, and irritation are the most common causes of conjunctivitis.

Infectious conjunctivitis may be viral or bacterial (Chapter 60).

Allergic conjunctivitis (3) may occur seasonally, year-round (perennial conjunctivitis), or as an isolated reaction to material in the eye (often ophthalmic medications, particularly those containing neomycin), and is more common in patients with atopic diseases such as eczema, asthma, and allergic rhinitis (2). Seasonal conjunctivitis is usually caused by airborne pollens and follows the

growth cycle of the responsible plant. Perennial conjunctivitis is usually caused by allergens present in the home, particularly dust mites and animal dander. Numerous irritants may also affect the conjunctiva; common examples include dust, smoke, and chemical fumes.

Symptoms include mild irritation, itching, and watery discharge. Vision is not intrinsically affected but may be blurred by copious discharge. The conjunctivae are globally injected (both tarsal and bulbar surfaces); both eyes are equally affected (1). *Allergic conjunctivitis* may also present with significant conjunctival edema, termed *chemosis,* which appears as a marked bulging of the conjunctiva. In chronic allergic conjunctivitis, fine papillae may develop on the tarsal surface, giving a velvety appearance. Follicular hyperplasia occurs in viral or chlamydial conjunctivitis, give a cobblestone appearance.

Keratitis

Keratitis may be caused by bacterial, viral, fungal, and UV sources. *Infectious keratitis* is discussed in Chapter 60. *Photokeratitis,* caused by UV light exposure, is characterized by foreign body sensation, photophobia, and superficial punctate fluorescein uptake on slit lamp exam; management is supportive, and ophthalmology referral is only required if symptoms persist beyond 48 to 72 hours.

Uveitis

The uveal tract consists of the iris, ciliary body, and choroid. Uveitis is classified as anterior, intermediate, and posterior. Only anterior uveitis typically produces a visibly red eye; it includes iritis and iridocyclitis (inflammation involving the iris and ciliary body). Approximately 50% of cases are idiopathic; most of the remainder are immune mediated (4,5), and a few are infectious.

Typical symptoms include pain (which may radiate to the temple or worsen with extraocular movements), photophobia, consensual photophobia (light in the unaffected eye produces pain in the red eye), and decreased vision. Physical findings include decreased visual

acuity, pupillary constriction, and fine vascular dilation concentrated in the area around the cornea (perilimbal or ciliary flush). The large, dilated vessels typical of conjunctivitis are absent. On slit-lamp examination, there are cells and flare in the aqueous humor, which in severe cases may contain fibrin clot or even pus (hypopyon).

Episcleritis

The episclera is a thin, membranous layer between the conjunctiva and sclera. Inflammation is usually idiopathic but is sometimes associated with immune-mediated disorders (6,7). It occurs mainly in young adults, most commonly women. Patients have mild discomfort, tearing, and an erythematous, injected patch on the globe. The injected area is usually localized, occupying less than half of the visible globe. Episcleritis poses no threat to vision and is self-limited, usually resolving within 2 to 3 weeks (2).

Scleritis

Scleritis is an inflammation of the sclera (the thick, white connective tissue covering the anterior surface of the globe). Inflammation (7) is often idiopathic, but about 50% are associated with systemic diseases (1), often immune-mediated disorders. Scleritis is most common between ages 30 and 60 and is somewhat more common in women. Within several years of an acute attack, up to one-third of patients suffer significant loss of visual acuity. Pain is severe, deep, and typically described as “boring”; pain may be worse with extraocular movements. The pain often interferes with sleep and may radiate to the forehead or jaw. The eye is diffusely hyperemic, often violaceous; sometimes only one quadrant is involved. The palpebral conjunctiva is not inflamed. An identifying feature of scleritis is tenderness of the globe to palpation. An avascular-appearing area amid the hyperemia suggests *necrotizing scleritis,* which can progress to globe perforation.

Acute Angle-Closure Glaucoma

A rapid increase in intraocular pressure results in severe pain, hyperemia, and impaired vision with a pupil that is classically

midposition and poorly reactive (Chapter 61).

Corneal Abrasion and Foreign Body

Significant eye trauma is typically clinically obvious; patients present with complaint of injury rather than red eye. However, minor corneal abrasions and foreign bodies may be present without recognized trauma, particularly in young children and infants (Chapter 57).

DIFFERENTIAL DIAGNOSIS

The differential for the red eye may be best summarized in tabular form (Table 56.1). Other disorders that might produce scleral injection include chemical irritation or infections of the surrounding structures.

TABLE 56.1
Differential Diagnosis of Red Eye

Factor	Infectious Conjunctivitis	Allergic Conjunctivitis	Keratitis	Anterior Uveitis	Episcleritis	Scleritis	Angle-Closure Glaucoma	Corneal Abrasion, Foreign Body
Injection	Diffuse bulbar and palpebral	Diffuse bulbar and palpebral	Diffuse	Diffuse ciliary flush	Focal erythema	Diffuse erythema; may have violet hue	Diffuse bulbar	Diffuse bulbar
Discharge	Viral: Watery Bacterial: Purulent	Copious, watery	Watery	Watery	Watery	Watery	Watery	Watery
Pain	Irritation	None	Severe	Photophobia	Mild	Severe pain, tender to palpation	Severe	Moderate irritation, foreign-body sensation
Itching	Minimal	Moderate	None	None	None	None	None	None
Systemic symptoms	Occasional URI symptoms, preauricular nodes	Sneezing, rhinorrhea	None	Occasional rheumatologic or gastrointestinal	Usually none; occasional rheumatologic	Usually none; occasional rheumatologic	Headache, nausea, vomiting	None
Visual acuity	Usually normal	Normal	Decreased	Decreased	Normal	Initially normal, may become decreased	Decreased	Normal; may be decreased with central abrasion
Pupils	Normal	Normal	Normal	Constricted, poorly reactive	Normal	Normal	Midposition, poorly reactive	Normal
Cornea	Normal	Normal	Diffuse punctate lesions	Normal; anterior chamber with cells and flare	Normal	Normal	Hazy or cloudy	Abrasion visible
Intraocular pressure	Normal	Normal	Normal	Normal	Normal	Normal	Elevated	Normal

ED EVALUATION

A systematic approach to the red eye should lead one to the correct diagnosis. Key symptoms and findings that are helpful in discriminating one cause from another are listed in Table 56.1.

History should focus on the eye and relevant systemic complaints, including any changes in vision, the presence or absence and type of pain/discomfort, foreign body sensation, photophobia, history of trauma, presence and type of discharge, contact lens use, and previous occurrences. Autoimmune or rheumatologic diseases or symptoms should also be elicited (1,8).

Physical examination of the eye (Chapter 54) includes visual acuity, evaluation of pupillary response, delineation of the nature and location of vascular dilation, slit-lamp examination including fluorescein staining, lid eversion for foreign-body detection and, in most cases, ocular tonometry (1,8). A drop of topical anesthetic can provide important diagnostic information: Superficial pain from conjunctivitis, foreign body, or corneal abrasion is relieved, but the deep pain of uveitis, scleritis, or glaucoma is unaffected. Similarly, drops of phenylephrine will not affect the hyperemia of scleritis (1) but will cause blanching in other causes of red eye (phenylephrine will also cause pupillary dilation, and is contraindicated in patients with a history of glaucoma or if acute glaucoma is suspected).

Laboratory testing is usually not helpful. Serologic tests are sometimes useful when immune-mediated disease is suspected but may be coordinated with the ophthalmologist and primary care physician.

ED MANAGEMENT

The treatment options depend upon etiology. Eye trauma, corneal abrasions, ocular infections, and acute angle-closure glaucoma are discussed in Chapters 25, 57, 60, and 61, respectively.

Allergic conjunctivitis should initially be treated with either a nonprescription topical antihistamine/vasoconstrictor such as naphazoline/pheniramine or prescription agents with combination antihistamine and mast-cell–stabilizing activity such as olopatadine or ketotifen. Other agents, including topical NSAIDs and

corticosteroids, may subsequently be added as needed by consultants.

Patients with *anterior uveitis* may get relief from photophobia with a topical cycloplegic, pending ophthalmology evaluation. Definitive treatment usually involves corticosteroids and sometimes immunosuppressives (9). These should be managed by consultants.

Episcleritis is self-limited and generally requires no specific treatment. However, the duration may be shortened by oral NSAIDs or topical corticosteroids.

The discomfort of *scleritis* may be reduced by oral NSAIDs. Definitive treatment should be initiated by consultants and involves systemic as well as topical corticosteroids, with immunosuppressives for necrotizing scleritis or unresponsive disease.

CRITICAL INTERVENTIONS

- Record visual acuity in all cases.
- Measure intraocular pressure to exclude acute angle-closure glaucoma.
- Carefully evert lids to search for a foreign body.
- Perform slit-lamp examination with fluorescein staining.

DISPOSITION

Patients with suspected uveitis or scleritis should be evaluated by an ophthalmologist within 24 hours. Patients with allergic conjunctivitis, episcleritis, or photokeratitis may have either ophthalmologic or primary care follow-up within 2 to 4 days.

Common Pitfalls

- Failing to adequately explain eye pain and decreased vision; these findings almost always indicate a serious disorder.
- Assuming that all causes of red eye are infectious.
- Failing to consider angle-closure glaucoma and measure intraocular pressure.
- Failing to detect a foreign body.

- Failure to refer scleritis and uveitis to an ophthalmologist within 24 hours.

ACKNOWLEDGMENT

The author gratefully acknowledges the contributions of Robert S. Porter to the content of this chapter.

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CHAPTER 57

Corneal Abrasion and Foreign Bodies

Lori A. Weichenthal

Corneal abrasions and foreign bodies are among the most frequent ocular conditions that present to the emergency department (ED). It is estimated that the incidence of nonpenetrating injuries to the eye is 15.7 per 100,000 persons per year (1). Although a corneal abrasion is usually a self-limited process, a persistent corneal foreign body or undiagnosed intraocular foreign body can cause unnecessary morbidity.

The emergency physician (EP) must be able to accurately diagnose and treat corneal abrasions and foreign bodies to reduce pain and prevent complications such as infection, ulceration, and vision loss. It is also important that the EP be aware of the potential for intraocular foreign body and be attentive to the historical and physical clues that suggest ocular penetration. This chapter provides an overview of the evaluation and management of corneal abrasions, corneal foreign bodies, and intraocular foreign bodies in the ED.

CLINICAL PRESENTATION

Corneal abrasions and corneal foreign bodies often present with a similar history. The patient often reports that something struck or flew into the eye, followed shortly by the development of pain. At times, the patient does not recall feeling an object entering the eye, but he or she reports being in a situation where such a possibility

exists (using a leaf blower, sawing wood, grinding metal, etc.). Contact lenses may also cause corneal abrasions, because of prolonged wear, an improper fit, foreign material under the lenses, or trauma associated with the placement or removal of the lenses. Some patients develop recurrent corneal erosions, which are characterized by pain upon awakening, usually at the site of a recent abrasion.

Whether a foreign body is present, the patient often complains of a persistent foreign body sensation. With this sensation, there is usually pain, tearing, photophobia, blepharospasm, and a minimal decrease in visual acuity. A headache may also be present but is usually mild.

An intraocular foreign body should be suspected when there is a history of a high-velocity injury to the eye. The injury may be caused by a blast effect or activities such as grinding metal or jack hammering cement without the use of protective eyewear. Patients with intraocular foreign bodies usually present with similar symptoms as patients with corneal abrasions or foreign bodies, although they often describe more visual disturbances.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of corneal abrasion, corneal foreign body, and intraocular foreign body should include all the disease processes that present with an acute red eye. For a complete discussion of the red eye, please refer to Chapter 56. When there is no history of a foreign body or trauma, the concern for an infection, inflammatory reaction, or acute angle-closure glaucoma should be heightened.

Infections of the conjunctiva (conjunctivitis) and the cornea (keratitis) are most common and are usually viral or bacterial, but in immunocompromised patients, fungal keratitis is also possible. Patients with eye infections will have symptoms similar to those described for corneal abrasions and foreign bodies. They may also describe mucopurulent discharge and other symptoms of infection (cough, congestion, etc.). The pain associated with eye infections

also tends to be more gradual in onset or is first noticed upon awakening (2).

Autoimmune and inflammatory disorders can also cause symptoms similar to those of corneal abrasions and foreign bodies. Anterior uveitis and scleritis are two examples. Patients with these disorders often have other systemic complaints that will help the EP in differentiating them from simple abrasions and foreign bodies.

Acute angle-closure glaucoma can present with a painful red eye. This disease process, however, is usually associated with a severe, unilateral headache and decreased visual acuity, which differs from abrasions and foreign bodies.

In contact lens wearers, although corneal abrasions are common, concern for more serious injury and infection should be heightened. Corneal ulcers and infectious keratitis can occur. Chemical irritation caused by the preservatives in contact lens solutions or the enzymes used to clean some contact lenses can also lead to symptoms similar to corneal abrasions or foreign bodies.

In the setting of trauma, the differential should include corneal or scleral lacerations, hyphema, globe rupture, and traumatic iritis (see Chapter 25). Corneal or scleral lacerations range from simple partial-thickness lacerations to injuries that penetrate the eye. When the laceration is extensive and deep enough, the injury is considered a ruptured globe, which is an ophthalmic emergency. Traumatic iritis can present with symptoms very similar to corneal abrasion and foreign bodies; however, it usually occurs after significant blunt trauma and is associated with headache, photophobia, and decreased vision. If the history is of a high-velocity impact to the eye, intraocular foreign body should always be suspected.

In patients presenting with the story of multiple episodes of corneal abrasions, the diagnosis of recurrent corneal erosions should be entertained. Recurrent corneal erosions often occur in people with epithelial basement membrane dystrophy and/or a history of trauma (3).

ED EVALUATION

When a patient presents to the ED with the complaint of a foreign body sensation to the eye, the history should focus upon the preceding events and a description of all symptoms, including pain, redness, visual changes, or discharge. The time of onset and progressions of symptoms should also be elicited. If the history suggests an actual foreign body, the suspected type of foreign body (wood, metal, organic material, etc.) as well as the setting (high velocity vs. low velocity) should be determined. Previous injuries or surgeries to the eye should be documented, as should the use of glasses or contact lenses. A thorough review of systems and a general medical history should be obtained to evaluate for systemic illness. If nothing in the history suggests a possible systemic problem or multisystem trauma, the physical examination can be focused on the eye.

Visual acuity should be measured as soon as possible. In patients with corneal abrasions and foreign bodies, the visual acuity is frequently normal or mildly decreased. When an intraocular foreign body is present, the visual loss can be significant. The use of a topical anesthetic (proparacaine 0.5% solution or tetracaine 0.5% solution), one to two drops in the affected eye, will make the patient more comfortable and aid the EP in the examination. The use of topical anesthetic can also be helpful in making the correct diagnosis. If the anesthetic does not relieve the patient's pain, it suggests that the pathology is deeper than the corneal epithelium.

A complete examination of the eye should follow instillation of the topical anesthetic. For a detailed discussion of the eye examination, please refer to Chapter 54. Patients with a corneal abrasion or foreign body often have a slightly swollen eyelid, and the conjunctiva and sclera will be hyperemic. It is particularly important to search the corneal and conjunctival surfaces for a foreign body. This examination should be done under magnification with a bright light or a slit lamp. As the superior tarsal plate is a common place for foreign bodies to lodge, lid eversion should be performed in all patients when suspicion of a foreign body exists. To perform lid eversion, ask the patient to look down, grasp the eyelashes of the upper lid, pull the lid down and out, place a cotton-

tipped applicator horizontally above the tarsal plate, and fold the upper lid over the applicator to expose the underlying conjunctival surface (4).

Also of importance in evaluation of the patient with a suspected corneal abrasion or foreign body is an examination with fluorescein. Fluorescein will permanently stain soft contacts, so they should be removed before instilling fluorescein. The patient should be advised to refrain from wearing contacts for several hours. Fluorescein should be instilled in the eye, and the patient should be asked to blink several times. The eye should then be examined with a cobalt blue light or a Wood lamp. Defects of the corneal epithelium will appear green. Particular patterns of uptake can suggest specific injuries. A simple abrasion from a low-impact foreign body will often appear as a single linear uptake. Uptake of multiple linear markings perpendicular to the eyelid suggests a retained foreign body in the superior tarsal plate. A dendritic lesion viewed on fluorescein examination should suggest herpes keratitis. Corneal ulcers and infectious keratitis may appear on fluorescein examination as corneal staining with surrounding opacification (Fig. 57.1).

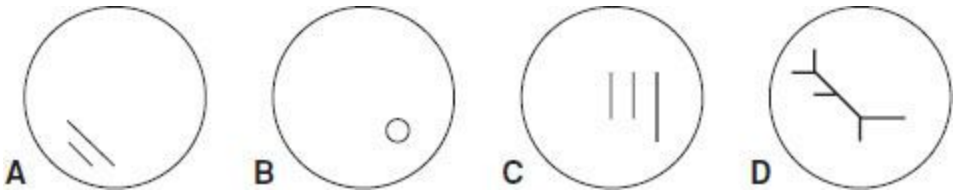

FIGURE 57.1 Corneal fluorescein uptake patterns for particular injuries. A: Typical abrasion. B: Abrasion around a corneal foreign body. C: Abrasion from a foreign body under the lid. D: Herpetic dendritic lesion.

The eye examination should be completed with examination of the anterior segment and fundus. The anterior segment is best examined using a slit lamp and is usually normal with abrasions and corneal foreign bodies. The funduscopic examination is done with an indirect ophthalmoscope and should also be normal.

Routine measurement of intraocular pressure (IOP) is not necessary in simple corneal abrasions and foreign bodies due to small and low-speed particles. Some argue that the use of a tonometer on an abraded cornea may even be harmful. In abrasions due to larger objects, or if the diagnosis is uncertain, IOP should be measured. IOP should not be measured in a suspected penetrating ocular injury, since pressure on the globe may result in extrusion of intraocular contents (4).

Some of the findings on examination of the eye that are suggestive of an intraocular foreign body or globe penetration include an irregular pupil, a prolapsed iris, a laceration to the sclera or cornea, hyphema, absence of a red reflex, significant reduction in visual acuity, and/or a positive Seidel test (5). The Seidel test involves flooding the eye with fluorescein and looking for a small stream of green using the cobalt blue light or Wood lamp, suggesting that fluid is leaking from the globe. If anything on history or physical examination is suggestive of an intraocular foreign body, imaging studies are indicated to make the diagnosis. Although plain films and ultrasonography have been used, computed tomography of the orbit is the preferred test. Magnetic resonance imaging (MRI) should not be considered if the foreign body could be metallic. Patients with suspected intraocular foreign body require immediate ophthalmologic consultation.

KEY TESTING

- Flourescein to highlight corneal epithelial defects
- Measurement of visual acuity in all cases, and IOP in selected cases
- Thorough search for foreign body, including lid eversion
- Imaging studies in case of suspected penetrating foreign body

ED MANAGEMENT

The management of the patient with suspected corneal abrasion or foreign body will be dictated by the history and findings of the eye examination. If a corneal, scleral, or conjunctival foreign body is

found, it must be removed. Frequently, removal is as easy as brushing the foreign body with a moistened cotton-tip applicator. Saline irrigation can also be used to rinse foreign bodies out of the eye. This technique is especially useful if there are multiple, small foreign bodies that are difficult to see.

If irrigation is needed, the eye should be well anesthetized. The lids should be held open with gauze pads or by the use of lid retractors. A saline stream can then be instilled in the eye. The irrigation can be done by using regular intravenous tubing attached to a bag of normal saline or a Morgan lens. The volume and duration of irrigation depends on the suspected foreign body, but at least a full liter is recommended (4).

If the foreign body is embedded in the sclera or cornea, it is best removed with a needle (25 to 27 gauge) attached to a syringe or with a commercial stud device (burr). For this to be done, the eye must be well anesthetized. The patient's head should be stabilized, and the procedure should be performed under magnification, preferably with a slit lamp. The patient is asked to focus on a distant spot. The stud device or needle is then held tangentially to the globe, and the foreign body is gently picked off. If the embedded foreign body is metallic, a rust ring may remain after removal of the metal object. The EP can attempt to remove this ring at the same time that the foreign body is removed by gently brushing it away with a stud device or needle. It is frequently easier to remove the rust ring 24 to 48 hours later when it has had a chance to mature or soften. If a patient has multiple embedded foreign bodies, as if from an explosion, they should be referred emergently to an ophthalmologist.

Once a corneal foreign body has been removed, the treatment is the same as for a corneal abrasion. Treatment for a simple abrasion consists of an antibiotic ointment or drops and oral analgesics as needed. (See Chapter 55 for a complete list of topical antibiotics.) Though there is little research supporting the use of topical antibiotics in this setting, this treatment remains the standard of care in many institutions, and the ointment itself is often soothing. Topical antibiotics are advised for corneal abrasions caused by

infected material (farm instruments, vegetable matter) or contact lens use, because these types of abrasions can rapidly progress to ulceration or keratitis. The offending agents are often gram-negative organisms. In contact lens wearers, there must be special concern about *Pseudomonas* sp. An ulcer due to *Pseudomonas* sp can destroy the cornea in as little as 24 hours. A broad-spectrum topical antibiotic, such as a fluoroquinolone, should be used in these cases.

Cycloplegics (1% cyclopentolate or 5% homatropine) have been recommended in the past because they were thought to relieve some of the pain of corneal abrasions by relaxing ciliary body spasm. A recent literature review revealed there is no evidence to support this practice (6). Similarly, patching the affected eye was once the standard of care, but studies in adults and children have failed to show any difference in the rate of healing or in the degree of pain between groups with or without a patch (1,7). Some studies even suggest that patching delays healing of corneal abrasions. In contact lens-related abrasions, the eye should never be patched, because it can lead to worsening infection and visual loss (8,9).

Traditional teaching discourages the prescribing of topical anesthetics such as tetracaine or proparacaine because of concern that home use may delay healing and enable further injury. However, one recent study suggested that prescribing dilute proparacaine 0.05% for patients with acute corneal injuries improves patient comfort and does not delay wound healing (10).

Other studies have shown that topical nonsteroidal anti-inflammatory drug (NSAID) drops may be useful to treat the pain of corneal abrasions (Table 57.1). Three studies showed a greater reduction of pain in patients using a topical NSAID compared to those receiving no topical analgesia (11–13). Topical NSAIDs can be expensive and have not been adequately tested against oral analgesics for controlling pain due to corneal abrasions and foreign bodies.

TABLE 57.1
Topical Ophthalmic NSAIDs

Ketorolac 0.5% solution
Diclofenac 0.1% solution
Indomethacin 0.1% solution

For corneal ulcers, the use of topical fluoroquinolones and topical steroids is recommended. The treatment should be done in consultation with an ophthalmologist and requires urgent follow-up. Recurrent erosions should be treated with topical lubricants, particularly at bedtime.

CRITICAL INTERVENTIONS

- Remove corneal foreign bodies.
- Treat abrasions due to infected material or contact lens use aggressively with antibiotics.
- Cycloplegics and eye patches are not routinely indicated.
- Provide adequate analgesia and close follow-up.

DISPOSITION

Patients with simple corneal abrasions, recurrent erosions, or corneal defects following foreign body removal should be followed up within 24 to 36 hours, either in the ED, by primary care, or by an ophthalmologist. Patients with abrasions caused by infected material or contact lenses or a corneal ulcer are at higher risk and need urgent ophthalmologic involvement. Patients with an intraocular foreign body need emergent ophthalmologic consultation. If an ophthalmologist is not available, a transfer should be arranged to a hospital with appropriate resources.

Return precautions should be given to all patients who are discharged home. Patients should be urged to return for any evidence of infection (drainage from the eye, increased redness, or pain) or any changes in vision. If a foreign body was the source of the patient's complaint, the use of eye protection should be urged when engaging in future activities that create the risk for injury to the eyes.

Common Pitfalls

- Failure to detect an extraocular foreign body.
- Failure to suspect an intraocular foreign body.
- Failure to provide adequate analgesia.

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CHAPTER 58

Acute Vision Loss

Catherine A. Marco

Loss of vision, whether unilateral or bilateral, partial or complete, is an emergent ophthalmologic complaint and requires rapid and thorough evaluation and management. Major eye diseases are particularly common among the geriatric population with the predominant disease entities affecting this group including diabetic retinopathy, glaucoma, and macular degeneration. Approximately 50% of patients older than age 65 have a major eye disease (1). Emergent evaluation includes taking the relevant ocular history, examination of the eyes and other relevant systems, pertinent laboratory evaluation, determination of the differential diagnosis, and rapid institution of appropriate therapy. Consultation with an ophthalmologist and/or other appropriate specialists is often indicated.

CLINICAL PRESENTATION

Patients may present with complete or partial vision loss, with or without a variety of associated symptoms. Typically, any degree of visual loss is disturbing to the patient and may lead to early evaluation; however, some patients may procrastinate and not seek medical evaluation. A thorough history can be crucial and is the most efficient approach to the wide differential diagnosis of visual disturbances.

Several historic points may be particularly useful in determining the etiology of symptoms. The onset of symptoms, whether gradual or abrupt, transient or persistent, constant or waxing and waning, may be of importance. The unilateral or bilateral nature of the

disturbance, and association of pain, may be valuable in the differentiation of certain disorders. Associated symptoms, including systemic symptoms (fever, weakness, rash, etc.), previous history of similar symptoms, history of trauma, and other ocular symptoms, including eye pain, redness, discharge, and so forth, should be sought when obtaining historical information from the patient. Following is a discussion of many conditions that cause vision loss.

Inflammatory Processes

Giant Cell Arteritis

Giant cell arteritis (GCA), an inflammatory disease of medium and large arteries, typically affects patients older than 60 with a female predominance of 3:1. Peak incidence occurs between the ages of 70 and 80. GCA is often associated with polymyalgia rheumatica (2). Visual disturbances are a common presenting symptom and may include painless visual loss or cranial nerve palsies. Patients may also present with malaise, headache, neck pain, fever, night sweats, anorexia, weight loss, depression, jaw claudication, or pain over the temporal or occipital arteries (Table 58.1). Helpful diagnostic tests include an elevated erythrocyte sedimentation rate (ESR) (typically 80 to 100 mm within the first hour; elevated in 98% of documented cases), elevated C-reactive protein (CRP), and an abnormal temporal artery biopsy (3). Elevated ESR has a sensitivity of 76% to 86%, and elevated CRP has a sensitivity of 97.5%. The sensitivity of ESR and CRP together is 99% (4).

TABLE 58.1
Diagnostic Criteria for Giant Cell Arteritis (5)

At least three of the following:
Age at onset of 50 yrs or older
Onset of a new headache
Temporal artery tenderness or reduced pulsation
Raised ESR (≥50 mm/hr by the Westergren method)
Histologic evidence of necrotizing arteritis in the temporal artery

Optic Neuritis

Optic neuritis is an inflammatory disorder that often affects young women and occurs from varying etiologies, including multiple sclerosis, sarcoidosis, systemic lupus erythematosus, leukemia, syphilis, collagen vascular diseases, alcohol abuse, tumor, and infection (meningitis, syphilis, Lyme disease, viral infection). Optic neuritis is often the initial manifestation of multiple sclerosis. Acute visual loss, often occurring within 1 week, is typical. Most patients (65%) have pain with eye movement. Typically, there is unilateral involvement and an afferent pupillary defect. Elevation of the optic disc may be seen on funduscopic examination. Visual field defects may be noted. Optic neuritis often resolves spontaneously over weeks to months (6).

Uveitis

Uveitis, inflammation of the iris, ciliary body, or choroid, may cause visual impairment. Uveitis may be caused by Reiter syndrome, ankylosing spondylitis, sarcoidosis, tuberculosis, collagen vascular disorders, and other diseases. Uveitis may also present as an inflammatory response to corneal abrasion, ulcer, infection, or trauma. The presentation generally includes conjunctival injection, pain, photophobia, and blurred vision.

Vascular Events

Central Retinal Artery Occlusion

Central retinal artery occlusion (CRAO) often presents with sudden, painless visual loss (Fig. 58.1). There may be a history of transient visual loss prior to this event. The cause is often due to emboli from carotid plaques, cardiac valves, fat emboli, arteriosclerosis, or a host of other underlying disorders (such as systemic lupus erythematosus), hypotension, coagulopathy, migraine, smoking, hypercholesterolemia, procedures such as cardiac catheterization, sickle cell disease, cocaine, certain medications (sildenafil, oral contraceptives, epinephrine, etc.), amniotic fluid embolism, and GCA. Elderly patients are more commonly affected, and men are more commonly affected than women. Visual loss is typically

profound, with 90% of patients sustaining losses that range from counting fingers to light perception. An afferent pupillary defect may be present. Physical findings include “cherry-red spot” of the fovea, retinal opacity in the posterior pole, “boxcars” of the arterioles, pallor of the involved retina, and optic disc edema (7). Ultrasound, including color Doppler imaging, may be helpful in elucidating the diagnosis (8). Echocardiography and carotid artery studies may reveal sources of emboli. Branch retinal artery occlusion (RVO) may occur and may present with sudden loss of visual field and reduction in visual acuity. The long-term prognosis is related to the duration of symptoms prior to resolution. Improved outcomes are seen if the condition is reversed within 90 minutes of onset of symptoms.

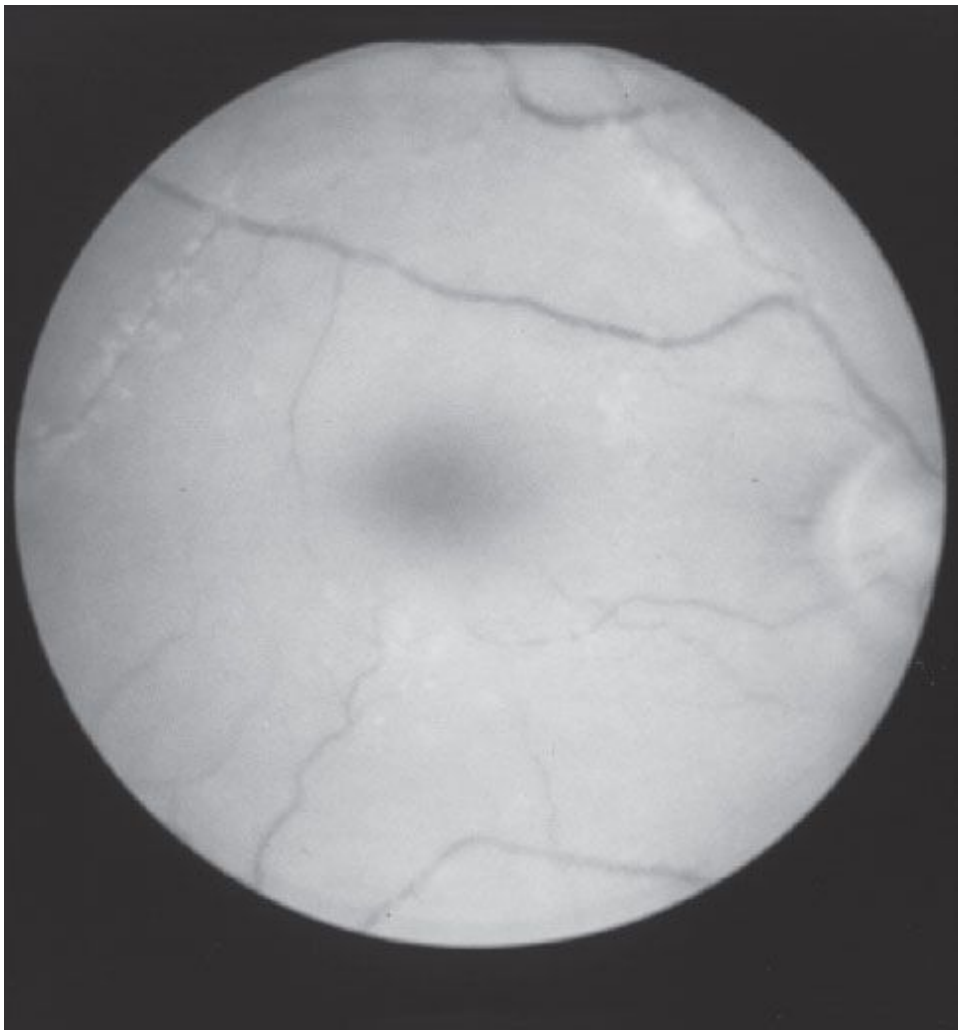

FIGURE 58.1 Central retinal artery occlusion.

Central Retinal Vein Occlusion

Patients with central retinal vein occlusion (CRVO) typically present with painless, sudden loss of vision (Fig. 58.2). Most patients are older than age 50, and many also have significant cardiovascular disease. Other associated disorders include hypertension, glaucoma, venous stasis, diabetes mellitus, tobacco use, vasculitis, and collagen vascular disorders. Physical findings may include retinal hemorrhage, which may be pronounced and diffuse, venous dilatation, cotton wool spots, and optic disc edema. Branch RVO may occur and may have segments of intraretinal hemorrhage. Complications may include macular edema, ischemia, and neovascularization with associated vitreous hemorrhage. The natural history of CRVO is often favorable even without specific intervention.

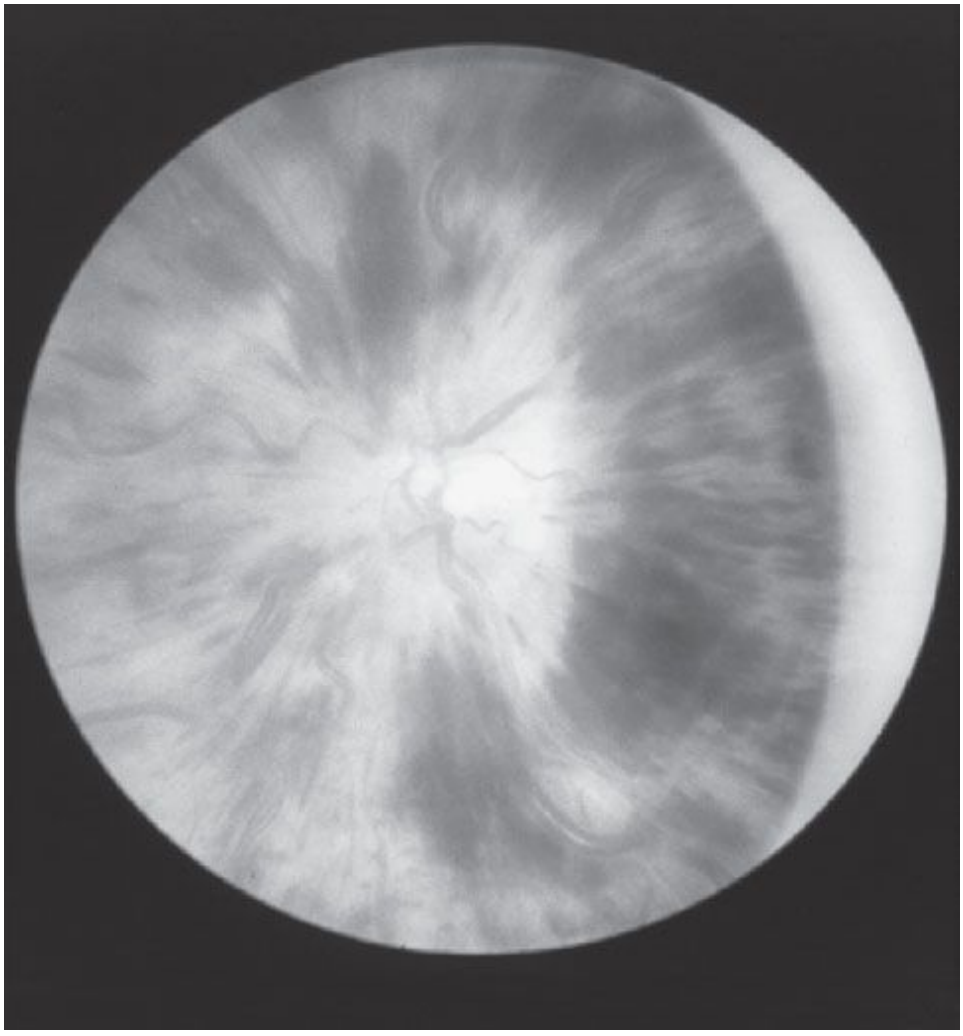

FIGURE 58.2 Central retinal vein occlusion.

Amaurosis Fugax

Amaurosis fugax, a unilateral transient obstruction of a retinal artery, may cause temporary loss of vision (up to 15 minutes). The visual loss is often described by the patient as a curtain being drawn across the visual field. Amaurosis fugax is usually caused by cholesterol emboli or fibrin-platelet emboli and may be associated with carotid artery disease, cardiac arrhythmias, anemia, sickle cell disease, hypertension, or episodic hypotension. Carotid and cardiac studies may be indicated to determine the source of the emboli.

Ischemic Optic Neuropathy

Ischemic optic neuropathy is typically found in patients older than 50 and often presents with painless decreased visual acuity. This disorder may result from an infarction of the optic nerve (90% of cases) or from GCA (10% of cases). An afferent pupillary defect may be found as well as a pale, elevated optic disc.

Vitreous and Retinal Disorders

Vitreous Hemorrhage

Vitreous hemorrhage typically presents with acute unilateral painless loss of vision and may be accompanied by symptoms of “floaters” or “cobwebs.” Associated visual disturbances may be mild or severe, depending on the extent of the hemorrhage. The normal red reflex of the fundus is absent. Diffuse, dark, particulate opacities may be seen. If severe, a black uniform reflex (“eight-ball hemorrhage”) will be seen instead of the normal retinal red reflex. Vitreous hemorrhage may be associated with numerous disorders including diabetes, trauma, malignancy, vitamin K deficiency, CRVO, leukemia, anemia, and thrombocytopenia.

Diabetic Retinopathy

Diabetic retinopathy is the leading cause of visual loss among retinal vascular disorders and may be divided into proliferative and nonproliferative disorders. This disorder may occur in type I or type II diabetes mellitus. Nonproliferative diabetic retinopathy is a progressive microangiopathy. Symptoms may be mild or nonexistent and may include hue discrimination abnormalities, scotomas, contrast sensitivity, or a variety of other visual complaints. Physical findings include multiple hemorrhages throughout the retina and macular edema. Proliferative retinopathy refers to ischemia as a result of microvascular occlusions and may present with cotton wool spots, retinal vein bleeding, and irregular dilation of the retinal capillary bed. Sudden visual loss may occur with massive vitreous hemorrhage from fragile neovascularization or from retinal detachment. Progressive loss of vision may be slowed or prevented by laser photocoagulation.

Retinal Detachment

Retinal detachment refers to a separation of the two layers of the retina: the pigment epithelium and neurosensory retina (Fig. 58.3). The most common type, rhegmatogenous, occurs as a result of tears, holes, or breaks in the sensory layer of the retina. Retinal detachment may be associated with advancing age, male gender, significant myopia, diabetes mellitus, sickle cell disease, or ocular contusion or penetrating injury, or it may be idiopathic. In addition, exudative or traction types of retinal detachment may be seen. Symptoms include photopsia (light flashes), floaters, or a shower of black dots in the periphery secondary to hemorrhage into vitreous humor, or a sensation of a shadow or curtain obscuring the visual field. Visual acuity may be normal if the macula is unaffected or severely impaired if involved. On examination, the detached area may appear gray, opaque, or translucent. Retinal folds may be seen, and vessels may appear dark red. Symptoms often resolve within 1 week.

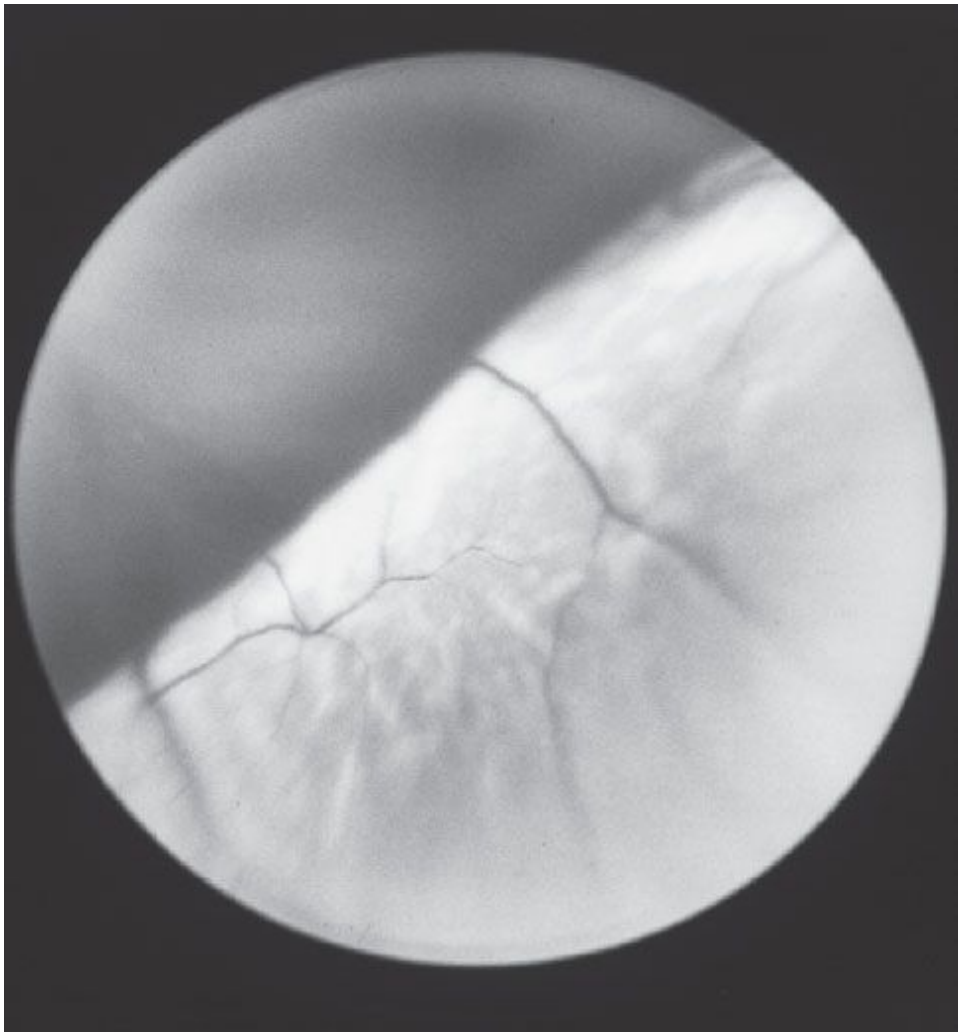

FIGURE 58.3 Retinal detachment.

Macular Degeneration

Age-related macular degeneration (ARMD) is the most common cause of permanent blindness among older patients and has an estimated incidence of up to 11.4 per 1,000. The disease can be divided into nonexudative (dry) macular degeneration, characterized by drusen (yellowish subretinal deposits) and exudative (wet) macular degeneration, characterized by submacular hemorrhage, yellowish exudates, or serous fluid. The incidence is associated with advanced age, family history, tobacco history, race (Caucasian), and gender (slight female predominance). The etiology is unknown. Symptoms include blurred vision, visual distortion, scotoma, or central visual loss. Physical findings include impaired visual acuity,

drusen (yellow–white deposits beneath the pigment epithelium), and clumps of pigment throughout the macula.

Neurologic Disorders

Cerebrovascular accidents and transient ischemic attacks may be associated with visual loss. A bilateral homonymous hemianopsia may result from involvement of the optic tract or occipital lobes. Involvement of both occipital lobes may produce complete blindness ("cortical blindness").

Cortical blindness may be caused by entities such as ischemia, mass lesions, hydrocephalus, anoxia, encephalitis, meningitis, edema, or hemorrhage into the occipital lobe(s) (9,10). Evaluation should be conducted promptly and may include computed tomography (CT), magnetic resonance imaging (MRI), and lumbar puncture.

The optic chiasm may be compressed by mass lesions such as pituitary adenomas, meningiomas, craniopharyngiomas, or aneurysms. These patients may present with bitemporal hemianopia, and advanced imaging is warranted.

Other Causes of Vision Loss

Cytomegalovirus Retinitis

Cytomegalovirus (CMV) retinitis may present with sudden or gradual visual loss when the infection invades the macula. It is seen most commonly in immunocompromised patients such as those with AIDS, on chemotherapy, or following organ transplantation. Symptoms include blurred vision, floaters, flashes of light, eye pain, and scotomas (11). Findings include retinal hemorrhagic areas combined with zones of white retinal necrosis ("tomato and cheese pizza" appearance).

Glaucoma

Patients with glaucoma may present with acute or chronic visual loss. Visual field testing may indicate a diminished perception in the nasal region. Optic nerve pallor and cupping is seen on examination. Elevated intraocular pressure (IOP) (often 50 to 70 mm Hg) is typically found. Associated symptoms often include eye pain, headache, nausea, and vomiting (Chapter 61).

Malignancies of the Eye

Although space does not permit a detailed study of ophthalmologic malignancies, it is prudent for the emergency physician to have an awareness of the spectrum of malignancies that may affect vision. Benign intraocular tumors may include retinal angiomas or astrocytic hamartomas. Malignant intraocular tumors include retinoblastoma (usually before age 1, presenting with leukocoria or strabismus) and malignant melanoma. Metastatic tumors may involve the eye, most often with choroidal metastasis (12). Complications of intraocular malignancies that affect vision include hemorrhage from tumor vascularization, retinal detachment, retinal degeneration, and retinopathy. Abnormal physical findings should alert the physician to the importance of timely ophthalmologic follow-up.

Methanol Toxicity

Methanol toxicity is associated with transient or permanent visual disturbances. Symptoms and signs usually occur within 18 to 48 hours of the ingestion. Associated symptoms include nausea, vomiting, headache, or abdominal pain. Findings include hyperemic, swollen optic discs, with retinal edema. A cherry-red spot may be observed.

Other Toxins

Numerous other toxins that may be associated with visual disturbances include carbon monoxide, lead, salicylates, sulfonamides, ergots, tin, quinine, barbiturates, chemotherapy, and nitroglycerin. Visual loss is usually bilateral, and therapy consists of the appropriate treatment of the underlying condition.

DIFFERENTIAL DIAGNOSIS

Vision loss may be caused by a variety of ophthalmologic conditions, or in association with other diseases. Some of the more common ophthalmologic causes are summarized in Table 58.2. In general, any abnormality of the cornea, lens, vitreous, retina, optic nerve, optic tract, optic radiations, or occipital cortex should be considered (13).

TABLE 58.2
Differential Diagnosis of Selected Causes of Visual Disturbance

Disease Process	Symptoms	Clinical Findings	Ancillary Tests	Management
Giant cell arteritis	Painless visual loss, sudden or gradual, HA, myalgias	Optic nerve edema, temporal artery tenderness	Elevated ESR, CRP, temporal artery biopsy	Steroids, ophthalmologic consultation
Optic neuritis	Painful visual loss, pain with EOM	APD, elevation of optic disc	MRI, consider LP	Consider steroids in MS; ophthalmologic consultation
Uveitis	Eye pain, blurred vision, photophobia	Cells in anterior or posterior chamber, flare in aqueous humor		Topical steroids, cycloplegics, ophthalmologic consultation
CRAO	Sudden, painless, profound visual loss	APD, pallor of retina, cherry-red fovea		Globe massage, paracentesis, acetazolamide, inhaled carbogen, ophthalmologic consultation
CRVO	Sudden, painless visual loss	Retinal hemorrhages, venous dilation, optic disc edema		Ophthalmologic consultation
Amaurosis fugax	Monocular visual loss (transient)		Carotid, cardiac studies	ASA, neurologic consultation
Vitreous hemorrhage	Visual floaters, cobwebs, or severe visual loss	Diminished or absent red reflex ("eight-ball" hemorrhage)		Treatment of underlying condition; ophthalmologic consultation
Retinal detachment	Acute, painless visual disturbance; filmy, cloudy vision; peripheral monocular visual loss ("veil")	Gray/translucent detached area with folds, bulging appearance		Ophthalmologic consultation
Macular degeneration	Gradual, painless disturbances; spots in visual field; distortion of straight lines	Drusen, macular pigment clumps		Ophthalmologic consultation
Diabetic retinopathy	Gradual visual disturbances, scotomas	Multiple retinal hemorrhages, macular edema		Ophthalmologic consultation
Ischemic optic neuropathy	Painless, diminished visual acuity	APD, pale, elevated optic disc		Ophthalmologic consultation
TIA	Transient binocular visual loss	Normal	Carotid, cardiac studies	Neurologic consultation, ASA
Cortical blindness	Sudden or gradual, complete visual loss or homonymous hemianopia, HA	Papilledema, other neurologic findings	CT, MRI, LP	Neurologic consultation, therapy of underlying disorder
Migraine HA	Transient visual loss	Normal		Neurologic consultation
Glaucoma	Sudden, painful visual disturbance, abd pain, N/V	Optic nerve pallor and cupping	Elevated IOP	Topical β-blocker; acetazolamide; ophthalmologic consultation; see Chapter 61
CMV retinitis	Sudden or gradual visual disturbance	Retinal hemorrhages, areas of pale retinal necrosis ("tomato and cheese pizza" appearance)	Consider CT/MRI	Foscarnet or ganciclovir, ophthalmologic consultation
Cavernous sinus thrombosis	Fever, visual loss, headache	Chemosis, proptosis, CN abnormalities	CT/MRI	IV antibiotics, admission
Methanol	Transient visual disturbance, N/V, HA	Hyperemic, swollen optic discs, cherry-red spot		EtOH, fomepizole, dialysis, see Chapter 302
Functional visual loss	Variable symptoms	Normal	Optokinetic nystagmus	Psychiatric consultation

This table represents only a summary of certain disorders, and is not an exhaustive information source for the above disease states.
HA, headache; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; EOM, external otitis media; APD, afferent pupillary defect; MRI, magnetic resonance imaging; LP, lumbar puncture; MS, multiple sclerosis; CRAO, central retinal artery occlusion; CRVO, central retinal vein occlusion; ASA, aspirin; TIA, transient ischemic attack; CT, computed tomography; abd, abdominal; IOP, intraocular pressure; CMV, cytomegalovirus; CN, cranial nerve; N/V, nausea/vomiting; EtOH, ethyl alcohol.

Patients with vascular disease may develop vision loss due to hemorrhages of various types, including preretinal, linear, punctate, subretinal, and white central hemorrhages (Roth spots). In addition, there may be acute ocular ischemia due to infarction of the optic disc (ischemic optic neuropathy), which presents with sudden visual loss and a pale, swollen optic disc. Causes of ocular ischemia include hypertension, atherosclerosis, choroidal infarction, retinal infarction,

and transient retinal ischemia (amaurosis fugax). Patients with AIDS may present with toxoplasmosis, candidal endophthalmitis, herpes zoster ophthalmicus, or optic neuropathy.

The diagnosis of functional visual loss, as seen in conversion disorder, should always be one of exclusion. There may be a variety of complaints, but no abnormalities are seen on examination. Optokinetic responses may be tested in a cursory fashion in the emergency department (ED) by passing a tape measure, or sheet of paper with prominent vertical lines, rapidly before the affected eye(s). Another simple test involves placing a mirror before the patient's face and rocking the mirror from side to side. The presence of optokinetic nystagmus (following movements with rapid returns to the primary position of the eye) indicates that vision is present. In addition, patients feigning blindness may demonstrate an inability to oppose outstretched forefingers while bringing outstretched arms together. This ability would not ordinarily be affected by blindness. Additional tests to differentiate organic from functional visual loss may be suggested by ophthalmologic or psychiatric evaluation.

ED EVALUATION

Complete details of the ophthalmologic examination are included in Chapter 54. Specifically, when evaluating the patient with loss of vision, visual acuity and visual field testing are of primary importance.

Visual acuity is an essential element of the physical examination and can be measured with a Snellen eye chart. For patients unable to adequately read from the eye chart, their ability to count fingers, detect movement, color, and perceive light should be evaluated. Visual field testing can be useful in determining the extent of visual loss and in developing the appropriate differential diagnosis. Eyes should be tested independently. In addition, the examiner should perform a slit-lamp examination and measurement of IOP.

Pupils should be evaluated utilizing the swinging flashlight test to detect an afferent pupillary defect. Funduscopic examination should be performed using a handheld ophthalmoscope. Pupillary dilation may be required to perform an adequate examination of the retina.

The fundus should be examined for evidence of papilledema, disc edema, pallor, hemorrhage, or exudates (14).

Ultrasound of the eye may be helpful in elucidating certain diagnoses such as retinal detachment and vitreous hemorrhage. Radiographic evaluation (including MRI or CT) may be indicated in cases where intracranial pathology or mass lesions involving the optic nerve or globe are suspected.

KEY TESTING

- Visual acuity, slit-lamp and funduscopic examination
- ESR and CRP (for suspected GCA)
- IOP (for suspected glaucoma)
- CT or MRI of brain
- Ultrasound of eye (for suspected retinal detachment)

ED MANAGEMENT

Many of the diseases that produce acute vision loss mandate immediate ophthalmologic consultation, intervention, or admission. The unique features of some of the causes are discussed here.

GCA should be treated expeditiously with early administration of corticosteroids (e.g., intravenous [IV] methylprednisolone, 2 to 4 mg/kg initial dose), to prevent blindness and other long-term visual defects, as well as contralateral eye involvement (common within 10 days without treatment) and may provide dramatic pain relief (15–19). Patients may have a 34% chance of improvement in visual function after steroid therapy. Aspirin may have additional protective effects when instituted in conjunction with steroid therapy. A biopsy should be performed within 7 to 10 days of steroid initiation, although most biopsies will remain positive up to 4 weeks after initiation of therapy. A negative biopsy does not exclude GCA.

Although the treatment of optic neuritis with steroids is not universally beneficial, IV methylprednisolone is indicated for patients with suspected multiple sclerosis (12,20). Interferon has also been suggested as a possible therapeutic adjunct. Investigation for an underlying predisposing condition, in consultation with the primary

care physician, is essential. Consultation with an ophthalmologist is indicated for patients with suspected optic neuritis.

Uveitis may be treated effectively with topical corticosteroids and cycloplegic agents. Systemic steroids may be indicated in severe cases. For cases resistant to steroid therapy, other therapies may include immunosuppressants such as antimetabolites or T-cell inhibitors. Therapy of the underlying disorder should be initiated.

Treatment for CRAO is often unsatisfactory but should be attempted if diagnosed within 90 minutes of onset of symptoms. Supplemental oxygen should be administered. Intermittent globe massage should be attempted to dislodge an embolus (moderate pressure for 5 seconds and release for 5 seconds). Other treatment modalities may include anterior chamber paracentesis (to decrease IOP and increase retinal perfusion), IV acetazolamide (to decrease IOP), topical timolol 0.5% or topical levobunolol 0.5%, inhaled carbogen (oxygen–carbon dioxide mixture of 95% to 5%) to induce retinal vasodilation and increase retinal PO_2. Hyperbaric oxygen and nifedipine have also been reported as successful therapies (21,22). Other treatments may include ophthalmic artery infusion of urokinase or tissue plasminogen activator, isovolemic hemodilution, oral acetylsalicylate, or oral pentoxifylline (23).

CRVO is difficult to treat successfully, but treatment should include a careful evaluation of the probable etiology to prevent contralateral eye involvement. Spontaneous resolution may occur in some cases. Treatment offered by an ophthalmologist may include intravitreal injection with vascular endothelial growth factor (VEGF) antibodies, intravitreal steroids, isovolemic hemodilution, retinal laser photocoagulation, or vitrectomy (24,25).

Amaurosis fugax should be treated with antiplatelet therapy such as aspirin, and ophthalmologic consultation should be obtained. Ischemic optic neuropathy should be treated with systemic steroids (methylprednisolone, 250 mg IV q6h) to prevent contralateral eye involvement.

Retinal detachment should be treated by an ophthalmologist, with options including diathermy, laser photocoagulation, or other intraocular surgical therapies. Treatment for macular degeneration

includes photodynamic therapy with verteporfin or intravitreal injection of pegaptanib. The use of low vision aids may be recommended.

CMV retinitis may be treated with IV or intravitreous antiviral therapy (fomivirsen, foscarnet, or ganciclovir) in consultation with an ophthalmologist.

Glaucoma may be treated with a miotic (e.g., pilocarpine), topical β-blocker (e.g., timolol), a carbonic anhydrase inhibitor (e.g., acetazolamide), mannitol or glycerin, and topical steroids (see Chapter 61).

Methanol toxicity may be treated with ethanol or dialysis and is discussed in Chapter 302.

CRITICAL INTERVENTIONS

- Rapidly recognize and obtain ophthalmologic consultation for patients with CRAO and amaurosis fugax
- Initiate steroids for patients with GCA or optic neuritis associated with suspected multiple sclerosis

DISPOSITION

For the majority of patients with acute visual loss, consultation with an ophthalmologist is indicated. The severity and nature of the disease process will dictate whether emergent or urgent consultation is necessary. Patients considered for hospital admission should be those patients who require IV medications, surgery, or other invasive procedures, or for whom serious worsening of vision is imminent.

Common Pitfalls

- Failure to measure visual acuity
- Failure to measure IOP and consider the diagnosis of glaucoma
- Failure to test visual fields adequately
- Failure to administer steroids rapidly to patients with GCA
- Delay in treatment of CRAO

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CHAPTER 59

Diplopia

Kurt Brueggemann and James A. Comes

Diplopia is an uncommon and frightening emergency department (ED) complaint. The differential diagnosis is complex and evaluation may require neuroimaging or consultation with subspecialists who may not be immediately available. Diplopia can be the sentinel finding of an insidious neurologic or metabolic disease, the sole symptom of a benign and self-limited microvascular (diabetic) mononeuropathy, or the lone warning sign of an impending intracranial aneurysm rupture. Diplopia can result from a unilateral ocular problem or binocular misalignment. It may present in isolation or as part of a constellation of findings.

Management varies from expectant to emergent depending on the presumed etiology. A comprehensive emergent management strategy has not been thoroughly established. Guiding principles and available evidence favor a meticulous, systematic, and conservative approach.

CLINICAL PRESENTATION

Diplopia has a wide variety of presentations, depending upon the neuroanatomic location of the lesion (if present) (1,2). Diplopia can be categorized as horizontal, vertical, or oblique/diagonal, and it may be noted to be worse with a particular direction of gaze. Strabismus may be evident at rest (*-tropia*) or upon provocation (*-phoria*). For example a medial deviation of the eye at rest is termed an esotropia.

Diplopia can be confused with a variety of other symptoms, including dizziness, lightheadedness, blurry vision, ghost-like images, and partial or full vision loss (3).

Diplopia, colloquially “double vision,” is the result of an inability to integrate the signals received by two retinas into a single sensible visual perception. This can result from a refractive error of an individual eye (monocular diplopia) or an extraocular cause producing misalignment of the eyes (binocular diplopia).

Monocular diplopia is almost invariably due to a problem with the single involved eye, and rarely requires emergent management. It can be distinguished from binocular diplopia by having the patient alternately close one eye and then the other. If diplopia persists with monocular vision, misalignment of the eyes is not the problem (3) and further attention should be directed to the affected eye. The focus of the remainder of this chapter is binocular diplopia.

During normal vision the brain integrates the sensory input from each eye into a single stereoscopic worldview (visual acuity and depth perception). The two eyes are normally entrained and aligned to place any object of interest over the fovea (central vision) of each retina. The inability of one eye to accurately “acquire the target” produces two distinct retinal projections which cannot be fused by the visual cortex, resulting in “double vision.”

Diplopia (pathologic binocular diplopia) results from dysfunction of the extraocular muscles (EOMs), also called ophthalmoplegia. This dysfunction can result from disorders and diseases anywhere from the orbit to the CNS including the muscles, their neuromuscular junctions, cranial nerve(s) or nuclei up through their respective interneurons. These neurons make possible the complex coordination of head and eye movements involving cortical, vestibular, proprioceptive, and cerebellar circuits.

Extraocular motility is provided by six EOMs; the medial rectus (EOM-MR) and lateral rectus (EOM-LR) adduct and abduct the eye, the superior rectus (EOM-SR) and inferior oblique (EOM-IO) elevate the eye while the inferior rectus (EOM-IR) and superior oblique (EOM-SO) depress the eye.

The abducens nerve (CN-VI) innervates the EOM-LR. The trochlear nerve (CN-IV) innervates the EOM-SO. The oculomotor nerve (CN-III) innervates the remainder of the EOMs, the major muscle of the eye lid, levator palpebrae superioris (LPS), and also carries autonomic parasympathetic fibers to the pupillary constrictor muscle.

Individual cranial nerve palsies present with typical clinical presentations. A patient may adopt several coping strategies to deal with the deficits. These coping strategies can help guide the identification of the palsy. If a compensatory head position is present, it mirrors the function of the inactive muscle(s).

The clinical presentation may also vary considerably secondary to the underlying cause. For example, a lesion in the cavernous sinus may involve all three extraocular cranial nerves as well as the ophthalmic and maxillary branches of the trigeminal nerve. Lesions of the carotid artery up through the cavernous sinus may produce a Horner syndrome (ipsilateral ptosis, miosis, and anhidrosis). A lesion of the pituitary may involve a characteristic visual field deficit and endocrinologic signs and symptoms. Diseases involving the orbit may be painfully obvious (e.g., an orbital fracture with EOM entrapment) or quite subtle (e.g., thyroid myopathy). Brainstem or other central lesions often involve other neurologic deficits including hemiparesis, anesthesia, discoordination or vertigo, facial weakness or anesthesia, dysphonia, dysphagia, or visual field deficits. Neuromuscular junction disorders can be elusive but may exhibit historical features such as fatigability, temporal variation, dysphagia, proximal muscle weakness, and dyspnea. CNS infection may also produce fever, headache, meningismus, or altered mental status.

Oculomotor (CN-III) Palsy

A complete CN-III nerve palsy will produce a “down and out” pupil, and ipsilateral ptosis with variable but critical pupillary involvement. The patient may complain of a diagonal diplopia which is worse in near-field gaze when looking inward and upward.

The accompanying ptosis (effectively closing the "bad" eye) may minimize the associated disability by obliterating the diplopia.

The cranial nerves supplying EOMs exit the brainstem and traverse the dura, subarachnoid space, and cavernous sinus before funneling into the superior orbital fissure. CN-III travels alongside the posterior communicating artery soon after it exits the brainstem. CN-III innervates four EOMs and includes fibers supplying pupillary and palpebral muscles.

A complete CN-III palsy with pupillary involvement is a posterior circulation aneurysm until proven otherwise. Pupillary involvement is particularly worrisome because the parasympathetic fibers lie in the periphery of the nerve sheath, making them more susceptible to external compression. Aneurysm and diabetic neuropathy are the two leading causes of CN-III palsy. An isolated, unilateral, atraumatic complete CN-III palsy *sparing the pupil* is often due to diabetic neuropathy. Cavernous sinus lesions can produce CN-III palsies with a concurrent Horner syndrome which can make the pupillary findings very ambiguous.

Partial, incomplete, or inconsistent palsies of CN-III are substantially more complicated and require neuroimaging and consideration of neuromuscular disease (4). A dysfunctional EOM-MR raises several diagnostic possibilities including internuclear ophthalmoplegia (INO), myopathy, and neuromuscular disease. These last examples serve to illustrate the point that any findings not consistent with a complete unilateral cranial nerve III palsy sparing the pupil require a very meticulous appraisal.

Trochlear (CN-IV) Palsy

A complete CN-IV nerve palsy may have a more subtle presentation. The patient may complain of a vertical diplopia with a torsional (rotational) component. Owing to the inaction of the functionally denervated EOM-SO the globe may appear elevated (hypertropia) and extorted. The diplopia will worsen with nasal deviation and downgaze, thus activities like reading, descending stairs or watching TV in bed may be difficult. The patient may adopt a compensatory

head posture or tilt consisting of the head tilted forward and away from the affected eye (mirroring the depression and intorsion action of the EOM-SO).

CN-IV exits the brainstem dorsally and passes alongside the edge of the cerebellar tentorium making it vulnerable in the setting of closed head injury. It has a long intracranial course, so diseases affecting the subarachnoid space should be strongly considered. CN-IV palsies are very unlikely to be aneurysmal.

The critical diagnostic consideration in patients presenting with vertical diplopia is skew deviation. Skew deviation results from a central lesion and can mimic a CN-IV palsy but is often distinguished by the presence of other neurologic findings. It results from a supranuclear lesion of the interneurons connecting the vestibular and ocular circuits and frequently presents with vertical diplopia present in all gaze directions.

Abducens (CN-VI) Palsy

Although the abducens nerve (CN-VI) innervates only a single muscle, EOM-LR, the associated diplopia is often the most severe. Horizontal diplopia is the rule and a compensatory head rotation (toward the affected side) may be present. The patient may close the eye "pseudoptosis" or cover it to minimize the symptoms.

CN-VI travels near the cavernous portion of the internal carotid artery and may be the first cranial nerve involved in vascular disease in this area. The abducens nerve ascends the clivus in a near vertical fashion and is tethered at the apex across the sharp ridge of the petrous portion of the temporal bone. This anatomic anchoring makes the abducens nerve very susceptible to increased intracranial pressure (ICP). Thus the examiner should look for headache and papilledema and have a low threshold for obtaining imaging to exclude obstructive hydrocephalus, mass lesions, idiopathic intracranial hypertension, or sagittal venous thrombosis.

Internuclear Ophthalmoplegia

Internuclear ophthalmoplegia (INO) clinically presents as an EOM-MR palsy. In normal abduction the medial longitudinal fasciculus (MLF) activates the contralateral EOM-MR to keep the eyes aligned. A lesion of the MLF manifests as an inability to adduct the eye on attempted contralateral abduction. The abducting eye will exhibit nystagmus as a response to the divergence. INO is by definition a central lesion requiring neuroimaging and consideration of neuromuscular disease. Bilateral INO is a hallmark of multiple sclerosis (MS). As the EOM-MR itself is not impaired, convergence should remain intact in an INO and be impaired in a neuromuscular disease affecting the EOM-MR.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of binocular diplopia can be simplified based on whether the findings suggest an isolated cranial nerve palsy. If an isolated unilateral cranial nerve palsy is present, and there is no history of antecedent trauma or orbital findings, the differential diagnosis can be narrowed considerably. CN-III palsy is most likely due to a posterior circulation aneurysm or diabetic neuropathy. CN-IV palsy must be differentiated from central causes of vertical diplopia and the physical examination may not be adequate to do so (5,6). The patient with CN-VI palsy must be evaluated for disease processes producing elevated ICP.

If the diplopia is not attributable to an individual cranial nerve palsy, the diagnostic considerations include myopathy or myositis (7), neuromuscular disease, demyelinating disease, descending paralytic disorders, or a CNS lesion including infection, inflammation, neoplasm, ischemia, thrombosis, aneurysm, hemorrhage, dissection, or demyelination.

Some selected diseases which can mimic or aggregate extraocular cranial nerve dysfunction include:

Cavernous Sinus Thrombosis: May involve all three extraocular cranial nerves as well as the ophthalmic and maxillary branches of the trigeminal nerve. It should be strongly considered in the thrombophilic or immunocompromised patient as the associated

infection can be bacterial or fungal. Diseases of the cavernous internal carotid artery including aneurysm or rupture may present similarly.

Giant Cell/Temporal Arteritis: Should be considered in any elderly patient complaining of unilateral headache and vacillating vision abnormalities (including diplopia). *Ophthalmoplegic migraine* must be considered a diagnosis of exclusion in all age groups.

Miller–Fisher Syndrome (MFS): Is a descending demyelinating inflammatory polyneuropathy which typically begins with diplopia and then progresses to ataxia, areflexia and potentially proximal muscle weakness, paresthesias, and respiratory failure from diaphragmatic insufficiency (8).

Botulism: Often begins with bilateral ophthalmoplegia but it can potentially involve any cranial nerve (e.g., dysphagia may be the presenting complaint). It progresses to symmetric descending weakness.

Myasthenia Gravis (MG): Can initially present with ocular symptoms of diplopia and ptosis. The ophthalmoplegia producing diplopia can involve any combination of EOMs and mimic any of the CN palsies described above. The pupils, however, are never affected in ocular myasthenia.

Multiple Sclerosis (MS): Patients may present with ophthalmoplegia resulting from cranial nerve palsies or INO.

Idiopathic Intracranial Hypertension (IIH): (Formerly pseudotumor cerebri) is an important diagnostic consideration as it can result in vision loss if left untreated. Since CN-VI is sensitive to increased ICP it is the EOM palsy associated with this condition. Funduscopic examination reveals papilledema and nonpulsatile distended retinal veins. Emergent neuroimaging is warranted to exclude obstructive hydrocephalus, venous sinus thrombosis or mass lesion.

Thyroid Extraocular Myopathy: It can produce diplopia in clinically euthyroid patients without alarming signs of an orbital process. The inferior rectus is most commonly the first muscle involved in this restrictive myopathy. Orbital findings can include

exophthalmos, ptosis, periocular inflammation, lid lag, and lid retraction.

Wernicke Encephalopathy: Must be considered in any patient presenting with altered mental status, ataxia, and oculomotor aberrations from ophthalmoplegia to nystagmus (9).

ED EVALUATION

The diagnostic approach must be guided by the overall condition of the patient and the associated signs and symptoms. Thus, if the patient is strongly suspected to have meningitis, the diagnostic and management process is governed by the preliminary diagnosis, regardless of diplopia.

The history and physical examination can be critical in lesion localization and establishing the diagnostic approach. In a stable and cooperative patient the examiner should first focus on the eyes, including tests of visual acuity, visual field integrity, pupillary reactivity, afferent defects and appearance (size and symmetry), extraocular movements, and alignment (looking for strabismus, gaze deviation, or nystagmus). The patient should be asked to report any changes in their symptoms with these maneuvers. Visual acuity and EOM testing should be performed with each eye individually and together. The examiner should then proceed to consideration of the face, looking for ptosis (if not already noted) and facial, orbital or ocular asymmetry (e.g., unilateral conjunctival injection). The presence of pain at rest or pain with movement should be noted (7,10–12). A full cranial nerve examination must be performed, as well as a complete cerebellar examination, gait testing, and evaluation of deep tendon reflexes, and extremity motor or sensory function.

Even with a careful physical examination in a cooperative patient the localization of the lesion may prove difficult (1,2). Consequently, consider broad neuroimaging and early subspeciality consultation if available. Patients with binocular diplopia without clinically evident ophthalmoplegia require careful evaluation as this can be a sign of MS.

Monocular diplopia, once identified, should prompt a thorough examination of the eye including cornea, lens, anterior/posterior chambers, retina, and possibly the optic nerve. Consideration should be given to disease processes producing monocular vision impairment or loss (13), monocular visual field deficits, and a monocular painful red eye. Ophthalmologic consultation is recommended.

In the setting of trauma, computed tomography (CT) should be the first choice for diagnostic imaging. In the absence of trauma, CT can be performed initially as it is often the most accessible, though a negative result may be falsely reassuring (14–16). If resources are available patients should be evaluated with magnetic resonance imaging, with angiography or venography, depending on the clinical picture.

Neurologic findings attributable to more than one cranial nerve (II to XII) or any other neurologic findings should prompt neuroimaging and consideration of neuromuscular disease, restrictive myopathy, demyelinating disease, or other causes of descending weakness (17). If aneurysm is strongly suspected, some authorities consider that a negative CT or MR angiogram is inadequate to exclude aneurysmal disease and thus suggest formal angiography in this setting (3).

Some authors have argued that all patients presenting with binocular diplopia require advanced neuroimaging because the potential etiologies may be life-threatening and there are no established clinical criteria for safely identifying the subset of patients who do not require an extensive workup.

KEY TESTING

- Careful neurologic examination
- MRI is indicated in most patients with binocular diplopia

ED MANAGEMENT

The most important goal is to rapidly identify patients with a serious underlying cause of diplopia, initiate therapy as appropriate,

and involve necessary specialists. Depending on the nature and severity of the underlying cause, appropriate initial actions may include intubation and respiratory support, hemodynamic support, ICP management, seizure and/or vasospasm prophylaxis, anticoagulation correction, thrombolytic consideration, or broad-spectrum antibiotics. Isolated cranial nerve palsies should undergo neuroimaging and early subspeciality consultation.

CRITICAL INTERVENTIONS

- Supportive care as needed with attention to the underlying pathology

DISPOSITION

Admission or transfer decisions largely rest on the condition of the patient, the presumed diagnosis, and the capabilities of the institution. Most patients presenting to the ED with binocular diplopia will require hospitalization, advanced neuroimaging, and subspecialty consultation. Patients with negative neuroimaging studies and histories suggestive of progressive or descending weakness require hospitalization for definitive diagnosis and close observation. As no clinical criteria exist for safely and effectively risk-stratifying potential expectant management patients, clinical judgment and the availability of specialty consultation and follow-up play a role in the disposition of these patients.

Common Pitfalls

- Failure to distinguish monocular from binocular diplopia
- Failure to identify diplopia in the patient complaining of dizziness or blurry vision
- Performing unenhanced CT in the patient with diplopia and regarding it as a definitive study
- Failure to perform lumbar puncture or opening pressure measurement in CN-VI palsy patients with a normal head CT to exclude IIH

- Failure to consider myopathy, neuromuscular or demyelinating diseases in the differential
- Failure to involve subspecialists in the diagnostic decision making

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CHAPTER 60 Acute Eye Infections

Tricia C. Loo

Eye infections are encountered in the ED in a broad spectrum ranging from minor to severe. The majority of infections seen in the ED are minor, but it is very important that the emergency physician learn to recognize the signs and symptoms of severe infections which, if missed, could lead to compromise of vision and be devastating to the patient. This chapter addresses a variety of eye infections, including conjunctivitis, keratitis, keratoconjunctivitis, endophthalmitis, and orbital and periorbital cellulitis (see Chapter 255).

CLINICAL PRESENTATION

Conjunctivitis refers to inflammation of the mucous membranes that line the eyelids and sclera. Causes of conjunctivitis include viral, bacterial, fungal, or parasitic (rare) infections, allergic, chemical exposure, and contact lens wear. The main bacterial pathogens include *Haemophilus Influenzae* and *Streptococcus pneumoniae* species in both children and adults, and *Moraxella catarrhalis* in children. The most common cause of viral conjunctivitis is adenovirus. Contact lens wearers are at risk for gram negative infections, including *Pseudomonas*. Most patients presenting to the ED with conjunctivitis have a self-limited condition, but the emergency physician must be wary of patients presenting with serious etiologies (i.e., bacterial or herpetic conjunctivitis) that could result in vision loss if left untreated.

Patients with bacterial conjunctivitis may present with symptoms of eye redness, mucopurulent discharge, and itching. Patients with

viral conjunctivitis present with bilateral watery discharge and foreign body sensation. Upper respiratory infection typically precedes viral conjunctivitis. Discharge from either cause can result in crusting and sticking of the eyelids, which is especially notable after sleep. The quality of discharge or associated findings such as an enlarged ipsilateral preauricular lymph node, are commonly used to differentiate between viral and bacterial conjunctivitis, but there appears to be little evidence of these associations or of any specific factors aiding this differentiation (1).

Keratitis refers to inflammation of the cornea. Infectious keratitis frequently involves the conjunctiva as well and is referred to as keratoconjunctivitis. This condition usually causes significant pain for the patient and may have viral or bacterial etiologies as well. Patients with keratitis usually present with intense eye pain, tearing, redness, and sometimes photosensitivity. Herpes keratitis may produce severe pain and a corneal dendritic lesion.

Blepharitis refers to inflammation of the eyelids and is one of the causes of a persistent red eye. Chronic inflammation can lead to the meibomian glands getting clogged. If the glands get infected, a painful lump forms, and this is known as a hordeolum/sty. A chalazion is not truly an infection but a chronic inflammatory process leading to granuloma formation surrounding blocked sebaceous or meibomian glands.

Blepharitis may result in red, swollen eyelids, a foreign body sensation, tearing, crusting of the eyelid margins, eye pain, or photophobia. With hordeolum, similar symptoms are often present, but typically a focal area of erythema and swelling of the eyelid is noticed. Similarly, a chalazion usually causes a focal area of inflammation that is usually subacute in onset and most times occurs proximal to the eyelid margin.

Endophthalmitis is inflammation of the intraocular structures (vitreous and/or aqueous humor). It most frequently results from exogenous causes (i.e., ocular surgery or penetrating trauma), but can also rarely occur from endogenous causes (i.e., bacteremic seeding of the eye). Patients with endophthalmitis often exhibit more significant clinical findings, including eye pain, vision loss,

headache, discharge, and photophobia. Acute endophthalmitis is a medical emergency and requires aggressive antibiotic therapy (both systemic and intravitreal) and urgent ophthalmology consultation.

Preseptal and *orbital cellulitis* are relatively uncommon and affect children more frequently than adults. Preseptal cellulitis refers to infections of the soft tissues anterior to the orbital septum (Fig. 60.1). Orbital cellulitis refers to infections posterior to the septum (fat and ocular muscles). Preseptal cellulitis is more common than orbital cellulitis, and most frequently arises from external sources (trauma, bites, foreign bodies). Orbital cellulitis most frequently arises from rhinosinusitis. Periorbital cellulitis typically involves erythema, edema, and warmth of the periorbital tissues and also may involve closure of the palpebral fissures. Fever may be present. There should be no complaints of ocular pain, pain with movement of the globe, nor any limitation of globe mobility, all of which suggest the more serious diagnosis of orbital cellulitis.

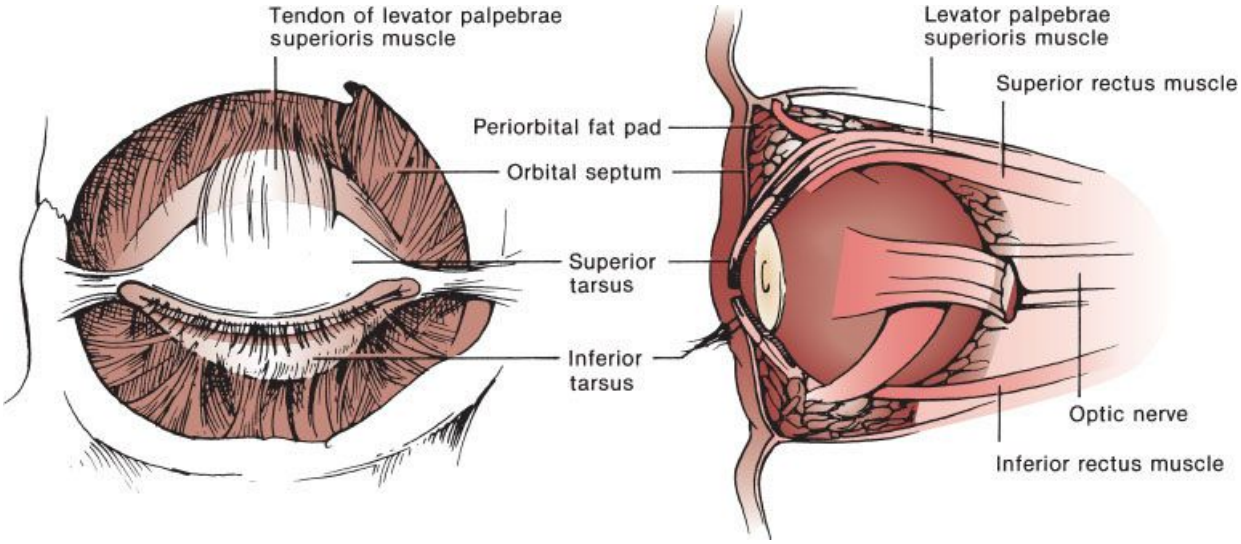

FIGURE 60.1 View of orbit–orbital septum.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the red or painful eye is broad (Chapter 56). Infection is a relatively common cause of these symptoms, but a variety of other causes must be considered, including allergic reactions, irritant causes, foreign body, chemical or thermal burns,

trauma, medication reactions, orbital disease related to other medical problems (e.g., thyroid disorders), glaucoma, uveitis, mucocutaneous syndromes (e.g., Kawasaki disease, Stevens–Johnson syndrome, etc.), and cancer (2). The differential diagnosis of periorbital cellulitis includes orbital cellulitis, insect bite, allergic response, and hordeolum. The differential for orbital cellulitis includes cavernous sinus thrombosis, endophthalmitis, and tumor.

ED EVALUATION

A thorough but focused history and a careful ocular examination are the keys to ED management of the painful or red eye. The relevant physical examination is described in more detail in Chapters 54 and 56. History should include documentation of previous visual problems or surgeries, current vision complaints, use of glasses or contact lenses, use of general or ophthalmic medications, other general medical problems, trauma, contact with other people who may have ocular infections, contact with or exposure to chemicals or toxins, symptoms of systemic illness (e.g., fever, tachycardia, etc.), history of immunocompromised state from medical conditions or medications, and the pattern of development of symptoms (one eye, both eyes, etc.). Visual acuity should always be documented, as visual acuity is the "vital sign" of the eye. This examination should take place before use of any ophthalmologic medications (e.g., topical anesthetics, mydriatics, etc.). Focused examination of the eye and periorbital areas should then be performed.

Lids

Examination of the eyelids is important to evaluate for crusting or other signs of infectious or dermatologic conditions. Any general or focal erythema or swelling of the lids should be noted. Eversion of the lids and inspection of the fornices for foreign body should also be performed.

Conjunctiva

Examination should identify chemosis or discharge. Membranes may be present in infections involving adenovirus but may be due to *S. pneumoniae,* diphtheria, or rarely, herpetic disease. Conjunctival hemorrhage may be present and is often petechial when caused by adenovirus. Copious discharge may be present in gonococcal conjunctivitis. Hemorrhage may also be secondary to other organisms such as *S. pneumoniae.* Follicular reaction, creating a "cobblestone" appearance in the lower palpebral conjunctiva, is typically seen with adenovirus infection but may be secondary to allergic or toxic causes (3).

Cornea

The cornea should be specifically examined for signs of ulceration. Most ulcers are centrally located, and fluorescein staining may reveal spots or specks of increased uptake over areas of corneal epithelial damage. Larger areas of corneal epithelial injury signify ulceration and require ophthalmologic consultation for further management because the possible complications include corneal scarring and vision loss. Fluorescein staining may also reveal the typical dendritic pattern associated with herpes simplex virus (HSV) infections. Varicella zoster virus (VZV) may also cause corneal ulcers. Care must be taken to examine the nose for involvement with the typical zoster lesions. Herpetic eruptions involving the nose may signify that the nasociliary branch of the ophthalmic nerve is involved. Corneal involvement is likely in this scenario and is referred to as the Hutchinson's sign. Corneal ulcers associated with blue or greenish discharge are often associated with *Pseudomonas aeruginosa* infection. Urgent (next-day) ophthalmology referral is often adequate for small corneal ulcerations, but larger or more extensive ulcerations require ophthalmologic consultation in the ED. Fungal ulcers are often caused by *Candida, Aspergillus,* or *Fusarium* species. The incidence of fungal infections is increasing secondary to the increasing number of patients with AIDS and because of the increasing use of immunosuppressive medications. Contact lens use also predisposes to corneal ulceration.

Anterior Chamber

Slit-lamp examination for evaluation of the anterior chamber is important to evaluate for signs of iritis (uveitis). White blood cells ("cell and flare") visualized in the anterior chamber are the key finding with iritis. Iritis may be related to significant corneal surface infections or ulcerations. A hypopyon, the layering of the white blood cells in the anterior chamber, may be seen and represents a true ocular emergency. Presence of a hypopyon requires immediate ophthalmology consultation.

Periorbital Areas and Skin

Erythema and swelling in the periorbital area may be secondary to local inflammatory causes or infection, but underlying preseptal or orbital cellulitis should be considered. There are a number of key points to remember when performing the physical examination of this area:

- Preseptal cellulitis may present with sufficient swelling to affect visual acuity and ocular motility.
- Fever is absent in as many as 24% of all patients with preseptal and orbital infections.
- Unilateral involvement is the rule rather than the exception for both preseptal and orbital cellulitis.
- Examination should be performed with the assumption that the patient has orbital cellulitis until proven otherwise.
- Proptosis and painful eye movements or extraocular movement impairment are more often associated with orbital cellulitis, although subperiosteal or orbital abscesses may cause similar findings (4).

The bacterial pathogens in orbital and preseptal cellulitis are typically the same organisms causing the predisposing condition: sinusitis, upper respiratory infection, local skin infection, dental infections, or postsurgical infections. Most commonly, *Staphylococcus aureus, Staphylococcus epidermidis, S. pneumoniae,* or other streptococcal species are causative agents, but many others have been implicated. *H. influenzae* type b vaccine has dramatically

decreased this organism's role as a pathogen in children with preseptal or orbital cellulitis (5). *Staphylococcus* sp are now seen most commonly in children with these infections. The prevalence of methicillin-resistant *S. aureus* (MRSA) continues to increase with rapidly growing numbers of ophthalmologic-related *S. aureus* isolates being reported as methicillin-resistant (6).

When preseptal or orbital cellulitis is considered, further diagnostic testing may be indicated. For the systemically ill patient, particularly pediatric patients, blood cultures may be useful. With orbital cellulitis, blood cultures are negative in two-thirds of children and 90% to 95% of adults (3). Cultures of eyelid aspirates and eye secretions are rarely helpful and are not recommended, unless there is a clear source of cutaneous infection. Cultures of cerebrospinal fluid are recommended only for infants in whom meningeal signs are evident.

Computed tomography (CT) scanning of the orbit is the preferred method of imaging for orbital infections. CT scanning of the orbit is advocated in all children in whom orbital cellulitis cannot be clearly ruled out by examination (7). Many authors recommend obtaining axial and coronal CT views to improve diagnostic yield in regard to subperiosteal or orbital abscesses that may be missed if only axial views are obtained (8–10). There is no advantage to using contrast-enhanced versus noncontrast CT scans. Orbital or subperiosteal abscesses are identified on CT scans in only 80% of cases (11), and diagnosis of orbital infection remains primarily a clinical one. Ultrasound has been used in some centers for diagnosis, and magnetic resonance imaging (MRI) may be a useful alternative for patients requiring surgical treatment.

KEY TESTING

- CT of the orbits, if orbital cellulitis is suspected

ED MANAGEMENT

Examination and other testing should allow somewhat focused treatment of eye infections. If bacterial conjunctivitis or keratitis is

suspected, topical antibiotics are generally appropriate. Although these infections are generally self-limited and rarely associated with sight-threatening complications, evidence suggests that the use of topical antibiotics may improve clinical remission rates (12,13).

Treatment of Ocular Surface and Lid Infections

Recent reviews have evaluated the antibiotic resistance of commonly used ophthalmic antibiotic preparations (14). In general, the narrow-spectrum antibiotics bacitracin, vancomycin, and cefazolin have retained their effectiveness against gram-positive infections. The broad-spectrum antibiotics include the aminoglycosides gentamicin, tobramycin, neomycin, trimethoprim, and the sulfacetamides. The aminoglycosides continue to have excellent activity against gram-negative bacteria and good activity against *Staphylococcus* sp but are less effective for *Streptococcus* sp. Trimethoprim provides excellent coverage for *Haemophilus* sp but poor coverage against *Moraxella* sp and other gram-negative bacteria. The sulfacetamides have excellent efficacy against *Streptococcus* sp and *S. aureus* conjunctival infections but less activity in cases of *S. aureus* keratitis.

Erythromycin has exhibited increased bacterial resistance rates, particularly with *Staphylococcus* sp infections. The fluoroquinolones have good activity against most gram-negative organisms and *S. pneumoniae,* but increased resistance has been seen for *Pseudomonas aeruginosa* and *S. aureus* (15,16). Failing to reach adequate concentrations of fluoroquinolones will inadequately treat infections and likely will increase bacterial resistance; therefore, frequent topical dosing is recommended. MRSA is increasing in prevalence, and initial antibiotic choices should be made with consideration of local resistance patterns. Vancomycin remains the drug of choice for serious MRSA infections (17).

Ophthalmic drops are generally well tolerated by adults, but ointment may be useful at bedtime. Ointments may be useful in children because of inherent difficulties in instilling ophthalmic drops in children. Care must be used to avoid complications caused by the topical antibiotics themselves. Neomycin is very sensitizing and can cause reactions with symptoms similar to the patient's initial

presenting complaints, thus confusing further management. Aminoglycosides, sulfa agents, and bacitracin may cause similar reactions, although less often. Cross contamination of ophthalmologic medications also occurs frequently during patients' use of these medications and highlights the importance of appropriate handwashing practices for the patient and for health care personnel. This practice should decrease the possibility of contracting or spreading the infectious agent.

Patients with herpetic corneal lesions may be treated with both a topical antiviral agent such as trifluridine (Viroptic 1%) and an oral antiviral (acyclovir, famciclovir, valacyclovir) with ophthalmologic consultation and follow-up. Gonococcal conjunctivitis should be treated with intramuscular (IM) ceftriaxone. If the infection involves the cornea or deep structures, ophthalmologic consultation and admission are recommended.

Some infections of the corneal surface may be complicated by iritis and may require treatment with cycloplegics for symptomatic relief. Steroid medications may also be indicated for patients with iritis, but use of these medications is generally deferred to the treating ophthalmologist. Topical steroids are usually not prescribed by emergency physicians without consultation with an ophthalmologist.

Initial treatment of uncomplicated blepharitis and hordeolum usually involves use of warm compresses several times daily. Typically, this is the only treatment required for hordeolum, although topical antibiotics may be indicated if there are signs of infection spreading from the area involving the hordeolum. Systemic antibiotics may be needed if there is evidence of a more significant infection.

The key to treatment of blepharitis is an adequate regimen of cleansing the eyelid margins. Topical combination preparations containing an antibiotic and a steroid (e.g., sulfacetamide and prednisolone) may also be useful but only for a short duration of treatment. Conservative management predominates in the early treatment of chalazion. Surgical excision by an ophthalmologist may be necessary, if improvement does not occur with initial treatment.

Treatment of Periorbital and Orbital Cellulitis

Outpatient treatment with oral antibiotics may be acceptable for the management of periorbital cellulitis in adults, if there is no evidence of orbital infection, and the infection is not severe. Antibiotics should cover *S. aureus,* group A *Streptococcus* sp, and Enterobacteriaceae. First-generation cephalosporins (cephalexin) or penicillinase-resistant synthetic penicillins (dicloxacillin) are appropriate choices for initial treatment. As with the treatment of conjunctivitis, local patterns of resistance must be taken into account when assigning initial antibiotic therapy. Treatment should generally continue for 7 to 10 days, unless the infection is suspected to be secondary to sinusitis. In these cases, treatment should continue for 2 to 3 weeks, and antibiotics should be targeted at typical organisms associated with sinusitis. Next-day ophthalmology follow-up should be arranged in patients when outpatient therapy is chosen. See Chapter 255 for orbital and periorbital cellulitis in children.

For orbital cellulitis and most cases of periorbital cellulitis, inpatient treatment with parenteral antibiotics is indicated. Common intravenous (IV) antibiotic doses are listed in Table 60.1. Combination therapy with vancomycin and a second- or third-generation cephalosporin (cefuroxime, cefotaxime, ceftriaxone, or ceftazidime) is recommended. Ticarcillin/clavulanate, piperacillin/tazobactam, and ampicillin/sulbactam are also reasonable choices.

TABLE 60.1
Common Parenteral Antibiotic Doses for Orbital or Periorbital Infections

Ampicillin/sulbactam: 3 g IV every 6 hrs (25–100 mg/kg IV every 6 hrs for children)

Ceftazidime: 1–2 g IV every 8 hrs (30–50 mg/kg IV every 8 hrs for children)

Ceftriaxone: 2 g IV once daily (50–100 mg/kg IV once daily or divided into every 12-hr dose for children)

Cefotaxime: 2 g IV every 4–6 hrs (50–180 mg/kg/d IV divided into every 6-hr dose for children)

Cefuroxime: 750–1,500 mg IV every 8 hrs (75–100 mg/kg/d IV divided into every 8-hr dose for children)

Chloramphenicol: 50–100 mg/kg/d divided into every 6-hr dose

Clindamycin: 600–900 mg IV every 8 hrs (20–40 mg/kg/d divided into every 6-hr dose for children)

Metronidazole: 500 mg IV every 8 hrs (7.5 mg/kg IV every 8 hrs for children)

Nafcillin: 500 mg–1 g IV every 6 hrs (150 mg/kg/d IV divided into every 6-hr dose for children)

Piperacillin/tazobactam: 4.5 g IV every 6–8 hrs (100–300 mg/kg/d IV divided into every 4–6-hr dose for children)

Ticarcillin/clavulanate: 3.1 g IV every 6 hrs (200 mg/kg/d IV divided into every 6-hr dose for children)

Vancomycin: 1 g IV every 12 hrs (40 mg/kg/d IV divided into every 6–8-hr dose for children)

CRITICAL INTERVENTIONS

- Practice strict handwashing policies to prevent the spread of ocular surface infections.
- Seek ophthalmology consultation for hypopyon, endophthalmitis, significant corneal ulcers, or orbital cellulitis.
- Initiate IV antibiotics for infections of the orbit.

DISPOSITION

Patients with signs of severe conjunctivitis, associated corneal ulcer or infiltrate, or with hypopyon require immediate ophthalmologic consultation. Other cases necessitating immediate consultation include severe conjunctivitis with suspected gonococcal source. Referral for early ophthalmologic consultation within 24 to 48 hours should be made for patients with conjunctivitis that does not improve within 24 to 48 hours and for patients with findings suggestive of herpetic disease.

Patients with deeper ocular infections, including endophthalmitis, severe corneal ulcers, or gonococcal conjunctivitis with corneal infiltrates, typically require hospital admission and urgent ophthalmologic consultation. It is uncommon for a patient with herpes simplex or herpes zoster infection to require admission. In-hospital care is geared primarily toward providing IV antibiotics, intravitreal injections, or very frequent topical antibiotic administration (18).

Patients with orbital cellulitis require admission, but mild cases of periorbital cellulitis may be managed in the outpatient setting in adults, if appropriate follow-up within 24 hours is available. IV antibiotics should be started in the ED when hospital admission is indicated.

Common Pitfalls

- Obtaining a culture of conjunctival or ocular secretions, which is not clinically useful for emergency physicians.
- Failure to recognize the distinction between preseptal and orbital cellulitis.
- Overreliance upon tests that are of little value in differentiating periorbital from orbital cellulitis, such as white blood cell count, sinus films, cultures of eyelid aspirates or eye secretions, and blood cultures.
- Failure to use CT scanning as the diagnostic test of choice for differentiating orbital and periorbital cellulitis and abscesses.

ACKNOWLEDGMENTS

Special thanks to Dr. Michael A. Bohrn for his past contributions to this chapter.

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CHAPTER 61

Acute Angle-Closure Glaucoma

Stacy Sawtelle

Glaucoma is a group of disorders characterized by increased intraocular pressure (IOP) sufficient to cause loss of vision. This definition has recently evolved, however, and currently isolated increased IOP is not considered to constitute glaucoma; rather it is the resulting damage to the optic nerve that defines the disease (1,2). Visual change, pain, or elevated IOP without signs of injury to the optic nerve is now termed *acute angle-closure crisis* (AACC) rather than acute angle-closure glaucoma (AACG) (2,3).

The underlying pathologic mechanisms of AACG, increased aqueous humor production and decreased aqueous humor outflow, cause varying degrees of increased IOP. Patients with only mildly elevated IOP can have findings consistent with glaucoma (low-tension glaucoma) whereas patients with significantly elevated IOP may lack criteria for glaucoma (ocular hypertension) (4). Glaucoma is classified in terms of both anatomy of the anterior chamber (angle) and presence or absence of comorbid disease. The anatomic classification describes whether the angle of the anterior chamber is *open* or *closed*. Each anatomic classification may be further subdivided into *primary* or *secondary* depending on the absence or presence, respectively, of pre-existing disease (4). Primary AACG is particularly important to the emergency physician, as it carries a high rate of visual morbidity if not quickly diagnosed and treated. Glaucoma is the second most common cause of blindness worldwide (5).

ANATOMY AND PATHOPHYSIOLOGY

The eye is a complex organ controlled by opposing effects from the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). Stimulation of the ciliary body receptors (β1) results in production of aqueous humor. The aqueous humor flows from the posterior chamber to the anterior chamber via the space between the posterior surface of the iris and the lens (Fig. 61.1). The area of this opening varies with miosis, mydriasis, and accommodation. The muscles controlling these functions also affect the trabecular meshwork in the anterior chamber angle and, thus alter the opening of the canal of Schlemm.

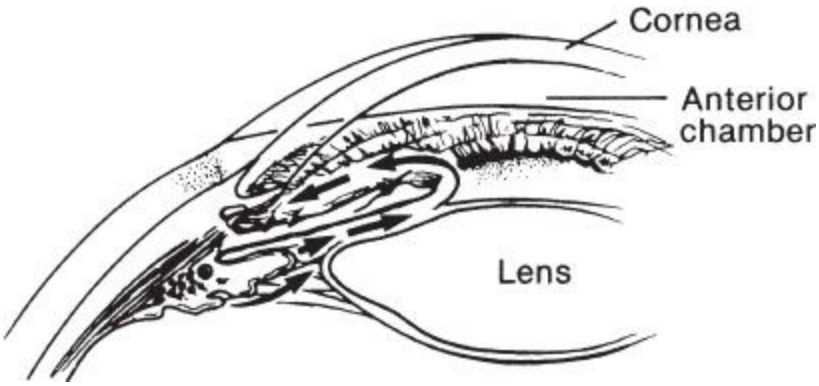


FIGURE 61.1 Normal anterior chamber angle. Aqueous passes from the posterior chamber through the pupil into the anterior chamber and out through the trabecular meshwork.

The iris contains two muscle groups, the radial and circular, whereas the ciliary body contains one group, the ciliary muscle. The radial muscle, which contains α_1-receptors, contracts when stimulated by the SNS, resulting in mydriasis. The circular muscle of the iris and the ciliary muscle both contain muscarinic receptors under the control of the PNS. Stimulation of the circular muscle causes contraction and thus miosis. Ciliary muscle contraction reduces the tension on the zonules of Zinn, thereby reducing tension on the lens. Zonule laxity allows the lens to “round up” for accommodation of near vision; however, this also increases the contact between the lens and posterior iris, potentially inhibiting

flow of aqueous humor from the posterior to the anterior chamber. Conversely, relaxed tension on the meshwork reduces resistance to outflow at the angle by enhancing the opening from the anterior chamber into the canal of Schlemm.

Elevated IOP in glaucoma most often results from an obstruction to aqueous outflow rather than excessive production (6). Obstruction to outflow from the anterior chamber occurs in both open-angle glaucoma and AACG. The location and mechanism of the resistance to outflow distinguish these two conditions. In open-angle glaucoma, the trabecular meshwork of the anterior chamber angle remains open, but the aqueous humor is unable to reach the canal. In AACG, the peripheral iris contacts the trabecular meshwork and blocks the flow of aqueous into the canal.

Several anatomic features predispose an eye to AACG, and patients may have any combination of risk factors. A shallow anterior chamber results in increased baseline narrowing of the entrance to the angle, with a greater area of contact between the lens and iris. This lens-to-iris apposition impedes the flow of aqueous from the posterior chamber to the anterior chamber through the pupil, produces a forward bowing of the peripheral iris, and effectively closes the angle (Fig. 61.2). Those with a shallow anterior chamber angle, at increased risk for the development of AACG, include the elderly, women, patients of Asian or Inuit descent, and farsighted patients (2,4,5,7). A pharmacologic or physiologic event in a susceptible person typically triggers an attack of acute angle closure by upsetting the equilibrium of aqueous humor dynamics.

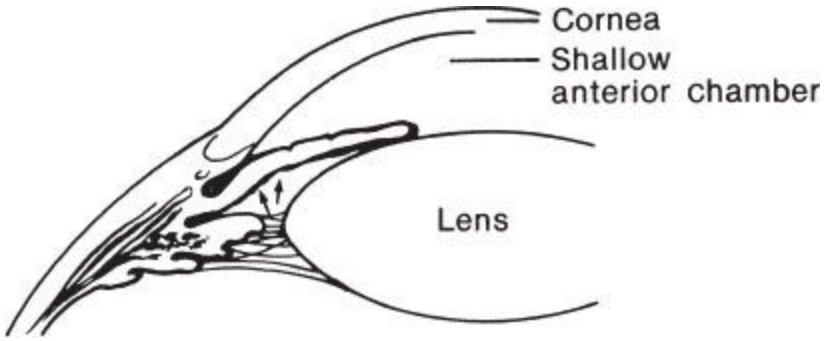


FIGURE 61.2 Angle closure with pupillary block. The angle is closed as the iris is pushed up against the trabecular meshwork.

Pupillary dilatation frequently precipitates an attack of acute angle closure. As the pupil dilates, the peripheral iris becomes more flaccid and may be pushed against the trabecular meshwork, blocking aqueous outflow. This may occur when a person is in a dimly lit environment or under emotional stress perhaps due to increased sympathetic tone. Medications that stimulate α_1- and/or β_1-receptors (sympathomimetics) and those that oppose M3 receptors (anticholinergics) cause pupillary dilatation and may precipitate AACC (Table 61.1) (3,4,8).

TABLE 61.1
Common Pharmacologic Preparations That May Precipitate AACG

Sympathomimetics
Prescription Sympathomimetics
Epinephrine compounds, norepinephrine compounds, levarterenol, terbutaline, amphetamine compounds, apraclonidine, phenylephrine, albuterol
Nonprescription Sympathomimetics
Propylhexedrine, naphazoline, tetrahydrozoline, tyzine, oxymetazoline, pseudoephedrine
Monoamine Oxidase Inhibitors
Tranylcypromine, phenelzine, isocarboxazid
Anticholinergic Activity
Mydriatic and Cycloplegic Agents
Ipratropium bromide, atropine, scopolamine, homatropine, cyclopentolate, tropicamide
Antispasmodics
Dicyclomine, oxyphencyclimine
Antipsychotics
Chlorpromazine, thioridazine, trifluoperazine, haloperidol
Antiemetics
Chlorpromazine, prochlorperazine, promethazine
Antihistamines
Diphenhydramine, dimenhydrinate, chlorpheniramine, brompheniramine, hydroxyzine, meclizine
Tricyclic Antidepressants
Imipramine, amitriptyline, doxepin, nortriptyline, desipramine
Selective Serotonin Reuptake Inhibitors
Paroxetine, venlafaxine, citalopram, escitalopram
Miscellaneous Agents
Trihexyphenidyl, topiramate, benztropine, ethopropazine

CLINICAL PRESENTATION

Most patients present with a complaint of sudden onset of severe pain localized to the orbit, or brow or more generally with a severe headache, often associated with nausea and vomiting. Occasionally, the presenting clinical picture is more systemic than ocular, leading to an erroneous or missed diagnosis (9). The physician should consider AACG in patients with headache and high-risk patients

with undifferentiated gastrointestinal illness. Blurred vision or the appearance of rainbow-colored halos around lights may occur shortly after the onset of pain (Table 61.2).

TABLE 61.2
Diagnosis of AACG

History
Acute onset of pain
Exposure to dim illumination at symptom onset (i.e., movie theater)
Emotional upset or fatigue
Precipitating medications (anticholinergics, sympathomimetics)
Symptoms
Pain
Blurred vision/halos around lights
Nausea/vomiting
Signs
Conjunctival injection
Corneal edema (light reflex irregular or steamy appearance)
Middilated, nonreactive pupil
Narrow anterior chamber (only temporal half of iris illuminated on flashlight test)
Anterior chamber cells may be present, but no keratic precipitates
Elevated IOP

The patient with AACC has a unilateral red eye with congested episcleral and conjunctival blood vessels, a nonreactive middilated pupil, corneal edema, a shallow anterior chamber, and a high IOP (Fig. 61.3). The IOP is elevated, usually ranging between 60 and 90 mm Hg (IOP <21 mm Hg is considered normal). If the attack has been prolonged, however, the IOP may be lower, due to ciliary body ischemia and decreased aqueous production. Corneal involvement varies with the duration of the attack but is often hazy or steamy appearing from epithelial edema. The anterior chamber appears shallow. Although mild anterior chamber inflammation is common, keratic precipitates (aggregates of white blood cells) on the corneal endothelium are not a typical finding.

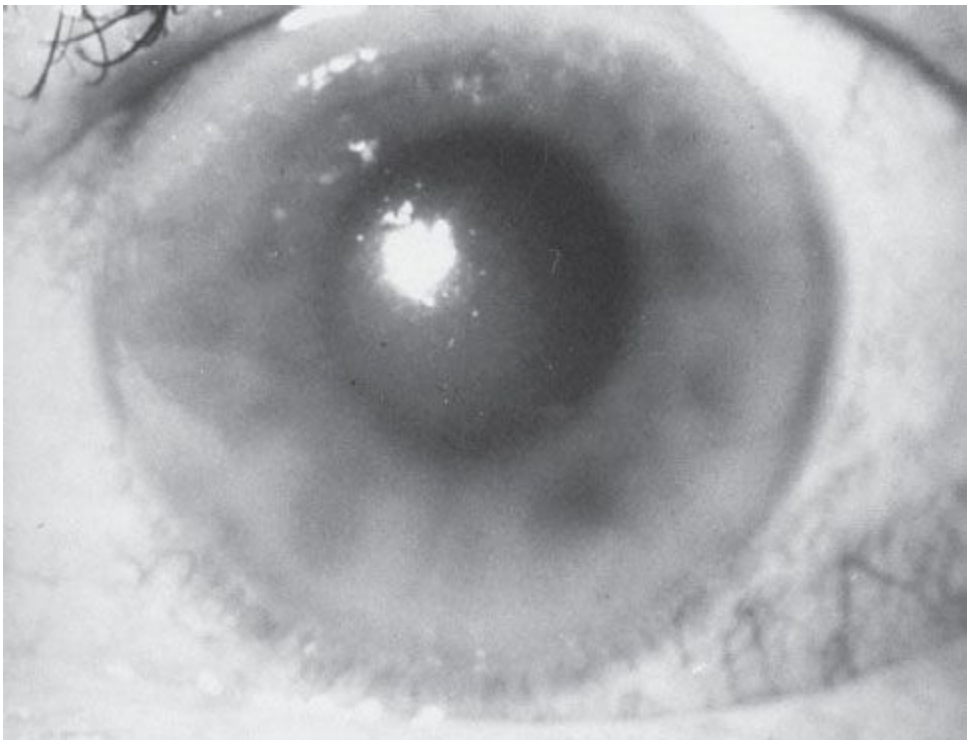


FIGURE 61.3 This eye demonstrates the hallmarks of acute angle-closure glaucoma: perilimbal injection, corneal edema, and a middilated nonreactive pupil.

The course of untreated AACG varies. An attack may damage the optic nerve as well as the corneal endothelium, lens, and retinal ganglion cell layer. In some undiagnosed patients, the attack will continue and, if untreated, can result in permanent blindness within 2 to 3 days. Visual prognosis improves with the initiation of prompt, effective treatment, but any damage to the optic nerve is irreversible.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the acutely painful red eye is extensive and is described in detail in Chapter 56. Because headache, nausea, and vomiting may be dominant symptoms in glaucoma, the differential should also include central nervous system and gastrointestinal disorders. Most conditions are readily distinguished by a careful history and physical examination. Other ophthalmic disorders that more closely mimic AACG are the secondary

glaucomas: glaucomatocyclitic crisis, neovascular glaucoma, glaucoma secondary to iritis or uveitis, and lens-induced glaucoma.

Glaucomatocyclitic crisis produces recurrent attacks of visual blurring and halos but, in contrast to AACG, pain is not a prominent feature. In addition, the anterior chamber is deep and keratic precipitates develop on the cornea after 2 to 3 days (10).

Neovascular glaucoma presents with a chief complaint of a painful red eye months after vision impairment in the affected eye. It is usually associated with disorders such as, diabetic proliferative retinopathy and retinal vascular occlusion. Retinal hypoxia serves as the underlying stimulus for neovascularization. If the condition progresses, a fibrovascular membrane may obstruct the drainage angle, leading to secondary AACG (4).

Acute iritis with secondary glaucoma presents with ocular pain, photophobia, and blurred vision. The onset is gradual in contrast to AACG. Clinical findings may mimic angle closure, with perilimbal conjunctival injection and corneal edema. However, a miotic pupil, keratic precipitates, and a deep anterior chamber differentiate acute iritis with secondary glaucoma from AACG.

Phacolytic glaucoma presents similarly to AACG, but the anterior chamber depth (ACD) is normal and there are cells in the anterior chamber. Keratic precipitates are also present, and a mature or hypermature cataract can be seen. The cause of phacolytic glaucoma is the release of soluble lens protein into the aqueous, which leads to elevated IOP when it occludes the trabecular meshwork and canal (4,11).

Lens particle glaucoma is associated with spontaneous or traumatic disruption of the lens capsule. As with acute iritis and phacolytic glaucoma, the anterior chamber is of normal depth. In addition, the pupil is often miotic, and lens cortical material is present in the anterior chamber. The particulate lens material reduces outflow in the trabecular meshwork, with resultant increased IOP (4,11).

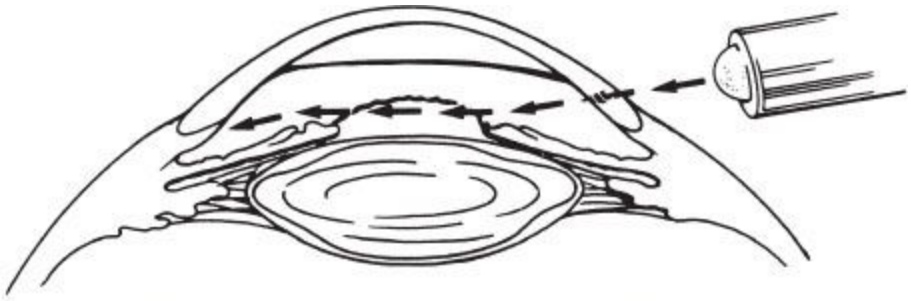
ED EVALUATION

A careful history is an essential part of the ED evaluation and should include *onset* of symptoms (sudden, gradual, subsequent to accidental or surgical trauma); history of similar symptoms previously (brief episodes of pain, blurred vision, and/or halos around lights); *visual impairment* in the affected eye and the unaffected eye; *pain* in or around the eye; *discharge* or secretions from the eye; and a detailed *medication history*.

The ocular examination is described in detail in Chapter 54. The following aspects of the ocular examination deserve special emphasis in relation to AACC and glaucoma. *Visual acuity* is probably one of the most important evaluations done during any ocular examination. If a distance or near visual acuity cannot be recorded owing to inability to read the chart, the following should be recorded (including the distance at which each is tested): finger counting, and the presence or absence of perception of hand motion and light. *Conjunctival injection* is often present but is nonspecific. The pattern of injection, however, may be helpful. Perilimbal injection suggests acute iritis or angle closure. Segmental injection characterizes episcleritis; diffuse injection is typical of keratoconjunctivitis. Finally, the presence of purulent discharge suggests an infectious cause. *Corneal edema* is apparent in many cases of AACG and is due to the rapid rise of IOP. Assessment of the *ACD* is essential in the evaluation of the painful red eye and in the diagnosis of AACG. In the ED setting, an adequate estimation of the ACD can be accomplished with the oblique flashlight test and slit-lamp examination.

Oblique Flashlight Test

In this test (Fig. 61.4), the examiner shines the light across the eye from the temporal side toward the pupil. In an eye with a normal depth anterior chamber, the entire iris is illuminated. In an eye with a narrow angle or shallow ACD, a shadow is cast on the nasal side of the iris (12).



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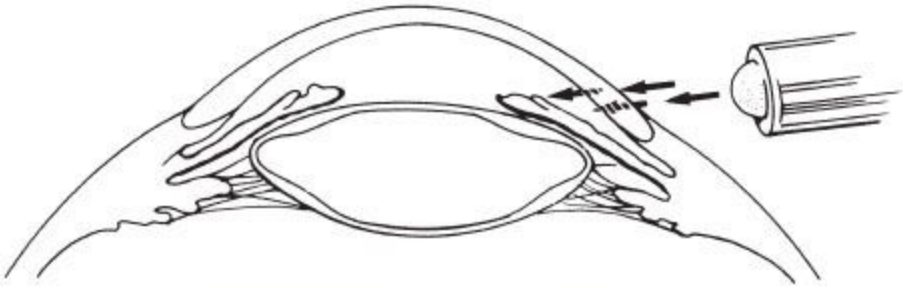

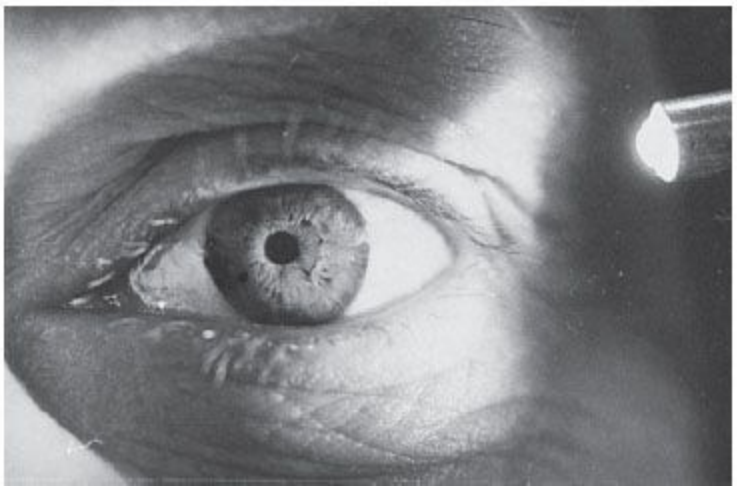

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FIGURE 61.4 Flashlight test for wide and narrow angles. A: Wide angle: Entire iris is illuminated. B: Narrow angle: Only temporal half of iris is illuminated. (Photo courtesy of D. R. Anderson, MD.)

Slit-Lamp Examination

The ACD can also be estimated during the slit-lamp examination. A narrow beam of light is directed obliquely at the surface of the iris. The corneal thickness is estimated, as is the distance between the corneal beam and the iris beam, and the ACD is calculated. If the peripheral ACD is less than one-fourth the thickness of the adjacent cornea, the angle is narrow and at risk of occlusion (4,12,13).

The size and shape of the *pupil* and pupillary reaction to light are recorded for each eye. Unequal pupil size (anisocoria) should be noted. A middilated, nonreactive pupil is characteristic of AACC and glaucoma. In contrast, many other conditions have a miotic pupil that is minimally reactive.

A mature (opaque) or hypermature (liquid cortex) *lens* may be associated with lens-induced glaucoma. Phacodonesis, movement of the lens, indicates a dislocated or subluxed lens. This may occur secondary to trauma, or it may be part of a systemic syndrome such as Marfan syndrome. A dislocated lens can increase pupillary block and result in a secondary ACG (11).

Intraocular Pressure

The range of IOP considered normal is 10 to 21 mm Hg, although the actual range found in population studies is dependent on a number of factors and varies significantly among different ethnicities (14). Three commonly used tonometers available in the ED are the air-puff noncontact tonometer, the Schiötz tonometer, and the Tono-Pen. The Goldmann applanation tonometer is frequently used by ophthalmologists and is considered the gold standard for measurement of IOP.

Air-Puff Noncontact Tonometer

The air-puff tonometer has the advantage of measuring the IOP without the application of topical anesthesia or contact between the instrument and the eye. A puff of air is blown against the cornea and the instrument records the force needed to flatten the cornea and displays the correlated IOP (4,15).

Schiötz Tonometry

Schiötz, or indentation, tonometry determines IOP by measuring the indentation of the cornea produced by a known weight. The patient is placed in a supine position and a drop of a local anesthetic is instilled. The patient is asked to look upward and fix on some object in the distance. While separating the eyelids, the instrument is gently placed in a vertical position directly over the cornea. The plunger is allowed to rest completely on the eye. With the instrument held steady, the pointer will stay fixed at a value on the scale. Each instrument is accompanied by a conversion table that expresses the scale readings in mm Hg. Inadvertent pressure on the globe can result in a falsely elevated reading. Scleral rigidity and corneal thickness can affect the measurement (4).

Tono-Pen

A handheld electronic applanation tonometer, the Tono-Pen is frequently used in EDs. After initial calibration, the sheathed tip of the Tono-Pen is repeatedly tapped on the anesthetized cornea. The instrument calculates and displays the average of 4 to 10 readings, as well as variability percentages (4). The Tono-Pen generally correlates well with Goldmann applanation tonometry, but the Tono-Pen underestimates IOP when it is high and overestimates IOP when the pressure is low (4,16).

Goldmann Applanation Tonometry

In applanation tonometry, the cornea is flattened and the instrument measures the area flattened and the force required to do so. A local anesthetic and fluorescein are instilled. Correctly positioned at the slit lamp, the patient looks straight ahead. Illuminated by the cobalt blue light, the examiner gently contacts the anterior corneal surface

with the tip of the Goldmann tonometer (Fig. 61.5). On contact, two fluorescein semicircles are seen. A calibrated dial is then adjusted until the semicircles are aligned such that the inner borders of each semicircle match up. The IOP is estimated from the value displayed on the dial (4).

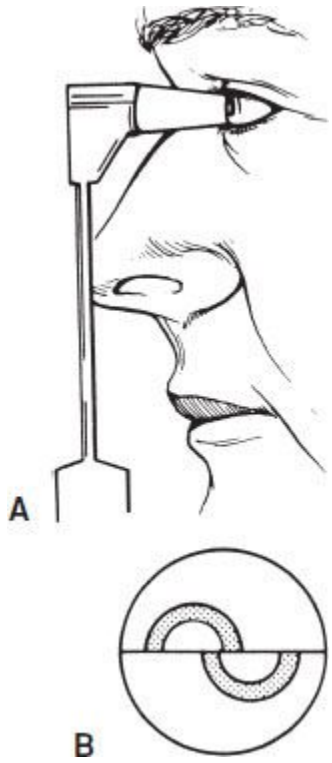

FIGURE 61.5 Applanation tonometry. A: The tonometer tip should just contact the patient's cornea. B: Viewed through the slit lamp are two fluorescent semicircles aligned edge to edge.

KEY TESTING

- Visual acuity
- ACD (use slit lamp or oblique flashlight test)
- IOP

ED MANAGEMENT

AACC, as the name suggests, is an ophthalmic emergency. Once the diagnosis has been established in the ED, the immediate goal is twofold: to obtain appropriate consultation with an ophthalmologist

and to begin treatment to decrease the IOP. The latter is directed at decreasing aqueous production, increasing aqueous outflow, and reducing vitreous volume with dehydrating agents. A combination of topical agents and systemic medications directed toward these three goals is often effective in reducing IOP and is first-line therapy (17). A number of agents can be used to acutely lower the IOP, but these medications are not without side effects and treatment should be tailored to each patient's medical status.

Topical Therapy

Timolol Maleate

Timolol maleate is a nonselective β-blocker that lowers IOP by decreasing the production of aqueous humor. It should be used with caution in patients with contraindications to β-blockers, such as asthma, heart block, and heart failure, as systemic absorption may occur. Side effects include bronchospasm, decreased pulse rate, and altered mental status. The recommended dosage is timolol 0.5% solution, one drop at 5-minute intervals initially for three doses, and then one drop every 12 hours.

Pilocarpine Hydrochloride

Pilocarpine is a direct-acting parasympathomimetic agent that causes miosis by stimulation of M3 receptors in the iris. Miosis improves the mechanical obstruction in AACG because the iris is pulled taut and away from the trabecular meshwork. Systemic side effects such as sweating, tremors, bradycardia, and hypotension, though uncommon, have been observed as a result of excessive administration of pilocarpine. Pilocarpine may be ineffective if IOP is more than 50, in which case its application can be delayed until the IOP is lowered with other agents (4). The recommended dosage is pilocarpine 2%, two drops every 5 minutes until the pupil constricts, and then one drop every 6 hours.

Apraclonidine

Apraclonidine is a topical α-2 agonist used in chronic glaucoma; it lowers IOP by reduction of aqueous humor production by an

indirect sympatholytic mechanism. Its effects are additive to those of topical β-blockers. Success in AACG treatment has also been reported, and its use should be considered (18). The recommended dosage is apraclonidine 1% solution, one drop every 5 minutes for three doses.

Prednisolone Acetate
Topical corticosteroids reduce inflammation and may be recommended by an ophthalmologist. Steroids may be used as a bridge to surgery. The recommended dosage is prednisolone acetate 1%, one drop every 30 to 60 minutes until surgical treatment is completed.

Topical Prostaglandins
Topical prostaglandin drops are thought to decrease pressure by increasing outflow of aqueous humor. The recommended dose is latanoprost 0.005% solution, one drop daily (19).

Systemic Therapy

Acetazolamide
Acetazolamide is a carbonic anhydrase inhibitor that inhibits aqueous humor formation. Because respiratory acidosis can occur with the use of carbonic anhydrase inhibitors, the drug should be avoided in patients with significant respiratory disease. Hypokalemia can also be seen with acute therapy and should be appropriately monitored. The recommended dosage for treating AACG is acetazolamide 500 mg IV every 12 hours or 500 mg PO every 6 hours.

Mannitol
Mannitol is a hyperosmotic agent that lowers IOP by increasing the serum osmolality, thus creating a gradient between the blood and the vitreous, and drawing water from the vitreous cavity. The recommended dosage is mannitol 20%, 1 to 2 g/kg IV over 30 to 60 minutes.

Glycerol and Isosorbide

Glycerol and isosorbide are hyperosmotic agents that can be administered by mouth in patients who are able to tolerate oral medications. Glycerol should be avoided in diabetic patients because it can produce hyperglycemia and ketosis. The recommended dosage is glycerol 50%, 1 to 1.5 g/kg PO (on ice with juice) or isosorbide 45%, 1.5 to 2 g/kg PO (4).

Corneal Indentation

When the IOP is higher than 50 mm Hg, topical miotics such as pilocarpine may be ineffective owing to ischemia of the iris constrictors (4). In this situation one might consider a maneuver to lower IOP known as corneal indentation. As the cornea is indented, the aqueous is displaced peripherally, temporarily opening the angle. This results in a prompt decrease in IOP. Typically, a cotton-tipped applicator, a glass rod, or an applanation prism is used, although any smooth instrument is appropriate (20). After application of a topical anesthetic, the tool is used to apply firm pressure to the inferior part of the cornea in 30-second intervals (30 seconds on 30 seconds off). The IOP is typically decreased after 3 to 4 cycles. Corneal indentation applied to the superior aspect of the cornea may result in epithelium disruption, complicating laser peripheral iridotomy (21).

Surgical Therapy

The definitive treatment of ACG is surgical release of pupillary block. Peripheral laser iridotomy has largely replaced incisional iridectomy due to its low-risk profile and ease of performance (20). In cases where the laser equipment is not readily available and the patient is refractory to medical management, the ophthalmologist may choose to perform an anterior chamber paracentesis to avoid further delays in lowering the IOP. At times, it is necessary to perform a surgical iridectomy emergently when the IOP is medically unresponsive and in which corneal clouding prevents laser iridotomy. Argon laser peripheral iridoplasty and lens extraction are other measures used in specific cases of ACG (20). The unaffected

eye should be examined for an anatomically narrow chamber and if present, prophylactic iridotomy is generally performed, since half of patients with AACG will have an attack in the other eye within 5 years (2).

CRITICAL INTERVENTIONS

- Initiate therapy to reduce the IOP.
- Consult an ophthalmologist in all cases of AACC and AACG.

DISPOSITION

AACG is an ophthalmic emergency, and an ophthalmologist should be consulted immediately.

Owing to vagal stimulation as a consequence of the rapid and severe elevation of IOP, patients with AACG are often systemically ill and require admission. Analgesic and antiemetic agents should be given if there is severe pain, nausea, or vomiting.

Parenteral administration of medications should be carried out in the hospital so that the patient can be closely observed for possible adverse reactions. Initially, IOP should be monitored every 30 minutes. If the eye is responding and IOP is decreasing, IOP can be measured every 1 to 2 hours while treatment is continued. However, if the eye is not responding well to medical maneuvers and the IOP remains elevated, laser iridotomy or iridoplasty should be performed by the ophthalmologist as soon as possible.

If emergent consultation with an ophthalmologist is unavailable at the initial hospital, therapy should be initiated and the patient should be transferred expeditiously, since delays in treatment are detrimental to the visual prognosis.

Common Pitfalls

- Failure to consider the diagnosis of AACG and to check IOP.
- Failure to obtain specialty consultation. Any patient with a painful red eye and decreased vision has an ophthalmic emergency and requires prompt consultation with an ophthalmologist.

ACKNOWLEDGMENTS

Special thanks to Dr. William Bozeman and Dr. R. Scott Everett for past contributions to this chapter.

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SECTION VI
ENT and Dental Emergencies

Section Editor: GREGORY W. HENDEY

CHAPTER 62 Dental Emergencies

Rawnica L. Ruegner

Dental emergencies prompt almost 3 million emergency department (ED) visits nationally, accounting for 0.7% of all ED patients (1). Factors such as poverty, a lack of dental insurance or a primary care dentist, and difficulty finding an "off-hours" dental clinic have contributed to an increasing number of patients with dental-related complaints presenting to emergency physicians (2,3,4). Despite the common nature of dental-related complaints, many physicians receive little training on dental emergencies (5).

This chapter addresses the common nontraumatic dental emergencies. Dental trauma and odontogenic infections of the face are covered elsewhere.

DENTAL ANATOMY

Human teeth are composed of three layers. The outermost layer, enamel, is an extremely hard protective cover that contains no nerve fibers. Enamel covers the visible portion, or crown, of the tooth. The corresponding outer layer in the portion of the tooth embedded in the gum or root is known as cementum and is much softer than enamel. Under the enamel and cementum is dentin, and at the center of the tooth is the pulp chamber through which the nerves and blood vessels connect to the alveolar bone. The tooth sits in a socket with relatively long apices extending into the bone. The tooth is anchored to the bone by the periodontal ligament.

The first set of teeth, known as primary or deciduous dentition, should be completely erupted by 3 years of age. This set consists of

10 maxillary and 10 mandibular teeth. The permanent teeth begin erupting at around 5 years of age. This set consists of 32 teeth divided equally into four quadrants (right upper, right lower, left upper, left lower). In each quadrant, there is a central incisor, a lateral incisor, a canine, two premolars, and three molars. The third molar is called the *wisdom tooth* and may not be visible if it failed to erupt or has been therapeutically removed. Several numbering systems have been developed to identify a specific tooth. The most commonly used system numbers the permanent teeth consecutively beginning with the upper right third molar (tooth 1), to the upper left third molar (tooth 16), then down to the lower left third molar (tooth 17), and across to the lower right third molar (tooth 32). Other numbering systems exist, and some patients will have teeth missing, which may make numbering difficult. Generally, physicians should simply describe the tooth involved, for example, the left upper second premolar.

The biting area of a tooth is the occlusal surface for molars or incisal surface for the incisors. In the direction of the occlusal or incisal surface is coronal and in the direction of the root is apical. The medial or mesial aspect faces toward the midline of the jaw, and the distal surface faces the ramus of the mandible. The portion of the tooth facing the tongue or palate is the lingual or palatal surface. The portion facing away from the tongue is the labial or buccal surface. The portion of the tooth in contact with an adjacent tooth is the interproximal surface.

The Dental Examination

Patients with dental complaints should first be examined for possible nondental causes of their symptoms. An examination of the external facial structures and neck can detect swelling, cellulitis, or odontogenic fistulae. When performing the intraoral examination, look first for trismus (restricted opening of the mouth) and for swelling of the tongue or lips. Examine the mouth for asymmetry, swelling, or signs of cellulitis. Determine that the uvula is midline and not shifted as a result of abscess formation. Confirm that the

tongue is not elevated and that the floor of the mouth is not tender or indurated (signs of Ludwig angina). Examine the teeth looking for signs of caries. Pay particular attention to the junction of the tooth and the socket, where foreign bodies can lodge. The tissue adjacent to the tooth along the alveolar bone should be examined carefully, because odontogenic abscesses typically form in this area. The gum overlying absent molars should be examined for evidence of erupting teeth (usually the wisdom tooth). Each tooth can be gently percussed, preferably with the end of a dental mirror, though a tongue depressor will suffice.

DENTAL ANESTHESIA

Patients with severe dental pain may require anesthesia for either temporary pain relief or for painful procedures such as incision and drainage of a periodontal abscess. Topical anesthesia of the mucosa can be achieved within 2 to 3 minutes by the application of a cotton swab soaked in 20% benzocaine or 10% lidocaine. This anesthesia can lessen the pain of needle injection for further anesthesia and, in some cases, may provide adequate anesthesia for incision and drainage of a superficial abscess. An individual tooth may be anesthetized by infiltration of lidocaine (2% with 1:100,000 epinephrine) or bupivacaine (0.5% with 1:200,000 epinephrine) at the root of the tooth using a supraperiosteal injection. Mandibular teeth may be anesthetized by blocking the inferior alveolar nerve where it enters the lower mandible. Dental blocks generally last between 1 and 7 hours depending on the anesthetic and choice of procedure (6).

CLINICAL PRESENTATION

Caries and Pulpitis

Among the most common dental conditions is dental caries, or “cavities.” As oral bacteria ferment dietary carbohydrates, an acid is formed, which demineralizes the tooth enamel. This demineralization initially is asymptomatic, until the erosion intrudes on the tooth pulp, resulting in inflammation (pulpitis). Caries

appear as either a whitish gray discoloration of the enamel or as a brownish visible defect of the enamel surface. Pulpitis, or inflammation of the pulp of the tooth, causes significant pain, which depends upon the extent of inflammation. Early or reversible pulpitis causes relatively well-localized pain that is usually triggered by hot, cold, or sweet stimuli, usually lasts only a few seconds, and resolves spontaneously. Late or irreversible pulpitis results in poorly localized, severe, and persistent pain.

Periodontitis

If the inflammation of the pulp goes unabated, it will extend to the tooth apices, expand outward from the pulp, and cause apical periodontitis. The pain of periodontitis is severe, persistent, and localized to a particular tooth (unlike irreversible pulpitis, which is usually poorly localized). Periodontitis usually results in a tooth sensitive to percussion.

Peri-Implantitis

Recent advances in reconstructive dentistry may cause patients to visit the ED with problems relating to their dental implants. These patients present similarly to those with periodontitis.

Abscess and Cellulitis

Should periodontitis progress unchecked, the inflammation may extend laterally from the tooth apex to cause an apical abscess. Alternatively, an abscess can form in the absence of dental caries when inflammation begins at the junction of the tooth and gum line, extends down the tooth apices, and involves the periodontal ligament and adjacent alveolar bone. This is termed a *periodontal abscess* and results from either chronic bacterial plaque (periodontal disease) or a foreign body lodged between the tooth and gum. Clinically, both abscesses appear as a small fluctuant swelling located adjacent to the involved tooth. The swelling may appear tense and painful or it may be draining pus. Periodontal abscesses

may result in teeth that are somewhat mobile due to bone destruction. The area surrounding the abscess should be examined for evidence of cellulitis.

Pericoronitis

A partially erupted molar creates a potential space between the occlusal surface of the tooth and the gingiva through which the tooth protrudes. If plaque or food particles become lodged in this space, the overlying mucosal flap will become inflamed. Pericoronitis presents as a painful, tender area over a partially erupted tooth often accompanied by a foul taste or odor due to extruded pus.

Gingivitis

Gingivitis is inflammation of the gingiva usually caused by bacterial plaque on the tooth. Simple gingivitis does not typically prompt an ED visit, as it is painless. Gingivitis appears as redness, swelling, and pocket formation of the gingiva. If the inflammation is significant, it can produce some bleeding from the gums after brushing the teeth.

Acute Necrotizing Ulcerative Gingivitis

If bacteria actively invade the gingiva, the inflammation may produce painful, swollen gums often accompanied by fever, malaise, grayish pseudomembranes, lymphadenopathy, a foul odor, and a metallic taste. This disorder is commonly called *trench mouth* and may be facilitated by immunocompromise or physiologic stressors.

Gum Hyperplasia

Unusual gum swelling may rarely prompt an ED visit. In addition to gingivitis and acute necrotizing ulcerative gingivitis (ANUG), other conditions that may cause generalized gingival hyperplasia or swelling include acute leukemic infiltration and drug-induced hyperplasia (most commonly phenytoin and nifedipine).

Postextraction Bleeding

Teeth are commonly removed for therapeutic reasons, and postextraction bleeding is a frequent complication. Although life-threatening hemorrhage may occur, most patients present with persistent oozing from the extraction site. In patients with acquired or congenital bleeding disorders, bleeding may be persistent and difficult to stop.

Alveolar Osteitis ("Dry Socket")

Following a tooth extraction, some sockets may lose the protective clot prematurely, exposing the socket down to the bone. Typically, patients present 3 to 5 days following the extraction with severe localized pain. Some patients complain of a foul odor or taste. Physical examination shows a nontoxic-appearing patient without signs of infection. The extraction site usually is unimpressive. In contrast, postextraction osteomyelitis often is associated with fever, malaise, leukocytosis, and the surrounding teeth and bone may be sensitive to palpation. A radiograph is usually indicated to rule out retained roots or foreign bodies.

Oral Candidiasis

Candidal infections of the mouth are relatively common, especially among children and the immunocompromised. Painful white plaques are present that typically can be easily scraped off to show an erythematous underlying mucosa.

Aphthous Stomatitis

Many individuals will experience painful recurrent oral ulcers. Aphthous stomatitis is a common cause, though ulcers from hand-foot-and-mouth disease, herpangina, and herpetic gingivostomatitis may appear similar. While most aphthous ulcers are <5 mm, they may coalesce to form large lesions. These ulcers are self-limited and rarely are complicated by a localized cellulitis requiring antibiotic therapy.

Herpetic Gingivostomatitis

In children younger than 5 years old, a primary herpes virus infection (herpes simplex type 1) may present with multiple painful, ulcerated vesicles in the oropharynx. Often there is accompanying fever, lymphadenopathy, erythema, and edema. Although the primary infection lasts about 2 weeks, recurrences are common, though these usually present with a lesion at the border of the lip. Eruptions are generally self-limited.

Other Systemic Diseases

Several systemic diseases can present with oral lesions, though most are nonspecific. Systemic lupus erythematosus, scleroderma, Wegener granulomatosis, pemphigus vulgaris, Stevens–Johnson syndrome, Behçet syndrome, varicella zoster, and several neoplasms all can present with oral manifestations.

DIFFERENTIAL DIAGNOSIS

Although most patients with apparent dental complaints ultimately are diagnosed with relatively minor conditions, a few will have a serious illness. Perceived dental pain can result from sinus infections, temporomandibular joint dysfunction, otitis media, migraine headaches, neuritis, or myocardial ischemia. A dental infection can occasionally spread to the cavernous sinus, face, mouth, or throat, causing a potentially life-threatening complication.

ED EVALUATION

The evaluation of the patient with dental pain begins with a relevant history and physical examination to determine if the complaint is truly odontogenic in nature. A history of recent dental procedures, medication allergies, and anticoagulant medications is particularly important. Radiographs may be helpful in the evaluation of some patients in a search for retained roots or foreign body after a dental procedure. Computed tomography (CT) scanning

is indicated if one suspects the extension of an infection to the cavernous sinus, neck, or deep spaces.

KEY TESTING

- Consider radiographs for suspected foreign body, or CT scan for deep space infection.

ED MANAGEMENT

The treatment of asymptomatic dental caries and reversible pulpitis is a dental filling, and irreversible pulpitis requires root canal therapy. In the ED, patients with dental pain caused by pulpitis or periodontitis should receive pain medications and a referral to a dentist. Pain medications may include a nonsteroidal anti-inflammatory drug (NSAID), acetaminophen, or a mild narcotic. Antibiotics are not necessary for simple caries, but there are diverging opinions on their role in periodontitis. Treatment of peri-implantitis consists of irrigation with saline or 0.12% chlorhexidine, antibiotic therapy for 10 days, pain medication, and referral to a dentist (7).

A large apical abscess may be incised and drained following appropriate anesthesia of the area, usually accomplished with a dental block or topical anesthesia. Smaller abscesses, especially in children, may respond to antibiotics alone. The use of antibiotics for drained abscesses without accompanying cellulitis is controversial. Some authorities recommend antibiotics (4,8), and others do not (9). As many as two-thirds of dentists in one study prescribed antibiotics liberally (10). If the cellulitis is relatively minor and localized, oral medications are appropriate, typically penicillin V potassium 500 mg/qid (or erythromycin 500 mg/qid for patients with penicillin allergy). Patients who do not respond to initial treatment within 3 days should be switched to clindamycin 300 mg/qid.

Patients with apical abscesses or cellulitis treated as an outpatient should be referred to a dentist within 1 to 2 days. For cellulitis that is severe, has spread into the deep spaces of the face or neck, or is

associated with a toxic appearance or an immunocompromised patient, hospital admission and parenteral antibiotics are recommended. These antibiotics are typically clindamycin 600 to 900 mg intravenously (IV) every 6 hours or ampicillin/sulbactam 1.5 to 3 g IV every 6 hours. If significant cellulitis is present, CT scanning of the involved areas should be performed to rule out deep space infection. Remember that incision and drainage of a dental abscess may lead to transient bacteremia, so antibiotics should be given for prophylaxis against endocarditis for individuals at risk.

Pericoronitis should be treated with mechanical irrigation under the flap following appropriate anesthesia. Some sources recommend antibiotic treatment with penicillin, erythromycin, or clindamycin in the same dosing regimens as noted previously. Patients should receive pain medications and follow up with a dentist within 48 hours. Cellulitis or abscess-accompanying pericoronitis should be evaluated and treated as discussed previously.

ANUG may be treated with systemic antibiotics and rinses with warm saline or 3% hydrogen peroxide. Improved oral hygiene is mandatory and may require prescription analgesics to alleviate the pain. Viscous lidocaine may also assist with pain relief and improve oral hygiene. ANUG requires referral to a dentist.

Postextraction bleeding can usually be stopped by having the patient bite down for 10 to 15 minutes on gauze placed over the site. Arterial bleeding may require ligation of the artery, a procedure that can be difficult without proper dental equipment. Patients taking anticoagulants or with bleeding disorders may require reversal, depending on the initial indication for anticoagulation and the extent of bleeding. Oozing that does not stop with direct pressure may require the topical application of procoagulant agents including Gelfoam, Oxycel, Surgicel, or Thrombogen (11).

For alveolar osteitis, the socket should be irrigated with chlorhexidine or warmed saline (12), dried thoroughly, and packed with eugenol-soaked Gelfoam. Analgesics should be prescribed, and the patient should be referred promptly because the packing will usually need to be replaced within 24 hours.

Oral candidiasis may be treated with an oral antifungal agent such as nystatin suspension (100,000 units/mL) (13). Five milliliters is rinsed in the mouth and held as long as possible before swallowing or spitting. Aphthous stomatitis should be treated symptomatically with hydrogen peroxide rinses or diphenhydramine syrup mixed half and half with bismuth subsalicylate (Kaopectate, 2 teaspoons as a rinse as needed). Oral corticosteroids such as triamcinolone may speed healing (Kenalog in Orabase: Dispense 5 mg and apply in a thin layer to the ulcer three times a day), and topical analgesics such as 2% viscous lidocaine or amlexanox (Aphthasol) 5% paste (apply to the lesion up to four times daily) may help with pain (14). *Herpes gingivostomatitis* may also be treated with analgesics such as acetaminophen or ibuprofen, adequate hydration, and oral application of agents such as "magic mouthwash," variably described as a mixture of equal portions of diphenhydramine elixir (12.5 mg/5 mL), 2% lidocaine, and Maalox or bismuth subsalicylate (Kaopectate). For adults with a herpetic prodrome of burning or tingling, antiviral therapy with acyclovir or valacyclovir may reduce the duration or severity of the eruption. Administer acyclovir 200 mg five times a day, valacyclovir 500 to 1,000 mg bid for 5 days, or valacyclovir 2,000 mg bid for 1 day (15).

CRITICAL INTERVENTIONS

- Treat dental infections and abscesses with incision and drainage as needed and antibiotics when appropriate.
- Provide adequate analgesia by using medications and/or dental blocks.

DISPOSITION

Most patients with dental disorders may be successfully treated and discharged from the ED with appropriate dental follow-up. However, as discussed previously, some disorders may necessitate emergent dental consultation or hospital admission, such as abscesses that are large or extending over the face and neck or

postextraction bleeding that cannot be controlled by simple measures.

Common Pitfalls

- Failing to identify a systemic cause, such as myocardial infarction, for face or jaw pain.
- Failing to recognize the spread of an odontogenic infection to the face or neck.
- Failing to ascertain antibiotic allergies before prescribing penicillin or other common dental antibiotics.
- Performing dental procedures prior to antibiotic prophylaxis in a patient at risk for endocarditis.

ACKNOWLEDGMENTS

The author gratefully acknowledge the contributions of Gregory T. Guldner and Thomas Forney to the content of this chapter.

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CHAPTER 63 Head and Neck Infections

Manon Kwon

Infections of the head and neck are both common and potentially life-threatening. Knowledge of the fascial layers and the potential spaces of the neck are important to clinical practice because of the potential complications that may arise.

CLINICAL PRESENTATION

The signs, symptoms, and complications of the infectious disorders of the head and neck are determined largely by the anatomic compartment of origin. The fascial layers serve as important barriers to infection and often determine the path of the spread of infection. In addition, comorbidities frequently found in severe presentations are diabetes mellitus, old age, alcohol abuse, systemic disease, and immunosuppressed states (such as in patients with AIDS or in those undergoing chemotherapy).

Patients with deep neck infections can present in a variety of ways with the most common signs and symptoms being fever, pain, swelling, and a variable period ranging from 1 day to several weeks. Decreased oral intake can result in mild to severe dehydration, and swelling may lead to airway compromise.

Deep neck infections may occur at any age, but there appears to be a somewhat bimodal distribution. Overall there is a predominance in patients over 50 with a higher prevalence in the lower socioeconomic groups mainly due to poor oral hygiene and lack of dental care (2–4,6,7). In pediatric patients, these infections can occur at any age, but most commonly occur between 3 to 5 years of age with a slight male predominance (5).

The most common etiologic sites of infection are the teeth and tonsils. Other common causes are postsurgical and trauma that disrupts the skin and soft tissues. Intravenous drug users can present with jugular vein infections from contaminated injections. Other less common causes include foreign bodies, sialolithiasis, parotid obstruction, osteomyelitis, and epiglottitis. In patients with recurrent deep neck infections, consider underlying congenital anomalies (branchial cleft cysts, lymphangiomas, and thyroglossal duct cysts) (2–7,19).

Although mortality from head and neck infections has decreased significantly since the emergence of antibiotics, resistant organisms are spreading into the community. Most infections are polymicrobial including anaerobic and facultative oral bacteria (5). The most commonly isolated organisms in the head and neck infections are gram-positive aerobes followed by anaerobes, gram-negative aerobes and fungi. *Streptococcus viridans* and *Staphylococci* species dominate the gram positives, while *Klebsiella pneumoniae* and *Neisseria* species are frequently the gram-negative culprits (6). Emergency physicians must also be cognizant that the onset may be insidious secondary to partial treatment with antibiotics.

Facial cellulitis of odontogenic origin usually involves the upper half of the face when the maxillary teeth are the source. Involvement of the middle and lower part of the face and neck suggests a mandibular origin. These infections are generally well contained, but in a compromised host there may be rapid spread of infection, which can be fatal (24,25). Infections that affect the midface are commonly caused by a dental abscess of the anterior maxillary molar teeth and the buccal space. Infections in these areas can lead to cavernous sinus thrombosis because of the pattern of venous drainage, airway compromise, and mediastinal extension (1). Odontogenic sinusitis refers to the secondary infection of the paranasal sinuses originating from dental infection. Although most paranasal sinus infections result from an upper respiratory tract infection, direct spread of the infection from the teeth and associated oral tissues can result in secondary sinusitis. Based on proximity, the maxillary sinuses are most often involved. Symptoms include headache, foul discharge,

fever, weakness, and drainage. Osteomyelitis may complicate odontogenic infection typically involving the premolar soft tissues, maxillary sinuses, infratemporal fossa, or the periorbital region.

Ludwig Angina

Ludwig angina is defined as an infection involving the submandibular, sublingual, and submental spaces with marked elevation of the tongue (2,4,10). A characteristic brawny edema, induration, or board-like swelling is present on the floor of the mouth. Tender and firm anterior neck edema without fluctuance is appreciated on physical examination. Patients may also complain of stridor, drooling, difficulty talking, tachypnea, and tender tongue with abnormal protrusion.

Ludwig angina typically begins as an infection of the second and third mandibular molars (odontogenic), progressing rapidly into tissues that cover the small muscles between the larynx and the floor of the mouth. Hemolytic Streptococcus sp is the most commonly identified organism. Mixed flora can also cause an overgrowth of gas-producing organisms such as *Bacteroides fragilis*. Although Ludwig angina is a cellulitis with diffuse infiltration, subsequent abscess formation is not uncommon. The mode of spread is typically direct and not lymphatic. Thus the infection is classically bilateral, but not always obvious on initial presentation. Ludwig angina may result in a life-threatening airway compromise and obstruction, and these patients tend to be quite toxic.

Mediastinitis

Although the most common cause of acute mediastinitis is esophageal rupture (due to instrumentation, foreign body, or trauma), descending necrotizing fasciitis from the retropharyngeal space, prevertebral space, or other anterior visceral spaces can also spread into the mediastinum. Symptoms include increased respiratory difficulty, tachycardia, chest pain, back pain, erythema/edema of the neck and chest, crepitus, and shock. It is important to have a low threshold for further workup in patients

with these symptoms (12,13,14,16). Comorbid conditions such as diabetes and immunocompromised patients are at higher risk for this severe infection. Mediastinitis may also result from direct extension from an adjacent source of infection, including osteomyelitis of the sternoclavicular joint, pulmonary infections, and spread of granulomatous disease from mediastinal lymph nodes.

Salivary Infections

Salivary infections can develop in three ways: (a) retrograde migration into the duct from the oral cavity, (b) contagious spread of a local infection, or (c) as a suppurative complication of salivary stasis secondary to an obstructing stone. New literature suggests that the infection is polymicrobial, consisting of Streptococcus sp, Staphylococcus sp, aerobes, anaerobes, or viral etiology (mumps, AIDS, influenza, coxsackieviruses) (2,3). Sialoadenitis is a suppurative inflammation of the Stensen duct or the Wharton duct. Infectious parotiditis is often seen in elderly, dehydrated, diabetic, or patients with granulomatous disease. This entity is usually bilateral and associated with fever and a toxic appearance. Drugs with anticholinergic and diuretic properties can contribute to the development of sialoadenitis (6,25).

Lemierre Syndrome

Lemierre syndrome is a form of septic thrombophlebitis, with or without metastatic abscesses, typically involving the internal jugular vein ipsilateral to a neck or throat infection. First described in 1936, however most cases have occurred in the postantibiotic era, and it was termed in 1984 as the “forgotten disease.” However, recent reviews of the literature suggest an increasing incidence. The offending organism is most commonly a Fusobacterium anaerobic gram-negative bacillus, which is part of the normal flora of the mouth. Predisposing factors include trauma, edema, anoxia, or tissue destruction after dental disease (18,20).

Cavernous Sinus Thrombosis

The cavernous venous sinuses are bilateral structures that communicate with the pterygoid plexus as well as the superior ophthalmic vein. Because these sinuses anastomose with facial veins which have no valves, paranasal sinus, odontogenic, and facial infections may spread into the cavernous sinus. Patients with cavernous venous sinus thrombosis often have a history of midface infection for the past 5 to 10 days. Presenting signs and symptoms include headache, fevers, and cranial nerve deficits, specifically CN III to VI. The patient may have orbital pain, visual disturbances, and fullness with periorbital edema or discrete abscess. Other symptoms include confusion, drowsiness, and coma as a result of central nervous system involvement and/or sepsis.

DIFFERENTIAL DIAGNOSIS

In addition to the processes discussed above, the differential diagnosis of head and neck infections is broad and includes simple pharyngitis, dental infections, and referred pain. Tumors may present as nonspecific swelling and can be difficult to differentiate from advanced primary infections. Viral infections involving the salivary glands (e.g., mumps) can present as facial swelling. Less common infections include tuberculous cervical lymphadenitis (scrofula), cytomegalovirus, catscratch disease, and actinomycosis. Failure to respond to conventional therapy should lead the clinician to suspect a complication or an alternative diagnosis. Certain fungal infections, such as mucormycosis, although rare, are more common in the head and neck regions and should be considered in the immunocompromised patient. Autoimmune diseases such as Sjögren syndrome and Mikulicz disease can also lead to facial swelling caused by enlargement of the salivary glands. Trauma-induced swelling (vascular and nonvascular), can also mimic facial infections (4).

ED EVALUATION

The initial evaluation must focus on an assessment of the ABC’s, as some patients with a deep neck infection present in septic shock and require emergent airway management. The patient’s alertness,

posture, work of breathing, stridor, and quality of voice may be assessed in the first few seconds. Once this assessment has been made, more stable patients may have a more detailed physical examination and diagnostic testing.

Protective eyewear, mask, and gloves should be worn when evaluating the oral cavity. Positioning the patient is also important, ideally at a 45-degree angle. Consider examining children on a parent's lap for patient comfort. It is important to have the following equipment readily available: a good light source, a tongue blade, gauze, suction, and a dental mirror. Providing topical anesthesia of the oropharynx may facilitate the examination in some cases. A MacIntosh laryngoscope blade is an excellent tongue depressor and light source for examination and or procedure.

Patients with dental pain should be examined for the presence of infection and localized dental pain. Pain to percussion with a tongue blade indicates involvement at the apex of the tooth (such as a periapical abscess). Tender swelling of the gingiva adjacent to a tooth may indicate either a periodontal abscess or extension of a periapical abscess through the cortex of bone into the subperiosteal space.

The EM physician should evaluate for facial swelling which can be subtle in some cases as well as adenopathy and other signs of infection. In patients with sialoadenitis, pus may be expressed from the meatus of the salivary duct with gentle pressure to the gland or "milking" along the duct. In severe head and neck infections such as Ludwig angina, trismus, the inability to open the mouth because of involvement of the internal pterygoid or masseter muscle, may be present. Overall, this sign is present in less than 20% of patients even in advanced head and neck infections. More commonly in severe infections, patients will have a toxic presentation or appear in respiratory distress with impending upper airway obstruction or concomitant pneumonia. Other significant clinical signs include torticollis from sternocleidomastoid (SCM) inflammation, neck pain with neck movement, drooling of secretions, stridor, otalgia, headache, and vocal quality changes (2–7,19). Advanced infections may also extend down to the mediastinal area or present as facial

cellulitis with closure of the eye indicating potential spread of infection to the periorbital spaces.

Imaging studies provide important information in identifying infection, discerning abscess versus edema, mass, or lymphadenopathy, guiding drainage procedures, and diagnosing complications. Computed tomography (CT) scanning with intravenous contrast is the most helpful and readily available advanced imaging study in most hospitals. Depending on the soft tissues involved, one should consider a maxillofacial CT with 1-mm cuts and/or a neck CT with intravenous contrast. MRI may be superior to CT in assessing the origin of infection and it is less prone to interference from dental artifacts. However most studies note that CT venography seems to be superior to MR venography in the identification of the cerebral venous sinuses and at least equivalent in the diagnosis of cerebral venous sinus thrombosis (1,2,5,9,11). Overall, CT remains the advanced imaging study of choice in most instances.

A lateral soft tissue radiograph of the neck may be a helpful screening tool for deep space infections since it may reveal a thickened prevertebral stripe, enlarged epiglottis, or soft tissue gas. However it gives little information on abscess, and CT is preferred. For patients with chest symptoms, a plain chest radiograph or a chest CT may be indicated to search for evidence of mediastinitis. For patients with evidence of cellulitis or phlegmon by CT but no definitive abscess, IV antibiotics alone are effective. Patients with Ludwig angina can develop complications including internal jugular thrombophlebitis, intracranial extension, and carotid hemorrhage. Findings on CT for sinusitis may include thickening of sinus walls, sclerosis, and perforation (12–16). Since most stones are radiopaque, CT is likely to demonstrate sialolithiasis and its infectious complications if present. The salivary gland demonstrates enlargement, hypodensity on precontrast scan, and avid postcontrast enhancement, with adjacent inflammatory stranding and fascial thickening. The salivary duct may be dilated and thick walled due to a stone obstructing the duct. MR imaging can display inflammation and edema, but is poor in detecting the actual stone. In Lemierre’s,

CT scan with contrast demonstrates enlargement and thrombosis of the internal jugular vein, with enhancement of the walls of the vein and perivenular soft tissues.

KEY TESTING

Imaging studies are critical:
CT scan is the imaging study of choice in most cases
Plain films may be a useful screening tool, but should not be relied upon
Consider imaging the chest, as infections may spread to the mediastinum

ED MANAGEMENT

In the patient with a head and neck infection, the emergency physician must determine the following: (a) the potential for airway compromise, (b) the extent of involvement of contiguous structures, and (c) the potential for spread of infection to the fascial planes of the head and neck. If the patient is in need of immediate stabilization, the initial resuscitation takes precedence over further evaluation or diagnostic imaging. See Table 63.1.

TABLE 63.1
Essential Features of Odontogenic and Parapharyngeal Infections

Fascial Space/Anatomic Area	Clinical Presentation	Diagnosis and Treatment	Disposition
Periapical abscess	Acute or chronic odontalgia; pain with percussion; no visible swelling	Periapical lucency on Panorex; analgesics/ antibiotics	Dental referral
Subperiosteal	Vestibular, palatal, or sublingual swelling/ fluctuance	Stab incision to alveolar bone, irrigation and drainage, analgesics/antibiotics	Dental/oral surgery referral 24–48 hrs
Buccal space	Massive cheek swelling	Analgesics/antibiotics; fluctuance usually easy to palpate	OMFS consult for abscess drainage
Masticator Spaces; submasseteric pterygomandibular temporal	Severe trismus is the clinical hallmark	Patients are often dehydrated and may require fluid resuscitation; CT scan may confirm diagnosis	OMFS or ENT consult; hospitalize for trismus, toxicity, or severe dehydration
Sublingual, submandibular, submental space	Prominent swelling	Airway assessment; IV antibiotics; fluid resuscitation if dehydrated	OMFS or ENT consult; admission if toxic
Ludwig angina	"Brawny edema" of the neck; upper airway obstruction with stridor	Airway stabilization; broad-spectrum antibiotics	OMFS or ENT consult; admission, possible surgery
Parapharyngeal infections; lateral, retropharyngeal space	Pharyngeal bulging, dysphagia, trismus; nuchal rigidity with prevertebral involvement	CT scan defines location and extent of abscess; lateral neck x-ray may show retropharyngeal thickening	OMFS or ENT consult; admission, possible surgery
Mediastinitis	Chest pain, severe dyspnea, systemic toxicity	Wide mediastinum on CXR. Gas or fluid on CT scan. IV antibiotics	Admission, possible surgery
Cavernous sinus thrombosis	Ocular pain, orbital edema, retinal hemorrhages early; CN III, IV, V, VI deficits	Usually dramatic findings; CT scan or MRI may confirm Dx	Admission

OMFS, oral and maxillofacial surgeon; CT, computed tomography; IV, intravenous; ENT, ear, nose, and throat; OR, operating room; CXR, chest x-ray; IV, intravenous; CN, cranial nerve; MRI, magnetic resonance imaging; Dx, diagnosis.

Patients with acute airway compromise or signs of sepsis must be treated quickly and skillfully to prevent further deterioration. Securing the airway is a priority in the ED treatment and should be done in the initial resuscitation. All patients with trismus must be presumed to be difficult intubations. Trismus may be due to muscle spasm, edema, or both, and may not respond to paralytic agents. Patients with Ludwig angina, other deep space infections, postoperative swelling or bleeding present difficult challenges in airway management. Oral intubation can be attempted, although the normal anatomic relationships may be distorted because of swelling or obscured by bleeding. A "backup airway" or alternative measures such as video laryngoscopy, nasotracheal intubation, tracheostomy, cricothyroidotomy, gum elastic bougie, or fiberoptic techniques should be carefully considered before attempts are made. Consultation with the appropriate services should be obtained as time and availability permit.

Parapharyngeal space infections (sublingual, submandibular, submaxillary, lateral pharyngeal, retropharyngeal, and pretracheal) are usually polymicrobial. Appropriate antibiotic therapy includes penicillin G (high dose) plus metronidazole or cefoxitin. Alternative therapy may include ticarcillin/clavulanate (Timentin), piperacillin/tazobactam (Zosyn), or clindamycin in the penicillin-allergic patient.

Patients with suspected deep neck infections require aggressive, early, empiric broad spectrum antibiotic therapy. Most patients are given IV antibiotics targeting gram-positive cocci and anaerobes, but broader coverage for gram-negative aerobes should be considered in diabetics and immunosuppressed patients. For deeper soft tissue head and neck infections like Ludwig angina, high-dose penicillin G (12 million units/d) is required. Unasyn (Ampicillin/Sulbactam) or Clindamycin also provide excellent anaerobic coverage. Chloramphenicol is reserved for extreme situations with few other alternatives (2,4,11). If the patient does not respond to treatment with antibiotics in the first 24 hours, surgical drainage may be required. Most of these cases require admission and consultation with appropriate services. There is no consensus on duration of oral antibiotic therapy but most recommend 7 to 10 days.

Mediastinitis is a surgical emergency in which IV antibiotics, surgical debridement, drainage, and airway management are typically necessary.

Patients with simple dental-related infections can be managed as outpatients with oral antibiotics, analgesia, and rinses. A simple incision and drainage may be indicated for abscesses and follow-up should be arranged the next day with the oral and maxillofacial surgeon (OMFS) or the family dentist (2,3). Penicillin V (phenoxymethyl penicillin) is an effective and inexpensive first-line choice, and unless penicillin allergy exists, it is the antibiotic of choice for outpatient therapy. Clindamycin has become a favorite in dentistry because of its bactericidal activity and its excellent penetration into soft tissue and bone. Clindamycin covers oral pathogens and can be an alternative choice in penicillin-allergic patients (1,2,4,5,10).

Sialoadenitis may be treated on an outpatient basis with an antibiotic that has gram-positive coverage (cephalexin, dicloxacillin), oral hygiene, and a sialagogue such as lemon juice. For immunocompromised patients, consider broader coverage with antibiotics like third-generation cephalosporins, piperacillin/tazobactam (Zosyn), imipenem, or meropenem (1,2,4,5,10).

The incidence of complications from deep neck space infections has remarkably decreased since the advent of antibiotic therapy. Despite this, the potentially devastating outcomes associated with these complications remind the physician to remain vigilant for subtle signs and symptoms. Airway obstruction and asphyxia is a potential complication of any deep neck infection, but has been most commonly associated with Ludwig angina. Other complications include sepsis, internal jugular vein thrombosis, upper GI bleeding, mediastinitis, and vocal cord palsy (4,6,7,19). Carotid artery rupture, although rare, carries a mortality rate between 20% and 80%. This can occur when infection involving the carotid sheath leads to arterial wall weakening, erosion, and eventual hemorrhage. Arterial rupture may be heralded by recurrent small bleeds from the ear, nose or mouth, the onset of shock, a protracted clinical course, and hematoma in the nearby tissue, Horner syndrome or unexplained cranial neuropathies (4,19). The EM physician should be wary of patients at risk for complications (e.g., advanced age, comorbid conditions including HIV, myelodysplasia, cirrhosis, and diabetes) (6,8).

CRITICAL INTERVENTIONS

- Initiate early parenteral broad-spectrum antibiotic coverage in the patient with a suspected deep neck or parapharyngeal infection.
- Assess and manage the airway early in patients with airway compromise. Be prepared to utilize alternate “difficult airway” techniques.
- Consult appropriate services early in the management of critically ill patients.

DISPOSITION

Patients with minor infections can be discharged home with oral antibiotics and close follow-up. Patients with deep neck infections or clinical toxicity generally require admission, and some will need surgical intervention. Depending on the institution, consultants may include Dentistry, Oral Maxillofacial surgery, Ear Nose and Throat,

critical care, anesthesia, or a general surgeon. Patients with Ludwig angina or those at risk for immediate airway obstruction should be admitted to a critical care setting for close observation. If appropriate physicians and resources are not available, the patient should be transferred expeditiously to an appropriate facility. Advanced life-support personnel should be used for monitoring the airway, and consideration should be given to establishing a definitive airway prior to transfer.

Common Pitfalls

- Failure to carefully examine patients to identify the source and follow the spread of infection along the fascial planes.
- Underestimation of the potential for spread of infection to the mediastinum.
- Failure to initiate appropriate antibiotics and consultation.
- Failure to recognize the potential for airway compromise from swelling or infection, leading to delay in early airway protection.

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CHAPTER 64 Temporomandibular Pain and Dislocation

Darria Long Gillespie

The temporomandibular joint (TMJ) consists of the head of the mandibular condyle as well as the articular tubercle and mandibular fossa of the temporal bone (Fig. 64.1) (1). The joint is held loosely by the TMJ capsule, which has a weak surface anteriorly—allowing the variety of movements required, but also the relative ease of dislocation (2,3). The muscles of mastication are divided into two groups: the temporalis, masseter, and internal pterygoid muscles elevate, retract, and close the mandible, while the suprahyoid, infrahyoid, and external pterygoids open and protrude (Fig. 64.2) (4).

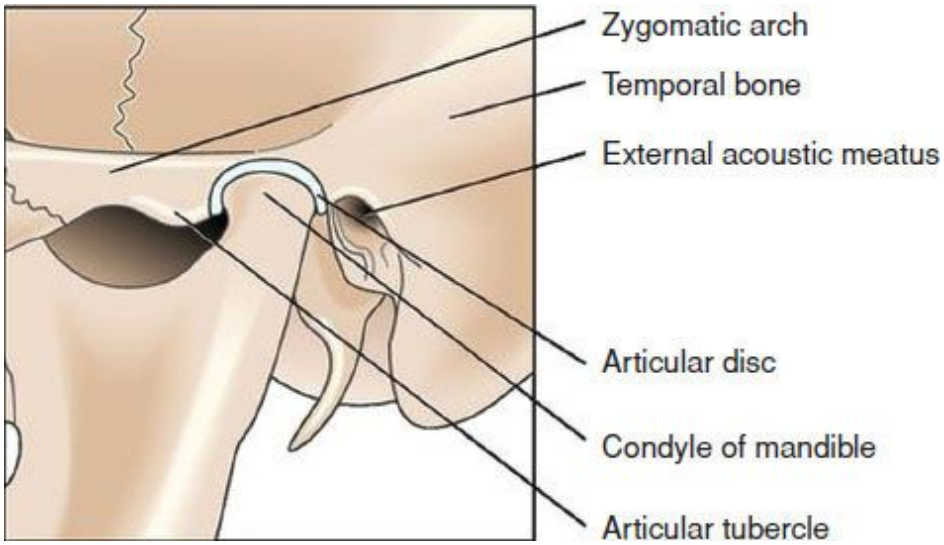

FIGURE 64.1 Bony Anatomy. (Adapted from Bickley LS, Szilagyi P. *Bates' Guide to Physical Examination and History Taking.* 8th ed.

Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

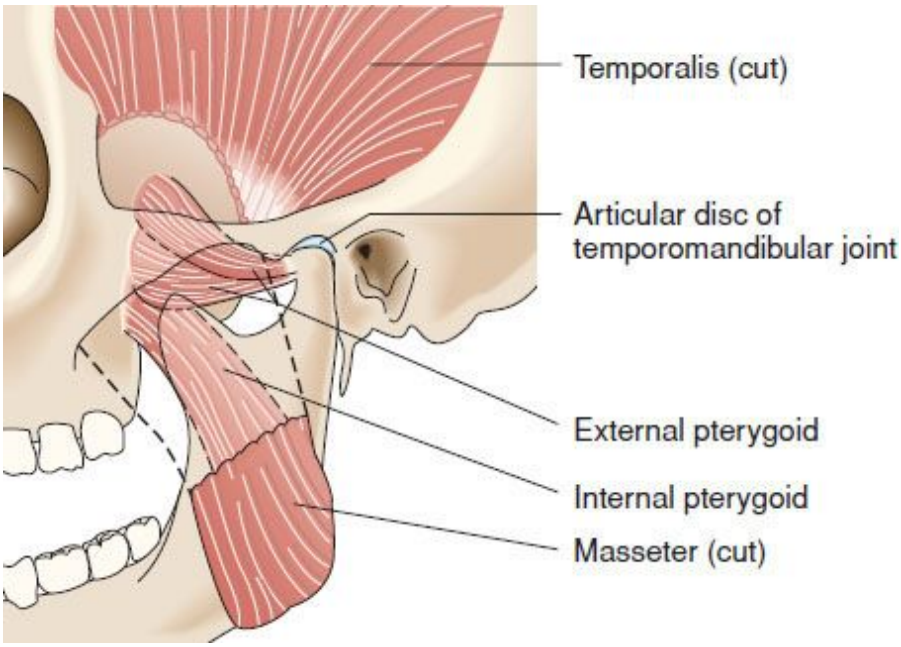

FIGURE 64.2 Muscular anatomy. (Adapted from Bickley LS, Szilagyi P. *Bates' Guide to Physical Examination and History Taking.* 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

CLINICAL PRESENTATION

Temporomandibular Myofascial Pain Dysfunction Syndrome (TMPDS): TMPDS is a neuromuscular disturbance, and its causes are debated. Contributing factors include anatomic abnormalities (congenital or traumatic), microtrauma from clenching/grinding, stress, and systemic arthritides (5,6,7,8). Recent research suggests that sleep bruxism is not a cause of TMPDS (9,10). However, increased clenching and grinding in times of stress contributes to TMPDS and triggers a cycle of muscle pain, dysfunction, and spasm (1,6). Patients who present to the ED are more commonly females in their 20s to 40s (1) and experience unilateral dull pain involving the TMJ, masseter, and temporalis muscles. Pain worsens throughout the day, as well as with chewing, and may refer to the supraorbital, cervical, and occipital regions. Patients may also complain of a "click" or sensation of catching with opening and closing of the jaw (7),

although clicking alone without pain is inadequate to make the diagnosis of TMPDS.

The TMJ is vulnerable to all conditions that affect joints in the body, including arthritis, ankylosis, and neoplasm (1). TMPDS secondary to systemic arthritides presents with pain and crepitus in periods of exacerbation and remission. Pain in secondary TMPDS typically is greatest in the morning, presents in younger patients, and has greater severity and joint erosion.

Acute mandibular dislocation: The most common dislocation direction is anterior, in which the condyle is trapped anterior to the articular tubercle due to muscle spasm, prohibiting jaw closure. Posterior, superior, and lateral dislocations are rare and usually associated with severe trauma and other injuries. Dislocations are more commonly bilateral; in unilateral dislocation, the jaw deviates away from the dislocation.

Acute dislocations can be caused by a direct blow to the jaw, seizures or dystonic reactions, and most commonly, due to maximum opening (yawning, laughing, vomiting, dental procedures). Predisposing factors include a shallow fossa and congenital or traumatic weakness of the joint capsule and ligaments (3,11). Patients present with the mouth stretched wide open, are anxious and uncomfortable, and have garbled speech and drooling due to the inability to swallow or move the tongue appropriately. They report exquisite pain due to masseter spasm.

DIFFERENTIAL DIAGNOSIS

In any patient presenting with facial, jaw, or head pain, the differential diagnosis includes deep space infections (peritonsillar abscess, retropharyngeal abscess, Ludwig angina), odontogenic pain (abscess, caries, tooth fracture), otologic referred pain, zoster, temporal arteritis, trigeminal neuralgia, or parotid gland pathology. Neck and shoulder pain are often reported with TMPDS, and the differential may include other disorders such as referred pain from cardiac ischemia.

Although most cases of TMJ dislocation are clinically obvious, some may be confused with mandibular fracture or acute dystonia.

Dislocations and fractures may coexist.

ED EVALUATION

The emergency physician should thoroughly examine the head and neck to evaluate the airway and rule out non-TMJ causes. Examination frequently reveals spasm and tenderness of the masseter externally and internal pterygoid intraorally. The joint itself can be palpated by placing a finger just anterior to the tragus, or in the external auditory meatus and pulling forward on the tragus (Fig. 64.3). Both muscle and joint examinations should be performed while the patient opens and closes the mouth. If this completely reproduces the patient's pain or demonstrates clicking or crepitus, a TMJ disorder is the likely cause. In severe cases, the jaw deviates toward the affected side, with myofascial spasm and trismus limiting full mouth opening. Examination may show facial asymmetry (12).

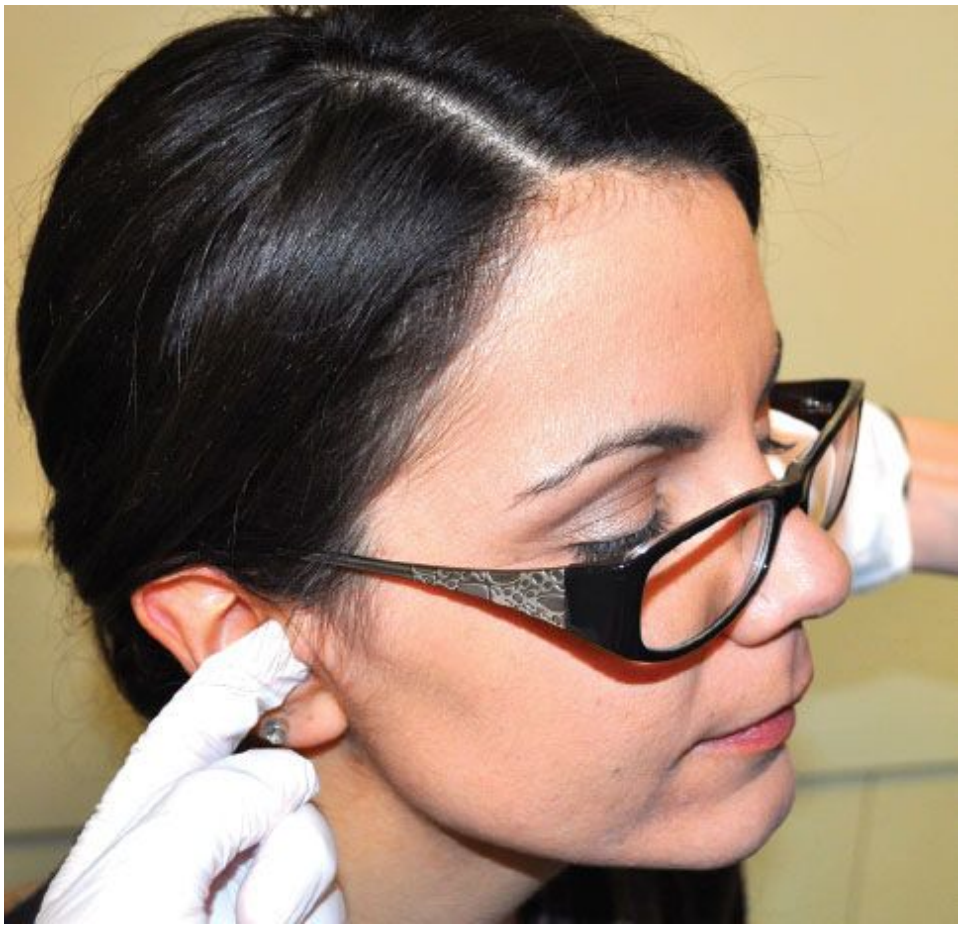

FIGURE 64.3 Palpation of the TMJ via pressure on tragus from external auditory canal.

For patients with a question of mandibular dislocation, evaluate for signs of trauma, including mandibular deformity or missing teeth, and for sensory deficit at the chin or mouth. With anterior dislocation, there is often a prominent-appearing lower jaw, as well as a depression in the preauricular area representing the empty temporal fossa.

Imaging

Atraumatic, subacute, or chronic TMJ pain: In the absence of trauma, signs of dislocation, acute change in bite, or asymmetry, emergent imaging is rarely required (7).

Mandibular dislocation: Spontaneous anterior mandibular dislocations that have no history of trauma, no atypical findings, nor evidence of fracture may be reduced without imaging (13). Otherwise, a mandibular x-ray or panorex view should be taken to exclude fracture (14). If these are unavailable, or there is high suspicion of fracture or internal derangement, a CT scan should be obtained (15).

KEY TESTING

- Obtain mandibular x-ray, panorex, or CT in cases of suspected fracture, trauma, or atypical or non-anterior dislocation

ED MANAGEMENT

TMJ pain or dysfunction: Regardless of cause, TMJ syndrome is initially treated with a combination of 1 to 2 weeks of physiotherapy, moist heated compresses, a soft/pureed diet, and nonsteroidal pain medication (5). Prescription pain medication or muscle relaxants may be of use acutely.

Acute TMJ dislocation: Anterior TMJ dislocation can be reduced in the ED.

1. Relief of anxiety, pain, and spasm is crucial (14,3), and procedural sedation or adequate analgesia is required. The physician may consider intra-articular anesthetic injection into the TMJ (3).
2. The patient should sit upright with a firm support behind his head, putting the mandible at the height of the physician's elbow (14).
3. Facing the patient, place both thumbs intraorally (Fig. 64.4) on either the mandibular ridge or over the occlusal surface of the molars, with fingers gripping the mandible. (CAUTION: Muscle spasm will cause the jaw to snap into place quickly, and thumbs should be protected with gauze wrapping and possibly tongue depressors). Alternative methods include standing behind the patient, using an external approach (16), or positioning the patient supine with the physician at the head of the bed.

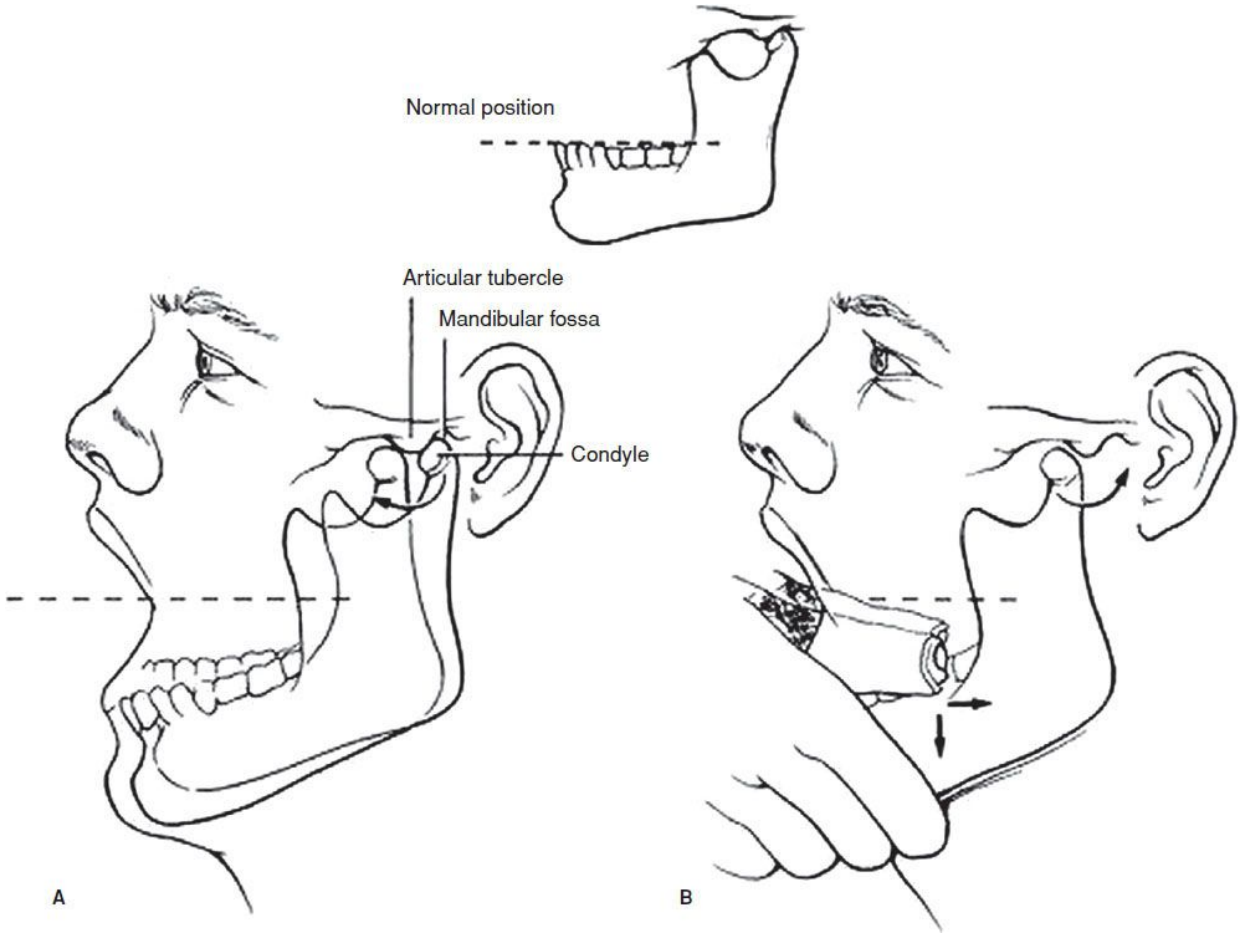

FIGURE 64.4 Anterior dislocation and reduction technique. (From Fleisher GR, Ludwig S, Henretig FM, et al. *Textbook of Pediatric Emergency Medicine.* 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)

4. Apply downward pressure to free the condyles from the tubercle. Consider gently rocking from one side to another instead of bilateral pressure, or tilting the chin up while pushing down on the posterior mandible (3,2). Once freed from the tubercle, the mandible quickly snaps posteriorly in a C-shaped direction. Success is followed by an immediate ability to close the mouth, reduced pain, and sense of relief (3).

Complications of reduction are rare and include fracture, cartilage injury, or operator bite injury. Postreduction imaging is only necessary in a difficult reduction or in cases of severe pain during/after the reduction (13).

Posterior, lateral, superior, or open dislocations, as well as those with associated fractures or that the emergency physician cannot reduce will likely require further intervention and the emergent evaluation by an oral/maxillofacial surgeon.

CRITICAL INTERVENTIONS

- Rule out non-TMJ etiologies of pain and any signs of potential airway compromise.
- Provide adequate sedation and analgesia to facilitate reduction of TMJ dislocation.

DISPOSITION

Patients with TMPDS should be referred to a general dentist or periodontist for occlusive therapy or intra-articular steroid injections. Many patients will improve with supportive measures (5); most tend to have periods of exacerbation and remission.

After successful reduction of an anterior dislocation, patients should use nonsteroidal analgesic for pain control. For the 2 weeks following a TMJ dislocation, patients must be instructed to avoid

opening of the mouth beyond 2 cm, eat a soft/pureed diet, apply warm compresses, and follow up with a dentist or maxillofacial surgeon.

Special attention should be paid to children with posttraumatic internal abnormalities of the TMJ, as they are at higher risk of asymmetry in facial growth (2,14,17).

Common Pitfalls

- Failure to carefully examine for infection or referred etiology of pain.
- Failure to identify mandibular fracture.
- Failure to provide adequate sedation and analgesia to facilitate TMJ reduction.

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CHAPTER 65 Upper Airway Obstruction

Louisa S. Canham and Jonathan Fisher

Upper airway obstruction occurs from a variety of causes including foreign-body obstruction, infection, swelling, and bleeding. Airway obstruction from choking on a piece of food can occur rapidly, although conditions such as epiglottitis may occur more insidiously. Early recognition and treatment of impending complete airway obstruction is essential to avoid catastrophic results. Evaluation, differential diagnosis, and emergency intervention all must occur simultaneously. Although not every patient with upper airway obstruction will require emergency airway management, for a subset of patients there is only a small window of opportunity to intervene before the airway is completely lost.

The major determinant of airway resistance is the radius of the airway, resistance being proportional to the fourth power of the radius. Therefore, a small decrease in diameter can have an extreme impact on the airway. Identification of high-risk presentations and clinical situations is the key to successful outcomes.

CLINICAL PRESENTATION

Nontraumatic airway obstruction can occur rapidly in a manner of seconds or through a period of days to months. The process may progress gradually or suddenly with little warning. The emergency physician must understand the disease processes at work and be prepared to intervene quickly.

The site of the obstruction, the size of the obstructing agent, and associated spasm and edema are important determinants of the

presentation. Historical factors may aid in arriving at the diagnosis. Physical findings may be nonspecific but can help to separate patients into a category of obstruction.

Increasing airway obstruction is first evidenced by subjective complaints of respiratory distress by the patient. Patients may complain of a sensation of “throat closing” or “something stuck in their throat.” Objective findings include the presence of respiratory sounds such as stridor or wheezing. Inspiratory noises tend to indicate an upper airway source of obstruction. In general, stridor is produced in large, upper airways during inspiration, while wheezing occurs in smaller, lower airways during expiration. However, the distinction may not always be so clear. Inability to swallow or handle one’s secretions can be an ominous finding. The patient’s positioning is important to note. An upright posture with the neck extended in the sniffing position is characteristic of the patient with supraglottic obstruction, such as epiglottitis. Forcing the patient to become supine can cause complete airway obstruction.

Although airway obstruction by a foreign body, such as food, occurs suddenly, obstruction by an expanding mass effect within the upper airway is more insidious. Abscesses may obstruct the airway by their location or can rupture into the airway, causing acute obstruction. Expanding hematomas behave similarly. Edema and soft tissue swelling owing to infection or allergy have a more diffuse mass effect.

DIFFERENTIAL DIAGNOSIS

Foreign-body obstruction, infection, hypersensitivity, hemorrhagic disorders, extrinsic mass, and neoplasia all may result in the syndrome of upper airway obstruction. Paradoxical vocal cord motion is a psychogenic form of stridor that mimics true airway obstruction. It is a diagnosis of exclusion, but it is an important entity to recognize to avoid harmful unnecessary interventions, such as intubation (1).

Foreign-Body Obstruction

The classic example of upper airway obstruction by a foreign body is the “cafe coronary” (2). Food that causes an obstruction has often been poorly masticated. The victim may have painful or poorly fitting dentures or otherwise poor dentition that hampers chewing. Alcohol consumption has been associated with an increased risk of choking. This type of obstruction is usually supraglottic and responds to the maneuvers prescribed by the American Heart Association, such as abdominal thrusts (3).

Aspirated toys or smaller pieces of food may pass the vocal cords and produce obstruction in the subglottic area. These obstructions may be intermittent and aggravated by the head-down position, which allows the object to move an obstructing position. Back blows and the head-down position may actually worsen these obstructions. The clinical presentation of a subglottic foreign body may be one of localized wheezing and atelectasis as the foreign body becomes lodged in a bronchus (4).

Infection

Infection of the upper airway structures may produce airway compromise within hours. Patients often present with fever, pain, hoarseness, and decreased ability to open the mouth or move the neck. *Ludwig angina* (cellulitis of the sublingual space) can quickly obstruct the airway. The condition is a true otolaryngologic emergency that requires airway maintenance and antibiotic therapy (5). Retropharyngeal or parapharyngeal abscess can cause gradual obstruction as it expands and then catastrophic deterioration if it suddenly ruptures into the airway (6). Epiglottitis may produce sufficient swelling to produce airway obstruction in the adult or child.

Hypersensitivity

Anaphylaxis presents suddenly after exposure to an antigenic stimulus. When there is laryngeal edema, prompt intervention is needed (see Chapter 175), and a delay in the initiation of medical therapy may make immediate surgical intervention necessary. Food,

drug, and insect sting allergies are the commonly encountered causes of anaphylactic airway emergencies. Severely ill patients may not be able to speak and therefore unable to relate a history of exposure.

Hereditary angioedema (HAE) is an autosomal dominant inherited condition that is manifested by sudden edema of the face, hands, abdominal viscera, and airway. Airway obstruction is the most dramatic and life-threatening complication of the disease (7). Episodes may be triggered by minor trauma, emotional distress, or surgery. There is no race or sex predilection. Despite the inherited nature of the disease (see Chapter 176), there is often no known family history.

Angiotensin-converting enzyme (ACE) inhibitor agents have also been associated with the development of angioedema (8,9). Moderate to complete airway obstruction may occur. It is important to note that this reaction may occur even in patients who have been taking ACE inhibitors for years.

Hemorrhagic Disorders

The widespread use of anticoagulants for the treatment of cardiac and cerebrovascular disease has increased the population who are at risk for the development of spontaneous hematoma. These hematomas may develop anywhere in the body, but when the pharynx, tongue, or soft tissues surrounding these structures are involved, airway compromise is a predictable consequence.

Airway compromise has been reported because of hematoma of the sublingual space, retropharynx, and hypopharynx (10,11). There is rapid, unexpected deterioration of a patient who, in most cases, was previously healthy. Pain is often noted early, frequently preceding other symptoms. Signs of airway obstruction may develop before the examiner's eyes. Physical examination often reveals an area of swelling, with or without ecchymosis. Close observation is essential to avoid an adverse outcome from unrecognized abrupt deterioration.

Extrinsic Mass

Airway obstruction owing to an extrinsic mass is occasionally seen. An example is the development of an obstruction in the esophagus caused by achalasia (12). The distended esophagus impinges on the airway in the neck and produces recurrent airway obstruction that resolves when the esophageal obstruction is cleared. Cystic lesions of various types may produce a similar syndrome that may require temporary airway support until the lesion is removed.

Neoplasia

Tumors located anywhere along the airway may cause respiratory distress via extrinsic compression or internal infiltration of the airway. Common culprits include mediastinal tumors, lung cancer, and Kaposi sarcoma. Patients present with dyspnea and noisy respirations, and may be misdiagnosed as having asthma or an airway infection. Some clues to the diagnosis of neoplastic etiology include hemoptysis and worsening of symptoms with lying flat (13,14).

Congenital tumors of the oropharynx or neck may present immediate and unexpected airway emergencies at birth. These conditions require the immediate availability of neonatal resuscitation capabilities and surgical resources (15).

ED EVALUATION

Regardless of the cause of the obstruction, the emergency physician must first gauge its severity by quickly placing the patient in one of four categories:

1. Stable airway, deterioration risk low
2. Stable airway, deterioration risk high
3. Compromised airway and respiration
4. Obstructed airway and agonal respirations

The evaluation and therapy process can then proceed with the appropriate degree of urgency.

The history should include questions about previous allergic reactions, medications, cancer, fever, pain with swallowing, and

hoarse voice. The vital signs, presence or absence of stridor, and degree of respiratory distress should be quickly assessed. The neck should be palpated for masses and lymphadenopathy, and the larynx and trachea should be moved from side to side to check if this "tracheal rock" elicits pain with gentle movement. Examination of the throat may reveal a partial view of a supraglottic foreign body, an abscess, or swelling of the tongue or pharynx.

A patient placed in the stable category with low risk of deterioration is in some ways the most hazardous for the emergency physician. It implies that the patient can be evaluated at a leisurely pace with a minimal degree of observation. However, airway obstructing lesions can deteriorate quickly and unexpectedly.

The second category reflects the appropriate degree of concern during the initial evaluation of any patient in whom airway obstruction is suspected. The risk of deterioration calls for constant observation and readiness to intervene if necessary. Measures intended to correct the underlying obstructive process should be instituted as soon as possible. Laboratory studies may be helpful in confirming an infectious or hemorrhagic etiology. A lateral cervical spine radiograph may reveal a thick epiglottis or signs of a retropharyngeal abscess, such as prevertebral thickening or gas. Computed tomography (CT) scan may further delineate a mass or abscess impinging upon the airway but must be used carefully in the patient who may not tolerate the time and positioning necessary to obtain this study.

The third category, with established airway compromise, calls for immediate decisions regarding airway intervention. The emergency physician must quickly assess the likelihood of success with a medical approach before intubation or surgical intervention is required. The decision to intubate is a clinical one. An arterial blood–gas analysis may add more supporting data, but such testing usually only delays needed therapy, with potentially catastrophic results.

The last category, with the patient in an agonal state, represents the most straightforward situation. The airway must be established emergently.

KEY TESTING

- Advanced imaging (usually CT scan), if the patient can tolerate the study

ED MANAGEMENT

The patient who is stable is a candidate for treatment that might obviate the need for airway intervention. Oxygen supplementation should be initiated in all cases. Consideration needs to be given to nebulization therapy with racemic epinephrine and steroids to decrease edema in hypersensitivity or croup syndromes. If infection is a possibility, appropriate antibiotic therapy should be initiated. Bleeding disorders require replacement of clotting factors.

A mixture of 80% helium and 20% oxygen (heliox) has been suggested as a temporizing measure in patients with airway obstruction caused by tumors (16). The density of the mixture is one-third that of air, and the less turbulent air flow may improve oxygenation in selected patients with a narrowed upper airway. Heliox may not be suitable for hypoxic patients, given the relatively low concentration of oxygen delivered.

When foreign-body obstruction is suspected, airway clearing maneuvers should be implemented promptly according to widely accepted protocols described by the American Heart Association (3). Failure to clear the airway should lead to more aggressive maneuvers to establish an airway. A supraglottic obstruction that is not removable may be bypassed by tracheal intubation or establishment of a surgical airway. With subglottic obstruction, intubation or a surgical airway may not solve the problem as the obstruction is beyond the part of the airway bypassed by the insertion of a tube. Magill forceps may allow removal of foreign bodies under direct vision (17). An aspiration technique uses a blunted (tip cut off) endotracheal tube, wall suction, and a meconium aspirator or “Y” connector attached to the tube (18). If the obstruction is in the lower trachea, attempts to remove the object have failed, and the patient’s condition continues to deteriorate it may be possible to push the obstruction into a

mainstem bronchus, so the other lung can be ventilated as a temporizing measure.

The incidence of acute epiglottitis in children under age 5 years has dramatically decreased with the use of *Haemophilus influenzae* type b vaccine. In 2000, the incidence was only 0.3 per 100,000 children (4). Adult epiglottitis can also lead to complete obstruction, but this is less likely because the adult airway is larger. However, patients may deteriorate unexpectedly and should be continuously monitored until the infection recedes. Preparations for immediate surgical airway placement must be made. Antibiotics should provide coverage against *Staphylococcus aureus, Pneumococcus* sp, group A streptococci, and *H. influenzae.* A standard regimen is ceftriaxone 1 g intravenously (IV) and vancomycin 1 g IV in an area where there is a high prevalence of methicillin-resistant *S. aureus.* Patients with other deep-space infections such as Ludwig angina and retropharyngeal abscess should receive antibiotics that also cover anaerobes, such as clindamycin 900 mg IV or metronidazole 500 mg IV. Steroids may be considered to help reduce swelling and potentially avoid the need for intubation (19). Emergent ENT consult should be obtained to determine the need for drainage.

The most common infectious cause of airway obstruction in children is croup, which is almost always viral in etiology. Standard treatment involves the use of nebulized racemic epinephrine, which provides fast relief but does not have a sustained effect. Steroids, given as a one-time dose, have become more widespread in the treatment of croup in recent years (6,20).

The patient with a hemorrhagic disorder associated with warfarin therapy requires aggressive therapy to reverse the coagulopathy. Correction is most rapid with administration of fresh frozen plasma (FFP) or prothrombin complex concentrates (10,11). FFP should be supplemented with vitamin K, which enhances the synthesis of clotting factors in the liver. Levels of the vitamin K–dependent factors II, VII, IX, and X begin to increase 2 hours after vitamin K administration with significant elevation in 6 to 8 hours, and vitamin K levels are frequently normal in 24 hours. Hemophiliacs should be treated with the appropriate factor concentrate.

The patient with hypersensitivity or anaphylaxis should be treated emergently with epinephrine (0.3 mL 1:1,000 subcutaneous [SC]), antihistamines (diphenhydramine 50 mg IV and ranitidine 50 mg IV), and steroids (methylprednisolone 125 mg IV) (see Chapter 175). There are no randomized controlled trials evaluating the use of these medications in nonallergic angioedema, but if the etiology of the edema is unclear the risks of empiric treatment are low (8). Patients with known HAE can be treated with FFP to supply the missing C1 esterase inhibitor (21); in addition, a plasma-derived C1 esterase inhibitor product was approved by the FDA in 2009 for use in patients with HAE (8).

Airway Opening Maneuvers

Airway opening maneuvers such as chin lift, head tilt, and oral and nasal airways are most useful in patients with a decreased level of consciousness (3). The situation is quite different if the comatose state is a result of hypoxia caused by airway obstruction and specific medical therapy and more aggressive airway intervention therapy are indicated.

Nonsurgical Management

A patient with significant airway compromise who does not improve with medical intervention often requires tracheal intubation. Blind nasotracheal or orotracheal intubation will suffice in many cases in which the decision is made before the airway is completely obstructed. Rapid sequence orotracheal intubation can often be accomplished, but the physician must weigh the risks of paralysis against its potential benefit in each case.

Useful adjuncts for difficult intubation include the gum-elastic bougie, video laryngoscopes, flexible video-optic devices, and the intubating laryngeal mask airway (ILMA). Inability to remove an obstructing object or to secure the airway with tracheal intubation is an indication to pursue surgical approaches to the airway. Nasal flexible endoscopic intubation performed by the emergency physician, anesthesiologist, or otolaryngologist may be extremely

helpful when the practitioner is comfortable with the technique. The nasal approach may allow passage behind a very proximal supraglottic obstruction. If the obstruction is in the lower trachea, standard tube placement will not relieve the obstruction. In such cases, the tube may need to be advanced further to the carina or into a mainstem bronchus.

Surgical Management

Transtracheal needle ventilation using a high-pressure oxygen source can temporarily provide oxygenation and minimal ventilation, provided that upper airway obstruction is not complete, so that exhalation can still occur through the upper airway. The technique is a temporizing measure that allows time to secure the airway by other, more definitive means. Cricothyrotomy is the emergency surgical airway of choice for most obstructing lesions in the upper airway. For subglottic obstructions, such as a laryngeal abscess, hematoma, or tumor, tracheostomy is preferred (22).

CRITICAL INTERVENTIONS

- Plan and prepare for airway management in the patient with impending airway obstruction before it occurs.
- Proceed with rapid assessment and treatment simultaneously.
- Administer appropriate specific therapies (epinephrine, FFP, antibiotics, steroids) in an effort to avoid the need for direct airway intervention.

DISPOSITION

The development of protocols for the treatment of acute upper airway obstruction should be initiated by the emergency physician. A cooperative team effort should be organized between the emergency, anesthesia, otolaryngology, pediatric, and internal medicine personnel who will be dealing with these patients.

The patient with airway obstruction needs to be under constant observation in an intensive care unit until the risk of airway obstruction has passed. Whenever there is doubt as to the

immediate future course of a patient with airway obstruction, intensive care unit admission is mandatory.

Common Pitfalls

- Underestimation of the potential for sudden deterioration
- Assumption that a sore throat is caused by simple pharyngitis when pharyngeal findings are absent
- Inadequate preparation of equipment and personnel

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CHAPTER 66 Sore Throat

Michael F. Murphy

Sore throat is a common presenting complaint in emergency medicine, particularly the acute variety. Although most causes of sore throat are not life threatening, some are life threatening.

The pharynx is a U-shaped fibromuscular tube extending from the base of the skull to the lower border of the cricoid cartilage, where it is continuous with the esophagus at the level of the sixth cervical vertebra. Posteriorly, the pharynx rests against the fascia covering the prevertebral muscles and the cervical spine. Anteriorly, the pharynx opens into the nasal cavity (the nasopharynx), the mouth (the oropharynx), and the larynx (the laryngo- or hypopharynx).

The oropharyngeal musculature has a normal tone similar to any other skeletal musculature. This tone serves to keep the upper airway open during quiet respiration. Respiratory distress is associated with pharyngeal muscular activity that attempts to open the airway further. Benzodiazepines and other sedative hypnotic agents may attenuate some of this tone. This fact explains why sedation may lead to total airway obstruction in patients presenting with partial airway obstruction.

The glossopharyngeal nerve (IX) supplies sensation to the posterior one-third of the tongue, lingual and faucial tonsils, the valleculae, the free edge of the soft palate, the superior surface of the epiglottis, and most of the posterior pharynx. This nerve also supplies sensation to a portion of the tympanic membrane, the carotid sheath, sinus and body, and the stylopharyngeus muscle. The innervation patterns, as they relate to the carotid sheath, and the epiglottis are important in identifying occult but potentially

lethal causes of sore throat. Stimulation of the glossopharyngeal nerve at any of these locations may be interpreted by the patient as a “sore throat.”

CLINICAL PRESENTATION

Most patients with sore throat are nontoxic appearing, have a clear voice, and have no difficulty with respirations. Since most causes of sore throat are infectious in origin the patient may experience fever, significant pain, and become dehydrated. The challenge for the clinician is to provide symptomatic relief and to identify those patients with serious pathology requiring specific treatment. Four conditions comprise the vast majority of adults that present to the ED with a chief complaint of sore throat: retropharyngeal abscess (RPA), peritonsillar cellulitis and peritonsillar abscess (PTA), epiglottitis, and acute pharyngitis.

The patient with RPA presents with fever, neck pain, and sore throat out of proportion to the oropharyngeal findings. Other symptoms and signs may include odynophagia, neck swelling, drooling, torticollis, meningismus, cervical adenopathy, and stridor. The voice may be normal, though if the abscess is high in the neck, nasal obstruction and a hyponasal voice result. A “hot potato” voice may be present if the swelling is above the level of the larynx (see Chapter 1). Chest pain associated with these symptoms strongly suggests mediastinal extension.

PTA is part of a continuum of illness from tonsillitis, through peritonsillar cellulitis (inflammation without fluid collection) to PTA. The patient may present at any point along this continuum, and symptoms and treatment vary accordingly though severe unilateral throat pain is typical.

Supraglottitis (epiglottitis), because of its occult nature and potential lethality, merits special discussion. The clinical presentation may be categorized into a spectrum that varies from a fulminating course developing over hours to a subacute form smoldering for days to weeks.

- Category 1: severe respiratory distress, imminent or actual respiratory arrest. Patients in category 1 typically report a history of a brief but rapidly progressive illness. Blood culture often reveals *Haemophilus influenzae* type b.
- Category 2: moderate to severe symptoms and signs of potential airway compromise. Symptoms and signs include inability to swallow or lie supine, dyspnea, severe sore throat, muffled voice, stridor, and the use of accessory muscles. The emergency physician should prepare to intervene if the airway should suddenly deteriorate, then undertake further evaluation of the airway.
- Category 3: mild to moderate illness without signs of airway compromise. Patients may report a 3- to 14-day history of a sore throat and pain on swallowing with minimal physical findings on examination. A patient can rapidly worsen with little warning.

DIFFERENTIAL DIAGNOSIS

Throat pain (pharyngalgia), has many causes and may be acute, subacute, or chronic. The most common cause of all forms of sore throat is pharyngitis, meaning "inflammation of the pharyngeal mucous membrane." "Sore throat" and "pharyngitis" are not identical, because many noninflammatory disorders (e.g., oropharyngeal carcinomas) can also cause pharyngeal pain. Local infection is the most common cause of inflammation of pharyngeal structures or acute pharyngitis. The most common and serious causes are discussed in more detail (Table 66.1).

TABLE 66.1
Differential Diagnosis of Sore Throat

Acute Pharyngitis
Bacterial Infections
• GABHS
• N. gonorrhoeae
• C. diphtheriae
Viral Infections
• Epstein–Barr virus
• Herpes virus
• Influenza virus
• Rhinovirus
• Coxsackievirus A
Noninfectious
• Stevens–Johnson syndrome
• Pemphigus
• Angioedema
Chronic Pharyngitis
• GERD
• Obstructive sleep apnea
• Fungal infections (e.g., *Candida albicans*)
• Chronic sinusitis with postnasal drip
• Inhalation of irritants (pyrethrins, chlorine gas, heavy smoking)
• Breathing dry air
• Glossopharyngeal neuralgia
• Carcinomas: pharyngeal, lingual, and tonsillar
• Monomyelocytic leukemia
• Thyroiditis
Retropharyngeal Abscess
Peritonsillar Abscess/Cellulitis
Supraglottitis/Epiglottitis

Acute Pharyngitis

Acute pharyngitis and tonsillopharyngitis are the most common causes of sore throat. Acute pharyngitis usually presents as the rather abrupt onset of pharyngeal pain, particularly with swallowing (odynophagia). The severity of the pain is variable, usually being worse in the morning. Odynophagia that is so severe as to preclude

swallowing is uncommon and should prompt one to consider conditions such as epiglottitis, and RPA or PTA. Important causes of acute pharyngitis include the following.

Group *A β-hemolytic streptococcus* (GABHS): GABHS is the most common cause of bacterial pharyngitis in children (see Chapter 260). The typical age range is 3 to 25 years, though sore throat can occur at all ages. Some historical and physical features favor a diagnosis of GABHS over viral etiologies of acute pharyngitis, including younger age, higher fever, absence of a cough, anterior cervical adenitis, and tonsillar exudates. However, weighted scoring systems utilizing these criteria have not demonstrated high sensitivity or specificity (Centor Criteria as modified by McIsaac) (1) though they may identify patients in whom testing is cost effective (Table 66.2) (2).

TABLE 66.2
Clinical Scoring Systems and Likelihood of Positive Throat Culture for Group A Streptococcal Pharyngitis

Criteria	Points
Fever (temp >38° C)	1
Absence of cough	1
Tender, swollen anterior cervical nodes	1
Tonsillar swelling or exudate	1
Age	
3–<15 yrs	1
15–<45 yrs	0
45+ yrs	−1

Neisseria gonorrhoeae: This sexually transmitted disease may occur independent of a genital infection and is of variable severity. Gonococcal pharyngitis is an important source of gonococcemia.

Corynebacterium diphtheriae: This bacterium is a potentially lethal cause of pharyngitis. Sore throat and dysphagia are prominent symptoms, and patients exhibit a grey–white pharyngeal mucosal membrane of varying size. Airway obstruction may follow. Despite

immunization, large portions of the adult population in the United States lack immunity to the diphtheria toxin.

Viral infections: Viruses are common infectious causes of pharyngitis in adults and children (Table 66.1).

Stevens–Johnson syndrome (SJS): SJS is an immune-mediated hypersensitivity disorder that is a severe expression of erythema multiforme. It usually involves the skin and the mucous membranes and may cause severe erythema, edema, sloughing, blistering, ulceration, and necrosis of the oropharyngeal mucous membrane. Four etiologic categories have been identified: infectious (e.g., herpes simplex virus and mycoplasma), drug induced (e.g., sulfonamides and phenytoin), malignancy related, and idiopathic. SJS may be fatal.

Pemphigus: This is a group of rare autoimmune blistering diseases of the skin and/or mucous membranes. Pemphigus vulgaris is characterized by sores and blisters that almost always start in the mouth and carries a moderate to high mortality rate if unrecognized and untreated.

Retropharyngeal Abscess

RPA is more often a disease of young children usually occurring when lymph nodes in the retropharyngeal space become infected. These lymph nodes involute by puberty. In adults, RPA may be caused by direct trauma or extension of a local infection, such as Ludwig's angina, odontogenic infections, or mycobacterial osteomyelitis of the cervical spine (Pott's disease) (3). Traumatic causes include blunt and penetrating neck wounds, which have the potential to develop the delayed complication of an abscess, and iatrogenic injuries secondary to intubation or endoscopy. Uncommon causes include sinusitis, and otitis media. RPAs tend to be polymicrobial, with *Streptococcus* sp, *Staphylococcus* sp, and anaerobes most commonly recovered when cultured.

Peritonsillar Cellulitis and Abscess

PTA is a complication of tonsillitis. It occurs more frequently in teenagers and younger adults, but it can present at any age, especially in immunocompromised or diabetic patients. The abscess forms in the potential space between the lateral aspect of the tonsillar capsule and the superior constrictor muscle of the pharynx. When tonsillitis spreads beyond the tonsil capsule, inflammation in this space results in cellulitis and abscess if left untreated. Abscess cultures tend to be polymicrobial, with the frequent presence of GABHS and anaerobes such as *Bacteroides*. *Lemierre syndrome* is septic thrombophlebitis of a neighboring internal jugular vein, usually caused by *Fusobacterium necrophorum*. It may be complicated by septic pulmonary emboli.

Supraglottitis/Epiglottitis

Supraglottitis is an acute disorder that usually produces substantial throat pain but is not generally considered a variant or a complication of acute pharyngitis. Strictly speaking, the term supraglottitis more appropriately defines the condition because the pathologic changes involve not only the epiglottis but also the aryepiglottic folds and false cords. *H. influenzae* type b was traditionally the most common bacterium found in blood cultures, but *S. pneumoniae* is also common.

ED EVALUATION

History

As with any presenting complaint, the onset, location, radiation, duration, quality, timing, and exacerbating and remitting factors of the pain or discomfort ought to be elicited. Throat pain of acute onset is common. If the diagnosis of acute infectious pharyngitis is obvious, an overly detailed evaluation is not necessary. If the etiology is not clear, a more complete evaluation is indicated and should include the following questions: Was pharyngeal trauma involved? Is a foreign body such as an impaled fish bone suspected? Has a caustic, irritative, or thermal agent been inhaled or ingested? Is this a single episode of throat pain, or recurrent? Does the pain

vary day to day, morning to evening, or is it seasonal? How long has the pain persisted? Is the pain positional? Does mouth opening or closing affect the pain? Is the pain associated with meals or certain types of foods?

The patient is often able to localize the origin of the pain (i.e., the nasopharynx, the oropharynx, or the hypopharynx). The pattern of pain radiation may indicate the location of a lesion, as painful swallowing is associated with faucial, lingual, oropharyngeal, or hypopharyngeal disorders. Pain in the throat brought on by exertion and relieved by rest may represent cardiac ischemia.

Associated symptoms such as the presence or absence of cough, fever, and coryza should be noted. Additional historical features such as earache, stiff neck, hoarseness, odynophagia, pain on protruding the tongue, trismus, facial pain, alterations in taste, or halitosis may be helpful. A history of contact with sources of infection is important, particularly in close social settings.

Physical Examination

Attention should be directed to the patient's general appearance and vital signs, including oxygen saturation. Signs suggestive of upper airway obstruction or sepsis must be quickly noted and addressed.

Patients with deep-space neck infections and epiglottitis may be much sicker and appear toxic, dehydrated, and febrile. The patient with an RPA may hold the head stiff or lean it to one side in the case of a PTA, as motion of the head and neck elicits pain. Anterior or lateral displacement of the larynx may be noted in an RPA or deep-space infection, and patients with Lemierre syndrome may present with anterolateral neck pain and swelling.

The face and anterior neck should be examined for sinus tenderness, parotid tenderness, or induration, fullness or masses in the mandibular space, lymphadenopathy, tenderness along the carotid sheath, pain on laryngeal manipulation (may indicate epiglottitis or parapharyngeal abscess), thyroid tenderness, and cervical spine mobility.

The carotids should be auscultated for bruits, and the oral cavity should be inspected. Trismus is often present with PTA but not with uncomplicated RPA or epiglottitis. Inflammation, mucosal ulcerations, purulence, and masses ought to be noted. There may be distortions of normal anatomy in patients with a deep-space abscess (e.g., palatopharyngeal arches, soft palate, posterior pharyngeal wall). In the case of RPA, the posterior pharyngeal wall may be displaced forward toward the uvula (Fig. 66.1). A PTA displaces the tonsil downward, medially, and deviates the uvula to the opposite side (Fig. 66.2). A process more caudal in the neck may show no abnormalities on oral examination.

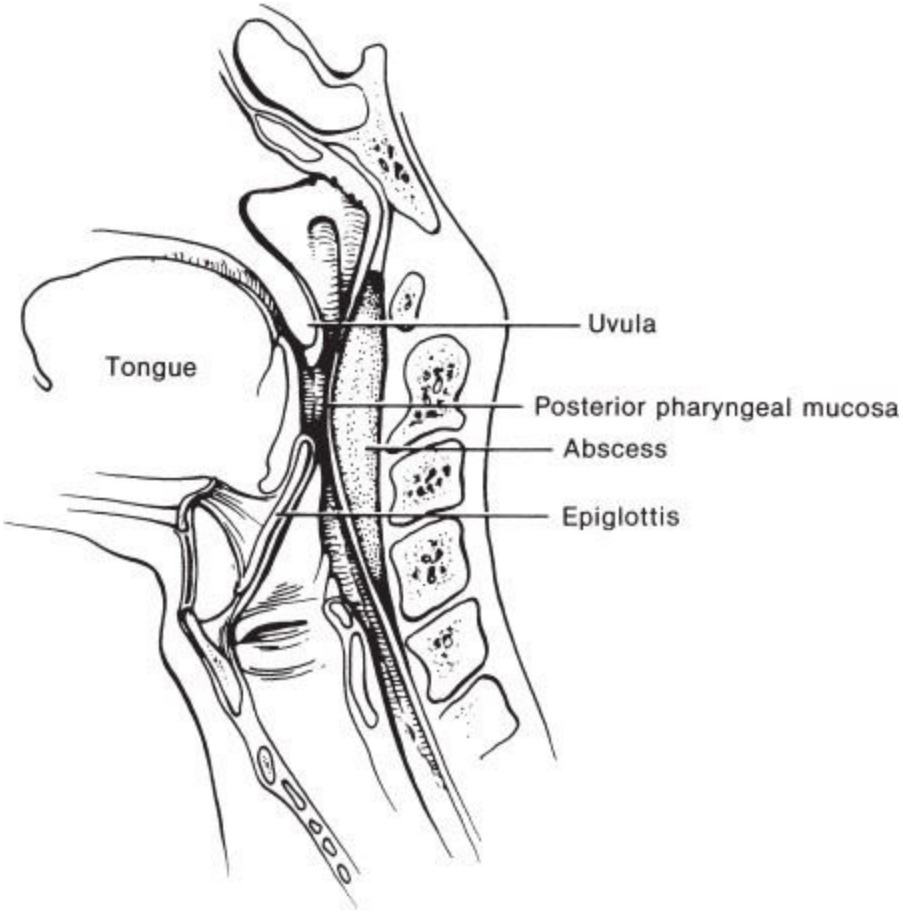

FIGURE 66.1 Retropharyngeal abscess.

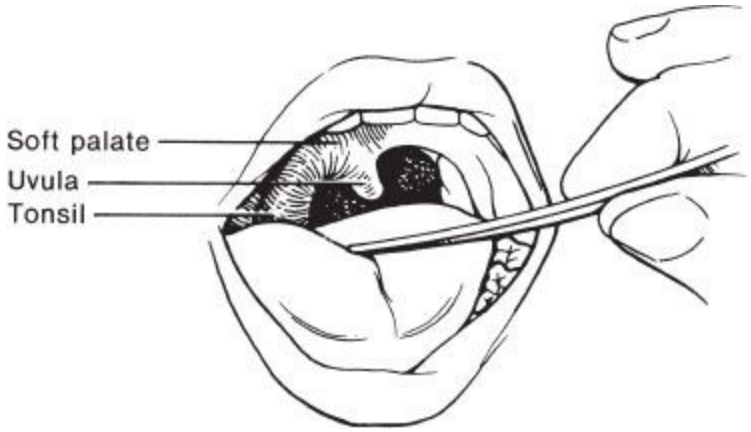

FIGURE 66.2 Peritonsillar abscess.

The use of a tongue depressor to facilitate the exposure of oral and pharyngeal structures has generated some controversy because of the prohibition placed on such a maneuver in evaluating the pediatric patient with suspected epiglottitis. With this exception, there ought to be no reluctance to utilize this maneuver. The patient is asked to protrude the tongue as part of this examination, and the presence of pain is noted.

Palpation of the floor of the mouth, the peritonsillar areas and the base of the tongue presents the risk of being bitten or provoking the gag reflex, but it may be indicated if an oral or lingual abscess or lesion is suspected. Lidocaine 5% ointment applied to the base of the tongue or lidocaine 4% aqueous to gargle prior to palpation may attenuate or eliminate these responses. Although palpation of the posterior pharyngeal wall may confirm the diagnosis of RPA, this maneuver is not recommended because of the risk of rupturing the abscess into an already compromised airway.

If a nasopharyngeal or hypopharyngeal lesion is suspected but not visible on direct examination, flexible endoscopic nasopharyngoscopy may be undertaken, particularly in the case where symptoms are ‘out of keeping’ with physical findings and supraglottitis is suspected. Preparation should include the administration of a vasoconstrictor nasal spray (e.g., 0.25% phenylephrine), topical anesthesia for the nasal mucosa (e.g.,

lidocaine 4% atomized or by pledgets), and oropharyngeal topicalization as described above.

Diagnostic Imaging

Radiologic studies are not indicated in most patients with sore throat. However, when one suspects the presence of RPA or supraglottitis, the following studies may be useful.

Lateral soft tissue x-ray: Plain films have some utility in detecting a thickened prevertebral stripe (as in RPA) or swollen epiglottis. Moderately sensitive and specific, these studies cannot be relied upon to exclude these potentially life threatening conditions (4).

Indirect endolaryngoscopy and ultrasound: Recent advances in ultrasound applications have identified this modality as effective in diagnosing upper airway conditions, particularly epiglottitis (5,6).

CT scan: Contrast-enhanced computed tomography scanning is the imaging study of choice in defining the extent of deep-space neck infection in peritonsillar, retropharyngeal, and parapharyngeal abscesses, if the patient is cooperative and sufficiently stable to lay flat for the study. Ultrasound and magnetic resonance imaging (MRI) may also be useful in some cases (5,6).

Laboratory

General laboratory studies such as complete blood count, coagulation profiles, electrolyte studies, and renal and hepatic function are not helpful unless otherwise indicated. A blood sugar determination may be useful in diagnosing an occult diabetic.

Culture of a throat swab on a sheep blood agar plate is considered the gold standard for confirmation of acute GABHS pharyngitis (7). Rapid antigen detection tests (RADTs) have supplanted throat culture in many clinical settings as they are easily done, reasonably reliable, and give immediate results. *N. gonorrhoeae* and *C. diphtheria,* if suspected, require specific collection techniques and culture media.

Guidelines promulgated by the American College of Physicians (ACP), the American Academy of Family Physicians (AAFP), and the

Centers for Disease Control and Prevention (CDC), the Infectious Diseases Society of America (IDSA), and the American Heart Association (AHA)–American Academy of Pediatrics do not recommend throat swabbing or rapid antigen detection testing when there are no clinical features suggestive of streptococcal infection as identified in Table 66.2 (2). In the event that clinical suspicion is high and RADT is negative throat swabbing has been recommended. The recent development of chemiluminescent single-stranded DNA probe that detects specific rRNA sequences unique to GABHS has been shown to be highly sensitive and specific and considered by some to be equivalent to throat culture as a confirmatory test. The IDSA recommends routine confirmation of negative RADTs by culture or DNA probe unless the patient is treated. However, the cost-effective nature and medical necessity of this practice in adults has been questioned because of its substantial cost, delay in antibiotic prescribing, and because suppurative complications are very uncommon (7).

KEY TESTING

For suspected supraglottitis:
- Video laryngoscopy (flexible, stylette, blade)

For suspected GABHS pharyngitis of intermediate suspicion, consider:
- Rapid antigen detection testing
- Throat swab or DNA probe (controversial)

For suspected RPA:
- CT scan

ED MANAGEMENT

Initial attention should be directed to the airway, breathing, and circulation (ABCs) and immediate life threats. The patient is observed for signs of airway compromise, and the vital signs are examined for evidence of cardiovascular compromise. The four cardinal signs of upper airway obstruction include muffled voice (hot potato voice), difficulty swallowing secretions, dyspnea, and

stridor. Although the first two may not herald imminent upper airway obstruction, dyspnea and stridor are much more sinister. The presence of stridor generally indicates that the airway has been reduced to 4.5 mm or less (8). Any of these findings in a patient who insists on sitting upright to breathe should prompt an immediate upgrade to an acute resuscitation area in the ED for possible airway management.

The treatment of sore throat without airway compromise is mostly symptomatic, utilizing gargles and mild analgesics. Ulcerated, extremely painful lesions may be dabbed with a cotton-tipped swab containing a solution of 4% lidocaine and bismuth subsalicylate (Kaopectate) (to make it adhere), though the efficacy of this therapy in relieving pain is anecdotal and unproven. Some have reported that adults with moderate to severe pharyngitis obtain relief of symptoms sooner if treated with IM or oral dexamethasone (9).

GABHS

A number of antibiotics have been shown to be effective in treating GABHS pharyngitis, including penicillins, cephalosporins, macrolides, and clindamycin. Penicillin remains the agent of choice because of its proven efficacy, safety, narrow spectrum, and low cost (2). Patients with acute infectious mononucleosis treated with ampicillin or amoxicillin may develop a rash.

Supraglottitis

Patients with severe airway compromise or obstruction must receive immediate airway management in the ED. Patients with mild dyspnea or respiratory complaints may be closely monitored in the intensive care setting. Indirect flexible or rigid videolaryngoscopy is helpful in evaluating the adequacy of the airway in these patients and as a guide to the aggression of therapeutic maneuvers. The antibiotic of choice on empiric grounds is cefuroxime, cefotaxime, ceftriaxone, or ampicillin–sulbactam (Unasyn). Though some

recommend the use of steroids, scientific evidence is lacking. Aerosolized epinephrine is not thought to be useful.

Retropharyngeal Abscess

Intravenous fluids and intravenous antibiotics such as high-dose penicillin (6 million units every 6 hours) and metronidazole (500 mg every 6 hours after a 1 g loading dose), or cefoxitin (2 g every 8 hours) should be started immediately. An otolaryngology consult should be obtained early. Patients should be admitted to the intensive care unit or taken directly to the operating room. Definitive management includes incision and drainage under carefully controlled circumstances. The presence of mediastinitis mandates a surgical consult.

Peritonsillar Cellulitis

Intravenous fluids should be given to correct dehydration, and intravenous antibiotics should be initiated. Penicillin (1 to 2 million units every 4 hours) or clindamycin (600 mg every 8 hours) are good choices. Early cellulitis may be treated with hydration and antibiotics alone, though it may be difficult to differentiate from abscess. Needle aspiration may provide both diagnostic information and therapeutic benefit if abscess is present. Lemierre syndrome is primarily treated with intravenous antibiotics with anaerobic coverage.

Peritonsillar Abscess

In addition to the antibiotic regimen described for peritonsillar cellulitis, diagnostic and therapeutic needle aspiration is indicated (10). With the patient in the sitting position and hunched slightly forward, topical anesthetic is applied to the posterior pharynx. The patient should be told that although an initial puncture will be felt, the procedure is likely to reduce the pain significantly. Aiming posteriorly toward the medial aspect of the enlarged tonsil, an 18- or 20-gauge needle is inserted to a depth of 2 cm, aspirating during

insertion. Insertion of the needle more than 2 cm runs the risk of puncturing the internal carotid artery.

CRITICAL INTERVENTIONS

- Provide emergency airway management for patients with impending airway obstruction, such as severe epiglottitis or RPA.
- Initiate antibiotic therapy promptly for serious throat infections.

DISPOSITION

All patients with signs of upper airway obstruction should be admitted. Immunocompromised patients may need to be admitted to hospital for aggressive intravenous antibiotic and fluid management and continuous observation.

All patients with epiglottitis or RPA, whether or not they are intubated, should be admitted to a high acuity unit for close observation.

Nonimmunocompromised patients with uncomplicated, peritonsillar cellulitis that can take fluids and medications orally may be discharged, provided they are in the company of a reliable caretaker and close follow-up is arranged.

Patients with PTA can be discharged on appropriate antibiotic therapy after successful aspiration or incision and drainage. If the treatment does not relieve severe symptoms, or if there is any suspicion of spread of infection beyond the peritonsillar area, admission for further evaluation and treatment will be required.

Almost all patients with simple pharyngitis can be treated as outpatients, with follow-up as needed.

Common Pitfalls

- Overtreatment of pharyngitis, most of which are viral in etiology, with antibiotics.
- In a patient with severe symptoms, excluding the diagnosis of supraglottitis without visualization of the epiglottis and surrounding structures.

- Underestimating the severity or potential for airway compromise in patients with RPA or PTA.

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CHAPTER 67

Sinusitis and Rhinitis

Hagop M. Afarian

Upper respiratory complaints, including sinusitis, are among the most common disorders encountered by the emergency physician. It is estimated that 14% of the US population, approximately 31 million people, are treated annually for diseases of the paranasal sinuses, costing approximately 5.8 billion dollars each year (1,2). Sinus disease is usually a harmless inconvenience; however, it occasionally presents as a fulminant, life-threatening entity in the ED.

Sinusitis is an inflammatory disease of the paranasal sinuses resulting from infectious, allergic, or autoimmune processes (3). Rhinitis strictly means inflammation of the nasal mucous membranes. Rhinitis may be caused by allergic (most common), nonallergic, infectious, hormonal, occupational, and other factors (4). This chapter will focus on rhinitis as part of a broader infectious disease spectrum. Rhinosinusitis has been proposed as a more precise definition, as inflammation frequently involves the nasal passages, and sinusitis without rhinitis is rare (5).

The human sinuses are composed of four paired, sterile cavities lined with ciliated, columnar epithelium. Maxillary and ethmoid sinuses are present at birth. Frontal and sphenoid sinuses develop in the 7th and 10th year of life, respectively (6). Individual sinus anatomy is highly variable, with frontal sinuses absent in 2% to 5% of the population (7). The posterior ethmoid and sphenoid sinuses empty into the superior meatus. The frontal, anterior ethmoid, and maxillary sinuses empty into the ostiomeatal complex within the middle meatus. Obstruction of the ostiomeatal complex (OMC)

caused by inflammation, anatomic abnormality, or other pathology is the critical event in the development of acute sinusitis (6). Maxillary sinusitis is most common, followed by ethmoid, frontal, and sphenoid (1).

A practice guideline published in the 2007 *Journal of Otolaryngology: Head and Neck Surgery* classified sinusitis into acute (<4 weeks), subacute (4 to 12 weeks), chronic (>12 weeks) with or without acute exacerbations, and recurrent acute (having four episodes of sinusitis within 1 year with complete resolution of symptoms between each episode) (2).

The exact incidence and prevalence of sinusitis is difficult to determine because of a lack of rigid criteria defining sinus disease. Women are affected approximately twice as often as men (8). An estimated 0.5% to 2% of upper respiratory infections (URIs) in adults and 5% of URIs in children are complicated by acute bacterial sinusitis (8). Furthermore, up to 16% of Americans suffer from chronic sinusitis (2,9).

Most cases of sinusitis follow a viral URI. Viruses injure the sinus epithelium, resulting in ciliary dysfunction and an inflammatory cascade. Mucostasis and a damaged epithelium make the sinuses susceptible to secondary bacterial invasion. Inflammation results in occlusion of the OMC, obstructing sinus drainage and creating a hypoxic, hypercarbic, acidic environment with negative pressure, promoting bacterial growth (10).

Other factors contribute to the development of sinusitis. Five percent to 10% of acute maxillary sinusitis occurs because of contiguous spread of dental infection (9). Ciliary motility disorders, both congenital (Kartagener syndrome) and acquired, predispose to sinusitis. Inflammatory changes and anatomic abnormalities (polyps, adenoids, tumors) can result in OMC occlusion. Nasal foreign bodies also result in OMC obstruction, leading to sinusitis; 95% of nasally intubated patients develop sinusitis (9). Immunocompromised patients are more susceptible to the development of sinusitis and are more likely to have severe disease (9).

Infectious sinusitis can be of viral, bacterial, or fungal origin. Viral rhinosinusitis is 20 to 200 times more common than bacterial

sinusitis (11). Over 200 viruses have been implicated, with subtypes of rhinovirus, parainfluenza, and influenza virus being the most common (12). *Streptococcus pneumoniae* (30% to 40%), nontypeable *Haemophilus influenzae* (30% to 40%), *Moraxella catarrhalis, Staphylococcus aureus,* other streptococcal species, and anaerobes of dental origin compose the primary pathogens in acute bacterial sinusitis (8). Viral infections predominate in the first 10 days followed by a predominance of aerobic bacteria for up to 3 months and then anaerobic bacteria thereafter (10). *Pseudomonas* sp is an important pathogen in patients with cystic fibrosis and HIV and those with nasal tubes. Fungal sinusitis may present as an acute fulminant or a chronic indolent process. Mucoraceae species including *Rhizopus* sp, *Mucor* sp, and *Absida* sp cause necrotizing invasive disease, most often in patients with diabetic ketoacidosis (13). *Aspergillus* sp are becoming a more common pathogen, manifesting in one of the three chronic forms in immunocompetent adults: indolent invasive, mycetoma ("fungus ball"), and allergic fungal sinusitis, the most frequent form of fungal sinusitis in the United States (14).

CLINICAL PRESENTATION

The clinical presentation of acute sinusitis is highly variable, but usually includes purulent nasal discharge, congestion, facial pressure, dental pain, fever, headache, cough, fatigue, halitosis, or a diminished sense of smell. Many of the symptoms are indistinguishable from those of a viral URI; thus duration of symptoms becomes critical in diagnosis. A patient with cold symptoms not resolving after 7 to 10 days has a higher likelihood of acute bacterial sinusitis (11).

Systemic toxicity, mental status changes, severe headache, and fever are signs and symptoms indicative of a more serious sinus disease and its complications (7). Periorbital cellulitis is the most common complication of sinusitis, usually originating from the ethmoid sinuses (15), and must be differentiated from orbital cellulitis (see Chapter 60). Intracranial complications of sinusitis

include meningitis, osteomyelitis, cavernous sinus thrombosis, and intracranial abscesses (epidural, subdural, and intracerebral). Fifteen percent of meningitis cases may be of paranasal sinus origin (7). Extension of acute frontal sinusitis with suppurative inflammation of cortical bone results in the Pott puffy tumor, a condition requiring aggressive surgical and antimicrobial therapy (15). Cavernous sinus thrombosis presents with periorbital edema, exophthalmos, papilledema, and cranial nerve III, IV, and VI palsies. Intracranial abscesses will usually present with fever and acute neurologic signs, and 33% of patients develop long-term morbidity, including blindness, hemiparesis, seizure disorders, and cognitive impairment (7).

Special consideration must be given to the immunocompromised host with sinus complaints, as invasive fungal sinusitis is much more common in this population. Patients are typically toxic and may present with moldy smelling, thick, brown or black nasal discharge. The nasal mucosa may become gray and eventually necrotic from fungal–vascular invasion. Perforation of the palate, nasal septum, or cribriform plate may be apparent (14). The invasive organisms cause ischemic necrosis of the bone and mucosa with hematogenous invasion of the orbit, skin, and brain. Progression to coma and death can occur within hours. Interestingly, acute fungal sinusitis is relatively rare in acquired immune deficiency syndrome (AIDS) patients, presenting as a late-stage phenomenon when CD4 counts drop to $<50/mm^3$ (14). Aspergillus is the most common fungal pathogen in this group.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for sinusitis is broad, as the signs and symptoms of sinus disease are neither sensitive nor specific. Viral URI, nasal polyps, cocaine abuse, allergic rhinitis, and vasomotor rhinitis all may present with symptoms of nasal discharge and congestion. Cerebral spinal fluid rhinorrhea should be considered in a patient with a history of head trauma. Persistent unilateral nasal discharge with epistaxis is concerning for neoplasm or nasal foreign

body (1). Tension, cluster, and migraine headaches and dental disease are alternative diagnoses in the patient whose sinus disease manifests as cephalgia or facial pain.

ED EVALUATION

Acute sinusitis is a diagnosis based primarily on clinical history and physical findings (Table 67.1). Unfortunately, physical examination findings are not specific for acute sinusitis (12). Findings may include mucosal hyperemia, purulent rhinorrhea, nasal airway congestion, crusting of the anterior nares, and facial pain. However, palpable facial tenderness is a poor indicator of underlying sinus infection, and "purulent" discharge is not a reliable indicator of bacterial sinusitis (8). Transillumination has poor correlation with the presence of fluid, poor intraobserver consistency, and poor specificity. Thus, transillumination is of little use in the diagnosis of acute sinus disease (12).

TABLE 67.1
Major and Minor Factors for Diagnosis of Acute Sinusitis[a]

Major[b]	Minor
Facial pain or pressure	Headache
Facial congestion	Cough
Fever	Fatigue
Nasal congestion/obstruction	Halitosis
Purulent anterior nasal discharge	Dental pain
Purulent posterior nasal discharge	Ear pain/pressure
Hyposmia or anosmia	

[a]From the Task Force on Rhinosinusitis (11) and Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis.* 2012;54(8):e72–e112 (8).
[b]Diagnosis requires two major OR one major and two minor factors in a patient with symptoms for more than 7 days.

Radiographic imaging has little role in the diagnosis of acute sinus disease in the ED. Abnormal findings are common in asymptomatic individuals, and findings such as air–fluid levels, sinus opacification, or mucosal thickening have poor sensitivity

(12). Plain radiographs are often normal in patients with acute disease and abnormal in those without disease (12).

Computed tomography (CT) scan is more sensitive than plain films in the detection of sinusitis but is overly sensitive in detecting "disease" (16). Eighty-seven percent of patients with viral URIs have abnormalities consistent with sinusitis on CT (9). Use of CT in the ED should be limited to ruling out other diagnoses such as malignancy. CT is indicated when serious complications of sinusitis are suspected and in patients who are not improving after antibiotic therapy (5,8,16).

Nasal cultures are not helpful in the diagnosis of acute sinusitis, as growth correlates poorly with cultures from sinus aspirates (9). Sinus aspiration, although more specific, is excessive and impractical in the ED. Blood tests are necessary only in patients who show signs of systemic toxicity, CNS involvement, or who have significant comorbid disease or immunosuppression.

As the ED applications of ultrasound expand, it may become one more tool to help in the diagnosis of sinusitis. One study reported high sensitivity and specificity of ultrasonography for sinusitis (17). However, it is operator dependent and feasible only for the frontal and maxillary sinuses.

The lack of a simple, accurate diagnostic test means that physicians must rely on a clinical diagnosis in most cases, but this creates a tendency to label many common colds as sinusitis (1). Duration and severity of symptoms may provide clues in the diagnosis. In acute bacterial sinusitis, symptoms generally last greater than 10 days, worsen after 3 to 4 days or after a period of improvement "double sickening," and are much more severe than those associated with a viral URI (8,11).

KEY TESTING

- Laboratory tests and imaging are not indicated in most patients with rhinosinusitis. Testing should be reserved for toxic, immunocompromised patients or those with a suspected intracranial complication

ED MANAGEMENT

The goal of therapeutic intervention in acute sinusitis is threefold: to relieve obstruction of the OMC, to restore mucociliary clearance, and to reestablish sinus sterility through eradication of infection (6). As acute sinusitis is not purely an infectious process, antimicrobial therapy alone will likely fail (1). Combination treatment with antibiotics, analgesics, topical and systemic steroids, nasal and oral decongestants, mucoevacuents, antihistamines, and nonpharmacologic measures may provide the best symptomatic and therapeutic outcome.

There is some evidence to suggest that both topical and systemic corticosteroids may provide benefit to patients with acute sinusitis. The use of topical steroids in acute sinusitis is attractive, as they are a potent anti-inflammatory agent with few side effects. Some studies have demonstrated improved symptom relief, but the clinical efficacy of topical and systemic steroids remains uncertain (9,12,18). The greatest benefit to both topical and systemic corticosteroids may be when used as adjunctive therapy to antibiotics (8,18).

Topical α-adrenergic agonists, such as oxymetazoline 0.05%, have been used to decrease mucosal edema, promoting sinus drainage. These agents should not be used for more than 3 days as this may elicit *rhinitis medicamentosa* because of rebound vasodilation. α1-Agonists, such as phenylephrine, do not reduce blood flow of the nasal mucosa to the same degree as α2-agonists and therefore are preferred (5). Oral systemic decongestants (ephedrine, pseudoephedrine, phenylephrine, phenylpropanolamine) may be helpful, but side effects, including nervousness, insomnia, hypertension, and tachycardia, may limit their use. Oral decongestants have a weaker effect on the nasal mucosa, but they do not cause the rebound vasodilation noted with topical agents.

The mucoevacuent guaifenesin can be used to increase mucous flow and decrease mucous viscosity (9). Side effects are minimal but may include abdominal discomfort and emesis (12). Antihistamine use in acute sinusitis remains controversial. Although antihistamines

may decrease rhinorrhea, some argue their use is contraindicated as they may cause xerostomia, increasing mucous viscosity, leading to inspissation and outflow obstruction (8). Nonpharmacologic therapy such as steam inhalation and saline rinses provide symptomatic relief by softening crusts and moisturizing dry mucosa. Both isotonic and hypertonic solutions can be used for nasal irrigation, without significant evidence to support one over the other (19).

Although treatment of acute sinusitis requires a multifaceted regimen, the main question remains whether or not to use antibiotics. In 2012 the Infectious Diseases Society of America (IDSA) published a clinical practice guideline to provide recommendations for the treatment of bacterial sinusitis (8). Antibiotics are frequently prescribed, but great controversy exists regarding indications for use, choice of antimicrobial agent, and duration of therapy (20). Many studies suggest that in the majority of patients, acute sinusitis resolves quickly with or without antibiotics. Mild cases of rhinosinusitis with symptoms lasting less than a week are most likely viral in etiology and should not be treated with antibiotics (11). Symptoms lasting more than 10 days, worsening after 3 to 4 days, or after a period of improvement "double sickening" are more likely to be bacterial (8). Severe cases with significant pain, fever, and comorbidities should be treated with first-line antibiotics, while nonsevere cases should only be treated with antibiotics if there are no signs of improvement after 7 to 10 days (2).

Amoxicillin is still a first-line agent of choice in acute sinusitis, however, with increasing rates of resistance, there is evidence, greater in children than adults, to support use of amoxicillin–clavulanate as first-line empiric therapy (Table 67.2) (8). Most studies show no difference in efficacy between antibiotics, although high-dose therapy is recommended in areas with higher rates of penicillin-nonsusceptible *S. pneumoniae* (3,8). Empiric therapy with trimethoprim–sulfamethoxazole and macrolides are no longer recommended in the treatment of acute bacterial rhinosinusitis because of high rates of resistance, while doxycycline continues to remain effective (8). While there have been reports of acute

bacterial rhinosinusitis due to methicillin-resistant *Staphylococcus aureus* (MRSA), routine empiric treatment for MRSA is not typically indicated (8). Recommendations for duration of therapy span from 5 to 7 days to 10 to 14 days (1). A small number of studies have shown 3 days of therapy can be as effective as longer courses of treatment (21). Second-line agents should be initiated in cases that fail first-line therapy (8,11). The natural course of untreated acute sinusitis is unknown, but it is estimated that many, if not most, cases resolve without treatment (3). In the midst of the antibiotic controversy, it is important to remember the importance of basic symptomatic treatment.

TABLE 67.2
Antibiotic Therapy Alternatives in Acute Sinusitis[a]

Drug	Dose (Adult)	Dose (Pediatric)
First-Line Therapy		
Amoxicillin (high dose)	1 g PO tid × 10 d	90 mg/kg/d max of 3 g/d PO divided bid × 10–14 d
Amoxicillin/ clavulanate	875/125 mg PO bid × 10 d	45 mg/kg/d Amox + 6.4 mg/ kg/d Clav PO divided bid × 10–14 d
Second-Line Therapy		
Amoxicillin/ clavulanate	2,000/125 mg PO bid	90 mg/kg/d Amox + 6.4 mg/ kg/d Clav PO divided bid × 10–14 d
Doxycycline	100 mg PO bid or 200 mg PO qd	Not recommended for children
Cefprozil	250–500 mg PO bid × 7–14 d	7.5–15 mg/kg PO divided bid 10–14 d
Cefdinir	300 mg PO bid or 600 mg PO qd × 7–14 d	14 mg/kg PO divided qd or bid 10–14 d
Cefpodoxime proxetil	200 mg PO bid × 7–14 d	15 mg/kg PO divided bid × 10–14 d
Azithromycin	500 mg PO qd day 1 then 250 mg/d on days 2–5	10 mg/kg PO qid on day 1 followed by 5 mg/kg PO qid days 2–5
Clarithromycin	500 mg PO bid for 14 d	6 mos and older 15 mg/kg/d (divided bid) for 10 d, max 1 g/d
Third-Line Therapy		
Levofloxacin	750 mg PO qd × 5 d or 500 mg PO qd × 10 d	Safety and efficacy in children under 18 yrs of age have not been established
Moxifloxacin	400 mg PO qd × 10 d	

[a]Adapted from Gilbert DN, Moellering RC, Eliopoulos GM, et al. *The Sanford Guide to Antimicrobial Therapy 2010.* 40th ed. Sperryville, VA: Antimicrobial Therapy, Inc.; 2010:47; and Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis.* 2012;54(8):e72–e112(24).

PO, by mouth; qd, once daily; tid, three times a day; bid, twice a day; qid, four times a day.

Special consideration is needed for managing sinusitis in children, the elderly, and immunocompromised patients. Children with recurrent acute sinusitis or chronic sinusitis, despite aggressive therapy, should be referred for evaluation for cystic fibrosis or underlying immune dysfunction (6). In elderly patients, the threshold for treating acute sinusitis should be lower, as aggressive

medical intervention may be important in reducing morbidity in this group (12). In immunocompromised patients, increased alertness for fulminant sinusitis and its complications is necessary. The initial treatment of acute sinusitis is essentially the same regardless of HIV status, except for duration of antimicrobial therapy: 21 days of therapy is recommended (22). In patients with CD4 counts of $>200/mm^3$, opportunistic sinus infections are more common and are more resistant to standard therapy (23). In addition, those patients who have had a recent hospitalization within the last 5 days or who have taken antibiotics within the last month are at higher risk for failure of first-line therapy, and second-line therapy should be considered instead (8).

Patients with severe headache, altered mental status, systemic toxicity, meningeal signs, or visual complaints suggestive of intraorbital or intracranial extension require aggressive evaluation and management. Administration of broad-spectrum antibiotics, generally a third-generation cephalosporin plus vancomycin, should not be delayed by diagnostic procedures (3). This treatment should be followed by CT, lumbar puncture, and appropriate consultation (1).

CRITICAL INTERVENTIONS

- Promptly initiate antibiotic therapy for severe cases of sinusitis in elderly, immunocompromised, or toxic patients.
- Order imaging studies and initiate parenteral antibiotics early in patients with suspected intracranial complication of sinusitis.

DISPOSITION

Most patients with acute, uncomplicated sinusitis or rhinitis can be safely discharged with instructions to return to the ED or follow up with their regular doctor if symptoms are worsening or not improving within several days. Patients should be educated on the signs of potential intracranial extension (severe headache, vomiting, and confusion) and advised to return to the ED immediately. Patients with sinus symptoms lasting longer than 1 month, despite a

complete course of therapy, should be referred to an otolaryngologist for further evaluation (1).

Patients with intracranial extension of sinus disease require aggressive parenteral antibiotics and hospital admission, often to a critical care setting. Transfer to a referral center is necessary if a specialist is not readily available for these patients. Appropriate stabilization efforts and intravenous antibiotic therapy should be initiated prior to transfer, and advanced cardiac life-support-capable transport by ground or air is necessary.

Common Pitfalls

- Routine radiographic imaging in the setting of acute uncomplicated sinusitis adds little to the evaluation and is often misleading.
- Overuse of antibiotics in healthy patients with symptoms for less than 1 week.
- Failure to recognize signs of a serious complication. Patients with sinusitis and marked headache and fever must be carefully evaluated, with increased concern in the elderly or immunocompromised patient.

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CHAPTER 68

Ear Infections in Adults

Michael Cole and Sukhjit S. Takhar

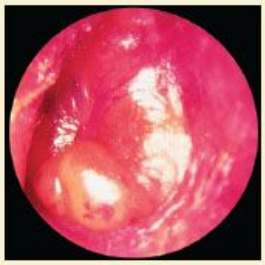
The vast majority of ear infections in the antibiotic era are benign and self-limited. However, there are certain life-threatening conditions that require prompt diagnosis and treatment (eTable 68.1).

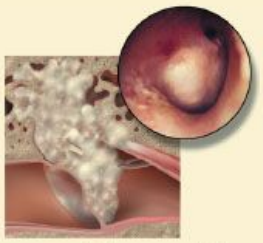
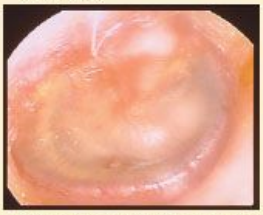
TABLE 68.1
Therapeutic Options for the Management of Otitis Externa[a]

Drug	Dosage	Comments
VoSol Otic HC (2% acetic acid)	4 drops every 6 h for 7–10 d	Use only in mild disease when the tympanic membrane can easily be visualized
Ciprofloxacin otic HC Ofloxacin otic HC	4 drops every 12 h for 7–10 d	More expensive. Very high topical levels may overcome resistance.
Neomycin/polymyxin B/hydrocortisone	4 drops every 8 h for 7–10 d	Can cause contact dermatitis. Do not use if the tympanic membrane is ruptured.

[a]Note: Removal of debris from the ear canal should always be performed prior to antibiotics administration.

eTABLE 68.1
Most Common Etiologies of Ear Pain

Diagnosis	Symptoms/Signs	Typical Treatment	Example
Acute Otitis Externa	Erythema of ear canal Edema of ear canal Otorrhea	Cleaning the ear canal Topical agents (e.g., antibiotics, acetic acid)	
Acute Otitis Media	Middle ear effusion Limited TM* mobility on pneumotoscopy Erythematous TM Bulging TM	Oral antibiotics Watchful waiting in otherwise healthy patients	
Mastoiditis	Inflammatory changes over the mastoid process Tenderness of the mastoid process Displacement of the auricle by inflammation and edema	Intravenous Antibiotics Consider emergent otolaryngology and/or Infectious disease consult in moderate to severe cases	 From Fleisher GR, Ludwig W, Baskin MN. *Atlas of Pediatric Emergency Medicine.* Philadelphia, PA: Lippincott Williams & Wilkins; 2004
Auricular Cellulitis	External Ear is: Erythematous Tender Warm Ear Lobule may be affected	Oral or Intravenous antibiotics depending on severity of disease	 Courtesy of Steven D. Handler, MD, MBE
Perichondritis	External Ear is: Erythematous Tender Warm Ear Lobule is spared Piercing often present	Oral or intravenous antibiotics depending on severity of disease Consider emergent otolaryngology and/or Infectious disease consult in moderate to severe cases	 Used with permission from Handler SD, Myer CM. *Atlas of ear, nose and throat disorders in children.* Ontario, Canada: BC Decker; 1998:12

Diagnosis	Symptoms/Signs	Typical Treatment	Example
Cholesteatoma	Collect of keratinized epithelial cells on TM Asymptomatic or hearing loss, dizziness	No acute treatment Otolaryngology referral	 Asset provided by Anatomical Chart Co
Bullous Myrinigitis	Painful vesicles on TM Often mycoplasma infection	Antibiotics—similar spectrum as acute otitis media	 The Wellcome Trust, National Medical Slide Bank, London, UK
Otitis media with effusion	Middle ear effusion without signs of acute inflammation	None. Self limiting	 Courtesy of Alejandro Hoberman, Children's Hospital of Pittsburgh, University of Pittsburgh

[2]TM = Tympanic Membrane.

ACUTE OTITIS EXTERNA

Acute otitis externa (AOE) is a diffuse inflammatory condition of the external ear canal. Knowledge of the anatomy helps to understand AOE and its complications. The external ear is composed of the external auditory canal (EAC) and the auricle. The outer portion of the external canal is cartilaginous with a well-developed dermal layer. The inner, or osseous, portion is lined by a thin layer of epithelium that is firmly attached to the periosteum of the temporal bone (Fig. 68.1). The narrowest part of the canal is the osseous–cartilaginous junction. Cerumen is produced by the apocrine glands and is required for a healthy ear canal. It is a thin, acidic, protective coat that is inhospitable to many microorganisms including those most commonly implicated in AOE (1).

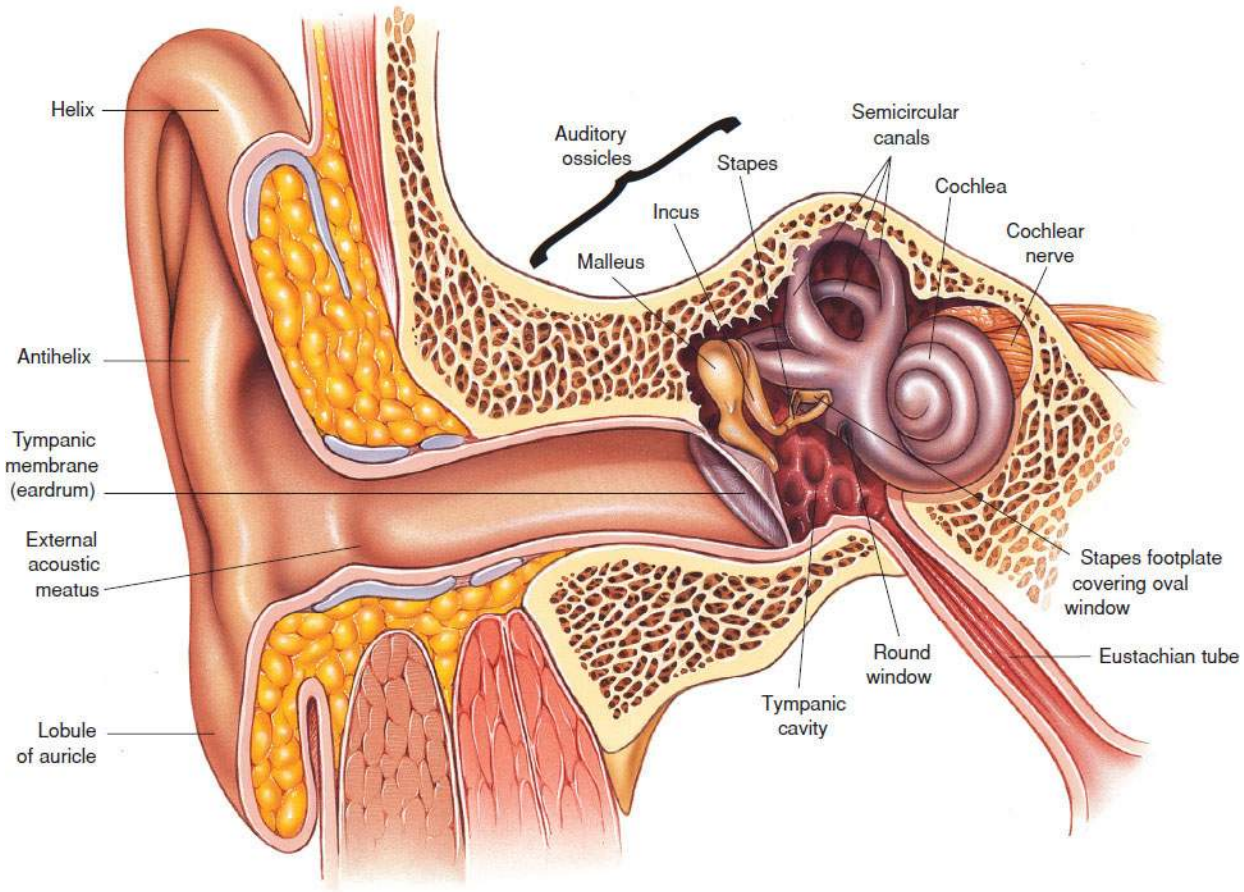


FIGURE 68.1 Anatomy of the middle ear. Asset provided by Anatomical Chart Co.

The overlying squamous epithelium of the inner portion can be disrupted by direct trauma, prolonged use of ear plugs, ear phones or hearing aids, or maceration from prolonged water exposure, providing the initial insult that leads to infection (2). A warm, humid environment promotes bacterial growth. AOE, often known as *swimmer's ear,* occurs most often in the summer months and in tropical climates with *Pseudomonas aeruginosa* and *Staphylococcus aureus* being the most common pathogens (3,4). Fungal infections are typically seen in chronic disease and occasionally cause AOE.

Invasive otitis externa, also called necrotizing otitis externa or malignant otitis externa, is a rare complication of otitis externa. Essentially it is osteomyelitis of the temporal bone, occurring when the infection spreads from the auditory canal to the temporal bone

and nearby structures, like the cranial nerves. It was originally called *malignant otitis* due to the high associated mortality. It occurs most often in the elderly diabetic patient and occasionally in other immunocompromised patients. *P. aeruginosa* is the responsible organism in up to 98% of cases (5,6).

ACUTE OTITIS MEDIA

Acute otitis media (AOM) is an inflammatory process of the middle ear. It occurs most commonly in young children. In adults, the pathophysiology and treatment are quite similar, with a few noteworthy differences.

Eustachian tube dysfunction is critical in the pathogenesis of otitis media. The tube connects the middle ear cavity to the nasopharynx and provides ventilation and drainage (see Fig. 68.1). Eustachian tube dysfunction may result from an upper respiratory tract infection, allergy, barotrauma, or nasopharyngeal tumor. These inciting factors may lead to congestion and accumulation of fluid behind the tympanic membrane (TM). If this fluid subsequently becomes infected by nasopharyngeal organisms, AOM is the result.

The most common organisms involved in AOM are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* (7,8). Viruses are often present as coinfection agents. Patients with chronic disease can be infected with *Pseudomonas* or *S. aureus.*

Complications of otitis media occur when the infection spreads beyond the confines of the middle ear. Intracranial spread may lead to meningitis, brain abscess, or lateral sinus thrombosis, whereas extracranial spread leads to TM perforation, mastoiditis, subperiosteal abscess, facial nerve paralysis, or petrous apicitis (9,10). Complications have decreased dramatically in the antimicrobial era.

It is noteworthy that the mastoid air cells are connected to the middle ear. In uncomplicated otitis media, patients often have fluid in the mastoid air cells. Therefore the finding of fluid in the mastoid air cells on imaging is nonspecific and requires clinical correlation. Mastoiditis is clinically diagnosed when there is tenderness over the

mastoid prominence, displacement of the auricle posteriorly and inferiorly, and signs of inflammation.

AURICULAR CELLULITIS AND PERICHONDRITIS

Infections of the external ear structures are usually the result of local trauma or extension from a severe case of otitis externa. Auricular cellulitis is an infection of the dermis overlying the external ear and it is most often caused by streptococci or staphylococci.

Perichondritis is infection or inflammation of the perichondrium of the auricular cartilage. Piercing the upper third of the pinna ("high piercing") has become fashionable, and it allows the introduction of bacteria into a poorly vascularized area. Although most infections are due to staph and strep, patients with recent (<1 month) piercings appear to have an increased incidence of pseudomonal infection (11,12). Cosmetic deformity following perichondritis is common and difficult to avoid.

CLINICAL PRESENTATION

The initial symptoms of otitis externa may be pruritus and a sensation of fullness, which can progress to more severe pain, mucopurulent discharge, and hearing loss (13). Infection may spread beyond the ear canal, leading to pain in surrounding soft tissues and lymph nodes. Potential spaces, tissue planes, and fissures in the external ear canal can allow the spread of bacteria to the temporal bone, parotid gland, and the temporomandibular joint. Infection may also spread through the thin, osseous portion of the ear canal to the skull base. Patients with necrotizing external otitis complain of severe, unrelenting pain, often worse at night. Cranial nerve VII (facial) is the most commonly affected, leading to facial paralysis, although others may be involved (5,6).

Patients with AOM develop progressive pain as fluid accumulates in the middle ear, bulging the TM outward. There can also be hearing loss, vertigo, and low-grade fever. Perforation of the TM leads to drainage of pus or blood. This differs from otitis externa in that the pain improves after perforation and drainage occur.

Auricular cellulitis resembles soft tissue infections in other parts of the body. The ear is tender and erythematous in the absence of systemic complaints. Perichondritis is a deeper infection. Patients may present days to weeks after a high piercing. There is localized tenderness and possible purulent drainage and the ear may also appear deformed. The ear lobule is devoid of cartilage and is not involved in perichondritis.

DIFFERENTIAL DIAGNOSIS

A variety of conditions can mimic otitis externa. These conditions may cause otalgia, otorrhea, and/or inflammation of the external ear canal. Commonly, otitis media with a perforation of the TM is misdiagnosed as otitis externa as a result of fluid drainage into the EAC. Chronic otitis media (COM) is defined as recurrent or chronic middle ear infections in the presence of a perforated TM, which may drain either serous or purulent fluid (i.e., chronic suppurative otitis media). Patients with COM have fluid drainage with less inflammation and tenderness of the external ear canal when compared with AOE. Cholesteatoma is a keratinized collection of epithelial cells diagnosed by its distinct appearance with patients being asymptomatic or presenting with hearing loss, dizziness and otorrhea. Herpes zoster oticus (Ramsay Hunt syndrome) presents with vesicles on the TM and adjacent tissues, otalgia and, classically, facial nerve palsy. Bullous myringitis, also characterized by small vesicles on the TM, is classically a manifestation of mycoplasma infection but occurs with other organisms as well. Localized abscesses also occur in the ear canal and are most often due to *S. aureus*. Squamous cell carcinoma of the external ear canal should be considered in an older patient who fails standard therapy for otitis externa. Fungal otitis externa should be considered if the physical examination shows a white or black discharge. Contact dermatitis and seborrheic dermatitis are also mimickers of AOE.

A variety of disorders cause middle ear pain and may be confused with otitis media. Otitis media with effusion (OME) presents with a middle ear effusion without any signs or symptoms of acute inflammatory disease. Antibiotic therapy is not appropriate in these

patients. COM, as described above, may also be mistaken for AOM. Frequently a cholesteatoma is also present. These patients need otolaryngology referral.

Relapsing polychondritis is an autoimmune disease that can involve the auricular cartilage in addition to the cartilaginous tissues in the respiratory tract and aorta. These patients present with complaints and physical examination findings similar to those of infective perichondritis. However, the ear lobe lacks cartilage and thus is spared in relapsing polychondritis.

ED EVALUATION

Acute Otitis Externa

Otitis externa is diagnosed based on history and physical findings. Patients should be questioned about predisposing factors such as water exposure, instrumentation of the ear canal, and immune status. The patient should be questioned about hearing loss, vertigo, and prior infections.

A thorough examination of the head and neck should follow. Patients almost invariably complain of pain with tragal manipulation or otoscope insertion. The ear canal is edematous and narrowed and may be filled with cellular debris. If possible, the external canal should be cleaned for better visualization of the deeper structures and to aid in treatment.

Patients with systemic toxicity should be evaluated for a deeper, invasive infection. The most common organisms are *S. aureus* and *P. aeruginosa.* Patients with a chronically weeping, wet ear are more often infected with *Pseudomonas.* Staphylococcus tends to be associated with a more acute onset of symptoms. Appearance of granulation tissue on the floor of the EAC at the bony–cartilaginous junction is a typical finding in invasive disease. Although patients with invasive otitis externa may be in severe distress, they may remain afebrile with a normal white blood cell count (5,6). High-resolution, CT scan with thin cuts through the temporal bone, is generally the initial imaging study for patients with suspected invasive disease (6).

Acute Otitis Media

Patients with suspected AOM should also be asked about risk factors such as recent respiratory tract infections, a history of tobacco exposure (both primary and secondhand tobacco exposure increases risk), and barotrauma (e.g., air travel or scuba diving). To diagnose acute otitis media, the patient should have 1) acute symptoms, 2) a middle ear effusion, and 3) symptoms of middle ear inflammation. Classic findings (erythema and bulging of the TM) have been shown to be highly suggestive of disease, and a normal TM (one that is concave, gray, and translucent) is helpful in ruling out disease. To avoid overdiagnosis, pneumatic otoscopy is often recommended to confirm middle ear effusion; however this requires a cuffed speculum, and is often impractical in the emergency department. The physical examination should also focus on possible complications of otitis media. In addition to the ear itself, the mastoid process, nasopharynx, and oropharynx should be examined and a cranial nerve examination should be performed. If invasive infection or severe disease is suspected, CT scan with thin cuts through the temporal bone is the initial imaging study of choice (14). Contrast-enhanced CT scans or an MRI should be considered if one is concerned about intracranial complications. Note that fluid in the mastoid sinus found on imaging, *radiologic* mastoiditis, is a nonspecific finding and does not correlate with clinical mastoiditis since other diseases of the ear (AOM, COM, etc.) may result in fluid in the mastoid sinus (15,16). Laboratory tests are often not helpful in the initial examination.

Auricular Cellulitis and Perichondritis

The patient should be questioned about trauma and other exposures such as bites, as well as comorbid conditions. A careful inspection of the external ear is critical. One should also ask about previous history of similar episodes. The external ear structures should be palpated and any deformities or obvious abscesses noted. Early perichondritis can present as tenderness without erythema.

KEY TESTING

- Consider CT scan if invasive disease is suspected.

ED MANAGEMENT

Acute Otitis Externa

The EAC should be cleaned if possible. Purulent debris, cerumen, and desquamated skin should be removed using a wire loop or suctioning. EAC irrigation (aural toilet) using a tepid solution of dilute hydrogen peroxide is also reasonable provided the TM is intact. Cleaning of the EAC can be difficult and painful, but it is a necessary step to allow topical agents to reach the underlying infected tissue. A wick (1/4 inch ribbon gauze or a preformed cellulose sponge) should be placed in the canal if there is significant edema (17). Pain control must also be addressed, with acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or opioids being used as needed.

After cleaning the EAC, topical treatment is recommended for *uncomplicated* AOE (13,15,18–20). Topical agents are safe and effective and provide a high concentration of medication at the site of infection. Typically the active ingredient is an antibiotic or an acid, often combined with a steroid (Table 68.1). If the TM is intact, multiple agents are available to treat AOE (e.g., cortisporin otic, topical aminoglycosides, or topical fluoroquinolones). However, acidifying agents and aminoglycosides should be avoided in patients with a perforated TM owing to an increased risk of ototoxicity. In patients with AOE with a perforated TM, the drug of choice is a topical fluoroquinolone. Regardless of the type of topical agent chosen, therapy should be continued for 7 to 14 days and after each dose it is recommended that the patient lie on their side for 15 to 20 minutes (21). Of course, final antibiotic choices should be made with regards to cost and local microbiologic susceptibilities, when available (21). Although MRSA infections have been increasing, initial treatment for AOE does not need to include specific MRSA coverage (15).

Oral antibiotics for AOE are required in more severe disease and in patients that are severely immunocompromised (e.g., patients with AIDS or those on chemotherapy or immunomodulators) (Table 68.2). Ciprofloxacin 750 mg every 12 hours should be used in suspected pseudomonal infections and cephalexin or dicloxacillin 500 mg PO every 6 hours are appropriate for staphylococcal infections.

TABLE 68.2
Antibiotic Therapy for Invasive Otitis Externa

Drug	Dosage	Comments
Ciprofloxacin	400 mg IV every 12 h 750 mg PO every 12 h	High resistance. Only oral drug for pseudomonas
Piperacillin/tazobactam	4.5 g IV every 6 h	
Ceftazidime/cefipime	2 g IV every 8 h	
Aztreonam	2 g IV every 8 h	If penicillin allergic
Gentamycin/tobramycin	5 mg/kg IV every 24 h	Combine with a β-lactam

Invasive otitis externa requires intravenous antibiotics (see Table 68.2). Pseudomonas is the causative agent in more than 90% of the cases. Pseudomonas has become increasingly resistant to quinolone monotherapy (22), and thus an antipseudomonal β-lactam antibiotic (piperacillin/tazobactam, ceftazidime, imipenem) is the preferred agent in most parts of the United States. A bacterial culture of the ear canal should be sent in patients who require systemic antibiotics.

Acute Otitis Media

There are few good studies on antibiotic treatment of AOM. According to the most recent guidelines from the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) and from the National Institute for Health and Clinical Evidence (NICE) high dose of amoxicillin is currently recommended as first-line treatment (23,24). Placebo studies have demonstrated that patients are much more likely to clear infections due to *H. influenzae* and *M. catarrhalis* than those due to *S. pneumoniae.* There is increasing penicillin resistance in *S. pneumoniae,* but it can be

overcome with higher doses of amoxicillin (Table 68.3). *H. influenzae* and *M. catarrhalis* both produce β-lactamase, an enzyme that can degrade amoxicillin. Patients with more severe disease should be given amoxicillin/clavulanic acid to cover these organisms. Macrolides, cephalosporins or respiratory quinolones such as levofloxacin or moxifloxacin are appropriate for patients with penicillin allergy (23,24). The duration of treatment should be 5 to 10 days, depending on severity of disease and the antibiotic choice.

TABLE 68.3
Antimicrobial Therapy for Uncomplicated Acute Otitis Media

High-Dose Amoxicillin	1 g PO every 8 h, 7 d	First-line therapy
High-dose Amoxicillin/ clauvulanate	2,000/125 mg PO every 12 h, 7 d	Use in patients that are more ill or who fail amoxicillin
Azithromycin	500 mg PO d one then 250 mg PO daily for 4 d	If penicillin allergic
Levofloxacin	750 mg PO daily for 5 d	If penicillin allergic
Moxifloxacin	400 mg PO daily for 7 d	

Observation without antibiotics or delayed antibiotic administration is an option in the treatment of adults with uncomplicated otitis media (23,24). This is a reasonable choice in a healthy adult with mild or ambiguous signs of AOM. In delayed antibiotic administration, the patient is discharged with a prescription for the antibiotic and told to initiate use only if symptoms either worsen or do not improve in 3 to 4 days (23,24). Decongestants and antihistamines have not been shown to be helpful in the treatment of AOM, but oral analgesia should certainly be prescribed. Provided the TM is intact, topical anesthetic agents such as benzocaine may also help alleviate pain associated with AOM.

Patients with a serious complication of otitis media require IV therapy (Table 68.4). Pneumococcus is the most common organism in acute complicated disease. Patients with mastoiditis should have broad-spectrum antibiotics, specialty consultation, and be admitted to the hospital.

TABLE 68.4
Antimicrobial Therapy for Complications from Otitis Media

Cerebral abscess	Vancomycin + ceftriaxone + metronidazole	Pneumococcus, polymicrobial	Use meningitis dosing of antibiotics
Meningitis	Vancomycin + ceftriaxone	Pneumococcus, *H. Influenza*	Use meningitis dosing of antibiotics
Acute mastoiditis	Ceftriaxone ± vancomycin	Pneumococcus, *H. Influenza*, Staphylococcus, Group A streptococcus	Use osteomyelitis dosing of antibiotics
Chronic mastoiditis	Piperacillin/tazobactam ± vancomycin	Polymicrobial, staphylococcus, pseudomonas	

Auricular Cellulitis and Perichondritis

The management of external ear infections is determined by the severity. Auricular cellulitis may be treated with cephalexin, dicloxacillin, or clindamycin. More severe disease, however, requires admission and treatment with intravenous antibiotics. Severe infection or infected bite wounds receive broader antibiotic coverage such as amoxicillin/clavulanate. In penicillin-allergic patients, combination therapy with clindamycin and ciprofloxacin is appropriate.

It is important to recognize that infections involving cartilage can spread quickly and are difficult to cure. Earrings or other foreign bodies must be removed. Consultation with an otolaryngologist and/or an infectious disease specialist is often needed.

In mild cases of perichondritis, treatment consists of oral antibiotics. Patients with a recent upper ear piercing should be treated with ciprofloxacin 750 mg PO q12 hours for 10 to 14 days to cover pseudomonas and should have close follow-up. More severe cases should be treated aggressively with intravenous antibiotics covering both staphylococcus and pseudomonas. Patients often need surgical intervention for subperichondrial abscesses.

CRITICAL INTERVENTION

- Initiate broad-spectrum IV antibiotics in patients with invasive otitis externa, complications of otitis media, or perichondritis.

DISPOSITION

Patients with simple otitis externa can be discharged with topical antibiotics and follow-up in 2 to 3 days to ensure clearance of the infection. They should also be instructed to avoid water immersion

for several days. Patients who do not respond to topical antibiotics may have either resistant organisms or involvement of the bony structures. Those with invasive otitis externa need admission or transfer to a hospital with urgent otolaryngology and infectious disease consultation.

The majority of patients with otitis media may be discharged home on oral antibiotics with follow-up. Patients with complications from otitis media should be admitted for intravenous antibiotics and specialty consultation.

The disposition of patients with auricular cellulitis depends on the severity. Patients with minor infections can be discharged with oral antibiotics and an early recheck. Those with more severe disease should be admitted for intravenous therapy. Most patients with perichondritis should be admitted for IV antibiotics, except in mild cases.

Common Pitfalls

- Using systemic antibiotics in uncomplicated otitis externa.
- Failing to use a wick in patients with otitis externa and significant canal edema.
- Using ototoxic agents in patients with a perforated TM.
- Failing to adequately visualize the TM.
- Not removing a foreign body (e.g., earrings) in patients with perichondritis.
- Underestimating the potential severity of cartilage infections.
- Failing to obtain specialty consultation in complicated cases.

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CHAPTER 69

Epistaxis

Trevor J. Lewis

Epistaxis is a frequent problem encountered by the emergency physician, accounting for approximately 1 in 200 emergency department (ED) visits in the United States (1). The incidence is bimodal, with peaks at ages younger than 10 and between 70 and 79 years of age (2). The higher incidence in children is attributed to local digital trauma in combination with reduced humidity during winter months (1,3). Pediatric epistaxis is usually benign and treated with local measures (4). Elderly patients are more likely to require invasive therapy and admission, because of both systemic causes of epistaxis and increased endothelial degeneration (3). Epistaxis is rarely life-threatening, and a majority of patients can be managed definitively by the emergency physician. When bleeding is not controlled by local measures, the source is usually posterior, and urgent otolaryngology consultation is required. Most posterior bleeds occur in older patients with the mean age of occurrence reported as 64 years of age (5).

The vascular supply to the nose is extensive, consistent with its function of warming and humidifying air. The blood supply to the nasal mucosa arises from the internal maxillary and facial arteries via the external carotid as well as from the posterior and anterior ethmoidal arteries via the internal carotid (6). The sphenopalatine artery, the terminal branch of the maxillary artery, supplies the lateral nasal wall below the middle turbinates and is the vessel responsible for most posterior epistaxis (7). The superior labial artery and greater palatine artery, terminal braches of the facial and maxillary arteries, respectively, supply the anterior portions of the

septum and floor of the nasal cavity. The anterior and posterior ethmoidal arteries supply both the septum and the lateral aspect of the nose superiorly. The confluence of these terminal arteries is referred to as *Kiesselbach plexus* or Little area. The majority of anterior nosebleeds occur in this area (Fig. 69.1).

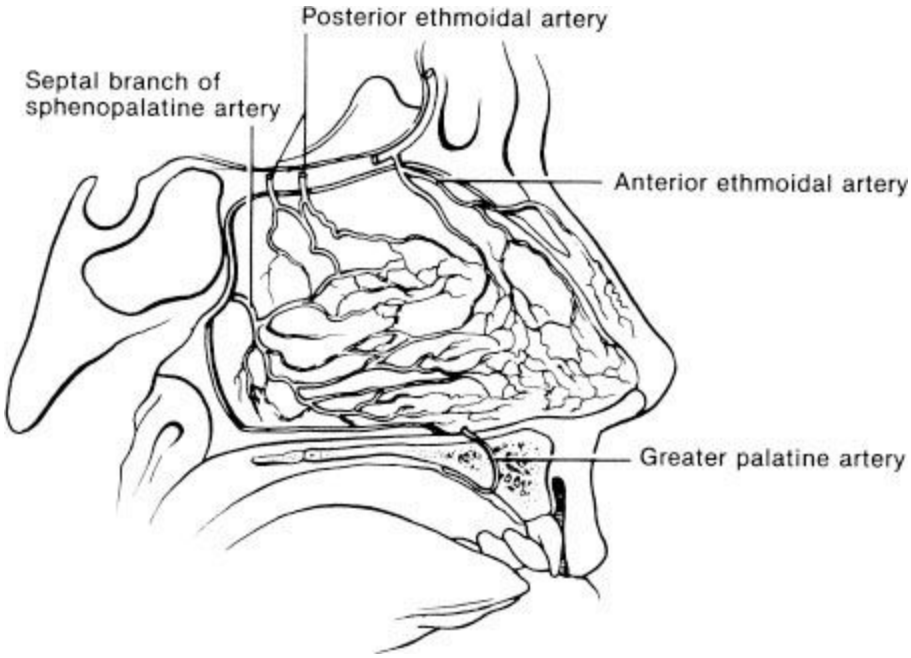

FIGURE 69.1 Blood supply to Kiesselbach plexus.

CLINICAL PRESENTATION

Epistaxis usually presents as spontaneous unilateral bleeding from a discrete lesion. Bilateral epistaxis is more commonly due to trauma or a posterior source of bleeding. Approximately 90% of nosebleeds are anterior, which means the bleeding source can be visualized in the anterior portion of the nasopharynx. The remaining 10% are posterior hemorrhages, in which a bleeding source is not directly visible. Posterior bleeds may present with nausea, hematemesis, anemia, hemoptysis, or melena (7) or may present with sudden copious bleeding due to involvement of larger vessels.

Patients with an underlying coagulopathy may present with other manifestations of bleeding such as bruising, petechiae, bleeding gums, hematuria, or gastrointestinal bleeding. Patients with a significant amount of blood loss may present with signs and

symptoms of hypovolemia such as lightheadedness, fatigue, tachycardia, or hypotension.

DIFFERENTIAL DIAGNOSIS

Epistaxis usually occurs from an interaction of factors that damage the superficial blood vessels of the nasal mucosa. The differential diagnosis includes both local and systemic causes, although the majority of cases are idiopathic (8). Local causes include direct facial trauma, nose picking (epistaxis digitorum), and chemical nasal irritants such as cigarette smoke, cocaine, and steroid nasal sprays. Epistaxis may be due to inflammatory disorders such as upper-respiratory infection, sinusitis, and allergic rhinitis. Environmental causes such as dry air during the winter months have been correlated with higher rates of admission for epistaxis (9). Other causes include foreign bodies (especially in children, the developmentally delayed, and elderly institutionalized patients), iatrogenic causes such as nasogastric and nasotracheal intubation, surgical complications, and overzealous treatment of self-limited hemorrhage.

Hypertension has been cited as a cause of epistaxis, but the relationship is controversial. Although studies have shown a higher prevalence of hypertension in epistaxis it is postulated that the sight of blood may cause a hypertensive or “white coat” response (8). Many hereditary bleeding disorders can present with epistaxis, including hemophilia, von Willebrand disease, and thrombocytopenia. Heavy alcohol use and a history of renal failure also increase the risk of epistaxis.

Numerous medications increase the risk of epistaxis via inhibition of normal clotting mechanisms. The most common class is nonsteroidal agents (including aspirin), which interfere with the cyclooxygenase pathway and inhibit platelet aggregation (6). Other commonly implicated medications include warfarin and other antithrombotic agents as well as antiplatelet medications. Many herbal supplements have anticoagulant properties including those that contain garlic, gingko, ginseng, and vitamin E (9).

Occasionally, patients present with massive epistaxis that is initially confused with hemoptysis or hematemesis. Blood from an episode of epistaxis that is swallowed or aspirated may further confuse the issue. If blood is coming from the nose and mouth and the source is unclear, the patient should be asked to sit upright, blow the nose, and rinse the mouth with water, and the oropharynx should be examined under suitable light. Blood dripping from the posterior nasopharynx confirms nasal hemorrhage. Table 69.1 lists some causes of epistaxis.

TABLE 69.1
Causes of Epistaxis

Spontaneous or idiopathic
Trauma
Digital trauma
Facial fractures
Foreign body
Infection
Bacterial rhinitis or sinusitis
Nasal diphtheria
Tumors
Juvenile angiofibroma
Paranasal sinus tumors
Surgery
Chemical irritants
Systemic toxins
Medications
Aspirin
Nonsteroidal anti-inflammatory drugs
Warfarin
Heparin
Dipyridamole
Clopidogrel, Ticlopidine
Thrombolytics
Coagulopathy
Thrombocytopenia
Disseminated intravascular coagulation
Hemophilia
von Willebrand disease
Hepatic failure
Leukemia
Venous congestion
Congestive heart failure
Mitral stenosis
Forceful coughing or nose-blowing
Other
Osler–Weber–Rendu syndrome
Barotrauma
Endometriosis
Allergic rhinitis

ED EVALUATION

Initial evaluation of the patient with epistaxis should focus on control of the bleeding to facilitate a directed history and physical examination and to alleviate the patient's anxiety. These measures should be initiated in triage and include the direct application of pressure by the thumb and index finger to the nasal alar area and the anterior septal area. The patient should be instructed to bend forward at the waist and spit out any blood that may pool in the throat. Swimmer's clips may be applied to the nasal area to control hemorrhage (10). Patients presenting with massive epistaxis or unstable vital signs require immediate resuscitation and airway management as well as direct control of the bleeding site. This precludes a lengthy history and physical examination. Once the patient has been stabilized, a more detailed history and examination can be obtained.

The history should focus on the initial site, duration, and amount of bleeding. One should inquire about precipitating events, including trauma and intranasal medications (illicit or otherwise) (3) as well as previous episodes of bleeding and whether control was achieved at home or in the hospital. Episodes of hematemesis may suggest a posterior source of epistaxis. Easy bruising or prolonged bleeding after minor surgical procedures suggests the possibility of coagulopathy, and recurrent episodes of epistaxis, even if self-limited, should raise suspicion for intranasal tumors. Use of alcohol and medications, especially aspirin, nonsteroidal anti-inflammatory agents, warfarin, or other antithrombotic or antiplatelet agents, should be noted, as these not only predispose to epistaxis but make treatment more difficult.

KEY TESTING

- Clotting studies (PT [INR], PTT): only for suspected bleeding diathesis, liver disease, or the anticoagulated patient (11,12).
- CBC, Platelets: if the patient relates a history of easy bruising, platelet disorder, neoplasia, or recent chemotherapy.

ED MANAGEMENT

The first priority in the management of epistaxis is to address the airway, breathing, and circulation (*ABC*s). Patients with unstable vital signs or severe hemorrhage should have intravenous access, as well as continuous cardiac monitoring and pulse oximetry. Massive hemorrhage may require endotracheal intubation to protect the airway and facilitate nasal packing. Elderly patients with massive bleeding may deteriorate rapidly, so aggressive resuscitation is vital (8). Rapid control of epistaxis that is associated with multiple trauma or significant facial injuries is best secured immediately with epistaxis balloons (13). This allows other life-threatening injuries to be addressed expeditiously. In patients with nontraumatic massive epistaxis, rather than making lengthy attempts at locating a bleeding source, the physician should proceed directly to packing with nasal balloons or tampons.

Most cases of epistaxis, however, are minor, and the episode frequently terminates with the proper application of pressure. When simple compression fails to stop the bleeding, the source of epistaxis must be located and then treated appropriately. Available treatments include topical vasoconstrictors, chemical or electrical cautery, nasal packing using prefabricated nasal tampons or epistaxis balloons, or traditional nasal packing. Every ED should have a prepackaged epistaxis tray or have key materials readily available (Table 69.2).

TABLE 69.2
Equipment Used for Management of Epistaxis

ENT chair
Headlamp
Nasal speculum (short and long)
Bayonet forceps
Frazier suction tips (No. 7 and 9)
Yankauer suction tip
Emesis or kidney basin
Gown, gloves, mask
Silver nitrate sticks
Electrocautery (optional)
Cotton balls
Dental roll
4- × 4-in gauze
Facial tissue
0.5- × 72-in petrolatum gauze
Antibacterial ointment (Neosporin, Polysporin, or Bacitracin)
0-silk sutures (straight needle)
Silk tape
Tongue depressors
Small plastic cups
Foley catheters (16 or 18Fr with 30-mL balloon)
Red rubber catheters (two 8Fr)
Umbilical clamps
Topical anesthetics (Cocaine 4%, Lidocaine 4%)
Topical vasoconstrictors (Phenylephrine 0.25%, Oxymetazoline [Afrin], Epinephrine 1:1,000)
Prepackaged nasal tampons (Rhino rocket and Rapid Rhino)
Prepackaged nasal balloons (Epistat, Simpson, Brighton)
Merocel nasal sponges
Avitene, Fibrin Glue, Surgicel, Oxycel, or Gelfoam

Preparation is the key to successful management. The physician should wear gown, gloves, and protective eyewear in anticipation of droplet spread of blood. The patient should be seated in an adjustable examination chair and draped from the neck down. A headlamp or mirror provides an excellent light source for optimal visualization.

The patient should be sitting upright or leaning slightly forward to prevent blood from tracking into the pharynx. The chair should

be adjusted so that the patient is just below eye level and the patient's head comfortably positioned against the headrest to prevent sudden movements during treatment. The patient should hold an emesis basin under the chin to catch blood running from the nose or mouth.

The patient should be instructed to blow the nose to clear the nasopharynx of blood and clots, even if bleeding has ceased, as local fibrinolysis of clots can result in persistent oozing or recurrence of epistaxis. This also allows for improved access for topical anesthesia (8). An initial attempt to locate the bleeding site should then be undertaken. The nasal speculum is used to spread the nares vertically, with the instrument held in such a manner that the index finger rests on the bridge of the nose for stabilization. The examination begins at Kiesselbach plexus, moving superiorly and posteriorly along the nasal septum, and concludes with the turbinates and lateral wall. Particular attention should be directed to common sites of bleeding: Kiesselbach plexus, the posterior floor of the nasal cavity, the junction of the anterior third and posterior two-thirds of the nasal septum, and the high anterior septum (11). With a well-illuminated and thorough examination, a bleeding point can almost always be identified.

Control of Anterior Epistaxis

If the bleeding point is identified and bleeding is not too brisk, application of oxymetazoline (Afrin) alone, or in combination with chemical cautery (silver nitrate), has been shown to be effective in the management of anterior epistaxis. Studies have indicated Afrin alone controlled 65% of nosebleeds in consecutive patients presenting to the ED (14). Other topical vasoconstrictors include phenylephrine (Neo-Synephrine) or epinephrine (1:1,000) applied to the area via cotton pledgets.

Electrical cautery has little advantage over chemical cautery with silver nitrate sticks (15). The nasal mucosa should be preanesthetized with 4% lidocaine solution on a cotton pledget to reduce discomfort. The principle of cautery is to injure the nasal

mucosa and underlying vasculature, resulting in immediate coagulation and vasoconstriction and immediate cessation of bleeding (3). The proper technique is to gently roll the applicator tip over the mucosa for no more than 5 seconds (16) until a grey eschar forms. Brisk bleeding may be slowed by cauterizing the four quadrants around the bleeding site or any identifiable vessel just proximal to the area of bleeding. Brisk bleeding may also decrease the effectiveness of the cautery by rapidly washing away the silver nitrate. Diffuse or extensive cautery should be avoided, and only one side of the septum should be cauterized at one time, so as to avoid septal necrosis or perforation.

For bleeding that is more brisk, pledgets soaked with an anesthetic-vasoconstrictor solution should be inserted into the nose on the side of the bleeding to provide hemostasis and anesthesia (17). An acceptable pledget can be fashioned by winding a piece of cotton tightly around the bayonet forceps. The cotton is pulled off the forceps and soaked in 4% cocaine or a 1:1 solution of 4% topical lidocaine and epinephrine (1:1,000), phenylephrine, or oxymetazoline. Oxymetazoline is suggested for increased safety in the elderly and hypertensive patients (18). Multiple pledgets may be placed, one above the other, onto the floor of the nasal cavity and allowed to remain in place for 10 to 15 minutes. If this fails to stop the bleeding, then cautery should still be attempted over the now well-anesthetized area.

If direct attempts to cauterize a bleeding point fail, anterior nasal packing should be placed. At this point, it may be a good idea to reconsider whether bleeding is posterior, because placing a posterior pack will necessitate first removing any anterior packing. Furthermore, if the site of bleeding is from the meatus, or from the medial surface of a turbinate, packing may prove to be of little value, and attempts to arrest the bleeding with other methods will be needed.

Traditional anterior nasal packing with Vaseline gauze has been supplanted by preformed nasal tampons or epistaxis balloons. Several nasal tampons are currently available, including Merocel, Rhino Rocket, and Rapid Rhino Nasal Pac with Gel Knit. The 85%

success rate of Merocel anterior packing is similar to that of traditional Vaseline gauze (8). After sufficient anesthesia is obtained, the Merocel tampon is lubricated with antibiotic ointment and inserted at a 45-degree angle into the nasal cavity for a distance of 1 to 2 cm. Antibiotic ointment is used to minimize infection as well as to lubricate the packing during insertion. The length of the Merocel is grasped with bayonet forceps and the long axis of the Merocel is rotated into the horizontal plane and then pushed straight backward into the nasal cavity. Merocel is supplied in different lengths that may be trimmed with scissors for both anterior and anterior–posterior hemorrhage. If an anterior–posterior sponge is employed, it should be inserted until it touches the back wall of the posterior nasal space. If the pack does not fully rehydrate with blood, then saline should be applied. The drawstring is secured to the patient's cheek.

The Rhino Rocket is a nasal tampon that is inserted using a supplied applicator. The nose should first be anesthetized with 4% lidocaine. The tampon is lubricated with antibiotic ointment and inserted along the floor of the nose. The Rapid Rhino Nasal Pac with Gel Knit is the newest nasal tampon. This is an inflatable balloon coated with a carboxymethylcellulose hydrocolloid compound. The compound acts as a platelet aggregator and lubricant when soaked in water (7). To insert the Rapid Rhino, the tampon is soaked in sterile water for 30 seconds and then completely inserted into the patient's nostril. The attached balloon is then inflated with 10 to 15 cc of air. Compared to the Rhino Rocket, the Rapid Rhino appears to be less painful to insert and easier to remove and to have similar effectiveness in stopping epistaxis (17).

Traditional anterior nasal packing is more difficult but may be considered if the foregoing measures are unavailable or unsuccessful. The nose should be packed with sterile petrolatum ribbon gauze (0.5 to 1 in wide), to which is added an antibacterial ointment to prevent toxic shock syndrome. Packing begins by grasping the ribbon with the bayonet forceps about 6 in from its end. The ribbon is then placed in the nasal cavity as far back as possible, while making sure that the free end still protrudes from the

nose. This first pass is pressed onto the floor of the nasopharynx with the closed forceps. The ribbon is then grasped about 4 to 5 in from the nasal alae, the nasal speculum is repositioned so that the lower blade holds the ribbon against the lower border of the nasal alae, and a second strip is brought into the nose and pressed downward. This process is continued superiorly in a stair-step fashion until there is no room left in the nose. Both ends of the ribbon must protrude from the anterior end of the nose, and the nostril is covered with a piece of gauze and secured with tape (19).

Other alternatives to the traditional anterior nasal pack include calcium sodium alginate (Kaltostat), Oxycel, Avitene, and balloon tamponade. Topical thrombogenic agents such as fibrin glue, gelatin sponge (Gelfoam), and microfibrillar collagen powder (Avitene) are useful in cases of epistaxis associated with coagulopathy when applied directly to the bleeding area. Floseal, a hemostatic sealant composed of collagen-derived particles and topical-derived thrombin, is applied as a gel to control epistaxis. When compared to traditional nasal tampons Floseal was found to be better tolerated and to provide superior epistaxis control. It is more costly, however (2). Thrombin-JMI epistaxis kit is a bovine derived topical thrombin that is reconstituted with saline and applied via a nasal mist device.

Control of Posterior Epistaxis

Bleeding that begins with the sensation of blood in the posterior pharynx, bleeding that cannot be localized anteriorly, or bleeding that fails to arrest with anterior packing is considered posterior and needs to be managed in consultation with an otolaryngologist. However, bleeding should be initially controlled by the emergency physician using one of a number of available techniques.

The traditional method of posterior packing with gauze rolls attached to strings is cumbersome and should be replaced with the use of an epistaxis balloon or inflatable Foley catheter. Balloon catheters are easier to install and just as effective as traditional posterior nasal packs (20). Posterior nasal packing should always be accompanied by anterior nasal packing. When the posterior balloon

is inflated and pulled forward, it acts to seal the posterior choana. The anterior naris is then packed with a nasal tampon or by inflation of an anterior balloon, effectively tamponading the entire cavity. Hence, it must be kept in mind that if the posterior pack dislodges, a large amount of blood can be aspirated (20). Posterior packs are uncomfortable when placed and usually require opioids for analgesia. Continuous pulse oximetry and cardiac monitoring are mandatory as posterior packing can cause hypoxemia, apnea, and cardiac dysrhythmia because of stimulation of the nasopulmonary reflex (3).

The commonly used balloons for control of posterior epistaxis include the Epistat nasal catheter, the Brighton balloon, and the Simpson balloon. The Epistat catheter is placed by inserting the catheter's entire length along the floor of the nose. The posterior balloon (white valve) is inflated with 10 cc of saline and pulled forward to occlude the posterior choana. The anterior balloon (clear valve) is then inflated with up to 30 cc of saline, unless the bleeding stops or the septum starts to bow. Rapid Rhino has a similar 9 cm dual port posterior pack.

If a Foley catheter is to be used, a 12 to 16Fr catheter with 30-cc balloon is placed into the nose along the floor of the nasopharynx until the tip is visible through the mouth in the posterior pharynx. It is then slowly inflated with 15 mL of saline, pulled anteriorly until it is firmly set against the posterior choana, and secured into place with an umbilical clamp wrapped around a dental roll or matted 4- $\times$ 4-in gauze, so as to avoid direct pressure necrosis of the ala or columella.

A traditional posterior pack is fashioned from a 4- $\times$ 4-in gauze rolled into a 1-in roll and secured with 3-silk sutures or umbilical tapes. This pack is brought into position in the posterior choana by passing a small red rubber catheter through each nostril and back out of the mouth, securing each of the two outer sutures to the catheters and pulling the catheters out of the nose again, drawing the pack through the mouth and into position. Each of the sutures is tied together over a gauze buttress to prevent pressure necrosis of the columella. The third suture is brought out through the mouth

and taped to the cheek to facilitate removal. Posterior packing is successful in stopping posterior bleed 70% of the time (21).

If unable to control posterior bleeding with traditional packing, emergent otolaryngology evaluation is necessary for possible endoscopic evaluation and cautery/ligation. Many otolaryngologists opt for early management of posterior bleeds with endoscopic cautery under direct visualization in the operating suite, early surgical control using arterial ligation, or referral to interventional radiology for selective arterial embolization (22). If time permits and bleeding is not severe, early consultation may spare patients with posterior nasal hemorrhage the discomfort of posterior packing altogether.

CRITICAL INTERVENTIONS

- Aggressively resuscitate patients with significant hemorrhage and signs of hypovolemia.
- Instruct patients who present to triage with epistaxis to apply squeezing pressure to the nose, as most nosebleeds are anterior and will terminate with this maneuver.
- For posterior epistaxis, control the hemorrhage with a balloon catheter, consult an otolaryngologist, and admit to the hospital.

DISPOSITION

Patients with a history of severe epistaxis or recurrent episodes of bleeding should be referred to an otolaryngologist for an outpatient examination to rule out a neoplastic process. Children with recurrent events should be evaluated for bleeding disorders (23). Patients with anterior packing should have follow-up for packing removal in 48 to 72 hours.

All patients with posterior packing should to be admitted to a high-acuity setting. These patients are at risk for cardiac and pulmonary complications and necessitate close monitoring. Clinicians should also strongly consider admitting elderly patients or those with cardiac or pulmonary disease who require anterior

packing. Patients who are coagulopathic or anemic often require admission for transfusion.

Patients who are discharged from the ED should be instructed to avoid blowing or picking the nose, straining, bending over, or participating in sports and strenuous activities and to sneeze with their mouth open. First aid instructions should be given on how to control epistaxis at home and when to seek medical help. Home humidifiers and saline nasal sprays may be helpful in drier, colder months, and patients should avoid any manipulation of the nose. Topical Naseptin cream or petroleum jelly may limit recurrent bleeds (8). Patients discharged with nasal packing should be prescribed an antibiotic, such as ampicillin/sulbactam or a second-generation cephalosporin, to prevent toxic shock syndrome or sinusitis (24). Aspirin may be discontinued if the benefit is felt to offset any risk of thromboembolic events. Anticoagulated patients with an INR in the therapeutic range can continue warfarin without interruption (25).

Common Pitfalls

- Failure to prepare the necessary equipment for control of epistaxis leads to unnecessary inconvenience and delays.
- Epistaxis in young children should prompt a search for a foreign body.
- Failure to identify the source of bleeding or to place an anterior pack properly leads to rebleeding and necessitates a return to the ED for repacking.
- Failure to prescribe antibiotics for patients discharged with an anterior pack can lead to sinusitis or toxic shock syndrome.
- Failure to identify posterior epistaxis until after an anterior pack has been placed necessitates completely unpacking the nose so a posterior pack can be placed.

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of Jeffrey A. Evans and Todd C. Rothenhaus to the content of this chapter.

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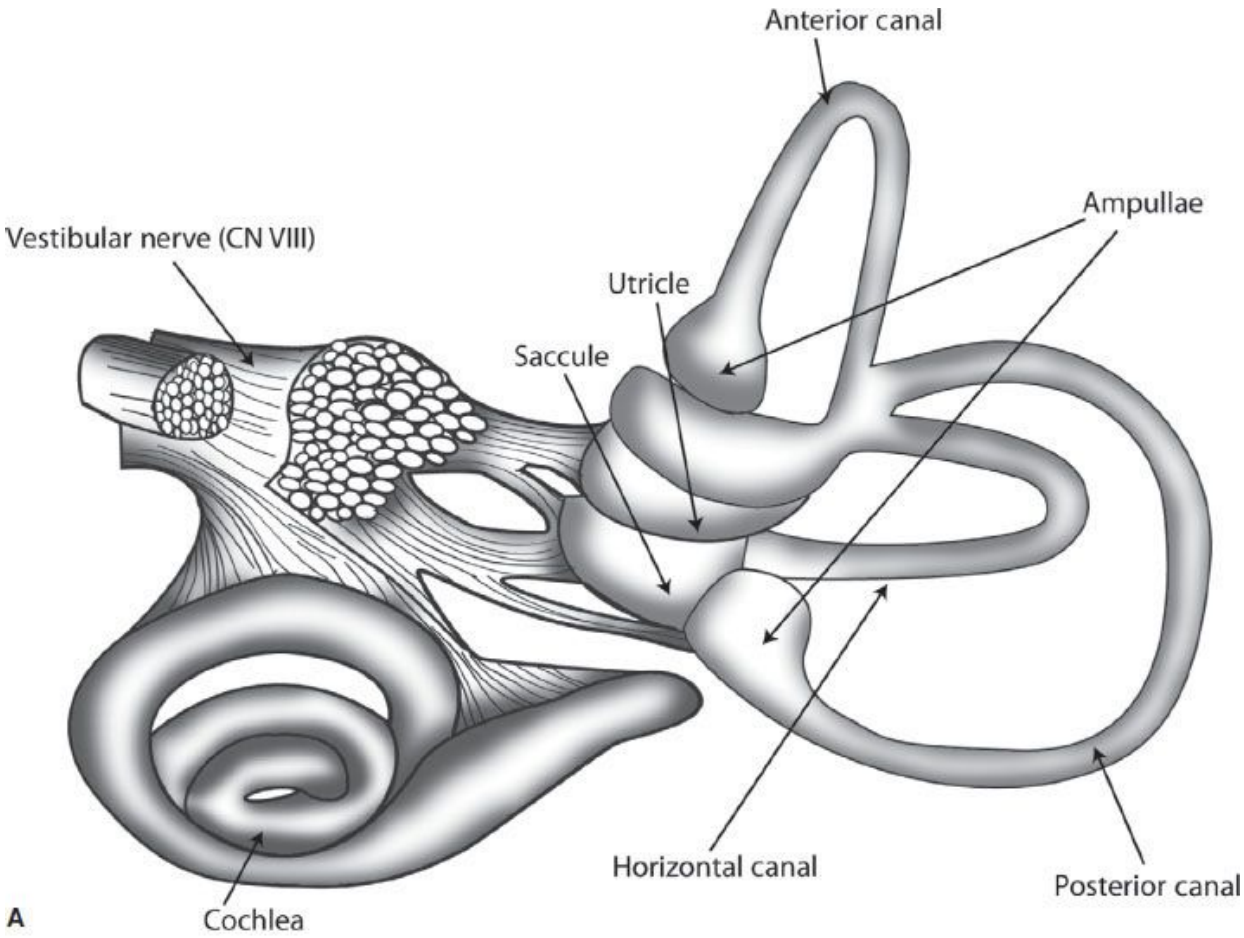
CHAPTER 70 Vertigo

Brian Chinnock

Vertigo, along with dizziness and other balance disorders, affects up to 70% of people during their lifetime. Vertigo is often categorized into peripheral and central causes. Peripheral disorders may cause considerable symptomatology but are rarely life-threatening, whereas those of central etiology may have significant morbidity and mortality.

PERIPHERAL AND CENTRAL VESTIBULAR ANATOMY

Maintenance of balance and coordination of eye movements is managed by a complex interaction of the vestibular system, the cerebellum, the brainstem, the ocular muscles, the visual cortex, and their interconnecting pathways. The peripheral vestibular system consists of three semicircular canals and two otolithic organs, the utricle, and saccule (Fig. 70.1A). Together they respond to head movement in all directions. Each canal is filled with endolymph, and has a dilated end called the ampulla which has the sail-like cupula. With head movement, the vestibular hair cells embedded in the cupula are stimulated and send input to the vestibular nerve (vestibular branch of CN VIII). Each semicircular canal is paired, and on head movement, one will give an excitatory input to the vestibular nerve, whereas the other will give an equal inhibitory input. With a unilateral peripheral vestibular deficit, the affected semicircular canal will not send in an inhibitory input to the vestibular nuclei, thus giving sensation of movement even if the head is still.



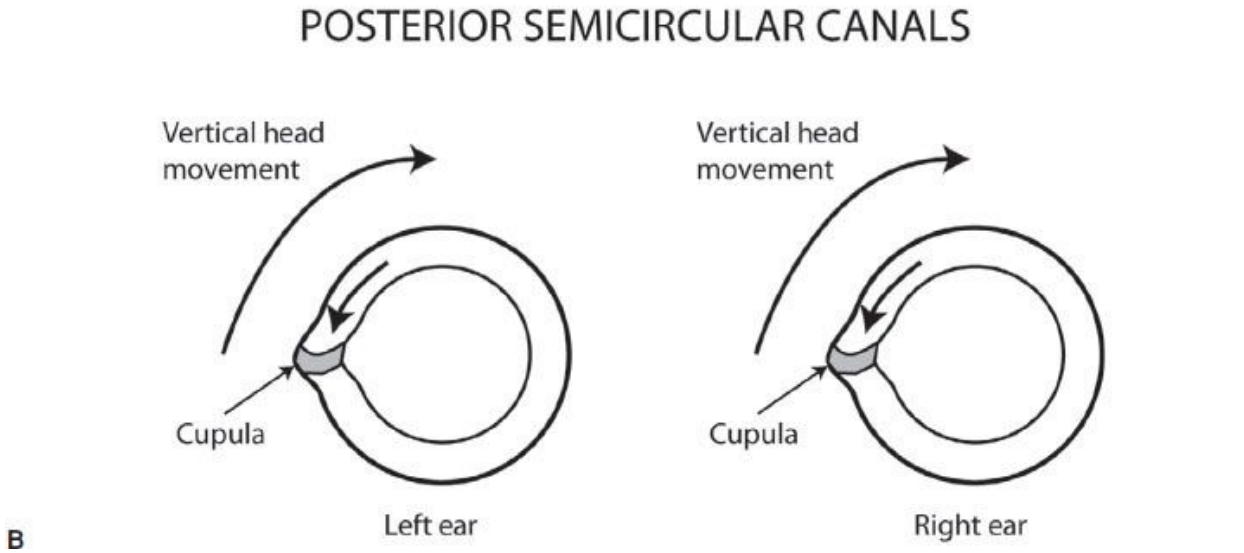


FIGURE 70.1 **A**: demonstrates the organs of the peripheral vestibular system. B: demonstrates the paired posterior semicircular canals, with vertical head movement causing the more static endolymph

inside the canal to cause pressure against the cupula, which stimulates the vestibular nerve.

The central vestibular system receives input through the vestibular nerve to the vestibular nuclei located in the brainstem. From the vestibular nuclei, there are neuronal connections through the medial longitudinal fasciculus to the ocular muscles. This pathway is responsible for the vestibuloocular reflex (VOR), which does not involve the cerebellum, and is tested with the head impulse test (HIT) (see Figure 70.3). The cerebellum is the main organ of the central vestibular system, coordinating vestibular, visual, and somatosensory input to help fine-tune motor activity. The cerebellum is composed of the lateral hemispheres and the midline vermis. The lateral hemispheres are responsible for limb movement, whereas the vermis is responsible for truncal motion. The cerebellum receives its blood supply from the posterior-inferior cerebellar artery (PICA), the anterior-inferior cerebellar artery (AICA), and the superior cerebellar artery (SCA). All originate from the vertebrobasilar system. Importantly, the cerebellum is supplied by the distal branches of each of these arteries, with the proximal parts supplying the lateral brainstem. For this reason, it is common for cerebellar CVA to also present with brainstem findings.

PERIPHERAL VERSUS CENTRAL VERTIGO

While there are many causes of vertigo, there are four primary diagnoses of significance to the emergency physician evaluating a patient with acute vertigo: (1) benign paroxysmal positional vertigo (BPPV), (2) vestibular neuronitis (VN), (3) migrainous vertigo, and (4) cerebellar/brainstem ischemia (CBI). The discussion will focus on these four diagnoses as they are the most common and important. CBI, which includes cerebellar/brainstem transient ischemic attack/cerebrovascular accident (TIA/CVA) or vertebrobasilar insufficiency, only represents 1% to 3% of vertigo patients, but has a mortality rate of up to 40% (1). It is thus the most important differential diagnosis for any vertigo patient. Other causes of peripheral and central vertigo are listed in Table 70.1.

TABLE 70.1
Less Common Causes of Peripheral and Central Vertigo

Peripheral Vertigo—Other Causes	Diagnostic Clue
Ménière disease: A chronic, progressive disease with endolymph hydrops affecting the vestibular and cochlear apparatus. Characterized by intermittent attacks of vertigo lasting 20 min–24 hrs, hearing loss that is at first episodic, but then constant, and a low pitch tinnitus. Vertigo attacks occur most commonly in clusters, and can decrease as hearing loss progresses over yrs	Intermittent vertigo, hearing loss, tinnitus
External canal and middle ear disorders: otitis media, serous otitis with effusion, tympanic membrane rupture, cholesteatoma, herpes zoster oticus, cerumen impaction and malignant otitis externa can all cause peripheral vertigo	Adequate otoscopic examination
Labyrinthine concussion: traumatic peripheral vestibular injury due to head trauma. Most patients have improved symptoms in days, but can last for weeks to months.	Vertigo after concussive head trauma
Perilymphatic fistula: Fistula develops at the otic capsule which separates the inner ear from the middle ear. May occur due to trauma or barotrauma. The defect allows middle ear pressure changes to be transmitted to the inner ear, causing episodic vertigo and/or hearing loss	Episodic vertigo and/or hearing loss caused by sneezing, heavy lifting, straining, or coughing
Labyrinthine hemorrhage: This is a rare cause of spontaneous vertigo and deafness. It has been described in patients with clotting problems related to leukemia, sickle cell disease, antiplatelet and anticoagulant therapy, cocaine ingestion and systemic lupus erythematosus. It can be detected on T2-weighted images on MRI.	Vertigo and hearing loss in a patient with clotting disorder
Cogan's disease: autoimmune disease affecting the eye and inner ear. Peak age of incidence is 22 yrs old. Causes Ménière-like attacks of vertigo, hearing loss, and tinnitus.	Vertigo/hearing loss in association with keratitis
Medications: aminoglycosides (usually IV/oral; rarely topical), loop diuretics, aspirin or nonsteroidal anti-inflammatory drugs (especially in overdose)	Medication history
Central Vertigo—Other Causes	
Vestibular schwannoma (acoustic neuroma): tumor growing from the vestibular nerve. As it slowly grows, there is gradual compressive involvement of the cochlear nerve (95%) with hearing loss, vestibular nerve (63%) with mild gait imbalance and vertiginous symptoms. Continued growth can affect the trigeminal nerve, facial nerve, and even compress the brainstem and cerebellum	Long-standing indolent hearing loss and vertigo/imbalance
Temporal lobe seizure: One type of this can involve a prodrome of vertigo and auditory hallucinations, which can occur in isolation as a simple partial seizure, or can progress to a complex partial seizure with automatisms such as lip smacking, chewing, picking, fidgeting.	Vertigo preceding complex partial or generalized seizure
Medication/ toxicology: Medications such as sedatives, antidepressants, neuroleptics, and anticonvulsants can cause central vestibular dysfunction. Alcohol is a common cause of central vertigo. PCP use, while not causing vertigo, can give a multidirectional nystagmus that mimics that seen with CBI	Medication history and examination for intoxication

BPPV: This is the most common cause of vertigo, representing up to 50% of cases. It has a cumulative incidence of nearly 10% by the age of 80. It is caused by otoconia, calcium carbonate crystals present in the utricle, that become dislodged and migrate into the semicircular canal. The presence of otoconia in the endolymph of one ear will cause increased excitatory input to the vestibular nuclei compared to the unaffected ear on head movement, causing vertigo. BPPV is characterized by intermittent episodes of sudden severe vertigo precipitated by head movement, commonly with nausea and vomiting, which usually last for less than 1 to 2 minutes. When the head stops moving, the vertigo will abate as the movement of the otoconia is the only source of abnormal input; the rest of the vestibular structures are fully functional. As the posterior canal is the most dependent of the semicircular canals and the most likely location for otoconia to settle by gravity (see Fig. 70.1A), 85% of BPPV is caused by posterior canal otoconia. While BPPV is commonly idiopathic, it may also be due to otoconia dislodged due

to minor trauma or whiplash injuries, or as a residual effect of Ménière disease.

VN: VN is caused by a selective inflammation of the vestibular nerve, likely due to a post viral cause. Concomitant involvement of the cochlear nerve is termed “labyrinthitis,” and has the same physical examination findings as VN, in addition to hearing loss. Unilateral vestibular nerve involvement will give unequal input to the vestibular nuclei, and cause vertigo. Unlike BPPV, though, keeping the head completely still will not significantly affect the vertigo, as the defect is in the nerve itself, not the canals which give output based on movement. Resolution of symptoms typically takes weeks as recovery is dependent on the vestibular nerve regenerating, and central vestibular compensation mechanisms to develop, as the nerve regeneration is typically incomplete.

Migrainous vertigo: In neurootology clinics, this is the most common cause for referral. Criteria have been developed for the diagnosis of migrainous vertigo and are listed in Table 70.2. Despite these criteria, migrainous vertigo is a diagnosis of exclusion and can be the most difficult diagnosis to make as the vertigo can have either peripheral or central features (2). In addition, the quality and duration of vertigo can range from the mild, indolent quality of CBI which lasts for days, to the severe quality of BPPV or VN, lasting for minutes or over a day, respectively.

TABLE 70.2
Neuhauser Criteria for Migrainous Vertigo

Definite

1. Episodic vestibular symptoms of at least moderate severity
   - vertigo; positional dizziness and head motion intolerance
2. Migraine according to International Headache Criteria
3. One or more of the following features during at least two vertigo attacks
   - migrainous headache
   - headache
   - photophobia
   - photophobia
   - migraine aura
4. Other diagnoses excluded by appropriate tests

Probable

- Criteria 1 and 4 as above plus at least ONE of the following:
  - Criteria 2 or 3 as listed above
  - migraine-specific triggers of vertigo
  - response to antimigraine drugs

CLINICAL PRESENTATION

A good history is extremely important in ruling out CBI in the vertigo patient. In one study, patients with isolated dizziness and no findings suggestive of CVA had a $<1\%$ incidence of CVA (3). Risk factors for CBI are the same as for other types of CVA: previous CVA, diabetes, hypertension, advanced age, atrial fibrillation, hypercholesterolemia. In a case series of patients with vertigo who had a final diagnosis of cerebellar CVA, and who had negative initial diffusion-weighted MRI (DW-MRI), the mean age was 72 years old and all had significant risk factors for CVA (4).

BPPV is usually easy to differentiate from VN and CBI by its sudden onset, short duration, and complete resolution of symptoms in between episodes (Table 70.3). Vertigo that is associated with particular head positioning is almost always due to BPPV (Table 70.3). However, rarely, a patient may have central positional vertigo due to a very localized infarction of CN VIII at the brainstem or of the vestibular nucleus. Either of these may cause a positional vertigo without other neurologic findings. The Dix–Hallpike maneuver (described below) may be particularly helpful in differentiating in this circumstance. Patients with migrainous vertigo usually have a

previous history of migraines, with new vestibular symptoms which may or may not occur at the same time as the migraine.

TABLE 70.3
Features of BPPV in Comparison with VN and CBI

	BPPV	VN	CBI
Onset	Sudden, with head movement	Minutes–hours	Sudden
Duration	Seconds–minutes	Days–weeks	Days–weeks
Improvement with keeping head still, eyes closed	Complete	Minor	Minor
Emesis	Common	Common	Less common
Dix–Hallpike maneuver	Positive	Negative	Negative

DIFFERENTIAL DIAGNOSIS

Traditional teaching emphasizes the differentiation of vertigo from presyncope, disequilibrium, or nonspecific dizziness. However, this approach may be problematic. A large ED-based study found that the incidence of CBI was similar in patients with vertigo versus nonvertiginous dizziness (3). Another ED study found that patients' descriptions of dizziness were unclear, imprecise, and unreliable (9). Therefore the many causes of vertigo should be at least considered in patients without a clear description of vertigo.

ED EVALUATION

Physical Examination

Standard neurologic examination: All the standard elements of a neurologic examination should be completed, as the presence of any abnormalities can suggest CBI as the cause. Finger–nose testing for dysmetria by itself is not an adequate test of cerebellar function, since it tests only lateral hemispheric function. Large cerebellar vermal CVAs can have a completely normal finger–nose test. Testing of gait is extremely important as patients with peripheral vestibular disorders, while often having significant symptomatology trying to

walk, will still be able to walk. Inability to walk (or sit or stand), strongly suggests CBI.

Nystagmus testing should be done by having the patient follow the examiner's finger in all horizontal and vertical directions. It is also important to hold the finger for 10 to 15 seconds at eccentric vertical and horizontal gaze positions (testing for gaze-evoked nystagmus [GEN]), and then allowing the eyes to return to normal position (testing for rebound nystagmus). When doing this, it is important to not test at the very extremes of gaze as this can evoke a sustained nystagmus even in normal patients. In VN, the nystagmus will be unidirectional, horizontal, with perhaps a slight rotatory component, suppressible by fixating on a target. CBI is more likely if the nystagmus is vertical, purely rotatory, or is not suppressible. Physiologic end-point nystagmus (EPN) occurs upon extreme lateral gaze, when a few beats of low-amplitude nystagmus occur before normal brainstem mechanisms allow the eyes to maintain the eccentric gaze without further nystagmus.

GEN occurs on far eccentric gaze, with sustained, large-amplitude nystagmus. This is caused by an abnormality in the cerebellum or cerebellar pathways. A small lesion of CBI will only manifest at very extremes of gaze. A larger lesion can appear as soon as the eyes deviate from straight-ahead. A vertical GEN, in particular, is diagnostic of cerebellar or brainstem dysfunction. With VN, as the eyes move eccentrically in the direction of the fast phase of nystagmus, the nystagmus will increase until it eventually suppresses with fixation, whereas fixation is unlikely to suppress with CBI.

Rebound nystagmus occurs after holding the eccentric gaze position for 10 to 15 seconds, then returning to the primary gaze position. Nystagmus with the fast phase in the opposite direction of the preceding eccentric gaze indicates CBI. Reversible nystagmus occurs when the direction of the fast phase changes when looking side to side, and is indicative of CBI.

Smooth pursuit is assessed by watching eye movements while performing the nystagmus assessment. It is normal for patients to have slight saccades (fast, jerky eye movements) interrupting smooth pursuit during downward gaze, but should otherwise be smooth

without saccades. Significant asymmetry of saccadic motion between each eye is suggestive of a structural brainstem/cerebellar lesion. Saccades due to slow eye movements (eyes have to make saccades to catch up with pursuit) can also be seen with medication/drug usage (alcohol, benzodiazepines).

Skew deviation is tested by asking the patient to fixate on the examiner's nose, covering one eye, then uncovering that eye while simultaneously covering the other, alternating simultaneous cover and uncover every 1 to 2 seconds. Normally, there is little or no eye movement to regain fixation on the examiner's nose. With CBI, fixation is not maintained and the eyes make a movement, usually vertical, to regain fixation. For example, as the left eye is uncovered it makes a vertical downward movement to regain fixation, and then, as the right eye is uncovered while the left eye is covered, the right eye makes a vertical upward movement to regain fixation. While not sensitive for CBI, the presence of skew deviation is very specific for CBI.

Dix–Hallpike: The Dix–Hallpike test should be performed if BPPV is a diagnostic consideration. The Dix–Hallpike test positions the head so that otoconia in the posterior semicircular canal move to cause maximal stimulation, with nystagmus and vertigo (Fig. 70.2, panels S and 1). The maneuver has an approximately 50% to 88% sensitivity in detecting BPPV (5).

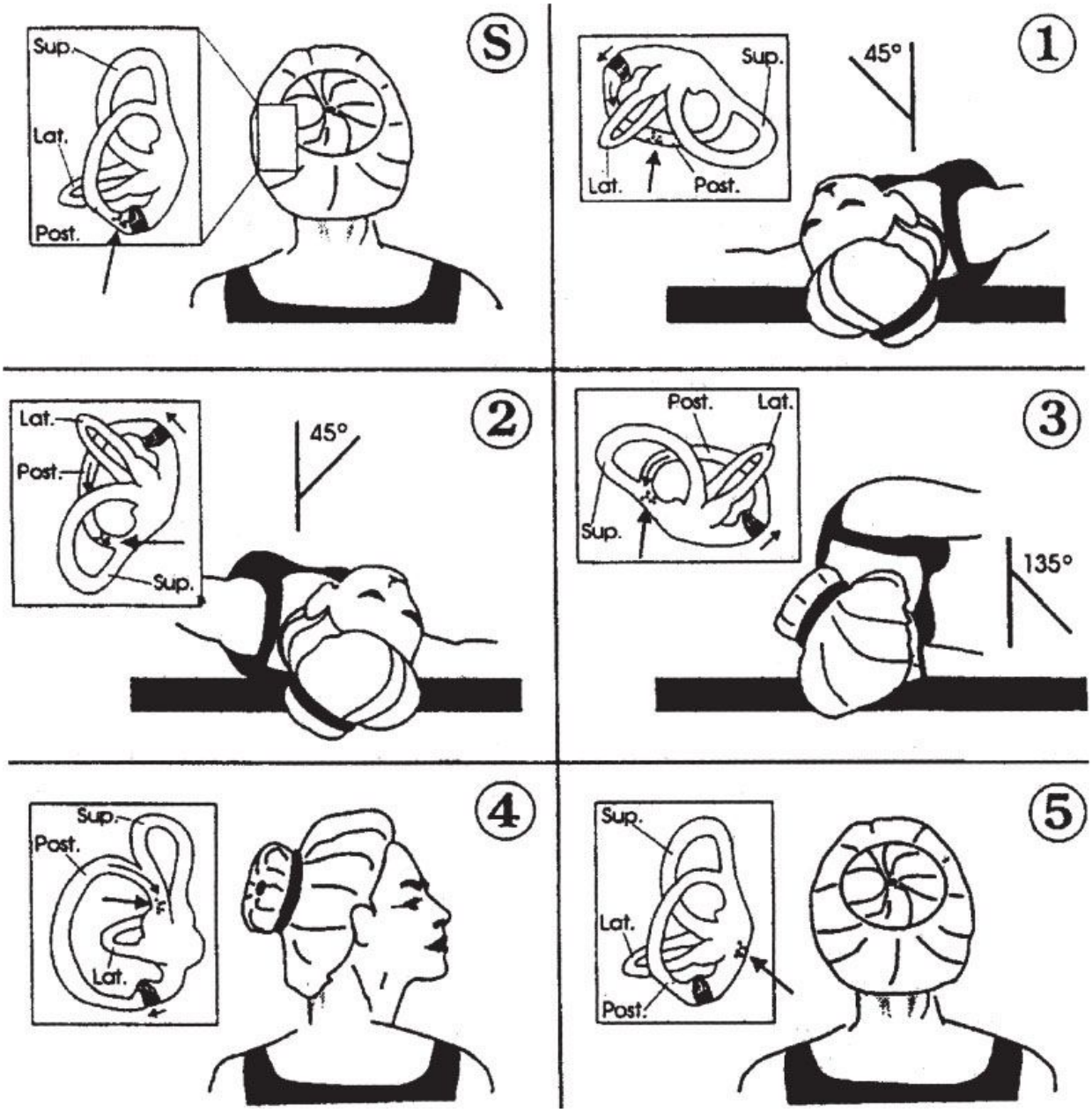


FIGURE 70.2 Dix–Hallpike test and Epley maneuver. Positioning sequence for left posterior semicircular canal as viewed by operator (behind patient). Small boxes show the labyrinth and migration of particles (large arrow). (S) and (1) represent a Dix–Hallpike test of the left posterior semicircular canal, while the entire sequence demonstrates the Epley maneuver. (S) Start-–patient seated. 1: Place head over end of table, 45 degrees to the left. For Dix–Hallpike test, with a positive test, there will be a short latency period, followed by an upward and torsional nystagmus and vertigo, which fatigue in

about 15 to 30 seconds. When the nystagmus fatigues, the patient is returned to the sitting position, at which point the vertigo and nystagmus return briefly, the nystagmus now in the opposite direction. 2: Keeping head tilted downward, rotate to 45 degrees right. 3: Rotate head and body until facing downward 135 degrees from supine. 4: Keeping head turned right, bring patient to sitting position. 5: Turn head forward, chin down to 20 degrees. Pause at each position until induced nystagmus approaches termination, or for approximately 30 seconds if no nystagmus. If able, keep repeating entire series (1 to 5) until no nystagmus in any position.

"Bow and lean" test: Patients who have symptoms consistent with BPPV, but a negative Dix–Hallpike maneuver, should have this maneuver performed to test for horizontal canal otoconia, which can represent up to 10% to 20% of BPPV cases. In this maneuver, the seated patient first bends the head forward ("bow"), aligning the horizontal canal with gravity, and then leans their head backward quickly, flipping the canal 180 degrees. The examiner looks for nystagmus in each position. With right ear horizontal canal otoconia, there will be a right-beating nystagmus on the bow, and a left-beating nystagmus on the lean. Knowing which canal is involved is important in determining the treatment maneuver.

Head impulse testing: The HIT evaluates the VOR, and is vital at differentiating VN from CBI. It is described in Figure 70.3. The sensitivity of HIT for detection of VN is 72% when done by "nonexperts" (6). A study in which the HIT was used in patients at high risk for CVA showed that 31/34 patients with a final diagnosis of CVA had a negative HIT (7). In patients suspected to have VN, the triad of a positive HIT, unilateral nystagmus, and absent skew deviation excluded 91% acute CVAs and identified 78% of peripheral vestibular lesions (8). These studies demonstrate that a positive HIT by itself must be viewed with caution in ruling out CBI, however, in association with the lack of other findings suggesting CBI (see Table 70.4). The ability to rule out CBI is similar to that of MRI, especially within the first 24 hours.

FIGURE 70.3 Head impulse test. This is a test of the VOR. The examiner grasps the sides of the patient's head and asks the patient to fixate on the examiner's nose (A). The examiner asks the patient to relax the head, and then performs a low-amplitude, high-velocity, random movement of the head to one side or the other, while having the patient maintain fixation on the nose. With an intact VOR (intact vestibular system), the patient's eyes will maintain fixation (B). C demonstrates an abnormal VOR: On movement of patients head to the right, the patient briefly loses fixation on the examiner's nose, and then has a rapid saccade of the eyes to the left to regain fixation (D).

TABLE 70.4
Features Differentiating VN from CBI

	VN	CBI
History		
Onset	Over minutes–hours	Sudden
Duration	Days–weeks	Days–weeks
Imbalance, more than vertigo	No	Yes
Headache	Yes	Yes
Vomiting	Common	Less common
Nystagmus		
On primary gaze (looking straight-ahead)	Common (first 24 hrs)	Common
Pure torsional (no horizontal component) on primary gaze	No	Yes
Suppression with visual fixation on a target in lighted conditions	Yes	Little or none
Fatigable on lateral gaze	Yes	No
High amplitude on lateral gaze	No	Yes
Up- or downbeating with vertical gaze	No	Yes
Increases during eccentric gaze toward fast phase of nystagmus	Yes	
Rebound	No	Yes
Reversible	No	Yes
Other Eye Testing		
Smooth pursuit	Normal (can be interrupted by unilateral nystagmus)	Saccadic; possibly asymmetric
Skew deviation	No	Yes
Other Neurologic Findings		
Gait—inability to walk	Rare	Common
Neurologic (especially brainstem) deficits	No	Common
Complete hearing loss	No	Yes (but rare)
Romberg examination	Abnormal—but should be able to stand with eyes open	Abnormal —but may not be able to stand with eyes open
Head impulse test	Abnormal	Normal

Laboratory Testing

Laboratory testing has a very limited role in the evaluation of vertigo. Consider evaluating for hypoglycemia, anemia, thyroid dysfunction, uremia, or electrolyte abnormalities in the patient who has a broader differential diagnosis than vertigo.

Imaging

Imaging has little role in the evaluation of BPPV or VN, except to evaluate for the serious alternative, CBI. CT scan may reveal hemorrhagic CVA. Beyond that, it has no role in the evaluation of CBI since the sensitivity for ischemic CVA is only 40%, and possibly lower for posterior fossa pathology. DW-MRI has become the standard of care in the diagnosis of ischemic CVA. DW-MRI can demonstrate an acute ischemic CVA even in the first few hours. However, the false-negative rate is 19% within 12 hours and 24% within 3 hours (10). The same artifacts that make CT difficult to evaluate the posterior fossa, also make MRI difficult to evaluate in the acute setting. For this reason, a normal DW-MRI is not reliable in ruling out CBI in the first 24 hours of symptom presentation.

KEY TESTING

- Physical examination maneuvers to detect findings consistent with central causes.
- Obtain MRI when central vertigo is suspected, but be cautious of a normal result in the first 24 hours.

ED MANAGEMENT

Vestibular neuritis: In the acute phase, medications that work either as vestibular "sedatives" (decreasing abnormal input from the vestibular system) or antiemetics can be used to decrease symptomatology. These medications include antihistamines, benzodiazepines, antiemetics, and scopolamine. Little evidence supports the use of one treatment over another. One trial examining the IV use of dimenhydrinate 50 mg versus lorazepam 2 mg found less sedation and better symptomatic relief in the dimenhydrinate

group (11). Another study showed equivalent effect of IM dimenhydrinate 50 mg and droperidol 2.5 mg (12). All of these classes of drugs can have significant side effects in elderly patients, and the risk–benefit ratio should be carefully weighed in this patient population. For more long-term relief, the use of steroids has been examined. Two studies, one using methylprednisolone in a 22-day taper and another using prednisone 1 mg/kg for 5 days with a 15-day taper, showed no better symptom improvement than placebo at 12-month follow-up (13,14). However, the smaller study using prednisone demonstrated better symptom improvement than placebo at 3- and 6-month follow-up. Therefore, if there is not a contraindication, it is reasonable to give a short course of steroids.

Posterior canal BPPV: Epley and Semont are maneuvers designed to move the head in a way that moves the otoconia out of the semicircular canal and into the utricle, where it can then be washed away. Studies show that Epley and Semont maneuvers perform equally well. As Epley is the most commonly used and most well studied, the discussion will center on this maneuver. The Epley maneuver (Fig. 70.2) has been shown to improve the symptoms in both the short and longer term in randomized controlled trials (RCTs). An ED-based RCT with 11 patients each in Epley and sham maneuver groups, had six Epley-treated patients with complete resolution of symptoms on completion of the maneuvers, compared to only one in the sham arm (15). The average time to complete the maneuvers was 2 to 3 minutes. Another RCT with 67 patients demonstrated 80% improvement in vertigo and nystagmus at 24 hours compared to 10% improvement in patients who did sham maneuver (16). Improvement in Epley-treated patients has also been demonstrated at 1 month post procedure.

Horizontal canal BPPV: Numerous maneuvers have been described, but with little supporting evidence. In the Asprella–Gufoni maneuver, the patient starts in a sitting position, lies down onto the side of the unaffected ear with the head resting on the bed with the eyes looking straight-ahead. Position is held for about 2 minutes, then head is rotated 45 degrees looking toward the bed (toward the unaffected ear). After another 2 minutes, the patient sits up with the

head still turned 45 degrees looking toward the unaffected ear. This maneuver is approximately 80% effective in resolving symptoms.

Studies of beneficial medications are scarce. Benzodiazepines have not been shown to be better than placebo. Meclizine is commonly prescribed for this condition but has only demonstrated benefit in one small study (17). Both medication classes have significant side effects, particularly in elderly patients.

Migrainous vertigo: Treatment of migrainous vertigo is similar to that of migraine headache (see Chapter 153), and includes antiemetics (prochlorperazine, metoclopramide, droperidol), and serotonin agonists (triptans, dihydroergotamine).

CRITICAL INTERVENTIONS

- Differentiate BPPV, VN, and CBI with a focused history and physical, with particular concentration on gait and nystagmus testing, Dix–Hallpike test, and HIT
- Obtain MRI in the patient with suspected CBI
- Perform an Epley maneuver and demonstrate home exercises in the patient with BPPV

DISPOSITION

Patients with peripheral vertigo should be instructed to decrease or stop activities such as driving, operating heavy machinery, or work duties until such time as the symptomatology abates. Particular caution needs to be exercised with the elderly, as they can have significant morbidity and mortality from falls due to vertigo/imbalance. Depending on the patient's functional status, home social situation, and outpatient and ED service capability, consideration should be given for prescribing walking aids, physical therapy referral in the ED to assess gait, home health referral, or admission to hospital or rehabilitation facility. Referral to ENT, a neurootology clinic, or a clinic that specializes in vestibular rehabilitation is indicated as proper rehabilitation can significantly decrease the severity of symptoms and increase functionality. Patients with vestibular neuritis should be counseled that severe

symptoms last for 1 to 2 days, with a gradual resolution over weeks to months. Recurrence is rare. BPPV patients should receive instruction on how to do the Epley home maneuvers for the appropriate affected ear. Studies have demonstrated significantly improved resolution rates in patients who were additionally given instruction in how to perform the Epley maneuver at home compared to those who only had the maneuver performed by the physician (18). BPPV does have a significant risk of recurrence: 15% to 18% at 1 year, and 37% to 50% at 5 years. Admission is indicated for workup when CBI is suspected. Neurology consultation is helpful in this setting.

Common Pitfalls

- Using a patient's description of "dizziness" symptoms to rule out vertigo.
- Using a normal finger–nose test to rule out CBI.
- Failure to use the HIT and nystagmus testing in the differentiation of VN from CBI.
- Failure to perform a Dix–Hallpike test in the patient suspected of BPPV.
- Failure to perform horizontal canal diagnostic maneuvers in patients with BPPV symptoms when the Dix–Hallpike test is negative for posterior semicircular canal involvement.
- Using CT to rule out CBI.
- Failure to recognize that a negative DW-MRI does not rule out CBI in the first 24 hours.
- Treating BPPV with medications of unproven benefit, rather than a potentially curative Epley maneuver.

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CHAPTER 71 Acute Hearing Loss and Tinnitus

Carolyn Chooljian

CLINICAL PRESENTATION

Acute hearing loss (AHL) is defined as hearing loss occurring over 3 days or less and involves the loss of 30 decibels (dB) of hearing over three or more contiguous audiologic frequencies. AHL may present in isolation or with tinnitus and/or vertigo. The presence or absence of associated symptoms is useful in its evaluation. The etiology of AHL may be obvious or obscure. When it is due to trauma of the temporal bone or associated with the effusion of acute otitis media the etiology is readily apparent. However, AHL may also occur spontaneously without an obvious etiology. The patient may complain of hearing loss in one ear or both.

Auditory Pathway

Knowledge of the auditory pathway (1) is helpful in understanding the presentation, type, and cause of AHL. The auditory system can be divided into peripheral and central parts. The peripheral auditory system consists of the external ear, middle ear, and the inner ear located within the temporal bone. The external ear includes the auricle, external auditory canal, and tympanic membrane (TM). The middle ear is an air-filled space that contains the auditory ossicles—the malleus, incus, and stapes. Sound waves reach the TM and are transmitted via the ossicles of the middle ear to the fluid-filled cochlea of the inner ear. The cochlea contains the specialized

hearing organ of Corti where sound is converted from mechanical pressure to electrical signals through its neuroepithelial hair cells. Projections from the organ of Corti proceed to the bipolar spiral ganglion. The centrally projecting processes of the spiral ganglion constitute the auditory portion of the eighth cranial nerve, the cochlear nerve. These project to the ventral and dorsal cochlear nuclei, which are located in the brainstem at the level of the lower pons.

The central segment of the auditory system extends from the cochlear nuclei up to the auditory cortex of the temporal lobe. The cochlear nuclei send projections to the superior olivary nucleus of the pons. Here most of the auditory input crosses to the contralateral side via the trapezoid body to form the lateral lemniscus. The lateral lemniscus is the auditory tract that traverses the pons to the inferior colliculus of the midbrain. At this level the inferior colliculi intermingle information from both ears. Inferior colliculi axons project on to the medial geniculate bodies of the thalamus. From there the auditory radiations project to the primary auditory cortex of the temporal lobe. Each auditory cortex receives input from both ears. As a result, lesions of the central auditory pathway cause bilateral hearing loss, though the loss is greater on the contralateral side. Peripheral lesions cause unilateral ipsilateral loss. Cortical deafness only occurs when both temporal lobes are injured. Unilateral temporal insults do not clinically affect hearing.

Types of Hearing Loss

Hearing loss is divided into two broad categories—conductive hearing loss (CHL) and sensorineural hearing loss (SNHL). Mixed hearing loss is a combination of the two.

CHL involves problems of the external and middle ear. SNHL involves the cochlea, cochlear division of the eighth cranial nerve, and the central nervous system portion of the auditory pathway.

Tinnitus

Tinnitus is the perception of sound without an auditory stimulus. Ninety-four percentage of healthy young people report perceiving tinnitus at times (2). Ringing, buzzing, whistling, and humming are some descriptors of tinnitus. It may be a symptom of disease though not necessarily. Fifty percentage of persons with sudden hearing loss will describe associated tinnitus. Tinnitus may be associated with CHL or SNHL.

DIFFERENTIAL DIAGNOSIS

Acute Conductive Hearing Loss

Acute causes of CHL include cerumen impaction of the external auditory canal, TM perforation secondary to trauma or infection, acute effusion of the middle ear from otitis media, ossicular chain dysfunction, and eustachian tube obstruction. TM perforation leads to 15 to 20 dB of CHL. Acute barotrauma from the inability to equalize pressure between the external and middle ear during scuba diving or altitude changes during air flight or driving can lead to painful, temporary CHL.

Acute Sensorineural Hearing Loss

SNHL has many causes including ototoxic drugs, acute infections, chronic meningitis, loud noise, vascular disease, barotrauma, Ménière's disease, multiple sclerosis, migraine (3), and autoimmune inner ear disease (AIED). Acute SNHL may also be idiopathic. Drugs known to cause ototoxicity include aminoglycosides, intravenous erythromycin, loop diuretics, salicylates, antineoplastic agents such as cisplatin and vincristine, and has been newly reported in patients using the phosphodiesterase five inhibitors sildenafil, tadalafil, and vardenafil for erectile dysfunction (4). Aminoglycoside ototoxicity is related to the total serum concentration of the drug, though it is heightened by increasing age and appears to have a genetic component. Tinnitus is a common early symptom. Loop diuretic–associated ototoxicity is usually temporary, but can be permanent. Salicylate concentrations of 20 to 50 mg/dL can cause up to 30 dB of hearing loss. Tinnitus increases as the plasma levels exceed 40

mg/dL. Bacterial meningitis causes hearing loss in up to 35% of infections by injuring the inner hair cells of the cochlea. Viruses that have caused hearing loss include measles, mumps, rubella, CMV, herpes zoster, herpes simplex, and HIV. Spirochete infections of early and late syphilis and Lyme disease may cause unilateral or bilateral SNHL. Syphilitic hearing loss may be fluctuating and associated with vertigo resembling Ménière's disease. Chronic meningitis involving the auditory nerve—both infectious and noninfectious—may cause or present with acute SNHL. Sarcoid, mycotic, lymphomatous, carcinomatous, and tuberculous infiltrations have been described. Other cranial nerves may or may not be involved. Extreme noise levels may lead to cochlear spiral ganglion degeneration and SNHL by damaging sensory hair cells. This is often temporary, though prolonged exposure to sounds above 85 dB may cause permanent hearing loss. Hearing loss has also been described with automobile airbag detonation (5). Cerebrovascular accidents and transient ischemic attacks involving the vertebrobasilar circulation may lead to acute SNHL. The anterior-inferior cerebellar artery serves the lateral pons, middle cerebellar peduncle, and the inner ear. Strokes in this distribution cause vertigo, severe SNHL loss, and ataxia (6). Infarction in the distribution of the superior cerebellar artery leads to contralateral partial hearing loss by involving the lateral lemniscus. Cochlear anoxia due to poor microcirculation or vasculitis may cause acute SNHL. Hyperviscosity states in Waldenstrom macroglobulinemia and polycythemia can impair cochlear circulation. Spontaneous hemorrhage of the inner ear has occurred with leukemia, sickle cell disease, thalassemia, subarachnoid hemorrhage, trauma, and hypercoagulable states. Sudden SNHL and vertigo occurring within hours or days may be due to a perilymphatic fistula (PLF). PLF from rupture of the round or oval window between the air-filled middle ear and fluid-filled inner ear may be caused by barometric pressure changes from scuba diving, airplane flight, mountain travel, and even vigorous sneezing. Ménière's disease is a syndrome that causes recurrent fluctuating hearing loss, vertigo, and tinnitus. The hearing loss usually resolves within 24 hours, though it eventually becomes

permanent. Multiple sclerosis may present with acute SNHL or vertigo. Migraine headache can be associated with acute SNHL, likely due to vasospasm, and may cause migrainous infarction (3). AIED is an immune-mediated cause of SNHL which may present with rapidly progressive hearing loss. It has been associated with relapsing polychondritis, Wegener granulomatosis, systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, Behcet syndrome, giant cell arteritis, sarcoidosis, and Cogan Syndrome—an interstitial keratitis and vestibuloauditory syndrome which presents with abrupt vertigo, tinnitus, hearing loss, and ataxia. AIED with immune-mediated hearing loss but without systemic symptoms can present as rapidly progressive bilateral deafness as well. Sudden idiopathic SNHL may present acutely with immediate onset or progressive hearing loss over 3 days. It may be bilateral but is unilateral in 90%. Four thousand new cases/year occur in the United States. Any age group may be affected, though it occurs more often between ages of 30 and 60 years. Associated symptoms may include vertigo, tinnitus, or both. The natural history of acute idiopathic SNHL is complete recovery without medical intervention in as many as two-thirds, often within first 3 days to 2 weeks. Hearing worsens over time in 15% (7).

Mixed Hearing Loss (CHL Plus SNHL)

Processes that extensively involve the temporal bone such as tuberculosis and trauma can cause mixed hearing loss. Temporal bone fractures can be longitudinal or transverse, though 70% to 90% are longitudinal. AHL associated with longitudinal fractures involving the external auditory canal, middle ear, and long axis of the petrous pyramid is predominantly CHL, though SNHL occurs in 35% and facial nerve paralysis in 15%. Transverse fractures involving the cochlea and/or auditory nerve can cause total sudden SNHL and may be associated with facial nerve paralysis as well. Penetrating trauma can cause both CHL and SNHL depending on the trajectory and force of the missile.

Blast injuries can cause TM disruption, ossicular discontinuity, cochlear injury, and temporal bone fracture, leading to CHL and SNHL. If a PLF develops, there may be progressive hearing loss and disequilibrium. Lightning and electrocution may produce TM perforation and CHL as well as temporal bone fracture–related SNHL. Bilateral oval window PLF from lightning strike can cause SNHL. Cerebellopontine angle tumors may present with AHL in as many as 20%. Unilateral tinnitus is often present. Meningiomas and cholesteatomas also have presented with AHL. Primary or metastatic tumors to the temporal bone may cause CHL or SNHL. Breast, prostate, and renal cell carcinoma are the most common metastatic tumor types.

ACUTE HEARING LOSS AND ASSOCIATED SYMPTOMS

AHL and Tinnitus

Acute CHL due to otitis media as well as cerumen impaction may have associated tinnitus. Acute SNHL is associated with tinnitus in Ménière's disease and other causes of sudden SNHL such as ototoxic drugs including salicylates and loop diuretics. Sixty-five percentage of patients with vestibular schwannomas will have constant tinnitus. Pulsatile tinnitus may be a sign of neoplasm; arterial, venous, and intracranial hypertension; and great vessel bruits. Paragangliomas (glomus jugulare tumors) present initially with pulsatile tinnitus and CHL.

AHL and Vertigo

Vertigo can be associated with both CHL and SNHL. Labyrinthine disorders, PLF, Ménière's disease, multiple sclerosis, and cerebellopontine angle tumors can cause both. Brainstem, cerebellar, and higher causes of vertigo do not usually affect hearing (8).

ED EVALUATION

The ED evaluation of AHL should include a directed history and physical examination regarding the hearing loss complaint; an

assessment of hearing, differentiating between CHL and SNHL; recognition of the presence of tinnitus, vertigo, and other focal neurologic findings as well as underlying diseases such as cancer and autoimmune disease; and assessment of the medication list for ototoxic medications.

The ED physician's tools to differentiate CHL from SNHL include the tuning fork tests. Using a 256- or 512-Hz tuning fork, the Weber test is performed by placing the tuning fork on the patient's forehead or front teeth. Normally sound is heard the same in both ears. With CHL sound is louder in the poorer-hearing ear (lateralizes to the bad ear). In SNHL sound is louder in the better-hearing ear (lateralizes to the good ear). The Rinne test is performed by first placing the tuning fork on the mastoid bone. When the patient no longer hears sound, the fork is then placed at the auditory meatus. Normally sound should still be heard because air conduction is greater than bone conduction. Inability to hear in front of the ear indicates CHL. In SNHL hearing at both positions will be decreased.

CT scan of the temporal bone is indicated in the setting of head trauma and AHL. CT is best at evaluating fractures and the integrity of the middle ear ossicular chain. MRI is best for fluid, blood, and soft tissue masses. Nontraumatic acute idiopathic SNHL is best evaluated by MRI with gadolinium contrast. Routine laboratory tests and CT scan of the head are not recommended in the evaluation of acute idiopathic SNHL (9). Tinnitus with concerning characteristics —persistent unilateral, pulsating, or fluctuating, and associated with vertigo warrants investigation.

KEY TESTING

- Differentiate CHL from SNHL by physical examination
- Carefully assess for associated symptoms or neurologic deficits
- Consider MRI for acute idiopathic SNHL

ED MANAGEMENT

If the cause of hearing loss is obvious, the management should be directed toward it, for example, remove cerumen from the ear canal,

treat infections, including otitis media or meningitis, or reduce or discontinue ototoxic medications. An Ear, Nose, and Throat (ENT) specialist should be consulted for patients with hearing loss associated with temporal bone trauma. Acute idiopathic SNHL is considered a medical emergency (10). Patients with acute idiopathic SNHL may be candidates for special interventions including high-dose corticosteroids orally, intravenously, or intratympanically. It is recommended that if oral corticosteroid therapy is used it should be initiated immediately, ideally within the first 14 days of hearing loss. The initial dose of prednisone is 1 mg/kg/d (maximum 60 mg/d) at full dose for 7 to 14 days and then tapered over a similar time period. Immediate consultation with the ENT specialist is ideal (9–11). Intratympanic steroids may be used as salvage therapy, although there is now evidence that the intratympanic approach is equivalent to oral therapy in outcome. Intratympanic steroids may be preferred for patients who are not good candidates for high-dose oral corticosteroids due to other comorbidities, for example, diabetes (12). Other therapies may include hyperbaric oxygen, antiviral medications, carbogen inhalation, and bed rest although empiric antiviral therapy is not currently recommended (9). The ENT specialist may choose to hospitalize the patient. PLF may require surgery. As many as two-thirds of patients with acute SNHL improve without intervention (7). Most of the patients who will improve usually do so within 2 weeks. Evaluating the efficacy of interventions is beyond the scope of this discussion. A clinical guideline published by the American Academy of Otolaryngology-Head and Neck Surgery in 2012 outlines the current recommendations of the ENT community for the evaluation and management of sudden hearing loss (9).

CRITICAL INTERVENTIONS

- Emergent discussion with ENT specialist for acute SNHL

DISPOSITION

Most cases of AHL may be discharged home with appropriate follow-up, depending on the suspected cause and underlying comorbidities. If the patient has acute SNHL, emergent discussion with an ENT specialist is recommended.

Common Pitfalls

- Not distinguishing between CHL and SNHL.
- Not contacting ENT emergently for patients with acute SNHL.
- Not considering ototoxic medications, autoimmune disease, neurologic disease infections, cancer or hematologic disease as a cause of acute SNHL.
- Not considering simple causes such as cerumen impaction for hearing loss.
- Not considering tumor as a cause of acute unilateral tinnitus and/or hearing loss.

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CHAPTER 72

Complications of Tracheostomies

Valerie Dobiesz, Samreen Vora, and Carissa Tyo

Tracheostomy placement is a mainstay in airway management of critically ill patients. A tracheostomy tube is placed because of mechanical obstruction, inability to clear secretions, or need for prolonged ventilation. A tracheostomy provides access for mechanical ventilation, clearance of secretions, and protection of the airway. Placement may be done in the operating room using an open technique, or at the bedside in the intensive care unit (ICU) using a percutaneous dilational tracheostomy (PDT) technique. This surgical procedure has been known for centuries, with references to this practice in Eber's Papyrus (1550 BC) and the ancient Rig Veda texts (two of the three oldest known medical works) (1,2).

Complications of these devices range from minor inconveniences for the patient to life-threatening emergencies and may occur immediately postoperatively or may be delayed in nature. Complications include local bleeding, obstruction, infection, stenosis, tracheoesophageal fistula, pneumothorax, pneumomediastinum, air leaks, dislodgement, false passage, tracheostomy tube fractures with aspiration, and decannulation. Rarely, an extra-long tube can lead to right mainstem bronchus intubation recognized in the immediate postoperative period. The overall mortality rate is $<1\%$ with a total complication rate of up to 65%. A greater mortality rate and complication rate are seen in emergency situations, ICU patients, and pediatric patients (3,4). Because the tracheostomy tube is frequently encountered in the

emergency department (ED), emergency physicians must be aware of the purpose, structure, and proper maintenance of these devices, so they will be prepared for complications.

HEMORRHAGE

Major hemorrhage during and soon after tracheostomy is rare but can be life threatening. Bleeding complications account for 20% of ED tracheostomy visits (5). There are numerous vessels in the vicinity that can bleed and cause problems, including the superficial blood vessels, thyroid vessels, carotid arteries, anterior jugular veins, and the innominate (brachiocephalic) artery. The lacerated thyroid gland can bleed, as can granulation tissue. Incisional or stomal bleeding may be controlled with cauterization or packing the wound with petroleum jelly gauze.

Of particular concern is the potential for a tracheoarterial fistula. This fistula is typically caused by erosion of the tip of the tracheostomy tube into the innominate artery, producing massive bleeding that is universally fatal if not recognized and treated immediately. Tracheo-innominate artery fistula (TIF) is reported in approximately 0.1% to 1% of surgical tracheostomy patients and 0.35% of PDT patients; moreover, delayed hemorrhage is underreported (6). Although rare, TIF has a mortality rate of 50% to 75% despite emergent management (5). The clinical presentation may include a sentinel bleed in the form of hemoptysis or mild bleeding at the tracheostomy site hours or days before massive bleeding occurs.

The ED evaluation should include a rapid assessment for airway patency and for signs of shock or coagulopathy. Basic laboratory studies and a type and screen are helpful in this regard.

The ED management should initially focus on resuscitation, if necessary. Vigorous resuscitation with isotonic fluids and possibly blood should be started for any brisk bleeding while emergent surgical consultation is obtained for definitive management. Bronchoscopy is the diagnostic method of choice. Temporizing measures should be attempted to control the bleeding, such as

hyperinflation of the tracheostomy cuff to compress bleeding vessels against the sternal wall. If cuff inflation is unsuccessful, digital pressure should be applied to the anterior tracheal wall through the tracheostomy, compressing the anterior tracheal wall against the sternum until definitive care can be provided (7,8).

OBSTRUCTION

A patient with a tracheostomy who presents with respiratory distress must first be assessed for either a partial or complete obstruction of the tracheostomy tube. Patients with tracheostomies lack the humidification of air inspired by nasal passages, and this often results in thick, dry secretions. Improper care and maintenance of tracheostomy tubes in the outpatient setting are common. Mucus, inspissated secretions, blood, or dislodgement of the tracheostomy tube may cause life-threatening obstruction. Secretions may act as a ball valve, allowing air in but restricting outward ventilation (9).

The clinical presentation may range from slow, progressive shortness of breath to sudden obstruction and respiratory arrest.

The initial ED management should include verification of proper placement of the tracheostomy tube, with repositioning as needed. Treatment with high-flow oxygen should be initiated. Saline, hypertonic saline, or N-acetylcysteine may be used to help loosen secretions, followed by suction with an endotracheal suction catheter. Nebulized sodium bicarbonate raises the pH of secretions and weakens the saccharide structure of the mucus, and may offer an additive benefit when combined with nebulized N-acetylcysteine (10).

The inner cannula should be removed and cleaned, as this is a common source of obstruction. However, if the problem persists, the outer cannula should be removed and replaced with a new tracheostomy tube. Mechanical problems with the tube such as cuff leak or tube fracture may also necessitate tube replacement or consultation for bronchoscopy (9,11). Replacement of the tracheostomy tube in nonemergent circumstances is described in

Table 72.1. However, the process may need to be abbreviated in the prehospital or emergency setting. A patient in respiratory distress not relieved by conservative methods such as suction, oxygen, and bronchodilators should be treated by immediate removal of the tracheostomy tube and tube replacement. Most obstructions occur in patients with long-standing tracheostomies, and those patients generally have uncuffed tracheostomy tubes that can be easily removed (12). If a new tracheostomy tube needs to be emergently replaced, the procedure may be simplified by passing a catheter or gum elastic bougie through the old tracheostomy tube and using it to guide the removal and replacement of the tube (12).

TABLE 72.1
Replacement of the Tracheostomy Cannula

1. Preoxygenate the patient and extend the head slightly to facilitate placement. Removal and replacement of tracheostomy tubes should follow the curved path of the tube itself.
2. Lubricate the new tube with a water-soluble lubricant, and place the obturator inside the tube to facilitate insertion. This obturator will be removed after tube placement.
3. A well-positioned tube can be advanced gently with little resistance. Tracheal hooks or a dilator may be used to hold the stoma open.
4. If force is necessary to place the tube, efforts should be discontinued because of the possibility of creating false passages, bleeding, and edema.
5. A safe method to ensure proper placement of a tracheostomy tube is to use a thin red rubber catheter as a guide. The catheter can be placed through the existing tracheostomy before removal. If the tracheostomy tube has accidentally fallen out, the catheter may be placed directly through the stoma. Once the old tracheostomy tube is removed, the new tube without the obturator can be passed over the catheter into place. The red rubber catheter can then be removed.[a]
6. Secure the tube with tracheal tube ties tightened enough so that only one finger can fit between the patient's neck and the tube tie.
7. Correct tube placement may be confirmed clinically, radiographically, or using end-tidal CO_2 detection.

[a]Adapted from Rowe BH, Rampton J, Bota GW, et al. Life-threatening luminal obstruction due to mucous plugging in chronic tracheostomies: Three case reports and a review of the literature. *J Emerg Med.* 1996;14(5):565–567.

INFECTION

Serious infection of the stomal site is rare, despite most fresh wounds being colonized by nosocomial organisms (13). The patient's underlying medical condition, the presence of an indwelling device, and exposure to flora-colonizing ventilator tubing predisposes to infection, including lower respiratory infections. Prophylactic antibiotics, however, are not indicated.

The clinical presentation ranges from cellulitis or drainage around the tracheostomy tube to tracheitis, bronchitis, pneumonia, or sepsis.

The ED management of peristomal cellulitis consists of outpatient antibiotics for mild cases. Rarely, the wound infection may spread inferiorly, causing mediastinitis, mediastinal abscess, and paratracheal abscess. Patients with signs or symptoms of systemic infection or pain with breathing and swallowing should be evaluated for these complications, usually by imaging with computed tomography (CT) scan, and given intravenous antibiotics. Antibiotics should cover common respiratory flora, though methicillin-resistant Staphylococcus aureus must also be considered.

STENOSIS

Constant pressure from the cuff may cause pressure necrosis, ulceration, and formation of granulation tissue that subsequently causes tracheal stenosis (14). This is a late complication presenting weeks to months after decannulation.

The clinical presentation is insidious. Typically, patients do not become symptomatic until the endotracheal lumen has been reduced by 50% to 75%, at which point they may complain of cough, dyspnea, and inability to clear secretions.

The ED evaluation includes consultation or referral, because the diagnosis of stenosis is typically made with bronchoscopy. Once identified, significant stenosis is treated with operative dilation or resection of granulation tissue.

TRACHEOESOPHAGEAL FISTULA

Tracheoesophageal fistula is a rare but potentially life-threatening complication. It is caused either by perforation of the posterior wall of the trachea during the tracheotomy or erosion into the esophagus by the tracheostomy tube.

The clinical presentation may include signs and symptoms of cuff leak, aspiration of food contents, abdominal distention, or copious secretions (4).

The ED evaluation includes making arrangements for bronchoscopy or swallowing studies to confirm the diagnosis. This complication has also been associated with PDT (1,15).

PERCUTANEOUS DILATIONAL TRACHEOSTOMY

An alternative technique to surgical tracheostomy is a PDT, which was first described in 1985 and has become a popular alternative and has recently been proposed as the new gold standard (16–19). This technique has several advantages compared to surgical tracheostomies, including lower rates of pneumothorax, major hemorrhage, and laryngeal granulation (18). PDT can be done at the bedside, thereby reducing the operative risk and the cost. A major advantage is the ability to gain and maintain competence with the procedure in the elective setting (20). Long-term complications are the same as for standard surgical tracheostomy, although there is a slight reduction in tracheal stenosis with PDT. This procedure also has some unique risks not encountered with surgical tracheostomy, such as paratracheal insertion of a tracheostomy tube and posterolateral tracheal wall laceration (21). However, these complications are not common and are rarely lethal with a reported mortality rate of 0.17% (3,14).

REPLACEMENT OF TRACHEOSTOMY CANNULA

Tracheostomy tubes may be cuffed or uncuffed and may come with an inner cannula that can be removed for cleaning (Table 72.1). Indications for replacement of the tracheostomy tube in the ED include cuff rupture or leak and complete or partial obstruction. Changing the tracheostomy should be avoided for at least 1 week

after the creation of the stoma, if possible. A replacement tube should be the same type and size as the original. In an emergency, replacement with a smaller size is preferred if maintaining a patent airway depends on it. If the appropriate-sized tracheostomy tube is unavailable in an emergency situation, a standard endotracheal tube may serve as a temporary replacement, typically a size 6 mm to 7.5 mm cuffed tube in an adult.

If the tracheostomy tube cannot be replaced and the airway is in jeopardy, the physician should consider oral endotracheal intubation. The original indication for the tracheostomy may hamper attempts at endotracheal intubation (e.g., laryngeal malignancy). If respiratory distress persists after adequate tube replacement, the physician must not overlook other causes such as pneumothorax, pulmonary embolus, pneumonia, or congestive heart failure.

CRITICAL INTERVENTIONS

- Obstruction of a tracheostomy tube can be life threatening. Remove the inner cannula and clear the obstruction to restore airway patency.
- Gain rapid control of hemorrhage, and consult a surgeon for definitive care.

DISPOSITION

Patients with minor bleeding or infection around a tracheostomy tube site may be treated and discharged with appropriate follow-up. Those patients with partial obstruction caused by deposits or secretion buildup on the tracheostomy tube may also be discharged after the tube is cleaned or changed and the symptoms are resolved.

Patients with persistent bleeding, more serious infection, or difficulty breathing mandate consultation and admission. Those patients with suspected tracheoesophageal fistula or early stenosis may be further evaluated on an inpatient or outpatient basis, depending upon the severity of symptoms.

Common Pitfalls

- Failure to rapidly clear or remove an obstructed tracheostomy tube.
- Inadequate control of hemorrhage around a tracheostomy tube. A tracheoarterial fistula should be suspected if a patient presents with brisk bleeding from the tracheostomy tube site.
- Overly aggressive application of force when replacing a tracheostomy tube must be avoided to prevent the creation of a false tract.

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SECTION VII
Pulmonary Emergencies

Section Editor: JEFFREY J. SCHAIDER

CHAPTER 73 Respiratory Failure

Micelle J. Haydel

Respiration is the exchange of gases at the level of the alveoli occurring by simple diffusion. Gas in the alveoli has a high concentration of oxygen and a low concentration of carbon dioxide relative to the deoxygenated blood passing through the alveolar capillary bed. Oxygen and carbon dioxide both diffuse freely through alveolar membranes. Oxygen molecules bind to hemoglobin to be off-loaded in the tissues to be used to generate cellular energy, and the by-product CO_2 which is then carried back to the alveoli for exhalation. The O_2–CO_2 gradient at the capillary-alveolar border is constantly maintained, permitting the passive diffusion of gases, while the contraction and relaxation of intercostal muscles actively draws oxygenated gases into the alveoli and then pushes the carbon dioxide–rich gas out of the alveoli. Any part of this process can be altered leading to respiratory distress and failure.

CLINICAL PRESENTATION

Respiratory distress implies that the work of breathing has increased to the point that a patient displays clinical evidence of difficulty in breathing, such as tachypnea, dyspnea, and accessory muscle use. *Dyspnea* is the sensation of difficulty breathing and is most commonly caused by congestive heart failure, asthma, chronic obstructive pulmonary disease, and pneumonia. *Respiratory failure* implies that a patient is not able to maintain adequate oxygenation and/or ventilation. Respiratory failure is a clinical diagnosis, although measurements of the partial pressure of oxygen and carbon

dioxide are used to assess the patient's respiratory status. In general, patients with clinical respiratory failure exhibit hypoxemia (PO_2 <60) and/or hypercapnea (PCO_2 >45) with a concomitant respiratory acidosis (pH <7.34) (1). Symptoms of respiratory distress and failure depend on the chronicity of the respiratory impairment, the presence of comorbidities, and the patient's physical ability to perform the increased work of breathing.

Hypoxia leads to a physiologic increase in respiratory rate and cardiac output to compensate for the oxygen deficit. As the patient attempts to compensate for the hypoxemia, clinical findings will include tachypnea, accessory muscle recruitment, abdominal paradoxical movements, and intercostal retractions. This increased work of breathing increases a patient's oxygen consumption to 10 times the resting state (2). Patients with mild–moderate hypoxemia display tachypnea, tachycardia, and hypertension, and may complain of headache. Patients with severe hypoxemia display somnolence, confusion, and seizures. As hypoxemia worsens, patients develop bradycardia and hypotension, leading to permanent hypoxic encephalopathy or death.

Hypercarbia leads to physiologic increase in rate and depth of respirations, and signs and symptoms of hypercarbia depend on the level and rate of increase in PCO_2. A high PCO_2 can be well tolerated if it develops slowly, minimizing acidemia via renal compensatory mechanisms. Acute noncompensated hypercarbia (PCO_2 >80) leads to intracellular acidosis, myocardial depression, dysrhythmias, cerebral vasodilation, and elevated intracranial pressure. Patients with hypercarbia may have agitation, confusion, headaches, seizures, and/or coma, although these neurologic effects of hypercarbia are reversible in patients without concomitant intracerebral injury or stroke (3).

DIFFERENTIAL DIAGNOSIS

Respiratory complaints account for up to 10% of emergency department (ED) visits and dyspnea as a chief complaint has the highest association with inhospital mortality (4). A differential

diagnosis can be based on the primary blood gas abnormality, such as hypoxic, hypercapnic, or mixed respiratory failure. In hypoxic respiratory failure, gas exchange is blocked in an area of the lungs due to disease processes such as pneumonia, pulmonary edema, pulmonary embolism, or pneumothorax. Carbon dioxide has a high diffusion capacity and may be unaffected by this "increased shunt," but will be greatly affected by hypoventilation. Hypercarbic respiratory failure is the inability of gas flow to maintain the necessary off-loading of carbon dioxide at the alveolar level, and is commonly seen in COPD, neuromuscular disease, and opiate toxidromes.

While the most common causes of dyspnea are pneumonia, asthma/COPD, congestive heart failure, and pulmonary embolism (5), several potentially lethal disease states can cause dyspnea and respiratory failure without hypoxemia or hypercarbia on blood gas analysis. When the etiology of dyspnea cannot be explained by the hypoxic/hypercarbic approach, a cognitive map based on four general categories: pulmonary, cardiovascular, neuromuscular, and systemic (Table 73.1), leads the clinician to consider less common causes of respiratory distress, to identify contradictory findings in the H&P, and to determine if more than one disease process is involved. The differential diagnosis of dyspnea in the trauma setting is listed in Table 73.2.

ED EVALUATION

Emergency patients with undifferentiated respiratory distress or impending respiratory failure should be approached in a logical, step-wise manner (Table 73.3) with a goal of:

1. Immediately detect and mitigate life-threatening hypoxemia and hypercarbia.
2. Formulate and initiate critical actions without a complete dataset.
3. Establish a differential diagnosis based first on the most lethal, and then the most likely diagnosis.

Assess Upper Airway

Clinicians must rapidly evaluate the upper airway of patients with dyspnea to rule out the possibility of obstruction, as well as to prepare for the possibility of difficult airway management. Patients with stridor, muffled voice, drooling, neck hematoma, or swelling should be examined for mechanical obstruction due to infection, foreign body, malignancy, or trauma. The presence of obesity, facial hair, poor or absent dentition, and older age are associated with a difficult bag-mask seal. Mallampati classification and measurement of the thyromental and inter-incisor distance can be used to assess for challenges in intubation (6) (see Chapter 1).

TABLE 73.1
Differential Diagnosis of Respiratory Distress and Failure

Upper Airway
Acute obstruction: Foreign body, trauma, tumor
Epiglottitis, laryngotracheitis
Angioedema, anaphylaxis

Lower Airway
Asthma, COPD, emphysema
Pneumonia, bronchiolitis
Acute lung injury, ARDS, pneumonitis, vasculitis, pulmonary contusion
Cystic fibrosis, interstitial lung diseases
Autoimmune lung diseases, lung cancer

Pleural Processes: Effusions, empyema, hemothorax, pneumothorax

Pulmonary Emboli

Cardiovascular Diseases
Congestive heart failure
Myocardial infarct
Valvular disease, congenital structural disorders
Dysrhythmias, cardiomyopathies
Pericardial tamponade, aortic dissection
High output heart failure (see systemic processes)

Neuromuscular Diseases
Guillain–Barré, Myasthenia gravis
Botulism, tetanus

Systemic Diseases
High output heart failure: Severe anemia, beriberi, thyrotoxicosis
Sepsis
Massive obesity, sleep apnea
Toxins: Cyanide, carbon monoxide, organophosphates, salicylates
Metabolic, acid–base or electrolyte disturbances

COPD, chronic obstructive pulmonary disease; ARDS, adult respiratory distress syndrome.

Assessment of Adequacy of Oxygenation

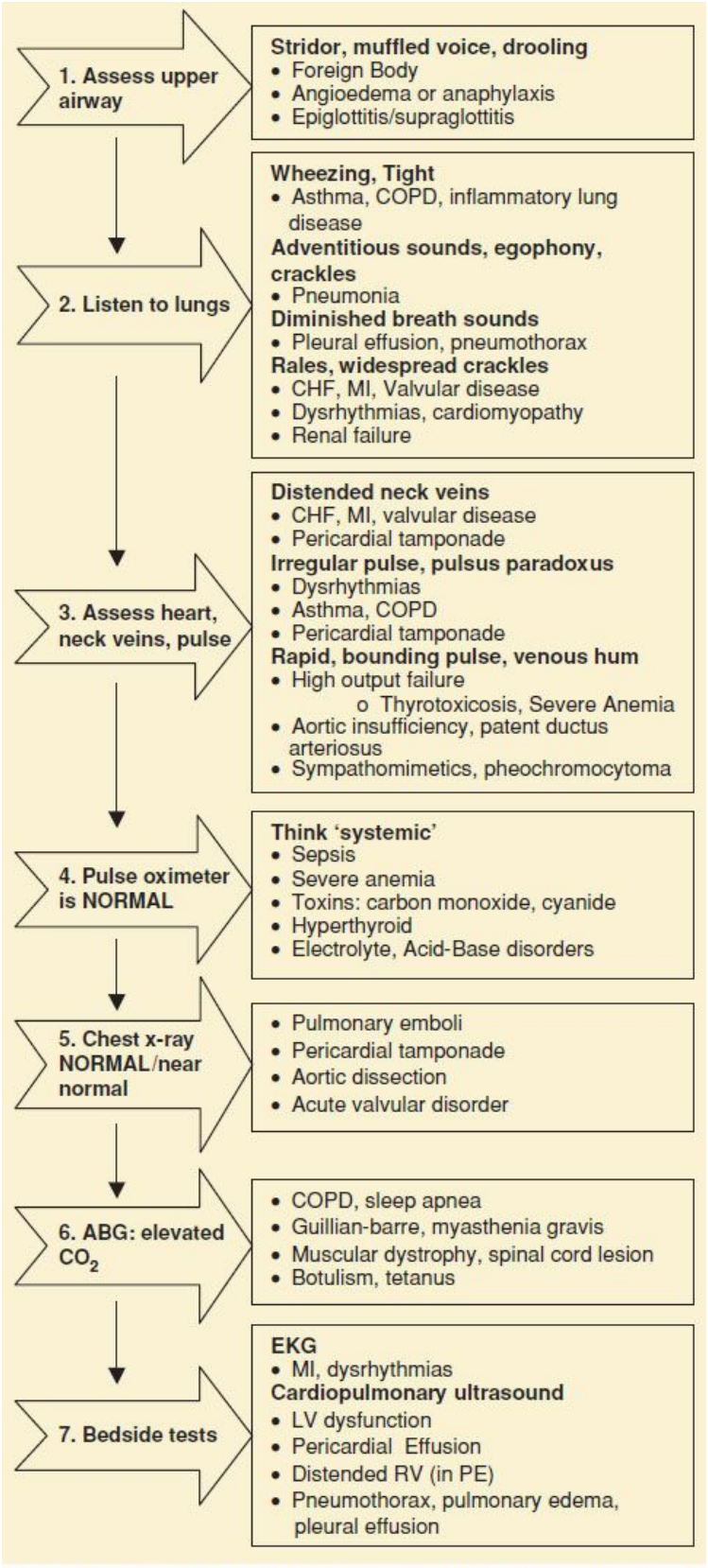
Oxygen delivery to vital organs is the cornerstone of the management of respiratory failure. Bedside pulse oximetry estimates hemoglobin oxygen saturation (SaO_2) by analyzing the transmission of light through a cutaneous vascular bed. Pulse oximetry will overestimate arterial oxygenation in the presence of poor perfusion or carboxyhemoglobin; it will underestimate it in the presence of

methemoglobin (7). An arterial blood gas (ABG) analysis, most commonly measures SaO_2 indirectly by plotting the PaO_2 on a standardized temperature- and pH-adjusted O_2–hemoglobin dissociation curve, while ABG analysis using a co-oximeter has the ability to directly measure the concentrations of oxygenated and deoxygenated hemoglobin.

TABLE 73.2
Differential Diagnosis of Dyspnea in the Trauma Setting

Hemothorax
Pneumothorax
Pulmonary contusion
Cardiac contusion
Severe hypovolemia
Flail chest
Pericardial tamponade

TABLE 73.3
Severe Undifferentiated Respiratory Distress



The vast majority of patients with respiratory distress can be diagnosed based on the physical examination (1, 2, 3). When the diagnosis remains elusive, bedside tests (4, 5, 6, and 7) will narrow the diagnosis.

TABLE 73.4
Formula to Predict Acid–Base Compensation

Acute Respiratory Acidosis
pH will change 0.08 for each 10 mm Hg change in PCO_2
HCO_3^- will rise 1 mEq/L for each 10 mm Hg rise in PCO_2

Acute Respiratory Alkalosis
pH will change 0.08 for each 10 mm Hg change in PCO_2
HCO_3^- will decrease 2 mEq/L for each 10 mm Hg decrement in PCO_2

Chronic Respiratory Acidosis
pH will decrease 0.03 for each 10 mm Hg increase in PCO_2
HCO_3^- will rise 3.5 mEq/L per 10 mm Hg increment in PCO_2

Chronic Respiratory Alkalosis
pH will increase 0.02 for each 10 mm Hg decrease in PCO_2
HCO_3^- will fall 5 mEq/L per 10 mm Hg decrement in PCO_2

Winter's formula for mixed disorders: Calculate the expected $PCO_2 = (1.5 \times HCO_3) + 8$ (if measured PCO_2 on an ABG is higher than the expected PCO_2, then a respiratory acidosis is also present)

Assessment of the Adequacy of Ventilation

While pulse oximetry is used routinely in most emergency settings, it does not provide information about ventilation, and can be falsely reassuring if the clinician assumes that a normal pulse oximetry reading reflects adequate alveolar ventilation. Noninvasive measures of ventilation (exhaled CO_2) have gained widespread use in the ED as an adjunct to pulse oximetry. Bedside capnography provides a numeric and waveform representation of exhaled CO_2 ($ETCO_2$), corresponding to arterial PCO_2. Patients with a normal baseline (35 to 45 mm Hg) $ETCO_2$ can be expected to have an increase in their $ETCO_2$ during hypoventilation and a decrease during hyperventilation. $ETCO_2$ measures only the exhaled CO_2, not the actual $PaCO_2$ and therefore a low $ETCO_2$ can also be seen in the setting of reduced cardiac output and pulmonary embolism.

ABG analysis remains the time-honored gold standard for assessing the adequacy of gas exchange and the acid–base balance. Many diseases are neither acute nor found in isolation, and the ABG is very useful in helping to determine the chronicity of the process, as well as the presence of a mixed respiratory–metabolic disorder. Commonly used acid–base formulas are listed in Table 73.4.

Physical Examination

In the early stages of respiratory distress, vital signs may reflect tachycardia, tachypnea, and hypertension, with the patient demonstrating increased work of breathing and accessory muscle use. As respiratory distress progresses, the patient is unable to speak in complete sentences and must rely on the tripod position to maintain respirations. Increasing hypoxemia or hypercarbia may lead to confusion and combativeness, progressing to a patient who is obtunded or comatose. Depending on the etiology of the respiratory distress and the patient's physical abilities, the progression from dyspnea to respiratory failure can be gradual or precipitous. In order to prepare for the possibility of a difficult airway, the initial assessment of any patient with respiratory complaints should include assessment of visibility of the soft palate, sternomental distance, and thyromental distance (6) (see Chapter 1).

Diagnostic Studies

An electrocardiogram (ECG) should be obtained in any adult with risk factors for coronary disease or cardiac symptoms. Dyspnea can be a symptom of cardiac as well as pulmonary disease; therefore, the ECG is useful in the evaluation of both adult and pediatric patients with undifferentiated dyspnea.

The measurement of peak expiratory flow rate as a surrogate index for forced expiratory volumes and should be standard practice in the management of patients with respiratory distress due to asthma or COPD. Flow rates $<50\%$ of personal best or baseline indicate a severe exacerbation and typically require consideration of

inpatient therapy if there is no satisfactory improvement after treatment.

Chest radiography can detect disease processes not identified by physical examination alone, while computed tomography (CT) is useful in patients when lung parenchymal or pleural disease cannot be delineated by plain radiography alone. CT angiogram has largely replaced ventilation–perfusion scanning in detecting pulmonary embolism. Bedside ultrasound can be used to identify pneumothorax, pleural effusion, and pulmonary edema. Ultrasound has more recently been proven to be very useful in the approach to the undifferentiated patient with respiratory distress (8).

Routine complete blood count, electrolytes, glucose, and renal indices should be obtained in patients with respiratory distress of unknown etiology. Other studies that may be indicated when specific diseases are suspected include cardiac enzymes (acute coronary syndromes), brain natriuretic peptide (congestive heart failure), D-dimer assay (thromboembolic disease), coagulation profile, liver enzymes (multisystem involvement), erythrocyte sedimentation rate (autoimmune diseases, pericarditis, myocarditis), and lactate dehydrogenase (LDH) (*Pneumocystis carinii* pneumonia).

ED Management Approach to the Undifferentiated Patient with Impending Respiratory Failure

1. Exclude upper airway obstruction: Foreign body, hematoma, infection, cancer, angioedema
2. Assess and ameliorate hypoxia
3. Assess ventilation and ameliorate hypercarbia
4. Initiate mechanical ventilation for hemodynamic instability, unstable dysrhythmias, fatigue, progressive respiratory acidosis and/or hypoxemia, loss of airway protective reflexes, alteration in level of consciousness, expected clinical course or lack of response to NIPPV
5. Bedside testing: Portable chest radiograph, electrocardiogram, ultrasound
6. Targeted treatment based on differential diagnosis (Table 73.1)

Oxygen Supplementation

The first step in the management of patients with respiratory distress is the addition of supplementary oxygen, titrating to optimize the individual clinical situation (9). Supplementary oxygen may be provided using a nasal cannula, simple face mask, and nonrebreathing face mask. Nasal cannula provides 24% to 40% oxygen via 1 to 6 L of flow, but high flow rates are poorly tolerated. A face mask provides supplemental O_2 concentrations of 40% to 60% when set to 10 to 12 LPM, whereas a nonrebreathing mask with a collapsible bag reservoir of high flow O_2 (10 to 15 LPM), optimally delivers O_2 concentrations of more than 70%. If these modalities do not provide adequate oxygenation, then mechanical modalities should be initiated to add positive pressure.

Noninvasive Ventilation

Noninvasive positive pressure ventilation (NIPPV) delivers mechanically assisted breaths without the need for intubation. The positive pressure improves oxygenation and gas exchange by increasing both tidal volume and functional residual capacity, and recruiting collapsed alveoli. NIPPV does reduce the work of breathing, but does not "protect the airway" and is therefore contraindicated in patients at high risk for aspiration, those with impaired level of consciousness or need for prolonged ventilator support (Table 73.5). NIPPV has been established in a variety of disease states in the emergency setting, including COPD, cardiogenic pulmonary edema, hypoxemic respiratory failure, and in patients with an acute respiratory exacerbation who do not wish to be intubated (10–12). NIPPV can be used cautiously as a bridge in patients with asthma or pneumonia, but these patients continue to require close monitoring (typically ICU) for deterioration (10). NIPPV failure is not uncommon, and can be predicted during the first hour of use by monitoring closely for continued respiratory distress, or failure to normalize respiratory rate and ABGs (13).

TABLE 73.5
NIPPV—Exclusion Criteria

Severe cardiopulmonary instability
Respiratory arrest
Hypotension or shock
Serious dysrhythmia
Acute myocardial infarction
Anatomic problems
Recent facial, esophageal, or gastric surgery
Craniofacial trauma or burns
Chronic anatomic abnormalities of the upper airway, nasopharynx, oropharynx
Inability to clear or maintain a patent airway and prevent aspiration
Impaired protective reflexes

NIPPV ventilators used in the ED are usually set to either continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP). CPAP provides the patient with airway pressure above the ambient atmospheric pressure and is held constant throughout the respiratory cycle, conceptually similar to extrinsic positive end-expiratory pressure (PEEP). BiPAP provides two distinct airway pressures cycled during inspiration (IPAP) and exhalation (EPAP). The work of breathing is a function of initiating and maintaining airflow throughout the inspiratory phase. The tidal volume is set by the clinician, and peak inspiratory pressures can be monitored to minimize the risk of barotrauma.

Suggested Protocol for Initiation of Noninvasive Positive-Pressure Ventilation

With the ventilator set in CPAP mode, the selected mask should be held to the face, allowing a brief period of acclimatization. Once patient cooperation is established, the mask is secured with straps. After the patient is accustomed to CPAP, the ventilator may be changed to BiPAP.

- CPAP settings: Start with 5 cm H_2O and titrate to a maximum of 20 cm H_2O.

- BiPAP settings: Start with IPAP of 10 cm H_2O and EPAP of 5 cm H_2O.
- IPAP is then incrementally adjusted to obtain exhaled tidal volume of 7 to 9 mL/kg ideal body weight, and RR <30. Maximum IPAP is typically 25 cm H_2O.
- EPAP is adjusted to maintain adequate oxygenation, with a typical maximum of 15 cm H_2O.
- FiO_2 is typically started at 40% and titrated to maintain oxygen saturations of $>90\%$.
- Tidal volumes: 10 to 15 mL/kg, which is typically higher than invasive ventilators due to the expected air leak around mask.

Endotracheal Intubation

No specific set of laboratory or clinical criteria can be used to identify all patients who require endotracheal intubation. The decision to intubate should begin with consideration of the patient's underlying disease process, cardiopulmonary reserve, and initial response to other medical therapies. Patients with respiratory distress and hemodynamic instability, dysrhythmias, fatigue, progressive respiratory acidosis and/or hypoxemia, loss of airway protective reflexes, alteration in level of consciousness, expected clinical course or lack of response to NIPPV should prompt plans to intubate (Table 73.6) (see Chapters 1 and 2).

TABLE 73.6
Indications for Initiation of Invasive Mechanical Ventilation in Adults with Respiratory Failure

Apnea or impending respiratory arrest
Cardiovascular hemodynamic instability
Altered mental status with need to protect the airway for:
Patency
To reduce risk of aspiration
To manage or control secretions
Acute ventilatory insufficiency in neuromuscular disease with one of the following:
Acute respiratory acidosis
Progressive decline in vital capacity to <10–15 cc/kg
Progressive decline in maximum inspiratory pressure to <20–30 cm H_2O
Failure of intensive therapy, possibly including NIPPV, in these states:
Acute exacerbation of COPD or asthma
Acute hypoxemic respiratory failure
Acute traumatic brain injury
Traumatic thoracic injury
Acute respiratory distress, any cause

NIPPV, noninvasive positive-pressure ventilation; COPD, chronic obstructive pulmonary disease.

Selection of a Ventilator Mode

The goal of mechanical ventilation in the acute care setting is to take over the work of breathing and maintain adequate gas exchange. The ventilator mode that accomplishes this most effectively is assist control (AC), and is the initial mode of choice in many ED scenarios. Oxygenation is optimized by titrating the FiO_2 quickly down from 100% to a goal of $<60\%$, whereas the PEEP is titrated up from 3 to 5 cm H_2O to prevent alveolar collapse. Ventilation (carbon dioxide off-loading) is optimized with a tidal volume of 8 mL/kg (ideal body weight) and a respiratory rate of 10 to 12 per minute. Patients with asthma or COPD benefit from a prolonged expiratory phase, achieved by lowering the rate to 8 per minute and tidal volume of 6 mL/kg. These settings must be tailored to the individual patient to avoid iatrogenic lung injury.

AC mode provides the highest level of ventilator assistance, because every breath the patient receives is at a predetermined tidal volume. The clinician sets both the tidal volume and the minimum rate. In AC mode, the ventilator delivers the set tidal volume each

time the patient initiates a breath, and also provides ventilator-initiated breaths at the same set tidal volume if the patient's respiratory rate is lower than that set by the clinician.

Synchronized intermittent mandatory ventilation (SIMV) differs from AC mode because the patient is allowed to control the tidal volume and flow rate of any spontaneous breaths exceeding the ventilator's set rate. When the patient breathes below the set rate, the mandatory breaths are synchronized with patient-initiated breaths and the work of breathing is similar to the AC mode. In contrast, spontaneous breaths above the set rate require the patient to generate enough negative force to pull air through the ventilator and to expand the chest cavity against the elastic recoil of the lungs. This increased work of breathing can be great enough to result in respiratory or metabolic acidosis. Clinicians can reduce the work of breathing by adding positive pressure (typically 20 cm H_2O) during the spontaneous breaths that exceed the set rate. In SIMV with pressure support, the patient initiates and terminates inspiration, thereby determining tidal volume.

In selected cases, when the reason for intubation is protection of the airway and the patient's ventilatory drive is intact, CPAP (+/– pressure support) may be appropriate. Positive pressure is provided during inhalation and exhalation, but the patient initiates and terminates each breath, controlling the tidal volume. The work of breathing occurs as the patient initiates each breath and maintains inspiratory effort throughout inhalation.

Monitoring Ventilator Pressures

Mechanical ventilation can cause damage to the lungs at both the macroscopic and microscopic levels. Ventilator-induced lung injury (VILI) encompasses all forms of injury, including pneumothorax, pneumomediastinum, bronchial rupture, and alveolar overdistension.

Peak inspiratory airway pressure is the highest pressure that is generated during inflation of the lung. Peak pressures are highly variable, dependent on lung compliance and airway resistance.

Plateau pressure is the end inspiratory airway pressure, measured just after airflow has ceased, and represents the pressure at the alveolar level. Plateau pressures in an adult with normal lung compliance is usually in the range of 5 to 15 cm H_2O, but is higher in patients with lung disease or overdistension. Plateau pressures should be maintained below 30 cm H_2O.

Auto-PEEP is ventilator-induced lung overdistension caused by inhalation initiated before exhalation is complete. Auto-PEEP and plateau pressures can be reduced by an incremental decrease in the tidal volume and respiratory rate.

CRITICAL INTERVENTIONS

- Anticipate difficult intubations to avoid unexpected failed airways.
- Use the AC ventilator mode as the initial mode after intubation.
- Monitor and control plateau pressure delivered to the alveolar level to help prevent VILI.

Disposition

The overwhelming majority of patients who present with acute respiratory failure require admission to the hospital. Indications for admission to the ICU include hemodynamic instability, respiratory failure requiring mechanical ventilation, need for frequent respiratory therapy and monitoring, rapid progression of respiratory failure, and failure to respond to intervention. Patients who improve with therapy and become stable may be managed on observation units or inpatient wards. Occasionally, a patient with asthma or mild congestive heart failure responds rapidly to treatment and remains stable during further observation in the ED. These patients may be cautiously discharged with close outpatient follow-up, if the patient's primary care physician is agreeable and can assure prompt follow-up.

Common Pitfalls

- Failure to recognize impending respiratory failure.
- Failure to consider alternative etiologies of respiratory failure.
- Failure to consider initiating noninvasive ventilation, leading to endotracheal intubation that might have been avoided.
- Overreliance on pulse oximetry to predict adequacy of oxygenation and ventilation.
- Failure to monitor airway pressures after initiation of mechanical ventilation.
- Failure to individualize ventilator settings, with consequent VILI.
- Use of CPAP or SIMV modes without sufficient pressure support, causing increased work of breathing.

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CHAPTER 74 Pneumonia

Gregory J. Moran and David A. Talan

In the United States, more than 3 million persons contract community-acquired pneumonia (CAP) annually, resulting in about 500,000 hospital admissions. Pneumonia is the most common infectious cause of death in the United States. Most deaths occur in the elderly or immunosuppressed, but pneumonia also occurs in otherwise healthy persons. To manage patients with pneumonia successfully, emergency physicians must maintain an awareness of the expanding spectrum of pathogens, changing antibiotic-resistance patterns, and availability of new antimicrobial agents.

Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, and viruses continue to be the most common causes of CAP, with *Legionella* sp and *Chlamydophila pneumoniae* less frequently diagnosed (1). Less common etiologies include gram-negative bacilli and oral anaerobes. *Staphylococcus aureus* was considered an uncommon cause of CAP, but recent studies indicate it is among the more common pathogens, particularly in seriously ill patients (2). *Pneumocystis jirovecii* (previously known as *P. carinii*) and *Mycobacterium tuberculosis* are important as pathogens related to pulmonary infections in patients with acquired immunodeficiency syndrome (AIDS). Knowledge of local prevalence patterns for pathogens of CAP is important to make appropriate choices regarding evaluation and treatment.

CLINICAL PRESENTATION

Typical and Atypical Pneumonias

Pneumonia is often divided into typical (pyogenic bacterial) and atypical categories, but this division is somewhat artificial. Prediction of these etiologies based on clinical and radiographic findings is inaccurate. The classic presentation of typical pyogenic bacterial pneumonia is the abrupt onset of fever and chills, followed by development of productive cough with purulent sputum and pleuritic chest pain. Elderly or debilitated patients can present with nonspecific complaints, such as altered mental status. Tachypnea and tachycardia are usually present. Physical examination signs of pneumonia include findings of consolidation such as dullness to percussion, coarse rales, bronchial breath sounds, or increased tactile fremitus.

The atypical pneumonia syndrome is caused by organisms such as *M. pneumoniae, C. pneumoniae,* viruses, *Legionella* sp, or rickettsial organisms such as *Coxiella burnetii.* Patients with this type of pneumonia generally present with a subacute onset of systemic complaints, such as fever, headache, malaise, and myalgias, associated with a nonproductive cough. Although mucopurulent sputum generally indicates the presence of pyogenic bacterial pneumonia or bronchitis, it can also be present with mycoplasmal or viral pneumonia. Chest examination often reveals scattered rhonchi or rales. Signs of consolidation are less common.

The high degree of overlap between the clinical and radiographic features of typical pyogenic and atypical pneumonia makes it impossible to accurately predict the specific type of pneumonia. Typical and atypical pathogens sometimes coexist in the same patient, and bacterial infections often coexist or follow viral respiratory infections. It is usually not possible to determine the specific etiology of pneumonia within the timeframe of an emergency department (ED) evaluation, however, certain clinical factors can suggest a likely etiology and guide empiric therapy. The clinical characteristics of several types of pneumonia are noted next.

Common Etiologies

S. pneumoniae is the single most common identified etiologic agent among adults with CAP. The classic presentation of pneumococcal

pneumonia is the abrupt onset of a single shaking chill, followed by fever, cough productive of rust-colored sputum, and pleuritic chest pain. However, many patients have a more insidious onset. Patients with a history of asplenia, sickle-cell disease, AIDS, multiple myeloma, or agammaglobulinemia are at increased risk of pneumococcal bacteremia and sepsis. Extrapulmonary complications such as meningitis, endocarditis, or arthritis occasionally develop.

In a recent study of hospitalized ED patients, staphylococcal pneumonia was the second most common identified etiology of CAP. Although CAP due to methicillin-resistant *S. aureus* (CA-MRSA) occurred in less than 3% overall, patients were distinctly more seriously ill and had chest radiographs with cavitation characteristic of necrotizing pneumonia (2). Intravenous (IV) drug users can present with pneumonia due to septic emboli from hematogenous spread of *S. aureus* (often associated with tricuspid-valve endocarditis), and with multiple small bilateral infiltrates.

H. influenzae is a common pathogen in adults with chronic obstructive pulmonary disease (COPD), alcoholism, malnutrition, malignancy, or diabetes. *Moraxella catarrhalis* is a gram-negative rod that can be found in patients with COPD and appears to be associated with exacerbations of chronic bronchitis much more frequently than it is associated with pneumonia.

Klebsiella pneumoniae is a rare cause of CAP, but it can cause severe pneumonia in debilitated patients with alcoholism, diabetes, or other chronic illness. *Pseudomonas aeruginosa* is also uncommon, but it can be present in patients with underlying lung disease, such as bronchiectasis or cystic fibrosis, or in patients who have recently been in a hospital or nursing home.

C. pneumoniae is a relatively common etiology of CAP, accounting for at least 8% of cases in adults; however, this is probably an underestimate because of the difficulty in diagnosing infection with this organism. Most infections in young adults cause a minor, self-limited upper-respiratory illness; radiographically evident pneumonia is more common in the elderly, in contrast to the common perception that atypical pneumonias occur in the young.

M. pneumoniae is one of the most common causes of CAP in previously healthy patients <40 years of age. It tends to be a more mild illness, with extrapulmonary manifestations such as maculopapular, vesicular, urticarial, or erythema-multiforme–type rashes and rarely pericarditis, glomerulonephritis, aseptic meningitis, and Guillain–Barré syndrome. Many patients complain of sore throat or ear pain, but the classic finding of bullous myringitis is less common and is nonspecific. *Legionella* sp is an intracellular organism that lives in aquatic environments, including tap water. There is no person-to-person transmission but outbreaks can occur due to a common water-related point-source exposure. Some patients present with a mild, self-limited atypical pneumonia, but older patients with chronic disease are at risk for more severe systemic illness. Gastrointestinal symptoms such as diarrhea are often prominent.

Winter influenza outbreaks, usually caused by influenza type A, result in an average of 20,000 deaths yearly in the United States, mostly among persons age 65 years or older (3). Cytomegalovirus (CMV) can cause pneumonia in persons with severe immunosuppression (e.g., transplant recipients). Varicella zoster virus (chickenpox) may rarely cause pneumonia; it is seen more often in adults and especially with pregnancy. Periodically, new viral pneumonia threats emerge in various parts of the world, including avian influenza strains, some with high case fatality, and novel coronaviruses. Emergency physicians should be aware of newly emerging pathogens, and screen for geographic exposures when appropriate. Up-to-date information on outbreaks can be found on the US Centers for Disease Control and Prevention (CDC) website, cdc.gov.

Although *P. jirovecii* pneumonia (PCP) does not occur in normal hosts, the possibility of opportunistic infection and unrecognized AIDS must always be considered. Many patients are unaware of their human immunodeficiency virus (HIV) status. All patients who present with pulmonary complaints should be questioned about HIV risk factors, and clinicians should search for signs of immunosuppression, such as weight loss, lymphadenopathy, and oral

thrush. PCP typically presents subacutely with fatigue, exertional dyspnea, nonproductive cough, pleuritic chest pain, and fever.

Lower-respiratory infection caused by anaerobic organisms generally results from the aspiration of oropharyngeal contents. These infections are typically polymicrobial, including many anaerobes such as *Peptostreptococcus* sp, *Bacteroides* sp, *Fusobacterium* sp, and *Prevotella* sp. Clinical factors that suggest an anaerobic infection include risk for aspiration (e.g., central nervous system depression or swallowing dysfunction), severe periodontal disease, fetid sputum, and radiographic appearance (e.g., location in posterior segment of right upper lobe or superior segment of lower lobe, lung abscess).

Fungal infections caused by organisms such as *Histoplasma capsulatum, Blastomyces dermatitidis,* and *Coccidioides immitis* commonly present as pulmonary disease. These organisms are present in the soil in various geographic areas of the United States: *H. capsulatum* in the Mississippi and Ohio River valleys, *B. dermatitidis* in a poorly defined area extending beyond that of *H. capsulatum,* and *C. immitis* in desert areas of the Southwest. These infections should be considered in persons in appropriate geographic areas, especially those near activities that disturb the soil (e.g., construction, dirt bike riding), or those who fail to respond to antibacterial treatment. The clinical presentation ranges from an acute or chronic pneumonia to an incidental finding of asymptomatic granulomas on chest radiography.

Unusual Causes of Pneumonia

Hantaviruses have been associated with a syndrome of severe respiratory distress (hantavirus pulmonary syndrome) and shock that has occurred in persons in several areas of the United States. Infection appears to occur from inhalation of aerosols of material contaminated with rodent urine and feces. Characteristic laboratory findings include thrombocytopenia, hemoconcentration, leukocytosis, and mild elevation of hepatic transaminases. The chest radiograph demonstrates bilateral interstitial lung infiltrates that are more pronounced in dependent areas. While there is no known

effective antiviral therapy, if the patient can be adequately supported, including the use of extracorporeal membrane oxygenation (ECMO) if necessary, then recovery is usually complete.

Plague, caused by *Yersinia pestis,* is endemic in many parts of the world and has been implicated as an organism that could be used in biologic terrorism. Plague occurs in the southwestern states of the United States in persons bitten by fleas from infected rodents or carnivores. Hematogenous spread may lead to severe pneumonia that is highly contagious.

Anthrax (caused by *Bacillus anthracis*) has been used as an agent of biologic terrorism. Inhalation of anthrax spores can cause a syndrome that presents as severe sepsis with or without pneumonia and meningitis. Chest radiography may reveal a wide mediastinum caused by swelling of mediastinal nodes.

Tularemia is a febrile illness, caused by *Francisella tularensis,* that is spread by contact with body fluids of infected mammals (especially rabbits) or the bite of an infected arthropod. The illness usually begins with an ulcerated skin lesion and painful regional lymphadenopathy. Some patients have a typhoidal form, with only fever, malaise, and weight loss. Pneumonia can occur with either form.

Psittacosis is a chlamydial infection that can be spread to humans from infected birds. Illness often begins rapidly with chills, high fever, myalgias, and nonproductive cough; severe headache is often the major complaint.

Q fever is an acute febrile illness caused by the rickettsial organism *C. burnetii* that may present as pneumonia, often with severe headache. Q fever is most common in persons with occupational exposure to animals.

DIFFERENTIAL DIAGNOSIS

Cough is a very common presenting complaint; however, only a small fraction of patients presenting with cough have pneumonia. Most patients with acute cough have a viral upper-respiratory infection or bronchitis. Several noninfectious etiologies can also result in inflammatory lung processes. These include exposure to

mineral dusts (e.g., silicosis), chemical fumes (e.g., chlorine, ammonia), toxic drugs (e.g., bleomycin), radiation, thermal injury, or oxygen toxicity. Immunologic diseases such as sarcoidosis, Goodpasture syndrome, and granulomatosis with polyangiitis (GPA, previously known as Wegener's) may cause pneumonia. Tumors can mimic pneumonia radiographically or present initially as a postobstructive infection. Pulmonary emboli and infarcts must be considered in patients who present with tachypnea, hypoxia, tachycardia, or chest pain in the appropriate clinical setting. Cardiac illness often presents with respiratory complaints such as dyspnea. Aspiration of a foreign body may cause a focal pulmonary infiltrate, and should be considered in at-risk patients (e.g., toddler).

No microbial etiology can be determined in one-third to one-half of CAP cases, even after thorough investigation. To a great extent, the likely etiologies must be predicted based on epidemiologic considerations and prevalence of pathogens in research studies (Table 74.1). In general, the likelihood of *S. pneumoniae* is higher with greater severity of illness, accounting for as many as 50% of intensive care unit (ICU)-admitted and fatal cases, with CA-MRSA also now associated with severe disease. Atypical organisms such as viruses and *Mycoplasma* sp account for a relatively higher proportion of pneumonias in those who have milder illness amenable to outpatient therapy.

TABLE 74.1
Most Common Etiologies of Community-Acquired Pneumonia

Patient Type	Etiology
Outpatient	*Streptococcus pneumoniae*
	Mycoplasma pneumoniae
	Haemophilus influenzae
	Chlamydophila pneumoniae
	Respiratory viruses[a]
Inpatient (non-ICU)	*S. pneumoniae*
	M. pneumoniae
	C. pneumoniae
	Staphylococcus aureus
	H. influenzae
	Legionella sp
	Aspiration
	Respiratory viruses[a]
Inpatient (ICU)	*S. pneumoniae*
	S. aureus
	Legionella sp
	Gram-negative bacilli
	H. influenzae

ICU, intensive care unit.
[a]Influenza a and b, adenovirus, respiratory syncytial virus, and parainfluenza.
Table is adapted from Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44(suppl 2):S27–S72.

ED EVALUATION

ED evaluation should focus on establishing the diagnosis of pneumonia, identifying host factors that will influence decisions regarding the need for hospitalization, and determining the presence of clinical features associated with specific infectious etiologies that will guide choice of antibiotics. In most healthy older children and adults, the diagnosis of pneumonia can be reasonably excluded on the basis of history and physical examination, with suspected cases further evaluated by chest radiograph. Absence of any abnormalities in vital signs or chest auscultation substantially reduces the likelihood of pneumonia. No single clinical finding is highly reliable in establishing or excluding a diagnosis of pneumonia (4).

Chest Radiography

The chest radiograph is generally the most important test to determine the presence of pneumonia. Predictive models have been developed to optimize chest x-ray use in patients with cough in whom pneumonia is suspected. Clinical findings found to be associated with radiographically confirmed pneumonia are fever, tachycardia, and tachypnea; rales or decreased breath sounds, sputum production. Absence of rhinorrhea or sore throat have also been predictive in some models. Predictive models can reduce unnecessary chest x-rays but appear to be less sensitive than physician judgment (5). Chest x-ray, because of its relatively low cost and risk, is appropriate when management will be affected by the result (e.g., hospital admission, antimicrobial use, exclusion of other diagnoses). Chest x-ray can be particularly useful in groups who often have subtle clinical signs of pneumonia, such as the elderly and those at risk for tuberculosis (TB), to quickly establish the need for isolation. Healthy adults who will receive outpatient treatment with empirical antimicrobials can have the chest radiograph deferred unless there is suspicion of immunosuppression or other unusual features of disease. Routine chest radiography for patients with exacerbation of chronic bronchitis or COPD is of low yield and can be limited to those with other signs of infection or heart failure. Computed tomography (CT) of the chest is more sensitive than plain radiography for detecting the presence of pulmonary consolidation, although the natural history of CT-positive, plain-radiograph–negative pneumonia is unclear.

Certain radiographic patterns tend to be associated with specific pathogens. In pyogenic bacterial pneumonias, radiographs usually show an area of segmental or subsegmental infiltration and air bronchograms. Lobar consolidation is present in a minority of cases of bacterial pneumonia and is often caused by pneumococcus or *Klebsiella* sp. Bronchopneumonia resulting from spread of infection along the intralobular airway causes fluffy or patchy infiltrates in the involved areas of the lung. Viruses and a wide variety of bacteria can cause this pattern, including *C. pneumoniae, M. pneumoniae, Legionella*

sp. An interstitial pattern on the chest radiograph is typically caused by *M. pneumoniae,* viruses, or *P. jirovecii.* Tiny nodules disseminated throughout both lungs represent a miliary pattern typical of granulomatous pneumonias such as due to *M. tuberculosis* or fungal infection. The location of infiltrates can also give a clue to the etiology. Aspiration pneumonia occurs in dependent areas of the lung, most commonly the superior segments of the lower lobes or the posterior segments of the upper lobes. Pneumonia produced by hematogenous spread (such as due to staphylococci) tends to be multifocal and peripheral. Apical infiltrates suggest TB. An infiltrate associated with hilar or mediastinal adenopathy suggests the presence of TB or fungal disease or pneumonia associated with a neoplasm. Cavitation is most commonly present with infections caused by anaerobes, gram-negative organisms, fungi, or *S. aureus:* Cavitation can also be present in fungal disease or TB. Pneumatoceles or spontaneous pneumothorax can be seen in AIDS patients with PCP. Pleural effusions can be seen with a wide variety of organisms, including many types of pyogenic bacterial pneumonia, *C. pneumoniae, Legionella* sp, and TB. Anaerobic infections are especially prone to the development of empyema.

However, despite these characteristic associations, radiographic presentations vary greatly among patients with a specific infection etiology and are also modified by the host response. Immunocompromised patients are particularly likely to have atypical radiographic appearances. Occasionally, patients with a clinical picture strongly suggestive of pneumonia have a normal chest radiograph. The absence of findings on the chest radiograph should not preclude the use of antimicrobial therapy in patients thought to have pneumonia on clinical grounds.

Other Tests

Patients with respiratory complaints should be screened with pulse oximetry at triage because hypoxia may not be otherwise clinically suspected and its presence has therapeutic implications (6). Severe hypoxia is an indication for hospital admission.

Most laboratory studies available in the timeframe of ED care are of limited utility in establishing the diagnosis and specific etiology of pneumonia. Although an elevated peripheral white blood cell (WBC) count can increase the likelihood of a pyogenic bacterial etiology, this finding is of limited value in making decisions regarding therapy in an individual patient and must be considered in light of other clinical and epidemiologic features (i.e., the pretest probability of various etiologies). A WBC count may be helpful if it yields evidence of immunosuppression, such as neutropenia, or if it reveals lymphopenia that may indicate immunosuppression from HIV. Serum lactate dehydrogenase (LDH) can be helpful in evaluating possible PCP in patients at risk of AIDS. Rapid HIV tests are available that can be helpful in this situation. Serum chemistry studies can be helpful in identifying patients with metabolic acidosis or renal–hepatic dysfunction associated with sepsis or with underlying disease that predicts a complicated course and influence decisions regarding disposition, choice of antimicrobial agents, and dosages. In addition, elevated lactic acid levels, even in the absence of fluid-unresponsive hypotension, can indicate the need for early and aggressive hemodynamic resuscitation. These ancillary tests are not necessary in patients with mild illness. B-type natriuretic peptide (BNP) or echocardiography can be helpful in cases in which heart failure is a consideration.

Inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein have not been demonstrated to be helpful in clinical decision-making regarding pneumonia. Procalcitonin level has been suggested as a means to assess risk of a bacterial etiology, response to antimicrobial therapy, and prognosis in pneumonia. However, its utility in the ED, such as to assess need for hospitalization or ICU admission compared to other risk-stratification systems (see below) has not been established (7).

Although a Gram stain of the sputum is often recommended as a means to identify a bacterial pathogen, the use of the Gram stain as a basis for empiric therapy in the ED can be problematic due to difficulty obtaining an adequate sputum specimen and infection control hazards associated with sputum induction. Moreover,

correlation between pneumococcal identification on Gram stain and by sputum culture is poor even with an adequate specimen, and Gram stain is even less likely to demonstrate gram-negative pathogens. If sputum Gram stain and culture are considered, they should be reserved for the subset of patients with more serious illness (e.g., admitted to the ICU), in whom the bacteriologic diagnosis is highly uncertain, and for whom it is felt that the outcome may be most dependent on optimal antimicrobial therapy. For example, in the ED, those patients with pneumonia and respiratory failure requiring intubation should have endotracheal suction specimens obtained. Patients with a pleural effusion should have a diagnostic thoracentesis performed, with fluid sent for cell count, differential, pH (pH <7.2 is predictive of a need for chest tube), Gram stain, and culture. Although it is preferred to obtain pleural fluid specimen as early as possible, because of time constraints it is not always possible to perform diagnostic thoracentesis in every patient with pleural effusion in the ED. For most patients, thoracentesis can be safely deferred until after hospital admission. However, patients in significant respiratory distress or with evidence of tension and mediastinal shift require emergent therapeutic thoracentesis.

The utility of routine blood cultures is questionable because studies of nonimmunocompromised adults with pneumonia have demonstrated a low prevalence of noncontaminant bacteremia, and management is rarely changed based on the results (8–10). The follow-up of false-positive blood cultures can be costly, labor intensive, and may lead to unnecessary use of antibiotics such as vancomycin or linezolid when results are initially reported as gram-positive cocci. Blood cultures should be obtained from immunocompromised patients, those with severe sepsis or shock, or those with risk factors for endovascular infection (e.g., prosthetic valves or IV drug use). When cultures are drawn, they should be obtained prior to the initiation of antibiotics (although antibiotics should not be delayed for this reason).

Serologic tests are available for the diagnosis of a number of organisms, including *C. pneumoniae, Legionella* sp, and fungi. Serologic tests to determine the etiology of pneumonia may be

helpful retrospectively, but both acute and convalescent serum titers are usually required; therefore, they are of little use to the emergency physician. Urine-antigen tests for organisms such as *S. pneumoniae* and *Legionella* sp can give results quickly. Rapid diagnostic tests for viral antigens are available for several viruses, including RSV and influenza. These tests may be useful for infection-control decisions in hospitalized patients and may provide an indication for influenza therapy. In the future, rapid testing using technology such as the polymerase chain reaction may provide emergency physicians with a reliable method for determining the specific etiology of pneumonia.

KEY TESTING

- Chest radiograph
- Pulse oximetry
- For seriously ill patients:
  - Blood culture
  - Serum lactate level
  - Complete blood count
  - Chemistry profile
  - Blood and sputum culture

ED MANAGEMENT

Initial attention should focus on ensuring adequate ventilation, oxygenation, and perfusion. Hypoxic patients with pneumonia should receive supplemental oxygen. Those patients with severe respiratory compromise may require endotracheal intubation. Patients with underlying asthma or COPD who present with wheezing may benefit from bronchodilator therapy. Seriously ill patients who present with volume depletion or septic shock will require fluid resuscitation and may require more intensive management with vasopressors, transfusion, and inotropic agents as part of sepsis resuscitation (11).

It is usually necessary to begin empiric antimicrobial therapy for pneumonia before a definite microbiologic etiology is established.

Antimicrobials should be started in the ED for patients who are being admitted to the hospital: deferring treatment until arrival on the ward can cause significant delays. Timely administration of antimicrobials has been associated with improved outcomes for hospitalized pneumonia patients (12). However, a rush to treatment without a diagnosis of pneumonia can result in inappropriate antibiotic use.

The antibiotics chosen must provide coverage of the likely etiologies based on clinical, laboratory, radiologic, and epidemiologic information. Though care must be taken not to miss possibly dangerous pathogens, the regimen should be as selective as possible to avoid problems with drug toxicity, promotion of antimicrobial resistance, and excessive cost.

The prevalence of drug-resistant *S. pneumoniae* (DRSP) has increased steadily in recent years. In most areas of the United States, high-level penicillin resistance occurs in approximately 15% to 20% of outpatient pneumococcal sputum isolates. Isolates that are resistant to penicillin are often also resistant to other β-lactams as well as macrolides, tetracyclines, and trimethoprim-sulfamethoxazole (TMP/SMX). Most remain susceptible to third-generation cephalosporins such as ceftriaxone. Extended-spectrum fluoroquinolones such as levofloxacin and moxifloxacin have activity against DRSP as well as other typical and atypical organisms that commonly cause pneumonia and may offer additional alternatives to vancomycin if DRSP is a concern. However, it is not clear that in vitro resistance is related to adverse clinical outcome. Most cephalosporins and macrolides will achieve adequate levels in serum and tissues to successfully treat *S. pneumoniae* respiratory tract infections, even if the laboratory reports that the organism is resistant.

CA-MRSA has rapidly emerged as the most common pathogen isolated in community-acquired skin and soft-tissue infections and is also increasingly recognized as a cause of severe, rapidly progressing pneumonia with sepsis, often in children or healthy young adults. Antimicrobials with consistent in vitro activity against CA-MRSA isolates include vancomycin, ceftaroline, TMP/SMX, and linezolid.

Although vancomycin is used most often for suspected or documented MRSA infections, vancomycin may be losing efficacy, at least as based on increasing minimum inhibitory concentrations (MICs) observed during the last few years. Daptomycin is active against CA-MRSA but is inactivated by pulmonary surfactant, so is inappropriate for pneumonia. Although it is not necessary to provide empiric coverage of MRSA for all pneumonia cases, it should be strongly considered for patients with severe pneumonia associated with sepsis, especially those with concurrent influenza, contact with someone infected with MRSA, or radiographic evidence of necrotizing pneumonia (13).

Guidelines have been issued for empirical antibiotics for patients with CAP (14). For patients whose illness is severe enough to require hospital admission and parenteral antibiotics, options include a combination of a third-generation cephalosporin and a macrolide (e.g., IV or oral azithromycin) or an extended-spectrum fluoroquinolone alone. These regimens will treat the most common bacterial pathogens, such as *S. pneumoniae,* methicillin-susceptible *S. aureus, H. influenzae,* and atypical pathogens such as *Mycoplasma* sp, *Chlamydophila* sp, and *Legionella* sp. A regimen with activity against atypical pathogens (e.g., macrolide) is recommended in guidelines, but studies have not clearly demonstrated better outcomes in hospitalized patients compared to regimens without atypical activity (15). If anaerobic organisms are suspected (e.g., with aspiration), clindamycin or metronidazole could be added to the regimen, or a β-lactam–β-lactamase-inhibitor antibiotic such as ampicillin-sulbactam or piperacillin-tazobactam could be used. Moxifloxacin is also active against anaerobes.

Severely ill and compromised patients are at relatively greater risk of infection caused by *S. pneumoniae, S. aureus* including MRSA, aerobic gram-negative bacilli, and, in some areas, *Legionella* sp. Because antimicrobial resistance is more likely to impact the outcome in these patients, it is important to include agents with activity against DRSP and CA-MRSA. Appropriate empirical therapy could include a combination of a third-generation cephalosporin or a β-lactam–β-lactamase-inhibitor antibiotic plus vancomycin, plus a

fluoroquinolone. Outcomes with severe pneumonia appear to be better with combination therapy when compared with a single agent such as a fluoroquinolone alone (16,17).

Healthcare-associated pneumonia (HCAP) characterizes patients in nursing homes or other extended-care facilities who are at increased risk for infection with resistant organisms such as *P. aeruginosa, K. pneumoniae* (including strains producing extended spectrum β-lactamases [ESBL]), *Acinetobacter* sp, and hospital-associated strains of MRSA (18). Other risk factors for infection with multidrug-resistant pathogens include (a) hospitalization for 2 or more days in an acute-care facility within 90 days of infection; (b) patients who attended a hemodialysis clinic; and (c) those who received IV antibiotic therapy, chemotherapy, or wound care within 30 days of infection. It is therefore appropriate to give broader-spectrum empiric therapy to patients with HCAP, usually with a combination of antimicrobials to increase the chance that at least one antibiotic will be active against the causative pathogen. Appropriate combinations would include an antipseudomonal β-lactam agent such as piperacillin/tazobactam, cefepime, imipenem, or meropenem combined with either an aminoglycoside or a fluoroquinolone, and vancomycin or linezolid to cover for MRSA (19).

Studies of antiviral agents for influenza have generally focused on uncomplicated cases in which benefit appears to be limited to patients treated within 48 hours of symptom onset. Arrival treatment may also benefit patients hospitalized with influenza or bacterial complications of influenza. If influenza is suspected (or confirmed by testing), empirical antiviral treatment should be considered, based on clinical judgment, for patients with severe or progressive illness. These would include those with pneumonia, as well as those with the following: age <5 (particularly <2) and ≥ 65 years, chronic comorbidities, immunosuppression, pregnancy or within 2 weeks post-partum, age ≤ 18 years on chronic aspirin treatment, long-term care facility residence, morbid obesity (BMI ≥ 40), or hospitalization (3). Neuraminidase inhibitors such as oseltamivir are a better choice than amantadine and rimantadine, because they are active against influenza A and B and because many circulating strains are resistant

to these older agents (3). Zanamavir is given by inhalation and is not recommended for patients with underlying reactive airway disease because it can induce bronchospasm.

For patients with AIDS, it is important to treat *P. jirovecii* and bacterial pathogens such as *S. pneumoniae.* TMP/SMX is the treatment of choice: the usual regimen is 20 mg/kg of TMP and 100 mg/kg of SMX in four divided doses (3 amps IV q6h for most adults) to be continued for 21 days. For patients allergic to sulfa, pentamidine can be given in a dose of 4 mg/kg throughout 1 hour. Because pentamidine has no activity against *S. pneumoniae* or other bacterial pathogens, it is important to add a cephalosporin or other antibacterial agent to the initial empiric regimen. Other options include clindamycin 600 mg IV q8h plus primaquine 30 mg po daily or TMP plus dapsone, atovaquone, or trimetrexate. The addition of steroids (prednisone 40 mg PO bid) has been shown to reduce mortality and clinical deterioration in patients with Pa_{O_2} $<$70 mm Hg or A-a gradient $>$35 mm Hg.

Outpatient Management

Appropriate agents for outpatient treatment of adults include macrolides (erythromycin, clarithromycin, azithromycin), respiratory fluoroquinolones such as levofloxacin or moxifloxacin, or doxycycline. Alternative options that would be appropriate in those patients with a higher likelihood of a "typical" bacterial etiology include amoxicillin-clavulanate or an oral cephalosporin such as cefdinir, cefpodoxime, or cefprozil. These β-lactam agents do not have activity against atypical pathogens. In patients properly identified as low risk for complications, use of a macrolide or doxycycline is reasonable, even when there is concern about DRSP. Use of more expensive and more broad-spectrum agents, such as respiratory fluoroquinolones, may be justified based on convenience, avoidance of side effects and drug interactions, or concern about DRSP in patients with a higher likelihood of bacterial etiology. Some agents, including azithromycin and levofloxacin (750 mg daily), can be given as a 5-day course. Use of ampicillin or amoxicillin is not

generally recommended because of the high incidence of β-lactamase production in pneumonia pathogens, although these have been used successfully in higher doses (e.g., amoxicillin 1 g tid) in other conditions with a high prevalence of DRSP. TMP/SMX has also been largely abandoned for treatment of pneumonia because of increasing resistance. Except for the administration of fluoroquinolones, these recommendations also apply to school-aged children and adolescents, in whom *Mycoplasma* sp is common.

Many EDs initiate outpatient therapy in moderately ill patients who previously might have been hospitalized with an initial parenteral dose of a long-acting antibiotic such as ceftriaxone and employ extended observation (i.e., 12 to 24 hours) while administering supportive care such as hydration, antipyretics, and bronchodilators before discharge on an oral regimen. Certain patients may also be brought back to the ED for follow-up in 24 hours and receive a second parenteral or observed oral dose of antibiotics. Extended-spectrum fluoroquinolones are another option that may be employed in this strategy, and they have additional activity against atypical pathogens and DRSP. Oral administration of these agents results in blood and tissue levels similar to those with IV therapy, provided that intestinal absorption is normal.

Empiric therapy for pneumonia is summarized in Table 74.2.

TABLE 74.2
Empiric Therapy for Pneumonia

Clinical Setting	Antibiotic Regimen	Comments
Parenteral Regimens		
Community-acquired, nonimmuno-compromised	Ceftriaxone 1 g q24h + azithromycin 500 mg q24h IV or PO	Could substitute cefotaxime, ceftaroline, or ertapenem for ceftriaxone
	Respiratory fluoroquinolone (levofloxacin 750 mg IV q24h or moxifloxacin 400 mg IV q24h)	Treats most common bacterial and atypical pathogens. Active vs. DRSP
Severe pneumonia ICU	Ceftriaxone 1 g IV q24h + levofloxacin 750 mg IV q24h + vancomycin 1 g IV q12h	Can substitute cefotaxime, cefepime, ertapenem or β-lactam–β-lactamase inhibitor for ceftriaxone. Can substitute moxifloxacin for levofloxacin. Can substitute linezolid for vancomycin
Severe pneumonia with neutropenia, bronchiectasis, or recent hospitalization (risk for *Pseudomonas* sp)	Cefepime 2 g IV q12h + ciprofloxacin 500 mg IV q12h + vancomycin 1 g IV q12h	Can substitute other antipseudomonal β-lactam such as piperacillin-tazobactam, imipenem, or meropenem for cefepime. Can substitute aminoglycoside plus macrolide for ciprofloxacin
Presumed pneumocystis pneumonia	TMP/SMX 160/800 mg IV q6h	Add ceftriaxone to TMP/SMX if severe, until PCP confirmed. Alternatives for sulfa allergy include pentamidine + third-generation cephalosporin; clindamycin + primaquine; atovaquone + ceftriaxone
Oral Regimens		
Previously healthy, no antimicrobials in last 3 mos	Doxycycline 100 mg PO bid	Preferred for adolescent/young adult when likelihood of mycoplasma is high; variable activity vs. *S. pneumoniae*
	Azithromycin	Treats common typical bacterial and atypical pathogens. Variety of dosing regimens: 500 mg once followed by 250 mg daily for 4 d; 500 mg PO daily for 3 d; 2 g PO extended release suspension once. Can substitute clarithromycin
Comorbidities or antimicrobials in last 3 mos	Levofloxacin 750 mg PO daily for 5 d	Can substitute moxifloxacin. Treats common typical and atypical bacterial pathogens; active vs. DRSP. Use if recently received β-lactam or macrolide
	Cefpodoxime 200 mg PO bid + azithromycin 500 mg PO daily	Use if recently received fluoroquinolones. Can substitute cefdinir, cefprozil, or amoxicillin/clavulanate for cefpodoxime. Variable activity against DRSP

Doses are for 70 kg adult with normal renal and hepatic functions.
IV, intravenous; PO, by mouth; DRSP, drug-resistant *S. pneumoniae;* TMP/SMX, trimethoprim-sulfamethoxazole; PCP, *P. jirovecii* pneumonia.

CRITICAL INTERVENTIONS

- Obtain blood cultures from immunocompromised patients, those with severe sepsis or shock, or those with risk factors for endovascular infection (e.g., prosthetic valves or IV drug use).
- Initiate antimicrobials in the ED for patients who are being admitted to the hospital.
- Isolate patients who may be infected with organisms that could put hospital staff and other patients at risk, such as TB or influenza.

DISPOSITION

Disposition of patients with pneumonia is dictated by the patient's underlying medical conditions, severity of illness, likelihood of clinical deterioration, and feasibility of home care and outpatient follow-up. Outpatient treatment is 15 to 20 times less expensive than inpatient treatment, and most patients prefer the home environment. There is tremendous variability in physician admission decisions for pneumonia (20). The more common tendency is overestimation of disease severity, leading to hospitalization of patients at low risk for death or serious complications. The decision to hospitalize for

pneumonia does not necessarily commit the patient to a prolonged inpatient stay. Twelve- to 24-hour ED or hospital-ward observation may allow the early discharge of certain moderate-risk patients.

Scoring systems have been developed to assist with decisions regarding hospitalization for pneumonia. One commonly used system is based on the Pneumonia Patient Outcomes Research Team (PORT) study, a prospectively validated predictive rule for mortality among immunocompetent adults with CAP (21), also known as the pneumonia severity index, or PSI. This is a two-step approach to assess risk. Patients in the lowest-risk class may not need testing and can be treated as outpatients. These patients include those younger than age 50 years, without significant comorbid conditions (neoplasm, congestive heart failure, cerebrovascular disease, renal disease, liver disease, or HIV), and without the following findings on physical examination: altered mental status, pulse $\geq$125 beats/min, respiratory rate $\geq$30 breaths/min, systolic blood pressure $<$90 mm Hg, and temperature $<$35°C or $\geq$40°C. Patients who do not fit the lowest-risk category are classified into categories based on a scoring system that accounts for age, comorbid illness, physical examination findings, and laboratory abnormalities (Table 74.3). Hospitalization is recommended for those with a score $>$91 (class IV–V), and brief admission or observation may be considered for those with a score of 71 to 90 (class III).

TABLE 74.3
Pneumonia Severity Index: Scoring System for Pneumonia Mortality Prediction

Patient Characteristics	Points
Demographic factor	
Age	
Male	Years of age
Female	Years of age-10
Nursing home resident	10
Comorbid illness	
Neoplastic disease	30
Liver disease	20
Congestive heart failure	10
Cerebrovascular disease	10
Renal disease	10
Physical examination findings	
Altered mental status	20
Respiratory rate >30 breaths/min	20
Systolic blood pressure <90 mm Hg	20
Temperature <35°C or >40°C	15
Pulse >125 beats/min	10
Laboratory or radiographic findings	
Arterial pH <7.35	30
Blood urea nitrogen >30 mg/dL	20
Sodium <130 mEq/L	20
Glucose >250 mg/dL	10
Hematocrit <30%	10
Arterial P_{O_2} <60 mm Hg	10
Pleural effusion	10

Table is adapted from Bartlett JG, Dowell SF, Mandell LA, et al. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Diseases Society of America. *Clin Infect Dis.* 2000;31(2):347–382.

Although this method of assessing the likelihood of successful outpatient management is helpful in establishing general guidelines, it can be cumbersome to use, has not been modeled to predict acute life-threatening events, does not take into account dynamic evaluation over time, and has many important exceptions (e.g., an otherwise low-risk patient with severe hypoxia would be discharged by its strict interpretation). Additional discharge criteria could include improving and stable vital signs during a several hour observation period, ability to take oral medications, an ambulatory

pulse oximetry >90%, home support, and ability to follow-up. A study in which physicians were taught this system and provided the patient's risk score revealed a significantly lower overall admission rate, cost savings, and similar quality-of-life scores compared to patients conventionally managed by their physicians (22).

A simpler tool is the CURB-65 rule (23). This rule uses only five simple criteria to identify patients at lower risk for adverse events: confusion, uremia (blood urea nitrogen [BUN] ≥20 mg/dL), respiratory rate ≥30, blood pressure <90 systolic or ≤60 diastolic, and age 65 years or greater. The risk of 30-day mortality increases with a greater number of these factors present: 0.7% with no factors, 9.2% with two factors, and 57% with five factors. It is recommended that patients with zero to one feature can receive outpatient care, those with two should be admitted, and ICU-level care should be considered for those with three or more. No randomized trials of hospital-admission strategies have directly compared the PSI to the CURB-65 score. In a comparison of scores in the same population of CAP patients, the PSI gave a slightly higher percentage of patients in the low-risk category, with a similar low mortality rate (24). Most emergency physicians do not routinely use these scoring systems for admission decisions (20).

In some cases it is obvious that ICU admission is indicated, including those patients who are intubated or require vasopressors for hemodynamic stabilization. It is more difficult to identify those patients who do not require these interventions initially but may be at greater risk for deterioration. Objective criteria using the PSI (class V) and CURB-65 have been proposed but have not been prospectively validated for the ICU-admission decision (14). ICU admission may be indicated for patients with signs of more serious infection such as severe hypoxia, confusion, multilobar infiltrates, or the need for aggressive fluid resuscitation. Another ICU risk-stratification score is abbreviated SMART COP; intensive respiratory or vasodepressor support was predicted by several clinical features (Table 74.4). A SMART-COP score of ≥3 points identified 92% of patients who received intensive respiratory or vasodepressor support,

including 84% of patients who did not need immediate admission to the ICU (25).

TABLE 74.4
SMARTCOP Scoring System for ICU Admission Decision

Clinical Feature	Points Assigned
Systolic blood pressure <90 mm Hg	2
Multilobar infiltrates	1
Albumin <3.5 mg/dL	1
Respiratory rate (age ≤50, 25/m; >50, 30/m)	1
Tachy ≥125/min	1
Confusion (new)	1
Oxygen saturation (age≤50 <93%; >50 <90%)	2
pH <7.3	2
Score Interpretation	
≥7 points	Very high risk of needing ICU (2 in 3)
5–6 points	High risk of needing ICU (1 in 3)
3–4 points	Moderate risk of needing ICU (1 in 8)
≤2 points	Low risk of needing ICU

Table is adapted from Charles PG, Wolfe R, Whitby M, et al. SMART-COP: A tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. *Clin Infect Dis.* 2008;47:375–384.

Most patients with CAP do not need respiratory isolation. Those patients who are suspected of having an etiology of pneumonia that could pose a threat of transmission to other patients (e.g., influenza, varicella, TB, plague) should be isolated. Persons with fever and respiratory symptoms who have been in an area with possible exposure to agents such as avian influenza or coronavirus should be immediately isolated. Frequent hand washing and use of masks to prevent droplet exposure are also helpful to prevent transmission of pathogens. Neutropenic patients are generally placed in reverse isolation. HIV-infected patients who present with any form of pneumonia should be considered for isolation until TB can be ruled out by sputum acid-fast bacillus (AFB) smears, because delayed diagnosis of TB in these patients is a well-recognized cause of

nosocomial TB outbreaks. The chest radiograph cannot be relied on to rule out TB in AIDS patients because it often does not have the typical appearance of TB or is negative. Isolation should be strongly considered for others at high risk for TB, such as inner-city homeless persons or IV drug users.

Common Pitfalls

- Delay in initiating of antibiotics for seriously ill patients.
- Failure to consider treatment of influenza.
- Failure to question patients who present with respiratory complaints about HIV risk factors.
- Failure to recognize TB and initiate respiratory isolation in a patient with HIV infection or other TB risk factors.
- Failure to ask about travel and exposure history during outbreaks of new respiratory pathogens.

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CHAPTER 75 Pleural Effusion

Micelle Haydel

The visceral and parietal pleura are serous membranes that line the outer surface of the lung, mediastinum, diaphragm, and the inner surface of the thoracic wall, forming the right and left pleural spaces. Under normal homeostatic conditions, the parietal pleura secretes about 0.01 mL/kg/hr of pleural fluid which is continuously resorbed by the pleural lymphatics, maintaining a steady state of less than 10 mL in the pleural space (1). About 30% of healthy men have 3 to 5 mm of fluid visible on ultrasound, whereas 80% of women have up to 5 to 7 mm visible on MRI (2,3). A pleural effusion occurs when fluid formation increases beyond the capacity of lymphatic clearance, or when lymphatic clearance is impaired. Pleural fluid has a chemical composition similar to that of interstitial fluid, but is altered in the setting of inflammation, infection, malignancy, or trauma. Fluids that collect in the pleural space include transudative, exudative, hemorrhagic, and chylous.

CLINICAL PRESENTATION

The clinical presentation of pulmonary effusions ranges from incidental findings to life-threatening cardiopulmonary distress or sepsis. Patients with a pleural effusion often present with complaints related to the underlying disease process rather than to the pleural effusion itself. Pleural effusions are graded as small when up to 25% of the pleural cavity is involved, moderate when 25% to 50% is involved, and large when more than 50% is involved (4). Signs and symptoms in patients with pleural effusion vary based on the size

and cause of the effusion, as well as associated underlying disease processes.

- Fever: A pleural effusion caused by infection is typically associated with fever.
- Pain: Inflammation of the parietal pleura causes referred pain to the overlying chest wall, whereas irritation of the diaphragmatic pleura causes referred pain to the ipsilateral shoulder. The visceral pleura is not innervated, therefore does not cause pain.
- Cough: Lung compression with bronchial irritation can cause a nonproductive cough.
- Dyspnea: Large pleural effusions can compromise pulmonary mechanics, impair gas exchange and cause dyspnea, tachypnea, and respiratory distress. A pulmonary embolism or infarct often will cause dyspnea that is out of proportion to the associated effusion.
- Tachycardia and hypotension: A large pleural effusion can cause cardiac collapse during diastole, physiologically mimicking cardiac tamponade.
- Weight loss: The review of systems often reveals unexplained weight loss in patients with tuberculosis, malignancy, and HIV.
- Ascites: Cirrhosis, ovarian cancer, and Meigs syndrome are associated with ascites.
- Size: The size of an effusion can suggest its etiology. Large or massive effusions are associated with malignancy, but can also be found in tuberculosis and bacterial parapneumonic effusions.
- Laterality: Most bilateral effusions are caused by a transudative process, such as heart failure, renal or hepatic failure, or low protein states. Bilateral effusions are rarely seen in malignancy, pulmonary embolism, and rheumatoid arthritis. When bilateral effusions are of unequal size, more than one etiology should be suspected.

DIFFERENTIAL DIAGNOSIS

Pleural effusions are quite common, diagnosed in over 1 million patients each year in the United States (5). Over 50 etiologies are known, and in the United States the most common causes are heart

failure, pneumonia, malignancy, and pulmonary embolism (6). In children, pneumonia is the most common cause of pulmonary effusion. The medical history and symptoms (or lack thereof) can be very helpful in developing a differential diagnosis and management plan. The most common causes of pleural effusions include the following.

- Congestive heart failure: Over 80% of patients with decompensated CHF have some degree of bilateral or unilateral transudative pleural effusions due to elevated pulmonary capillary pressure (7,8).
- Pneumonia: About 40% of patients with bacterial pneumonia have an exudative pleural effusion, known as a parapneumonic effusion. Most are uncomplicated and resolve with antibiotic therapy, but about 1% progress to an empyema with the potential for rind formation and constrictive pleuritis (9). Parapneumonic effusions are further classified in Table 75.1.

TABLE 75.1
Stages of Parapneumonic Effusion

Stages	Clinical Course	Macroscopic	Cell Count and Chemistry of Fluid	Treatment
Uncomplicated	Improves with antibiotics	Small, sterile, free-flowing, clear to slightly cloudy fluid	LDH <200, pH >7.2 glucose >60 mg/dL WBC count <1,000 No bacteria	Antibiotics and monitor for resolution
Fibropurulent	Fails antibiotics, fever, sepsis	Cloudy to frank pus; fibrin sheets causing loculations	LDH >200, pH <7.0, glucose <40 mg/dL WBC >50,000 Bacteria invasion	Antibiotics and chest tube
Organization	Fever, sepsis Fibroblasts restrict lung movement	Inelastic, fibrous peel in pleura space	As above, plus fibroblastic invasion with fibrin deposition	Antibiotics and surgery

- Malignancy: Patients with malignant effusions typically present with a complaint of dyspnea or chest pain. Malignant cells in a pleural effusion imply disseminated disease and a reduced life-expectancy. Malignant effusions tend to recur within a month of being drained, with lung and breast cancer accounting for ~60% of malignant effusions (10). Paramalignant effusions are caused by lymphatic obstruction, superior vena cava syndrome, or postobstructive atelectasis; but do not involve pleural metastasis (11). Malignant effusions can be hemorrhagic or chylous (lymphoma).

- Pulmonary embolism: One-third to one-half of patients with pulmonary embolism have a small, unilateral, frequently hemorrhagic, exudative effusion (12). Dyspnea is typically out of proportion to the size of the effusion, and the presence of pleuritic pain and a pleural effusion is suggestive of pulmonary embolism (6,13).

Less common causes of pulmonary effusions are very diverse, but the past medical history and physical examination can offer important diagnostic clues and include the following.

- Tuberculosis: In the United States about 5% of patients with tuberculosis have plural effusions, but in countries with a higher prevalence of tuberculosis, TB is often the primary cause of pulmonary effusions (14).
- HIV: Pulmonary effusions are frequently found in hospitalized patients with HIV, most commonly due to infections (including tuberculosis) and malignancy (lymphoma and Kaposi) (15). Parapneumonic effusions in patients with HIV are caused by the bacteria encountered in the general population, as well as *Mycobacterium, Pneumocystis, Cryptococcus,* and *Histoplasmosis.*
- Cirrhosis, ascites, and peritoneal dialysis are all associated with transudative pleural effusions due to the imbalance of pleural oncotic and hydrostatic forces.
- Nephrotic syndrome can cause a transudative pleural effusion, but the associated hypercoagulable state also predisposes to pulmonary embolism.
- Trauma and postsurgical: While small left-sided pleural effusions are expected in the first week post-CABG, up to 10% of patients will develop moderate to large or persistent effusions (16). Large pleural effusions develop after a complete pneumonectomy. Potentially lethal causes of pleural effusions include hemothorax and ruptured esophagus.
- Disruption of the thoracic duct (due to trauma or malignancy) causes a chylous effusion due to fatty acids that give lymphatic fluid a milky appearance.
- Autoimmune diseases such as lupus, rheumatoid arthritis, and sarcoidosis are rare causes of pleural effusions.

- Drug induced: Numerous medications have been associated with a pleural effusion. Most resolve with cessation of the culprit drug, but some continue long after the medication has been stopped. The most common drugs associated with pleural effusion are methotrexate, phenytoin, nitrofurantoin, β-blockers, and amiodarone (6). Procainamide and hydralazine can cause lupus syndrome with effusions. Ovarian hyperstimulation syndrome secondary to infertility treatments can cause pulmonary effusions.
- Sympathetic effusion: Virtually any abdominal infection or inflammatory process can alter the surrounding capillary permeability leading to an effusion. Examples include pancreatitis, hepatitis, cholecystitis, hepatic amebiasis, splenic abscess, pyelonephritis, glomerulonephritis, peritonitis, pelvic inflammatory disease, and abdominal abscess.

ED EVALUATION

The physical examination of a patient with a pleural effusion can be benign or markedly abnormal, depending on the size of the effusion. As the pleural space fills with fluid, the involved cavity increases in total volume while the lung parenchymal volume decreases. The chest may be visibly asymmetrical with bulging or retraction of the intercostal spaces, and tracheal deviation. The cardiac apical pulse may be displaced due to a shift in the heart's location due to fluid accumulation. Diminished breath sounds and/or a pleural rub may be appreciated. Dullness to percussion and tactile fremitus are the most useful physical examination signs of pulmonary effusion (17). The change in the sound of percussion can identify the upper limit of a pleural effusion.

Upright posteroanterior (PA) and lateral chest radiographs should be part of the initial evaluation of the patient with suspected pleural effusion. The subpulmonic space is the most dependent area of the diaphragm below the lungs where effusions initially collect. Easily mistaken for an elevated hemidiaphragm, a 25- to 50-mL subpulmonic effusion is seen as a shifting of the peak of the right diaphragm laterally (see arrow in Fig. 75.1) or an increased distance

between gastric bubble and left lobe lung on upright PA chest film. Blunting of the costophrenic angles can be seen on the lateral film when more than 50 mL of fluid has collected, and can be seen on the PA film when more than 150 mL has collected. A meniscus can typically be seen on the PA film when 200 mL has collected, and when 500 mL has collected the diaphragm is obscured (18). Lateral decubitus films (Fig. 75.2) are useful to determine layering of the fluid, and a dependent fluid layer more than 10 mm thick is considered significant.

FIGURE 75.1 Subpulmonic effusion. Note (arrow) shifting of the peak of the diaphragm laterally. (From Crapo JD, MD, Glassroth J, MD, Karlinsky JB, MD, MBA, et al. *Baum's Textbook of Pulmonary Diseases*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

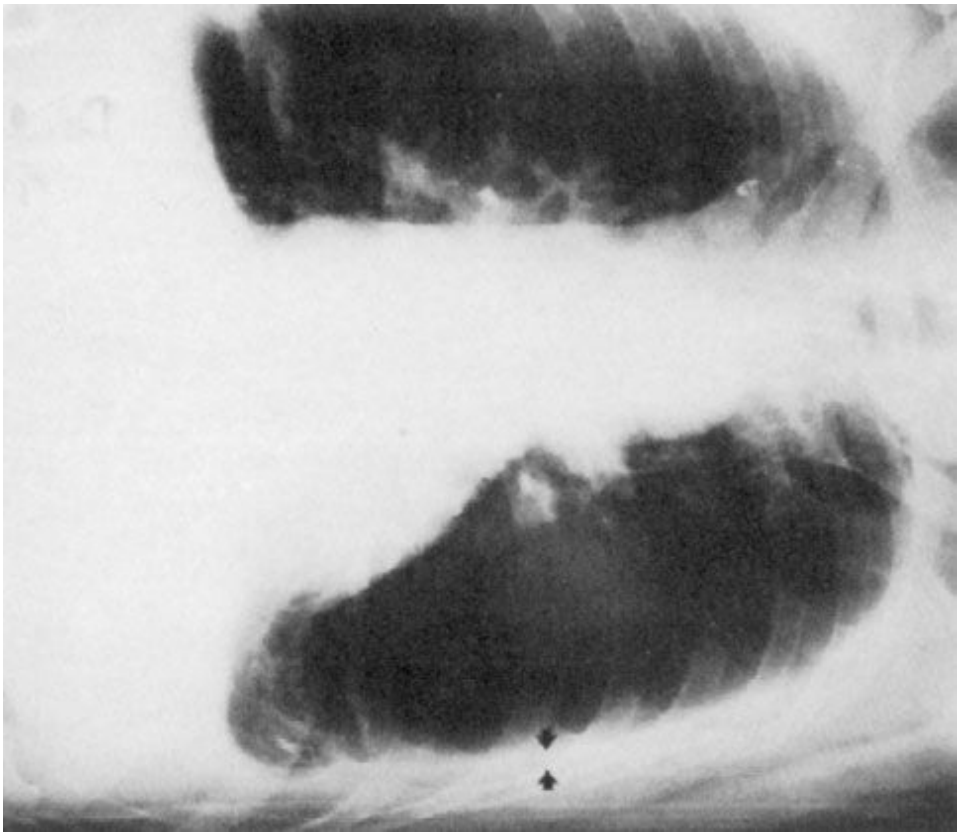

FIGURE 75.2 Lateral decubitus film showing layering out of effusion. Courtesy of LifeArt 2014.

Ultrasonography has been shown to have better sensitivity than plain radiographs in identifying effusions, especially in the setting of small effusions or loculations (1). With a 5- to 10-MHz linear transducer and the patient supine or upright, the hemidiaphragms are visualized just above the liver and spleen. As shown in Figure 75.3, fluid is demonstrated above the diaphragm and between the kidney and liver. The normal pleural space appears as a black line <0.5 mm thick between the two pleural (white) lines which appears to glide during respiration. A pleural effusion is seen as an echo-free (black) space which may change in size with respiration. The volume of the effusion (in milliliters) can be estimated using the following equation: (mL $=$ 16 $\times$ D), where D (depth) is the maximum size of effusion measured from parietal to visceral pleura in millimeters (19). If the effusion is large, the lung size is reduced and is seen as a free-floating hyperechoic/white area within the effusion. If the

effusion is organized or loculated, the septa will appear hyperechoic (white) within the effusion.

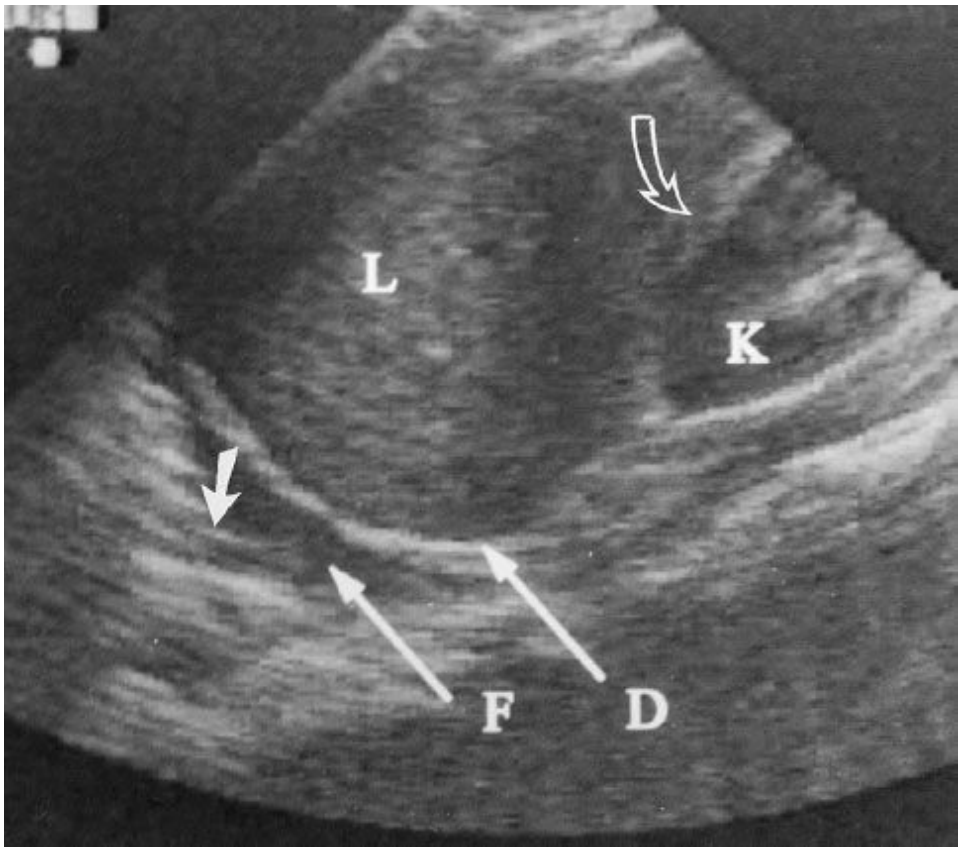

FIGURE 75.3 Morrison's pouch demonstrating free fluid between the liver and kidney (curved open arrow), as well as above the diaphragm (short arrow).

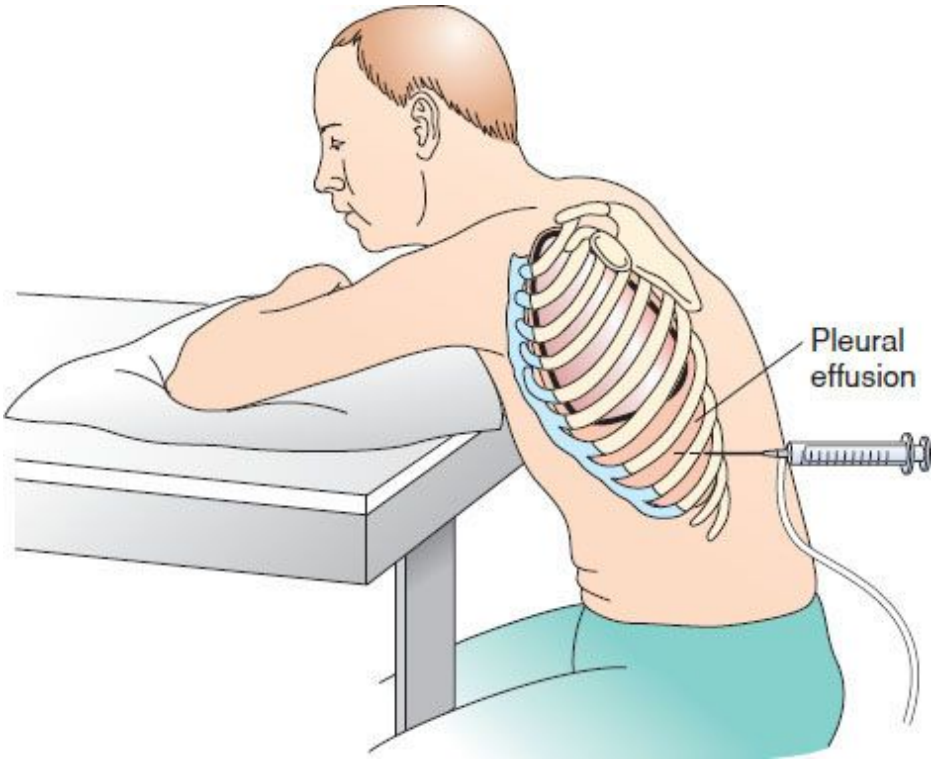

FIGURE 75.4 Position for patient undergoing thoracentesis. From Smeltzer SC, Bare BG, Hinkle JL, et al. *Brunner & Suddarth's Textbook of Medical Surgical Nursing*. 11th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

Computed tomography (CT) is indicated for suspected pulmonary embolism, malignancy, or ambiguous parenchymal findings on plain films.

KEY TESTING

- CXR—upright PA and lateral films should be initial evaluation. Perform lateral decubitus if cannot obtain upright CXR or to check if effusion layers out.
- Ultrasound—better sensitivity than plain radiographs to identify effusions and useful in small or loculated effusions.
- CT—indicated for suspected pulmonary embolism, malignancy, or ambiguous parenchymal findings on CXR.

ED MANAGEMENT

Once a pleural effusion is identified in an ED patient, the management involves the following four key considerations.

1. Is the effusion most likely transudative? Most transudative effusions (CHF, low protein states, ascites, peritoneal dialysis) can be identified based on the history and physical examination alone, and do not require intervention unless the presentation is atypical and/or does not respond to appropriate therapy.
2. Are antibiotics indicated? Antibiotics should be initiated early in the setting of parapneumonic effusions, and selection should be based on the source (community- vs. hospital-acquired pneumonia) and severity of illness.
3. Is an ED thoracentesis indicated? Indications for emergent thoracentesis include symptomatic large effusions or sepsis with suspected empyema. Small (<10 mm), free-flowing parapneumonic effusions do not require thoracentesis, unless the patient is septic or fails to respond to appropriate antibiotics (20). Pleural effusion in the setting of pulmonary embolism, or medication-related effusions that resolve with cessation of the offending medication do not require thoracentesis.
4. Is a chest tube indicated? Chest tubes are indicated in patients with frank pus or an infected effusion with a pH <7.20. Chest tubes are also indicated in patients with large or symptomatic pneumothorax after thoracentesis.

Thoracentesis

Contraindications to thoracentesis are generally relative. An INR >2 or platelets <25,000 represent relative contraindications to thoracentesis, while the decision to give platelets, clotting factors, or fibrinogen should be made on an individual basis (21). A technically difficult thoracentesis, or one with higher risk of complications, should be expected in the setting of mechanical ventilation, a loculated effusion, congenital or acquired diaphragmatic structural abnormality, bleb disease or scarring from past disease or trauma. Thoracentesis in the settings of both very small and very large effusions have a higher risk of complications. If a difficult thoracentesis is anticipated, consultation with an invasive radiologist

or pulmonologist may be the most appropriate course of action. Bedside ultrasound increases the yield, reduces the complication rate, and should be used if available (22). The following steps outline the thoracentesis procedure.

1. After informed consent, the patient should be upright, leaning forward on a raised bedside table, as shown in Figure 75.4. The lateral decubitus position may be used if the patient cannot tolerate sitting.
2. Using a bedside ultrasound, mark the location of the effusion and the area to be punctured. The diaphragm excursion should be marked at full inspiration and expiration to avoid puncturing.
3. The puncture site should be 8 to 10 cm lateral to the midline, toward the posterior axillary line, typically in the seventh to ninth intercostal space, one to two interspaces below the fluid level, and above the diaphragm marks.
4. After sterile preparation of the aspiration site, local anesthesia is injected.
5. Using Seldinger technique, a small-gauge catheter covered needle is inserted over the superior margin of the rib avoiding the intercostal vessels.
6. The catheter is advanced into the chest, and a maximum of 1,500 mL of fluid should be removed.
7. A postprocedural chest radiograph or ultrasound should be obtained to rule out iatrogenic pneumothorax. While a small amount of air entering the pleural cavity during thoracentesis leads to a clinically insignificant pneumothorax, inadvertent puncture of the lung parenchyma can lead to a large and/or symptomatic pneumothorax which may require a chest tube (23). Less common complications of thoracentesis include hemothorax, hemoperitoneum, shearing of the catheter tip, and infection.
8. Trapped lung due to malignancy or pleural inflammation should be suspected when the lung remains unexpanded despite adequate thoracentesis. If symptomatic, a chest tube and/or surgical consult will be indicated.

TABLE 75.2
Etiology of Pleural Effusions

Transudate	Exudate
Common Causes	

• Congestive heart failure
• Cirrhosis
• Renal:
  • Nephrotic syndrome
  • Glomerulonephritis
  • Peritoneal dialysis
	• Parapneumonic effusion:
	  • Bacterial
	  • Viral
	  • Tuberculosis
	• Malignancy: Metastatic, lymphoma, leukemia, and mesothelioma
	• Pulmonary embolism

Less Common Causes	

• Other low protein states
• CSF leak after spinal surgery or ventriculopleural shunt
• Atelectasis due to increased negative pressure
• Urinothorax due to obstructive uropathy
	• Infection
	  • Fungal or parasitic
	  • Hepatic or splenic abscess
	• Trauma or surgical
	  • Post cardiac surgery
	  • Traumatic hemothorax
	  • Esophageal rupture/Boerhaave's
	• Drug-induced
	• Collagen vascular disease
	  • Rheumatoid arthritis
	  • Systemic lupus erythematosus
	  • Sarcoidosis
	• Uremia
	• Chylothorax : Traumatic injury or malignancy
	• Sympathetic effusions: Pancreatitis, pericarditis, hepatitis, radiation-induced pleuritis
	• Ovarian hyperstimulation syndrome

Can Cause Either Transudate or Exudate	
• Meigs syndrome • Hypothyroidism • Lung entrapment • Superior vena cava obstruction • Pulmonary embolism can *occasionally* be transudative • Malignancy can *occasionally* cause transudative effusion if blocking lymphatic outflow	

Evaluation of the Fluid

After gross examination of the pleural fluid, the differential diagnosis can be narrowed by determining if the fluid is a transudate or an exudate. The most common causes of transudative effusion are congestive heart failure and cirrhosis; the most common causes of exudative effusion are pneumonia (bacterial, viral, and tuberculosis), malignancy, and pulmonary embolism (Table 75.2). Light's criteria (24) is the most widely accepted method to identify exudative effusions (Table 75.3), using pleural LDH and protein levels as markers of capillary permeability. Exudates have a large differential diagnosis and require further fluid analysis to help identify the etiology. Markers of increased cellular metabolism (pH and glucose) help identify and grade infectious processes, while cell counts, cultures, specific stains, and cytology measures assist in identifying exact organisms or malignancy. Additional pleural fluid biomarkers may aid in the identification of congestive heart failure (BNP), tuberculosis (adenosine deaminase), pancreatitis (amylase), chylothorax (triglycerides), and malignancy (mesothelin, fibulin-3, immune-cytochemical stains).

CRITICAL INTERVENTIONS

- ED thoracentesis is indicated in patients with effusions (>10 mm) associated with respiratory distress or sepsis, and in patients thought to have a complicated parapneumonic effusion.
- Antibiotics should be initiated early in parapneumonic effusion.
- Ultrasound should be routinely used to guide thoracentesis.
- A chest tube is indicated in patients with frank pus, loculations, or fluid with a pH <7.20.

DISPOSITION

The patient's condition and underlying disease process dictate the need for admission. The presence of a pleural effusion, in and of itself, does not necessitate admission, but does require a discussion with the primary care physician regarding the timing and setting of thoracentesis. If thoracentesis is performed, hospital admission is

usually indicated for further treatment of the underlying disease, although the occasional patient with an uncomplicated effusion might be discharged after 4 to 6 hours of observation.

TABLE 75.3
Gross, Microscopic, and Biochemical Examination

Differential Diagnosis	Gross Appearance	Biochemical Profile (PF = Pleural Fluid)	Microscopy
Transudative effusion	Straw-colored, clear, odorless	• Light's criteria: Exudate if any are present: • PF: Serum protein ratio >0.5 • PF: Serum LDH ratio >0.6 • PF LDH >2/3 normal serum LDH Additional markers of exudate: • PF cholesterol >45 mg/dL • PF protein >2.9 g/dL • Glucose <60 mg/dL • WBC >1,000/mm (3)	
Exudative effusion	Clear to cloudy depending on protein and cell content		
Differential Diagnosis of Exudates:			
Infectious (see Table 75.1)	Cloudy to purulent	Glucose <60 mg/dL pH <7.4	WBC >50,000/mm (3)
Malignancy	Serosanguinous to bloody	Elevated protein and decrease pH if rapid cellular turnover	Variable
Pulmonary embolism	Serosanguinous to bloody	Variable	Variable
Hemothorax	Bloody	Similar to serum	Hemothorax: PF-whole blood HCT >0.5
Tuberculosis	Serosanguinous to bloody	Variable TB: Protein >5 g/dL	WBC >10,000, with Lymphocytosis
Chylothorax	Milky	Elevated lipids and triglycerides	Variable, but typically elevated WBC

Common Pitfalls

- Failure to identify an effusion, leading to inadequate or delayed evaluation and treatment.
- Failure to initiate antibiotics in patients with parapneumonic effusion.
- Failure to identify patients with complicated parapneumonic effusions that require chest tube to prevent rind formation and constrictive pleuritis.
- Failure to consider pulmonary embolism in patients with pleural effusion.
- Failure to identify hemothorax or esophageal rupture.
- Presumption that an effusion is old and unchanged can result in an inadequate evaluation or treatment. Comparison with previous radiographs is essential.

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CHAPTER 76

Asthma

Lauren M. Smith

Asthma is characterized by increased airway responsiveness to various stimuli. Asthma is caused by a variety of processes including bronchoconstriction, widespread bronchial wall edema, and increased mucous secretions. However, airway inflammation is the primary pathophysiologic mechanism. Although the reversibility of airflow obstruction was once considered a cornerstone of the diagnosis, it is now recognized that reversibility may be incomplete in some patients because of airway remodeling (1).

Asthma affects between 5% and 10% of adults in the United States and the prevalence of asthma has been on the rise for the last three decades. However, mortality has declined. Asthma accounts for just over 2 million emergency department (ED) visits per year, adult and pediatric. Most deaths occur prior to hospital arrival and the highest rates of death occur in those older than 65. About half of all cases are diagnosed before the patient reaches age 10, and another one-third are detected before age 40. The male-to-female ratio of this disease is higher during childhood but reverses in adulthood. Higher asthma prevalence is seen in lower socioeconomic households and in the Afro-American population (2).

The natural course of asthma has not been investigated thoroughly, but studies suggest that 50% to 80% of patients have a good prognosis, especially those with mild disease or disease that develops in childhood. Chronic asthma is categorized by severity, ranging from intermittent to mild, moderate, or severe persistent. Treatment is focused on reduction of impairment and reduction of risk. Periods of symptom-free intervals are interspersed with

exacerbations, which trigger visits to the ED. Only about l0% or less of asthmatics are considered to have severe or refractory asthma, and it is these patients that are difficult to control and are prone to exacerbations.

Asthma is a heterogeneous disease. Clinically, it can be separated into two groups: allergic or extrinsic asthma, and nonallergic or intrinsic asthma. Many patients have components of both types. *Extrinsic asthma* accounts for $<10\%$ of patients with asthma and tends to develop early in life. It is associated with a well-defined sensitivity to inhaled allergens, a family history of allergic diseases, increased serum levels of immunoglobulin (Ig) E, positive immediate skin tests, and blood eosinophilia. It may be seasonal (trees, grasses, and spores) or perennial (animals, gardens, and house dust). A good response to bronchodilator therapy is usually observed.

Intrinsic asthma is the more common type of the disease. An inciting allergen cannot be identified, a family history of allergies is less common, IgE levels may be normal or low, and skin tests are negative. Intrinsic asthma is perennial, tends to be more severe than extrinsic asthma, and has a limited response to bronchodilator therapy.

All individuals with asthma have hyperresponsive airways that narrow when exposed to various stimuli: allergic, infectious, pharmacologic, environmental, occupational, exercise-related, or emotional stimuli.

Allergic asthma occurs when inhaled allergens bind to IgE molecules that are bound to mast cells in the lining of the tracheobronchial tree. During the early response, various mediators are released, causing increased vascular permeability, mucosal edema, and bronchial smooth-muscle contraction. A second wave of reaction, the late response, is seen hours to days later and involves the accumulation of inflammatory cells in the bronchial mucosa, thereby perpetuating the reaction.

Although several theories attempt to explain the pathophysiologic changes that occur in nonallergic asthma, none adequately explains all clinically observed phenomena. Research suggests that even

patients without atopy have the same pathophysiologic basis for the disease as atopic patients.

Respiratory infections, particularly viral infections, commonly precipitate bronchospasm. Viruses cause mucosal inflammation and lower the firing threshold of the subendothelial vagal receptors, resulting in enhanced airway reactivity. This hyperactivity may last up to 8 weeks, even in nonasthmatic persons.

Pharmacologic agents also may induce acute asthma. The agents most frequently implicated are aspirin and nonsteroidal anti-inflammatory compounds, coloring agents, and β-adrenergic antagonists.

Up to 10% of adults with asthma experience the triad of aspirin-induced bronchospasm, nasal polyps, and eosinophilia. Ingestion of aspirin, nonsteroidal anti-inflammatory compounds, and tartrazine (FDC yellow dye no. 5) and other dyes may induce severe asthma in these patients, possibly by diverting arachidonic acid metabolism toward the lipoxygenase pathway and causing the production of leukotrienes, which are potent bronchoconstrictors.

Sulfating agents are used widely as food preservatives and antioxidants in pharmaceutical products. Exacerbation of asthma has been reported after food ingestion and after the use of sulfite-containing drugs, including some inhalation bronchodilators.

A large variety of occupational dusts and fumes may provoke acute airway obstruction. Patients with occupational asthma typically give a cyclic history. They are symptom-free during weekends, vacations, and on arrival at work. As the workday progresses, wheezing develops. A history of similar symptoms in fellow employees may be noted. Three mechanisms are involved in occupational asthma: immunologic reactions (e.g., animal handlers), direct liberation of bronchoconstrictors (e.g., cotton workers), and direct irritant effects (e.g., meat wrappers).

Exercise also may stimulate an asthma attack. Exercise-induced bronchospasm is usually noted within 5 to 20 minutes after the completion of exercise and is related to thermal changes in the respiratory tree. Exercising in a cold, dry environment causes a more marked response than exercising in a warm, humid environment.

Endocrine factors have been recognized as yet another cause of airway hyperresponsiveness. Normal variations in progesterone and estradiol levels are believed to modulate airway reactivity.

Psychological factors also influence asthma exacerbations, probably through modification of vagal efferent activity. The extent to which psychological factors participate in the induction and continuation of an asthma attack is unknown but probably varies from patient to patient and from episode to episode.

Regardless of the underlying precipitant, airway narrowing, bronchial wall edema, bronchial smooth muscle contraction, and mucosal plugging ensue. These changes result in increased airway resistance, decreased forced expiratory volumes and flow rates, lung hyperinflation, increased work of breathing, and ventilation–perfusion mismatch.

CLINICAL PRESENTATION

The classic triad of symptoms during an asthma attack is cough, dyspnea, and wheezing, but chest tightness and nonproductive cough may precede dyspnea and wheezing. Asthmatic patients coming to the ED are frequently anxious, tachypneic, tachycardic, and mildly hypertensive. As airway obstruction worsens, the expiratory phase becomes prolonged and lung hyperinflation, accessory respiratory muscle use, muscle retraction, and pulsus paradoxus may be noted. Patients may attempt to sit upright or lean forward (tripod position) in an effort to ease the work of breathing. However, these signs may be absent despite severe airway obstruction. A silent chest indicates insufficient air movement or extensive mucous plugging and is an ominous sign. Cyanosis may appear only immediately before respiratory arrest and should not be relied on as an indication of the severity of the attack. The termination of an exacerbation is often marked by a cough productive of thick mucous plugs and bronchial casts (Curschmann spirals).

A subset of asthmatic patients experiences the sudden onset of severe symptoms. These individuals tend to respond rapidly to treatment but appear to be at significant risk for a fatal outcome.

Occasionally, an asthmatic patient may complain of intermittent dyspnea or cough on exertion. Patients with cough-equivalent asthma tend to have normal breath sounds on examination, even during an exacerbation, but reversible bronchospasm may be demonstrated on pulmonary function testing.

Complications of asthma include pneumothorax, pneumomediastinum, and subcutaneous emphysema. Pneumothoraces may require insertion of a chest tube for evacuation. Mild atelectasis may occur as a result of bronchial mucous plugging but rarely requires intervention other than conventional bronchodilator therapy. In addition, rib fractures and costochondral strain may occur as a result of excessive coughing. Cough syncope, a rare complication of asthma, is noted most frequently in moderately obese, middle-aged asthmatic men. Finally, dysrhythmias may occur as a result of hypoxia, especially in patients who have received oral adrenergic agents.

DIFFERENTIAL DIAGNOSIS

Wheezing, coughing, and dyspnea are present in many conditions. Common problems include pneumonia, bronchitis, croup, bronchiolitis, chronic obstructive lung disease, congestive heart failure, pulmonary embolism, allergic reactions, and upper airway obstruction from edema or a foreign body. Less common problems include cystic fibrosis, hypersensitivity pneumonitis, carcinoid syndrome, and exposure to odors, dust, and gas. A careful history and physical examination should help differentiate asthma from these conditions.

ED EVALUATION

The ability to perform a thorough history and physical examination before initiating treatment is often limited by the patient's dyspnea. Aggressive therapy directed at relieving airway obstruction begins as soon as a diagnosis of asthma is established. Meanwhile, an attempt is made to obtain a history from family members or the patient. Important points to establish include the following (3,4).

- Duration and onset of the current attack

- Identification of precipitating causes
- Type and amount of medications (inhaler/nebulizer) used before arrival in the ED
- Response to prior therapy, including current or previous use of steroids
- Frequency of ED visits and hospitalizations
- Previous need for intubation or ventilation
- History of concurrent medications and allergies
- History of concurrent medical problems
- History of illicit drug use

Patients at high risk of asthma-related death include those with previous intubations; more than two hospitalizations or more than three ED visits in the past year; use of more than two canisters of short-acting β_2-agonist (SABA) per month; difficulty perceiving airway obstruction or worsening asthma; low socioeconomic status or inner-city residence; illicit drug use; major psychosocial or psychiatric disease; age; and comorbidities such as cardiovascular or other chronic lung diseases.

Immediate attention is also directed to the patient's appearance and work of breathing (i.e., use of accessory muscles), vital signs, chest, heart, mental status, and skin examination. The presence of a pulsus paradoxus (a drop of SBP of more than 12 mm Hg during inspiration) may be noted. However, judging the state of a patient's ventilatory status and pulmonary function on clinical grounds alone can be misleading. The failure to recognize impending respiratory failure is a key contributor to patient death. The degree of tachycardia and tachypnea often do not correlate well with the degree of airway obstruction. Pulsus paradoxus may be absent in up to one-third of severe asthmatics (5). Furthermore, wheezing is absent if airflow is minimal. To complicate matters, all of the aforementioned clinical parameters can normalize with even minimal improvement in pulmonary function (6). Therefore, quantification of airway changes must be assessed by using either the forced expiratory volume in 1 second (FEV_1) or the peak expiratory flow rate (PEFR). An initial FEV_1 of <1 L ($<30\%$ predicted) or a PEFR of

$<$100 L/min ($<$20% predicted) indicates very severe obstruction (3,4).

Hypoxemia is not common during most acute exacerbations. Pulse oximetry may be useful in assessing and following oxygenation. A saturation of $<$91% generally correlates with severe hypoxemia. Arterial blood gas (ABG) measurements are rarely needed in the management of acute asthma, unless the practitioner desires to know the pCO_2 or pH. In general, hypercapnia, severe hypoxemia, or metabolic acidosis does not occur until the PEFR or FEV_1 is $<$25% of predicted values (7), but young children and elderly patients commonly present exceptions to this rule. The degree of hypoxemia determined by ABG generally reflects the extent of ventilation–perfusion mismatch. A normal or increased $PaCO_2$ indicates severe airway obstruction and impending ventilatory failure (7).

Expectorated sputum may appear purulent because of the presence of eosinophils, but this finding may not reflect infection. A wet preparation of sputum may contain Charcot-Leyden crystals (eosinophilic granules), Curschmann spirals (mucous casts), and bacteria.

Chest radiographs may demonstrate hyperinflation and atelectasis but are usually nondiagnostic. A chest radiograph is necessary only if pneumonia, pneumothorax, or pneumomediastinum is suspected or if the patient fails to respond to aggressive bronchodilator therapy.

Although electrocardiography occasionally reveals evidence of right ventricular strain, it is generally not helpful except to rule out concurrent cardiac problems. However, all older patients, especially those with cardiac disease, should be monitored during therapy.

Blood tests, including a complete blood count, are unlikely to help guide the acute management of an asthma attack. Asthma scores that incorporate subjective and objective criteria (pulse, respiratory rate, pulsus paradoxus, subjective dyspnea, accessory muscle use, wheezing, and PEFR) should not be relied on for predicting emergency treatment or determining disposition.

ED MANAGEMENT

ED interventions are guided by pulmonary function tests (FEV_1, PEFR), vital signs, chest, heart and mental status examinations, and the patient's subjective assessment of dyspnea. The goal of emergency treatment is to ensure adequate oxygenation and to relieve airflow obstruction.

Supplemental oxygen, inhaled β-adrenergic agonists, oral or intravenous corticosteroids, and, to a lesser extent, inhaled anticholinergic agents are the mainstays of asthma treatment in the ED. It is now thought that timely administration of glucocorticoids for serious exacerbations is the single most effective strategy for reducing ED visits and hospitalizations (8,9). The methylxanthines (e.g., theophylline) are not a component of emergency care (10). The benefits of ketamine remain largely anecdotal and have not been substantiated in controlled trials (11). The National Asthma Education and Prevention Program (NAEPP) Expert Panel (Fig. 76.1) (3,4) has established guidelines for the diagnosis and management of acute exacerbations of asthma. Acute pharmacologic therapy can be divided into three categories: β-adrenergic agonists, glucocorticoids, and anticholinergics. Chronic management is primarily composed of treatment with inhaled corticosteroids and long-acting inhaled β-agonists; however, these have no role in the acute setting. Despite effective therapies for chronic management, there is still frequently poor compliance, leading to poor control (1). Much work is being done to develop medications that further address the inflammatory component of asthma. This includes anti-IgE therapy and blockers of specific mediators (e.g., IL-5, 9, and 13) or receptors. These remain under investigation and their potential utility in the acute setting remains unclear (1).

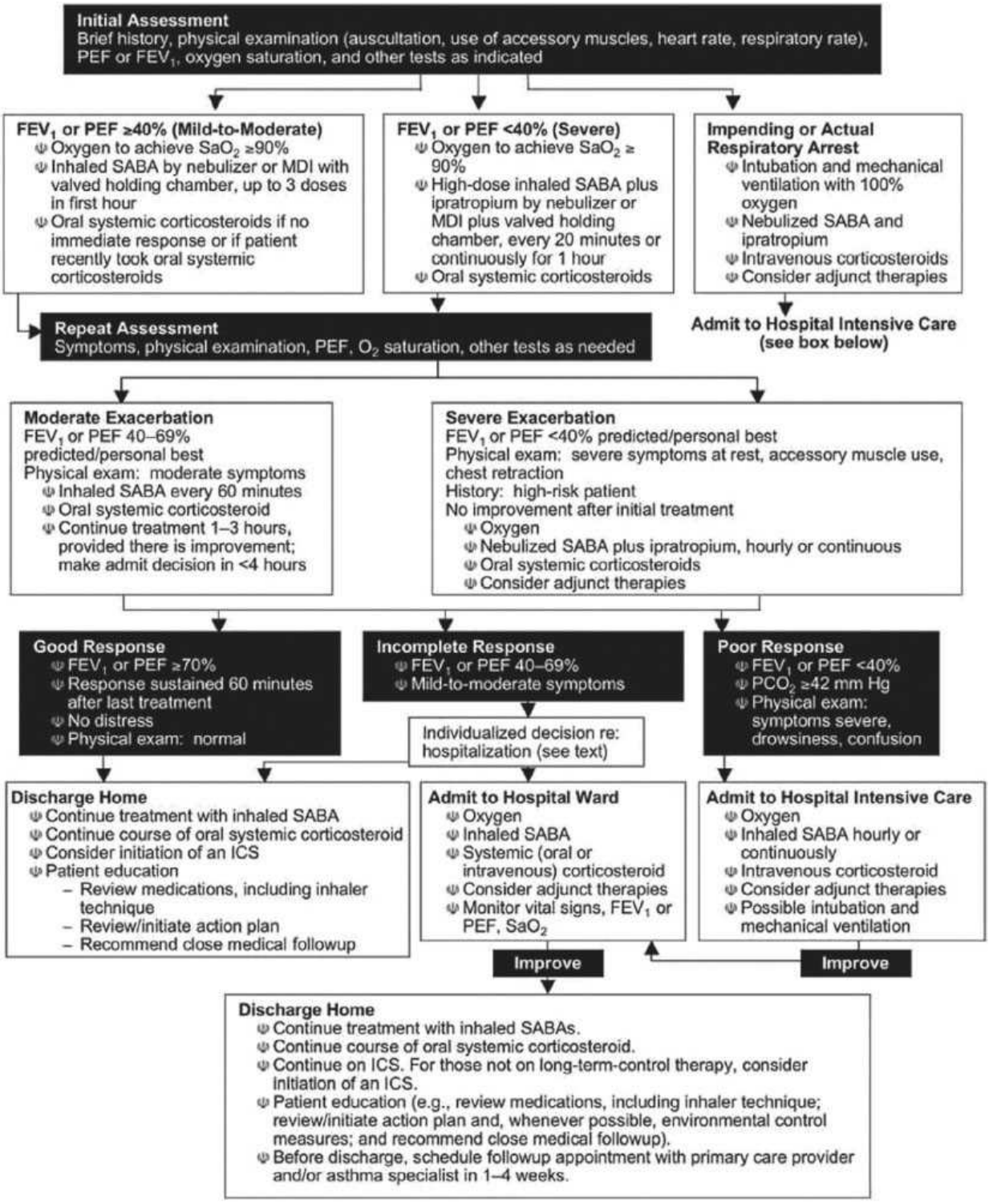

FIGURE 76.1 Management of asthma exacerbations: Emergency department and hospital-based care. Key: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; MDI, metered-dose inhaler; PCO_2, partial pressure carbon dioxide; PEF, peak expiratory

flow; SABA, short-acting β_2-agonist; SaO_2, oxygen saturation. (Adapted from National Asthma Education and Prevention Program, *Expert Panel Report 3: Guidelines of the Diagnosis and Management of Asthma* (NIH Publication Number 08–5846). Baltimore, MD: Department of Health and Human Services, National Institutes of Health, 2007.)

Table 76.1 outlines the preferred treatments recommended by the NAEPP Expert Panel (3,4).

TABLE 76.1
Dosages of Drugs for Asthma Exacerbations in Emergency Medical Care or Hospital

Medication	Dosages		
	Adult	Child[a]	Comments
Short-Acting Inhaled β_2-agonists			
Albuterol			
Nebulizer solution (5 mg/mL, 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)	2.5–5 mg every 20 min for 3 doses, then 2.5–10 mg every 1–4 hrs as needed, or 10–15 mg/hr continuously	0.15 mg/kg (minimum dose 2.5 mg) every 20 min for 3 doses, then 0.15–0.3 mg/kg up to 10 mg every 1–4 hrs as needed, or 0.5 mg/kg/hr by continuous nebulization	Only selective β_2-agonists are recommended. For optimal delivery, dilute aerosols to a minimum of 3 mL, as gas flow of 6–8 L/min.
MDI (90 µg/puff)	4–8 puffs every 20 min up to 4 hrs, then every 1–4 hrs as needed	4–8 puffs every 20 min for 3 doses, then 1–4 hrs inhalation maneuver; use spacer/holding chamber	As effective as nebulized therapy if patient is able to coordinate
Bitolterol			
Nebulizer solution (2 mg/mL)	See albuterol dose	See albuterol dose; thought to be half as potent as albuterol on a milligram basis	Has not been studied in severe asthma exacerbations; do not mix with other drugs
MDI (370 µg/puff)	See albuterol dose	See albuterol dose	Has not been studied in severe asthma exacerbations
Levalbuterol (R-Albuterol)			
Nebulizer solution (0.63 mg/3 mL, 1.25 mg/3 mL)	1.25–2.5 mg every 20 min for 3 doses, then 1.25–5 mg every 1–4 hrs as needed, or 5–7.5 mg/hr continuously	0.075 mg/kg (maximum dose 1.25 mg) every 20 min for 3 doses, then 0.075–0.15 mg/kg up to 5 mg every 1–4 hrs as needed, or 0.25 mg/kg/hr by continuous nebulization	0.63 mg of levalbuterol is equivalent to 1.25 mg of racemic albuterol for both efficacy and side effects
Pirbuterol			
MDI (200 µg/puff)	See albuterol dose	See albuterol dose; thought to be half as potent as albuterol on a milligram basis	Has not been studied in severe asthma exacerbations
Systemic (Injected) β_2-Agonists			
Epinephrine			
1:1,000 (1 mg/mL)	0.3–0.5 mg every 20 min for 3 doses subcutaneously	0.01 mg/kg up to 0.3–0.5 mg every 20 min for 3 doses subcutaneously	No proven advantage of systemic therapy over aerosol
Terbutaline (1 mg/mL)	0.25 mg every 20 min for 3 doses subcutaneously	0.01 mg/kg every 20 min for 3 doses then every 2–6 hrs as needed subcutaneously	No proven advantage of systemic therapy over aerosol
Anticholinergics			
Ipratropium Bromide			
Nebulizer solution (0.25 mg/mL)	0.5 mg every 30 min for 3 doses then every 2–4 hrs as needed	0.25 mg every 20 min for 3 doses, then every 2–4 hrs	May mix in same nebulizer with albuterol; should not be used as first-line therapy; should be added to β_2-agonist therapy
MDI (18 µg/puff)	4–8 puffs as needed	4–8 puffs as needed	Dose delivered from MDI is low and has not been studied in asthma exacerbations.
Ipratropium with Albuterol			
Nebulizer solution (each 3 mL vial contains 0.5 mg ipratropium bromide and 90 µg of albuterol)	3 mL every 30 min for 3 doses, then every 2–4 hrs as needed	1.5 mL every 20 min for 3 doses, then every 2–4 hrs	Contains EDTA to prevent discoloration. This additive does not induce bronchospasm.
MDI (each puff contains 18 µg ipratropium bromide and 90 µg of albuterol)	4–8 puffs as needed	4–8 puffs as needed	
Systematic Corticosteroids			
Prednisone			
Methylprednisolone			
Prednisolone	60 mg initially 120–180 mg/d in 3 or 4 divided doses for 48 hrs, then 60–80 mg/d until PEF reaches 70% of predicted or personal best	1 mg/kg every 6 hrs for 48 hrs then 1–2 mg/kg/d (maximum: 60 mg/d) in 2 divided doses until PEF 70% of predicted or personal best	For outpatient "burst" use 40–60 mg in single or 2 divided doses for adults (children: 1–2 mg/kg/d, maximum 60 mg/d) for 3–10 d.

Note: No advantage has been found for higher dose corticosteroids in severe asthma exacerbations, nor is there any advantage for intravenous administration over oral therapy, provided that gastrointestinal transit time or absorption is not impaired. The usual regimen is to continue the frequent multiple daily dose until the patient achieves an FEV or PEF of 50% of predicted or personal best and then lower the dose to twice daily; this usually occurs within 48 hrs. Therapy following a hospitalization or emergency department visit may last from 3 to 10 d.

[a]Children = 12 yrs of age.

EDTA, ethylenediaminetetraacetate; FEV, forced expiratory volume; MDI, metered-dose inhaler; PEF, peak expiratory flow.

From National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma: update on selected topics—2000. *J Allergy Clin Immunol* 2002; 110:S1–S209, with permission.

β-Adrenergic Agonists

SABAs are the drugs of choice for the management of acute bronchospasm. They produce bronchodilation by stimulating β-

receptors, resulting in the formation of cyclic adenosine monophosphate (cAMP), which results in relaxation of bronchial smooth muscle, inhibition of mediator release, and increase in mucociliary clearance. Drugs in this category include resorcinols, saligenins, and catecholamines (Table 76.1).

Resorcinols and saligenins available in the United States include albuterol (salbutamol), levalbuterol, pirbuterol, formoterol, metaproterenol, and terbutaline. Aerosol forms are available for albuterol, levalbuterol, and metaproterenol. All are available in metered-dose inhalers (MDIs). Aerosol agents and MDIs are rapid-acting, are theoretically long-lasting, and may be repeated every 20 to 30 minutes in an acute situation. Levalbuterol, the R-isomer of albuterol, offers little advantage over albuterol and is more expensive. Salmeterol is a chemical derivative of albuterol with an extended duration of action and a bronchodilator effect 10 times that of albuterol. Formoterol is similar but is even longer acting than salmeterol. Neither is appropriate for use in acute exacerbations of asthma. Albuterol, metaproterenol, and terbutaline are also available in oral form. Terbutaline and epinephrine are available for subcutaneous injection.

The resorcinols and saligenins are highly β_2-selective and are virtually devoid of cardiac side effects when given in inhaled or aerosol form. A frequent noncardiac side effect is tremor. Inhaled or aerosolized β-agonists rapidly promote bronchodilation comparable with that produced by parenteral agents, appear to be longer lasting, and cause fewer side effects. Treatments given every 20 to 30 minutes or in a continuous fashion result in more effective and sustained improvement of pulmonary function than treatments given less frequently (12). The use of spacer devices enhances drug delivery and reduces oral deposition of the medication. Recent studies suggest that albuterol by MDI/spacer is as efficacious as higher doses of albuterol delivered by nebulizer (13).

Subcutaneous administration of β-agonists (epinephrine or terbutaline) may be of use in the treatment of asthmatics who cannot use inhalation devices effectively, in patients in extremis, in patients for whom initial treatment with aerosol β-adrenergic agents fails, or

when preparation of aerosol or metered-dose agents for acute use risks delaying the initiation of therapy.

The catecholamines (epinephrine, isoproterenol, and isoetharine) have largely been supplanted by their more selective and longer-acting derivatives. Epinephrine, a nonselective α- and β-adrenergic agonist, may be given by oral inhalation (in a nonprescription preparation) or subcutaneously. The usual subcutaneous dose in adults is 0.3 to 0.5 mL of a 1:1,000 solution, which may be repeated every 20 minutes to a total of three doses. Epinephrine reaches peak blood levels 20 to 40 minutes after injection, and its bronchodilating effects last up to 4 hours. Side effects include increased myocardial irritability, dysrhythmias, and nervousness. Although some studies suggest that epinephrine may be safely used in asthmatics older than 40 years of age, extreme caution should be used in patients with coronary artery disease (14).

Isoetharine is more β_2-selective than epinephrine and is an effective a bronchodilator. It is supplied as a 1% aerosol solution or in an MDI preparation. Its duration of action is 30 to 90 minutes. Doses may be repeated every 20 to 30 minutes during an acute attack.

Isoproterenol is a potent selective β-adrenergic agent. It is available in aerosol form, in a new MDI, and as an intravenous solution. The duration of action of the inhaled form is 3 hours, and inhalations may be repeated every 3 hours. Use of isoproterenol inhalants was associated with a number of asthmatic deaths in England and Wales in the 1960s, suggesting that the agent should be used cautiously, although a cause-and-effect relationship was not demonstrated. In addition, inhaled isoproterenol may cause paradoxical bronchospasm. Intravenous isoproterenol should be reserved for dire emergencies, and strict monitoring of heart rate, rhythm, and blood pressure is required.

Glucocorticoids

Glucocorticoids should be administered to any patient whose acute airway obstruction is not promptly relieved by an inhaled β-

adrenergic agent. Patients who receive glucocorticoids early require fewer hospital admissions and sustain fewer relapses after discharge from the ED (8). Corticosteroids are thought to exert their effect on acute asthma by reducing airway inflammation. The initial dose is 60 to 125 mg of intravenous methylprednisolone or 40 to 80 mg of oral prednisone (3). Additional doses of methylprednisolone (60 to 80 mg intravenous) or prednisone (40 to 80 mg PO) with a frequency range of daily to every 6 to 8 hours should follow the initial dose. *Oral administration of corticosteroids is equivalent to intravenous administration.* Inhaled corticosteroid use has led to improved asthma control; however, data on the use of inhaled corticosteroids during the acute ED treatment of asthma has yet to be clearly defined (15,16). Because the effects of steroids are not noted for 4 or more hours, vigorous concomitant bronchodilator therapy must be continued.

Anticholinergic Agents

There has been a resurgence of enthusiasm for the use of anticholinergic agents to treat acute bronchoconstriction. These medications, including ipratropium bromide and glycopyrrolate, antagonize the neuromuscular transmitter acetylcholine at the postganglionic parasympathetic receptor, reducing vagally mediated bronchoconstriction in the larger central airways. There appears to be an additive effect when β-adrenergic agents and anticholinergic agents are used together, although this effect is not dramatic (17). Nebulized ipratropium (see Table 76.1) mixed with albuterol should be used in severe asthmatics. Peak anticholinergic bronchodilation is achieved within 1 to 2 hours. Aerosolized atropine sulfate and glycopyrrolate, although effective, have fallen out of favor because of the high incidence of anticholinergic side effects (tachycardia, restlessness, irritability, dry mouth, thirst, and difficulty swallowing).

Other Agents

Magnesium sulfate, a physiologic regulator of intracellular calcium flux, is an effective bronchodilator. In addition to preventing

histamine release from mast cells and opposing the action of acetylcholine, magnesium directly inhibits bronchial smooth-muscle contraction. Both aerosolized magnesium (0.66 g in 10 mL of saline) and intravenous magnesium solutions (2 g over 20 minutes) have been used investigationally to treat patients with asthma for whom maximal standard therapy has failed, although neither form is currently approved for this indication in the United States. Bronchodilation is observed within 2 to 5 minutes after administration, but it disappears rapidly after treatment is discontinued; therefore, additional bronchodilator therapy must accompany the use of magnesium. Side effects include hypotension, malaise, and a warm sensation. Cardiac rhythm, blood pressure, pulse, neurologic status, and renal function must be monitored closely. Magnesium appears to be safe and may be helpful in some patients with severe asthma exacerbations (18).

Nedocromil and *cromolyn* inhibit the release of inflammatory cytokines from mast cells, but they have no role in acute management. Likewise, leukotriene inhibitors, although useful in long-term management, are not indicated for ED treatment.

Heliox, an 80:20 mixture of helium and oxygen, is sometimes considered for treatment in patients with respiratory acidosis who fail conventional therapy. Helium is a low-density, biologically inert gas that lowers airway resistance and decreases respiratory work. Significant improvement may be noted within 10 to 20 minutes of initiating therapy but there are currently insufficient data on whether heliox can avert tracheal intubation or change intensive care and hospital admission rates and duration or mortality; so while safe and well tolerated, no evidence exists that supports its use in the emergency setting (19,20).

Theophylline and its salts have been used to treat acute bronchospasm for more than 50 years. Studies suggest that the methylxanthines, when used alone or in combination with β-agonists during an acute episode, are associated with an increased incidence of side effects but do little to relieve bronchospasm. Methylxanthines have a narrow therapeutic-toxic window, are subject to many interactions with other drugs, and should not be used in the

treatment of acute asthma exacerbations. Toxicity may result in life-threatening cardiac dysrhythmias or seizures.

Noninvasive Assisted Ventilation

Noninvasive assisted ventilation can be in the form of continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP). Noninvasive ventilation decreases the load on the respiratory muscles, improves oxygenation, and can prevent the need for intubation and invasive ventilation (21). Noninvasive ventilation does have some advantages over intubation, including the avoidance of sedation and ventilator-associated complications. Although this intervention is widely used and is reported anecdotally to be successful, literature is lacking to support its use and no guidelines currently exist. Patients most likely to benefit from noninvasive ventilation are those with a high work of breathing a $pCO_2 < 45$, and who are alert cooperative, and hemodynamically stable, with minimal coughing or vomiting (7). Bronchodilator treatments may still be administered via the ventilation circuit. Frequent monitoring must be maintained, as some patients do not improve with this internvention and may become hypercapneic and require intubation and invasive ventilation.

Invasive Assisted Ventilation

If the patient's condition deteriorates or fails to improve despite intensive therapy, use of intubation and mechanical ventilation must be considered. Although there are no absolute criteria other than respiratory arrest and coma, the following patients should be considered for intubation and mechanical ventilation, via RSI (rapid sequence intubation).

- Those with worsening pulmonary function tests despite vigorous bronchodilator therapy
- Those with decreasing PaO_2, increasing $PaCO_2$, or progressive respiratory acidosis
- Those exhibiting respiratory muscle fatigue or exhaustion
- Those with declining mental status

Ventilatory strategies yielding low tidal and low respiratory rates are recommended to minimize the risk of producing or exacerbating dynamic lung hyperinflation (11). Expiratory airflow obstruction can result in air-trapping and higher lung volumes in mechanically ventilated asthmatics. This condition may result in "auto-PEEP," a continuously increased intrathoracic pressure that may decrease venous return and cause hypotension. Auto-PEEP may be avoided in mechanically vented patients by using a rapid inspiratory flow rate, a reduced respiratory frequency, and a prolonged expiratory phase. This type of mechanical ventilation is commonly referred to as "permissive hypercapnea." Hemodynamic instability or hypoxemia may occur after intubation; possible causes to consider besides "auto-PEEP" include displaced endotracheal tube, pneumothorax, over-sedation, and equipment failure.

Opioids, sedatives, and tranquilizers should be avoided in acute asthma, because respiratory arrest may occur after their use. Mucolytics, expectorants, and hydration do not aid in the treatment of asthma. Antibiotics are advisable only for those patients with fever and purulent sputum, evidence of pneumonia, or suspected bacterial sinusitis (3).

Asthma in Pregnancy

Asthma is the most common chronic medical condition that complicates pregnancy, and affects an estimated 4% to 8% of pregnancies. One-third of pregnant patients with asthma improve during pregnancy, one-third of patients remain unchanged, and one-third become worse. Asthma therapy during pregnancy is directed at providing adequate oxygenation for both mother and fetus. The management of pregnant asthmatics is essentially the same as that for nonasthmatics. The use of subcutaneous or inhaled β-adrenergic agents and corticosteroids appears to be safe during pregnancy (22).

CRITICAL INTERVENTIONS

- Measure either the FEV_1 or the PEFR to quantify the degree of airway obstruction.

- Administer IV or oral glucocorticoids early to patients whose acute airway obstruction is not promptly relieved by an inhaled β-adrenergic agent.
- Prescribe oral corticosteroids on discharge to patients who have received glucocorticoids in the ED.
- In intubated patients, avoid auto-PEEP by using a rapid inspiratory flow rate, a reduced respiratory frequency, and a prolonged expiratory phase.

DISPOSITION

Several asthma-scoring indices have been proposed to predict the need for hospitalization, but all have proven disappointing. The following patients should be admitted to the hospital or observation unit.

- Those whose condition deteriorates in the ED
- Those with repeat exacerbations after previous recent ED visits
- Those who have dyspneic and significant hypoxemia (PaO_2 <60), hypercapnea, or acidosis
- Patients with a pretreatment FEV_1 of <10 L ($<30\%$ predicted) or a PEFR of <100 L/min ($<20\%$ predicted), and a post treatment FEV_1 <2.1 L ($<60\%$ predicted) or a PEFR <300 L/min ($<60\%$ predicted)
- Patients who remain subjectively dyspneic after aggressive therapy
- Patients with continued abnormal vital signs after therapy
- Unreliable patients

Even patients who improve enough to be discharged from the ED have residual airway obstruction for up to several weeks after the acute episode subsides. Therefore, arrangements must be made for ongoing treatment and early follow-up. A nontapering 3- to 10-day course of oral corticosteroids (40 to 60 mg/d of prednisone) and a 5- to 10-day treatment regimen of a β_2-adrenergic MDI with spacer (two puffs as needed, up to every 4 to 6 hours) should be prescribed. In addition, a chronic regimen of inhaled corticosteroids (preferred) or leukotriene modifier-inhibitor should be prescribed for all patients

who have persistent asthma in accordance with NAEPP guidelines (3,4). Instruction in the proper use of the inhaler is essential, as is a brief educational intervention, as well as cessation of smoking and illicit drug use. Patients receiving chronic theophylline therapy should be continued on a long-acting preparation pending follow-up with their physician.

Common Pitfalls

- Failure to recognize that a silent chest or a normal $PaCO_2$ is a sign of severe obstructive disease that may result in respiratory arrest.
- Withholding β-agonist therapy in the ED because of β-agonist use at home.
- Failure to use objective measurements of pulmonary function, in addition to clinical and subjective parameters of dyspnea, when judging the adequacy of bronchodilator therapy.
- Failure to give glucocorticoids to all but the mildest asthmatics, especially those who fail to respond to one or two doses of β-agonists.
- Failure to consider chronic asthma management in discharge planning.

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CHAPTER 77

Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) comprises a spectrum of chronic respiratory illnesses characterized by cough, sputum production, dyspnea, airflow limitation, impaired gas exchange, and inflammation (1–3). The mortality rate is greater than 50% within 10 years of diagnosis. COPD is the fourth leading cause of death in the United States and is expected to become the third leading cause of death worldwide by 2020 (4). The overall prevalence of symptomatic COPD in selected countries is 10.1% (5).

The term COPD includes conditions, other than asthma, that have the common feature of airflow obstruction and inflammation of the small airways and alveoli. The inflammatory response in COPD is different than that seen in asthma and involves the recruitment of neutrophils, macrophages, and cytotoxic T lymphocytes. Inflammation of the small airways leads to airway wall thickening and fibrosis, resulting in decreased airway diameter and increased resistance to flow. This is chronic obstructive bronchitis (1,6). Chronic bronchitis is characterized clinically by a productive cough caused by excessive production of bronchial mucus that must be present for 3 months in a year in at least 2 successive years. Pulmonary emphysema, in contrast, is defined from a pathologic standpoint by inflammatory infiltrates in the alveolar wall, leading to an irreversible enlargement of the alveolar air spaces with destruction of the alveolar wall and pulmonary capillary bed (1,6). The result is a reduction in the elastic pressure that generates

expiratory flow (6). Most patients with COPD will have remodeling of both their small airways and their alveoli due to abnormal inflammation, and will therefore exhibit characteristics of both chronic bronchitis and emphysema.

The predominant risk factor for COPD is tobacco use; half of smokers develop airflow obstruction (4). However, 5% to 10% of patients with COPD have never smoked, implicating other causal factors (1). Other risk factors include inhalation of organic and inorganic dusts and fumes, that is environmental pollution, passive smoke inhalation, and occupational exposure (7). α_1-Antitrypsin deficiency is a genetic risk factor and is present in 1% to 2% of patients with COPD (4). Regardless of etiology, the ultimate outcome is irreversible airflow limitation.

The natural course of COPD is one of progressively worsening dyspnea, hypoxemia, and diminished exercise tolerance, with recurrent exacerbations. Most patients with COPD have modest reversible airway obstruction. Although the forced expiratory volume in 1 second (FEV_1) is classically considered the best single prognostic indicator of disability and death, disease severity is better assessed by considering FEV_1, body mass index (BMI), and exercise performance (3). The onset of chronic hypoxemia leads to progressive clinical deterioration caused by *cor pulmonale,* which worsens already diminished lung function. Recurrent episodes of infection and respiratory failure ultimately result in death. Long-term ambulatory oxygen therapy prolongs life in patients with advanced COPD.

CLINICAL PRESENTATION

All patients with COPD exhibit airflow obstruction, but the pure forms of emphysema and chronic bronchitis have distinctive clinical features. Patients with emphysema tend to hyperventilate to compensate for the decreased ability of the lungs to oxygenate the blood due to their decreased alveolar surface area. These classic “pink puffers” work hard to establish a near-normal partial pressure of arterial oxygen (Pa_{O_2}), and they appear barrel-chested, dyspneic,

and tachypneic. They use pursed lips breathing to create positive end-expiratory pressure (PEEP) to prevent early airway closure. Breath sounds are markedly diminished, with a prolonged expiratory phase.

In contrast, patients with chronic bronchitis tolerate hypoxemia well and make no effort to hyperventilate. Chronic hypoxia induces a secondary polycythemia that, combined with the cyanosis of marked desaturation of hemoglobin, produces a plethoric appearance. These patients tolerate an elevated partial pressure of arterial carbon dioxide ($Paco_2$) and have a less labored respiratory pattern. With the decreased work of breathing, the patient with chronic bronchitis does not experience muscle wasting like the emphysematous patient. These features produce the picture of the "blue bloater." Lung examination reveals rhonchi, rales, and variable wheezing. The severity of COPD as classified by Global Initiative for Chronic Lung Disease (GOLD) is listed in Table 77.1 (8).

TABLE 77.1
Global Initiative for Chronic Lung Disease Severity of Chronic Obstructive Pulmonary Disease

Stage	Category	FEV_1	Comments
I	Mild	80%	May be asymptomatic
II	Moderate	≥50% and <80%	Dyspnea on exertion and cough
III	Severe	≥30% and <50%	Reduced exercise capacity and impact on quality of life
IV	Very severe	<30% or <50% with chronic respiratory failure	*Cor pulmonale*

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Most patients who present with an acute exacerbation of COPD do not fit either picture precisely. Patients with COPD exacerbation present with worsening of baseline dyspnea, cough, and/or sputum

that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication (8). Physical examination may reveal a variable degree of respiratory distress, tachypnea, accessory muscle use, retractions, and cyanosis. On auscultation, one may hear diminished breath sounds, a prolonged expiratory phase, wheezing, rales, or rhonchi. Signs of *cor pulmonale* should be sought: a centrally displaced point of maximal impulse, heart gallop, tricuspid murmur, peripheral edema, jugular venous distention, hepatojugular reflux, and hepatomegaly. This complication of long-standing hypoxemia is associated with substantial mortality.

The causes of exacerbation include respiratory infection, noncompliance with (or under dosing of) medications, changes in weather, exposure to certain drugs (e.g., sedatives or β-blockers), cardiac dysrhythmias, left ventricular dysfunction, and environmental exposure to allergens or other irritants. Most exacerbations are caused by infections, either viral or bacterial, with bacterial infections accounting for 50% of COPD exacerbations. Air pollution and other environmental conditions account for approximately 15% to 20% (9). Table 77.2 lists common respiratory agents associated with COPD exacerbations (10–12). Patients typically present with a gradual, but progressive, deterioration, taking hours to days.

TABLE 77.2
Bacterial and Viral Agents Associated with Chronic Obstructive Pulmonary Disease Exacerbations

Bacteria	Viruses
Haemophilus influenzae	Rhinovirus
Streptococcus pneumoniae	Influenza
Moraxella catarrhalis	Parainfluenza
Pseudomonas aeruginosa	Respiratory syncytial virus
	Coronavirus
	Adenovirus

Acute decompensation may be the result of a number of other conditions. Spontaneous pneumothorax in COPD carries a significantly higher complication and mortality rate than in patients with a normal cardiorespiratory status. The patient with chronic bronchitis is predisposed to embolic and thrombotic phenomena because of the hyperviscosity associated with polycythemia. Other disorders, such as congestive heart failure (CHF), pneumonia, acidosis, or renal or hepatic failure, may also overwhelm the COPD patient's limited reserves, resulting in respiratory failure.

DIFFERENTIAL DIAGNOSIS

Other conditions must also be considered in the patient who presents to the emergency department (ED) with wheezing, cough, dyspnea, or respiratory failure. Pneumonia or acute bronchitis may present with varying degrees of shortness of breath, cough, and bronchospasm, and previously undiagnosed COPD may be discovered after an acute pneumonic process has resolved. The onset of respiratory symptoms in the presence or absence of chest pain, when associated with risk factors such as recent surgery, malignancy, immobility, or extended travel, or leg findings consistent with deep venous thrombosis, strongly suggest pulmonary embolism.

Acute left ventricular dysfunction may mimic many findings of COPD including cough, dyspnea, and hypoxemia, and patients may exhibit wheezing, referred to as "cardiac asthma." Orthopnea, paroxysmal nocturnal dyspnea, and cardiomegaly favor CHF, but COPD patients with *cor pulmonale* may demonstrate jugular venous distention and peripheral edema. Classically, chest radiography helped distinguish between these entities, with a lack of cardiomegaly and pulmonary venous redistribution and the presence of bullae and hyperinflation of the lungs suggesting COPD. However, patients with both CHF and COPD who present with dyspnea can present a diagnostic challenge. The rapid laboratory quantification of B-type natriuretic peptide (BNP) may allow more accurate distinction between an acute exacerbation of COPD versus

CHF. BNP is secreted from ventricles in response to pressure and volume expansion. Low levels of BNP are consistent with exacerbations of COPD, asthma, bronchitis, or pneumonia, whereas a BNP level of 100 pg/mL or greater is a strong predictor of CHF. Pulmonary embolism or COPD triggering *cor pulmonale* may also produce elevated BNP levels of 200 to 600 pg/mL (3). Therefore, it is best to use the patient's physical examination, history, and ancillary studies, together with the BNP level to make the most informed clinical diagnosis and therapeutic decisions.

ED EVALUATION

If the patient's respiratory status allows a brief history to be taken, attention should be directed to the rapidity of onset, duration of symptoms, precipitating factors, the dosage of medications, and when medications were last taken. Information should be sought regarding the character of the sputum, the course of previous exacerbations, and any history of concomitant disease processes.

The physical examination focuses on the patient's mental status and the degree of respiratory distress. Hypercapnia and hypoxia can cause confusion, somnolence, and irritability. The cardiac and pulmonary examinations are vital, and repeated examinations are mandatory after therapeutic interventions to monitor the response to treatment.

Pulse oximetry is useful in monitoring oxygen saturation and the effectiveness of oxygen supplementation. Arterial blood gas (ABG) analysis provides information on the $Paco_2$ and pH, reflecting adequacy of ventilation. The pH is the best single laboratory marker for gauging the severity of acute respiratory insufficiency, because it reflects the speed and degree of change in $Paco_2$ (8). Baseline or prior ABG results may be useful for comparison; in general, hypercapnia with acidemia suggests acute respiratory failure.

The chest radiograph (CXR) is usually done at the bedside, unless the patient is stable and can tolerate being transported to the radiology suite for posteroanterior (PA) and lateral films. The CXR is useful when findings of COPD are present, but it is even more

helpful in evaluating for other disease processes, such as pneumothorax, atelectasis, infiltrate, lung mass, or CHF.

Measurements of airflow do not always yield accurate assessments of the severity of illness but may be useful in judging the response to therapy. The peak expiratory flow rate (PEFR) is most commonly used in the ED setting, but, in contrast to the asthmatic patient's response, it does not correlate well with COPD severity during exacerbations, and does not improve as rapidly as the asthmatic patient's in response to therapy.

Laboratory studies are generally of limited value. β-Agonists may cause hypokalemia, although this is rarely clinically significant. A complete blood count may reveal anemia, which can compound the problem of hypoxemia, or a high white blood cell count, which may be a clue to pneumonia or other systemic infections. If there is suspicion for CHF or cardiac injury, BNP and troponin assays may be ordered. D-Dimer may be useful for evaluating low-risk patients when pulmonary embolism is being considered.

A 12-lead electrocardiogram (ECG) may suggest right atrial enlargement, low voltage, right ventricular hypertrophy, or strain (*cor pulmonale*). Acute ischemic patterns must be appreciated to identify an acute coronary event that may be triggering or complicating the acute COPD attack. Continuous ECG monitoring may be useful in revealing dysrhythmias that may aggravate an acute exacerbation.

Thoracic ultrasound is sensitive for ruling out pneumothorax when used by experienced operators. However, it should not be used to diagnose pneumothorax in patients with COPD because there is a high false-positive rate in this population (13).

Thoracic ultrasound is sensitive for ruling out pneumothorax when used by experienced operators. However, it should not be used to diagnose pneumothorax in patients with COPD because there is a high false-positive rate in this population (13).

KEY TESTING

- Order an ABG or VBG to obtain the pH, and thereby gauge the severity of the patient's acute respiratory insufficiency.
- Obtain a CXR to evaluate for infection, pneumothorax, mass, and edema.
- Consider a CBC and basic metabolic panel to screen for anemia, a high WBC, and hypokalemia.
- A BNP should be ordered if CHF is suspected (14).
- A troponin assay and an EKG should be ordered if symptoms or signs of cardiac ischemia or dysrhythmia are present.
- A D-dimer is useful in evaluating low-risk patients for whom PE is being considered.

ED MANAGEMENT

The effective management of the COPD patient with an acute decompensation includes rapid estimation of severity, prompt therapy, frequent reevaluation, and recognition of treatable entities that may have precipitated the ED visit or that complicate the patient's course. The patient should be placed on a cardiac monitor and intravenous (IV) access should be established. Dysrhythmias such as rapid atrial fibrillation usually reflect coexisting heart disease that is worsened by acute hypoxemia; current evidence suggests that most patients with a COPD exacerbation who exhibit ventricular dysrhythmias have underlying left ventricular diastolic dysfunction. Table 77.3 provides a summary to the approach to patients with moderate-to-severe COPD exacerbations.

TABLE 77.3
Overview of Emergency Department Management of Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease[a]

Oxygenation and Ventilation

- Supplemental oxygen—Titrate oxygen to maintain saturation 90–92%
- Noninvasive positive-pressure ventilation—Provide to reduce work of breathing
- Endotracheal intubation—Use when NIPPV fails or is contraindicated in patients with respiratory failure

Bronchodilators

- Albuterol 2.5 mg nebulized every 20–60 min

or

- Levalbuterol 1.25 mg nebulized every 30 min to 8 hrs

and

- Ipratropium 500 µg nebulized

Steroids

- Prednisone 40–60 mg PO

or

- Methylprednisolone 125 mg IV

or

- Decadron 10 mg IV

Antibiotics

- Moxifloxacin 400 mg IV/PO every 24 hrs for 5 d

or

- Levofloxacin 500 mg IV/PO every 24 hrs for 7–14 d or 750 mg IV/PO every 24 hrs for 5 d

or

- Amoxicillin/clavulanate 500 mg PO every 8 hrs or 875 mg PO every 12 hrs

Additional Considerations

- Magnesium sulfate 2 g IV given over 30 min

PO, by mouth; IV, intravenous.
[a]This table presents a focused list of therapies. Other agents may be used. See text for greater detail.

Treatment with oxygen is critical because hypoxemia is the major immediate threat to life. The goal is to maintain a $Pa_{O_2} > 60$ mm Hg or a pulse oximetry reading of 90% to 92% to minimize further risk of hypercapnea and respiratory acidosis (15). A controlled oxygen-delivery system is preferable; a Venturi-mask system can deliver a precise oxygen concentration ranging from 24% to 50%. Adjustments in oxygen delivery should be guided by continuous pulse oximetry and ABG determinations as needed. In the acutely

hypoxemic patient, the administration of oxygen is paramount and far outweighs the risk of hypercarbia caused by blunting of the hypoxemic drive in a chronic CO_2 retainer.

Sympathomimetics, specifically β_2-agonists, are the initial pharmacologic agents of choice for acute COPD exacerbations. Effectiveness is dependent in part on the reversible component of the patient's obstructive lung disease; however, a significant benefit of bronchodilator therapy is to decrease dynamic hyperinflation by improving lung emptying during expiration (3). Side effects include tremor, agitation, insomnia, headache, cardiac tachyarrhythmias, and mild hypokalemia. Nebulizer aerosolization is the preferred delivery method in the ED. Although there are many β_2-agonists available, albuterol, is the most widely used agent. Albuterol, 2.5 mg, is used either in repeated treatments every 20 to 60 minutes, or by continuous nebulization in severe cases. Levalbuterol, the active (R) isomer of racemic albuterol, is available for treatment of COPD by nebulizer; the "on-label" dosage is 1.25 mg every 6 to 8 hours, although dosages of up to 1.25 mg every 30 minutes have been reported in clinical studies. The inactive (S) isomer found in racemic albuterol is thought to promote hypersensitivity and bronchospasm in susceptible individuals, but though patients treated with levalbuterol may require less medication and experience a longer therapeutic duration of action as compared with those given racemic albuterol (16), the considerable added expense outweighs the questionable clinical significance of these minor differences (16).

The slower onset of action renders anticholinergic agents to second-line treatment in the acute setting. Ipratropium bromide, a congener of atropine, has little systemic absorption when inhaled, thus minimizing undesirable anticholinergic effects, and has been shown to have an additive effect when combined with a β_2-agonist. This agent may be administered at a dose of 500 μg per nebulizer treatment.

Corticosteroids are considered useful in acute exacerbations of COPD. Even patients who do not respond to steroids when stable

may still benefit from them during acute attacks. Because steroid use may suppress the adrenal–pituitary axis, patients with current or recent use may require steroids for the stress of any acute illness. IV methylprednisolone at a dose of 125 mg or oral prednisone 60 mg are commonly used in the treatment of exacerbations of COPD. Patients may be given oral prednisone 30 to 40 mg daily for 7 to 14 days if they are discharged from the ED (10).

Before the widespread availability of oral or inhaled β_2-agonists, methylxanthines, most commonly theophylline, were used as monotherapy for COPD. However, methylxanthines have since been proven to be of no benefit in acute COPD exacerbations, and have potentially serious side effects (17).

Other medications may be utilized in the management of acute COPD. Magnesium sulfate has modest bronchodilatory effects and may be given a trial as adjunctive therapy to patients with severe exacerbations who have normal renal function. Some authors have shown benefit of magnesium sulfate only when administered before β-agonists (18).

Cessation of tobacco use may well be the most important intervention for COPD. Brief counseling can be effective, and an effort should be made to advise the patient to stop smoking and seek further counseling from a primary care physician (1,3). COPD patients in the ED are also candidates to receive polyvalent pneumococcal and influenza vaccines to potentially decrease the risk of future exacerbations (19).

COPD exacerbations are commonly ($>50\%$) associated with acute respiratory tract infection. The most common agents are outlined in Table 77.2 (10–12). Antibiotic therapy is indicated if dyspnea is associated with a change in the volume or purulence of sputum or with a new infiltrate on CXR. Antibiotics should also be considered for any patient with a severe COPD exacerbation, or an exacerbation requiring admission. Antibiotic treatment has been associated with better inpatient outcomes (20). Former first-line agents such as trimethoprim/sulfamethoxazole, amoxicillin, and doxycycline have proven to be inferior to advanced-generation quinolones, second-

and third-generation cephalosporins, and amoxicillin/clavulanate. Antibiotic therapy increases treatment success and decreases mortality when used to treat acute exacerbations of COPD associated with increased sputum purulence and volume production (12,21,22). Increasing resistance of *Streptococcus pneumoniae* to macrolides also limits use of this antimicrobial (12). The choice of antibiotic should be based on local resistance patterns, particularly among the bacterial species commonly isolated from sputum during exacerbations: *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* (19). Broad-spectrum coverage should be instituted to reduce the incidence of antibiotic resistance.

For patients who do not respond to acute interventions and who begin to show signs of respiratory failure (such as deterioration of mental status, worsening hypoxemia [Pa_{O_2} of <50 mm Hg], or worsening respiratory acidosis [pH 7.25]), assisted ventilation is indicated. Noninvasive positive-pressure ventilation (NIPPV) should be considered for patients who present with moderate exacerbations of COPD and should be instituted for patients with severe exacerbations of COPD who have a relatively normal mental status and who do not require immediate endotracheal intubation. Contraindications to NIPPV include impending respiratory arrest, cardiovascular instability, and vomiting. NIPPV decreases the work of breathing and has been shown to decrease the rate of endotracheal intubation, to decrease hospital mortality, and to shorten hospital stay in patients with severe exacerbations of COPD (23). Recent studies have shown that NIPPV may safely and effectively be used in patients with altered mental status who are arousable and able to follow simple commands (24). However, for patients who are not candidates for these modalities or for whom noninvasive ventilation has failed, endotracheal intubation with mechanical ventilation is the treatment of choice.

After performing endotracheal intubation and implementing mechanical ventilation, the clinician must be aware of the potential complications associated with positive-pressure ventilation in the COPD patient. Complications include hypotension and

cardiovascular collapse caused by decreased venous return secondary to increased intrathoracic pressure. The increased intrathoracic pressure occurs in patients who "stack" breaths because of the inability to completely exhale the mechanically provided inspired volume that results in greater intrathoracic volume and pressure. If hypotension does not resolve with administration of IV fluids, the patient's endotracheal tube should be temporarily disconnected from the ventilator to relieve excessive positive intrathoracic pressure. Mechanical ventilation should be adjusted to allow for a short inspiratory and long expiratory time with a low tidal volume of 5 to 7 mL/kg. The frequency of ventilation may be gradually increased to allow for resolution of the acute respiratory acidosis and gradual normalization of pH. Extrinsic PEEP may be added to nearly equal intrinsic or auto-PEEP in an effort to keep distal small airways from collapsing with attendant gas trapping. Short-term administration of paralytics eliminates patient-ventilator dyssynchrony and reduces the risk of hyperinflation.

It is paramount that proper sedation is provided to the patient if paralytics are administered. However, hypotension can result from the administration of sedative agents that reduce sympathetic tone. Hypotension should be treated with IV fluids and pressors in more extreme cases.

CRITICAL INTERVENTIONS

- Obtain an arterial or venous pH to determine the severity of acute respiratory insufficiency, because it reflects the speed and degree of change in $Paco_2$. Hypercapnia with acidemia suggests acute respiratory failure.
- Administer oxygen in the acutely hypoxemic patient: the administration of oxygen far outweighs the risk of hypercarbia owing to blunting of the hypoxemic drive in a chronic CO_2 retainer.
- Use a controlled oxygen delivery system (Venturi mask) to maintain a Pao_2 >60 mm Hg or a pulse oximetry reading of

90% to 92% to minimize further risk of hypercapnia and respiratory acidosis in stable hypoxemic patients.
- Adjust oxygen delivery based on continuous pulse oximetry and serial ABGs.
- Start antibiotic therapy in patients with increased sputum volume and purulence, and patients being admitted with severe COPD exacerbations.
- Use NIPPV in patients with moderate-to-severe exacerbations to decrease the work of breathing when endotracheal intubation is not immediately indicated.

DISPOSITION

Many patients who present with an acute exacerbation of COPD require admission to the hospital. However, if the patient responds to therapy and the vital signs and pulmonary function tests approach baseline, discharge may be considered if good follow-up is assured. The bronchodilator regimen should be maximized: mono, dual, or triple therapy may be selected from long-acting β_2-agonists, long-acting anticholinergics, and inhaled corticosteroids (25). A short-acting β-agonist should be prescribed as a rescue inhaler. Systemic steroids should be continued for a short course, as they reduce the relative risk of treatment failure by about 30% as compared to placebo (19). Antibiotics should be prescribed for exacerbations associated with increased sputum volume or purulence. It should be recognized that approximately 15% of patients with COPD who are discharged from the ED require readmission.

Accepted criteria for hospitalization of patients with COPD include poor response to outpatient therapy, severe limitation of function, inability to eat or sleep because of dyspnea, presence of significant comorbid conditions, worsening respiratory failure, new or progressive *cor pulmonale,* and the need for invasive procedures, especially those requiring analgesics or sedatives. Guidelines for admission to the intensive care unit are not as well defined. Treatment in an intensive care unit is indicated when the close

observation, monitoring, and therapeutic interventions (including assisted ventilation) required by these patients cannot be provided elsewhere.

If transfer to another institution is required, it must be done carefully, because transfer is often associated with an interruption in treatment and increased patient fatigue. The transport team must be capable of managing the airway if decompensation occurs.

Common Pitfalls

- The COPD patient should not be expected to have disease that reverses as rapidly as the asthmatic patient. Look for a slower course of improvement, and have a lower threshold for admission.
- If patients have not slept well in the last 2 days, they are tired and the risk of respiratory failure is high. Such patients must be admitted to the hospital.
- Precipitating or complicating conditions (e.g., CHF, PE) may be overlooked when treating only the exacerbation of COPD.
- Oxygen should never be withheld because of concern about respiratory depression. If inadequate ventilation occurs, ventilatory support should be provided.
- It is easy to underestimate the severity of illness in patients with chronic dysfunction. Utilize radiography, pulse oximetry, and ABG analyses. Respect the patient's estimation of the severity of illness.
- If hypotension occurs during mechanical ventilation, the most common cause is "stacked" breaths caused by incomplete exhalation, with attendant rise in intrathoracic pressures and impaired venous return; the patient must be disconnected from the ventilator and allowed to "exhale."

ACKNOWLEDGMENTS

Thanks to previous edition author Marc A. Bellazini.

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CHAPTER 78

Spontaneous Pneumothorax and Pneumomediastinum

Susan M. Dunmire

Spontaneous pneumothorax and pneumomediastinum are sometimes challenging, yet critical to diagnose and treat for patients presenting in the emergency department (ED). These entities should be considered in any individual who presents with the acute onset of shortness of breath, chest pain, or subcutaneous emphysema.

A *pneumothorax* is defined by the presence of gas within the pleural space. When it occurs in the absence of penetrating or blunt injury to the chest wall, it is termed a *spontaneous pneumothorax.* A *primary spontaneous pneumothorax* occurs in individuals with no clinical or radiographic evidence of lung disease, whereas a *secondary spontaneous pneumothorax* occurs in individuals with underlying lung pathology. With large accumulations of air in the pleural space, a *tension pneumothorax,* characterized by hypotension due to impaired venous return, may develop (Fig. 78.1).

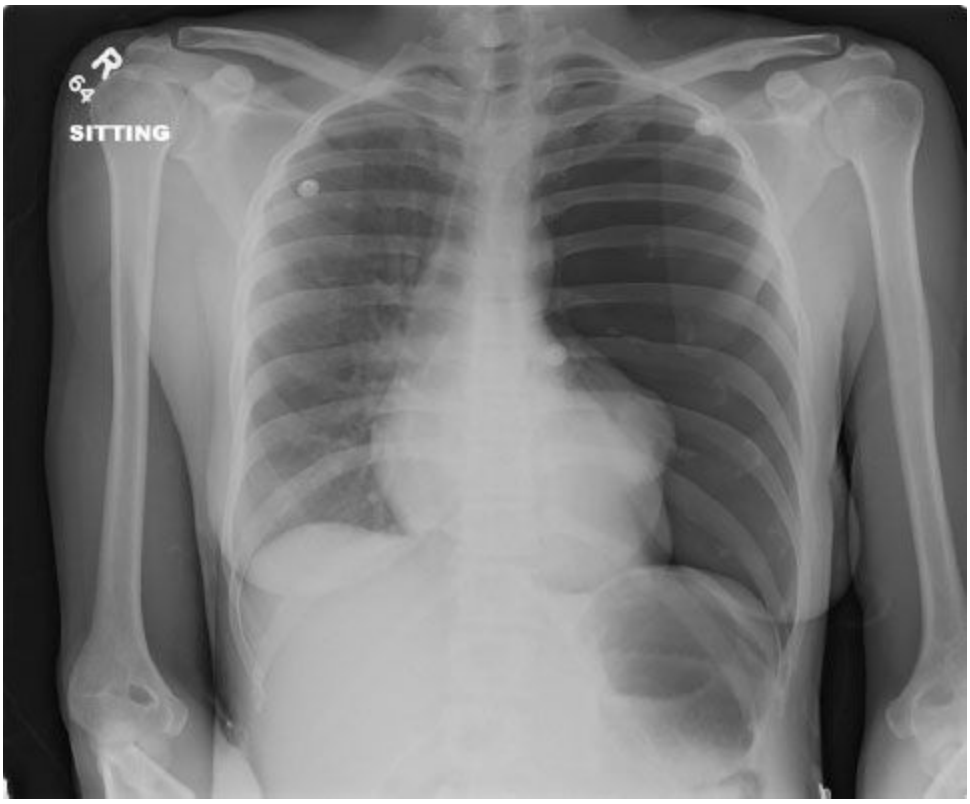

FIGURE 78.1 Left tension pneumothorax with shift of mediastinum to the right.

A primary spontaneous pneumothorax is often the result of rupture of small subpleural cysts or blebs. More than 10% of patients will report a positive family history of spontaneous pneumothorax. A mutation in the gene encoding for folliculin (FLCN) has been identified in individuals with familial spontaneous pneumothorax (1). Spontaneous pneumothorax recurs in up to 50% of patients within 2 years.

One of the most common causes of secondary pneumothorax is chronic obstructive pulmonary disease with rupture of bullae through the visceral pleura. The presentation can be misleading in that patients may report only a worsening of chronic dyspnea. The unsuspected pneumothorax is often found on chest radiography during the evaluation of a suspected exacerbation.

Pneumocystis carinii pneumonia has become an increasingly common cause of secondary pneumothorax. A subgroup of patients with *Pneumocystis* pneumonia has an accelerated inflammatory

response, with spontaneous rupture of necrotic lung tissue, resulting in pneumothorax (2). Other less common causes of secondary pneumothorax include malignancy, asthma (sometimes presenting as sudden severe respiratory compromise), cystic fibrosis, pulmonary infarction, histiocytosis X, and Hamman–Rich syndrome (acute interstitial pulmonary fibrosis). Patients with cystic fibrosis who experience a spontaneous pneumothorax have a significantly higher morbidity and mortality (3). Patients with significant underlying lung pathology may have respiratory decompensation with a relatively small pneumothorax, and therefore require aggressive therapy and close monitoring.

Another less common entity is *catamenial pneumothorax*. This is a spontaneous pneumothorax occurring in young females at the time of menstruation. Although its etiology is multifactorial, in some patients it is due to small implants of endometrial tissue in the pleural lining (4,5).

Spontaneous *pneumomediastinum* occurs when there is a sudden increase in intra-alveolar pressure resulting in alveolar rupture and dissection of air into the mediastinum. In a recent retrospective study, the use of illegal drugs (inhaling cocaine, smoking crack cocaine, and smoking marijuana) was the most common precipitating factor for a spontaneous pneumomediastinum (6). Other causes include vomiting, retching, Valsalva maneuver, and a history of recent endoscopy. Although a spontaneous pneumomediastinum is usually a benign entity, more serious causes such as esophageal rupture must be considered.

CLINICAL PRESENTATION

Primary spontaneous pneumothorax commonly occurs in young adults (male-to-female ratio 5:1) between the ages of 20 and 40 (7). Affected individuals tend to be tall and thin and frequently have a history of cigarette smoking (8). There is also a strong association with Marfan syndrome (9).

Patients with spontaneous pneumothorax typically present with the sudden onset of constant ipsilateral chest or shoulder pain that

may or may not increase with inspiration. The majority of patients complain of dyspnea, although the severity depends on the size of the pneumothorax. Most patients have the onset of symptoms at rest or during sleep. Rarely, spontaneous pneumothorax can present as a tension pneumothorax with severe cardiopulmonary compromise.

Symptoms in adults with spontaneous pneumomediastinum include retrosternal chest pain and, less frequently, subcutaneous emphysema due to tracking of air into the chest wall, neck, face, abdominal wall, and scrotum. If enough air accumulates in the mediastinum, the pleura can rupture, resulting in an associated pneumothorax in 6% to 10% of patients (10,11). Spontaneous pneumomediastinum in infants is a much more serious entity and can cause cardiopulmonary compromise by compression of the hilum (12).

DIFFERENTIAL DIAGNOSIS

Pulmonary embolism, exacerbation of chronic obstructive pulmonary disease or asthma, pneumonia, thoracic aortic dissection, and myocardial ischemia should all be in the differential diagnosis of a patient with shortness of breath and chest pain. Often the diagnosis of spontaneous pneumothorax is not considered until the chest radiograph is obtained.

Spontaneous pneumomediastinum usually presents as substernal chest pain. The differential diagnosis includes myocardial ischemia, gastroesophageal reflux, pulmonary embolism, and pneumonia.

Once the diagnosis of pneumothorax has been made, the physician should reevaluate the history and physical examination to ensure that there is no sign of blunt or penetrating trauma. An elderly person may have forgotten a recent fall that resulted in rib fractures and an underlying pneumothorax. A puncture site in the neck or supraclavicular area can easily be missed in an unsuspected drug abuser who has penetrated the pleural space.

ED EVALUATION

Physical findings are frequently not helpful in making the diagnosis of a small to moderate sized spontaneous pneumothorax. Patients often exhibit mild resting tachycardia and tachypnea. Depending on the extent of the pneumothorax, breath sounds may be diminished unilaterally. The presence of hypotension, tachycardia (>140 beats/min), or tracheal deviation should immediately alert the emergency physician to the possibility of a tension pneumothorax requiring emergent decompression.The diagnosis of pneumothorax is usually made by chest radiography, which reveals a peripheral lucent area containing no lung markings. It is unnecessary to perform inspiratory and expiratory films as they are equally sensitive for the diagnosis of a pneumothorax (13).

A chest CT is helpful in the detection of a small pneumothorax and pleural blebs. This can guide therapy, as video-assisted thoracoscopic surgery (VATS) may be considered in patients with PSP with visible blebs on CT. CT also allows for assessment of pleural blebs on the contralateral lung.

Bedside ultrasound as a diagnostic tool for pneumothorax has a higher sensitivity and similar specificity to chest radiography (14). It can be useful in the setting of patient who is too unstable to have an upright chest radiograph. Positive findings for pneumothorax include an absence of the lung sliding sign and the comet tail.

Patients with a significant (>25%) pneumothorax have an increase in the alveolar–arterial oxygen gradient, although an arterial blood gas is rarely necessary. The electrocardiogram is not helpful for diagnosis. Nonspecific changes, including T-wave inversion in the precordial leads, decreased amplitude of the R wave, and left axis deviation, are often noted.

The diagnosis of a spontaneous pneumomediastinum is often overlooked and requires a thorough examination and a high index of suspicion. Auscultation of the heart may reveal a “crunching” sound during systole (Hamman sign). Rarely, subcutaneous air may be present. A very thin lucent stripe can be seen outlining the heart and the mediastinum (Fig. 78.2). A lateral neck radiograph may reveal subcutaneous air. Up to 10% of clinically suspected pneumomediastinum will negative chest x-rays. CT scan is 100%

sensitive and specific in detecting pneumomediastinum (Fig. 78.3) (15). The electrocardiogram is useful only in helping to rule out ischemia in the patient presenting with substernal chest pain. Additional diagnostic testing, including esophagography, bronchoscopy, and esophagogastroduodenoscopy in nontraumatic pneumomediastinum is rarely indicated unless there is a high clinical suspicion of esophageal rupture (a history of recent instrumentation or forceful vomiting) (16).

FIGURE 78.2 Chest radiograph with pneumomediastinum.

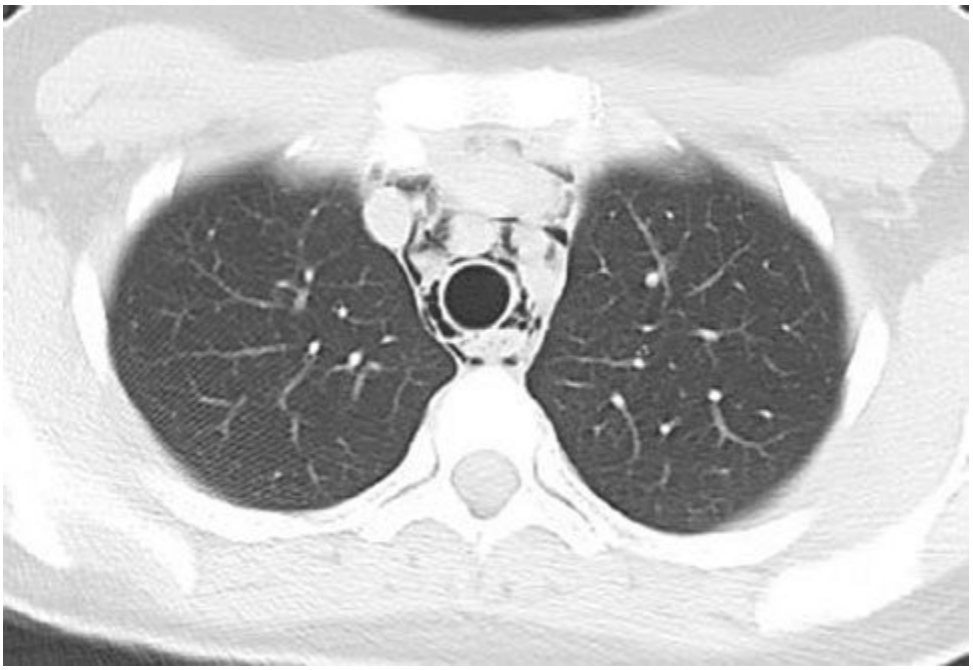

FIGURE 78.3 CT scan demonstrating pneumomediastinum.

KEY TESTING

- CXR
- CT chest—to detect small pneumothoraces/blebs and for diagnosis of pneumomediastinum
- Bedside chest ultrasound—for patients too unstable for upright CXR and more sensitive than CXR for small pneumothoraces

ED MANAGEMENT

Most patients with primary spontaneous pneumothorax do not have significant cardiopulmonary compromise. Any hemodynamic instability should suggest the presence of tension pneumothorax, which requires immediate needle decompression followed by tube thoracostomy.

Conservative treatment (observation) of a pneumothorax involving $<15\%$ of the total hemithorax volume is recommended by most experts. It is estimated that pleural air is spontaneously reabsorbed at a rate of 1% to 1.5% of the volume of the hemithorax

per day. Therefore, a small pneumothorax (<15%) would be expected to be reabsorbed within 10 to 15 days.

Evacuation of a larger pneumothorax by simple aspiration, pigtail catheter placement or tube thoracostomy is recommended. Surgical management is indicated in patients with recurrent spontaneous pneumothorax or a persistent air leak 5 to 7 days after placement of pigtail or chest tube.

A pneumothorax that occurs in the setting of chest wall trauma should be treated with a tube thoracostomy to drain a possible coexisting hemothorax. These patients require admission to the hospital and close monitoring.

Management of pneumomediastinum is conservative studies have shown that there is no need for antibiotics or further diagnostic testing unless there is a history of recent instrumentation or vomiting.

CRITICAL INTERVENTIONS

- Perform immediate needle decompression on patients with suspected tension pneumothorax.
- Insert a chest tube or pigtail catheter for patients with a moderate to large pneumothorax (>15%).
- Perform CT chest on individuals with suspected pneumomediastinum and negative chest radiograph.
- Perform an esophagoscopy on patients with pneumomediastinum and suspected esophageal rupture (e.g., history of recent instrumentation or forceful vomiting).
- Look for underlying trauma or needle penetration as a cause of the pneumothorax or pneumomediastinum.

DISPOSITION

Appropriate disposition of patients with spontaneous pneumothorax depends on the size of the pneumothorax, the therapeutic approach chosen, the reliability of the patient, and the availability of outpatient follow-up.

Patients with a small primary spontaneous pneumothorax (<15%) for which the physician has opted for conservative management (i.e., observation and spontaneous reabsorption) should have a follow-up radiograph within 6 hours to make sure the pneumothorax has not enlarged. If it has not, a follow-up radiograph should be performed in 7 to 10 days. Patients should be instructed to return for any increase in shortness of breath or chest pain or the development of fever.

Patients who have undergone placement of a pigtail catheter or a tube thoracostomy must be admitted to the hospital. The catheter or thoracostomy tube is connected to continuous suction. These patients do not require monitoring and do not require admission to an intensive care unit unless there is significant underlying pulmonary or cardiac disease.

Patients with spontaneous pneumomediastinum are usually admitted for 24 hours of monitoring, although patients with reliable follow-up could potentially be discharged. Studies indicate that, in the absence of risk factors for esophageal perforation, this is a benign entity with an uneventful course.

Common Pitfalls

- Failure to perform esophagoscopy in patients with spontaneous pneumomediastinum and suspected esophageal rupture.
- Management of spontaneous pneumothorax by observation alone can save hospitalization and healthcare costs only if employed in the appropriate circumstances and only if the patient is compliant and receives appropriate discharge instructions.

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CHAPTER 79

Pulmonary Embolism

Prathap Sooriyakumaran and Jeffrey A. Tabas

Pulmonary embolism (PE) is a relatively common, life-threatening condition that presents a diagnostic dilemma for the emergency practitioner. The incidence in the United States is estimated at 650,000 to 900,000 patients per year, resulting in as many as 200,000 deaths per year (1). This makes PE the third leading cause of cardiovascular death. Correct diagnosis and treatment significantly decreases morbidity and mortality (2). Accurate diagnosis is essential, as a missed or delayed diagnosis is associated with increased rates of adverse outcomes (3), and over diagnosis subjects a patient to the risks of unnecessary anticoagulation as well as to the psychological and financial implications of carrying such a diagnostic label.

CLINICAL PRESENTATION

Pulmonary emboli may result from a myriad of causes. Most commonly, emboli arise from thrombi in the legs, but they may also originate from anywhere in the venous system proximal to the pulmonary arteries, such as pelvic veins, nonportal abdominal veins, upper-extremity veins, or right-sided heart valves. Other sources include fat emboli, usually in association with long-bone fractures, amniotic fluid emboli (in the setting of labor and delivery), air emboli, and septic emboli.

The signs and symptoms of pulmonary emboli result from the effects of obstructed pulmonary vasculature. This may result in local tissue ischemia or infarct, increased ventilation–perfusion mismatch that can cause increased alveolar dead space or increased alveolar–

arterial oxygen gradient, and increased pulmonary vascular resistance that can cause right heart strain or failure. The spectrum of presentation varies from asymptomatic patients to those with mild subjective complaints to hemodynamically unstable patients with severe hypotension, respiratory failure, or pulseless electrical activity. The terms “submassive” and “massive” PE both describe symptomatic PE, with a systolic blood pressure less than 90 typically used to distinguish “massive” hemodynamically unstable PE, from “submassive” hemodynamically stable PE that nonetheless has some degree of right ventricular dysfunction and increased pulmonary hypertension. Differences in size, quantity, and location of emboli as well as underlying patient characteristics (such as cardiopulmonary reserve) contribute to the wide spectrum of presentation.

The most common signs and symptoms associated with the presence of PE are listed in Table 79.1 (4). A prospective cohort study of 7,940 patients with diagnosed PE found that patient history of PE or deep vein thrombosis (DVT), unilateral leg swelling, surgery within the previous 4 weeks, current estrogen use and hypoxemia (saturation $<95\%$) were the strongest predictors of PE, with odd ratios (OR) between 2 and 3 (5). Common symptoms investigated include dyspnea (OR 1.26), pleuritic chest pain (OR 1.53), and symptoms of DVT such as unilateral leg swelling (OR 2.60). Although low-grade fever is not infrequent, temperatures $>38.5^{\circ}C$ are less common and suggest other causes (temperature $>38.5^{\circ}C$ had an OR of 1.13, but this was not statistically significant). Unfortunately, many of these signs and symptoms are manifestations of other conditions, and there is no combination of clinical findings that has been shown to be diagnostic for PE. In addition, the “classic” triad of hemoptysis, pleuritic chest pain, and tachypnea is uncommon.

TABLE 79.1
Relative Frequency of Presenting Symptoms and Signs in Patients with PE

Symptom	Sign
Dyspnea, 73%	RR >20/min, 70%
Pleuritic pain, 66%	Rales, 51%
Cough, 37%	Tachycardia, 30%
Leg swelling, 28%	Loud P2, 23%
Leg pain, 26%	Temp. >38.5°C, 7%
Hemoptysis, 13%	Wheezes, 5%

PE, pulmonary embolism; RR, respiratory rate; Temp., temperature.

Classic risk factors (Table 79.2) for thrombosis include Virchow's triad of hypercoagulability, venous stasis, and endothelial injury. Commonly acquired hypercoagulable states include cancer, pregnancy, and estrogen therapy. There is increasing understanding and discovery of heritable thrombophilias, but these risk factors are often unknown at the time of presentation. Venous stasis may result from prolonged immobilization, recent surgery, extended travel, or medical conditions such as paraplegia or previous stroke. Damage to the vascular endothelium may result from fractures, surgery, catheter placement, or other forms of trauma. Demographic factors, such as advanced age, should also be taken into consideration. However, up to 30% of patients with a diagnosed PE have no known risk factors. In summary, although the presence of risk factors increases suspicion for PE, lack of known risk factors does not exclude the diagnosis.

TABLE 79.2
Risk Factors for PE

Prior thrombus or thromboembolism
Family history of thrombosis
Cancer
Prolonged immobilization—paralysis, lower-extremity cast, travel
Pelvic or lower abdominal surgery, <6 mos
Cerebral vascular accident
Congestive heart failure
Lower-extremity or pelvic trauma/fractures/surgery
Obesity
Estrogen therapy—oral contraceptives, hormone replacements
Pregnancy or postpartum
Inflammatory bowel disease
Age >40 yrs
Smoking
Thrombophilias (e.g., Factor V Leiden, Protein C or S deficiency, etc.)

PE, pulmonary embolism.

DIFFERENTIAL DIAGNOSIS

Given the wide spectrum of signs and symptoms associated with PE, the differential diagnosis in most presentations is extensive. Other causes of dyspnea or chest pain include pulmonary and cardiac causes such as chronic obstructive pulmonary disease (COPD) or asthma, congestive heart failure (CHF), pulmonary infections, pericarditis, acute coronary syndrome, aortic dissection, pneumothorax, trauma, or musculoskeletal pain. Abdominal sources such as biliary colic or pancreatitis may mimic a PE. The evaluation can be complicated by the fact that conditions such as CHF can both mimic signs and symptoms of PE as well as be a risk factor for PE. Musculoskeletal pain and anxiety are always diagnoses of exclusion and should be made only after more life-threatening causes have been confidently eliminated.

ED EVALUATION

Initial management of PE consists of rapid assessment and stabilization for immediate life-threatening conditions. When appropriate, intravenous access should be established, and cardiac and pulse oximetry monitors should be placed. Laboratory testing,

electrocardiography, and chest radiography should be expedited. The probability of disease (see subsequent text) should be determined based on the patient's signs, symptoms, identifiable risk factors, and the presence of an acceptable alternate diagnosis.

A complete blood count and serum chemistry panel are usually indicated in the general assessment of any patient with chest pain or shortness of breath. A creatinine level is helpful if contrast administration is planned. All patients suspected of having a PE should undergo an electrocardiogram (ECG). The ECG is a nonspecific test for PE, and the primary purpose is to detect other disease processes such as pericarditis or acute coronary syndromes. The most common ECG findings in patients with PE are nonspecific ST and T-wave abnormalities. Other common findings include tachycardia and T-wave inversion in the anterior precordial leads (V1 to V4). The classic ECG finding of S1Q3T3, consisting of an S wave in lead 1, and a Q wave with a flipped T wave in lead 3, is neither sensitive nor specific for PE. In a secondary analysis of a prospective, observational cohort of 6,049 ED patients who were tested for PE and had an ECG, both the findings of S1Q3T3 and T-wave inversions in V1 to V4 had positive likelihood ratios (LR+) of 3.7 and tachycardia had a LR+ of 1.8 (6). These findings were infrequent overall, but were observed more frequently in patients with the final diagnosis of PE compared to patients who did not have PE.

A chest radiograph should be obtained for patients with suspected PE. Given the lack of specific findings for PE, the primary purpose is again to detect other disease processes, such as a pneumothorax, pulmonary edema, malignancy, or pneumonia. In one large study of patients with proven PE, the most common chest radiographic interpretations were cardiac enlargement (27%), normal (24%), pleural effusion (23%), elevated hemidiaphragm (20%), pulmonary artery enlargement (19%), atelectasis (18%), and parenchymal pulmonary infiltrates (17%). Cardiomegaly is a common associated finding with PE, given that CHF is a risk factor. Classic radiographic findings, which occur infrequently, include Westermark sign (a prominent central pulmonary artery with decreased pulmonary

vasculature distally) and Hampton's hump (a wedge-shaped, pleural-based opacity representing pulmonary infarct) (7).

Arterial blood gases are rarely helpful in the evaluation of PE. One analysis of more than 100 patients with PE who lacked prior cardiopulmonary disease revealed that 38% had a normal alveolar–arterial (A–a) gradient. Patients with prior cardiopulmonary disease who proved not to have PE, had an elevated A–a gradient 24% of the time (8). One potentially useful scenario may occur when a patient is found to have a large, unexplained A–a gradient. However, these authors rarely obtain arterial blood gases for suspected PE alone.

Based upon the history, physical examination, and preliminary laboratory evaluation, the clinician should categorize a patient into very low (<2%), low (2% to 15%), moderate (15% to 40%), or high probability (>40%) suspicion for PE. Several clinical decision rules have been developed in an attempt to improve implicit clinician judgment, however, they appear to be no better than gestalt assessment by experienced providers in predicting probability of PE (9,10). These rules appear to be most effective at improving risk stratification for the clinically inexperienced practitioner and to provide some uniformity of approach within a department. The Wells Criteria (Table 79.3) is the most extensively tested decision rule. A modified approach, in which patients with a score less than or equal to 4 are considered safe for D-dimer testing and those greater than 4 are not, has been shown to be safe and effective (11).

TABLE 79.3
Criteria of Wells et al. for Assessment of Pretest Probability for PE

Criterion	Points
Suspected DVT	3.0
An alternative diagnosis less likely than PE	3.0
Heart rate, >100 beats/min	1.5
Immobilization or surgery in previous 4 wks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy (on treatment, treated in the past 6 mos or palliative)	1.0
Score range (points)	Interpretation of risk
0–2	Low
3–6	Moderate
>6	High

DVT, deep venous thrombosis; PE, pulmonary embolism.

Evaluation for PE should be based on pretest probability. See Figure 79.1 for an algorithm summarizing our recommendations for how to proceed with the evaluation for PE. The results of diagnostic testing should be used to determine sequentially what further evaluation is needed to exclude or confirm the presence of PE. A posttest probability of 1% to 2% is a generally accepted risk level. This would presumably lead to a subsequent complication rate of $<0.7\%$. Some patients and physicians may be willing to accept more or less risk.

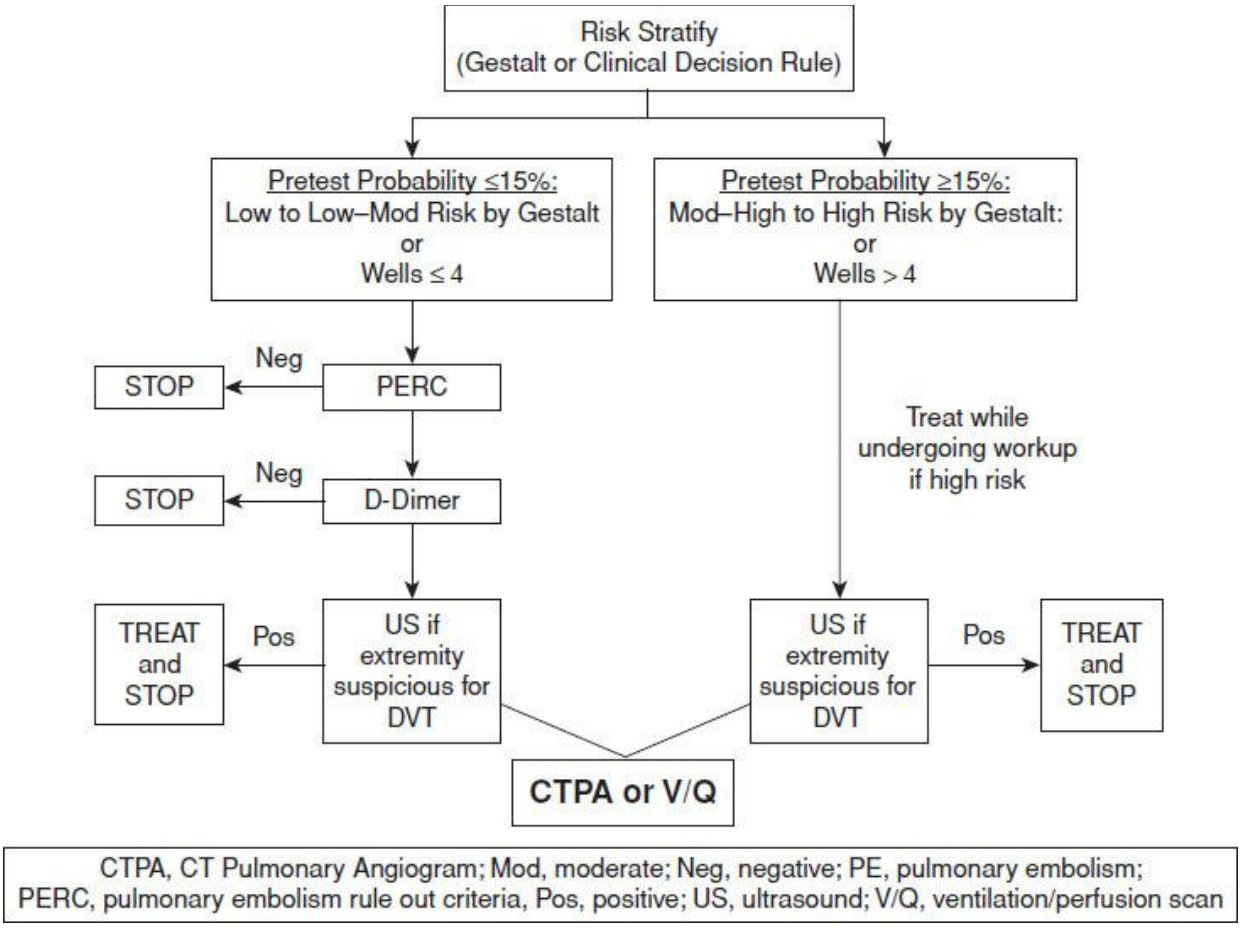

FIGURE 79.1 Workup of PE in the ED.

For patients who are low to low-moderate probability (less than 15%) stratified either by clinical decision rule or gestalt, Kline et al. (12) have demonstrated that patients with a zero score on the Pulmonary Embolism Rule Out Criteria (PERC) do not need further evaluation for PE. PERC consists of 8 criteria (Table 79.4). When none of these are present in patients with low to low-moderate pretest probability, the risk of PE or death is similar to that of patients with negative V/Q or CT pulmonary angiography. In a meta-analysis of 11 studies investigating the diagnostic performance of PERC for PE, the pooled sensitivity and specificity was 0.97 (95% confidence interval 0.96 to 0.98) and 0.23 (95% confidence interval 0.22 to 0.24), respectively (13). For patients with less than 15% pretest probability who are PERC positive, the next step in evaluation is a D-dimer test. D-dimers are degradation products of

cross-linked fibrin and are therefore elevated when there is activation of the coagulation pathway, as occurs in the setting of PE. Because of their nonspecific nature, D-dimers are also elevated in other conditions such as cancer, pregnancy, recent trauma, and even CHF. When used appropriately, a sensitive D-dimer assay is an effective screening test for PE, eliminating the need for further radiologic imaging. Most current assays show sensitivities as high as 90% to 95%. Bayesian analysis reveals that in a patient with 15% pretest probability (the upper limit of "low probability"), a negative likelihood ratio of 0.12 or less is required to provide a posttest probability of <2%. Most of the rapid, sensitive D-dimer tests demonstrate negative likelihood ratios within this range. Therefore, a negative result using currently available rapid, sensitive D-dimer assays is adequate to exclude PE in a patient with low to low-moderate pretest probability (14,15). Note that a positive D-dimer result has little impact on posttest probability.

TABLE 79.4
Pulmonary Embolism Rule-Out Criteria (PERC)

Criterion (All must be met to apply PERC)
Age ≤50
Heart rate <100
Oxygen saturation on room air >94%
No prior history of DVT/PE
No recent trauma or surgery
No hemoptysis
No exogenous estrogen
No clinical signs suggesting DVT

DVT, deep venous thrombosis; PE, pulmonary embolism.

For low to low-moderate pretest probability patients (<15%) with positive PERC and D-dimer testing, and for moderate to high risk patients, imaging is required. When discussing the diagnostic accuracy of radiographic imaging of patients with suspected PE, it is important to remember that the goal of imaging is to detect the presence of any venous thromboembolism (VTE) to guide the

initiation of treatment. Although patients with small or subsegmental pulmonary emboli may present with milder signs and symptoms, there is insufficient evidence to conclude that patients with "clinically insignificant" presentations are at a lower risk of recurrence than those with more clinically evident presentations (2).

Lower-extremity imaging for DVT in the assessment of suspected PE is most useful when there are clinical signs and symptoms in that extremity. Fifteen to twenty-five percent of patients with PE have clinically evident DVT (16). Bilateral lower-extremity imaging in a patient without clinical findings of DVT is probably of limited value except for unusual circumstances.

Ventilation/perfusion (V/Q) scanning involves low radiation exposure and displays high sensitivity. However, frequently indeterminate results and lack of information about other diagnoses have limited the use of the test in the evaluation of PE. Administration of an intravenous radioactive isotope is used to measure perfusion of the pulmonary vasculature, and administration of an inhaled radioactive isotope is used to measure pulmonary ventilation. A normal or near-normal result is 98% sensitive for the exclusion of PE. As with most tests, the V/Q scan should be interpreted within the context of pretest probability (Table 79.5). A low pretest probability with a low probability V/Q scan makes PE unlikely, and a high probability scan with a high pretest probability is considered diagnostic for PE. However, discordant results or intermediate probability scans, which account for a significant portion of results, mandate further studies. An indeterminate result is most common in patients with COPD, pre-existing cardiopulmonary disease, or markedly abnormal chest radiographs. V/Q scanning for assessment of suspected PE is appropriate when it is the only imaging modality available, in patients with a normal chest radiograph (and therefore likely to obtain a diagnostic result), or in patients who have contraindications to other imaging studies, such as contrast allergy or renal insufficiency. V/Q scanning is most likely to be diagnostic in patients with normal chest radiographs.

TABLE 79.5
Probability of Pulmonary Embolism Based on Clinical Suspicion and Results of Ventilation/Perfusion (V/Q) Scan

	V/Q Results			
Clinical Suspicion	High (%)	Intermediate (%)	Low (%)	Normal or Near-Normal
High	96	66	40	N/A
Intermediate	88	28	16	6%
Low	56	16	4	2%
All patients	87	30	14	4%

Adapted from The PIOPED Investigators. Value of the ventilation perfusion scan in acute pulmonary embolism: Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *JAMA*. 1990;263:2753–2759.
NA, not applicable.

Computed tomography pulmonary angiography (CTPA) has high sensitivity and specificity for PE and, in about one-third of cases, demonstrates an alternative diagnosis, such as pneumonia, cancer, or aortic dissection. It is not particularly invasive and requires only a single breath-hold. Reported sensitivities for CTPA vary depending on scanner technology. A prospective multicenter study designed to assess the efficacy of multidetector CTPA (4, 8, and 16 row), reported a sensitivity of 83% and specificity of 96%. The addition of CT venography to CTPA increased sensitivity and specificity to 90% and 95%, respectively (17).

Pulmonary angiography, the traditional gold standard for the diagnosis of PE, is rarely performed. It has a false-negative rate of 1% to 2% and an indeterminate study rate of 3%. Significant complications include death in 0.5%, major nonfatal complications in 1%, and minor complications in up to 5%.

Transthoracic or transesophageal echocardiography may be helpful in the assessment of PE, especially in the unstable patient. Echocardiographic findings in patients with PE include right ventricular dilatation and hypokinesis, septal flattening and paradoxical motion, failure of the inferior vena cava to collapse during inspiration and, rarely, direct visualization of the thrombus.

Evaluation of the pregnant patient poses a particular challenge for the emergency department (ED) practitioner. Pregnancy increases risk of venous thrombosis up to fivefold. For women whose pregnancies result in a live birth, PE is the leading cause of death. Although exposure of the fetus to radiation is clearly undesirable, the safety of the mother takes priority. Evaluation of the stable pregnant patient with symptoms of PE may include a rapid sensitive D-dimer test in a low-suspicion patient (although specificity in pregnancy will be significantly decreased), ultrasonographic evaluation of the lower extremities (which if positive, will allow initiation of anticoagulation and deferral of further evaluation), and V/Q scanning or CTPA. Current literature suggests that radiation exposure from CTPA to the fetus, especially in the first or second trimester, is lower than radiation exposure from V/Q scanning (18).

ED MANAGEMENT

As with any critically ill patient, the emergency physician should start with the "ABCs." Intravenous access, cardiopulmonary monitoring, and oxygen therapy should be initiated. The patient's airway should be maintained and, if severely hypoxic, the patient should be emergently intubated. Hypotensive patients should be fluid resuscitated while more definitive treatments are being considered.

The goal of treatment in PE is primarily aimed at life-saving restoration of flow through occluded pulmonary arteries, or the prevention of potentially fatal early recurrences as well as long-standing damage from the initial insult (pulmonary hypertension and symptomatic right ventricular dysfunction). Anticoagulation remains the primary treatment for patients with PE. Anticoagulation should be initiated for high-risk patients while confirmatory studies are pursued. Typically patients are treated with 6 to 12 months of Coumadin, with initial treatment with heparin until a therapeutic INR is achieved. Intravenous unfractionated heparin or low-molecular-weight heparin (LMWH) has been shown to be equally effective in the treatment of pulmonary emboli. The advantages of LMWH are thought to include ease of use (subcutaneous instead of intravenous) and lack of need for laboratory monitoring, though the

disadvantages include cost. However, a trial comparing fixed-dose unfractionated heparin, delivered subcutaneously without laboratory monitoring (333 U/kg SC initial dose, then 250 U/kg SC every 12 hours), to LMWH (100 IU/kg every 12 hours SC) found them to be of equivalent safety and effectiveness in patients with VTE (20% with PE) (19).

The FDA has approved the use of enoxaparin and tinzaparin: the dosing for enoxaparin is 1 mg/kg subcutaneously every 12 hours and for tinzaparin 175 anti-Xa IU/kg subcutaneously once daily. Contraindications include renal insufficiency, obesity, or weight <40 kg. If intravenous unfractionated heparin is used, weight-based dosing has been shown to be superior to standard dosing, with more rapid time to therapeutic levels and decreased rates of recurrence and complications. Patients should receive an initial bolus of 80 U/kg and then an infusion of 18 U/kg/hr. The activated partial thromboplastin time is measured every 4 to 6 hours and should be maintained at 1.5 to 2.3 times the control, with adjustment based on an established nomogram.

New anticoagulants being developed may ultimately show improvement over unfractionated heparin and LMWH. These new agents include direct thrombin inhibitors, direct and indirect factor Xa inhibitors, activated protein C, and tissue factor pathway inhibitors. Some of their superior properties include once-daily dosing without monitoring, oral administration, and improved pharmacodynamic profiles. The FDA has recently approved rivaroxaban, a factor Xa inhibitor, for VTE prophylaxis and treatment. EINSTEIN-PE, a randomized, open label study with 4,832 PE patients, showed noninferiority of rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) compared to standard treatment with enoxaparin followed by an adjusted-dose vitamin K antagonist for 3, 6 or 12 months (20). The advantages of rivaroxaban compared to vitamin K antagonists such as warfarin, which patients who are started on unfractionated heparin or LMWH are transitioned to, include more stable pharmacokinetic and pharmacodynamic profiles which allows for it to be prescribed in a fixed dose without the requirement of frequent monitoring. A significant disadvantage is

a lack of an antidote. Prothrombin complex concentrate (PCC) has been shown to reverse the effects of rivaroxaban on coagulation tests such as prothrombin time although the benefit in clinically reversing bleeding effects has not been studied (21).

For patients with hemodynamic instability resulting from PE, thrombolytic therapy is considered the treatment of choice. Despite this, in a modern cohort of ED patients with massive PE, analysis of the Emergency Medicine Pulmonary Embolism in the Real World Registry (EMPEROR) showed only 12% of these patients received thrombolytic therapy (22). Thrombolytics rapidly improve hemodynamic status by acutely reducing clot burden. The FDA has approved recombinant tissue plasminogen activator (r-TPA), streptokinase, and urokinase for the treatment of massive PE. The dosage used for r-TPA, which has been shown in several small studies to be associated with slightly better outcomes, is a 10-mg intravenous bolus and 90 mg over the next 2 hours. If streptokinase is used, the dosage is 250,000 IU over 30 minutes and then 100,000 IU an hour for 24 hours. Urokinase dosage is 4,400 IU/kg over 10 minutes followed by 4,400 IU/kg an hour for 12 to 24 hours. Before initiation of thrombolytic therapy, unfractionated heparin should be administered in full therapeutic doses (i.e., bolus followed by infusion). The heparin infusion should be suspended during delivery of thrombolytic therapy. The activated partial thromboplastin time should be checked immediately after completion of thrombolytic therapy and repeated until it is <80 seconds, at which point the heparin infusion should be restarted (without a bolus).

Current evidence is still insufficient to strongly support (or oppose) administration of thrombolytics to patients with acute right ventricular dysfunction or pulmonary hypertension from PE (i.e., patients with “submassive” PE). The Moderate Pulmonary Embolism Treated with Thrombolysis (MOPETT) trial tested the efficacy of half dose or “safe dose” thrombolysis in submassive PE. There is face validity that reducing the dose for PE would result in reduced complications while maintaining efficacy. Because the pulmonary vasculature receives the entire cardiac output, a given dose of drug would be expected to have greater effect than in the brain, which

receives 15% of cardiac output, or coronary arteries, which receive 5%. This treatment resulted in statistically significant benefit for the composite outcome of recurrent PE and death ($p = 0.0489$) (23). The Pulmonary EmbolIsm THrOmbolysis (PEITHO) study (24) compared full dose thrombolytics versus heparin therapy in 1,006 randomized patients with submassive PE over a 10-year period. Preliminary data presented at the American College of Cardiology 2013 Summer Sessions, showed significant benefit (absolute risk reduction of 3% in death or hemodynamic collapse) which was balanced by significantly higher rates of major bleeding.

Pulmonary embolectomy (catheter-directed or surgical) is an uncommon procedure, but it may be used as treatment for hemodynamically unstable patients with contraindications to thrombolytics or when thrombolytics are not available.

CRITICAL INTERVENTIONS

- Risk-stratify patients into low, moderate, or high probability for PE based upon the history, physical examination, and preliminary laboratory evaluation.
- Anticoagulate patients with a high clinical suspicion for thromboembolism before definitive studies are performed. Significant delays in initiation of anticoagulation can negatively impact outcomes.
- Administer thrombolytic therapy for patients with hemodynamic instability caused by PE.

DISPOSITION

Patients diagnosed with PE are generally admitted to the hospital. An RCT of outpatient versus inpatient treatment in low-risk PE patients found no difference in safety (25). However, the exclusion criteria were so stringent, including patients with BP <100 or hypoxia, patients deemed unreliable (broadly defined), patients who were obese and patients who received IV pain medication, that very few patients meet these criteria. If admitted, patients who are hemodynamically stable may go to a nonmonitored setting. If

unstable, they should be observed in the intensive care unit or a telemetry bed. Patients diagnosed with DVT who show no evidence of PE are routinely treated as outpatients, initially with LMWH and warfarin (see Chapter 96, "Deep Venous Thrombosis and Thrombophlebitis"). These patients transition off heparin in the outpatient setting.

Common Pitfalls

- Failing to consider PE in a patient presenting with pleuritic chest pain, dyspnea, or tachypnea in whom there is no convincing alternative diagnosis
- Failing to recognize that lack of risk factors does not exclude PE
- Failing to recognize atypical presentations, such as syncope, in the elderly
- Mistaking nonspecific radiographic findings of PE for an alternative diagnosis such as pneumonia in a patient with atelectasis on chest radiography
- Failing to apply PERC or D-dimer testing to avoid radiographic imaging in appropriate patients
- Failing to recognize that PE can recur in a patient who is adequately anticoagulated

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CHAPTER 80

Hemoptysis

Sanjay Bhatt

Coughing up blood is a significant cause of concern to both the provider and patient. While a common symptom in adults, it is an uncommon presentation in children. The differential diagnosis can be diverse and includes pulmonary pathology as well as pseudohempotysis caused by ear, nose, and throat (ENT) or gastrointestinal pathology. Although typically indicative of primary pulmonary pathology, hemoptysis may result from numerous systemic illnesses. It is important to note that the severity of bleeding does not correlate with the gravity of the underlying disease.

Hemoptysis is attributed to multiple underlying pathophysiologic mechanisms. Bleeding sources include bronchial and pulmonary arteries. In general, bronchial arteries are under high-pressure systems whereas pulmonary are under low-pressure systems. Massive bleeding, which accounts for 1.5% of cases, usually arises from injury to the high-pressure bronchial arteries (1–3). The cause of bleeding depends on the underlying etiology. Exsanguination is rarely the cause of death in hemoptysis; rather, blood can obstruct distal alveoli thereby impairing gas exchange. In these cases, death can result from hypoxemia. There are several possible causes for bleeding; Table 80.1 lists the multitude causes of bleeding in a patient presentation to the emergency department (ED).

TABLE 80.1
Mechanisms of Bleeding in Hemoptysis

Malignancies: Invade vessels, or the tumor itself may become necrotic
Inflammatory and infectious problems: Vascular engorgement of the tracheo-bronchial mucosa
Bronchiectasis: Associated with abnormal vascular anastomoses between bronchial and pulmonary arteries
Lung abscesses: Bronchial ulceration and necrosis
Mycetomas of cavitary TB: Rupture and cause life-threatening hemorrhage
Left ventricular failure or mitral stenosis: Increased intravascular pressure with capillary and venous rupture
Pulmonary embolism: Infarction of lung parenchyma
Goodpasture syndrome: Breakdown of the alveolocapillary basement membrane
Aortic aneurysm: Erosion into adjacent vascular structures
Coagulopathy: Exacerbation of an underlying reason for bleeding
Cocaine: Intense vasoconstriction with cell injury

TB, tuberculosis.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Patients may present to the ED with a chief complaint of "coughing up blood." The extent of this bleeding can range from minor to copious. While the vast majority of patients have stable vital signs, those with pulmonary compromise may reflect some degree of tachycardia. Those with severe bleeding may show signs of hypoxemia, hemodynamic instability, and/or airway compromise. Patients with systemic diseases, such as Goodpasture syndrome, may present with hematuria and hemoptysis.

Pseudohemoptysis should be excluded before the pulmonary causes of hemoptysis are entertained. An appropriate history and physical examination can eliminate gastrointestinal and otolaryngologic sources. The vomitus of gastrointestinal bleeding tends to be darker in color and may contain food particles. In comparison, true hemoptysis is typically bright red and frothy. Mouth, throat, and nasopharyngeal sources of bleeding may be visualized with direct, indirect, or fiberoptic laryngoscopy.

The etiology of hemoptysis worldwide can vary by country (4). In the United States, the most common causes include infections, malignancy, bronchiectasis, bronchitis, and cardiovascular disorders

(5–7). Chronic obstructive pulmonary disease is an independent risk factor for hemoptysis (1). Worldwide, while tuberculosis (TB) is still the most common cause of hemoptysis, it is much less common in the United States (8). In areas such as New York City or Los Angeles that house a large TB population, this diagnosis must be considered.

While uncommon, patient with systemic lupus erythematous (SLE) may present with alveolar hemorrhage and resultant hemoptysis (9). Travelers or immigrants, especially those from Asia, the Middle East, and South America, may have parasitic infections (3). Catamenial hemoptysis, which is hemoptysis during menstruation, may occur in women with thoracic endometriosis (1,10). In those who are immunocompromised, bacterial pneumonia is a common diagnosis while in the HIV population, Kaposi's sarcoma must be considered (1).

Independent of coagulation parameters, patients on immunosuppressive medications, or those with a history of transbronchial biopsy or lung transplant, are at an increased risk for hemoptysis after bronchoscopy (11). It is important to note that the mortality rate among lung transplant patients who present with hemoptysis is high (12). Occult malignancy should always be considered, especially in those with a long-standing smoking history.

Three potential biologic weapons that may present with hemoptysis include plague, tularemia, and T2 mycotoxin (2). Table 80.2 lists the common causes of hemoptysis by category.

TABLE 80.2
Common Causes of Hemoptysis

- Inflammatory
  - Bronchitis
  - Bronchiectasis
  - Lung abscess
  - Pneumonia (viral, bacterial, and fungal)
  - Tuberculosis
  - Parasites (e.g., ascariasis and schistosomiasis)
- Neoplastic
  - Bronchial adenoma
  - Bronchogenic carcinoma
- Cardiovascular
  - Arteriovenous malformation
  - Arteriovenous fistula
  - Congestive heart failure
  - Aneurysm
  - Pulmonary thromboembolism
  - Primary pulmonary hypertension
  - Mitral stenosis
  - Vascular injury (e.g., foreign body)
- Congenital
  - Cystic fibrosis
- Immunologic
  - Collagen vascular disease
  - Vasculitis
  - Goodpasture syndrome
- Extrapulmonary Disease
  - Thrombocytopenia
  - Coagulopathies
  - Trauma
- Drugs
  - Anticoagulants
  - Cocaine
  - Thrombolytics

In pediatric patients, lower respiratory tract infections account for almost 40% of all presentations of hemoptysis. Other causes include cystic fibrosis (CF), foreign-body aspiration, bronchial adenomas, and trauma. All providers must be aware of accidental as well as deliberate trauma; bleeding caused by deliberate suffocation has

been described (1). CF may be associated with recurrent, severe bleeding in both children and young adults. Hemoptysis in children with CF occurs with increasing age and advancing disease and almost 60% of children will have at least one episode. Most of these episodes are not life-threatening (13). Although congenital heart disease and mitral stenosis after rheumatic fever are still reported causes of hemoptysis, corrective surgery for the former and decreasing incidence of the latter make them infrequent causes of bleeding (13). Other uncommon causes include bronchiolitis obliterans organizing pneumonia (7), pulmonary embolism, Wegener granuloma, primary pulmonary hemosiderosis, and arteriovenous malformations (AVMs) (5,13).

ED EVALUATION

Patients with massive hemoptysis require initial focus on the airway, breathing, and circulation (ABCs) of support; as noted above, especially given concern for asphyxiation and lesser so exsanguination. The ABCs take precedence to making a definitive diagnosis. While providers agree that massive hemoptysis describes the expectoration of a large amount of blood *or* a rapid rate of bleeding, the thresholds that define massive hemoptysis remain controversial. Thresholds range from 100 to 1000 mL (14) over 24 hours though none has been generally accepted. Some clinicians argue that abnormal gas exchange and hemodynamic instability, generally tachycardia or tachypnea, should be part of the definition.

Nevertheless, patients who present with what is termed “massive” hemoptysis have a mortality rate close to 50% (6). Similar to the adult definition, the pediatric definition of massive hemoptysis can vary; some sources define the rate of bleeding as 8 mL/kg/24 hrs (13). While massive versus submassive bleeding carries both diagnostic and prognostic implications, this differentiation is difficult to perform in the ED. Similar to adult presentation, mortality is primarily due to asphyxiation and lesser so exsanguination.

Most series list TB and bronchiectasis as the most common causes of massive hemoptysis; other diseases include lung abscesses, malignancy, Goodpasture syndrome, Behçet disease, AV malformations, trauma, coagulopathies, and aspergillomas (3).

As almost any amount of bleeding may prove detrimental to patients with limited cardiopulmonary reserve or significant underlying disease, baseline cardiopulmonary status, and overall physical condition must weigh into a physician's decision to pursue aggressive measures. History, physical examination, and laboratory studies can help evaluate the patient's ability to respond to the physiologic stress of hemoptysis and the therapy it necessitates.

Once a patient has been stabilized, efforts to determine the cause of hemoptysis should include a thorough history and physical examination. Laboratory studies should include: a complete blood count to determine the chronicity and magnitude of bleeding and the need for a platelet transfusion; a urinalysis and creatinine values in those whom pulmonary renal syndromes are being considered; arterial blood gas analysis and a pulse oximetry to determine oxygenation; coagulation studies to determine whether fresh-frozen plasma may be of benefit; and sputum evaluation in those whom TB is considered, radiograph studies should include a chest x-ray to evaluate for a multitude of diagnosis including neoplasm and focal infections. A chest computed tomography may better identify malignancies, infections, and pulmonary emboli. The combination of high-resolution CT scan and bronchoscopy is the standard by which a diagnosis is established (2,4,15). Definitive diagnosis may require sputum cytology, pulmonary function testing, angiography, or specialized sputum studies (2,15).

Aggressive management must occur at the same time as evaluation. Some diagnostic modalities, most notably bronchial artery embolization, are both diagnostic and therapeutic (4,16–18). Some centers are now using a new technique of bronchoscopic endobronchial sealing with cyanoacrylate (19).

Even after exhaustive study, 10% of cases will have no identifiable etiology (3). These patients are classified as having idiopathic or cryptogenic hemoptysis; in these cases, it is presumed

that subtle airway or parenchymal disease is the culprit. Close follow-up to exclude repeat presentation and malignancy is especially important (20).

KEY TESTING

- Pulse oximetry
- CXR
- CBC
- Coagulation studies

ED MANAGEMENT

The primary goals of therapy are threefold: airway control to prevent asphyxia and less likely exsanguination, termination of bleeding, and diagnosis and treatment of the underlying cause. As noted above, patients with massive hemoptysis require initial focus on the ABCs of support. Airway control and adequate oxygenation are the immediate priorities. Endotracheal intubation, which may be technically challenging especially in this setting, is the intervention of choice, especially in those with poor gas exchange, hemodynamic instability, rapid ongoing hemoptysis, and at physician discretion. Placing a large 8.0 lumen tube can facilitate suctioning and the passage of a fiberoptic laryngoscope. Bag-valve-mask ventilation may be difficult in the patient with massive bleeding as blood may further block the tracheobronchial tree. The provider should consider selective intubation and, if readily available may consider a double-lumen endotracheal tube. Unilateral intubation, often performed in conjunction with a localizing bronchoscopic examination, can ventilate the nonbleeding lung. A localizing bronchoscopic examination is essential because of the importance of ventilating the proper lung as well as ensuring that the right upper lobe bronchus is not blocked as a result of the procedure. Another option is selective intubation using a fiberoptic laryngoscope. If the suspected bleeding lung or pathologic lesion is on the left side, the right mainstem bronchus may be selectively intubated by advancing an endotracheal tube past the carina. Normal lung anatomy

frequently allows passage of the tube into the right mainstem bronchus. As noted above, given the potential problem that the right upper lobe bronchus may become blocked, it is imperative that direct visualization is performed during or soon after the intervention.

In addition, patients with massive hemoptysis should be placed in a dependent, lateral decubitus position. Thus, in a patient with massive bleeding from the left lung, the patient should be intubated into the right mainstem and placed in a left lateral decubitus position. This position may protect the uninvolved lung from filling with blood and, in so doing, maximize gas exchange.

Special care is given to IV fluids and blood and resuscitation measures. Isotonic fluids and blood products should be rapidly infused. In addition to intravenous isotonic fluids, packed red blood cells, platelets, and fresh-frozen plasma are imperative in the proper clinical situations. Coagulation and platelet abnormalities should be corrected with fresh-frozen plasma and platelet infusions, as indicated. Significant coughing may exacerbate the bleeding and can be reduced with small doses of intravenous morphine. Antibiotics should be administered for suspected infectious etiologies. Pulmonary, ENT, interventional radiology, and surgical consultants will assist in localizing the bleeding site. Bronchoscopy and angiography may be both diagnostic and therapeutic. Bleeding control may be achieved with selective bronchial artery embolization, topical vasoconstrictors, and catheter tamponade. Selective bronchial artery embolization is an effective nonsurgical treatment for massive hemoptysis but carries a risk of systemic and spinal artery embolization (3,16). Although high success rates are frequently cited, spontaneous recanalization may occur and result in a recurrence of bleeding. Flexible endoscopy may be done at the bedside and rigid endoscopy may be performed in the operating room. Bronchoscopically administered topical hemostatic tamponade with a cellulose mesh has been reported as effective (21). Finally, recombinant factor VII may be effective in select cases (22). Hemoptysis may be best controlled by addressing the underlying source. As an example, mitral valve surgery may be

considered in patients with severe stenosis. Bleeding associated with CF may respond to intravenous pitressin therapy and bronchial artery embolization (23).

Medical therapy is successful in most patients-–even those with massive hemoptysis. However, when massive bleeding is caused by AV malformations, aortic aneurysms, chest trauma, pulmonary rupture, bronchial adenomas, or fungal lesions that do not respond to medical therapy, surgical options should be considered (2,3).

CRITICAL INTERVENTIONS

- For massive hemoptysis, place the patient in a lateral decubitus position. This will protect the uninvolved lung from filling with blood and allow adequate gas exchange.
- Use large endotracheal tubes when intubating (8.0 in the average adult) to facilitate suctioning and a fiberoptic laryngoscope.
- Selectively intubate the left or the right mainstem bronchus in the proper setting.
- Adequately resuscitate patient with IV isotonic fluids and blood products as appropriate.

DISPOSITION

Most patients respond to medical treatment and require admission to an intensive care setting; a smaller number of patients will require emergent operative intervention. As in all situations of potentially exsanguination, the operating room must be readily available. When definitive care is not available at the presenting institution, a patient may need to be transferred. The transferring physician should optimize the hemodynamic and respiratory status before transfer. Personnel involved in transferring a patient must be competent in emergency airway management. Admission to the hospital is indicated for all patients who are at high risk for deterioration; that includes those with limited pulmonary reserve, respiratory compromise, mycetomas or cavitary TB, and immunocompromised patients with likely infectious etiologies.

Patients with minimal hemoptysis may be discharged after the initial ED evaluation and institution of therapy. Follow-up bronchoscopy is indicated, especially in men, smokers, patients over the age of 40, those with a localized abnormality on chest radiography or CT, and those in whom bleeding has lasted more than 7 days.

Common Pitfalls

- Hemoptysis must be recognized and differentiated from nasopharyngeal and gastrointestinal bleeding.
- The bleeding rate must be accurately estimated. Special concern is appropriate even with only a few ounces of hemoptysis,
- Cardiopulmonary reserve and clinical status must be evaluated. A small amount of hemoptysis may have potentially devastating consequences for a patient with significant underlying disease.
- Close monitoring is essential; clinical deterioration may respond to measures including repositioning the patient and endotracheal intubation.
- In situations requiring transfer to another facility for higher level of care, measures must be taken to assure airway and hemodynamic stability, including prophylactic intubation when indicated.
- Radiographic lesions may be subtle; the radiologist's final report must be followed-up closely in all patients with hemoptysis.

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CHAPTER 81

Sarcoidosis

Sanjay Bhatt

Sarcoidosis is a multisystem, chronic granulomatous disease with diverse manifestations and a variable clinical course. It is characterized by a heightened cellular immune response at the site of disease activity; the lungs are the primary target organ and are involved in 90% of cases (1,2). Other organs of lesser involvement include the skin, lymphatic system, and eyes. While no single etiology has been identified, a number of them have been postulated. These include exposure to infectious agents, including *Mycobacterium tuberculosis, Propionibacterium acnes,* and HHV 8, and noninfectious occupational and environmental agents, including beryllium, and autoantigens. Until 1995, only nine patients infected with human immunodeficiency virus (HIV) had coexistent sarcoidosis (3,4) with a resulting postulation that a low CD4 count is "protective" against the granuloma formations seen in sarcoidosis (5).

In the United States, the prevalence of sarcoidosis is 10 per 100,000 in Caucasians and 40 per 100,000 in African Americans (6). Among African-American patients, women outnumber men two to one in the prevalence of disease. Curiously, sarcoidosis is virtually unknown on the continent of Africa, giving credit to an environmental etiology. While the peak incidence of diagnosis and symptoms are between 20 and 40 years of age, the disease has been reported in children and the elderly. Sarcoidosis has also been identified in twins, husband–wife pairs, and in coworker firefighters (7,8).

With or without treatment, most cases of sarcoidosis resolve spontaneously. Indicators of a favorable prognosis include acute manifestations of inflammation including erythema nodosum, polyarthritis, fever, and bilateral lymphadenopathy. Poor prognostic indicators include African-American race, lupus pernio, and chronic bone, lung, or nasopharyngeal involvement (2,6,7).

CLINICAL PRESENTATION

In the United States, approximately 50% of patients with sarcoidosis are asymptomatic and diagnosed on routine radiograph that shows hilar lymphadenopathy (6,7). Those with suspected sarcoidosis can be referred for follow-up and confirmation of the disease. In the emergency department (ED), however, the more important issue revolves around when to suspect and how to treat active disease (Table 81.1).

TABLE 81.1
Characteristics at Clinical Presentation

Characteristics	Incidence (%)
Age (yrs)	
<40	75
>40	25
May occur in children and the elderly	
Gender	
Male	60
Female	40
Race	
Black	90
White	10
Asymptomatic	10–20
Acute/subacute (fever, fatigue, malaise, anorexia, weight loss, respiratory symptoms)	20–40
Insidious (respiratory complaints without constitutional symptoms)	40–70

From Cox CE, Donohue JF, Brown CD, et al. The Sarcoidosis Health Questionnaire: A new measure of health-related quality of life. *Am J Respir Crit Care Med*. 2003;168:323–329.

In 20% to 40% of cases, acute sarcoidosis develops over a period of several weeks. The symptoms are usually mild and may include fever, malaise, anorexia, and weight loss (7,9). Those with chronic sarcoidosis develop a more indolent form over months. Most have vague respiratory complaints and are likely to have symptomatic relapses. It is the group with a slow evolution of symptoms that is more likely to develop chronic disease and organ damage.

As sarcoidosis is a multisystem disease, it can present as a multitude of symptoms. The lungs, however, are almost always (90%) involved, and the clinical presentation is consistent with the presence of interstitial lung disease. Patient often present with exertional dyspnea and a dry cough. The physical examination may reveal dry rales or wheezing, suggestive of reactive airway. Airway hyperreactivity is especially prominent in patients with endobronchial involvement (10). Ninety percent of patients have an abnormal chest radiograph and some may develop pulmonary hypertension related to decreased lung volumes (11,12).

There are four stages of sarcoidosis; these stages are classified by the Scadding scale. Radiographic evaluation is helpful to define pulmonary involvement and also stage the disease. These four stages of involvement are shown on chest films (Table 81.2). Stage I is defined by the presence of bilateral hilar adenopathy and can often be accompanied by right paratracheal node enlargement (Fig. 81.1). Stage II is characterized by bilateral hilar adenopathy and reticular opacities. Stage III consists of reticular opacities, which are generally distributed in the upper lung zones with shrinking hilar nodes. Finally, stage IV is defined by reticular opacities in the upper lung zones with general lung volume loss (2,8).

TABLE 81.2
Radiographic Stage and Prognosis in Sarcoidosis

Stage	% of Patients	Prognosis (Likelihood of Resolution) (%)
0	5–10	—
I	50	60
II	25–30	46
III	15	12

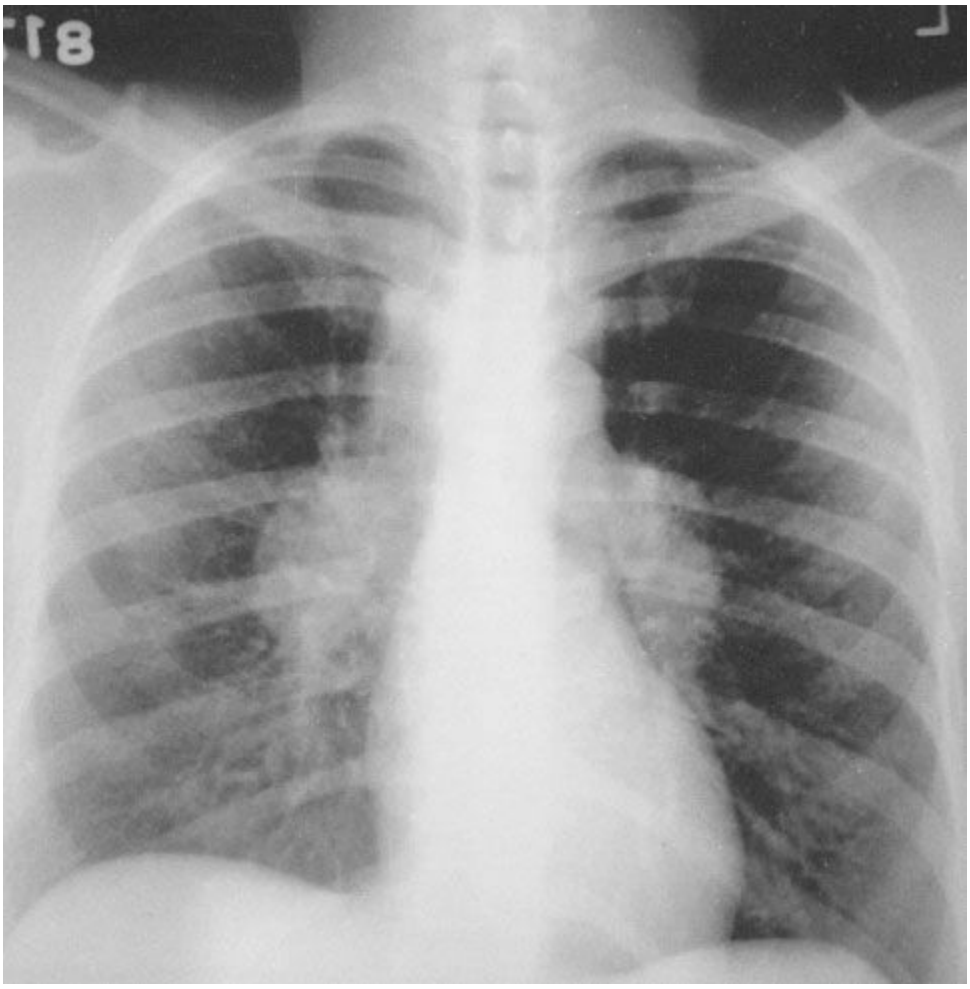

FIGURE 81.1 Typical type I radiograph. (Courtesy of Murray K. Dalinka, MD, Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia.)

Radiographic staging has limited prognostic significance. While staging provides a guide to lung involvement, it does not assess functional ability or disease activity. Stage I changes of bilateral hilar adenopathy may resolve whereas changes in stage II to IV are generally chronic. It is important to recognize that these are not

stages of the disease but rather represent different radiographic manifestations (7).

While pulmonary manifestations of sarcoidosis account for 90% of disease, extrapulmonary manifestations account for the remaining 10%. These extrapulmonary manifestations can involve most organs including the skin, lymph nodes, and heart. Although myocardial involvement of sarcoidosis is found in 25% of autopsied cases, only 10% of those patients without cardiac symptoms have an abnormal electrocardiogram. Granulomatous involvement of the conduction system and ventricular walls can lead to dysrhythmias including complete heart block and sudden cardiac death. Life-threatening ventricular dysrhythmias may be related to QT prolongation (13). As many as 25% of patients with cardiac manifestations of sarcoidosis die as a result of congestive heart failure (CHF) (7). CHF may be due to local infiltration of the mitral valve or diffuse granulomatous disease (1). Myocardial magnetic resonance imaging may be a useful modality for tracking the clinical course of disease (14).

Abnormalities related to calcium are the most common renal and electrolyte abnormalities among patients with sarcoidosis. The defect in calcium metabolism is due to increased intestinal calcium absorption owing to overproduction of 1,25-dihydroxyvitamin D_3 by activated macrophages. Hypercalciuria (30%) and hypercalcemia (10%) are common presentations of sarcoidosis; patients may present with renal colic from nephrolithiasis, hypertension, and renal arteritis; primary renal infiltration with sarcoid granulomas is rare (7).

While severe hypercalcemia is unusual, corticosteroids can control hypercalcemia by inhibiting the action of 1,25-dihydroxyvitamin D_3. Before corticosteroids are considered, treatment begins with conservative measures including intravenous (IV) fluids and decreasing oral calcium intake (15).

Ocular involvement of sarcoidosis involves approximately 25% of patients; 5% of patients initially present with ocular symptoms. The most common ocular presentation is anterior uveitis. Uveitis may

develop rapidly and can become chronic eventually leading to glaucoma, cataracts, and blindness (9). Other ocular diagnoses include posterior uveitis, conjunctivitis, cataracts, and retinal hemorrhages.

Skin lesions occur in about one of every four patients. Cutaneous manifestations include lupus pernio (Fig. 81.2), plaques, and symmetric maculopapular eruptions. In addition, erythema nodosum is a hypersensitivity reaction that may be seen in women of childbearing age. While a nonspecific finding (7,8), erythema nodosum is often considered the hallmark of the disease (8).

FIGURE 81.2 Lupus pernio. (Courtesy of Gerald S. Lazarus GS, MD, Department of Dermatology, Hospital of the University of Pennsylvania, Philadelphia.)

Musculoskeletal presentations of sarcoidosis are common with 10% to 20% of patients presenting with chronic arthritis or acute polyarthritis. Acute polyarthritis is associated with erythema

nodosum and can be incapacitating, requiring corticosteroid therapy. Chronic arthritis is associated with chronic persistent disease and is most frequently seen in black patients (7).

Sarcoidosis that involves the upper respiratory tract should be suspected in all patients with systemic sarcoidosis and upper respiratory tract symptoms. The granulomatous disease can involve the larynx, pharynx, nares, and sinuses. Nasal and laryngeal involvement occurs in up to 16% of patients with sarcoidosis; extensive disease may cause severe airway compromise (9).

Less than 10% of patients have neural involvement. While the initial manifestations of neural involvement are central nervous system (CNS) related, peripheral nerve and skeletal muscle involvement is characteristically seen in the later stages. The granulomatous component of sarcoidosis can compress local structures. Patients can present with cranial neuropathy, especially seventh nerve palsy from brainstem compression, central diabetes insipidus from pituitary and hypothalamic lesions, and seizures from hydrocephalus. Neurologic symptoms usually improve with corticosteroid therapy (7,16).

Two other syndromes have been described. Löfgren syndrome includes the triad of erythema nodosum, bilateral hilar adenopathy, and arthralgias. Löfgren syndrome is associated with a good prognosis with over 90% of patients experiencing disease resolution within 2 years. A second syndrome, Heerfordt–Waldenström, also referred to as uveoparotid fever, is a rare presentation of sarcoidosis. The symptoms include chronic fever, anterior uveitis, facial nerve palsy, and parotid enlargement (9,17).

Symptomatic sarcoidosis is rare in children. It has been shown that children of African descent have more severe disease than Caucasian and Asian counterparts. There are two distinct forms of pediatric sarcoidosis. Children under the age of 4 years, those with an early onset of disease, are likely to present with the triad of rash, uveitis, and arthritis. Children between the ages of 8 and 15 develop multisystem disease similar to that described in adults with lymphadenopathy, pulmonary involvement, and the typical generalized signs and symptoms of fever and malaise (18).

DIFFERENTIAL DIAGNOSIS

While there is no classic presentation of sarcoidosis, a common presentation entails a young adult who presents with a fever, subjective shortness of breath, blurry vision, and erythema nodosum; the chest radiograph shows bilateral hilar adenopathy. Most cases, of course, are not this typical. As sarcoidosis is a multisystem disease, the differential diagnosis is broad. Sarcoidosis can be confused with tuberculosis, or other mycobacterial infections, lymphoma, and some fungal disorders including coccidioidomycosis. Other systemic diseases to be considered include leprosy, berylliosis, and hypersensitivity pneumonitis.

HIV infection must also be considered in patients suspected of having sarcoidosis. Patients with HIV commonly have several of the features found in sarcoidosis, including chest radiograph abnormalities and lymphocytopenia. Only a small number of patients with concurrent HIV and sarcoidosis have been recorded. It has been postulated because CD4 cells are required for clinical expression of sarcoidosis, they may be “protective,” against the viral illness. Although the clinical suspicion may be high, a definitive diagnosis of sarcoidosis cannot be made with certainty on initial clinical presentation. A patient who carries a diagnosis of sarcoidosis, however, may present with a complication of the disease.

ED EVALUATION

On presentation to the ED, a physician should direct the initial patient history to determine the duration and severity of symptoms, a previous diagnosis of sarcoidosis, and any previous need for corticosteroid therapy.

The major complications of systemic sarcoidosis include upper airway obstruction from laryngeal involvement (19,6), cardiac dysrhythmias and conduction disturbances including complete heart block, CHF, advanced pulmonary fibrosis with cor pulmonale (20), superimposed tuberculosis or bacterial infection (7), sudden loss of vision from ocular complications (1), incapacitating arthritis or

arthralgias (11), space-occupying lesions of the brain and hydrocephalus (21), and hypercalcemia with its cardiac, neurologic, and renal sequelae. In the proper clinical setting, abrupt corticosteroid withdrawal may cause signs and symptoms of adrenal insufficiency (15,22).

The physical examination should first focus on airway and cardiopulmonary systems. As sarcoidosis is a multisystem disease, attention should be given to all potentially involved organ systems. Ocular, neurologic, skin, and joint complaints necessitate more specialized examination and testing. Like all patients who present with altered mental status or abnormal neurologic findings, a funduscopic examination may be useful.

Diagnostic studies in the ED should be directed toward detecting both current and potential sarcoidosis-related problems. Patients may benefit from a 12-lead electrocardiogram and outpatient Holter monitoring. Chest radiography, pulse oximetry, and arterial or venous blood gas analysis may be indicated in those with respiratory complaints. Benefit may be realized from renal function studies, electrolytes, and calcium and platelet counts.

Strict criteria must be satisfied to diagnose sarcoidosis. They include compatible clinical and radiographic findings (6,19), histologic finding of noncaseating granulomas, and exclusion of other diseases with similar findings (20,21,23,24). It is unlikely that an emergency physician will establish that a patient meets these exacting criteria. A diagnosis based on only one of these features may be misleading. Definitive diagnosis requires specialty assistance.

Additional evaluation often includes cerebrospinal fluid (CSF) and isotopic imaging studies, extrapulmonary biopsy, and bronchoalveolar lavage. The ATS Sarcoidosis Consensus Group believes that transbronchial biopsy should be performed on patients suspected of sarcoidosis (2). Fine-needle biopsy is an important diagnostic tool (21), and bronchoalveolar lavage may be performed at the same time as biopsy. An elevated CD4:CD8 ratio in the fluid confirms the diagnosis and occurs in the majority of those with pulmonary disease (2,21,22). Advances in gallium scanning have

improved diagnostic accuracy; however, this test is not diagnostic of sarcoidosis. Likewise, although CT scanning may be helpful to rule out other diseases, it cannot establish a definitive diagnosis (21). Most patients will eventually have a 24-hour urinary calcium level (7) and serum and CSF angiotensin–converting enzyme levels.

KEY TESTING

- CXR and pulse oximetry for respiratory complaints
- ECG to detect conduction abnormalities
- Calcium level, electrolytes, BUN, creatinine, if suspected hypercalcemia
- CT head if altered mental status

ED MANAGEMENT

Most patients with sarcoidosis do not require treatment. This is especially true as most patients have asymptomatic disease. For those individuals who have more severe pulmonary or extrapulmonary symptoms, treatment is aimed at reducing the burden of granulomatous inflammation. While no specific treatment exists, oral glucocorticoids have been most widely used to control symptoms. Incapacitating disease that interferes with normal life activities merits consideration for corticosteroid therapy. Conversely, mildly symptomatic disease warrants conservative management without corticosteroids. In those who require treatment, systemic corticosteroids of prednisone 40 mg/d remain an effective and safe form of treatment (16,19).

Indications for treatment with corticosteroids in patients with pulmonary sarcoidosis include progressive and worsening radiographic imaging, pulmonary symptoms, and deteriorating lung function as measured by pulmonary function testing. Therapy is generally withheld in all asymptomatic patients despite the stage of therapy. Lung transplantation is a final option for end-stage pulmonary disease (7,23).

Treatment of extrapulmonary sarcoidosis is based on the affected organ and the degree of damage. As a general rule, treatment of

neurologic, ocular, myocardial, or renal sarcoidosis and hypercalcemia is indicated. Treatment is generally started to prevent further complication leading to loss of vision, sudden cardiac death and fatal arrhythmias, or renal failure.

Because of mortality rates approaching 10%, patients with neurosarcoidosis require treatment with prednisone 1 mg/kg/d followed by a taper. For severe or fulminant cases, IV steroids (1 g/d methylprednisolone) are administered for 2 to 3 days (16). Topical corticosteroids are used for anterior ocular and dermatologic disease (7,15,19).

Patients with cardiac conduction abnormalities resulting from granulomatous infiltration are usually refractory to conventional pharmacotherapy and often need to be admitted to the hospital to determine the most appropriate pharmacologic or electrical therapy. Cardiac transplantation has been performed successfully in younger patients with severe heart failure. Refractory dysrhythmias may require resection of a ventricular aneurysm (19,23). Hypercalcemia, if severe or symptomatic, may be treated as per conventional treatment. High-dose corticosteroid therapy may be required. Milder elevations of serum calcium levels may be treated with corticosteroids and frequent monitoring (15,19).

Although corticosteroids remain the mainstay of treatment, other agents have also been used. These agents include methotrexate, azathioprine, cyclophosphamide, chlorambucil, cyclosporine, nonsteroidal anti-inflammatory agents, chloroquine, infliximab, and hydroxychloroquine.

CRITICAL INTERVENTIONS

- Obtain a serum calcium level in patients with suspected or diagnosed sarcoidosis
- Treat hypercalcemia as an inpatient; aggressive treatment is warranted, especially in patients with significant signs and symptoms of hypercalcemia
- Obtain an electrocardiogram to diagnose cardiac conduction abnormalities

- Begin corticosteroid therapy in selected cases in conjunction with the appropriate primary care physician or consultant

DISPOSITION

The ED physician may require the assistance of specialty consultants in diagnosing and managing a patient with suspected sarcoidosis. Pulmonary, ophthalmologic, dermatologic, and neurologic consultation may be necessary before definitive therapy is undertaken.

In those patients who carry a diagnosis of sarcoidosis, hospital admission is indicated for patients with cardiac or neurologic symptoms, hypercalcemia, severe thrombocytopenia, or any degree of airway compromise.

Because long-term care is usually required, the family physician, internist, or pulmonary specialist is most commonly called on to provide primary outpatient therapy for sarcoidosis.

Common Pitfalls

- Sarcoidosis is frequently asymptomatic; it should be considered in patient with eye findings, suggestive skin lesions, hypercalcemia, persistent cough or dyspnea, or unexplained fever and weight loss
- The emergency physician should arrange follow-up so that a definitive diagnosis can be made and an appropriate treatment plan begun
- Specialty consultation should be obtained before treating with systemic corticosteroids and when dealing with cardiac, neurologic, or ocular disease
- Children can develop sarcoidosis
- The presence of wheezing may incorrectly suggest reactive airway disease. Corticosteroids may not be indicated in this setting

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SECTION VIII
Cardiac Emergencies

Section Editor: JEFFREY J. SCHAIDER

CHAPTER 82

Acute Coronary Syndrome

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Acute coronary syndrome (ACS) is the leading cause of death and disability in developed nations and creates one of the largest economic burdens on the health care systems. More than 1 million deaths occur annually in the United States due to ACS, with many of these in patients younger than age 65 (1). Although millions of people are assessed for chest pain in emergency departments (EDs) in the United States each year, fewer than one-fourth are ultimately diagnosed with ACS. The case-fatality rate has dropped significantly owing to myriad factors, including societal education about risk factor modification, treatment of associated conditions such as diabetes and hypertension, current medical therapies, and the institution of reperfusion strategies. Despite aggressive workups and the use of several strategies for risk stratification, emergency physicians still discharge about 2% of patients with myocardial infarction (MI) (2), with an associated increase in short-term mortality. These patients tend to be younger, have atypical presentations, and have nondiagnostic electrocardiograph (ECG). Approximately 20% of all malpractice dollars are awarded to plaintiffs in cases involving ACS, and this fear often leads to altered decision making and an associated increase in testing and hospitalization in low-risk patients (3).

ACS encompasses three specific presentations of coronary artery disease (CAD): unstable angina (UA) pectoris, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).

UA is defined by its clinical presentation, usually a change in class as defined by the Canadian Cardiovascular Society (Table 82.1 and 82.2). The distinction between UA and NSTEMI is based ultimately on the detection of markers of myocardial necrosis in the blood, so the two entities are indistinguishable at presentation, and their management is initially the same. Neither UA nor NSTEMI have characteristic historical, physical examination, or ECG findings. STEMI is defined by the electrocardiographic findings and the need for initiation of emergent reperfusion strategies. Each of these conditions is due to a lack of perfusion of the myocardium, which causes an imbalance between oxygen supply and demand. Atherosclerosis of the coronary arteries with occlusion of the vessel is the most common cause of myocardial ischemia. Regardless of the specific etiology, the beneficial effects of therapy are greatest when performed soon after presentation to the hospital.

TABLE 82.1
Canadian Cardiovascular Society Grading of Angina Pectoris

Grade	Description
Grade I	Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina is caused with strenuous or rapid or prolonged exertion at work or recreation
Grade II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more then one flight of ordinary stairs at a normal pace and in normal conditions
Grade III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
Grade IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

Patients with stable angina usually have a smooth-surfaced atherosclerotic plaque that permits sufficient coronary arterial flow at rest or minimal exercise to meet the metabolic demands of the myocardium. During physical exertion or other increases in

metabolic demand, myocardial oxygen demand increases owing to elevation of both heart rate and blood pressure. Coronary perfusion cannot increase sufficiently to meet the augmented demands, and ischemia with classic symptoms of angina develops.

In contrast to stable angina, the pathologic substrate for ACS is a complex and irregular atherosclerotic plaque. Unstable plaques are prone to rupture, resulting in a cascade of inflammatory events, thrombus formation, and platelet aggregation that can cause acute obstruction of the arterial lumen and myocardial necrosis. Other etiologies of ACS include dynamic obstruction (coronary spasm such as in Prinzmetal's variant angina) and progressive mechanical obstruction, such as re-stenosis after percutaneous coronary intervention (PCI). The definition of myocardial infarction (MI) requires evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Specific examples include (i) a rise and/or fall of cardiac biomarkers with at least one of the following: symptoms of ischemia, ECG changes, or imaging evidence of new loss of viable myocardium or of wall motion abnormality; (ii) sudden, unexpected cardiac death accompanied by symptoms of myocardial ischemia or ECG abnormalities or autopsy findings; (iii) PCI and coronary artery bypass grafting (CABG), giving rise to elevated cardiac biomarkers with or without ECG findings. MIs can be classified according to Table 82.3.

CLINICAL PRESENTATION

The history is the most sensitive test for the ED detection of ACS, far surpassing both ECG and measurement of cardiac markers. The hallmark of ACS is chest pain, typically located in the substernal region or epigastrium that frequently radiates to the neck, left shoulder, and left arm. All patients presenting with chest pain should therefore have a detailed history and should be asked for particulars on onset of pain (abrupt or gradual), quality of pain (squeezing, sharp, pleuritic, etc.), radiation (can be either left or right shoulder/arm, neck, back, etc.), site of the pain (substernal, diffuse or poorly localized, chest wall, etc.), provocation (with exertion, breathing or spontaneously, etc.), and timing (episodic or constant,

duration of each episode, etc.). Anginal equivalents such as dyspnea, nausea, vomiting, and diaphoresis may also occur and compose up to 30% of presentations of ACS. These atypical symptoms are classically found in the elderly, in women, in non-Whites, or in those who have comorbid diseases such as diabetes, heart failure, prior stroke, or hypertension. Atypical presentations of ACS are associated with longer delays to presentation and ECG acquisition and a 3-fold increase in mortality associated with delay in the initiation of therapeutic interventions and a decreased intensity of treatment regimens (4). Classic ischemic chest pain associated with ACS usually occurs abruptly, increases in intensity over time, and reaches peak intensity within 2 to 5 minutes of onset. Anginal pain generally lasts for <15 minutes, whereas that associated with MI lasts longer. Certain chest pain characteristics have a low likelihood of representing ACS (seconds of pain or constant pain lasting hours to days, pleuritic pain, and reproducible chest wall pain), but this likelihood is not negligible and is one of the reasons why ACS is so difficult to diagnose (5). Patients may also present with a myriad of other symptoms like nausea, vomiting, diaphoresis, altered mental status, weakness, and even belching.

TABLE 82.2
Clinical Presentation of Unstable Angina

Angina at rest (usually >20 min) within 1 wk of presentation
New-onset angina of Canadian Cardiovascular Society Classification class III or IV within 2 mo of presentation
• Class III angina: pain when walking less than two blocks or climbing less than one flight of stairs
• Class IV angina: inability to carry out any physical activity without discomfort
Angina increasing in Canadian Cardiovascular Society Classification class to at least class III or IV

TABLE 82.3
Myocardial Infarction

Type 1

Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

Type 2

Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply (e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension)

Type 3

Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood

Type 4a

Myocardial infarction associated with PCI

Type 4b

Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

Type 5

Myocardial infarction associated with CABG

CABG, coronary artery bypass grafting; LBBB, left bundle branch block; PCI, percutaneous coronary intervention.

Reproduced with permission from Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Eur Heart J.* 2007;28(20):2525–2538. Kristian Thygesen, Joseph S. Alpert and Harvey D. White on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction.

Traditional risk factors (smoking, diabetes, hypertension, hypercholesterolemia, and family history) are weak predictors of the likelihood of ischemia in an acute presentation by an individual patient. These risk factors were developed retrospectively and are of limited utility in ED patients. These risk factors have no predictive value in the elderly, and even in those younger than 40 years of age, their predictive value is limited and should not dictate diagnostic and management decisions (6). The stronger risk factor for ACS is a previous history of ACS. Patients with a history of a positive stress testing or angiographically documented CAD have an extremely high likelihood of recurrent ischemic disease if they present with anginal or anginal-equivalent symptomatology.

Physical examination findings are nonspecific in the ACS patient, and the utility of the physical examination lies in identifying other etiologies for the patient's symptoms. Identification of acute cardiac dysfunction, in the form of shock or heart failure, mandates urgent initiation of treatment, but one-fourth of patients with ACS have a normal cardiac examination. Moreover, valvular heart disease, congenital heart disease, cardiomyopathy, and chronic ischemic heart disease have physical examination findings similar to those of the ACS patient, so care should be used in attributing these findings to other pathophysiologic processes. Thus, the physical examination is often not helpful in diagnosing ACS. Table 82.4 lists signs associated with the pathologic changes that occur with ischemia.

TABLE 82.4
Physical Signs That Occur During Myocardial Ischemia

Physical Sign	Underlying Pathophysiology
Soft S1	Decreased LV d*p*/d*t* or first-degree AV block
Paradoxically split S2	Prolonged LV ejection time
S3 and/or S4	Decreased LV compliance
Mitral regurgitation	Papillary muscle ischemia
Palpable precordial systolic bulge	Anterior or lateral dyskinesis
Bibasilar rales	Increased preload

AV, atrioventricular; LV, left ventricular; d*p*/d*t*, rate of pressure rise.

DIFFERENTIAL DIAGNOSIS

A detailed discussion of the differential diagnosis of chest pain is included elsewhere in the text. Cardiac, pulmonary, musculoskeletal, and gastrointestinal systems all give rise to symptoms of ACS. Life-threatening diseases which may be confused with ACS include aortic dissection, pulmonary thromboembolism, pneumothorax, mediastinitis, pericarditis, myocarditis, hypertrophic obstructive cardiomyopathy, and pericardial tamponade. Pneumonia and pleural diseases, valvular heart disease, pericarditis, takotsubo cardiomyopathy, gastroesophageal reflux disease, peptic ulcer disease, and chest wall pain (such as costochondritis and trauma to

the chest wall) should also be included in the differential diagnosis. Particular attention to the character of the pain, precipitating factors, associated symptoms, and the physical examination usually allows the clinician to rule out a number of these other causes of chest pain.

ED EVALUATION

The emergency physician must perform a rapid triage and assessment of patients with potential ACS. Risk stratification will need to be based on history, physical examination, ECG, cardiac markers, and potentially imaging. The estimation of risk is complex, but several investigators have proposed useful risk-stratification schemes (Tables 82.5 and 82.6).

Electrocardiography

The ECG is a mainstay of the initial diagnosis of ACS. It can dictate management, response to therapy, and appropriate admission disposition and is also predictive of the risk of subsequent major adverse cardiac events (MACE). In patients with suspected ACS, a standard 12-lead ECG should be obtained and interpreted within 10 minutes of presentation. Although the ECG remains the best immediate test for identification of AMI, a single ECG performed during the patient's initial presentation detects less than half of AMI. ECG abnormalities of myocardial ischemia or MI include characteristic changes in the PR segment, the QRS complex, the QT interval, and the ST segment or T waves. However, fewer than half of patients who are eventually discharged with a diagnosis of acute MI have a diagnostic initial ECG. Rather, "nonspecific" or "nondiagnostic" findings are more frequent. The ECG should be obtained when the patient is having symptoms, if possible, but a normal ECG obtained while a patient is having symptoms is no more likely to be associated with ACS than a normal ECG when there are no symptoms (7). Serial ECG recordings can aid in determining whether the patient's symptoms are due to ACS and have been shown to increase the sensitivity of identification of ACS to almost 90%, but the specificity remains poor at 50% (8). Whenever there is

a change in symptomatology or clinical status, a repeat ECG should be performed. Thus, if the ECG is either normal or nondiagnostic but there is still a high clinical suspicion of ACS, it is recommended that the ECG be repeated in 5- to 10-minute intervals to look for diagnostic changes (9).

TABLE 82.5
Likelihood That Signs and Symptoms Represent an Acute Coronary Syndrome Secondary to Coronary Artery Disease

Feature	High Likelihood *Any of the following:*	Intermediate Likelihood *Absence of high-likelihood features and presence of any of the following:*	Low Likelihood *Absence of high- or intermediate-likelihood features but may have:*
History	Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina Known history of CAD, including MI	Chest or left arm pain or discomfort as chief symptom Age > 70 yr Male sex Diabetes mellitus	Probable ischemic symptoms in absence of any of the intermediate likelihood characteristics Recent cocaine use
Examination	Transient MR, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation (≥0.05 mV) or T-wave inversion (≥0.2 mV) with symptoms	Fixed Q waves Abnormal ST segments or T waves not documented to be new	T-wave flattening or inversion in leads with dominant R waves Normal ECG
Cardiac markers	Elevated cardiac TnI, TnT, or CK-MB	Normal	Normal

Reproduced with permission from Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—summary article: A report of the American College of Cardiology/American Heart Association task force on practice guidelines [Committee on the Management of Patients with Unstable Angina]. *J Am Coll Cardiol.* 2002;40(7):1366–1374.

The electrographic manifestations of acute myocardial ischemia by the 2012 Joint ESC/ACCF/AHA/WHF Task Force include the following (10).

- For ST elevation: New ST elevation at the J point in two contiguous leads with the cut-points: ≥0.1 mV in all leads other than V2-V3 where the following cut-points apply: ≥0.2 mV in men 40 years; ≥0.25 mV in men <40 years, or ≥0.15 mV in women.
- For ST depression and T-wave changes: New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or T-wave inversion ≥0.1 mV in two contiguous leads with prominent R wave or R/S ration >1.

The 12-lead ECG shows the anterior myocardial wall well but is limited in identifying ischemic areas in the lateral, posterior, and right myocardium. Nonstandard surface ECG recordings are of value in some patients with ACS. The 15-lead ECG includes leads V4 r, V8,

and V9 to look for ischemic changes in the right ventricle and posterior portions of the myocardium. The addition of the 15-lead ECG increases the sensitivity for MI without sacrificing specificity. Although a 15-lead ECG should be obtained whenever there appears to be ischemia in the anterior or inferior leads, it can be used in every patient to increase the sensitivity of detection of MI. ECG with up to 192 leads has been utilized to improve sensitivity and to identify more patients who would benefit from reperfusion therapy. This body surface mapping has been shown to augment the traditional ECG in the identification of transmural infarction (ST elevation) and may get these patients to definitive therapy more readily. However, the vast majority of STEMI patients are picked up with the regular 12-lead ECG.

TABLE 82.6
Short-Term Risk of Death or Nonfatal Myocardial Infarction in Patients with Unstable Angina

Feature	High Risk *At least 1 of the following features must be present:*	Intermediate Risk *No high-risk feature but must have one of the following:*	Low Risk *No high- or intermediate-risk feature but may have any of the following features:*
History	Accelerating tempo of ischemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease, or CABG, prior aspirin use	
Character of pain	Prolonged ongoing (>20 mis) rest pain	Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of CAD Rest angina (<20 min) or relieved with rest or sublingual NTG	New-onset or progressive CCS Class III or IV angina in the past 2 wk without prolonged (>20 min) rest pain but with moderate or high likelihood of CAD
Clinical findings	Pulmonary edema, most likely due to ischemia New or worsening MR murmur S_3 or new/worsening rales Hypotension, bradycardia, tachycardia Age >75 yr	Age > 70 yr	
ECG	Angina at rest with transient ST-segment changes >0.05 mV Bundle branch block, new or presumed new Sustained ventricular tachycardia	T-wave inversions >0.2 mV Pathological Q waves	Normal or unchanged ECG during an episode of chest discomfort
Cardiac markers	Elevated (e.g., TnT or TnI >0.1 ng/mL)	Slightly elevated (e.g., TnT >0.01 but <0.1 ng/mL)	Normal

Reproduced with permission from Braunwald E, Jones RH, Mark DB, et al. Diagnosing and managing unstable angina. Agency for Health Care Policy and Research. *Circulation.* 1994;90(1):613–622.

ECG abnormalities have been classically divided into high- and low-risk criteria for MACE. High-risk abnormalities include ST-segment depression, pathologic Q waves, T-wave changes, left bundle branch block (LBBB), left ventricular hypertrophy (LVH), abnormal conduction, ventricular-paced rhythm, and any abnormality that is reversible or associated with the patient's symptoms. Abnormalities associated with a low risk of subsequent

cardiac events include normal ECG, nonspecific ST and T-wave changes, and absence of change from a previous ECG. Patients with a low-risk ECG still have more than a 10% chance of MI after presentation with ischemic symptoms. Patients with high-risk ECG findings have a 40% chance of MI and high risks of major cardiac events and mortality.

Early ECG signs of myocardial injury are ST-segment and T-wave changes that may also be seen with early or transient reversible ischemia. Nondiagnostic, new, or presumably new ST-segment elevation or depression of $\geq$0.5 mm (0.05 mV) or T-wave inversion to $\geq$1 mm (0.1 mV) observed during symptoms may indicate ACS. The magnitude of this ST-segment depression may be predictive for death and recurrent MI.

The presence of new nonspecific ECG changes increases the likelihood that chest pain is caused by myocardial ischemia; however, the predictive value is only about 50%. Any dynamic changes, including pseudonormalization of the ECG, should raise suspicion for ACS. New ST-segment deviations of $\geq$1 mm (0.1 mV) are more consistent with STEMI or NSTEMI and should prompt therapeutic intervention. It is important to note that the magnitude of the change is prognostic for morbidity and mortality from ACS. The greater the ST-segment depression on ECG, the more likely that the patient is having UA or a NSTEMI and worse the prognosis for outcome. A prominent R wave, or an R/S ratio $>$1, may also be indicative of myocardial ischemia, especially when it is seen in the anterior precordial leads. Patients with ST-segment elevation resulting from acute MI have either obliquely flat or convex-upward waveforms, whereas patients with noninfarction ST-segment elevation (i.e., early repolarization or LVH) tend to have a concave-upward waveform. ST-segment and T-wave changes are not always associated with ACS, so the differential diagnosis should be carefully considered before initiating treatment. Common nonischemic causes for ST-segment elevation or depression and T-wave inversions suggestive of ACS are listed in Table 82.7. Although a nonconcave ST-segment elevation pattern is more commonly encountered in acute STEMI than in other nonischemic causes of ST-elevation, the

sensitivity of the morphologic pattern, approximately 75%, precludes complete reliance on its presence or absence to make the diagnosis. The ECG can identify STEMI, but it is not sensitive or specific for the identification of other types of ACS.

TABLE 82.7
Nonischemic Causes of ECG Changes

ST-Segment Elevation	ST-Segment Depression	T-Wave Inversion
Left bundle branch block	LVH	Intracranial event
Left ventricular hypertrophy	Left BBB	Strain pattern
Pericarditis/myocarditis	Digoxin effect	Myocarditis
Paced ventricular rhythm	Hypokalemia	Early repolarization
Hypothermia (Osborne J waves)	Hypomagnesemia	Normal variant
Hyperkalemia		
Brugada syndrome		
Drug-induced (tricyclic antide-pressants)		
Left ventricular aneurysm		

BBB, bundle branch block; ECG, electrocardiogram; LVH, left ventricular hypertrophy.

Evidence of previous ischemic disease may be seen on the ECG. Q waves or QS complexes are usually pathognomonic of a prior MI. Q waves usually develop by 12 hours after the infarction and may be permanent ECG findings. The specificity of the ECG for diagnosing MI in the setting of previous MI is greatest when Q waves occur in anatomic groupings.

The degree of ST-segment changes is also predictive of the extent of myocardial disease, with higher mortality figures for both higher ST-segment elevation and deeper ST-segment depression.

T-wave inversions are a nonspecific finding and can occur in a normal ECG, especially in leads V1 and V2. They are more specific for ACS if they are narrow and symmetrically inverted, if they are associated with symptoms, or if they are reversible. Deep T-wave inversions across the anterior precordial leads or biphasic T waves in the same leads have an association with proximal left-sided coronary lesions. Wellens syndrome refers to this ECG finding, which is

associated with an increased incidence of sudden cardiac death during stress testing. These patients should thus undergo coronary angiography for definitive diagnosis.

STEMI is defined by distinctive changes on the ECG. The earliest finding of transmural ischemia may be prolongation of the corrected QT interval, then hyperacute T waves, followed by ST-segment elevation. The hyperacute T wave usually occurs within minutes of the interruption of blood flow. The T wave is often asymmetric, with a broad base. The height of the hyperacute T waves generally correlates well with the acuteness of the injury. There is no cellular death at this stage. The hyperacute T wave evolves rapidly to ST-segment elevation over a 5- to 30-minute period. It is important to note that ST-segment elevation in the setting of MI represents a region of the myocardium that is at risk for necrosis if blood flow is not restored; this has important implications for treatment. ST-segment elevation evolves from J-point elevation and maintenance of a concave configuration to a more pronounced elevation that becomes more convex or rounded upward. The ST segment may eventually become indistinguishable from the T wave and resemble a monophasic action potential (commonly referred to as *tombstoning*). The degree of ST-segment elevation correlates with the immediate risk for acute complications of infarction.

By definition, the diagnosis of STEMI is dependent on new ST elevation in two contiguous ECG leads. Specific criteria are new ST elevation at the J-point or dynamic ST-elevation in two contiguous leads, with cutoff points of $\geq$2 mm (0.2 mV) in men or $\geq$1.5 mm (0.15 mV) in women in leads V2-V3 and/or $\geq$1 mm (0.1 mV) in other leads. ST–T-wave depressions in leads oriented toward the presumably noninfarcted myocardium are termed *reciprocal changes.* These changes may also precede ST-elevation, emphasizing the importance of obtaining serial ECG. These ST–T wave depressions usually reflect more extensive infarction and a worse prognosis (Table 82.8).

TABLE 82.8
Anatomic Representation of Myocardial Ischemia by ECG

Findings

ECG Lead Changes	Infarct/Ischemia Location
V1–V6/I and aVL	Anterior wall
V1–V3	Anteroseptal or apical
II, III and aVF	Inferior wall
Right-sided precordial leads	Right ventricle
Posterior leads V7–V9 (ST depression in V1–V4)	Posterior wall

ECG, electrocardiograph.

Anatomic Localization of Ischemia by Electrocardiography

The localization of MI by ECG is important for immediate risk stratification for MACE.

Anterior and apical infarctions represent the large left ventricular wall, which makes up the greatest muscle mass of the heart. Infarction in this area is associated with the highest incidence of mortality and MACE. ST elevation or waves in one or more of the precordial leads (V1-V6) and leads I and aVL have classically been used to suggest anterior wall ischemia or infarction. Septal involvement classically refers to involvement solely in V1-V3 but this may represent an apical injury. Changes in V4-V6 suggest anterolateral ischemia or infarction. The reciprocal leads for anterior ischemia are the inferior leads. Anterior infarctions are due primarily to left-sided coronary lesions such as obstructions of the left main artery or the left anterior descending artery. Patients that have ST elevation in the anterior precordial leads and any of the following electrocardiographic findings are at risk of a proximal left lesion and thus have a higher risk of morbidity and mortality: presence of ST elevation in lead aVR, complete right bundle branch block (RBBB), ST depression in lead V5, an abnormal Q wave in aVL, and inferior ST elevation $\geq$1 mm plus ST elevation in aVL (11). ST elevation in lead aVR $\geq$ ST elevation in lead V1 may be indicative of a left main coronary artery obstruction (12).

Lateral infarctions may be associated with anterior, inferior, or posterior infarctions, depending on the dominance of the area by the left anterior descending, right coronary artery (RCA), or circumflex vessels. The ECG manifestations of lateral infarction are noted in

leads I, aVL, V5, and V6. The reciprocal leads for lateral infarctions can be seen in leads III, aVF, and V1.

Inferior infarctions are identified by ischemic changes in leads II, III, and aVF and may involve either the RCA or the circumflex artery. If there is ST elevation in lead III exceeding that in lead II, especially when combined with ST depression in I and aVL, there is a very high probability of involving the proximal or mid-RCA. If the ST-segment elevation in lead II is equal to lead III, especially combined with ST depression in leads V1-V3 or ST elevation in leads I and aVL, it is usually a circumflex arterial occlusion (13). The RCA supplies the atrioventricular (AV) node in 90% of patients (in the other 10% it is supplied by the circumflex). Thus, bradycardia and blocks are common with involvement in this region. When there is evidence of inferior myocardial ischemia and/or infarction, right-sided leads V3R and V4R should be placed to assess for possible right ventricular ischemia or infarction (see below for right ventricular infarctions [RVMIs]). The reciprocal changes can be seen in I, aVL, or both. Care must be taken in diagnosing anterior changes as reciprocal, as ST depression may be indicative of posterior infarction as well (see further).

True isolated posterior infarctions are rare, as the majority of posterior infarctions are extensions of either inferior or lateral infarctions (RCA or circumflex). Inferior and lateral MIs associated with posterior extension have a higher mortality than each in isolation, and posterior infarctions may be involved in up to 20% of all MI. The posterior wall is, however, poorly represented on the standard 12-lead ECG. A posterior MI should be suspected with any ST-segment depression in the anterior precordial leads or any inferior or right-sided MI. Posterior and inferior MIs can be differentiated from anterior wall ischemia by the presence of ST-segment elevations in the inferior leads (II, III, and aVF) and posterior leads V7-V9. Utilization of these posterior leads V8 and V9 improves diagnostic sensitivity. ECG criteria for posterior MI include a tall, upright T wave, a tall, wide R-wave ≥ 0.04 seconds in lead V1 (corresponds to the appearance of pathologic Q waves in the posterior leads), a R/S amplitude ratio of >1, and horizontal ST depression in the anterior

precordial leads. Posterior MI is amenable to reperfusion therapy, so identification has important implications.

The ECG diagnosis of RVMI offers special challenges. The right side of the heart is another poorly represented region on the standard ECG, and RVMI usually occurs in the presence of an inferior left ventricular infarction, which can mask the specific ECG manifestations. Because there are anatomic variations of the blood supply to the right ventricle, interruption of blood supply in any of the coronary arteries can lead to a right-sided infarction. Thus, right-sided infarction should be a consideration with all MIs and especially so in inferior infarctions. Thirty to fifty percent of inferior infarctions show extension to the right ventricle. RVMI is associated with higher mortality and in-hospital morbidity than patients without RV involvement. Although about half of RVMI have profound hemodynamic and electrical complications, the long-term prognosis is generally good for those who survive the event (14). The sensitivity of the ECG can be improved by utilizing right-sided chest leads (V1R-V6R), which are the mirror images of the left-sided leads. RV infarction is indicated by ST-segment elevation of ≥ 1 mm in lead V3R or V4R, or both. RV infarction is also suggested in an inferior MI with an isolated ST-segment elevation in V1, owing to the rightward axis of this lead. Although elevation of the right-sided limb leads is specific for RVMI, it is not sensitive. It is important to recognize right ventricular involvement on ECG, as these patients are dependent on preload for the maintenance of left ventricular outflow. Administration of agents, such as nitrates, that reduce preload can result in profound hypotension. RV contractile dysfunction becomes hemodynamically significant in only about 10% of patients; individuals with hemodynamically significant RV infarction typically present with arterial hypotension and jugular venous distention but clear lung fields. These patients are usually amenable to fluid resuscitation, as it will in essence improve hemodynamic parameters on these preload-dependent patients.

Bundle Branch Blocks

Bundle branch blocks (BBB) can make the interpretation of MI more difficult. RBBB usually does not interfere with the diagnosis of STEMI. A RBBB usually affects the terminal phase of ventricular depolarization, producing a wide R¿ wave in the right chest leads and a wide S wave in the left chest leads. This is due to the delayed depolarization of the right ventricle, while most of the STEMI involvement involves the LV and therefore ECG tracings will not be affected in this regard. In the setting of RBBB block, MI can be diagnosed relatively easily, with the ECG showing a wide QRS, a positive terminal deflection in lead V1, and a wide S wave in V6. In the presence of LBBB, ECG indicators of acute MI are much less reliable. No single or group of ECG criteria are completely sensitive for the detection of MI. Three ECG findings that have shown a specificity of 90% for MI include (i) ST-segment elevation of 1 mm or more in the same direction as the QRS complex, (ii) ST-segment depression of 1 mm or greater in leads V1 to V3, and (iii) ST-segment elevation >5 mm opposite to the direction of the QRS complex. A paced rhythm produces a pattern similar to that of LBBB, so ST-segment elevation of >5 mm in predominantly negative QRS complexes (usually the anterior precordial leads) is the only criterion that is useful in the setting of diagnosis of MI when there is a paced rhythm.

Biochemical Markers

After history and ECG, risk stratification continues with biochemical markers of cardiac injury. Disruption of normal cardiac myocyte membrane integrity by ischemia/infarction leads to biologically active intracellular contents such as troponin, creatine kinase (CK), and myoglobin to leak into the extracellular space. The patterns of appearance of these markers in the blood depend on their intracellular location and molecular weight, the local blood and lymph flow, and their rate of elimination from the blood. Cardiac markers are not only useful for diagnosis but can provide prognostic information as well. There is debate as to whether release of these markers is due solely to irreversible damage to the heart. This question arises because of the minor troponin elevations seen after

athletes that have run marathons or triathlons or rises of troponin with some patients with pulmonary embolism. These troponin elevations are transient and resolve much more quickly than troponin elevation from AMI (15).

CK, specifically the CK-MB fraction, has been historically used as the primary cardiac marker, but its diagnostic utility over time is in favor of troponin assays. CK-MB is far less sensitive and specific for myocardial infarction than troponins and should not be used in isolation to make the diagnosis of myocardial infarction. CK-MB usually begins to rise within 4 hours of an ischemic event, peaks at 18 to 24 hours, and returns to baseline by 36 to 48 hours. However, some CK-MB is normally present in skeletal muscle, limiting its specificity for cardiac ischemia. Its relatively short half-life assists in temporally identifying the ischemic event when used with other markers, such as troponins.

Cardiac troponins (TnI and TnT) are much more specific for cardiac muscle necrosis. These are proteins that are highly specific for myocardial tissue as they are immunologically distinct from skeletal muscle troponins. There is great variation in the sensitivity of the troponin assays currently in clinical use, from initially developed “standard” assays to the new “high sensitivity” assays that have come into use. Being able to rapidly diagnose ACS or to identify patients at high risk of events with cardiovascular disease is the premise of using “high sensitivity” troponins (16,17). There is little standardization of these assays against each other and there is only recommendation of utilizing an elevation above the 99th percentile, no matter what assay is being used. There are trade-offs between sensitivity and specificity, especially at the very low levels of troponin measurements in whatever troponin assay used. Using standard 99th percentile cut-off values, elevated serum cardiac Tn levels are detectable 2 to 3 hours after acute MI in 80% of patients with AMI (18). This sensitivity improves to 100% by 10 hours. Troponin reaches peak concentrations in approximately 12 hours and remains elevated for 3 to 10 days after an infarction. Even small troponin elevations that are accompanied by a normal CK-MB have been shown to correlate with focal myocyte necrosis. Troponin peak

values also correlate with size of infarct on scintigraphy and MRI (19,20). In patients presenting with chest pain who do not have ischemic changes on ECG, an elevated troponin is associated with significant increases in the incidence of CAD in those who undergo angiography and adverse cardiac events over the subsequent year. Troponins can thus be used as prognostic indicators in patients with ACS. NSTEMI is differentiated from UA on the basis of troponin elevation and is associated with four times the mortality in the first month and 2.5 times the mortality at 3 years. In STEMI patients, an elevated troponin has been shown to be an independent predictor of mortality in both the immediate postinfarction period and 1 month to 3 years after infarction (21). The degree of elevation of troponins also has significant prognostic value: Higher troponins are associated with progressively increased mortality, decreased TIMI flow, decreased LV function, and abnormal Q waves when compared with lower troponin elevations (22).

The demonstration of a rising or falling pattern is needed to distinguish myocardial injury from background elevated troponin levels. Troponins can also provide information about reinfarction. Patients with recurrent infarction have an increase in the troponin of more than 20% above the baseline elevation. Although elevations in troponins reflect myocardial necrosis, they do not indicate its mechanism. Thus, an elevated troponin in the absence of clinical evidence of ischemia should prompt a search for other etiologies of myocardial necrosis (Table 82.9).

TABLE 82.9
Etiologies of Elevated Troponins in the Absence of Ischemic Heart Disease

Cardiac Contusion (Trauma, Surgery, Pacing, etc.)	Congestive Heart Failure (Both Acute and Chronic)
Aortic dissection	Aortic valve disease
Hypertrophic cardiomyopathy	Tachy- or bradyarrhythmias
Rhabdomyolysis with cardiac injury	Renal failure
Pulmonary embolism	Acute neurologic disease (stroke or subarachnoid hemorrhage
Drug toxicity or toxins	Critically ill patients with respiratory failure or sepsis
Burns (especially if >30% body surface area)	Extreme exertion
Infiltrative diseases (amyloid, sarcoid, scleroderma)	Inflammatory diseases (myocarditis and pericarditis)

Reproduced with permission from Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Eur Heart J.* 2007;28(20):2525–2538. Kristian Thygesen, Joseph S. Alpert and Harvey D. White on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction.

Myocardial Imaging

Strong clinical suspicion and/or nondiagnostic ECG or laboratory findings have usually led to stress testing in the past to further risk stratify patients. Stress testing utilizes physiologic evidence to identify the relationship between coronary artery stenosis and symptoms, characteristic changes on the ECG, regional wall motion abnormalities on echocardiogram, and myocardial perfusion defects on nuclear medicine studies. If there are nondiagnostic stress test results or a strong clinical suspicion, anatomical assessment of the coronary artery may be required. Classically, invasive coronary angiography is then performed to assess whether significant coronary arterial occlusion has occurred. Recently, with the advent of improved coronary CT angiography (CCTA), multidetector CT scanning provides another option to assess anatomically the integrity of the coronary arteries. Multidetector CT scanning detects coronary artery calcification (CAC) and also offers direct imaging of the coronary arteries. Image quality and diagnostic accuracy have improved with each successive generation of scanners (23). Any CAC found on CT scanning is associated with an increased risk of death, infarction, bypass surgery, or PCI (24). Mortality increases linearly with increasing CAC score (calculated scores done by radiologist

specifically trained in CAC reading); patients with no detectable calcium have been reported to have a 12-year survival rate of 99.4% with regard to cardiac disease. The low specificity may lead to increased referral for invasive angiography in patients without significant obstructive disease. However, 64-slice CT angiography not only detects calcium but also has the ability to image the coronary arteries with a detail approaching that of invasive coronary angiography. In reviewing single-center studies of CCTA with classical angiography, there is a sensitivity for significant ($\leq$50%) stenosis of 98% and a pooled specificity of almost 90% (25). In multicenter studies, the sensitivity for significant stenosis is lower (85%) and specificity remains at 90% (26). Nevertheless, the negative predictive value of CCTA ranges from 95% to 100% (27). This has led some institutions to institute low-risk chest pain patients getting a "rule out" CCTA. This practice has not yet been adequately validated and cannot be recommended at this time. Both low-risk patients and high-risk patients do not benefit from CT angiography, because of false-positives and false-negatives, respectively. There is a lack of cost-effectiveness studies as well, and CCTA involves a much higher radiation exposure than the traditional ACS workup. So, although CT angiography and other newer imaging modalities may hold great promise for the future, it is premature to recommend their routine use at the current time.

KEY TESTING

- ECG—Repeat if initially non-diagnostic and there is on-going chest pain
- CXR
- Cardiac Troponin—Repeat at 2 to 4 hours if initial result is negative and recent onset of chest pain
- CBC
- Electrolytes, BUN, creatinine, glucose

ED MANAGEMENT

The initial management of all patients with chest pain and suspected acute ischemic heart disease should include immediate ECG, administration of oxygen, and establishment of vascular access, with laboratory assessment that includes cardiac markers, continuous cardiac rhythm monitoring and pulse oximetry, and close observation of vital signs.

Interventions in Patients with Chest Pain and Suspected Unstable Angina or non-ST-Segment Elevation Myocardial Infarction

ED interventions for intermediate- and high-risk patients with UA and NSTEMI are similar. Management is directed toward decreasing myocardial oxygen demand and stabilizing thrombogenic atherosclerotic plaques.

Anti-Ischemic Therapy

Nitroglycerin

Nitroglycerin (NTG) improves symptoms of myocardial ischemia by (i) reducing oxygen demand through venodilation (low doses: preload reduction; higher doses: preload and afterload reduction) and (b) enhancing oxygen delivery by dilating coronary arteries and arterioles. Despite extensive clinical use, there is remarkably little objective information documenting the effectiveness of NTG in NSTEMI. NTG can relieve anginal pain and may transiently improve LV function but has not been shown to lessen mortality (28,29).

To achieve rapid beneficial effects, NTG therapy should be initiated with sublingual tablets or sprays. Usual protocols include 0.4 mg as a starting dose, with repeated doses every 5 minutes to a total of three doses, based upon symptoms. IV NTG may be initiated by continuous infusion if there is inadequate resolution of symptoms with sublingual therapy or if titration of blood pressure is necessary. The goal of IV NTG therapy is relief of symptoms or a mean arterial blood pressure 10% below baseline in normotensive individuals and up to 30% reduction in hypertensive individuals. NTG should also be avoided in patients who have taken erectile dysfunction medications

such as sildenafil and tadalafil within the preceding 24 hours. Such administration can lead to profound hypotension, MI, and death. Hypotension due to administration of NTG should be treated with a crystalloid bolus infusion.

Morphine

Morphine (2 to 5 mg IV) is a reasonable addition for pain control in myocardial ischemia if symptoms do not resolve with NTG. Morphine has additional benefits beyond its analgesic and anxiolytic effects. It causes venodilation and reduced preload. It also has vagal effects, which reduce heart rate.

Beta Adrenergic Blockers

Beta blockers reduce myocardial oxygen demand by reducing contractility, sinus node rate, and AV nodal conduction. These agents also have antidysrhythmic properties and may counteract the effects of catecholamines on the myocardium. The primary immediate benefits are due to decreased myocardial oxygen demand. No randomized trials have specifically addressed the NSTEMI patient, but the multiple studies that show benefit of beta blockade of UA and STEMI can be extrapolated to the NSTEMI population (30). Beta blockers reduce the odds of death by 23% in the setting of acute MI.

Typically, a cardioselective beta blocker is preferred, such as metoprolol or atenolol or, if an ultrashort agent is required, esmolol (Table 82.10).

TABLE 82.10
Beta-Blockade Agents and Dosages

Agent	Dosage
Metoprolol	5-mg increments by slow intravenous administration (1–2 min) for a total initial dose of 15 mg. Oral therapy can be initiated after 15 min of IV therapy at 25–50 mg q6 h for the next 48 h
Atenolol	5 mg IV q10 min for two doses, then 50 mg 10 min after the last IV dose and repeat in 12 h, then 100 mg/d divided qd—bid
Esmolol	500 µg/kg/min IV bolus over 1 min, then 50 µg/kg/min IV with titration upward for control of heart rate or blood pressure but 50 µg/kg/min q4 min

Early aggressive beta blockade poses a significant hazard in hemodynamically unstable patients with STEMI and should be avoided; this philosophy is generally extrapolated to UA/NSTEMI patients as well (31). It has also been noted that there has been no mortality benefit in receiving IV beta blockers rather than oral preparations in the early stages of AMI.

Chronic oral therapy decreases long-term mortality and should be part of routine care. Carvedilol, begun in low doses with subsequent titration upward 3 to 10 days after MI in patients with left ventricular dysfunction, decreases subsequent death or nonfatal reinfarction when given in conjunction with other interventions for ACS.

The relative contraindications for beta blockers are well known: marked first-degree AV block; any form of second- or third-degree AV block; history of asthma; severe LV dysfunction with congestive heart failure; and marked sinus bradycardia or hypotension.

Calcium Channel Blockers

Calcium channel blockers (CCBs) reduce calcium flux into cells, which inhibits both myocardial and vascular smooth-muscle contraction. Some CCBs affect the cardiac conduction system to slow AV conduction and depress the sinus node. Decreased myocardial oxygen demand results from a reduction of afterload, contractility, heart rate, and improved myocardial flow. There are conflicting data as to whether CCBs are useful in NSTEMI. Trials in patients with UA found no difference in the incidence of MI or death in a comparison of CCBs to placebo (4). No CCB has been shown to reduce mortality

in MI, and in certain patients they may be harmful (e.g., those with heart failure, left ventricular dysfunction, or conduction disorders). CCBs can be used in patients who have ongoing symptoms despite adequate NTG and beta blocker therapy, inability to tolerate either NTG or beta blockade, or coronary artery spasm. The short-acting agent nifedipine must be avoided in the absence of concurrent beta blockade in ACS. Rate-controlling agents (verapamil and diltiazem) can be administered to patients who have no evidence of heart failure or in whom there are contraindications to beta blockers. Care should be used when administering a CCB to a patient already on a beta blocker, as the two synergistically depress LV function and both sinus node and AV node conduction.

Antiplatelet Therapy

Aspirin

All ACS trials evaluating aspirin in UA/NSTEMI have consistently demonstrated a striking benefit. Aspirin blocks the cyclooxygenase pathway that inhibits production of prostaglandins and thromboxanes from acarchidonic acid. Aspirin in conjunction with other medical therapy produces an almost 50% relative reduction in the combined endpoint of subsequent nonfatal MI, nonfatal stroke, or vascular death in UA patients and a 30% reduction in patients with myocardial infarction (32). One of every 11 patients treated with aspirin over 2 years avoided a cardiovascular event that would have occurred in the absence of aspirin therapy. These results were independent of time given, duration, and dosages. Aspirin should be given immediately upon presentation in doses of 75 to 325 mg and be continued indefinitely. It should be noted that the addition of a second antiplatelet agent significantly lowered the combined end point.

Adenosine Diphosphate Receptor Antagonists

Clopidogrel, prasugrel, and ticagrelor block the adenosine diphosphate receptor P2Y12 on platelets, thus inactivating platelet adhesion. The benefit of aspirin and adenosine diphosphate receptor

blockers was established with the CURE trial using clopidogrel. NSTEMI patients treated with clopidogrel have a relative risk reduction of 20% for death, MI, or ischemic stroke. The benefit of clopidogrel was seen both in patients treated with medical therapy alone and in those who underwent coronary catheterization. This reduction also led to a significant reduction in cardiovascular death, nonfatal myocardial infarction, or stroke at 9 months (33). The major disadvantage of clopidogrel is an increased incidence of bleeding. The actual risk of major bleeding is difficult to determine, as multiple studies have used different definitions of major bleeding. The risk of major bleeding (hemodynamic instability and/or requiring blood transfusions) is best estimated to be about 4%. Ideally, patients who subsequently require CABG should not receive clopidogrel for at least 5 days before their operation, so as to avoid excessive bleeding complications. Patients scheduled for elective PCI who had received clopidogrel prior to the procedure had a 70% relative risk reduction (1.9% absolute reduction) of major cardiac events versus placebo.

In general, NSTEMI patients should receive clopidogrel early. Even if clopidogrel is given prior to CABG, the benefits in terms of morbidity and mortality outweigh the risks of bleeding complications (34). The optimal loading dose of clopidogrel seems to be 600 mg rather than the previously accepted 300 mg dose. Although there was not a decrease in overall mortality, patients who received 600 mg and subsequently went on to get PCI had fewer deaths, MIs, and strokes, and fewer stent thromboses. However, the larger dose was associated with more major bleeding (2.5% versus 2.0%) (35). Aspirin therapy should continue with clopidogrel.

Prasugrel has a faster onset of action and has a greater degree of platelet inhibition than clopidogrel. In comparing prasugrel with clopidogrel in the form of a 300 mg loading dose, prasugrel has less cardiovascular death nonfatal MI and stroke irrespective if they had PCI or not. Prasugrel does appear to cause more major bleeding and life-threatening bleeding than clopidogrel after the first 3 days of therapy (36). Patients should not receive prasugrel in the ED, as patients with NSTEMI did not have a reduction in death, MI stroke,

urgent revascularization, and BPIIb/IIIa-inhibitor rescue therapy. In fact, pretreatment with prasugrel prior to PCI significantly increased bleeding risk (37). This recommendation is different than those for other agents in this class.

Ticagrelor not only has a faster binding time to platelets and inhibits platelets more than clopidogrel, but it also is a reversible. Ticagrelor showed a significant reduction in the rate of death from vascular causes, AMI, or stroke without an increase in the rate of overall major bleeding when compared to clopidogrel for patients that were schedule for coronary angiogram (38). In patients that were managed conservatively, ticagrelor once again outperformed clopidogrel with reduction of the same indicators as those above with only slightly nonsignificant bleeding rates (39).

In summary, outcomes after STEMI are better with aspirin and adenosine diphosphate receptor antagonists, with either conservative treatment or invasive management. In patients managed conservatively, ticagrelor has shown to be superior to clopidogrel and is therefore recommended. If ticagrelor is not available, then clopidogrel is recommended over prasugrel due to the reduced cost and less potential for bleeding complications. In patients who are being invasively managed, if the drug is being withheld until the coronary anatomy is known, ticagrelor and prasugrel are preferred over clopidogrel. If on the other hand a drug is given at the time of diagnosis, ticagrelor is recommended over clopidogrel. Prasugrel should not be used in this instance.

Glycoprotein IIb/IIIa Inhibitors

Glycoprotein (GP) IIb/IIIa inhibitors act by occupying the receptor responsible for the binding of platelets to fibrinogen, the final common pathway of platelet aggregation. Platelets are then unable to bind together, and aggregation is avoided. The major benefit of this class of drugs is prevention of complications associated with PCI in UA/NSTEMI (40). Abciximab, eptifibatide, and tirofiban are the specific agents that have been associated with a reduction in death and subsequent MI in patients undergoing PCI. For NSTEMI patients that will be getting PCI and have heparin is the anticoagulant

chosen, GP IIb/IIIa inhibitors should be added if the patient is troponin positive. As GPIIa/IIIb are often now given intracoronary with very high platelet inactivation rates, GPIIb/IIIa inhibition is not needed in the ED setting (41,42).

Anticoagulants

Unfractionated Heparin

Unfractionated heparin (UFH) has been one of the mainstay treatments of UA/NSTEMI. An 89% reduction of subsequent MI and a 63% reduction in refractory angina have been documented. Meta-analyses have shown a reduction of death or recurrent MI by 56% in the first 5 days and 33% in the subsequent 2 to 12 weeks (43). These benefits do not continue over the long term; however, there may be a "rebound" phenomenon with increased thrombin activity after heparin is discontinued.

Most trials use a standard 5000-unit loading dose followed by a 1000 U/h infusion. However, this regimen has been found to be inferior to a weight-based formula of an initial bolus of 60 to 70 U/kg (maximum of 5000 U) to be followed by an infusion of 12 to 15 U/kg/h (maximum 1000 U/h). The therapeutic endpoint of adequate anticoagulation is a PTT between 60 and 80 seconds.

There are several disadvantages of UFH. The bioavailability is poor; frequent monitoring of the PTT is necessary; and severe heparin-induced thrombocytopenia occurs in 1% to 2% of patients.

Low-Molecular-Weight Heparin

Low-molecular-weight heparin (LMWH) is an attractive alternative to UFH, as it addresses the shortcomings of UFH and is associated with a much lower incidence of severe heparin-induced thrombocytopenia.

Multiple studies have compared LMWH and UFH. The odds ratio for MI or death was similar with both UFH, and as with UFH, there was no benefit to long-term use of LMWH. Moreover, there is no difference in recurrent angina or major or minor bleeding between the two drugs. However, LMWH significantly reduced the risk of MI,

revascularization, and thrombocytopenia compared to UFH (44). Dosages and other information about LMWH can be found in Table 82.11.

TABLE 82.11
Low-Molecular-Weight Heparins in Treatment of UA/NSTEMI

Agent	Dosage
Enoxaparin	1 mg/kg subcutaneously every 12 h (maximum of 100 mg)
Dalteparin	120 international units/kg every 12 h (maximum of 10,000 international units)

Though patients on LMWH have overall more bleeding complications, most are minor and do not require treatment; major bleeding has not been shown to be statistically different from UFH.

Fondaparinux, a new LMWH that has FDA approval for the prevention and treatment of deep venous thrombosis associated with orthopedic procedures, may have an advantage over enoxaparin in terms of bleeding complications. Major bleeding was reduced by almost half when compared to enoxaparin with similar rates of death, recurrent MI, or refractory ischemia (45).

For NSTEMI patients who are managed with a conservative strategy, the recommendation is fondaparinux or enoxaparin over UFH or bivalirudin. Fondaparinux is preferred if there is a higher risk of bleeding. For NSTEMI patients who are managed invasively, fondaparinux would be recommended as the initial anticoagulant.

Bivalirudin

Bivalirudin is an example of a direct thrombin inhibitor that inactivates clot-bound thrombin. Clot-bound thrombin is a stimulus for thrombosis, so this inactivation will overcome some of the limits of standard heparin therapy.

Bivalirudin has been shown to be equivalent to GP IIb/IIIa inhibitors combined with LMWH in reducing death and recurrent MI and urgent need for revascularization in patients undergoing PCI. The main benefit is that the rate of major bleeding in these patients

is about half that associated with the GP IIb/IIIa inhibitor and LMWH group. Bivalirudin may be an attractive alternative to GP IIb/IIIa inhibitor and LMWH in light of the decreased bleeding rates and the simplicity of monotherapy (42). Bivalirudin has not been compared with fondaparinux.

Angiotensin-Converting Enzyme Inhibitors

The use of angiotensin-converting enzyme (ACE) inhibitors in the acute management of MI is a subject of debate. In the NSTEMI patient, indications for administration of ACE are clinical heart failure, pulmonary congestion, or a left ventricular ejection fraction $<40\%$. Outcomes appear to be best when administration occurs within the first 24 hours of ischemia. Oral medication is recommended owing to the risk of hypotension with IV administration. ACE inhibition in these patients results in a relative reduction of mortality by 7%, with a number-needed-to-treat of about 200 (46). Patients who have the greatest benefit are those with large anterior MI and clinically apparent heart failure. It is felt to be prudent to wait to administer this oral medication until few hours after presentation.

Reperfusion Therapy

Thrombolytics

There is no benefit to and there is strong recommendation against adding thrombolytic therapy to standard treatment in patients with UA/NSTEMI. Angiographic data show that the infarct-related artery in these patients is not occluded 60% to 85% of the time. The mechanism of ongoing ischemia and microinfarction is more likely to be embolization rather than complete vessel occlusion. Angiography after thrombolytic treatment has not shown a statistically significant improvement in flow compared to patients who did not receive thrombolysis. Furthermore, there was no difference in clinical parameters. Fatal and nonfatal MI occurred more frequently with thrombolytics and, not surprisingly, there was a trend more hemorrhagic complications (30).

Percutaneous Coronary Intervention

PCI therapy has shown tremendous promise, with a reduction of death, recurrent MI, and urgent need for revascularization in STEMI patients. There is limited data on PCI in NSTEMI patients.

UA/NSTEMI patients who should undergo immediate PCI include those with hemodynamic instability, refractory symptoms despite maximal medical therapy, refractory dysrhythmias secondary to ischemia, mechanical complications of ischemia (such as acute mitral regurgitation), and progressive symptoms in patients who had had prior PCI or CABG.

Patients without any of these high-risk characteristics can be managed in one of the two ways: an early invasive strategy that utilizes PCI or a conservative strategy that does not include PCI. Patients with ST depression, older than 65, and, most important, with troponin elevation seem to benefit most from an invasive approach, the primary benefit of which appears to be a reduction in subsequent MI (30).

A number of randomized clinical trials have compared the early invasive strategy to a conservative strategy in patients with a UA/NSTEMI. The rate of death or MI was 18% lower in the invasive group in these trials, primarily owing to the decrease in subsequent MI. There was a slight increase in immediate in-hospital mortality (procedural complication) that was more than compensated for by a significant reduction in mortality after discharge from the hospital. Several trials found that patients with an elevated troponin, with ST depression, and older than 65 derived particular benefit from the early invasive approach. Other studies have highlighted a strategy of selective invasive therapy in which patients are initially managed medically and stabilized before going for PCI. These trials found no difference in composite endpoints at 1 year between an early invasive and a selective invasive strategies (47).

In summary, patients with high-risk stratification for NSTEMI (see above) benefit from an early invasive approach, although optimal timing has yet to be determined.

Interventions in the Patient with ST-Segment Elevation MI

Acute STEMI is most commonly caused by abrupt thrombotic occlusion of a coronary artery at the site of an atheromatous plaque. Therapeutic interventions in this setting are directed toward reopening the occluded coronary artery (reperfusion) and decreasing myocardial oxygen demand.

Reperfusion Therapy

All STEMI patients should undergo rapid evaluation for reperfusion therapy and have a reperfusion strategy implemented promptly. The restoration of flow can be achieved by pharmacologic means (fibrinolysis or thrombolysis), by PCI with balloon angioplasty and coronary stent placement, or by surgical measures. The goal for all methods is rapid reperfusion to minimize myocardial necrosis.

Percutaneous Coronary Intervention

When it is available in a timely manner, high-quality PCI is preferred over thrombolytic therapy. Death, nonfatal reinfarction, and hemorrhagic stroke occur less often in patients receiving PCI, compared to those receiving thrombolytic therapy. PCI also has less short-term mortality at 30 days, less nonfatal reinfarction, and less hemorrhagic stroke. Should primary PCI occur with any acute STEMI, the patient can undergo the procedure in a timely manner by persons skilled in the procedure. Timely was defined as within 90 minutes or less from first medical contact for patients presenting or being transported to a PCI-capable hospital or 120 minutes or less for patients who present or are transported to a non-PCI-capable hospital with subsequent transport to a PCI-capable hospital (48). In the absence of contraindications, fibrinolytic therapy should be given to patients with STEMI and onset of ischemic symptoms within the previous 12 hours when it is anticipated that primary PCI cannot be performed within 120 minutes of first medical contact. Thrombolytics may even be given if there is clinical and/or ECG evidence of ongoing ischemia within 12 to 24 hours of symptom

onset and a larger area of myocardium at risk or hemodynamic instability.

In STEMI patients with delayed presentations of 12 to 24 hours, PCI is recommended over thrombolytics, especially if patients have symptoms of heart failure, ischemia, or malignant dysrhythmias (49).

The standard of care in STEMI patients presenting to the ED is to initiate PCI with balloon inflation within 90 minutes from arrival in the ED. Multiple measures can be instituted to lower the time for PCI (Table 82.12).

TABLE 82.12
Measures to Lower the Time for Percutaneous Coronary Intervention

Factors Shown to Reduce Door-to-Balloon Times in PCI	Time Saved (min)
Expectation of PCI team to arrive within 20 min	19.3
Use of prehospital ECG to activate PCI team	15.4
On-site cardiologist	14.6
Single call to activate PCI system	8.6
Weekly feedback to the emergency department and PCI lab	8.6
Emergency physician activation of the PCI team	8.2

ECG, electrocardiograph; PCI, percutaneous coronary intervention

Reproduced with permission from Bradley EH, Herrin J, Wang Y, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med.* 2006;355(22):2308–2320.

Given the superiority of PCI over thrombolytics, consideration must be given to the issue of patient transfer from non-PCI-capable centers to PCI-capable centers. The impact of delay can be substantial. Each half-hour delay of reperfusion therapy is associated with an increase of 1.075 in the relative risk of 1-year mortality (49).

Facilitated PCI refers to a strategy of planned immediate PCI after administration of thrombolytic therapy. Despite the theoretical advantages of this two-tiered approach, facilitated PCI has not demonstrated any benefit in reducing infarct size or improving outcomes (50).

Rescue PCI refers to patients who have failed thrombolytic therapy. Patients who do not show a 50% reduction in ST-segment elevation within the first 1 to 3 hours have been shown to have decreased myocardial blood flow, increased infarct size, and a poorer prognosis. Patients with continuing symptoms of ischemia, or continued or new ischemic changes on the ECG, also have a worse prognosis. Patients who fail thrombolytic therapy have a 5-fold increase in mortality. PCI in this setting has resulted in higher rates of early infarct arterial patency, improved regional infarct-zone wall motion, and fewer adverse in-hospital events compared to a deferred PCI strategy or medical therapy alone. As time is an important factor, patients receiving thrombolytic therapy must be observed closely. If there has not been a reduction in ST-segment elevation within the first few hours, or if there is any hemodynamic or electrical instability or persistent ischemic symptoms, rescue PCI should be instituted.

Thrombolytics

Although PCI should be the primary reperfusion strategy, thrombolytics do improve survival in patients with STEMI and are indicated if PCI is unavailable. Intravenous thrombolysis improves coronary flow at 90 minutes after administration in 50% to 85% of patients. There is a reduction on average of 18 deaths per 1000 patients treated, and this survival benefit remains evident even after 10 years. The greatest benefits occur when thrombolytics are administered within 2 hours of symptom onset; there is a decline of approximately 1.6 lives saved per 1000 patients treated for every hour of delay beyond 2 hours, but beyond 12 hours from symptom onset, the benefit of thrombolytic therapy is minimal. This has led to extensive education, preparation, and continuous quality improvement measures to expedite thrombolytic administration (48).

Streptokinase is the prototypical thrombolytic and still has clinical utility to this day. The addition of streptokinase to STEMI treatment regimen reduced the relative risk of death by almost 25%. The adverse effects of streptokinase include bleeding, allergic reactions, and hypotension. Major bleeding is rather uncommon, and the risk of

hemorrhagic stroke is <1% in patients younger than 70 and 1.6% in patients older than 70.

Streptokinase induces a global lytic state within the body, whereas fibrin-specific thrombolytics act on the fibrin-rich organized clot. The most commonly used fibrin-specific thrombolytics are alteplase (tPA), reteplase, and tenecteplase. tPA has a short half-life (3 to 4 minutes) and is not associated with allergic reactions or hypotension. The difference in reduction in absolute mortality between tPA and streptokinase is about 1%.

All the fibrin-specific thrombolytics have similar rates of morbidity and mortality. Major hemorrhagic events occur in 2% to 3% of patients, and intracranial hemorrhage in about 1%. The intracranial bleeding usually occurs within the first 24 hours after administration. Of the patients who have a major bleeding event, there is a 20% mortality rate, and this accounts for 10% of all hospital deaths (51). Predictors of higher rates of intracranial hemorrhage are age older than 75, black race, female gender, prior history of stroke, systolic blood pressure >160 mm Hg, and weight <65 kg for women and <80 kg for men. If one or more of these factors are present and the patient does not have access to PCI, streptokinase should be strongly considered for reperfusion rather than fibrin-specific thrombolytics, as it is associated with a risk of hemorrhagic stroke that is about half as great as the fibrin-specific agents.

There are major limitations to thrombolytic therapy. Thrombolytics have their major benefit when they are given early in the course of STEMI, with a delay of <3 hours. Although the timely use of thrombolytics restores patency in up to 90% of infarct-related vessels, only 50% are restored to normal patency. After what appears to be successful treatment, early recurrence of ischemia or ST-segment shifts have been observed in 20% to 30% of patients, with complete coronary reocclusion and reinfarction in some individuals. Around 20% to 30% of patients have contraindications to thrombolytic therapy (Table 82.13).

TABLE 82.13
Absolute Contraindications to Thrombolytic Therapy

Active internal bleeding
CNS neoplasm, AV malformation, or aneurysm
CNS procedure or CVA within 2 mo
Severe uncontrolled hypertension (over 200/130 or complicated by retinovascular disease or encephalopathy)
Known bleeding diathesis
MI due to aortic dissection
Allergy to either streptokinase or anistreplase, if streptokinase or anistreplase will be used
Relative contraindications to thrombolytic therapy
Age older than 75
Cerebrovascular disease
Pregnancy or early postpartum
Recent major surgery (<10 d), noncompressible vessel puncture, or organ biopsy
Recent trauma, including CPR of over 2-min duration
Recent GI bleeding or active ulcer disease (<10 d)
Acute pericarditis or subacute bacterial endocarditis
Septic thrombophlebitis
High likelihood of left heart thrombus (e.g., mitral stenosis with atrial fibrillation)
Known coagulation defects, including anticoagulant therapy
Significant liver dysfunction
Conditions associated with bleeding risks, such as diabetic retinopathy.
Menstruation
Terminal cancer or other end-stage disease
Recent streptococcal infection, if streptokinase or anistreplase will be used

CVA, cerebrovascular accident; MI, myocardial infarction.

Anti-Ischemic Therapies

Nitroglycerin

Nitrates have an important role in the management of patients with STEMI, despite the absence of a mortality benefit. It can be of value in reducing pain due to myocardial ischemia, improving symptoms of pulmonary congestion, and lowering blood pressure in hypertensive patients.

Care should be taken in patients with systolic blood pressure <90 mm Hg, marked bradycardia, tachycardia, or known or suspected RVMI. The initial dose of NTG is 0.4 mg sublingually and repeated as needed, with conversion to an intravenous drip if there is continuing pain or a need to control hypertension.

Morphine

Pain management should be directed toward acute relief of ischemic symptoms and general relief of anxiety and apprehension, thus reducing circulating catecholamines. An initial dose of 2 to 4 mg can be administered and then titrated accordingly for symptom relief.

Beta Blockers

The current literature is far from unanimous regarding the use of beta blockers in STEMI. Early studies showed that in patients who had received reperfusion therapy, the rate of death, recurrent reinfarction, and intracerebral hemorrhage was less in patients receiving beta blockers. These earlier studies have come into question, however. Although early IV beta blockade has become an accepted ancillary treatment in patients undergoing thrombolysis for STEMI, there is no convincing evidence of a mortality benefit. The most recent data suggest that the benefit of beta blockade by reduction of ventricular dysrhythmias and recurrent infarction is completely offset by the incidence of cardiogenic shock associated with beta blockade (31). There are no studies evaluating beta blockade with primary PCI, but the general recommendations are the same as for patients receiving thrombolytics.

It is reasonable to administer IV beta blockers to STEMI patients with tachycardia and hypertension. Intravenous beta blockers should not be administered in patients with the following: (i) signs of heart failure, (ii) evidence of a low output state, (iii) increased risk for cardiogenic shock (age >70, systolic blood pressure <120 mm Hg, sinus tachycardia >110 bpm or heart rate <60 bpm, and increased time since onset of symptoms of STEMI), or (iv) other relative contraindications (PR interval >0.24 seconds, second- or third-degree heart block, active asthma, or reactive airways disease). Oral

beta blocker therapy should be initiated in the first 24 hours after presentation to the hospital with ACS, unless there are contraindications.

Antiplatelet Therapy

Aspirin

Aspirin should be given to the patient with suspected STEMI as early as possible and continued indefinitely, regardless of the strategy for reperfusion and regardless of whether additional antiplatelet agents are administered. The relative risk reduction of mortality for this easily administered intervention is 23%. Doses ranging from 160 to 325 mg have been shown to be effective in STEMI. Aspirin reduces reocclusion and reduces ischemic events after fibrinolytic therapy with either fibrin-specific or fibrin-nonspecific agents (48).

Adenosine Diphosphate Receptor Antagonists

This class of medications includes clopidogrel and prasugrel. There are currently no trials evaluating clopidogrel in addition to aspirin in the context of STEMI, but the NSTEMI trials have been extrapolated to STEMI patients. Clopidogrel has been shown to result in a relative risk reduction of 36% over placebo in STEMI patients (52). The impact of clopidogrel on STEMI patients is quite dramatic with a benefit showing that for every 1000 STEMI patients, pretreatment with clopidogrel prevented nine cardiovascular events (31).

For patients undergoing PCI, clopidogrel has been compared to prasugrel in STEMI patients and prasugrel has been shown to have less mortality, nonfatal MI, and nonfatal stroke primarily driven by the reduction in subsequent MI. There has also been shown to be less stent thrombosis with prasugrel with no increased risk of bleeding (53). The dosing for clopidogrel for patients receiving PCI is 600 mg, which is increased from the previous recommendation of 300 mg due to a reduction of MACE. Prasugrel is recommended to have a loading dose of 60 mg (54).

Ticagrelor differs from clopidogrel and prasugrel in that it binds reversibly rather than irreversibly and has a more rapid onset of

action. It is similar to prasugrel in that it has a more intense platelet inactivation than clopidogrel. Patients given a 180 mg loading dose of ticagrelor were less likely to die, have an MI or stroke than those given clopidogrel (38).

The timing for platelet inactivation is inherent to the agent chosen. Clopidogrel has been shown to take 8 hours for acceptable platelet inactivation, whereas prasugrel and ticagrelor are at 2 hours for similar parameters (55).

Therefore for patients receiving PCI for STEMI either prasugrel or ticagrelor have advantages compared to clopidogrel.

For patients receiving fibrinolytics, clopidogrel is recommended over prasugrel and ticagrelor simply because clopidogrel is the only medication that has been studied in this setting. The dosage in this setting is 300 mg for those who are less than 75 years and 75 mg for older patients (48).

In patients that are unable to receive either PCI or thrombolytics, ticagrelor is recommended over clopidogrel or prasugrel (48).

Glycoprotein IIb/IIIa Inhibitors

The major initial indication for the use of GP IIb/IIIa inhibitor therapy in STEMI was for patients that were having immediate PCI. These initial recommendations were made prior to the use of potent $P2Y_{12}$ inhibitors like prasugrel and ticagrelor. Prior to standard use of the $P2Y_{12}$ inhibitors GP IIb/IIIa inhibitors (primarily abciximab) did lower the absolute rate of death for PCI patients by 1%. Further analysis of many trials showed that although more patients achieved TIMI 3 flow (normal) at the time of PCI, final TIMI flow rates or any other major clinical outcomes were no different. The limited studies in patients with $P2Y_{12}$ inhibitors being utilized have given mixed results showing either no benefit or little benefit to the addition of GP IIb/IIIa inhibitors. It should be noted that, GP IIb/IIIa inhibitors, originally given systemically, are now given by the intracoronary route as this has been shown to reduce infarct size and mortality (56). The most recent recommendation for patients at low risk for bleeding getting primary PCI after being given heparin and either a

$P2Y_{12}$ inhibitor or not is the patients should have a GP IIb/IIIa inhibitor added but only after diagnostic angiography assures that the patient does not need immediate coronary arterial bypass grafting. Therefore, routine administration of GP IIb/IIIa inhibitors in the ED should be avoided. In the context of bivalirudin being used as a sole agent for ACS in patients at high risk for bleeding, it is a moot point, as heparin and GP IIb/IIIa is not recommended in this clinical context.

The addition of GP IIb/IIIa inhibitors to thrombolysis in the primary treatment of STEMI is not recommended due to no increase in survival and an elevated bleeding risk especially in patients over the age of 75 (48).

Anticoagulants

Heparin: Unfractionated and Low-Molecular Weight

Anticoagulant therapy is a mainstay in the management of STEMI due to its ability to prevent vessel closure in patients receiving PCI with or without stents. Several trials have compared UFH to LMWH. Enoxaparin and dalteparin are the two most studied LMWH. LMWH has been shown to have less death or recurrent MI but slightly more major bleeding at 30 days as compared to UFH (57). The weight-adjusted dose of UFH varies depending on the reperfusion strategy. For PCI, a weight-adjusted bolus of 70 to 100 U/kg (reduced to 50 U/kg if GP inhibitors have been instituted) should be given, followed by an infusion to keep the PTT at 250 to 350 seconds (200 seconds if GP inhibitors are also used) (48). For patients receiving the recommended LMWH, the dose of enoxaparin for patients younger than 75 years is an initial IV bolus dose of 30 mg followed 15 minutes later by subcutaneous injections of 1.0 mg/kg every 12 hours. For patients older than 75 years of age, the bolus dose is eliminated, and the subcutaneous dose is 0.75 mg/kg every 12 hours.

Fondaparinux, a newer agent in this class, has shown some promise, with reductions in death and reinfarction beyond that seen with other LMWHs and with UFH (58). The dose of fondaparinux in

STEMI is 2.5 mg IV, followed by subsequent subcutaneous injections of 2.5 mg daily.

In patients receiving thrombolytic therapy, the recommendation for heparin administration depends on which fibrinolytic agent is used. The nonspecific fibrinolytic agents (e.g., streptokinase) produce a systemic coagulopathy and are anticoagulants themselves, so heparinization is not required. For fibrin-specific thrombolytics (tPA, reteplase, and tenecteplase), there is less systemic anticoagulant activity and even less procoagulant activity of the breakdown products, which makes the rationale for heparinization evident. Patients undergoing reperfusion with fibrinolytics should receive anticoagulant therapy for a minimum of 48 hours, and preferably for the duration of the hospitalization, up to 8 days. If fibrin-specific thrombolytic therapy is utilized, a 60 U/kg bolus dose followed by an infusion of 12 U/kg/h (maximum of 4000 U bolus and 1000 U/h infusion) is recommended. The data for LMWH in STEMI shows that it is similar to UFH in safety and efficacy and is preferred for the above listed reasons.

Angiotensin-Converting Enzyme Inhibitors

Patients with STEMI in the anterior precordial leads, evidence of heart failure, or a left ventricular ejection fraction of $<40\%$ should receive an oral ACE inhibitor within the first 24 hours of therapy. Caution is necessary to avoid causing hypotension in the first few hours after the infarction. Oral ACE inhibitors should not be initiated in patients who have received vasoactive medications until hemodynamic parameters have stabilized after treatment. An angiotensin II receptor blocker can be given either alone, if the patient is intolerant of ACE inhibition, or in addition to an ACE inhibitor.

Complications of Acute Ischemia or Infarction

Dysrhythmias

Cardiac rhythm disturbances, most typically of ventricular origin, are common during UA or acute infarction. Ventricular tachycardia and ventricular fibrillation can occur without warning in ACS patients.

Premature ventricular contractions are noted in the vast majority of patients who experience AMI. In the past, frequent, multifocal, or early diastolic premature ventricular contractions were routinely treated with antidysrhythmic medications to reduce the risk of development of hemodynamically unstable rhythms such as ventricular tachycardia and ventricular fibrillation. However, pharmacologic therapy is reserved now for patients with sustained ventricular dysrhythmias. Prophylactic therapy has been shown to increase the risk of bradycardia and asystole in ACS patients but to have no impact on mortality.

Accelerated idioventricular rhythms occur in approximately one-fourth of STEMI patients, most commonly during reperfusion therapy, but with minimal hemodynamic effects. Sinus tachycardia is the most common supraventricular dysrhythmia; atrial flutter and atrial fibrillation can also be seen. Sinus bradycardia occurs in 30% of myocardial infarctions, especially when ischemia affects the conduction pathways; sinus bradycardia should be treated only if hemodynamic compromise is present, as a slow heart rate is protective in ischemia.

Conduction Disturbances

Mortality rates are markedly higher for patients who develop complete AV block. Heart blocks are usually related to ischemia of the conduction system, increased vagal tone, or a combination of the two. Patients with conduction disturbances may require emergent pacing to correct hemodynamic abnormalities. Transcutaneous pacing is the most readily available modality for rapid restoration of heart rate (Table 82.14).

TABLE 82.14
Indications for Placement of Emergent Transcutaneous Patches and Active Transcutaneous Pacing

Sinus bradycardia with symptoms of hypotension that is unresponsive to drug therapy
Symptomatic Mobitz II second-degree AV block
Symptomatic third-degree AV block
Bilateral BBB (alternating BBB, or RBBB and alternating left anterior fascicular block (LAFB), left posterior fascicular block (LPFB)[a]
Newly acquired or age indeterminate LBBB, LBBB and LAFB and LPFB[a]
RBBB or LBBB and first-degree AV block[a]

AV, atrial ventricular; BBB, bundle branch block; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LPFB, left posterior fascicular block; RBBB, right bundle branch block.
[a]Apply patches and attach to system but may only need to activate if sudden symptomatic or hemodynamic compromise.
Reproduced with permission from Yusuf S, Mehta SR, Chrolavicius S, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: The OASIS-6 randomized trial. *JAMA*. 2006;295(13):1519–1530.

Ventricular Dysfunction

The left ventricle undergoes dynamic changes with any ischemic insult. AMI leads to dilation of the left ventricle, expansion of ischemic tissue, and thinning of the ventricular walls. These changes may result in heart failure and a subsequent poorer prognosis.

Cardiogenic Shock

The most severe form of ventricular dysfunction leads to inadequate forward flow and decreased perfusion of vital organs. Patients who develop cardiogenic shock usually have had a large anterior MI or have diffuse disease with multiple areas of myocardial dysfunction. Those younger than age 75 should immediately undergo PCI, as this has been shown to save 13 lives per 1000 patients (59). Patients older than 75 should also undergo PCI, provided they are suitable candidates for revascularization. Rapid transfer to a facility where PCI can be performed is indicated. In patients who present in cardiogenic shock within 3 to 6 hours of symptom onset and whose transport is expected to be delayed, fibrinolytic therapy may be initiated with close consultation from the accepting cardiology team (60).

Pericarditis

STEMI patients may develop pericardial friction rubs or pericardial pain. Infarction pericarditis occurs soon after AMI and is transient.

Most cases of infarction pericarditis have a benign course. The majority of rubs are audible in the first few days after an AMI. Postcardiac injury syndrome, often called *Dressler's syndrome,* is a late complication, developing weeks to months after an AMI. These patients develop pleuritic chest pain, a pericardial friction rub, fever, leukocytosis, and sometimes pulmonary infiltrates or pleural effusion. Most of the symptoms resolve with nonsteroidal anti-inflammatory drugs; rarely, corticosteroids may be required.

Left Ventricular Aneurysm

Local paradoxical expansile wall motion or dyskinesis has been termed *left ventricular aneurysm.* This occurs weeks to months after an AMI. Patients with large LV aneurysm are more prone to congestive heart failure, arterial embolism, and ventricular dysrhythmias.

Recurrent Chest Pain

Recurrent ischemic symptoms may develop in one-fourth or more of patients with AMI, especially when thrombolytics are used. The only way to determine whether medical or reperfusion therapy has failed is by prompt coronary angiography.

CRITICAL INTERVENTIONS

- Obtain an ECG quickly in patients presenting with symptoms consistent with myocardial ischemia.
- Initiate continuous cardiac monitoring to avoid missing significant cardiac dysrhythmias.
- Administer aspirin to all patients with potential ACS, unless there are specific contraindications such as aspirin allergy.
- Treatment decisions depend on risk stratification based on history and physical examination, ECG and serum cardiac markers, myocardial imaging, stress testing, and rest imaging.
- Recognize ST-segment elevation so that reperfusion therapy can be initiated promptly.
- Obtain informed consent for patients undergoing reperfusion therapy.
- Initiate anticoagulants and antiplatelet agents early in the course of ACS, as indicated.

DISPOSITION

Patients with suspected ACS should be admitted to the hospital. Patients with UA of MI should be admitted to an intensive care setting for close monitoring and treatment. When acute MI or refractory anginal symptoms are suspected, the consulting cardiologist should be contacted as soon as possible to facilitate medical management and, if indicated, interventional therapy. Patients often present with a low risk for ACS, however, and must be stratified for risk of short-term morbidity and mortality.

Low-risk patients are good candidates for admission into an observation unit for an accelerated protocol to determine whether ACS is present. Patients who have symptoms suggestive of myocardial ischemia but a nondiagnostic ECG and normal cardiac markers and no recurrent symptoms are candidates for stress testing. The safety of observation units for these low-risk patients has been established, and there is significant economic advantage to such an abbreviated hospital stay. Patients can be tested by standard treadmill exercise stress testing, myocardial scintigraphy at rest and during exercise, stress echocardiography, or CT coronary angiography. The sensitivities, specificities, and positive and negative predictive values of these test have been determined largely in the population of patients with a moderate-to-high pretest probability of CAD, so care must be used in their application to a low-risk population. Patients who have positive evaluations in the observation unit should be admitted to the hospital for further testing or management.

Stress echocardiography, to identify regional wall motion abnormalities, is another modality that can be used in low-risk patients. A negative dobutamine stress echocardiographic test is reported to have a negative predictive value of 99%.

Thallium and technetium sestamibi testing can be used for stratifying low-risk patients as well. These agents are taken up by the myocardium in proportion to regional blood flow and are capable of demonstrating myocardial perfusion defects. Negative tests in low-risk patients make them suitable for discharge, as they have less than a 1% chance of experiencing a cardiac event in the subsequent year.

Patients who are discharged from the ED with atypical or low-risk chest pain should have prompt follow-up arranged to further delineate and treat the etiology.

Common Pitfalls

- Failing to admit patients in whom the diagnosis of ACS is uncertain
- Failing to consider myocardial ischemia equivalents such as shortness of breath and syncope in the risk stratification of ACS patients
- Assuming that a negative or nondiagnostic ECG excludes ACS
- Assuming that negative biomarkers exclude ACS. Negative biomarkers can only exclude myocardial infarction. Cardiac markers are not released in UA.
- Failing to check posterior and right-sided ECG leads in patients with abnormal inferior and anterior precordial ST findings on ECG
- Failing to obtain serial ECGs to detect ACS in patients with a normal or nondiagnostic initial ECG
- Failing to appreciate that the 1-year mortality of STEMI and NSTEMI are the same
- Failing to consider the diagnosis of ACS in women. ACS is the leading cause of death in women.
- Failing to consider other potentially lethal diagnoses such as aortic dissection and pulmonary embolism in patients with chest pain

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CHAPTER 83

Congestive Heart Failure and Cor Pulmonale

Christopher I. Doty

CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) is a complex clinical syndrome that represents a broad spectrum of disease stretching from stable pedal edema to fulminant cardiogenic shock. CHF can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. Ultimately, CHF is the inability of the heart to pump enough blood to meet the body's needs. Often this manifests as increased left ventricular filling pressures. The common causes of CHF are listed in Table 83.1.

TABLE 83.1
Functional Classification and Causes of Left Heart Failure

Contractile Dysfunction
Ischemic heart disease
Idiopathic dilated cardiomyopathy
Myocarditis

Systolic Pressure Overload
Aortic stenosis
Systemic hypertension
Left ventricular outflow tract obstruction

Systolic Volume Overload
Aortic regurgitation
Mitral regurgitation

Restricted Diastolic Filling
Mitral stenosis
Left atrial myxoma
Hypertrophic cardiomyopathy

High-Output States
Hyperthyroidism
Anemia
Large arteriovenous fistula
Paget disease of the bone

Acute cardiogenic pulmonary edema or acute decompensated heart failure (ADHF) is characterized by the development of dyspnea associated with the rapid accumulation of fluid within the lungs' interstitial and alveolar spaces, which is the result of these acutely elevated left ventricular filling pressures (1).

The burden of CHF morbidity and mortality for the US health care system is staggering with over 6 million patients in the United States alone. The yearly incidence is over 500,000 new patients, making CHF a very deadly disease (2). The prognosis after the onset of clinical signs and symptoms of CHF has not changed substantially over the last 15 years; the 1-year mortality rate for severely symptomatic CHF (class III or IV) is about 45% (3,4). A new diagnosis of CHF carries a 5-year mortality risk of approximately 50%, which is worse than most solid tumors (1).

CHF continues to be predominantly a disease of the elderly. It is estimated that 80% of patients who present to the emergency

department (ED) with ADHF will be hospitalized, and repeat admissions are very common.

In CHF patients, there are three principal compensatory mechanisms that maintain systemic perfusion: (a) the Frank–Starling principle that relates preload to contractile force, (b) ventricular hypertrophy, and (c) central neural and peripheral neurohumoral responses to maintain systemic perfusion pressure and effective intravascular volume. These compensatory responses, unfortunately, are often maladaptive. These responses may further impede ejection of blood from the compromised ventricle. Therefore, manipulating the compensatory response to the fall in cardiac output (CO) (e.g., by the use of β-blockers, angiotensin-converting enzyme inhibitors [ACEIs]) has become a therapeutic focus in the management of chronic CHF (5).

The neurohumoral compensatory mechanisms for CHF actually result in an increase in systemic vascular resistance (SVR) and maintenance of effective intravascular volume through increased endogenous levels of biogenic amines, angiotensin, aldosterone, arginine vasopressin, B-type natriuretic peptide (BNP), prostaglandin E2, and prostacyclin. This increase in SVR and intravascular volume exacerbates the baseline pathology in CHF and worsen the patients symptoms. The pathophysiology of cardiogenic pulmonary edema is given in Figure 83.1.

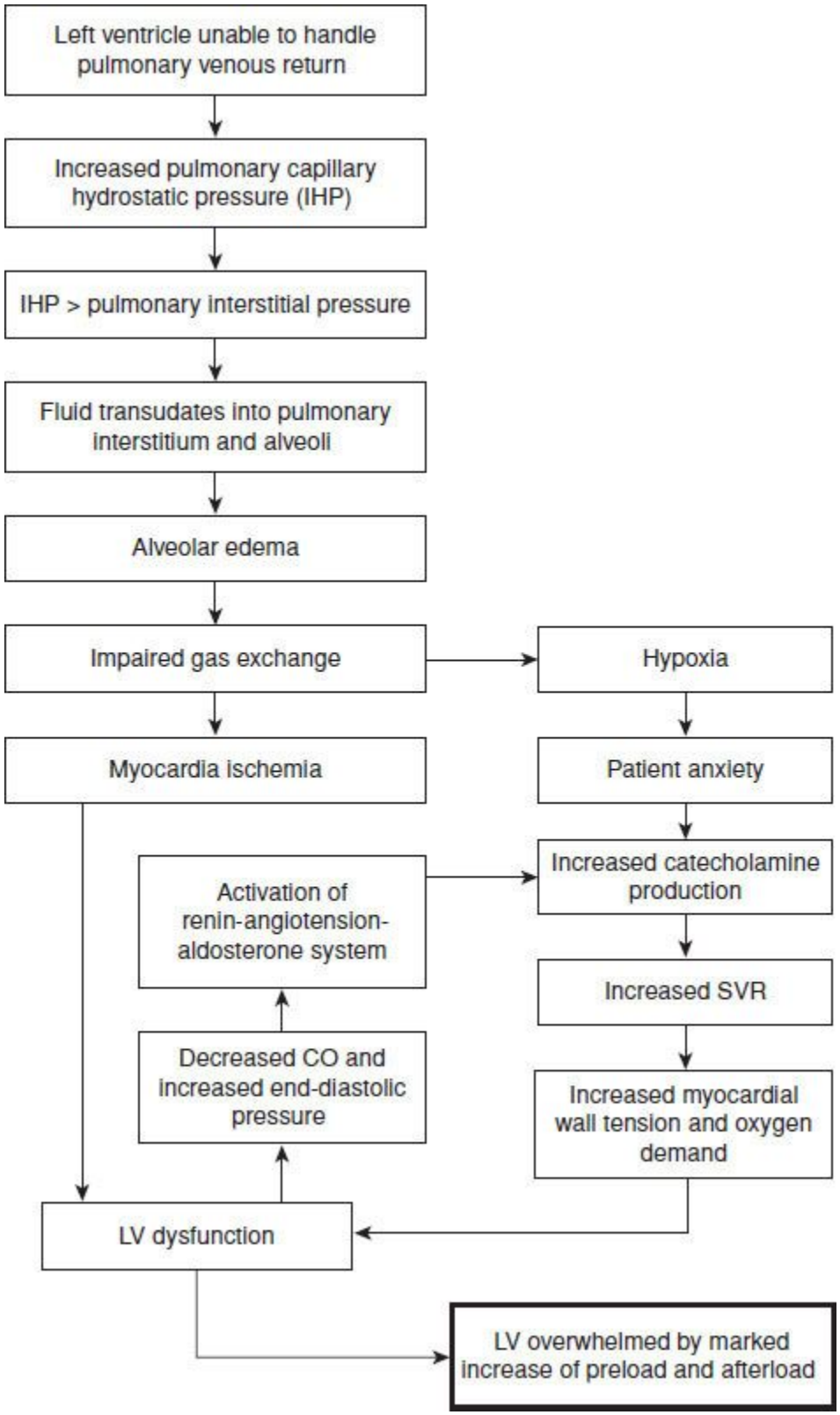

FIGURE 83.1 Pathophysiology of cardiogenic pulmonary edema.

CLINICAL PRESENTATION

The clinical symptoms of CHF usually present through one of two mechanisms. The first is by increasing of hydrostatic pressures in capillary beds. Often, this is in the capillary beds of the lung where the increased hydrostatic pressures in the capillaries lead to transudation of fluid into the alveolar air spaces. This inhibits effective gas exchange and leads to the feeling of dyspnea and to hypoxia. This increased hydrostatic pressure may also present in the capillaries of the systemic circulation. This would be most evident in dependent areas and is usually manifested by pedal edema, or in severe cases, ascites.

The second mechanism of clinical symptoms is through a decrease in CO or forward flow from the heart. This leads to the classic signs and symptoms of a low flow state. These include weakness, altered mental status, hypertension, and easy fatigue. Often these two mechanisms will often present simultaneously.

Patients with left-sided heart failure (LHF) usually present with dyspnea and exercise intolerance, whereas patients with right-sided heart failure often present with peripheral edema and ascites. No single feature or physical examination finding reliably distinguishes patients with CHF resulting from systolic dysfunction (decreased ejection fraction) from those with diastolic dysfunction (increased left heart filling pressures and pulmonary capillary wedge pressures [PCWPs]). It is important to remember that only a little over half of CHF patients have a systolic dysfunction (6). Patients with systolic dysfunction often have increased LV filling pressures owing to a decrease in compliance and a decrease in ejection fraction.

Rales, one of the classic findings in heart failure, may also be found in pneumonia, interstitial lung disease, ARDS, or chronic obstructive lung disease. Wheezing, or “cardiac asthma,” is caused by interstitial edema and is common in ADHF. However, wheezing has poor sensitivity for CHF as it is present in many other diseases.

Acute pulmonary edema is LHF in its most extreme form and is a life-threatening emergency. Dyspnea and respiratory distress are the major presenting symptoms. A past history of heart failure has a

specificity of 90% for the present dyspneic episode being caused by CHF, and patients with prior heart failure are approximately four times more likely to have ADHF when presenting to the ED with acute dyspnea (6). The typical patient is anxious, agitated, diaphoretic, in a tripod position, and will often appear as if they are in shock. There is usually hypertension caused by intense vasoconstriction, tachypnea hypoxia, and tachycardia. Clinical findings usually include (a) rales, (b) peripheral edema, (c) jugular venous distention, (d) a third heart sound, and (e) sometimes a fourth heart sound. Peripheral edema and hepatomegaly may not be seen when acute decompensation develops abruptly, unless it is superimposed on chronic fluid overload.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes pneumonia, asthma exacerbation, cor pulmonale, chronic obstructive pulmonary disease exacerbation, pulmonary embolism, and other conditions that cause dyspnea. Volume-overloaded states such as renal failure, nephrotic syndrome, and hypoproteinemia (e.g., due to liver failure) may also mimic heart failure. Table 83.2 outlines conditions that may precipitate or worsen heart failure.

TABLE 83.2
Precipitating Causes of Heart Failure

Cardiac	Noncardiac
Myocardial ischemia or infarction	Pulmonary embolism
Dysrhythmias	Increased metabolic demand (infection, trauma)
Noncompliance with therapeutic regimen (e.g., increased sodium intake, failure to restrict fluid intake, noncompliance with medications)	Systemic illness (e.g., severe hypertension, severe anemia, thyrotoxicosis, heavy alcohol consumption)
Acute or chronic valvular heart disease	Drugs: cocaine, amphetamines, excessiveness use of bronchodilators
	Pregnancy

ED EVALUATION

A thorough history and physical examination is the best diagnostic tool the emergency physician has in evaluating a patient for ADHF. ADHF often presents as a muddled picture in patients with the clinician having to weigh several diagnostic possibilities. However, there are several other diagnostic modalities that can help confirm the diagnosis. The chest plain radiograph (CXR) is readily available and often useful (7,8). Radiographic stages reflecting the severity of LHF have been described, but the classic radiographic progression is often not seen. In addition, the chest radiograph may not correlate temporally with the patient's immediate condition; that is, there may be a lag of as much as 12 hours from the onset of CHF to the appearance of diagnostic changes on X-ray. Similarly, after treatment of LHF, there may be a lag of up to 4 days from clinical resolution of CHF until radiographic resolution. The specificity of the CXR for CHF (67% to 78%) is low enough that it cannot exclude left ventricular dysfunction; however, it can often indicate other diagnoses, such as pneumonia or COPD (8). These causes of dyspnea can have very different appearances from CHF on CXR.

The earliest radiographic finding of increased preload is redistribution or "cephalization" of blood flow. Normally, there is more blood flow to the dependent portions of the lungs. As PCWP increases, flow to the lower lung fields is reduced because of the vasoconstriction and the flow to the upper lung fields increases. Cephalization is best detected on an upright film and is most commonly seen in the setting of chronic CHF. As PCWP continues to rise, fluid accumulates in the interstitial spaces of the lung, producing Kerley B lines. Often the radiographic shadows of the pulmonary vessels begin to blur. As PCWP rises further, the increased hydrostatic pressure causes alveolar edema, and a classic butterfly pattern of bilateral perihilar infiltrates is seen on CXR. In almost all patients with chronic CHF, the cardiac silhouette is enlarged (cardiothoracic ratio $>50\%$) and pleural effusions are common. The frequency of CXR findings that confirm CHF increases with the severity of diastolic dysfunction. A systematic review of the

utility of CXR in the diagnosis of LV dysfunction concluded that redistribution and cardiomegaly were the best predictors of increased and reduced ejection, respectively (7).

The availability of point-of-care ultrasound is quickly becoming ubiquitous in EDs. This modality allows the physician to rapidly and repeatedly assess the dyspneic patient without sending the patient to the radiology suite nor exposing the patient to ionizing radiation. There is increasing literature about the reliability and the ease of using point-of-care ultrasound in the evaluation of ADHF patients. Sonographic evidence of interstitial edema called B-lines or "lung comets" has been shown to be very sensitive for CHF and even predictive of PCWP (9). Liteplo et al. showed that rapid bedside thoracic lung sonography had very good likelihood ratios ($+OR = 4.7$, $-OR = 0.3$) for predicting or eliminating CHF if examined in two lung zones bilaterally (10). This evaluative technique for lung sonography has been shown to be easy to learn and very reproducible for novice ultrasound practitioners (11).

The electrocardiogram (ECG), although of limited diagnostic value, should be performed on every ADHF patient to rule out acute coronary syndrome as a precipitating cause, which requires CCU admission and a more aggressive approach to treatment. However, chronic ischemic changes are very common and can make new ischemia difficult to diagnose. In chronic CHF, the ECG usually shows enlargement or hypertrophy of one or more chambers.

Arterial blood gas analysis reliably shows hypoxemia caused by impaired gas exchange, but it is of no value in diagnosis and of limited use in guiding therapy. Other blood tests show typical but nondiagnostic abnormalities (e.g., abnormal liver function tests caused by passive hepatic congestion or hyponatremia caused by of excess free water retention).

BNP and NT-proBNP levels correlate well with the presence and severity of heart failure (HF). BNP is secreted by the myocardium in response to increased wall stretch and an increase in LV end-diastolic pressure (preload), both of which are hallmarks of ADHF. Pre-pro BNP is synthesized within myocytes and is cleaved to proBNP. ProBNP is released into the circulation and then cleaved to

the active BNP and an inactive N-terminal fragment, called NT-proBNP. The two peptides have a high degree of correlation (12). BNP is a compensatory peptide with venous, arterial, and coronary vasodilator properties but has no direct inotropic or chronotropic effects. Plasma BNP levels of <100 pg/dL and NT-proBNP levels of <300 pg/dL make HF highly unlikely; BNP levels >500 pg/dL and NT proBNP levels >1,000 pg/dL make HF very likely. In patients with a BNP level of 100 to 500 pg/mL, the baseline BNP level may be elevated owing to a stable underlying dysfunction, including right ventricular failure from cor pulmonale, acute pulmonary embolism, or renal failure. BNP level has been shown to be affected by age, gender, drug use, and several comorbidities such as liver cirrhosis or primary pulmonary hypertension. Conversely, BNP levels are lower than expected in flash pulmonary edema, obesity, and CHF secondary to mitral valve dysfunction. BNP levels should not, therefore, be used as the sole diagnostic tool in assessing patients with suspected heart failure (2). A plasma BNP >100 pg/mL diagnosed HF with a sensitivity and specificity of 90% and 76%, respectively (12,13).

Data from the BNP Multinational Study indicate that BNP levels can be used to improve diagnostic accuracy beyond clinical judgment. A rapid BNP immunoassay test is currently available and has been shown to be better than the clinical examination in detecting CHF in ED patients and identifying CHF as the etiology of dyspnea of unclear etiology (13). Coupling thoracic sonography with NT-proBNP has shown to increase the physician's diagnostic accuracy for ADHF tremendously (10). However, as BNP will not add significant diagnostic value in patients who have clear-cut findings, the test should not be used when the clinician has a very high or a very low pretest probability of ADHF.

Cardiac enzymes, including troponin, CBC, and a complete metabolic profile should be obtained in patients presenting with ADHF. Other testing may be indicated depending on the patient's medications and the patients past medical history.

KEY TESTING

- Chest radiograph
- EKG
- Transthoracic lung ultrasound
- Transthoracic echo
- NT-proBNP or BNP if unclear cause of dyspnea
- Troponin (I or T)

ED MANAGEMENT

All patients with ADHF should receive supplemental oxygen. An IV line should be placed, and the patient should be placed on a cardiac monitor with pulse oximetry. The treatment goals for treating ADHF have not changed significantly over the past 30 years. The pharmacologic goals of therapy are relief of pulmonary congestion by reducing preload and improvement in systemic tissue perfusion by improving myocardial contractility or reducing SVR (afterload) while maintaining or improving myocardial oxygen balance.

Patients presenting to the ED with ADHF can be treated in a stepwise manner and according to their underlying cause of heart failure. Recently we have begun to understand that there are several subtypes and pathways to heart failure.

There appears to be a “hypertensive” or “vascular pathway” to ADHF that is characterized by profound hypertension and relatively little peripheral edema. It is felt these patients are not truly volume overloaded but rather are in the state where the heart cannot empty its contents against the overwhelming afterload. The key step to treating these patients is aggressive vasodilation and afterload reduction to allow the heart to move the stroke volume forward. In these patients, fluid shifting to the vascular space, rather than total body water overload, is felt to be the culprit of the increased preload (2,14,15).

There is also a more gradual pathway that is characterized by a milder course and more progressive worsening of symptoms. This pathway, termed the “normotensive” or “volume overload” pathway, is marked by infrequent pulmonary edema but frequent hepatomegaly, peripheral edema, and jugular venous distention. In

this pathway, precipitating factors are commonly detected, which often include nonadherence to diet and medical plans, and concomitant pharmacologic therapy that exacerbates heart failure (14). As these patients tend to be truly volume overloaded, use of a diuretic is often useful.

TREATMENT OF MILD TO MODERATE ADHF

Initial ED therapy for patients in ADHF includes vasodilation with sublingual, oral, or transdermal nitroglycerin to increase venous capacitance and lower preload. Diuresis is not an efficient mechanism for preload reduction because ADHF patients have dramatically lowered renal blood flow secondary to vasoconstriction and therefore a relative inability to diurese. Furthermore, studies have shown that diuretics have several deleterious physiologic effects on CHF patients (2). However, patients that are clinically fluid overloaded and have peripheral edema can receive loop diuretics to assist in the reduction of total body water. Blood pressure (BP) should be monitored as many agents used for preload reduction can lower the BP (afterload) as well. Afterload reduction is required in patients with significant hypertension. This can be accomplished with high-dose nitrates, ACEIs, or direct vasodilators like nitroprusside (2,14).

Furthermore, the use of noninvasive positive pressure ventilation has been shown decrease mortality in several studies (16).

Tachydysrhythmias should be aggressively rate controlled to facilitate ventricular filling; this will decrease preload and improve CO. The most common supraventricular tachydysrhythmia (excluding sinus tachycardia) encountered in ADHF is atrial fibrillation. It is usually chronic; therefore, cardioversion is neither necessary nor likely to be effective. The ventricular response rate can be slowed quickly with an IV calcium channel blocker or amiodarone. Digoxin alone should not be used; however, it is a useful medication in concomitant CHF and atrial fibrillation, as it has positive inotropic and AV nodal blocking properties.

Treatment of Severe ADHF and Acute Pulmonary Edema

Nitrates

Nitrates are recommended as initial therapy for ADHF in the ED. At low doses, IV nitroglycerin induces venodilation; at high doses, it causes arteriolar dilation and dilation of coronary arteries. This simultaneously and efficiently lowers both preload and afterload.

Sublingual nitroglycerin at 400 μg per dose, repeated every 3 to 5 min as necessary, should be administered while IV nitroglycerin is being prepared for administration. High-dose sublingual nitroglycerin should be used in hypertensive patients with ADHF and is particularly useful in the prehospital setting. IV nitroglycerin should be initiated at 50 to 100 μg/min, with a range of 5 to 200 μg/min. Tachycardia and hypertension usually resolve as the patient gets symptomatically better, and the intravenous nitroglycerin dose can be titrated down gradually. The transdermal route is ineffective in these severe patients.

Despite the common use of nitrates, no prospective studies on their effects on mortality have been published. In a large randomized controlled trial involving patients with pulmonary edema, a regimen of high-dose nitrates and low-dose diuretics provided more consistent clinical improvement than a regimen of high-dose diuretics and low-dose nitrates. It was also associated with lower rates of mechanical ventilation and myocardial infarction (17,18).

Hypotension with standard nitrate therapy is generally mild and transient. Severe or persistent hypotension should raise suspicion for “preload-dependent lesions” such as aortic stenosis, cardiac tamponade, right ventricular infarction, hypertrophic obstructive cardiomyopathy, or for recent use of medications used for erectile dysfunction. All of these lesions result in hypotension when preload is suddenly lowered with nitrates.

Diuretics

Diuretics are a mainstay of long-term outpatient therapy for patients with systemic volume overload and chronic CHF. However, patients who present to the ED with ADHF are often not volume overloaded.

Historically, loop diuretics such as furosemide were administered IV to alleviate lung edema due to presumed fluid overload. Recent literature has suggested that this is not clinically useful in patients who are not edematous (14,15). There is often a 30- to 120-minute delay in the onset of actual diuresis. Moreover, patients with chronic pulmonary edema often have a significantly reduced renal blood flow owing to increased afterload, and diuretics may ultimately worsen renal function further; this effect is more pronounced in elderly patients. There is no convincing evidence of any immediate venodilatory effect, which might reduce preload quickly. In fact, furosemide produces activation of the sympathetic nervous system, which in turn increases pulse and SVR, and thus myocardial oxygen demand, all worsening ADHF (17,18,19). However, there is a set of patients with ADHF who benefit from diuresis. These patients will clinically appear fluid overloaded with the hallmark finding of peripheral edema. In these patients, moderate diuresis leads to decrease in total body water and eventual clinical improvement (19).

Nesiritide

Nesiritide is a recombinant form of BNP that is identical to the endogenous hormone produced in the ventricles and has identical hemodynamic effects. BNP binds to the guanylate cyclase receptor of vascular smooth muscle and endothelial cells, leading to increased intracellular cyclic guanosine monophosphate, which serves to dilate veins and arteries. It causes vasodilation and increases renal blood flow and urine output. It has also been shown to produce dose-related decreases in PCWP (preload), SVR (afterload), and increases in CO. These favorable effects in ADHF occur while also avoiding increases in heart rate or incidence of arrhythmias. However, nesiritide causes hypotension in a significant portion of patients and is also a very expensive medicine.

Nesiritide has been studied in several clinical trials, and studies have reported a trend toward increased 30-day mortality (7.2% mortality in nesiritide, 4% in those without nesiritide) and worsening renal function in ADHF patients receiving nesiritide (20).

Morphine

Morphine sulfate administered in small IV doses historically has been a classic therapeutic agent in ADHF. Although morphine does have venodilatory actions, its effects on venous capacitance have not been well established in the setting of acute pulmonary edema, and respiratory depression may occur at doses below those affect hemodynamic parameters. Morphine probably exerts mild indirect hemodynamic effects through anxiolysis by decreasing catecholamine production and causing vasodilation. Conversely, morphine produces many adverse hemodynamic effects (increases in left and right heart filling pressures and reductions in cardiac index, caused by a direct myocardial depressant effect on the already reduced contractile state of the ischemic heart). Several retrospective studies have found that ED administration of morphine to patients with ADHF increases the odds ratio of endotracheal intubation and ICU admission (21). The use of morphine in ADHF has dramatically decreased because of the superiority of nitroglycerin for preload reduction and low-dose benzodiazepines for anxiolysis.

Angiotensin-Converting Enzyme Inhibitors

ACEIs reduce both preload and afterload, improve renal hemodynamics, decrease sodium retention, attenuate sympathetic stimulation, and maintain or enhance left ventricular function. The data on the use of ACEIs for chronic outpatient CHF show a very clear mortality benefit; however, the literature for their use in ADHF is limited. There are several small studies showing safety and efficacy of ACEIs as vasodilators in the treatment of ADHF. ACEIs can be given in the form of a one-time dose of oral or sublingual captopril or IV enalaprilat as a bolus or by continuous IV infusion. Hemodynamic effects have been seen within 10 to 60 minutes. ACEIs can be used safely with IV nitroglycerin to provide a combination of preload and afterload reduction. However, more data are needed before the routine ED use of ACEIs can be recommended (18).

Positive Pressure Ventilation

The role of noninvasive ventilatory support (NIV) in the treatment of ADHF has been growing recently. In the past, NIV was reserved for patients that did not respond to standard therapy. However, more recent literature suggests a broader role for NIV. In patients with persistent hypoxia or signs of fatigue, NIV in the form of continuous positive airway pressure and bilevel positive airway pressure should be strongly considered. Patients with altered mental status are not good candidates for NIV.

NIV improves lung mechanics by recruiting atelectatic alveoli, increasing intrathoracic pressure, improving pulmonary compliance, and reducing the work of breathing. NIV improves hemodynamics by reducing preload and afterload, thereby enhancing left ventricular performance. Several studies have shown that NIV reduced the need for endotracheal intubation, and a meta-analyses of several small studies show decreased mortality in ADHF patients treated with NIV. Recent studies show no advantage of continuous positive airway pressure over bilevel positive airway pressure for patients with cardiogenic pulmonary edema (16).

Endotracheal intubation may be required if pulmonary edema is accompanied by severe hypoxemia that does not improve with pharmacologic therapy and NIV. The most reliable indication of life-threatening hypoxemia is a decreasing level of consciousness, although it is a relatively insensitive sign.

Inotropes

The use of inotropes is reserved for patients in whom vasodilators and noninvasive ventilation are ineffective or in hypotensive patients who are unable to tolerate vasodilators. This is because these medicines all increase myocardial oxygen demand and therefore acutely worsen the myocardial oxygen inbalance. When inotropes produce sufficient improvement in BP, IV nitroglycerin or nitroprusside can be added to provide the desired preload reduction to relieve pulmonary congestion. The choices of inotropic support include catecholamines (such as dobutamine, dopamine, or noradrenaline) and phosphodiesterase inhibitors. Dobutamine has the added advantage of inducing mild reductions in preload and

afterload and providing inotropic support. However, it occasionally causes a reduction in BP that requires it to be discontinued. Dopamine or norepinephrine can be used instead, but these improve BP by increasing SVR; thus preload and afterload-reducing medications are needed. To date, there have been no studies to demonstrate a mortality benefit of any particular pressor over others in the setting of ADHF treatment in the ED (14,18).

A newer class of medicines that are "calcium sensitizers," such as Levosimendan, have shown promise in certain subgroups as an alternative to catecholamine inotropes in the treatment of ADHF. A recent meta-analysis showed that there is a survival benefit as compared to conventional inotrope therapy in patients undergoing cardiac surgery in patients admitted to the cardiac ICU. Further trials are needed to clarify whether levosimendan has a role in the ED (22).

CRITICAL INTERVENTIONS

- Initiate high-dose nitrates as the initial therapy for acute pulmonary edema.
- Use of NIV decreases both intubation rates and mortality in hypoxic ADHF patients.
- Use of diuretics should be reserved for edematous patients with fluid overload (usually normotensive).
- Consider the use of bedside thoracic echocardiography for the rapid diagnosis and reevaluation of patients with ADHF.

DISPOSITION

The majority of patients with severe ADHF should be admitted to an intensive care unit unless pulmonary edema has been completely reversed and the patient does not have any evidence of ischemia on ECG. Invasive hemodynamic monitoring (PCWP) may be required in patients who do not respond to ED therapy. Patients with chronic CHF and a mild gradual worsening of symptoms who respond to IV diuretics may be managed in an observation unit or discharged after adjustments in their chronic drug regimen and arrangements for

early follow-up with a physician. Patients with more severe symptoms or other complicating factors (e.g., new rhythm disturbances, new onset CHF, uncontrolled severe hypertension, or suspected ischemic event) should be admitted for observation, evaluation, and optimization of drug therapy. Typical indications for admission are listed in Table 83.3 (14).

TABLE 83.3
Acute Exacerbation of CHF: Admission Criteria

Clinical or ECG evidence of acute myocardial ischemia
Pulmonary edema or severe respiratory distress
Oxygen saturation <90% (not caused by primary pulmonary disease)
Severe complicating medical illness (e.g., pneumonia)
Anasarca
Hypotension or syncope
Heart failure refractory to outpatient therapy
Inadequate social support for safe outpatient management

Common Pitfalls

- It is difficult to distinguish cor pulmonale with acute respiratory failure from ADHF. In some cases, it may not be possible to distinguish between these conditions by physical examination alone.
- Beware of hypotension with high-dose nitrate therapy. However, the hypotension is generally mild and transient. Severe or persistent hypotension should raise suspicion for "preload-dependant lesions."
- CXR is an imperfect test for the diagnosis of ADHF with different lag times between chest X-ray findings, symptomatology, and resolution of findings.
- Measurement of BNP levels for the diagnosis of LHF should be reserved for patients with dyspnea of unclear etiology.

CHRONIC COR PULMONALE (PULMONARY HEART DISEASE)

Chronic cor pulmonale is a syndrome resulting from restricted blood flow through the pulmonary artery circulation, resulting in increased pulmonary vascular resistance. This causes right ventricular hypertrophy and dilation. The syndrome is also known as pulmonary hypertension. Although cor pulmonale may be acute (most commonly caused by pulmonary thromboembolism), only the chronic form is discussed here. The usual cause of the increase of peripheral vascular resistance is loss of pulmonary vessel lumen cross-sectional size. This is usually due to vascular remodeling produced by excessive cell proliferation, reduced apoptosis, and often excessive pulmonary vasoconstriction (23).

Hypoxemia is a potent pulmonary vasoconstrictor, and concurrent hypercapnia and acidemia are synergistic. Most cases of cor pulmonale are accompanied by these abnormalities. The rise in pulmonary vascular resistance impedes RV ejection, and a compensatory response results in hypertrophy or dilatation and increased preload. Causes of chronic cor pulmonale are listed in Table 83.4. In the United States, chronic bronchitis and emphysema are the major causes of this disease.

TABLE 83.4
Causes of Chronic Cor Pulmonale

Diseases that Primarily Affect Air Passages
Chronic bronchitis/emphysema
Asthma
Pulmonary fibrosis (e.g., pneumoconiosis)
Granulomas and infiltrates (e.g., sarcoid)
Pulmonary resection
Congenital cystic disease
High-altitude hypoxia
Obstructive sleep apnea
Chronic daytime hypoxia

Diseases that Primarily Affect Chest Bellows
Kyphoscoliosis
Thoracoplasty
Pleural fibrosis
Chronic neuromuscular weakness
Morbid obesity

Diseases that Primarily Affect Pulmonary Vasculature
Primary pulmonary hypertension
Pulmonary embolism
Polyarteritis nodosa
Other arteritides

CLINICAL PRESENTATION

The underlying disease process largely determines the clinical manifestations of cor pulmonale, and symptoms of pulmonary dysfunction most often precede manifestations of right heart failure.

These symptoms include dyspnea at rest or with minimal exertion, weight gain, ankle swelling, and, in severe cases, ascites. Physical signs usually include bibasilar crackles and scattered wheezes (caused by lung disease, not interstitial fluid accumulation) on auscultation. The pulmonic component of the second heart sound may be palpable, and the jugular vein may fill paradoxically during inspiration or exhibit no respiratory fluctuation. Tricuspid insufficiency may be present, manifested by a systolic murmur heard best at the lower left sternal border and increasing with inspiration; this is often accompanied by the finding of a pulsatile liver edge.

DIFFERENTIAL DIAGNOSIS

The signs and symptoms of cor pulmonale may mimic those of left heart failure (LHF), constrictive pericarditis, or cardiac tamponade. Severe and advanced mitral stenosis may present with predominant right heart failure or "silent mitral stenosis." When signs and symptoms of cor pulmonale are of abrupt onset, acute pulmonary thromboembolism should be considered.

ED EVALUATION

The CXR usually shows evidence of the underlying pulmonary disorder only, but it may be helpful in diagnosing the cause of an acute exacerbation (e.g., pulmonary infiltrate). The ECG is not a sensitive test for detecting RV hypertrophy or dilation, but some findings are reasonably specific. These include a P-pulmonale pattern (P-wave amplitude of at least 2.5 mm in lead II), right-axis deviation, R/S amplitude ratio in $V_1 > I$, low-voltage QRS, and right bundle-branch block pattern. The absence of radiographic or ECG evidence of RV hypertrophy or dilation does not rule out the diagnosis. Arterial blood gas analysis usually shows some combination of hypoxemia, hypercapnia, and acidemia. Liver function tests may be abnormal because of passive hepatic congestion. Pulmonary function tests are always abnormal, and the typical patient has a forced expiratory volume in 1 second of <1 L. The serum BNP level may also be elevated.

KEY TESTING

- Chest radiograph
- Electrocardiogram
- Arterial blood gas if need to determine degree of hypercapnia and acidemia

ED MANAGEMENT

Patients who present with acute exacerbations of chronic cor pulmonale usually have an exacerbation of the underlying lung disease. Superimposed additional physiologic stresses can

precipitate exacerbations of chronic cor pulmonale; however, thromboembolic disease should be considered if no other causes of exacerbation can be found. Therapeutic efforts should be directed toward improving oxygenation, decreasing hypercarbia, and normalizing pH (20,24). Therapy is directed at the underlying lung disease and often includes administration of low-flow oxygen, corticosteroids, antibiotics, and inhaled and systemic bronchodilators (25) (see Chapter 77, "Chronic Obstructive Pulmonary Disease").

DISPOSITION

Indications for admission for an exacerbation of chronic cor pulmonale are the same as for acute respiratory failure (see Chapters 1, "Airway Management" and 73, "Respiratory Failure").

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of the authors of this chapter in prior editions of the text.

Common Pitfalls

- Administering high-flow oxygen to a patient with suspected LHF who has cor pulmonale may result in worsening of clinical status, because of the loss of hypoxic drive.
- The diagnosis of cor pulmonale cannot be excluded by the absence of ECG or radiographic findings of RV hypertrophy or dilation.
- ED treatment should be directed toward improving pulmonary function and decreasing pulmonary vascular resistance rather than toward alleviating the signs of right heart failure (e.g., aggressive diuresis, which may decrease RV preload and worsen left heart outflow).

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CHAPTER 84

Bradydysrhythmias

David Hartman and David T. Overton

The cardiac conduction system consists of pacemaker cells, conducting cells, and contractile cells. Pacemaker cell possess the capacity to spontaneously depolarize (termed *automaticity*). The sinoatrial (SA or sinus node) is normally the predominant pacemaker of the heart, is located at the junction of the right atrium and the superior vena cava, and has an intrinsic basal rate of 60 to 100 bpm. The SA node is innervated by both sympathetic and parasympathetic nerves that alter its discharge rate. The arterial blood supply is either from the right coronary artery (55%) or the left circumflex artery (45%).

The atrioventricular (AV) node is located beneath the right atrial endocardium superior to the insertion of the septal leaflet of the tricuspid valve and can also function as a pacemaker, with an intrinsic rate of 45 to 60 bpm. The arterial blood supply of the AV node is from the posterior descending artery of the right coronary artery (90%) or the left circumflex artery (10%). This anatomy becomes clinically relevant in the AV nodal dysrhythmias associated with acute inferior myocardial infarction. The AV node fires in the absence of sinus node impulses, or it may usurp control from the sinus node. Other cells in the bundle branches and Purkinje network can function as pacemakers as well, but their intrinsic rate is quite low, approximately 30 to 40 bpm.

Electrical impulses in the heart travel over a network of conducting cells. Impulses normally originate in the sinus node. Passage through the AV node is relatively slow, accounting for a normal physiologic delay in ventricular depolarization. The AV node

blends into the bundle of His, which divides into bundle branches. The bundle branches arborize into a network of Purkinje fibers that transmit impulses to the ventricular myocardial contractile cells. Contractile cells in the atria and the ventricles do not depolarize spontaneously.

The electrocardiographic P wave represents atrial depolarization. The P–R interval (normally 0.12 to 0.20 seconds in the adult) reflects intra-atrial, AV nodal, and His–Purkinje conduction. The QRS complex, representing ventricular depolarization, has a normal duration of 0.04 to 0.10 seconds, and the following T wave represents ventricular repolarization. The U wave is seen in a variety of circumstances such as hypokalemia, although its electrophysiologic basis is uncertain. Two basic pathophysiologic mechanisms underlie the production of both tachydysrhythmias and bradydysrhythmias: (i) disorders of impulse formation and (ii) disorders of impulse conduction. Depressed automaticity may result in bradydysrhythmias, such as sinus bradycardia or sinus arrest. If SA node automaticity is sufficiently depressed, escape rhythms originating elsewhere in the heart may assume control. Depressed impulse conduction may lead to AV or fascicular blocks.

ED EVALUATION AND MANAGEMENT

When approaching patients with bradydysrhythmias, as with any patient, the priorities of airway, breathing, and circulation must be addressed first. The patient should be placed on a cardiac monitor, and an electrocardiogram (ECG) should be obtained expeditiously. The urgency and means of treating bradydysrhythmias depend on how symptomatic the dysrhythmia is, the clinical setting in which the dysrhythmia occurs, the propensity for the dysrhythmia to progress, and concurrent drug therapy. Bradydysrhythmias may produce hypotension, lightheadedness, dizziness, fatigue, mental status changes, angina, congestive heart failure, syncope, or even seizures. The elderly may be more susceptible to symptomatic bradycardia. Prompt therapy using electronic pacing or intravenous medications is required for these symptoms, which are caused by end-organ hypoperfusion. Many dysrhythmias are asymptomatic and

require no treatment. A dysrhythmia that occurs during an acute myocardial infarction often mandates a different treatment approach than a dysrhythmia incidentally discovered during a routine physical examination. Electrolyte imbalances and a wide variety of drugs (e.g., digitalis, β-blockers, calcium channel blockers, cocaine, methylprednisolone, fentanyl, and amiodarone) may cause bradydysrhythmias, and each case has its own implications for treatment (1–7).

Sleep apnea may also be a cause of bradycardia (8), as may seizure disorders (9). Propofol has also been implicated in causing acute refractory bradycardia especially at doses >4 mg/kg/h for a prolonged time (10). Many infectious diseases have been reported to cause a relative bradycardia, including typhoid, Legionnaires, malaria, and dengue fever (11). Symptomatic bradycardias are increasingly common with advancing age. General supportive measures such as oxygenation, ventilation, and correction of electrolyte abnormalities are usually the first step. Specific drug therapy or artificial cardiac pacing may also be required.

Among drug therapies, the cornerstone is atropine sulfate, a vagolytic agent that enhances sinus node automaticity and AV nodal conduction. The usual adult dose is 0.5 to 1.0 mg intravenous push every 3 to 5 minutes to a total maximum dose of 0.04 mg/kg (3 mg) in the adult. Atropine is also effective when administered via the endotracheal route. The suggested endotracheal dose is 2 to 2.5 times the recommended intravenous dose diluted in 10 mL of normal saline. Because atropine can increase myocardial oxygen consumption, it should be used with caution in the presence of myocardial ischemia. Adverse effects include sinus tachycardia, ventricular tachycardia, or ventricular fibrillation, as well as manifestations of anticholinergic toxicity. In patients with high-degree AV block, one may also see, in rare instances, a marked reduction in the heart rate after atropine use.

Glucagon has been found to be beneficial in treating bradydysrhythmias secondary to β-blockers and calcium channel blockers. The drug appears to be effective in both toxic and nontoxic patients. Glucagon stimulates the SA node, resulting in a modest

increase in the heart rate. Glucagon increases automaticity at the AV node, which may be helpful in slow junctional rhythms. Glucagon has also been shown to increase cardiac contractility, increasing coronary perfusion. The peak action of glucagon occurs approximately 5 to 10 minutes after intravenous administration. Suggested initial dosing ranges are 0.05 to 0.10 mg/kg in children and 0.05 to 0.15 mg/kg in adults. This dose may be repeated based on the clinical situation and the characteristics of the offending medication.

Isoproterenol, a β-adrenergic sympathomimetic drug with potent inotropic and chronotropic effects, is only used rarely currently, having been largely supplanted by the widespread availability of transcutaneous pacing. Still, isoproterenol may be useful as a temporary measure when other options fail. It is administered as an infusion at a rate of 2 to 10 mg/min. Isoproterenol markedly increases myocardial oxygen demand and may cause significant adverse effects, including ventricular tachycardia or fibrillation.

If drug therapy is ineffective, artificial pacing may be instituted. Transcutaneous pacing is more easily performed than internal pacing and should be attempted first. Emergent temporary pacing may improve organ perfusion and cognitive function (12).

Disorders of Impulse Formation

Atrial Bradydysrhythmias

Sinus dysrhythmia is a physiologic finding commonly seen in healthy young people. In it, the sinus discharge rate decreases with expiration and increases with inspiration. Sinus dysrhythmia is thought to be caused by changes in vagal tone during respiration. P wave morphology and P–R intervals are usually constant. No treatment is indicated.

Sinus bradycardia, arbitrarily defined as a sinus rhythm of <60 bpm, may be the result of organic heart disease and may cause symptoms, but it is also a common finding in healthy patients and particularly in conditioned athletes (13). The significance of sinus bradycardia depends on the clinical setting. It is common during

therapy with digitalis and β-blockers and may not warrant intervention. In contrast, the following findings should suggest nonphysiologic sinus bradycardia: (i) profound bradycardia in an individual not engaged in strenuous endurance training, (ii) sinus pauses longer than 3 seconds on a Holter monitor, or (iii) syncope or near-syncope at rest or after strenuous exercise. When sinus bradycardia is symptomatic, treatment with atropine is usually successful, although cardiac pacing is sometimes necessary.

The sick sinus syndrome encompasses a spectrum of conditions, including severe sinus bradycardia, SA block, sinus arrest, and the bradycardia–tachycardia syndrome. The latter refers to the intermittent occurrence of bradydysrhythmias and tachydysrhythmias (e.g., atrial fibrillation, flutter, or paroxysmal supraventricular tachycardia) in the same patient. The bradydysrhythmia typically occurs immediately after resolution of an episode of tachycardia. Symptoms such as syncope or chest pain may result from either the tachycardia or the bradycardia. Pharmacologic therapy that is effective for the tachycardia may exacerbate the bradycardia, so cardiac pacing may need to be initiated before proceeding with pharmacologic therapy.

Atrioventricular Nodal Bradydysrhythmias

An AV junctional rhythm may be a physiologic rhythm initiated by the AV node in the absence of an adequate sinus stimulus or may result from an abnormally rapid AV junctional focus that usurps control from the sinus node (e.g., accelerated junctional rhythm). Junctional rhythms usually exhibit a QRS morphology similar to the patient's sinus rhythm. The P waves are usually inverted if they are conducted in a retrograde manner. The P waves can fall before, during, or after the QRS complex, depending on the location of the focus within the AV junction and the degree of retrograde AV block. When the P wave occurs before the QRS complex, the P–R interval is usually <0.12 seconds. The absence of P waves may be caused by obliteration by the QRS complex or by retrograde block.

AV junctional escape beats occur singly or multiply in the absence of stimuli arriving at the AV node (Fig. 84.1). Their hallmark is

occurrence after an interval longer than the dominant cycle. The underlying disorder may be sinus bradycardia, sinus arrest, sinus exit block, or AV block. Digitalis or β-blocker therapy may also be responsible. Junctional escape rhythms may also be incidental findings in otherwise healthy people with increased vagal tone. Treatment is not indicated for asymptomatic patients with infrequent escape beats. If symptoms occur, the clinician should treat the underlying rhythm rather than attempt to obliterate the escape beats, as pharmacotherapy to obliterate the AV nodal escape beats may lead to asystole. Treatment involves withholding offending drugs or using atropine or artificial pacing.

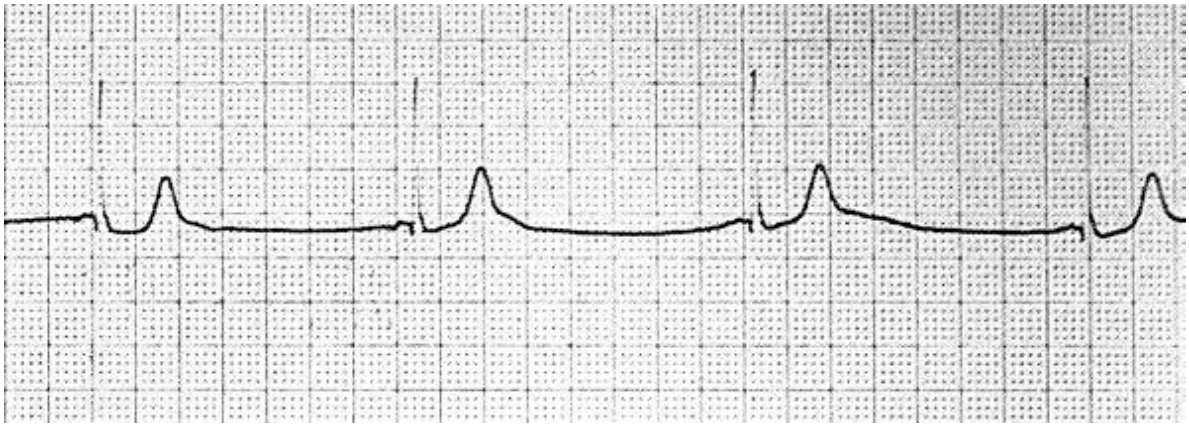

FIGURE 84.1 Junctional escape rhythm.

Ventricular Bradydysrhythmias

A ventricular rhythm with a rate of <50 bpm is termed a *ventricular escape rhythm* or *idioventricular rhythm.* Ventricular escape rhythm represents a physiologic safety mechanism that arises in the absence of stimuli from above, as in sinus bradycardia, sinus arrest, or, more commonly, AV block. Most patients with ventricular escape are symptomatic because the heart rate is low. Treatment is directed at the underlying dysrhythmia (i.e., atropine, or most often, cardiac pacing). Lidocaine, amiodarone, and other drugs that may abolish the ventricular rhythm are contraindicated because they have the potential for causing cardiac standstill.

Also known as idioventricular tachycardia or slow ventricular tachycardia, accelerated idioventricular rhythm has a rate of 50 to

100 bpm. Accelerated idioventricular rhythm is one cause of isorhythmic dissociation with occasional fusion beats demonstrating the continued presence of an intact AV node (Fig. 84.2). This rhythm may be associated with acute myocardial infarction (particularly after reperfusion), but it may also be seen in otherwise healthy patients. In the absence of symptoms, specific therapy is not warranted.

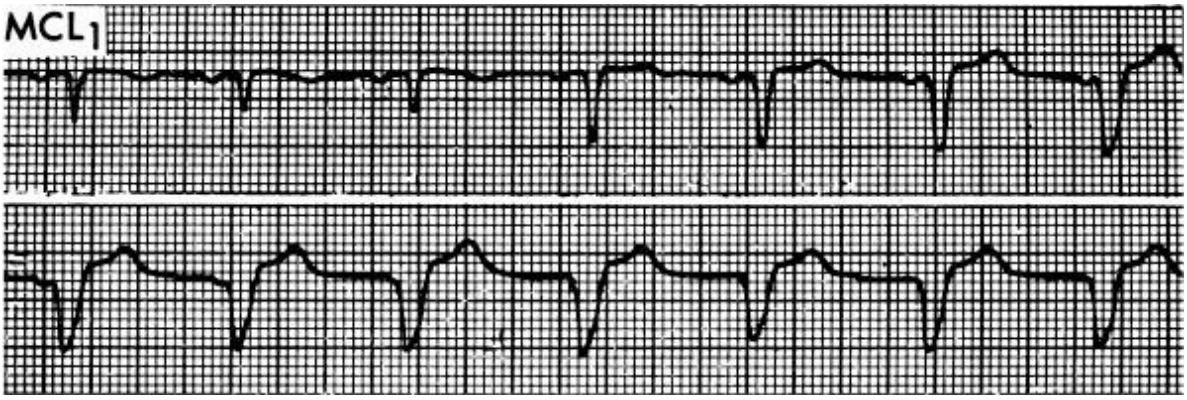

FIGURE 84.2 Idioventricular rhythm with isorhythmic dissociation and fusion beats.

Disturbances of Conduction

Disorders of Sinoatrial Conduction

The tissue surrounding the sinus node may delay or prevent conduction of sinus node impulses to the atria and AV node. Such conduction disorders are termed *SA block* and are classified in a manner analogous to AV block. Because of the limitations of the surface ECG, their precise diagnosis is more difficult than the varieties of AV block.

In first-degree SA block, there is a delay in the propagation of the sinus node impulse out to the atrial myocardium. Because every beat is transmitted, no abnormality is detected on the surface ECG.

Similar to AV block, second-degree SA block may be divided into types I and II. In type I (Wenckebach), there is, with each succeeding beat, a progressive delay in conduction from the sinus node to the atria, until conduction in totally blocked and a P wave is dropped (Fig. 84.3). The P–P interval shortens progressively before the

dropped P wave (analogous to the situation in second-degree AV block, in which the R–R interval shortens before the dropped QRS complex).

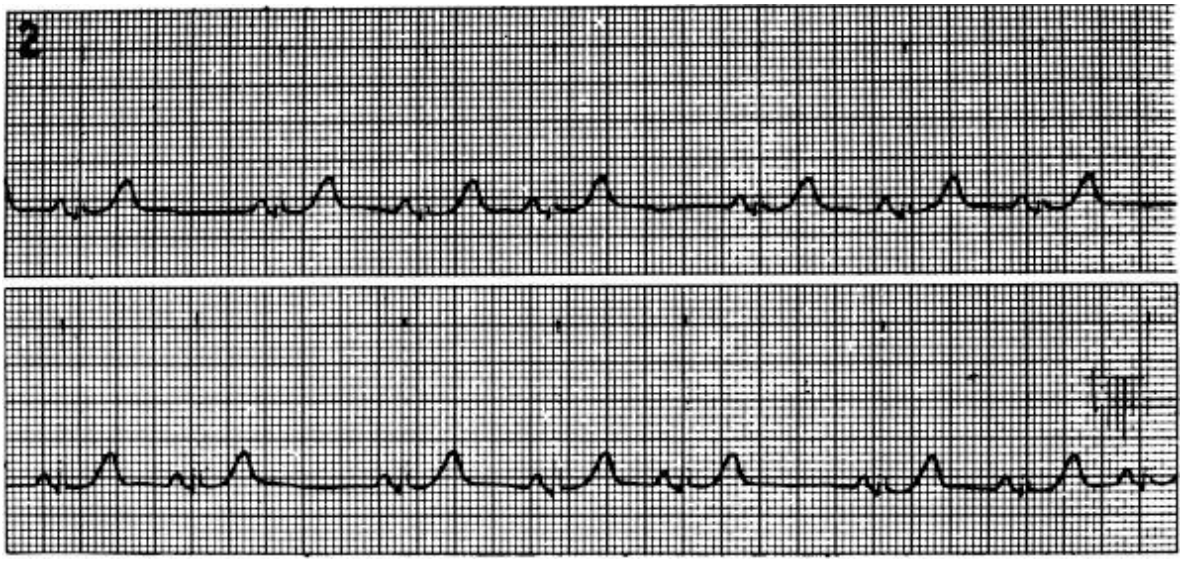

FIGURE 84.3 Type I (Wenckebach) SA block.

In type II second-degree SA block, there is intermittent failure of the sinus impulse to reach the atria, resulting in a missing P wave and a sudden lengthening of the P–P interval. The resulting P–P interval is usually a multiple of the previous one that is doubled in the case of 2:1 block (Fig. 84.4). This disorder can be mimicked by blocked premature atrial contractions, where the P wave is obscured by the preceding T wave (Fig. 84.5).

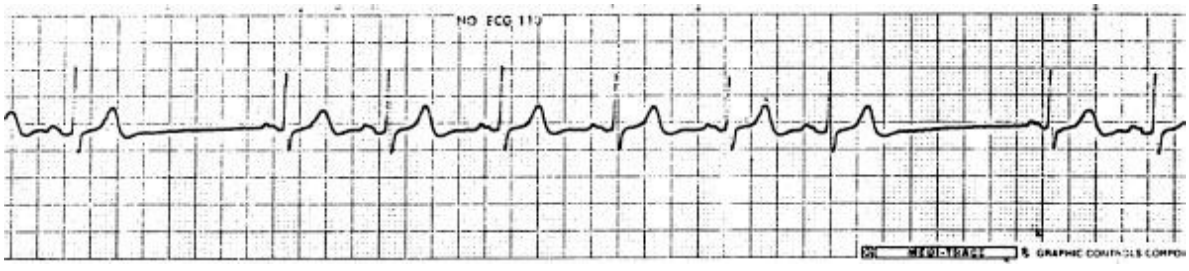

FIGURE 84.4 Type II SA block 2:1.

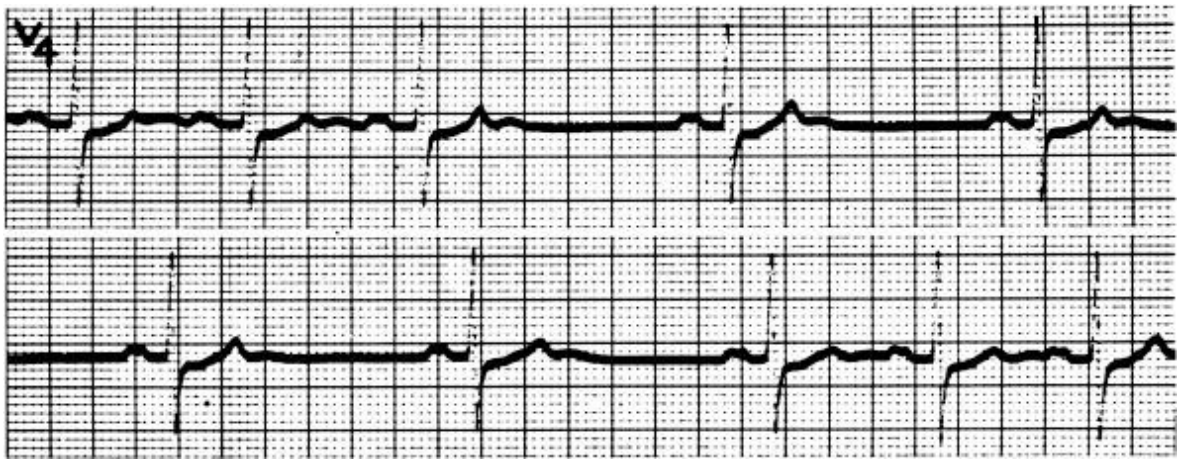

FIGURE 84.5 Blocked premature atrial contractions mimicking AV or SA block.

Third-degree SA block is where there is a failure of any sinus node impulses to be conducted to the atria (Fig. 84.6). Third-degree SA block is usually indistinguishable from sinus arrest, where there is a failure of impulses to arise from the sinus node.

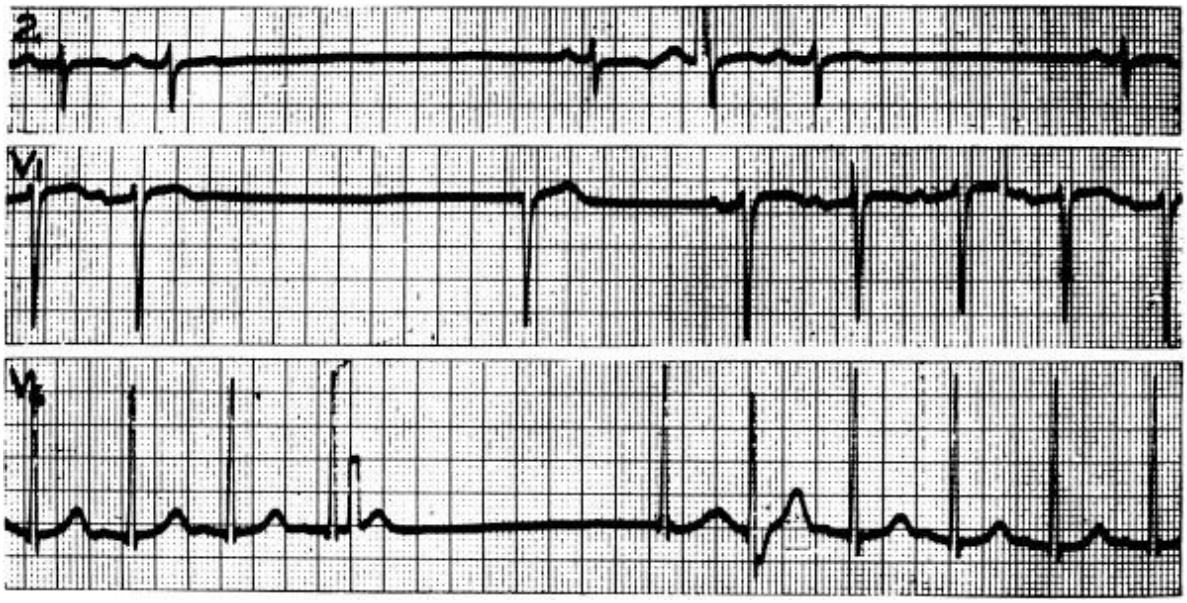

FIGURE 84.6 Third-degree SA block, with escape rhythm.

Disorders of Atrioventricular Conduction

Traditionally, AV blocks have been divided into first, second, and third degrees. However, AV block is a relative phenomenon, and the

physiologic delay normally present in the AV node is one end of a continuum. For example, in the patient with atrial flutter, “normal” AV conduction usually results in 2:1 block. In addition, the degree of block is rate dependent. One patient with mild AV disease may exhibit second-degree block at a particularly fast supraventricular rate, and another patient with more advanced AV nodal disease may exhibit 1:1 conduction if the supraventricular rate is slower.

A P–R interval of >0.20 seconds defines first-degree AV block. All P waves are conducted, 1:1 AV conduction is maintained, and the P–P and R–R intervals are consistent. Most commonly, the delay in AV conduction is within the AV node, and the QRS complex is of normal duration. Delays within the His bundle or His–Purkinje system are less common and are usually associated with widened bundle-branch block QRS patterns.

First-degree AV block may be associated with electrolyte disturbances or the use of digitalis, β-blockers, or calcium channel blockers. It becomes more prevalent as patients age. First-degree AV block may be seen during acute myocardial infarction, particularly inferior myocardial infarction. Treatment includes correction of electrolyte abnormalities or removal of the responsible drug. During acute myocardial infarction, close observation is warranted to detect progression to higher degrees of block. Otherwise, specific treatment is not indicated.

Second-degree AV block can be divided into Mobitz types I and II. Wenckebach distinguished between these two in the pre-ECG era, using only physical observation (14).

Mobitz type I second-degree AV block (Wenckebach) usually results from conduction delay in the AV node, although delays may occur in the bundle of His, bundle branches, or Purkinje system (Fig. 84.7). For this reason, the QRS complex in type I block is most often of normal duration and configuration. Mobitz type I AV block may be associated with inferior myocardial infarction or the use of digitalis, β-blockers, and calcium channel blockers. Mobitz type I AV block is usually transient, asymptomatic, and it has a good prognosis. If the patient is symptomatic, atropine can be given to enhance AV

nodule conduction. Pacing is usually not necessary. Offending drugs may need to be withheld.

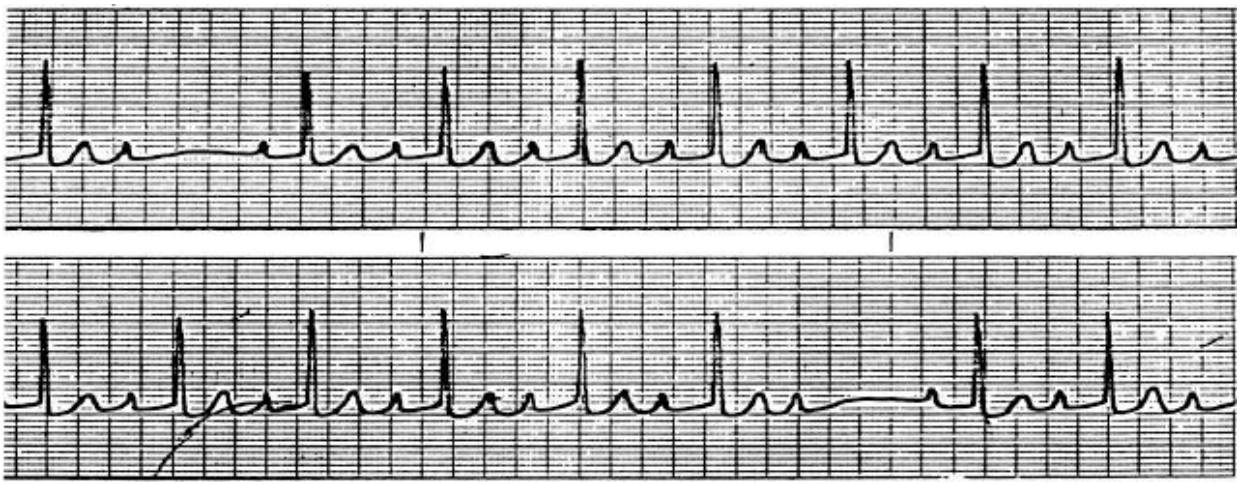

FIGURE 84.7 Mobitz type I (Wenckebach) second-degree AV block.

Mobitz type II second-degree AV block is less common. The site of block is usually within the His–Purkinje system, and a bundle-branch block QRS pattern is usually seen. In type II block, the P–R intervals are constant until single or multiple beats are suddenly dropped (Fig. 84.8). Type II block is usually symptomatic and has a higher likelihood of progressing to complete AV block. If associated with acute anterior myocardial infarction, type II block carries an ominous prognosis. Most authorities agree that Mobitz type II second-degree AV block requires permanent cardiac pacing. Because emergency drug treatment is often ineffective, temporary pacing may be necessary as a stabilizing measure.

FIGURE 84.8 Mobitz type II second-degree AV block.

A particular clinical problem is presented by the patient with 2:1 AV block. Although it is often assumed that such patients have type II block, type I block often presents as 2:1 block. The distinction is important given the difference in prognosis and treatment between the two entities. Although definitive proof may require intracardiac recordings, the following principles may aid in the clinical distinction:

- Type I block is more common than type II.
- A narrow QRS complex usually reflects type I block (although not all type I blocks have a narrow QRS complex). Type II block usually has a wide QRS complex.
- Coexisting acute inferior myocardial infarction suggests type I block, whereas anterior myocardial infarction suggests type II block.
- Digitalis, β-blocker, or calcium channel blocker therapy tends to be associated with type I block.
- In type I block, other areas of the rhythm strip may reflect other patterns of type I conduction such as 3:2 or 4:3.

In third-degree (complete) AV block, no atrial impulses reach the ventricles, and a subsidiary, escape pacemaker usually emerges. AV dissociation results with constant but independent P–P intervals and R–R intervals. The P–R intervals are variable, and P waves have no discernible relation to QRS complexes (Fig. 84.9). The site of block may be within the AV node, His bundle, bundle branches, or Purkinje system. In general, the lower the site of the block the more severe the symptoms.

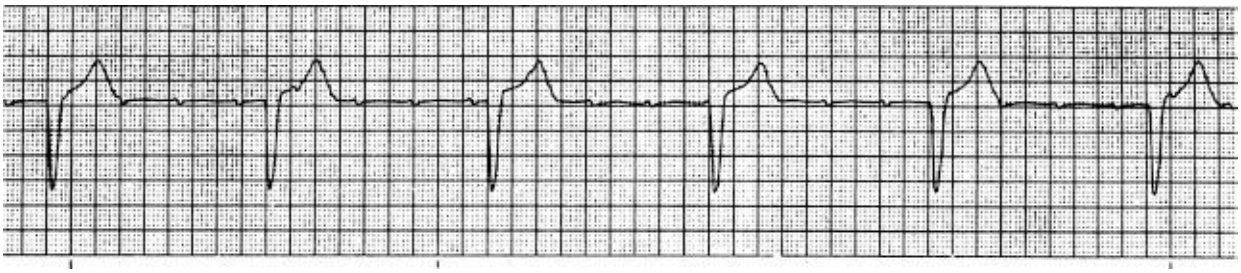

FIGURE 84.9 Third-degree atrioventricular block.

Third-degree AV block may be intermittent or self-limited. If the AV block is a complication of drug therapy, it usually resolves on withdrawal of the offending agent. Third-degree AV block may be associated with acute myocardial infarction but occasionally is an asymptomatic finding in an otherwise healthy person.

Like other bradydysrhythmias, the emergent treatment of third-degree AV block depends on symptomatology and clinical setting. Symptomatic patients may improve with atropine, particularly if the block is within the AV node. Symptomatic patients who are unresponsive to pharmacologic therapy require emergent pacing. Stable patients with acute inferior infarction may require only a prophylactic pacemaker. However, acute anterior infarction complicated by third-degree AV block is more ominous and requires emergent pacing.

The term *AV dissociation,* although commonly used interchangeably with the term *third-degree AV block,* encompasses a much broader range of rhythms. AV dissociation implies that the atria and ventricles are beating independently, a situation that includes not only complete AV block but also accelerated junctional and idioventricular rhythms (including ventricular tachycardia). In isorhythmic dissociation (Fig. 84.10), the sinus rate and the escape or ectopic rate are nearly identical, producing an electrocardiographic pattern characterized by varying P–R intervals as the sinus and ectopic foci slowly change their relative firing rates. Occasional fusion beats are an indication that the cause is not complete AV block.

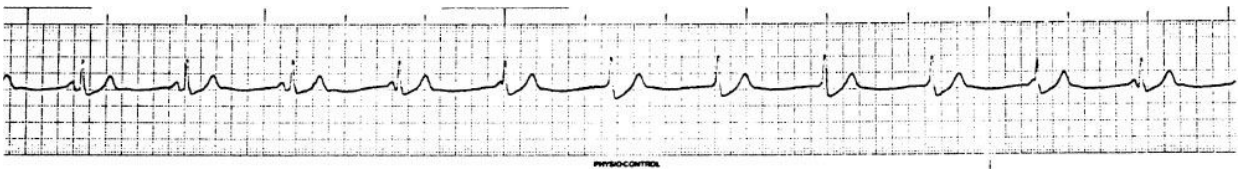

FIGURE 84.10 Atrioventricular dissociation with isorhythmic dissociation owing to a junctional focus.

Artificial Pacemakers

Temporary cardiac pacemakers are normally used in emergent or urgent circumstances, while most permanent pacemakers are placed electively. The emergency physician should be familiar with the indications and use of temporary pacemakers and with the principles of permanent pacemakers and their complications (see Chapter 86).

Temporary Pacemakers

Therapeutic emergency cardiac pacing is indicated in any hemodynamically unstable bradycardia that fails to respond to pharmacologic therapy. In addition, prophylactic emergent cardiac pacing may be indicated, even in the absence of symptoms, for patients with acute myocardial infarction in the following circumstances:

- First-degree AV block with new-onset bundle-branch block.
- Second-degree AV block type II.
- Third-degree AV block.
- Right bundle-branch block with left anterior fascicular block or left posterior fascicular block (either old or new).
- Left bundle-branch block (old or new) and placement of a Swan–Ganz catheter (because of the risk of inducing iatrogenic right bundle-branch block and then complete block).

Transcutaneous cardiac pacing involves the application of cutaneous electrodes to the chest and delivery of electrical impulses through the chest wall to the myocardium. Transcutaneous pacing is the technique of choice for emergent pacing in the emergency department and is the only option available for prehospital use.

The advantages of transcutaneous pacing are its ease and speed of use and the absence of serious side effects. The disadvantages include an inability to capture in some patients and the discomfort experienced by conscious patients because of chest wall contractions. The latter can usually be treated satisfactorily with analgesics or sedation. Transcutaneous pacing should be considered a stabilizing treatment, to be replaced with other pacing techniques, when possible.

Transvenous cardiac pacing involves the placement of the pacing electrode into the right ventricle by way of a central vein, often the

subclavian or internal jugular. Therefore, the procedure carries the risk of central venous catheterization but is the temporary modality that most closely approximates the function of a permanent pacemaker. Transvenous cardiac pacing does not involve painful muscle contractions or the hazard of direct cardiac puncture and can be used for relatively prolonged periods. Unfortunately, emergent transvenous pacemaker placement in the emergency department setting is often a lengthy and unsuccessful procedure associated with a high incidence of noncapture. Ideally, placement is performed under fluoroscopic guidance. Ultrasonographic guidance may make this procedure more effective, both in the initial placement of the central line and also in the correct placement of the pacing wire in the right ventricle. With the advent of transcutaneous pacing, transvenous pacing has been relegated to those situations in which fluoroscopy is available, stabilization has not been achieved by another modality, or attempts at transcutaneous pacing have been unsuccessful.

Transthoracic cardiac pacing is now rarely performed. It involves the placement of a pacing wire through the skin directly into the right ventricular cavity. Because of significant complications such as pericardial tamponade, pneumothorax, and coronary vessel injury, transthoracic pacing should usually be considered only in unusual circumstances.

Once capture has been achieved, regardless of the device used, the pacemaker settings will be dependent on the clinical situation. An initial rate of 80 to 100 bpm is appropriate for the majority of the patients. The initial output setting should be at maximum and decreased once capture is achieved. The mode should initially be asynchronous (sensitivity off) in those patients requiring emergency pacing for cardiac arrest. The mode should be set to synchronous in patients with bradydysrhythmias, as ventricular fibrillation may occur if the pacemaker fires during the vulnerable period (T wave).

CRITICAL INTERVENTIONS

- Initiate artificial pacing in unstable patients if drug therapy is ineffective.

DISPOSITION

Virtually all patients with symptomatic bradydysrhythmia require admission to the hospital. Patients with type II second-degree AV block and complete AV block usually warrant admission even if asymptomatic. Admission should be to a monitored bed in a unit with the capability of initiating emergent pacing.

If transfer to another facility is necessary, pacing should first be initiated if indicated and available. En route, the patient should have continuous cardiac monitoring and access to advanced cardiac life support. Transcutaneous pacing capability en route is also desirable.

Common Pitfalls

- Assuming that a 2:1 second-degree AV block is of the Mobitz type II variety, potentially leading to unnecessary treatment and intervention.
- Failing to take rate into account when evaluating AV blocks and fascicular blocks.
- Misdiagnosing blocked premature atrial contractions as significant AV block, potentially leading to unnecessary treatment and intervention.
- Blocking an escape rhythm, with the potential for causing cardiac standstill.

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CHAPTER 85
Tachydysrhythmias

Scott R. Votey and Eric Silman

The axiom that we must treat patients and not electrocardiograms (ECGs) or laboratory results is perhaps nowhere more relevant than in the emergency management of tachydysrhythmias. Decisions must be guided principally by the clinical presentation, and exact rhythm identification should be subservient to the goal of prompt appropriate management.

The acute and chronic management of tachydysrhythmias differ importantly. Acute management focuses on stabilization and typically involves emergent administration of intravenous (IV) medications or external electrical cardioversion, while chronic management increasingly relies on more advanced interventions which are beyond the scope of emergency medicine. This chapter focuses almost exclusively on acute management.

TACHYDYSRYTHMIA PATHOPHYSIOLOGY

Under normal circumstances, the sinoatrial (SA) node is the pacemaker for the heart. Depolarization is initiated in the SA node, and the impulse is conducted through the atrium to the atrioventricular (AV) node. Atrial depolarization corresponds to the P wave on the ECG. Conduction to the ventricles is slowed in the AV node, which provides a measure of protection against hemodynamically unstable tachycardias. The normal slowing in the AV node is seen on the ECG as the PR interval. After the impulse traverses the AV node, it is conducted first down the His bundle, followed by the left and right bundle branches, and then dispersed to the ventricular myocardium via the Purkinje fibers. Ventricular

depolarization corresponds to the QRS wave on the ECG. Normal impulse conduction produces a narrow QRS complex.

Tachycardias can be generated from any focus in the heart, because essentially all myocardial tissue has intrinsic pacemaker activity. There are two principal mechanisms by which tachydysrhythmias arise: reentry and enhanced automaticity. Reentry is a phenomenon in which an initial depolarizing impulse travels a closed-loop path that returns cyclically to its point of origin and, in doing so, generates a regular sustained tachydysrhythmia. The requirements for a reentrant tachydysrhythmia are (a) a closed-loop conduction path; (b) slower conduction and prolonged refractoriness in one limb of the loop; (c) propagation of the initiating impulse down the faster limb of the loop, with antegrade conduction down the slower limb blocked; and (d) retrograde excitation of the initially blocked slower limb, returning the impulse to its point of origin, where depolarization is reinitiated. Repetition of this cycle sustains the dysrhythmia with a premature beat as the typical precipitant.

Enhanced automaticity is an increase in the rate of the spontaneous depolarization of myocardial cells above their electrical threshold. Sinus tachycardia is the physiologic response to enhanced automaticity of the SA node. When enhanced automaticity results in more rapid depolarization of extranodal myocardial cells, these foci can produce ectopic tachydysrhythmias. Examples include paroxysmal atrial tachycardia (PAT) and junctional tachycardia. Enhanced automaticity often occurs as a result of increased sympathetic tone (e.g., with fever, thyrotoxicosis, or sympathomimetic overdose). Treatment of these dysrhythmias generally should be directed at removing the underlying stressor.

CLINICAL PRESENTATION

Patients with tachydysrhythmias can present with wide-ranging signs and symptoms, from palpitations to cardiac arrest. Most, however, complain of some constellation of palpitations and dizziness. Syncope is an important presenting complaint of patients with any arrhythmia and should prompt cardiac rhythm evaluation in the

emergency department (ED). Up to 70% of patients with tachydysrhythmias complain of chest pain, but it important to remember that not all chest pain in this situation reflects myocardial ischemia. Chest pain in a young otherwise healthy patient with a supraventricular tachycardia (SVT) rarely signifies ischemia, whereas the chest pain of an older patient with reasonable likelihood of coronary artery disease should be taken seriously. Other symptoms due to the dysrhythmia such as nausea and diaphoresis also overlap with those of myocardial ischemia. Symptoms of tachydysrhythmias depend on the hemodynamic consequences of the rate and rhythm, with those patients who are hypoperfused presenting with severe symptoms such as syncope, chest pain, or cardiac arrest. Hypotension and poor perfusion are more typically dependent on the heart rate produced by any dysrhythmia than they are on the source of dysrhythmia. Ventricular tachycardia (VT), for example, conjures up images of imminent catastrophe, and SVT is usually assumed to be benign. However, some patients with VT are relatively stable, at least in the short run; whereas, in other patients, SVT can be acutely life-threatening.

ED EVALUATION

In the ED, where diagnostic data are often limited and the patient's condition warrants prompt action, tachydysrhythmias are most successfully managed using an algorithmic diagnostic and therapeutic schema that is easily remembered and applied. The following approach is broadly applicable to the emergency management of tachydysrhythmias.

Step 1. Be Prepared for a Cardiopulmonary Arrest

Any patient with a tachydysrhythmia is at risk for deterioration, because of either the dysrhythmia or its treatment. Being prepared for a cardiopulmonary resuscitation by having advanced airway equipment and a defibrillator at the bedside is essential.

Step 2. Determine Stability

Determine what hemodynamic effect the rhythm is having on the patient. In this context, *unstable* is defined as a heart rate and blood pressure inadequate to maintain vital organ perfusion and function, manifested clinically by significant chest pain, pulmonary edema, altered mental status, syncope, or severe hypotension. Categorizing a patient as stable or unstable is complicated by the innumerable gradations on the continuum from asymptomatic health to cardiopulmonary arrest. Altered mental status and ischemic chest pain with ECG changes of ischemia are convincing evidence of instability. Electrical cardioversion should be used to treat unstable patients with any tachydysrhythmia except sinus tachycardia and multifocal atrial tachycardia (MFAT).

Blood pressure is one of the most commonly used determinants of patient stability. It is important to remember that arbitrary blood pressure cutoffs for defining stable or unstable do not take into account the patient's baseline blood pressure. A systolic blood pressure of 90 mm Hg is of far more concern in a hypertensive elderly patient than in a young and healthy 20-year old. It should be emphasized that stability is subject to change on a minute-to-minute basis, and therapy must be adjusted accordingly.

After clinical stability is assessed, the ECG should be rapidly and systematically evaluated. Although most therapeutic decisions can be made on the basis of a rhythm strip, it is prudent to obtain a 12-lead ECG as soon as it is feasible. A 12-lead ECG can help determine if myocardial ischemia is present and can aid in differentiating among tachydysrhythmias, especially between sinus tachycardia and other regular SVTs.

Step 3. Determine the Rate

The more extreme the ventricular rate, the more likely the patient is to become unstable. Sinus tachycardia rarely exceeds 160 to 180 beats/min in adults. Although SVTs typically have rates slower than 180 beats/min, they can be faster in the presence of a bypass tract. VT is not slowed by passage through the AV node and can thus be much faster (250 to 300 beats/min) but is usually less than 220 beats/min.

Step 4. Determine the QRS Complex Width

When emergent cardioversion is not required, subsequent decisions can be based on the duration of the QRS complex. In an adult, a QRS width of greater than 0.12 ms is considered "wide." In many adults with a wide-complex tachydysrhythmia, the QRS duration is substantially greater than 0.12 ms. In children, the QRS duration is age dependent, but any QRS duration >0.10 ms is considered prolonged. It is usually possible to determine if a rhythm is wide or narrow from a rhythm strip alone, but if there is uncertainty, the widest QRS complex in the 12-lead ECG should be used as the measure.

Narrow-complex tachycardias can be assumed to be supraventricular. Wide-complex tachycardias are the result of any of three distinct pathophysiologic processes:

1. The rhythm originates in the ventricle and does not use the normal conduction pathway.
   The origin of the tachycardia is supraventricular, but there is a block of the normal conduction pathway below the AV node (bundle-branch block), often referred to as "aberrancy."
2. The origin of the tachycardia is supraventricular, but there is an accessory conduction pathway that bypasses the normal conduction pathway.

With rare exceptions, a wide-complex tachycardia should be treated as VT for three reasons: (a) VT is the most common cause of a wide-complex tachycardia; (b) despite the existence of diagnostic criteria, VT cannot be reliably distinguished from SVT with aberrancy in the clinical setting (1), and treating VT as SVT can be fatal (although treating SVT as VT is not harmful); and (c) even if the tachycardia has a supraventricular origin, there may be an associated bypass tract, in which case, some standard SVT treatments (e.g., verapamil) are contraindicated. It is never safe to assume that a wide-complex tachycardia is caused by aberrancy.

Step 5. Assess the Regularity of the RR Intervals

An irregular narrow-complex tachycardia is usually caused by atrial fibrillation (AF), although it can occasionally be caused by MFAT or atrial flutter with variable AV block. Because VT is usually regular except during the first few beats, an irregular wide-complex tachycardia should also raise the suspicion of AF with a bundle-branch block (AF-BBB) or a bypass tract. Distinguishing which patients have AF with a bypass tract is important, because the treatment of choice for these patients is cardioversion, even if they are stable. Although this differentiation can be difficult, two characteristics are helpful. In contrast to patients with AF-BBB, patients with AF with a bypass tract may have (a) very rapid conduction, with some RR complexes intervals equivalent to >250 beats/min, and (b) bizarre morphology QRS complexes resulting from fusion and partial fusion of beats from normal AV and bypass-tract conduction.

Step 6. Determine the Presence or Absence of P Waves

Determine whether P waves are present, their morphologic characteristics, whether they are regular, and how they are related to the QRS complexes. Regular uniform P waves preceding the QRS complex help distinguish sinus tachycardia from other SVTs. A normal P wave axis is one with an upright P wave in lead II and negative in aVR. This axis strongly suggests the atrial activity is coming from the SA node and is indeed sinus in nature. Although similar P waves may be present with the much rarer PAT, an abnormal P wave axis or morphology should alert one to the ectopic origin of that rhythm. An irregular narrow QRS-complex rhythm with more than three P wave morphologies is indicative of MFAT. One should, in addition, look for the regular sawtooth deflections of the ECG baseline that characterize atrial flutter waves.

Application of this scheme organizes dysrhythmias into four major categories based on the ECG appearance, with the additional distinction of clinically stable or unstable. The four categories are (a) narrow complex, regular, P waves present or absent; (b) narrow complex, irregular, P waves present or absent; (c) wide complex, regular, no P waves; and (d) wide complex, irregular, no P waves.

Generally, each of the specific dysrhythmias that fall into each of these categories is treated in the same fashion, thus the simplicity of the approach. Occasionally, unstable patients need treatment initiated before analysis of the rhythm can be completed. In addition, once the rhythm is stabilized, the patient may require additional pharmacologic treatment to prevent recurrent dysrhythmias.

KEY TESTING

- Cardiac monitor strip
- 12-lead electrocardiogram
- Chest radiography*
- Chemistry*
- Cardiac enzymes*

*In select patients based on particular dysrhythmia and underlying comorbidities and risk factors.

DIFFERENTIAL DIAGNOSIS AND ED MANAGEMENT

Narrow-Complex Tachycardias

Narrow Complex, Regular, P Waves Present

Sinus tachycardia makes up the vast majority of these cases. Tables 85.1 and 85.2 outline the medical and electrical therapy for patients presenting with a wide variety of tachydysrhythmias. PAT is a rare alternative diagnosis. Therapy for sinus tachycardia is directed at the rhythm's underlying cause rather than at the rhythm itself. For example, patients with sepsis and sinus tachycardia or those with tachycardia due to hemorrhage require volume resuscitation and those with alcohol withdrawal or sympathomimetic intoxication benefit from benzodiazepines. There are a few conditions in which pharmacologic slowing of sinus tachycardia are beneficial. For example, β-blockers are important in thyroid storm to counteract the adverse consequences of extraordinary increases in sympathetic drive. While it was once standard to administer β-blockers to tachycardic patients with myocardial ischemia to decrease myocardial demand, routine early IV β-blockers are no longer

recommended in select ACS patients because of a lack of clear mortality benefit and an increased risk of cardiogenic shock in some patient groups (2).

TABLE 85.1
Selected Drugs for Tachydysrhythmias

Drug	Dosage	Contraindications	Side Effects	Comments
Adenosine	6 mg IV rapid push, followed by a saline flush Repeated doses of 12 or 18 mg may be used	• Known VT • AV node block • AF with WPW syndrome	Hypotension; transient Prolonged AV block (rare) Chest pain Flushing	Reduce dose in patients taking carbamazepine or dipyridamole (start at 3 mg), heart transplant patient, or administration via central line (start at 1–2 mg)
Amiodarone	150 mg over 10 min; 1 mg/min for 6 hrs; 0.5-mg/min maintenance infusion; 150-mg boluses for breakthrough VT/VF. 300 mg IV push in pulseless VT or VF	• AV block • Renal failure	Hypotension Bradycardia AV block Torsade de Pointes	Amiodarone has many side effects when given chronically but not acutely
Metoprolol	5 mg IV over 1–2 min; repeated every 5 min up to 15 mg if required	• Asthma/COPD • Hypotension • AF with WPW syndrome • AV node block	Hypotension High-degree AV block Bradycardia Bronchospasm	Secondary choice for most tachydysrhythmias because of negative inotropic effects. Atenolol is dosed identically
Diltiazem	5–10 mg IV slowly for AF Repeated to total of 50 mg in first 30 min, if required Infusion; 5–15 mg/hr	• Regular wide-complex tachycardias • AV node block • Hypotension • Digoxin toxicity • AF in WPW syndrome • Age <2 yrs	Hypotension High-degree AV block Bradycardia	Consider calcium pretreatment Use in patients with AF and class IV heart failure was safe in a small case series
Esmolol	0.5 mg/kg bolus over 1 min; followed by 0.1–0.3 mg/kg/min infusion titrated to effect	• As for other β-blockers	Hypotension High-degree AV block Bradycardia	A very short half-life makes this a good choice when it is unclear whether the patient can tolerate β-blockers
Lidocaine	1 mg/kg IV, repeated at 0.5–0.75 mg/kg IV to a total of 3 mg/kg, if required. Infusion of 1–4 mg/hr	• AF (increases AV conduction)	Seizures, confusion, lethargy, but only in overdose Bradycardia Asystole	Used for stable VT, but efficacy is poor. May reduce recurrent VT/VF but not helpful for primary prophylaxis
Magnesium	2–4 g IV over 5 min Infusion of 1–2 g/hr	• AV block • AF with WPW syndrome • Renal failure (infusion)	Hypotension Flushing Respiratory muscle weakness, bradycardia, and asystole with high doses	Patients with infusions running should be checked every few hours to determine respiratory status and reflexes. Decreasing reflexes suggest magnesium toxicity, and infusion should be stopped
Procainamide	17 mg/kg loading at no more than 50 mg/min	• Hypotension (relative contraindication)	Hypotension; give IV fluids, slow rate of infusion QRS widening QT prolongation	Effective in SVT with aberrancy. Reduces conduction though accessory pathways but may increase conduction through the AV node
Verapamil	5–10 mg IV at 2 mg/min for PSVT	• As for diltiazem	As for diltiazem	May cause more hypotension than diltiazem. Not extensively studied in patients with congestive heart failure

IV, intravenous; VT, ventricular tachycardia; AV, atrioventricular; AF, atrial fibrillation; WPW, Wolff–Parkinson–White; TdP, torsade de pointes; COPD, chronic obstructive pulmonary disease; VT, ventricular tachycardia; VF, ventricular fibrillation; SVT, supraventricular tachycardia; PSVT, paroxysmal supraventricular tachycardia.

TABLE 85.2
Electrical Therapy of Tachydysrhythmias

Rhythm	Biphasic Dose (J)	Notes
PSVT	50	Synchronized
Atrial flutter	50	Synchronized
Atrial fibrillation	50–200	Synchronized
Ventricular tachycardia	120–200	Synchronized
Torsade de Pointes	200	Unsynchronized (defibrillation)
Wide complex AF	50–200	Synchronized
Ventricular fibrillation	200	Unsynchronized, monophasic 200–360 J

Narrow Complex, Regular, No P Waves

The differential diagnosis includes paroxysmal supraventricular tachycardia (PSVT) and atrial flutter with a consistent AV block. Generally all these reentrant rhythms are treated in the same way with blockade of the AV node.

Paroxysmal Supraventricular Tachycardia

PSVT (Fig. 85.1) makes up the majority of cases in this category. The two main types of PSVT are atrioventricular nodal reentrant tachycardia (AVNRT) and atrioventricular reentrant tachycardia (AVRT), the differentiation of which is not important in the ED.

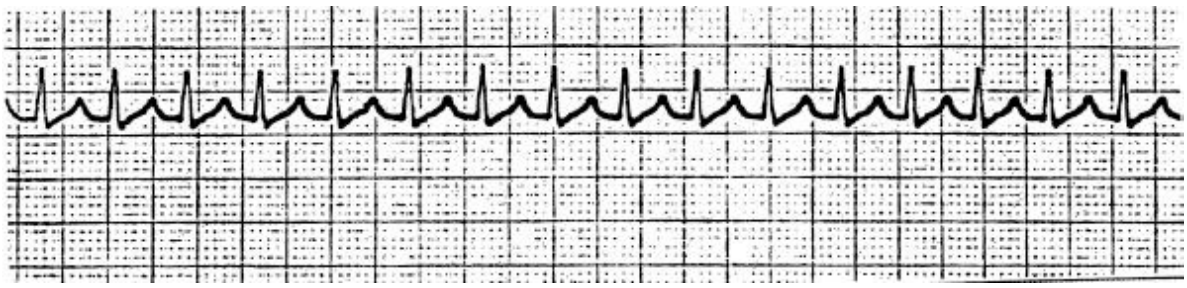

FIGURE 85.1 Paroxysmal supraventricular tachycardia.

Patients with PSVT who have severe signs of end-organ hypoperfusion should be cardioverted; more than 90% convert with small doses of electrical energy ($\leq$50 J). Pharmacologic treatment of PSVT, typically a reentrant tachycardia in which the AV node is part of the circuit, is directed at blockade of the AV node. Vagal maneuvers may be tried first: carotid massage, the Valsalva maneuver, and ice-water immersion work well in many patients.

However, because many patients with recurrent PSVT are familiar with vagal maneuvers, they often present for treatment only when these maneuvers have failed; therefore, these maneuvers are only occasionally effective in the ED.

Treatment options include adenosine, verapamil, diltiazem, and β-blockers. Adenosine, because of its brief duration of action and its resultant lack of sustained hemodynamic effect, is the drug of choice. The recommended initial dosage of adenosine is a 6-mg bolus over 1 to 3 seconds, followed by a rapid saline flush. If there is no response in 1 to 2 minutes, a 12-mg dose can be administered in the same manner. The use of doses of adenosine upward of 24 mg as a bolus have been reported in the literature, but are only marginally more effective than 12 mg. It is important that the drug be given as a rapid bolus to achieve high levels in the heart. In fact, adenosine is degraded so rapidly in plasma that the most proximal IV access possible (usually an antecubital vein) is desired.

In the absence of any of the standard contraindications to calcium channel blockers (hypotension, congestive heart failure, SA or AV nodal disease, or the previous use of IV β-blockers), diltiazem is a safe and effective alternative to adenosine. The standard initial dose is 10 mg IV and most patients convert to sinus rhythm within about 2 minutes. Incremental doses up to a total of 50 mg in the first 30 minutes are usually successful in those who do not. Verapamil is also effective. There is a substantial incidence of adverse effects when contraindications are present, so they should not be ignored. Many pediatric cardiologists consider it unsafe to use verapamil in children younger than 1 year of age and use adenosine exclusively in this age group.

Esmolol, an extremely short-acting β-blocking agent with a half-life of <10 minutes, is moderately effective in treating PSVT, although success rates are significantly lower than with either adenosine or verapamil and the incidence of hypotension is higher. Esmolol is, therefore, a secondary drug in the treatment of PSVT.

Atrial Flutter

Atrial flutter is a macroreentrant arrhythmia in which the circular current flow produces characteristic “sawtooth” waves, best seen in leads V1 and II, III, and aVF (Fig. 85.2). Atrial rates between 260 and 300 beats/min are typical, and the most common AV block of 2:1 produces ventricular rates of approximately 150 beats/min. Variable AV block can cause an irregular narrow complex rhythm. The ED management of atrial flutter is similar to that of AF. The decision to perform electrical cardioversion or attempt chemical rhythm control versus rate control must be made in the context of many factors: clinical stability, patient comorbidities and associate stroke risk, as atrial flutter carries a similar risk of stroke and many patients in atrial flutter also suffer from AF.

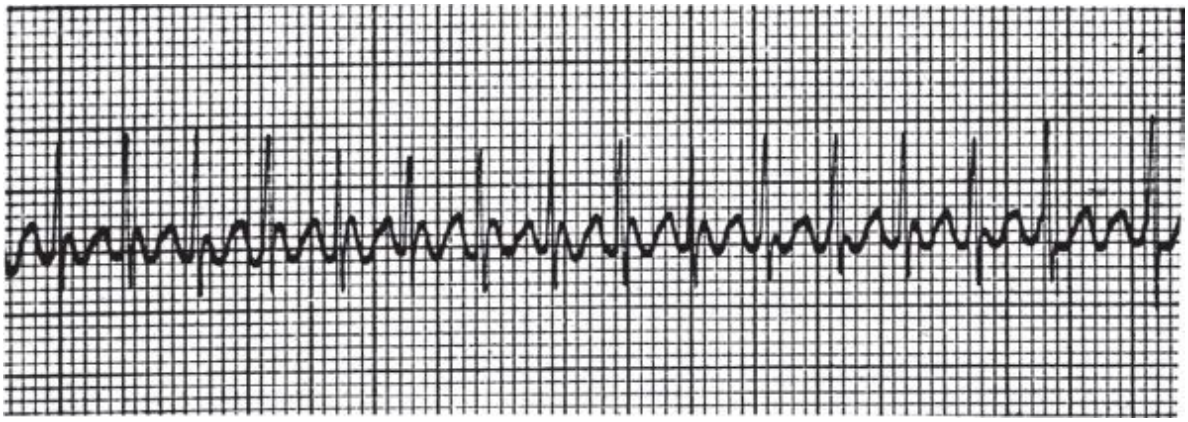

FIGURE 85.2 Atrial flutter.

The calcium channel blockers (verapamil and diltiazem), as well as digitalis, are capable of slowing the ventricular response in atrial flutter. Adenosine, although capable of slowing conduction for a few seconds, rarely results in cardioversion and has no role in the management of atrial flutter; however, it can occasionally be of diagnostic value in distinguishing atrial flutter and PSVT. Vagal maneuvers can sometimes slow the ventricular rate enough to bring out flutter waves (if they are present), but adenosine is particularly effective in this regard. Most authorities advocate electrical cardioversion given the high electrosensitivity of atrial flutter. Most patients convert with doses of 30 to 50 J. Despite the efficacy of electrical cardioversion, chemical cardioversion has advocates and

practice varies. As with AF, amiodarone and procainamide are currently commonly used agents in the ED.

Although the diagnosis of atrial flutter is often fairly easy, some patients with flutter at first glance appear to be in other rhythms. Therefore, it is important to consider and exclude flutter before using any drug (such as procainamide) that speeds conduction through the AV node. This is because atrial activity in flutter is typically much faster than the ventricular response and such drugs can change the conduction from 2:1 or 3:1 to 1:1, with serious hemodynamic consequences.

Since atrial flutter may increase the risk of systemic embolization, and since many patients with atrial flutter also have AF, anticoagulation is generally recommended in patients with atrial flutter in a similar manner as for AF (see section on *Atrial Fibrillation*) for risk assessment and anticoagulation recommendations.

Narrow Complex, Irregular, P Waves Present

Multifocal Atrial Tachycardia

MFAT is characterized by P waves of varying morphologies and by changing PR intervals. Because MFAT originates in the atria, it is associated with narrow QRS complexes, except in the presence of underlying bundle-branch block. MFAT occurs primarily in patients with chronic lung disease, and within this group, MFAT was most common in patients with high or toxic levels of theophylline. As the use of methylxanthines for the treatment of lung disease has declined, so apparently has the incidence of MFAT. Although MFAT is seldom life-threatening, the ability to control it can provide symptomatic benefit. Several small series have demonstrated slowing or conversion of MFAT with magnesium or verapamil (3). β-Blockers are probably less effective and should be used with caution in MFAT associated with chronic obstructive pulmonary disease (COPD).

Narrow Complex, Irregular, No P Waves

An irregular narrow-complex tachycardia is almost invariably AF or atrial flutter with variable block (Fig. 85.3). Occasionally, the P waves of MFAT are overlooked, and that rhythm is confused with AF.

FIGURE 85.3 Atrial fibrillation.

Atrial Fibrillation

AF is the most common arrhythmia treated in the ED and is marked by rapid disorganized atrial activation, often accompanied by rapid ventricular response (RVR). ED management of AF is both complex and controversial due to the heterogeneity of patients and their clinical presentations, and the lack of sufficient guiding evidence. When choosing therapy it is important to consider the ventricular response rate, hemodynamic consequences, duration of AF, presence of underlying heart disease, and precipitant of the patient's presentation.

In the majority of patients presenting with AF and RVR, the tachycardia itself (which profoundly decreases the time available for diastolic filling of the ventricles as well as coronary artery perfusion), rather than the loss of atrial systole, is responsible for the hemodynamic consequences. Patients with hypertrophic cardiomyopathy as well as other patients with significant diastolic dysfunction are an exception, because their stiff ventricles fill slowly and they thus rely on active atrial systole for an inordinate proportion of their end-diastolic ventricular volume.

At the other extreme, a slow ventricular response in new-onset AF is worrisome unless the patient is already taking medications that slow conduction in the AV node. Such patients may have AV node dysfunction, are rarely unstable, and often need to be admitted for consideration of long-term measures. Attempted cardioversion may lead to asystole or prolonged bradycardia and should be avoided.

Many patients seen in the ED with AF, particularly in circumstances in which AF is an incidental finding, have chronic AF, are taking medications for rate control, and are hemodynamically stable. Digitalis has long been used for chronic rate control.

Cardioversion in patients taking digoxin is a risk because of the potential for asystole. If cardioversion is required because of extreme hemodynamic compromise, it should initially be attempted at lower energy levels, such as 50 J. The calcium channel blockers diltiazem or verapamil, or a β-blocker are now preferred to digoxin for chronic rate control because these agents control rate not only at rest but also during exercise (4). Patients with chronic AF should be admitted to the hospital if they have signs of hemodynamic decompensation that requires cardioversion or if hemodynamic effects and RVR are not easily controlled.

Anticoagulation is an important management issue for patients with AF. Not only are patients with chronic AF at risk for systemic embolization, but evidence suggests that even shorter periods of AF may carry a risk of embolization, particularly following conversion to sinus rhythm, regardless of whether cardioversion is electrical or pharmacologic. All patients with chronic AF, except perhaps those <60 years old who have no other evidence of heart disease, should be on maintenance anticoagulant therapy unless there are substantial contraindications (5). Chronic anticoagulation may also benefit patients who experience recurrent paroxysmal AF (5,6). Even if accurate, a history of a brief duration of AF may fail to preclude the possibility of embolization caused by intra-atrial clot formation during the period of atrial standstill that can follow conversion to sinus rhythm. For this reason, some authorities suggest that in the absence of contraindications, patients with AF of >48 hours' duration be anticoagulated prior to electrical or chemical cardioversion, and for a minimum of 4 weeks after conversion to sinus rhythm. Other strategies involve risk stratification based on known risk factors for clot formation and a selective approach to anticoagulation in acute AF.

On the other hand, studies of transesophageal echocardiography (TEE) used to rule out an intra-atrial thrombus prior to conversion of AF suggest that a negative TEE reduces the risk of embolization enough to obviate the need for anticoagulation before cardioversion. Additional studies will be needed to more fully define the risks and benefits of these management strategies, and resolve this

controversy. Of course, if it is necessary because of hemodynamic instability, cardioversion should never be withheld.

For stable patients presenting with AF of >48 hours' duration and RVR treatment is directed at slowing the ventricular rate, and conversion to sinus rhythm is, at best, a secondary consideration. Prior to initiating rate control therapy it is important to consider what is precipitating the RVR. Just as an acute physiologic stress will increase catecholamine levels and result in sinus tachycardia in patient with a healthy heart, elevated catecholamines may precipitate an acute paroxysm of AF with RVR in a patient with an at-risk heart, or induce RVR in a patient with chronic AF. Consequently, an elderly patient with a history of chronic AF presenting with a fever, tachycardia, and evidence of urosepsis is better treated with IV fluids, antibiotics, and antipyretics than with pharmacotherapy directed at rate control.

Diltiazem has supplanted digoxin as the drug of choice for acute rate control of AF with RVR in stable patients. This change in practice is the result of evidence that, although digoxin is no more effective than placebo in slowing ventricular response in the first few hours, calcium channel blockers slow ventricular response within the first few minutes of IV administration (4). Neither diltiazem nor digoxin are particularly effective at producing cardioversion to sinus rhythm. In stable patients, diltiazem can be given at a dose of 5 to 10 mg IV over 2 minutes, repeated as necessary every 5 minutes to a total dose of 50 to 60 mg in the first 30 minutes. Following bolus injection, rate control can be maintained with an IV infusion of 5 to 15 mg/h. Although occasionally used to mitigate the hypotensive effects of diltiazem, IV calcium preparations are not supported by the literature in this regard.

Alternative rate control agents include β-blockers, digoxin, and magnesium. β-Blockers such as atenolol or metoprolol can be given in doses of 5 mg IV, repeated up to a total of 10 mg and 15 mg, respectively. β-Blockers are nearly as effective as diltiazem for rate control but may have a higher incidence of hypotension (7). Digoxin may be given as 0.5 mg IV or orally, followed by 0.25 mg, 4 and 8 hours later. Even when using these loading regimens, rate control is

no better than with placebo for at least several hours. Diltiazem may be given IV at the same time as digoxin, in the absence of other contraindications. Calcium channel blockers should be avoided in the presence of digitalis toxicity. There is evidence that IV magnesium is effective for rate control in AF, but although it is rarely used alone for this indication, it may be a useful addition to other therapies (8).

The ED management of stable patients with recent onset AF or flutter (RAFF) is controversial. RAFF, defined as <48 hours of symptoms, has many causes ranging from the benign to the life-threatening. It has long been standard practice to admit patients with RAFF to evaluate the possibility of serious underlying disease (e.g., acute myocardial infarction, mitral valve disease, pulmonary embolism, thyrotoxicosis, or drug effect) as its cause. However, 80% to 95% of stable patients with RAFF do not prove to have an acutely critical etiology, and those who do almost always have other worrisome clinical findings in addition to the dysrhythmia itself. Given the drive for cost-effective resource utilization and the emerging data, consideration may be given to discharging a reliable, hemodynamically stable, RAFF patient with no indications of serious underlying etiology, and prompt outpatient follow-up.

A second key management decision is intertwined with the decision to admit or discharge the patient with RAFF, whether to attempt cardioversion to sinus rhythm in the ED or merely control the ventricular response rate.

Rate control and admission is appropriate for high-risk but stable patients with RAFF. Rate control followed by discharge home on an oral rate control agent may be appropriate for low-risk patients for whom prompt follow-up can be arranged. Although this approach is widely used, evidence to support or refute its safety and efficacy is lacking. If this strategy is used the emergency physician should speak directly with the physician providing follow-up care to and agree on the time of the follow-up visit and the plan for rate control and anticoagulation.

In support of cardioversion of RAFF patients are several ED-based studies demonstrating a high success rate of cardioversion and an extremely low risk of stroke. In the largest prospective study of ED

cardioversion of RAFF patients, the authors observed no cases of stroke in over 600 patients discharged from the ED (8), albeit in a short follow-up period.

Pharmacologic agents that have been the subject of at least limited testing in the cardioversion of RAFF include amiodarone, clonidine, dofetilide, flecainide, ibutilide, magnesium, procainamide, propafenone, sotalol, and vernakalant. Rates of successful cardioversion and adverse effects vary. Of these procainamide has been more extensively studied for the cardioversion of RAFF. Procainamide has a 50% to 58% effectiveness rate and an acceptable safety profile when used in the ED (8,9).

The possible benefits of higher rates of earlier conversion using these drugs must be weighed against prodysrhythmic effects, a higher incidence of hypotension, and the fact that by 8 hours there is little difference from placebo in conversion rates. The spontaneous conversion rate of such patients is high, reaching 60% at 24 hours and 80% at 48 hours.

With the widespread adoption of safe and effective procedural sedation in the ED elective synchronized electrical cardioversion of PAFF has emerged as a viable therapeutic option. Often utilized following failed chemical cardioversion, success rates for electrical cardioversion are approximately 85% in selected patients with or without a preceding attempt at chemical conversion (10). Large ED case series have demonstrated a favorable safety profile (8).

Because of concerns about thromboembolic stroke, patient selection is important if either chemical or electrical cardioversion is to be attempted in the ED. Patients with AF >48 hours or of uncertain duration, and those at high risk of stroke (including a mechanical valve, rheumatic heart disease, prior stroke, and congestive heart failure) should not undergo elective ED cardioversion. To further reduce risk of stroke some centers perform TEE before elective cardioversion of RAFF.

In summary there is insufficient evidence to clearly guide the choice between rate versus rhythm control in stable patients with RAFF. The particulars of the specific patient and the local standard of

care will serve as a better guide for the practitioner than a blanket statement in support of either approach.

The therapy for unstable patients with AF and RVR is one of the most challenging situations in all of dysrhythmia management. Many of these patients have dilated atria and decreased ejection fractions. They do not easily cardiovert to sinus rhythm or remain in sinus rhythm if converted. In addition, cardioversion to sinus rhythm does not produce mechanical atrial contraction for hours to days. For this reason cardioversion should be considered a form of rapid rate control and not a therapy that immediately restores atrial systole. Finally, if the patient has been in AF for more than 2 days, intra-atrial thrombus may have formed and may embolize following cardioversion. For these reasons, cardioversion is considered by many a therapy of last resort, but if the patient is truly unstable, electrical cardioversion is required. The current American Heart Association (AHA) advanced cardiac life support (ACLS) recommendation is to cardiovert with a 120 to 200 J biphasic shock. Although traditional practice has been to cardiovert with an initial energy of 100 J, higher energies yield a somewhat greater success rate, and additional adverse effects appear to be minimal. Amiodarone has been used in unstable AF in a number of small case series and in one randomized trial in which it was found to be inferior to magnesium (11). Amiodarone slows ventricular rate and marginally increases the frequency of conversion to sinus rhythm. In rare cases, the cautious use of a vasopressor may be required to maintain blood pressure. The seriousness of this clinical situation cannot be overemphasized, and no therapy is without significant risk.

WIDE-COMPLEX TACHYCARDIAS

Wide Complex, Regular, No P Waves

Diagnostic possibilities include monomorphic VT, PSVT with aberrancy (bundle-branch block), and the antidromic SVT of WPW syndrome. Several clinical and ECG criteria have been devised to enable clinicians to distinguish between VT and SVT when the QRS

complex is wide. Useful indictors that make VT more likely include a history of heart disease, fusion and capture beats, and the presence of AV dissociation. Although such criteria are relatively accurate in predicting the source of tachycardia in series of patients, no single sign or combination of signs can definitively identify the origin of tachycardia (1). For this reason, wide-complex tachycardia should virtually always be treated as VT. Thus, drugs contraindicated in VT (e.g., verapamil) are almost never used to treat wide-complex tachycardia (12). Adenosine may be used to treat regular wide-complex tachycardia of uncertain etiology, because it is probably safe (if only very rarely effective) in VT and will convert most episodes of PSVT, including antidromic tachycardia associated with WPW syndrome.

Ventricular Tachycardia

VT (Fig. 85.4) is a macroreentrant rhythm that usually causes a life-threatening medical emergency. Although some patients have intermittent asymptomatic bouts of VT (usually episodes of <10 beats), patients who present to an ED with sustained VT are usually either suffering from significant hemodynamic effects or experiencing other acute cardiac problems—including, particularly, myocardial ischemia—that require emergent treatment.

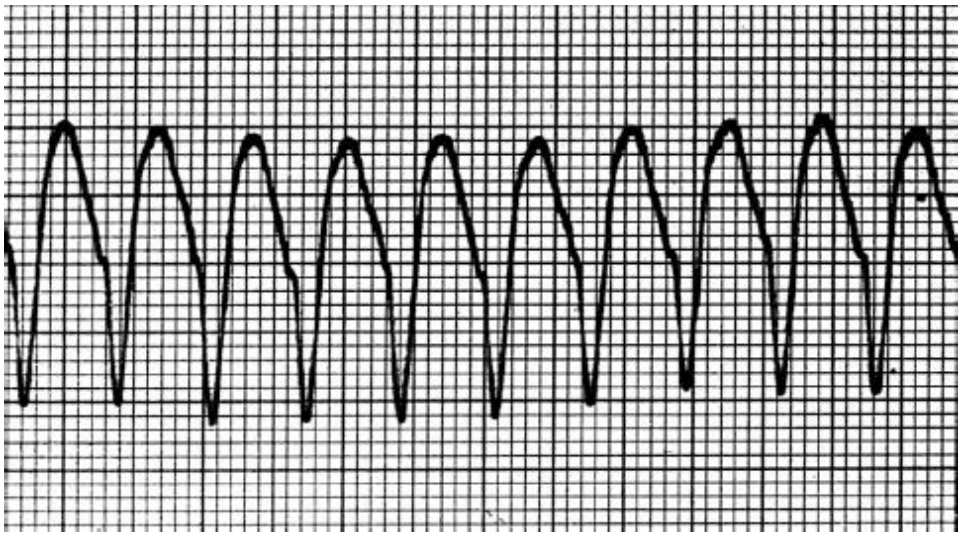

FIGURE 85.4 Ventricular tachycardia.

The very rapid heart rate of sustained VT usually causes hemodynamic deterioration. Such patients require emergent electrical cardioversion. Fixed dose single shocks have replaced the older “3-shock” protocol, and most guidelines recommend biphasic shocks of between 120 and 200 J (13). Cardioversion is performed in the synchronized mode to avoid precipitating VF. Amiodarone, procainamide, lidocaine, and magnesium are used to prevent recurrence of VT after successful cardioversion or to treat patients with recurrent VT. Despite a long history of use for this indication, lidocaine is of limited utility.

Sometimes, patients with sustained VT show no signs of hemodynamic instability in the short term. These patients can be treated with amiodarone, procainamide, or lidocaine, or magnesium. The medical literature does not provide a definitive basis for preferring one agent instead of another. Amiodarone is a common choice, but its efficacy has been questioned (14). Amiodarone can cause hypotension (treated with fluid bolus), AV nodal block, and rarely QT prolongation leading to torsade de pointes (TdP). Procainamide, an effective therapy for both VT and PSVT, should not be given at a rate of not more than 50 mg/min to avoid causing hypotension. Lidocaine is at best only moderately effective for the treatment of VT, and the literature in support of the use of magnesium for this indication is sparse. Failing pharmacologic conversion to sinus rhythm, synchronized cardioversion should be performed urgently, following appropriate sedation and analgesia. Essentially all patients with VT require consultation with a cardiologist and admission after ED therapy for the dysrhythmia.

Wide-Complex Paroxysmal Supraventricular Tachycardia

PSVT can manifest with wide QRS complexes when BBB (either underlying or rate-related) is present. The duration of the QRS complex in this circumstance is not likely to exceed 0.14 second, and heart rates usually range between 130 and 200 beats/min. Nevertheless, it is virtually impossible to be certain that a wide-complex tachycardia represents PSVT with bundle-branch block,

rather than VT; therefore, treatment should almost never be based on this assumption.

Wide QRS complexes are also seen in PSVT in association with the WPW syndrome when anterograde conduction occurs down the bundle of Kent and retrograde conduction occurs through the AV node. It may be possible to make this diagnosis from the ECG in patients with known WPW syndrome, although confusion with VT may still occur. When faced with a stable patient with a regular wide-complex tachycardia of uncertain etiology, adenosine is the preferred antiarrhythmic agent. Verapamil, diltiazem, β-blockers, and digoxin should be avoided in this circumstance.

When adenosine fails to convert regular wide-complex tachycardia or when VT is considered more likely, procainamide is a rational choice. Procainamide has antiarrhythmic effects on atrial and ventricular tissue, and it is generally safe and useful in most cases of wide-complex tachycardia, whether VT or PSVT with anterograde conduction through the bundle of Kent. Wide-complex tachycardia in the setting of possible drug overdose suggests cyclic antidepressant toxicity, in which case procainamide is absolutely contraindicated. Lidocaine can occasionally speed conduction through bypass tracts in experimental models and is therefore less attractive when wide-complex tachycardia is suspected to result from WPW syndrome-related PSVT.

Wide Complex, Irregular, No P Waves

Diagnostic possibilities include AF with bundle-branch block, AF with the WPW syndrome, polymorphic VT of which torsade de pointes is a subset, and VF.

Wide-Complex Atrial Fibrillation

A few patients with AF present with wide QRS complexes (Fig. 85.5), caused by an underlying or rate-related bundle-branch block or by the WPW syndrome. In the presence of known underlying bundle-branch block, treatment can be similar to that for routine narrow-

complex AF (i.e., cardioversion for severely unstable patients and diltiazem for rate control in stable patients).

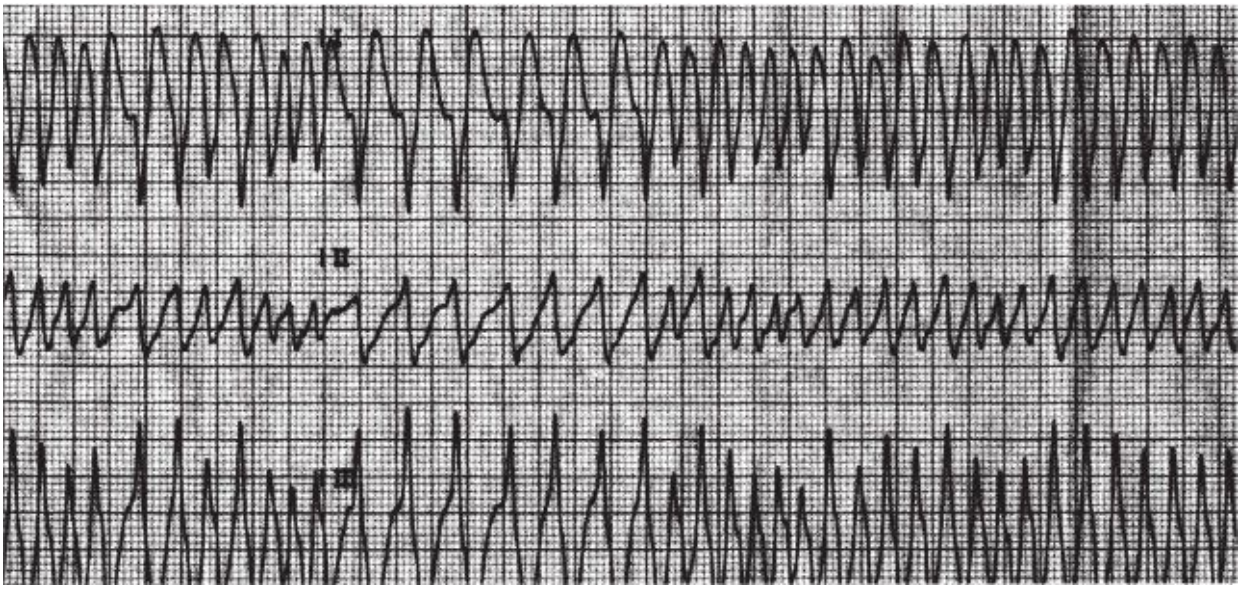

FIGURE 85.5 Atrial fibrillation in a patient with Wolff–Parkinson–White syndrome.

Patients with rate-related bundle-branch block often demonstrate both wide complexes (in beats that follow short RR intervals) and narrow complexes (in beats that follow longer RR intervals), but patients with AF and the WPW syndrome may also have both wide and narrow QRS complexes, depending on the conduction path followed by each depolarization. It is critical to recognize this latter entity, because agents that slow conduction through the AV node are absolutely contraindicated.

In WPW, the presence of rapidly conducting accessory pathways predisposes to a number of dysrhythmias, of which AF is the most dangerous. AF generates atrial impulses at 300 to 600 per minute. The accessory pathways of WPW syndrome, which bypass the AV node and its protective slowing, conduct impulses to the ventricle at rates exceeding 250 beats/min. The ventricle will fail or undergo fibrillation if these excessively rapid atrial impulses are conducted for more than a short period. Many patients are aware that they have WPW syndrome. Among patients who give no history of WPW

syndrome, the possibility should be considered when the irregular rhythm is wide and very fast and the QRS complexes are variable and bizarre.

Drugs such as adenosine, diltiazem, β-blockers, and digitalis are contraindicated in WPW syndrome with wide-complex AF, because they can actually increase the speed of conduction through the bypass tract. More importantly, relative blockade of the AV node causes preferential conduction through the bypass tract, thereby resulting in much higher ventricular response rates that can deteriorate into VF. Although amiodarone and procainamide are unlikely to be harmful in WPW syndrome-related AF, neither may be particularly effective in the acute setting. Therefore, even in the absence of acute hemodynamic deterioration, patients with WPW syndrome-related AF are best treated with electrical cardioversion.

Torsade de Pointes

Torsade de Pointes (TdP) is an unusual form of polymorphic VT characterized by the peculiar spiral pattern it produces on the surface ECG (Fig. 85.6). Drug-induced long-QT syndrome is the principle predisposing factor, with antiarrhythmic agents (e.g., ibutilide, procainamide, and sotalol) the most common inducing agents. Other drugs (most prominently, the phenothiazines and methadone), drug interactions, and many other conditions (especially hypocalcemia and hypokalemia) are also associated with TdP.

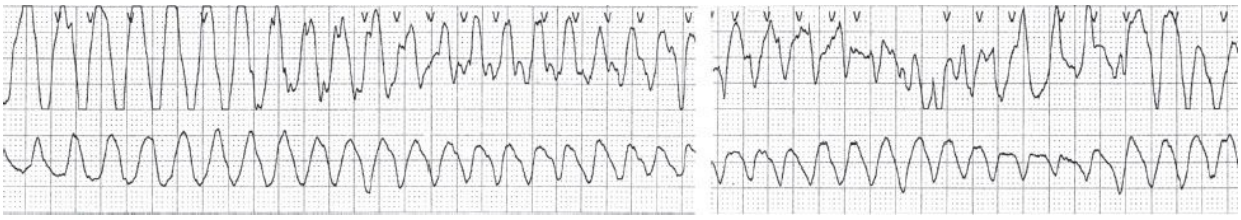

FIGURE 85.6 Torsade de Pointes.

Although most episodes of TdP are self-limited, they are nevertheless life-threatening, because any episode can precipitate VF. Because TdP usually converts spontaneously to sinus rhythm but

then recurs, treatment is directed at preventing recurrences rather than terminating a given episode. In the long term, this treatment often requires only withdrawal of the offending agent. In the ED, however, antiarrhythmic therapy is mandatory.

Magnesium, given as an IV infusion of 2 to 4 g over 5 to 10 minutes, is highly effective and is the treatment of choice for TdP (15). A normal serum potassium should be maintained. Alternately, overdrive electrical pacing can be used to speed the heart rate and thereby decrease the corrected QT interval and dispersion of refractoriness that is the underlying basis for this dysrhythmia. Infusions of isoproterenol have also been used with the same goal, although the prodysrhythmic effect of isoproterenol is worrisome.

Patients with polymorphic VT that is not TdP are almost invariably unstable and should be treated as VF with high-energy unsynchronized shocks. Patients with TdP may also have sustained episodes, may become severely unstable, and may require emergent unsynchronized electrical cardioversion. Since recurrence of TdP is so common, this treatment should be considered a temporizing measure, and magnesium should be promptly administered. Amiodarone and other antiarrhythmics that prolong the QT interval are contraindicated following cardioversion if TdP is suspected.

Ventricular Fibrillation

VF is the chaotic firing of the ventricle from multiple foci and never results in effective myocardial contraction. The only therapy shown to improve the outcome of patients with VF is electrical defibrillation (unsynchronized shocks), and delay in defibrillation is known to decrease survival. Accordingly, it has long been taught that when a defibrillator is available, no other activity should take precedence. Specifically, chest compressions (“cardiopulmonary resuscitation” or CPR) should be initiated only until the defibrillator is ready and charged, according to the 2010 AHAACLS guidelines for witnessed VF cardiac arrest (13). In unwitnessed VF cardiac arrest, the previous 2005 guidelines required 2 minutes of CPR before shocking. This strategy has been reversed in the 2010 guidelines based on two studies showing no benefit of intentionally delaying defibrillation to

perform CPR. Based on currently available evidence, defibrillation should be performed as soon as possible with CPR performed until the defibrillator is charged. This applies to both witnessed and unwitnessed VF, and pulseless VT arrest.

The previous practice of administering a single shock rather than three shocks at escalating energies has also been upheld in the 2010 ACLS Guidelines. The rationale for this change in strategy is the mounting evidence that reducing interruptions of CPR improves outcome, rather than convincing evidence that one or three shocks is more effective at terminating VF.

The optimal waveform and energy level for defibrillation of VF remain controversial. Biphasic waveform defibrillators have largely supplanted monophasic waveform defibrillators based on data demonstrating that biphasic defibrillation is more effective at terminating VF than monophasic defibrillation. Unfortunately, biphasic defibrillation has not been associated with any improvement in return of spontaneous circulation (ROSC) or survival to hospital discharge as compared to monophasic defibrillation (13). Although there is insufficient evidence to definitively determine an optimal energy for defibrillation using either waveform, the available evidence supports the following:

1. Biphasic defibrillation is effective at energy levels of 100 to 200 J. Biphasic defibrillators have differing waveforms and optimal energy levels for defibrillation. The specific energy level used should be based on manufacturer recommendation. Defibrillation with escalating higher energy levels was more effective than a fixed lower-energy protocol in a published randomized controlled trial (16). The 2010 ACLS guidelines recommend equal or greater energy levels be used for subsequent shocks (13).
2. Monophasic defibrillation is effective at 200 to 360 J. To date there is no evidence demonstrating superiority of the exclusive use of 360 J. On the contrary, defibrillation at 200 J may provide the greatest likelihood of success, and increasing the energy level may be detrimental (17).

Several adjunctive drugs are widely used when initial defibrillation is not successful. Although these drugs are considered standard therapy in this situation, it is important to remember that none of them has been definitively shown to increase the success of defibrillation or to improve long-term outcomes in humans with cardiac arrest. Thus, administration of these agents should never interfere with the rapid use of electrical defibrillation.

Specifically, no study has confirmed a positive effect of epinephrine use at either standard or high doses. Vasopressin has not been shown to be superior to epinephrine but remains on the ACLS protocol as an adjunct or alternative to epinephrine (18). Similarly, there is little evidence that amiodarone or lidocaine significantly improves outcomes in refractory VF. Amiodarone has supplanted lidocaine as the drug of choice, based on evidence suggesting that it is marginally more effective in achieving ROSC and survival to hospital admission (13,19).

IV amiodarone, procainamide, or lidocaine is used to help prevent recurrence of VF after successful defibrillation. Amiodarone is possibly more effective than lidocaine for this indication.

CRITICAL INTERVENTIONS

- Have a defibrillator and advanced airway equipment at bedside
- Perform immediate defibrillation for patients in VF
- Perform electrical cardioversion for unstable patients with a very rapid tachydysrhythmia except sinus tachycardia and MFAT
- Use a systematic approach to tachydysrhythmia identification

DISPOSITION

In most cases, the disposition of patients with tachydysrhythmia is apparent. The patient resuscitated from cardiac arrest resulting from VF obviously must be admitted to the intensive care unit. Similarly, there should be little controversy about discharging a healthy young patient with a brief, minimally symptomatic episode of PSVT that readily converted to sinus rhythm. In the few patients with a problematic disposition, the physician should remember that ED care

involves only initial therapy and not definitive management of the tachydysrhythmia. Several categories of patients should be admitted:

- Patients who are symptomatic after acute onset of tachycardia and who have failed appropriate therapy or responded only transiently.
- Patients who were clinically unstable as a result of a tachycardia, including all patients who require cardioversion because of end-organ hypoperfusion.
- Patients who were treated successfully before the development of serious symptoms but who have the potential for decompensation if the tachydysrhythmia recurs.

The basis of the dysrhythmia also plays a role in disposition decisions: Any patient with a realistic likelihood of a dangerous etiology (e.g., possible acute coronary syndrome) should be admitted, even if the dysrhythmia itself was benign. Finally, it may be appropriate to admit a stable patient for continuous ECG monitoring during initiation of chronic drug therapy.

Common Pitfalls

- Being overly concerned with definitive diagnosis. One should concentrate more on the hemodynamic effects of the rhythm than on its origin.
- Reliance on ECG and clinical findings to identify the likely anatomic source of a dysrhythmia. ECG and clinical findings are suggestive but not infallible guides.
- The use of a calcium channel blocker to treat a wide-complex tachycardia. Calcium channel blockers are appropriate for many narrow-complex tachycardias but can precipitate VF in wide-complex tachycardias, including those other than VT.
- Treatment of symptoms rather than the tachydysrhythmia precipitating those symptoms. In patients having symptoms related to a very rapid tachycardia, controlling the ventricular rate usually ameliorates the symptoms.
- Failure to seek and, if possible, correct the factors that precipitated a tachydysrhythmia. Examples include hypoxemia,

infectious or inflammatory processes, intoxications, and noncompliance with antidysrhythmic medications.

- Failure to consider myocardial ischemia in all patients. An acute coronary syndrome must be ruled out whenever it seems a reasonably likely cause of the dysrhythmia or when the dysrhythmia has itself produced a substantial period of ischemia as suggested by ECG changes or symptoms.
- Delays or errors in CPR and defibrillation during cardiac arrest. High-quality CPR and defibrillation are the only interventions shown to improve outcomes in cardiac arrest patients.

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CHAPTER 86

Pacemakers and Implantable Cardioverter–Defibrillators

Robert M. Rodriguez

PACEMAKERS

The first permanent cardiac pacemakers were implanted in the late 1950s; since that time, advances in microprocessor technology have led to the production of compact pacemakers that readily adapt to changes in patient physiology (14). Current dual-chamber pacemakers are rate-responsive to increased patient activity with batteries that may last longer than 10 years (16). Beyond simple treatment for bradycardia syndromes, the therapeutic utility of pacemakers has grown over the years. Recent trials have demonstrated the efficacy of pacemakers in the prevention and treatment of atrial fibrillation and as adjunctive therapy for patients with congestive heart failure and ventricular dyssynchrony (1,5,8).

Given that more than 1 million Americans currently have pacemakers and the rate of implantation is steadily increasing (14,19), the emergency department (ED) physician will undoubtedly care for many patients with these devices. Although detailed knowledge of the myriad complexities of pacemaker programming and operation is unnecessary, the emergency physician must understand the basics of pacemaker terminology and function and must be familiar with the presentation, evaluation, and treatment of common pacemaker-related problems.

Central to the understanding of basic pacemaker function are the five-letter codes used by the North American Society of Pacing and Electrophysiology–British Pacing and Electrophysiology Group (NASPE/BPEG) to characterize the modes of operation of current pacemakers (Table 86.1). In everyday practice, description of the mode of pacing is limited to the use of the first three code letters: position I, chamber(s) paced; position II, chamber(s) sensed; and position III, pacemaker response to sensing. A VVI pacemaker thus paces the ventricle only, senses only ventricular depolarizations, and inhibits pacemaker output in response to a sensed ventricular depolarization. The vast majority of currently implanted devices are DDD pacemakers (14), which pace the atria, the ventricles, or both; sense atrial depolarizations, ventricular depolarizations, or both; and either inhibit or trigger pacemaker output to the atria and ventricles in response to sensed depolarizations. Intrinsic ventricular depolarizations will inhibit both atrial and ventricular output; intrinsic atrial depolarizations will inhibit atrial pacemaker output and will trigger ventricular output if the ventricle itself does not respond after a programmed time interval.

TABLE 86.1
North American Society of Pacing and Electrophysiology–British Pacing and Electrophysiology Group (NASPE/BPEG) Defibrillator (NBG) Codes

First Position Indicates the Chamber Paced

V = ventricle
A = atrium
D = dual
O = no pacing

Second Position Indicates the Chamber Sensed

V = ventricle
A = atrium
D = dual
O = no sensing

Third Position Indicates the Response to a Sensed Event

I = inhibited
T = triggered/tracking
D = dual
O = no response

Fourth Position Indicates Programmability and Rate Response

O = not programmable
P = simple programming (three functions or less)
M = multiprogrammable (more than three functions)
C = communicating (M + telemetry capabilities)
R = rate responsive

Fifth Position Indicates Antitachydysrhythmia Functions

O = none
P = pacing
S = shock
D = dual (shock and pacing)

From Love C, ed. *Handbook of Cardiac Pacing*. Georgetown, TX: Landes Bioscience; 1998, with permission.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Syndromes of pacemaker malfunction can generally be divided into those that cause underpacing, with associated bradycardia, hypotension, light-headedness, and syncope and those that produce overpacing, manifested by tachycardia and palpitations with or without ischemia or hypotension symptoms.

The differential diagnosis of these nonspecific presenting complaints is broad, and the clinician should consider other disorders, including intrinsic dysrhythmias, vasovagal phenomena, anemia, hypovolemia, and nonrate-related syndromes of low cardiac output. Before attributing these nonspecific presenting symptoms to the uncommon entity of pacemaker failure, the physician must first determine whether the device is truly malfunctioning. Patient history, electrocardiographic (ECG) analysis, and identification of the current programming and specifications of the pacemaker are the keys to making this determination.

ED EVALUATION

In addition to elucidating standard history about the symptoms, time course, and precipitants related to the presenting complaint(s), the physician should also seek the following information regarding the pacemaker: pacemaker model, current programming, date of implantation, indication for implantation, history of pacemaker malfunction, and dates of last interrogation and battery check. Some of this vital information may be obtained from the pacemaker identification card, which the patient should carry at all times. If this card is unavailable, a chest radiograph may reveal the pacemaker's identifying serial number or code (15). For technical support or to find out other information about the pacemaker, the physician may call the pacemaker manufacturer's assistance department.

The emergency physician should also ask about exposure to potential sources of environmental electromagnetic interference with pacemaker function. Although most of the everyday appliances and devices pose virtually no risk to current pacemakers, electric toothbrushes, cellular telephones, induction ovens, and stove plates can markedly alter their operation. Most of the modern airport security gates pose minimal risk, but antitheft systems in stores emit signals of variable intensity, with unpredictable effects on pacemaker function (11).

Because pacemakers typically produce left bundle-branch block (LBBB) and other altered patterns of depolarization, the ECG diagnosis of myocardial ischemia or acute myocardial infarction (AMI) may be difficult, and patients with pacemakers have been shown to be less likely to receive reperfusion therapy and aspirin (27). In the absence of ischemia, discordant T waves after paced beats are the norm and minor ST-segment evaluations inferiorly and anteriorly (leads V_1 to V_3) and ST-segment depression (leads 1, V_1, V_5, and V_6) also occur commonly (4). Even after the patient's native, spontaneous rhythm emerges, transient ST-segment and T-wave abnormalities may be seen (4).

Despite these difficulties in AMI pattern recognition, the clinician should nonetheless look for ST-segment and T-wave changes in comparison to the patients' old ECG-paced rhythms. In the absence of such old ECGs, the physician may still diagnose MI in the patient with a pacemaker by applying the criteria used in the evaluation of patients with intrinsic LBBB (4). Concordant ST-segment elevations, ST-segment depression in leads V_1, V_2, and V_3, and markedly elevated (>5 mm) discordant ST segments are highly indicative of MI, especially when the T waves associated with these segments are of opposite polarity (4,23). A qR pattern after the pacemaker spike in leads I, V_1, and V_5 has low sensitivity but very high specificity for anteroseptal MI (4). In a meta-analysis of the diagnostic utility of the ECG algorithm of these patterns for the detection of MI in patients with intrinsic LBBB, investigators found that the algorithm had poor sensitivity (20%) but high specificity (98%) and a summary positive likelihood ratio of 7.9 for the prediction of MI (25). The few case series directly examining MI in patients with pacemakers have demonstrated similarly high specificity and low sensitivity of these Sgarbossa patterns (28,29). The emergency physician should therefore look for these patterns of MI, but, given their low sensitivity, their absence does not rule out ischemia or infarction.

Malfunction Associated with Bradycardia

Pacemaker malfunction leading to a slow pulse arises from noncapture, pacemaker output failure, or pacemaker oversensing. Noncapture refers to an absence of ventricular or atrial depolarization after a pacemaker spike (Fig. 86.1). The most common cause of this condition is pacemaker lead dislodgement, which typically occurs within a few weeks of implantation (11). Other mechanical causes include insulation breaks, lead fracture, and inflammatory reaction at the lead tip (11). Reversible metabolic abnormalities, such as hyperkalemia, and drug effects should also be considered. Of note, if a pacemaker spike occurs within 300 milliseconds of a prior ventricular depolarization, the ventricle may be in its refractory period and lack of capture is expected (11). In this case, the pacemaker may be firing early because of undersensing the prior depolarization, but it is not truly malfunctioning with regard to pacing (Fig. 86.2).

FIGURE 86.1 Noncaptured pacemaker spike between two captured spikes.

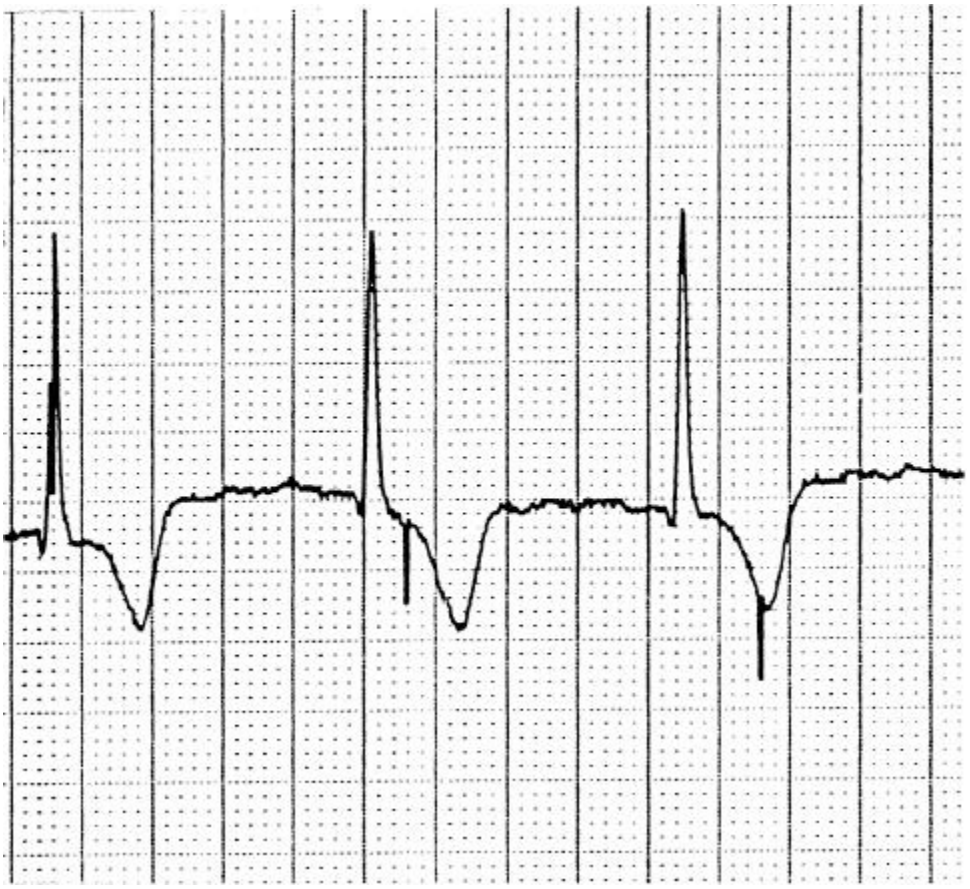

FIGURE 86.2 Pacemaker undersensing.

Absent or inappropriately delayed ventricular pacemaker spikes on the ECG of a patient with bradycardia indicate primary pacemaker output failure, battery depletion, or output failure secondary to oversensing (reading other signals as true ventricular depolarizations) (11). Causes of primary output failure include lead fracture or disconnection and various pulse generator component failures. Oversensed signals may be of cardiac (P and T waves) or extracardiac (myopotential) origin and lead to inappropriate inhibition of pacemaker ventricular output (11).

These causes of absent or delayed pacemaker spikes may be distinguished by performing a magnet test of the pacemaker.

Application of a ring magnet over a normally functioning pacemaker disables sensing and induces asynchronous pacing at model-specific rates, which may be determined by checking the patient's records or calling the pacemaker manufacturer (11,15). If the problem is oversensing, the magnet will induce asynchronous pacing at that model's characteristic rate. If battery depletion is the cause, asynchronous pacing will occur at a different, generally slower rate (11). If the malfunction is a result of lead displacement or some other circuit disruption, no pacing response to the magnet will be seen.

Malfunction Associated with Tachycardia

Pacemakers may produce inappropriate tachycardia by several mechanisms. When a pacemaker fails to sense intrinsic ventricular depolarizations, it will fail to inhibit pacemaker output, potentially causing a pacemaker-driven tachycardia, that is, "undersensing leads to overpacing" (15). In dual-chamber systems, the pacemaker circuit may act like an accessory pathway similar to those seen in Wolff–Parkinson–White syndrome, thereby propagating a re-entrant tachycardia known as pacemaker-mediated tachycardia or "endless-loop tachycardia" (15). This dysrhythmia may be terminated by vagal maneuvers, external magnet induction of asynchronous pacing, intravenous adenosine, or transthoracic cardiac pacing with 10 to 20 mA of output (9,15).

A final pacemaker-related tachycardia that occurs only rarely with current pulse generators is "runaway pacemaker," a potentially lethal disorder in which battery depletion or other component failure causes extremely rapid pacing, with rates restricted only by the pacemaker's upper rate limit (13). This disorder may not respond to traditional therapies to decrease the rate, including medications and cardioversion/defibrillation, and, in the setting of hemodynamic instability, the emergency physician should attempt to disable the runaway pacemaker by incising over the pacemaker pocket and disconnecting the pulse generator leads (13).

Pacemaker syndrome, a classic example of a pacemaker operating correctly according to its programming yet still causing bothersome symptoms, results from the loss of atrioventricular synchrony (15). Fatigue, light-headedness, syncope caused by decreased cardiac output (loss of atrial kick), and disturbing neck pulsations related to regurgitant cannon A waves (atria contracting against closed atrioventricular valves) are the predominant symptoms. Although this disorder is largely limited to patients with VVI pacemakers and is usually ameliorated with a change to synchronized dual-chamber pacing, it can occasionally occur in patients who have DDD pacemakers (11).

Infectious and Mechanical Complications of Pacemakers

In addition to rhythm and hemodynamic problems associated with pacemakers, foreign-body-related complications also occur. With *Staphylococcus* species being the most common pathogens, the incidence of pacemaker or implantable cardioverter defibrillator (ICD) infection is 1.9 per 1,000 device-years (26). In the patient presenting with fever and redness and tenderness over the pulse generator pocket, the diagnosis of pacemaker infection is obvious. Subtler presentations, however, are common, and the emergency physician should consider pacemaker-related infection as a potential cause of unexplained fever in any patient with a pacemaker. Notably, without superimposed endocarditis, embolic phenomena and murmurs are generally absent. Nuclear medicine scans may provide ancillary evidence of infected pacemaker hardware. Confirmed pacemaker infection mandates a course of parenteral antibiotics, and most authorities agree that removal of the device is indicated (19).

Pacemaker-associated thrombosis of the upper extremity vessels is uncommon, but it should be considered in the patient with unilateral arm swelling, erythema, or pain (7). Ultrasound or venography may be used to distinguish this entity from similar-appearing arm cellulitis. Anticoagulation without pacemaker removal has been reported to successfully treat the thrombosis (7).

ED MANAGEMENT

As with other ED problems, patient stability determines the urgency of intervention in the patient with a pacemaker. The cardiac arrest patient should receive standard advanced cardiac life support (ACLS)-guided resuscitation. During defibrillation or cardioversion, the physician should avoid placing pads or paddles directly over the pulse generator (9). Pacemakers of resuscitation survivors should be evaluated for damage or reprogramming arising from countershocks. In nonsurvivors, the pacemaker may continue to produce ECG spikes without associated ventricular capture, which represents isolated pacemaker activity and not true pulseless electrical activity.

The pacemaker patient with hypotensive bradycardia should receive the usual therapeutic measures (chronotropic support with medications, external pacing, or transvenous pacing). The physician may attempt to temporarily asynchronously pace the patient's rate with higher current by placing a ring magnet over the pacemaker, as described earlier in this chapter (11). This maneuver may be helpful if the pacemaker is oversensing, thereby suppressing output (absent or inappropriately slow rate of pacemaker spikes on ECG) or if low pacemaker current is leading to noncapture.

In the ED management of pacemaker patients, the physician must recognize that magnetic resonance imaging (MRI) and electrocautery may interfere with pacemaker function. Given that MRI may induce complete block of pacemaker output, severe pacemaker-driven tachycardias, and other potentially disastrous pacemaker malfunction, MRI is contraindicated for patients with pacemakers (11). If MRI is absolutely essential to patient management, some authorities have suggested switching the pacemaker to its "off" mode, turning pacemaker output down so that it will not capture, or surgically removing the device (3), all of which must be undertaken with the help of an electrophysiologist. Electrocautery may also induce a number of hazardous abnormalities in pacemaker function; precautions and steps to

minimize risk during surgical procedures are described elsewhere (3).

DISPOSITION

Disposition of the patient with a pacemaker-related problem largely depends on the severity of signs and symptoms and should be determined collaboratively with the patient's electrophysiologist. Patients with pacing malfunction, such as failure to capture or battery depletion, should be admitted to monitored settings. Patients requiring a higher level of care may need interhospital transfer. In these cases ACLS ambulance units should be used, and the patient's rhythm and hemodynamics must be stabilized prior to transfer; backup pacing modalities (transthoracic or transvenous) should be in place during transit.

IMPLANTABLE CARDIOVERTER&NDASH;DEFIBRILLATORS

The first ICD was placed in 1980, and, as with pacemakers, technologic improvements have produced smaller, "smarter" defibrillators that are more easily implanted (6). Early models were nonprogrammable shock or no-shock devices that required open thoracotomy for epicardial patch placement. Current programmable devices have defibrillator leads that are inserted transvenously and utilize improved rhythm-analysis algorithms to deliver sequential, tiered therapy. For example, slow ventricular tachycardia (VT) may be first treated with overdrive pacing; if this fails to convert the VT, low-energy shocks are delivered. If these shocks also fail, higher energy shocks are given (15). Many ICDs also incorporate pacing functions that may be activated if cardioversion or defibrillation produces a bradycardic or asystolic rhythm.

As with pacemakers, the indications for ICD implantation have also expanded. Major trials examining the treatment of patients with frequent ventricular dysrhythmias have demonstrated increased mortality with pharmacologic dysrhythmic therapy but markedly decreased mortality with ICDs (6). Prophylactic placement of an ICD

has also been demonstrated to increase survival in patients who have post-MI low ejection fractions even without electrophysiologic evidence of sustained dysrhythmias (20). In 2002, nearly 100,000 ICDs were placed in the United States (19).

NASPE/BPEG descriptive codes also characterize the types and functions of ICDs (15): position I, chamber(s) shocked; position II, chamber(s) for antitachycardia pacing; position III, method of tachycardia detection; and position IV, chamber(s) for bradycardia pacing (Table 86.2). In everyday practice, these codes are less commonly used than are pacemaker codes.

TABLE 86.2
North American Society of Pacing and Electrophysiology–British Pacing and Electrophysiology Group (NASPE/BPEG) Codes for ICDs

First Position Indicates the Chamber Shocked

V = ventricle

A = atrium

D = dual

O = no shock therapy

Second Position Indicates the Chamber for Antitachycardia Pacing

V = ventricle

A = atrium

D = dual

O = no antitachycardia pacing

Third Position Indicates the Method of Tachycardia Detection

E = electrogram

H = hemodynamic

Fourth Position Indicates Chambers for Bradycardia Pacing[a]

V = ventricle

A = atrium

D = dual

O = no bradycardia pacing

[a]Alternatively the three- or four-letter NBG pacing code may be used following the first three letters of the NBD code (e.g., VVE-VVIR, indicating ventricular shock, ventricular ATP, electrogram detection, and VVIR pacing capability).

From Love C, ed. *Handbook of Cardiac Pacing*. Georgetown, TX: Landes Bioscience; 1998, with permission.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

The rate of ICD malfunction is approximately 20-fold higher than that of pacemaker malfunction (18). Patients with ICD malfunction generally present with either defibrillation–cardioversion failure or inappropriate ICD discharge. Defibrillation–cardioversion failure may result from failure to deliver a shock, analogous to pacemaker output failure, or from failure of delivered shock(s) to convert the dysrhythmia, analogous to pacemaker noncapture. In recent studies, 7.4% to 7.9% of patients with an ICD experienced a discharge per year. Of these, less than half (approximately 45%) of shocks were deemed appropriate (10). Although the potential lethality of inappropriate ICD discharge is less than that of ICD failure to discharge, repeated shocks may cause myocardial injury, temporary

ventricular dysfunction, and rapid battery depletion (21). Furthermore, shocks may be very painful and anxiety-provoking. Because all ICDs use ventricular rate as the primary criterion for ICD activation, the most common causes of recurrent discharges are supraventricular dysrhythmias, sinus tachycardia, and nonsustained VT (13).

ED EVALUATION AND MANAGEMENT

In a study of the mechanisms of sudden death of patients with ICDs, the most common causes were (i) electromechanical dissociation (EMD) after ICD conversion of ventricular fibrillation (VF) or VT (29%); (ii) shock failure defined as VT or VF that was not terminated by the full complement of four to six ICD shocks (26%); (iii) primary EMD not involving VT or VF (16%); and (iv) VT/VF that was successfully converted but recurred again and again (13%) (18). Considering these primary causes, when treating the ICD patient in cardiac arrest, the physician should focus on treating potentially reversible causes of EMD and on further attempts to convert persistent or recurrent VT/VF. Resuscitation should generally follow the standard ACLS protocols for cardiac arrest (21). Most ICDs analyze and shock VF or VT within 30 seconds; therefore, if a patient presents in these rhythms, the physician should assume that ICD defibrillation–cardioversion has been unsuccessful and should immediately proceed with external countershocks (10). However, to prevent ICD absorption of current, defibrillator pads or paddles should not be placed directly over the device and, when feasible, should be positioned anteroposteriorly (10). Chest compressions should be given in the standard fashion. Without gloves, the rescuer may feel a slight, harmless shock if an ICD discharges during compressions (10).

After successful resuscitation, the emergency physician should investigate the events surrounding the arrest, focusing on the few causes of ICD failure (electrolyte imbalance, myocardial ischemia or MI, and drug effects) that may be treated without ICD reprogramming or surgery. The physician should ask the patient if

he or she recalls chest pain, palpitations, or ICD discharges. As with the pacemaker patient, the emergency physician should use direct history, the patient's ICD card, medical records, and telephone calls to the ICD manufacturer to gather information about the ICD, including recent ICD interrogation and prior ICD malfunction. Repetitive shocks occurring seconds apart during intense exercise are more likely to represent an inappropriate response to sinus tachycardia, and conversely shocks to the resting patient are likely to be appropriately treating ventricular dysrhythmias (10). The emergency physician should ask about exposures to the sources of environmental electromagnetic interference described earlier in the section on pacemakers. The many etiologies of ICD malfunction may be explored later by an electrophysiologist through interrogation. In addition, referral to an electrophysiologist is essential to evaluate the ICD for lead fracture or displacement caused by chest compressions and for pulse generator damage or reprogramming arising from external countershocks (21).

When rapid atrial fibrillation triggers frequent ICD discharge, the physician should attempt to slow the ventricular rate with the usual pharmacologic agents (21). If, after a period of close monitoring, it is determined that frequent ICD discharges are inappropriate or if frequent ineffective ICD discharges are interfering with resuscitation, the physician may disable the ICD by applying a ring magnet to the chest wall over the device (21). Occasionally, two magnets, stacked one on top of the other, are required to deactivate the ICD in markedly obese patients (21). Although the magnet suspends all antitachycardia functions (the ICD will not deliver a shock for VT), backup pacing functions of the ICD may persist.

If the ICD is delivering multiple appropriate shocks for ventricular dysrhythmias, the physician should consider administration of antiarrhythmic medications, such as amiodarone (10). Attention to hemodynamics, close monitoring, and sedation or analgesia for the anxious patient are other keys to ED management of frequent ICD discharges. The emergency physician must understand that although a ring magnet generally causes changes in pacemaker function only during application of the magnet (i.e., the pacemaker resumes its

normal function after removal of the magnet), a magnet may reset some ICD models to the "off " mode indefinitely (21). Therefore, if a magnet is either intentionally or inadvertently applied to an ICD, the physician should assume the device has been deactivated and should arrange for ICD interrogation and reprogramming.

The rate of ICD infections is higher than that of pacemakers (26). The presentation and management of infectious and thrombotic complications of ICDs parallel those of pacemakers, except that ICD infections may be more serious and difficult to treat (19). Hospital admission for administration of parenteral antibiotics and hardware removal is recommended for all infected ICDs (19). If the patient has an older model with epicardial patches, computed tomographic imaging of the heart and mediastinum is warranted to determine the extent of mediastinal involvement.

CRITICAL INTERVENTIONS

- Distinguish between causes of absent or delayed pacemaker spikes by performing a magnet test of the pacemaker, which, in a normally functioning pacemaker, disables sensing and induces asynchronous pacing at model-specific rates.
- Avoid placing pads or paddles directly over the pulse generator during defibrillation or cardioversion.
- Disable the ICD by applying a ring magnet to the chest wall over the device if frequent, inappropriate ICD discharges are causing substantial patient discomfort or are interfering with resuscitation. However, this action may reset the ICD to "off," even after removal of the magnet, so the ICD must subsequently be interrogated or reprogrammed.

DISPOSITION

Given the potentially catastrophic consequences of ICD failure, urgent referral to an electrophysiologist is recommended for essentially all types of ICD malfunction. ICD patients should be observed in or admitted to monitored settings until specialist evaluations are completed. If specialist evaluation or higher level of

care issues mandate transfer to another facility, ACLS units should be used and transthoracic (anteroposterior) defibrillation/pacing pads should be applied to the patient prior to transit. Patients who experience an ICD discharge, especially with associated lightheadedness or impairment of consciousness, should be instructed not to drive until they are cleared by their electrophysiologist (10).

Common Pitfalls

- Misdiagnosing pacemaker or ICD malfunction because of inadequate information about the current programming and operation of the device. The physician should gather as much information about the pacemakers or ICDs as possible from patient history, device identification cards, pacemaker or ICD registration departments, and patients' cardiologists or electrophysiologists.
- When evaluating the pacemaker patient for MI, failing to understand both the utility and the limits of 12-lead ECG interpretation. Several ECG patterns have high specificity and are reliable indicators of ischemia or infarction during RV pacing, but a normal LBBB pattern of pacing does not rule out infarction or ischemia.
- In a patient with cardiac arrest, allowing the presence of a pacemaker or ICD to change resuscitation procedures. Other than anteroposterior positioning of paddles and avoiding shocks over the devices, resuscitation should generally follow the usual ACLS protocols.
- Assuming that—after magnet application over an ICD or after cardioversion or resuscitation of a patient with an ICD or a pacemaker—the device has reverted to its normal programming and operation. The ICD or pacemaker must be re-evaluated after these procedures.
- Failing to make disposition decisions for most pacemaker problems and for essentially all cases of ICD malfunction in collaboration with an electrophysiologist.

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CHAPTER 87

Valvular Heart Disease

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A wide variety of diseases and conditions can affect the heart valves (Table 87.1). In the 1950s, virtually all patients with clinically significant valvular disease had complications of acute rheumatic fever or syphilis, or congenital heart disease. Since then, the pattern of disease responsible for valvular dysfunction in adults has changed dramatically in highly industrialized countries such as the United States. The major reasons for this shift are a marked decline in the incidence and better early treatment of acute rheumatic fever and syphilis; the wide availability of invasive and noninvasive testing to detect valvular heart disease; the development and perfection of surgical techniques for the repair or replacement of diseased valves; the increased longevity of the general population, allowing even normal valves to be subjected to more years of wear and tear; and sociocultural changes in our society (e.g., intravenous drug abuse).

TABLE 87.1
The Most Common Causes of Valvular Heart Disease in Adults

Cause	Specific Disease	Valves Affected	Murmur
Congenital	Bicuspid value	A	S, R
Rheumatic	Rheumatic fever	M > A > T > P	S, R
Infectious	Endocarditis	A, M (rheumatic) A, M, T, P (i.v. drugs)	R
Myxomatous degeneration	Prolapse	M:T	R
	Aortic root dilatation	A	R
Degenerative aging	Sclerosis	A	S

A, aortic; M, mitral; P, pulmonic; T, tricuspid; S, stenotic; R, regurgitant; i.v., intravenous.

Regardless of the cause, significant acute or chronic valvular dysfunction has predictable hemodynamic consequences. Regurgitant lesions (e.g., mitral or aortic regurgitation) cause volume overload of the affected atrium or ventricle. Although massive acute regurgitation can lead to shock and pulmonary edema rapidly, mild-to-moderate volume overload is usually tolerated well until after months or years, when the ventricle will often dilate and fail, leading to signs and symptoms of heart failure. Stenotic lesions above, at, or below the valve can cause pressure overload of the affected atrium or ventricle. Pressure overload is metabolically more costly to the myocardium than volume overload and leads to myocardial hypertrophy and eventual heart failure.

The combined hemodynamic effect of multiple valvular lesions is often complex. Some compound lesions (e.g., combined aortic regurgitation and stenosis) impose a tremendous burden on the myocardium by producing both volume and pressure overload of a single chamber (in this example, the left ventricle). Other combination lesions may be “protective” of a given chamber (e.g., in aortic stenosis combined with mitral stenosis, the volume of blood reaching the left ventricle is decreased, thereby “protecting” it to some extent from manifesting heart failure). However, the net effect may be to decrease forward, and thus net, cardiac output.

Some valvular lesions produce a rapidly downhill course. For example, acute, severe mitral, or aortic regurgitation can lead rapidly to pulmonary edema, shock, or both, which can usually be remedied only by immediate valve replacement. Other lesions, such as chronic

mitral or aortic regurgitation, can be tolerated well for decades. A structurally abnormal valve puts the patient at increased risk of developing infective endocarditis, which can further impair valvular function. Other concomitant diseases (e.g., coronary atherosclerosis, myocarditis), dysrhythmias (e.g., atrial fibrillation), or valvular calcification can also unfavorably influence the patient's symptoms and length of survival.

CLINICAL PRESENTATION

Patients with valvular heart disease may present to the emergency department (ED) with a complication of previously known disease, or they may challenge the emergency physician to evaluate a previously undetected and undiagnosed heart murmur (1). If complex congenital heart diseases, such as Tetralogy of Fallot, are excluded, complications of adult valvular heart disease are most often the result of left heart lesions (Table 87.2).

TABLE 87.2
Common Complications of Left Heart Valvular Disease in Adults

Valvular Lesion	Common Complications(s)
Mitral stenosis	Pulmonary edema, atrial fibrillation, systemic embolism
Mitral regurgitation	Heart failure, endocarditis
Aortic stenosis	Angina, syncope, heart failure, dysrhythmias, sudden death, endocarditis
Aortic regurgitation	Heart failure, endocarditis

When a patient with a heart murmur presents to the ED with symptoms that could be caused by valvular heart disease, an immediate question is whether the heart murmur is *causing, unrelated to,* or *caused by* the symptom complex. For example, if a 70-year-old man with dyspnea and moderate pulmonary edema on chest X-ray has a grade 3/6 systolic ejection murmur at the left upper sternal border and cardiac apex, the murmur may be caused by aortic stenosis or mitral regurgitation, either of which could cause heart failure. The patient's heart failure could also be caused by an

unrelated problem, such as ischemic heart disease, cardiomyopathy, myocarditis, or a congenital shunt lesion (e.g., atrial septal defect). Finally, left ventricular (LV) failure and dilatation could be causing a "functional" murmur owing to dilatation of the mitral valve and its supporting structures (papillary muscle dysfunction).

Myocardial ischemia (e.g., during angina) can also increase the murmur of papillary muscle dysfunction. "Functional" tricuspid regurgitation can be caused by right ventricular dilatation secondary to left heart failure. In practice, it is sometimes impossible to determine the relationship between the murmur and the patient's symptoms without further diagnostic evaluation, such as echocardiography or cardiac catheterization.

Common conditions affecting the heart valves in adults presenting to the ED are (i) mitral valve prolapse (MVP); (ii) aortic valve sclerosis in the elderly, with or (more typically) without significant stenosis; (iii) valvular aortic stenosis resulting from congenital bicuspid aortic valve; (iv) mitral regurgitation caused by papillary muscle dysfunction, rheumatic heart disease, infectious endocarditis, or ruptured chordae tendineae; (v) aortic regurgitation caused by rheumatic fever, infectious endocarditis, bicuspid aortic valve, or aortic root disease; and (vi) mitral stenosis resulting from rheumatic fever.

ED EVALUATION

A careful cardiovascular physical examination, beginning with the pulse and blood pressure, often identifies the cause of a heart murmur (2). A wide pulse pressure accompanied by a brisk (often bifid) carotid upstroke and a bounding ("water-hammer") peripheral pulse is common in moderate-to-severe aortic regurgitation; a narrow pulse pressure with a slow, delayed carotid upstroke ("pulsus parvus et tardus") is found in severe aortic stenosis. When a harsh systolic murmur suggesting valvular aortic stenosis is accompanied by a brisk carotid upstroke (and *no* aortic regurgitation), idiopathic hypertrophic subaortic stenosis (IHSS) should be suspected. In a young person (especially male), hypertension in the upper extremities and a *lower* arterial pressure in the legs with a weak

femoral pulse and a basal systolic murmur suggests coarctation of the aorta (which is associated with congenital bicuspid aortic valve in 40% to 80% of cases).

All normal and abnormal heart sounds should be noted carefully. A loud first heart sound (S_1) at the apex and/or an opening snap after the second heart sound halfway between the left sternal border and the apex are clues to the presence of mitral stenosis with a mobile valve. Paradoxical splitting of the second heart sound (S_2) (i.e., widening of the split on *expiration*) is seen in moderate-to-severe aortic stenosis. A widely ("fixed") split S_2 that fails to close fully during normal expiration in the upright position suggests atrial septal defect.

A high-pitched, early systolic click that is heard best along the left sternal border and that is followed by a systolic murmur usually signifies valvular pulmonic or aortic stenosis with a pliable, noncalcified valve. Systolic clicks heard later than the carotid upstroke or multiple systolic ("machine gun") clicks suggest MVP.

A third heart sound (S_3) is often heard in healthy children, adolescents, and young adults without heart or valvular disease. When the heart rate is rapid, the third heart sound is usually termed an S_3 gallop. In a person with heart disease, it usually indicates LV failure. Chronic or acute mitral regurgitation is often accompanied by an S_3, but its presence in this condition does *not necessarily* indicate heart failure, because its presence may indicate only the torrential inflow of blood from the left atrium into the left ventricle in early diastole.

A fourth heart sound (S_4) is abnormal in a young person; it can occur with hypertension or aortic stenosis. A loud S_4 accompanying mitral regurgitation indicates that the lesion is acute and substantial, the sound being caused by the valiant attempt of the left atrium to cope with overwhelming volume overload. With time, the left atrium dilates and the S_4 disappears.

Both an S_3 and S_4 can occur simultaneously, causing a quadruple cadence. Patients with severe, particularly acute, heart failure can have a mild sinus tachycardia (typically in the range of 110 to 120

beats/min) that shortens diastole, allowing an S_3 and S_4 gallop to superimpose into a loud "summation" gallop. Always suspect a summation gallop when a loud triple cadence is heard in the presence of a mild tachycardia. A few seconds of gentle carotid sinus massage during auscultation will usually slow the heart rate slightly, allowing the superimposed S_3 and S_4 sounds to separate into a quadruple cadence, thereby confirming the presence of a summation gallop.

The timing of heart murmurs should be studied carefully and characterized as systolic, diastolic, or continuous (Table 87.3). Innocent murmurs are virtually *never* accompanied by a thrill. In an older individual, a harsh, musical, vibratory murmur with a thrill at the base is usually caused by valvular aortic stenosis. A similar murmur with the thrill at the apex can be heard with mitral regurgitation. A new-onset musical "cooing-dove" murmur at the apex is almost always caused by rupture of the mitral valve chordae tendineae owing to underlying MVP, Marfan syndrome, or trauma. It is interesting that, although MVP occurs slightly more often in young women than in men, most complications (infective endocarditis, mitral regurgitation, and ruptured chordae) although unusual occur disproportionately more often in men.

TABLE 87.3
Classification of Common Murmurs by Timing

Systolic Murmurs
Aortic stenosis (valvular, supravalvular, and subvalvular)
Mitral regurgitation, including MVP
Tricuspid regurgitation
Pulmonic stenosis
IHSS
Coarctation of the aorta
Ventricular septal defect
Atrial septal defect
Innocent systolic murmur

Diastolic Murmurs
Mitral stenosis
Tricuspid stenosis
Aortic regurgitation
Pulmonic regurgitation

Continuous Murmurs (Extending Through S_2 Without Relationship to Aortic or Pulmonic Valve Closure)
Patent ductus arteriosus
Mammary souffle
Ruptured sinus of Valsalva aneurysm

IHSS, idiopathic hypertrophic subaortic stenosis; MVP, mitral valve prolapse.

The response of murmurs to "provocative" maneuvers, spontaneously occurring extrasystoles, changes in body position, brief exercise, and pharmacologic intervention can help emergency physicians to differentiate among causative entities. Virtually all systolic murmurs—except that caused by IHSS—get softer or disappear during the strain phase of the Valsalva maneuver (Table 87.4). After the Valsalva strain is released, right-sided systolic heart murmurs (such as pulmonic stenosis and many innocent murmurs) usually return during the next 1 to 4 beats as blood rushes back into the right side of the heart. Left-sided systolic heart murmurs (mitral regurgitation, valvular aortic stenosis) are usually not heard well for 8 to 10 heartbeats, until the right heart and pulmonary circulation have refilled.

TABLE 87.4
Differentiation of Common Heart Murmurs in Adults

Valve Lesion	Timing	Pattern	Pitch	Location	Valsalva Strain	Other
AS	Systolic	CD	High	Base, neck	Decr	Slow carotid
IHSS	Systolic	CD	High	Base	Incr	Bifid carotid with rapid upstroke
AR	Diastolic	D	High	LSB	Decr	Water hammer pulse
MS	Diastolic	Rumble	Low	Apex	Decr	OS
MR, rheumatic	Systolic	CD or Pan	High	Apex, axilla	Decr	Increase
MR, MV prolapse	Systolic	CD or Pan	High	Apex, axilla	Decr	Systolic click(s)
PS	Systolic	CD	Med or high	Pulmonic area	Decr	May have systolic ejection click
PR	Diastolic	D	High	Base, LSB	Decr	Slight delay from S_2 to murmur
TS	Diastolic	Rumble	Low	LSB or RSB	Decr	Increase on inspiration
TR	Systolic	CD or Pan	High	LSB	Decr	Systolic pulsation of jugular pulse

A, aortic; M, mitral; T, tricuspid; P, pulmonic; V, valve; S, stenosis; R, regurgitation; Med, medium; C, crescendo; D, decreascendo; Pan, pansystolic; Decr, decrease; Incr, increase; LSB, left sternal border; RSB, right sternal border; OS, opening snap; IHSS, idiopathic hypertrophic subaortic stenosis.

The isometric handgrip (squeezing two of the examiner's fingers tightly for 30 to 60 seconds) increases the systemic vascular resistance and typically increases the intensity and duration of mitral or aortic regurgitation. If the patient has extrasystoles or an irregular rhythm, as in atrial fibrillation, the murmur of valvular aortic stenosis usually becomes much louder in the beat following a long pause because of increased LV stroke volume and flow across the valve. In contrast, the murmur of mitral insufficiency generally does not change in intensity with the change in cardiac cycle length.

Listening to murmurs with the patient in different body positions may also be helpful. For example, most innocent systolic murmurs decrease or disappear in the sitting or standing position. These murmurs are often soft and blowing in quality, are heard best along the left sternal border without radiation, and are unaccompanied by any other abnormal clinical findings or symptoms. The diastolic rumble of mitral stenosis is heard best in the left lateral decubitus position with the bell of the stethoscope placed lightly over the apex (see Table 87.4). The high-pitched, early diastolic decrescendo murmur of aortic insufficiency is heard best along the left sternal border with the patient leaning forward and holding a maximal expiration. This murmur is almost always louder to the left of the sternum when aortic regurgitation is caused by rheumatic heart disease or a bicuspid valve. If the murmur is louder to the right of the sternum, one should suspect that aortic regurgitation results from aortic root dilatation caused by aortic dissection, hypertension, syphilis, ruptured sinus of Valsalva aneurysm, or Marfan syndrome.

Percutaneous catheter balloon valvuloplasty (3–5) can be performed to palliate or treat pulmonary, mitral, and aortic valve stenosis. Following a successful procedure, it is common to have a persistent stenotic murmur or a new murmur owing to valve regurgitation. Complications of this procedure include valve regurgitation, inadequate opening of the stenosis, endocarditis, arrhythmias, embolization, or atrial septal defect (mitral valvuloplasty only).

Prosthetic Valves

Surgically implanted or percutaneously inserted prosthetic valves present special diagnostic problems in the ED. Echocardiography and fluoroscopy are useful tools for assessing prosthetic valve dysfunction (6). Patients with such devices are at risk for (i) endocarditis (which may present with fever, chills, or peripheral embolic complications, including stroke); (ii) embolization resulting fro m clot formation (which may present as a new stroke, transient ischemic attack, or occluded peripheral artery); and (iii) prosthetic valve dysfunction caused by dehiscence of suture lines, thrombosis of the valve, valve degeneration (porcine heterografts or human homografts), hemolysis, or structural failure (disc devices). Patients with prosthetic valve dysfunction may develop heart failure or fatigue gradually, or may present suddenly with syncope or pulmonary edema.

The sounds and murmurs that should be heard after valve replacement vary from device to device. Mechanical disc valves should produce clicking or metallic opening and/or closing sounds. Most implanted mechanical valves are relatively stenotic compared with native valves, so it is common and permissible to have a short systolic murmur with a prosthetic aortic valve or a short diastolic rumble with a prosthetic mitral valve. Short whiffs of aortic regurgitation, common after aortic valve replacement, are often caused by a small periprosthetic leak at the suture line. Prominent mitral regurgitant murmurs are usually not present following mitral valve replacement unless there is a mechanical problem with the valve.

Because severe mitral or aortic regurgitation resulting from prosthetic valve dysfunction occasionally produces no audible murmur, the development of heart failure or the appearance of other potential indicators of valve failure always warrants immediate investigation as to the valve's integrity, even in the absence of a murmur. Surgical thrombectomy and fibrinolysis are the two treatment options for prosthetic valve thrombosis, with recent clinical series showing better hemodynamic results and fewer complications with surgery (7,8).

KEY TESTING

- Careful physical examination
- CXR
- Electrocardiogram (ECG)
- Echocardiogram

ED MANAGEMENT

All patients with a previously undiagnosed heart murmur should, of course, receive a thorough cardiovascular physical assessment, as described previously. A high-quality posteroanterior and lateral chest X-ray and an ECG complement the physical examination. Specific chamber enlargement (e.g., LV dilatation owing to aortic or mitral regurgitation, or left atrial enlargement resulting from mitral stenosis, regurgitation, or both) or poststenotic dilatation of the aorta or pulmonary artery on X-ray, or chamber hypertrophy on ECG (LV hypertrophy in aortic stenosis, left atrial enlargement in mitral stenosis, right ventricular hypertrophy in pulmonic stenosis) can help to disclose the cause of a murmur. Cardiomegaly, pulmonary vascular congestion, pulmonary edema, or pleural effusions on chest X-ray can detect or confirm heart failure.

Two-dimensional (2D) echocardiography with Doppler is a sensitive and precise means of detecting and evaluating the severity of valvular lesions noninvasively. It is particularly helpful in the patient who presents to the ED with cardiogenic shock and/or acute heart failure/pulmonary edema (9–11). It should be performed in the

ED or ordered electively for any patient who is being referred to a cardiologist for follow-up evaluation of a murmur that is suspected to result from valvular disease. This technique can often detect vegetations or intracardiac thrombi in patients with suspected endocarditis or evidence of systemic embolization and can be used to evaluate prosthetic valve motion and function. If transthoracic echocardiography cannot provide sufficient resolution to adequately define the anatomy, transesophageal echocardiography can be performed. The latter technique can produce spectacular images of the heart and great vessels.

Specific complications of valvular heart disease, such as heart failure, cardiogenic shock, embolization, or dysrhythmias, should be managed in the normal fashion. Severe heart failure, hypotension, and shock resulting from massive acute aortic or mitral regurgitation may be refractory to medical therapy. In such cases, it is often preferable to use dobutamine or low-to-medium doses (5 to 15 μg/kg/minute) of dopamine, or both, rather than potent alpha vasoconstrictors (e.g., high-dose dopamine or norepinephrine), because increases in afterload will only worsen valvular regurgitation. Intra-aortic balloon counterpulsation or other LV mechanical assist devices may be required for stabilization prior to cardiac catheterization or surgery.

Consensus guidelines for antibiotic prophylaxis against infective endocarditis in patients with valvular heart disease and/or prosthetic valves have changed dramatically in the last decade (12,13) (see Chapter 88, “Infective Endocarditis for specific recommendations”). Consultation with a cardiologist may be warranted for patients with significant valvular heart disease.

CRITICAL INTERVENTIONS

- Investigate for prosthetic valve dysfunction when heart failure develops even in the absence of a murmur because severe mitral or aortic regurgitation due to prosthetic valve dysfunction occasionally produces no audible murmur.
- In patients with significant valvular disease or prosthetic valves if they are undergoing a procedure that might result in bacteremia,

discuss with a cardiologist whether antibiotic prophylaxis against infective endocarditis is indicated.
- Listen to murmurs with the patient in different body positions to detect and distinguish the etiology of murmurs.

DISPOSITION

Indications for ED consultation with a cardiologist include (i) known or suspected valvular lesions that are accompanied by hemodynamic instability (heart failure or shock), fever, dysrhythmia, or embolization; and (ii) new onset or progression of these symptoms; (iii) significant hemolysis following valve surgery or valvuloplasty; and (iv) consideration of antibiotic prophylaxis for infectious endocarditis. Admission to the intensive care unit is usually indicated for significant dysrhythmia (particularly in new-onset cases or those causing hemodynamic compromise), pulmonary edema, hypotension, or when there are other concomitant life-threatening medical problems. Immediate cardiac catheterization and surgical intervention are indicated for new-onset severe valvular regurgitation, prosthetic valve malfunction, systemic embolization in the face of adequate anticoagulation, valve ring abscess, intractable heart failure, or shock.

If transfer to another facility is required, an emergency physician should consult by telephone with the receiving cardiologist to discuss the initial treatment and stabilization and the appropriate means of transportation. If available, an advanced cardiac life-support team with monitoring and resuscitation equipment should always accompany the patient. Air transport by helicopter or pressurized fixed-wing aircraft may be indicated if the patient is in need of urgent cardiac catheterization and operative intervention.

Most asymptomatic patients in whom a previously undetected heart murmur is found incidentally should be referred electively to a cardiologist for further evaluation. Pregnant patients with newly detected murmurs or abnormal heart sounds should also be referred for further cardiac evaluation if there is any question of the finding not being physiologic during pregnancy or if there is the slightest possibility that the patient may have structural heart disease.

Common Pitfalls

- Underestimating the severity of valvular disease during periods of severe heart failure, shock, or tachycardia, since decreased cardiac output results in decreased intensity of heart murmurs.
- Overestimating the value of physical findings in the elderly patient with valvular heart disease. The presence of concomitant atherosclerosis with rigid vessels may either mask or amplify pulse or blood pressure changes resulting from valvular disease. In addition, the location and radiation of murmurs are notoriously unreliable diagnostic indicators in older patients.
- Mistaking a normal heart sound or an innocent murmur in a young person for the presence of structural heart disease. Children or young adults may have a cervical venous hum, heard best in the upright position, at the base of the neck, and occasionally in the upper chest. The murmur is continuous, extending throughout the second heart sound, and can mimic a patent ductus arteriosus murmur. It can be correctly diagnosed by showing that it can be eliminated by having the patient lie down, by applying pressure at the base of the neck with the stethoscope while listening, and by turning the patient's head away from the examiner.
- The evaluation of murmurs is challenging during pregnancy (14). Murmurs may come and go as the cardiac output, blood volume, and vascular resistance change during the course of the pregnancy and in the postpartum period. A continuous, innocent "mammary souffle" murmur can often be heard along the right or left chest during late pregnancy or during lactation following delivery; it is caused by the increased flow of blood through the mammary arteries owing to hypertrophied breast tissue. It can often be eliminated by direct chest wall pressure or with changes in body position.
- Overlooking the fact that physical examination is often unreliable in detecting heart failure. For example, almost 60% of chronic heart failure patients with an elevated pulmonary capillary wedge pressure will not have jugular venous distension, rales, or

peripheral edema on physical examination. In such cases, a chest X-ray or brain natriuretic peptide level may be helpful.

- Failure to consider the possibility of infectious endocarditis in patients with known or suspected valve disease who present with suspicious signs or symptoms (e.g., unexplained fever, anemia, heart failure, hypotension, or signs of systemic embolization). When in doubt, consider infectious endocarditis to be present until proven otherwise.

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CHAPTER 88

Infective Endocarditis

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Infective endocarditis (IE) is an infection of the endothelial lining of the heart usually involving the heart valves. The first reported autopsy evidence of the disease dates to 1647. In 1885, Sir William Osler further reported on the autopsy and clinical findings of the disease in a series of classic papers published in the *British Medical Journal.*

Traditionally, IE has been divided into two forms: (i) a relatively insidious, chronic disease, subacute bacterial endocarditis (SBE), and (ii) a more abrupt-onset, fulminant form, acute bacterial endocarditis (ABE).

Although there is broad geographic variation in cases of IE, the overall incidence and mortality of IE had remained unchanged for the last 30 years (1). Despite the unchanged number of overall cases of IE, the proportion of cases involving increasing patient age, prosthetic valve infection, and nosocomial infection is increasing (2–4). As the incidence of these cases has increased, the incidence of IE from rheumatic heart disease has decreased and is now relatively uncommon (5). Additionally, the incidence of endocarditis due to *Staphylococcus aureus,* once primarily associated with intravenous (IV) drug abuse, is now the leading cause of IE in many parts of the world (6).

The incidence of IE is highly variable depending on predisposing anatomic risk factors, including prosthetic valves, anatomic valve abnormalities, degenerative valvular disease, and the presence of mechanical intracardiac devices such as pacemakers and implanted defibrillators (4). An increase in risk is also seen in patients with

prolonged exposure to indwelling IV catheters, hemodialysis patients, and intravenous drug users (IVDUs) (Table 88.1). Reviews of multiple studies have shown that IE remains uncommon in patients with healthy valves and no identifiable risk factors. Despite considerable advances in detection and therapy, IE remains a challenge to diagnose, and mortality continues to be high.

TABLE 88.1
Emergency Department Patients at Highest Risk for Endocarditis

Patients with valvular or structural heart disease
Intravenous drug users
Patients with prosthetic heart valves
Patients with repetitive indwelling catheters devices, especially hemodialysis shunts
Elderly patients who have recently undergone an invasive procedure
Patients with implantable cardiac devices including pacemakers and implantable defibrillators

The organisms most commonly causing IE have also changed. As IE has evolved, the frequency of *Streptococcus viridans* as a causative agent has decreased, whereas the incidence of *Staphylococcus* species has risen. *S. aureus* is now the most common cause of all types of IE and the incidence of methicillin-resistant *S. aureus* (MRSA) in these isolates has risen dramatically (3,6,7). *S. aureus* endocarditis also confers a higher risk of embolism, neurologic involvement, persistent bacteremia, and overall mortality than does infection caused by other organisms (6,7). In addition to the changing spectrum of infection, methods for elucidating the causative organism in endocarditis have been improved, including better culture techniques, serologic testing, and the use of polymerase chain reaction (PCR).

There are four steps in the development of SBE: (i) a hemodynamically defective valve produces turbulent blood flow and endothelial disruption; (ii) a sterile platelet–fibrin thrombus forms on the damaged valve lining; (iii) transient bacteremia infects the

thrombus; and (iv) high titers of antibodies to the infecting organism are produced. Furthermore, the infecting organism must have the capability to adhere to injured endothelium. Bacterial endocarditis may also develop on previously normal native and prosthetic heart valves. In these cases, the only necessary measure is an inoculum of a highly invasive organism.

Once endocarditis develops on a valve, the clinical manifestations are attributable to the following series of events: (i) local destruction and malfunction of the cardiac valve; (ii) invasive infection of contiguous structures of the heart; (iii) continuous bacteremia, leading to distant infections; (iv) embolization of vegetations that break off from the valve; and (v) an antigen–antibody response, leading to immune-mediated complications.

CLINICAL SUBGROUPS

IE is often classified into one of four distinct patient-centered clinical groups: (i) patients with a damaged native valve; (ii) patients with prosthetic valves (further classified as either early or late infection); (iii) IVDUs; and (iv) patients with nosocomial IE (3). A fifth category has also recently been described: health care-related endocarditis related to implantable intracardiac devices, invasive procedures, and chronic hemodialysis (8). IE in hemodialysis patients is becoming increasingly more common. It has been reported that patients on hemodialysis make up 30% of all cases of hospital-acquired IE and have a 50 to 60 times higher incidence of IE than the rate in the general population (9).

DAMAGED NATIVE VALVE

Any condition causing an alteration in the normal structure of the cardiac valves (e.g., rheumatic, degenerative, and congenital cardiac abnormalities) can predispose a patient to IE. Patients with native-valve IE are most likely to develop a syndrome similar to the classic SBE, a relatively chronic infection with only left-sided cardiac involvement, often with a streptococcal organism. The mitral valve is the most common valve to be infected in the native-valve group.

Isolated mitral involvement occurs in 35% to 45% of cases, isolated aortic valve involvement in 15% to 35%, and involvement of both valves in 15% to 30% (10). Mitral valve prolapse by itself is not a risk factor for IE unless accompanied by regurgitation (3). Tricuspid valve and pulmonic involvement is relatively rare in native-valve IE.

Staphylococcus species have now surpassed *Streptococcus* species as the most common organism causing native-valve IE, being responsible for 44% of native-valve IE, whereas *Streptococcus* and *Enterococcus* species account for 31% and 10% of cases, respectively (3). *S. aureus* and coagulase-negative *Staphylococcus* are probably introduced via the skin and are most likely to cause infection in patients on hemodialysis and those who have diabetes, implantable cardiac devices, chronic illness, and the elderly or otherwise debilitated (6,7). *S. aureus* is now the predominant pathogen in all types of IE (3,6). There has also been a significant rise in the percentage of these cases caused by MRSA. Though overall mortality is not statistically different, there is evidence that MRSA endocarditis may actually confer a lower risk for embolism but a higher risk for persistent bacteremia (6).

S. viridans is by far the most common *Streptococcus* species causing IE. *S. viridans* bacteremia and subsequent valvular seeding traditionally have been attributed to bacterial seeding during dental procedures in patients with pre-existing valvular or structural heart disease. This presumed cause-and-effect relationship has been increasingly questioned and, to date, there is no compelling evidence that dental procedures are the cause of a significant number of cases of IE. Additional organisms causing native-valve IE include *Streptococci bovis* and *Enterococcus faecalis* (3). These infections are more commonly introduced by bowel and urologic infections or procedures, especially in the elderly. Gram-negative organisms, fungi, polymicrobial infections, and diphtheroids are seldom contributors to native-valve IE (3,7).

INTRAVENOUS DRUG USERS

IVDUs are one of the leading groups at high risk for developing IE. Between 5% and 8% of hospital admissions in IVDUs are due to endocarditis (11). Because IV cocaine users inject themselves so frequently relative to other IVDU groups, they appear to have the highest risk of developing IE. Their increased relative risk may also be a result of factors such as lack of heating the drug before injection, needle sharing, immunosuppression from the drug, or direct valvular damage caused by cocaine (12). There are conflicting data in the literature regarding the predominance of right-sided versus left-sided endocarditis in IVDUs. Although left-sided endocarditis is seen in all patient populations, right-sided endocarditis is rarely seen outside of the IVDU population. Thirty-two percent of IE caused by IVDU involves the mitral valve, 19% the aortic valve, and almost all of the remaining cases involve the tricuspid valve (11). In right-sided endocarditis, pulmonic valve involvement is rare and is seen in $<1\%$ of patients (11).

Patients who inject illicit drugs often are infected with organisms that are normal skin flora. *S. aureus* is the most common causative agent in this group of patients, accounting for approximately 69% to 80% of cases *Streptococcus* species are the next most common. Interestingly, coagulase-negative staphylococci are rarely isolated from this patient population (3,11). Fungal infection and large (>2 cm) valve vegetations both portend a significantly worse prognosis in this patient population and may make these patients candidates for early surgery.

PROSTHETIC VALVE INFECTIVE ENDOCARDITIS

As the number of prosthetic valve surgeries increases, the number of cases of prosthetic valve infective endocarditis (PVIE) continues to rise. Once making up only 1% to 5% of the total number of cases of IE, PVIE now accounts for 20% of all cases of IE (13). Individuals with PVIE tend to be significantly older, have a lower likelihood of using injectable drugs, and have a higher likelihood of health care–associated infection and a higher mortality than patients with native valve infective endocarditis (13).

Early-Onset Prosthetic Valve Infective Endocarditis

Patients with early-onset PVIE either are contaminated intraoperatively or develop infection in the perioperative period, which is defined as 60 days after surgery (13,14). The rate of infection is highest in the first 3 months after surgery and diminishes to between 0.3% to 0.6% per year thereafter (14). Early prosthetic valve infections are predominantly nosocomial in etiology. The most common pathogens encountered in the first 2 months after surgery are *Staphylococcus* species (*S. aureus,* 36%, and coagulase-negative staphylococci, 15%) (13). *S. aureus* is now the most frequent organism associated with early-onset PVE with more than 50% of these isolates being methicillin-resistant (13). Though the overall number of cases of early-onset PVIE seems to be falling in comparison to late-onset PVIE, mortality remains very high, with cases due to *S. aureus* conferring a significantly higher mortality than infection from other organisms (13). Other organisms encountered less frequently include *S. viridans, Enterococcus* species, gram-negative organisms, and fungi.

Late-Onset Prosthetic Valve Infective Endocarditis

The predominant organisms responsible for late-onset PVIE continue to be *Staphylococcus* species. Coagulase-negative staphylococci (20%) and *S. aureus* (18%) were the predominant causative organisms in a recent large-scale observational study (13). In this same population, MRSA made up $<$20% of the staphylococcal isolates whereas *Enterococcus* species (12%), *Viridans streptococci* (10%), and *S. bovis* (7%) also caused a significant number of infections.

Mechanical valves and tissue valves have an approximately equal incidence of infection (overall incidence, 2.2% to 4.4%), but mechanical valves are more likely to develop early-onset PVIE. Mechanical valves tend to develop perivalvular abscesses, myocardial abscesses with conduction delays, pericarditis, and regurgitation caused by perivalvular leaks. An acute regurgitant murmur caused by partial dehiscence of the valve is a surgical

emergency because severe heart failure can develop rapidly or the valve can undergo total dehiscence. Tissue valves, however, are more likely to develop leaflet tears, also resulting in new regurgitant murmurs and heart failure. Valvular stenosis is also a potential complication with tissue valves.

CLINICAL PRESENTATION

Patients with IE may present acutely with fulminant heart failure and sepsis; with a chronic, indolent, nonspecific disease process; or with a syndrome intermediate between the two extremes. Because of the overlap, the artificial separation of ABE and SBE is usually not clinically helpful. Table 88.2 lists the historical and physical findings seen most often in IE.

TABLE 88.2
Historical and Physical Findings Suggestive of Endocarditis

	History	Physical Examination
General	Fever, chills, malaise, weakness, anorexia, weight loss, back pain, myalgia, arthralgia	Acute or chronically ill appearance, fever, diaphoresis pallor, splenomegaly, arthritis
Cardiopulmonary	Chest pain, dyspnea, edema	Murmurs, especially valvular insufficiency; signs of congestive heart failure
Neurologic	Headache, stiff neck, mental status changes, focal neurologic complaints, extremity pain or paresthesia	Meningismus, abnormal mental status, focal deficits
Other	Hematuria, abdominal pain	Skin: petechiae, Osler nodes, Janeway lesions, splinter hemorrhages
Risk factors	Intravenous drug abuse; heart disease; recent gastrointestinal, genitourinary, or dental procedure; poor dental hygiene	Embolic: mycotic aneurysm, visceral or extremity infarct, or ischemia Other: pneumonia, skin abscess, urinary tract infection

Complications

Cardiac

Cardiac complications of IE may involve any of the three layers of the heart. Endocardial damage of the valve may result in valvular destruction and variable degrees of congestive heart failure (CHF). CHF is the most common cause of death in patients with IE (15). Severe failure is usually a result of acute aortic insufficiency and, if not promptly amenable to medical intervention, is an indication for emergent valve replacement surgery (15). Myocarditis or perivalvular abscess results when the infecting organism invades the contiguous myocardium.

Electrocardiographic (ECG) abnormalities in cases of IE are much more likely to be seen with perivalvular spread of infection and confer a significant increase in mortality (16). The majority of ECG abnormalities are conduction abnormalities. The infection involving the conduction system results in conduction delays, bundle-branch block, or complete heart block. Mortality is significantly higher if there is a presence of infranodal block (15). Intracranial catastrophes may occur if thrombolytics are used in cases in which complications of IE cause ECG changes that mimic those of acute ischemia resulting from coronary artery disease.

Additional complications include aortocardiac fistula, perforated valves, or perforation of the myocardium (15). A perforated myocardial abscess may result in a purulent pericarditis. Large emboli to the coronary arteries can cause acute myocardial infarction or sudden death (17).

Central Nervous System

Central nervous system complications occur not only in 20% to 40% of patients with IE but may be the presenting complaints in a significant number of cases (7). Mortality is significantly higher in patients with IE and neurologic manifestations. Embolic cerebral infarction or stroke is the most common event and usually involves the middle cerebral artery or its branches (18). Intracerebral hemorrhage, isolated seizures, and transient ischemic attacks are also reported complications (18). Cerebral mycotic aneurysms

resulting from septic emboli eroding the vessel wall may remain asymptomatic or may enlarge, leak, or rupture and present as subarachnoid hemorrhage, cerebral abscess, or classic bacterial meningitis (19). A syndrome consisting of lethargy, delirium, hallucinations, and psychosis (i.e., toxic encephalopathy) may occur (17). When these findings are accompanied by a stiff neck and cerebrospinal fluid consistent with aseptic meningitis, the patient has meningoencephalitis. The cause is not clear, but multiple microinfarcts or microabscesses may be responsible. The likelihood of an embolic event decreases markedly after the initiation of antibiotics (18).

Emboli and Immunologic Responses

Peripheral embolization can occur anywhere in the body and is seen in up to one-third of patients with IE (19). In addition to the brain (50% of all events) and heart, other important areas of embolization are the splenic, renal, mesenteric, and extremity vasculature. The emboli result in endarteritis, mycotic aneurysm, local abscess formation, and distal infarction. Studies have shown that patients with large valve vegetations have a worse prognosis most likely because of a higher likelihood of embolic sequelae (17). It is not clear how many of the signs and complications of IE are immune complex–mediated, although it is thought that glomerulonephritis, aseptic arthritis, and most of the classic skin manifestations are immune-related. Prosthetic joint infections and vertebral osteomyelitis may, if seen, be likely a result of bacteremia during the acute phase of the infection (15).

ED EVALUATION

A definitive diagnosis of endocarditis relies on a combination of histologic, microbiologic, clinical, and echocardiographic findings. The Duke criteria, first proposed in 1994, have been well validated, and the modified Duke Criteria remain the gold standard for diagnosing IE. Because culture data are unavailable and most emergency departments (EDs) have limited access to

transesophageal echocardiography (TEE), a definitive diagnosis of IE is often impossible to obtain at the time of initial presentation. Therefore, the Duke criteria are of limited use in ED patients, and the clinician must rely on history, physical findings, and other rapidly available tests that will support a presumptive diagnosis of IE and the initiation of additional directed diagnostic testing and empiric antibiotic therapy.

Patients with IE often have numerous vague and nonspecific complaints. The classic patient presenting with persistent fever of unknown origin represents only a fraction of endocarditis cases (15). Most patients have nonspecific extracardiac complaints including fever, malaise, anorexia, and weakness. Approximately one-half of patients report headache, weight loss, night sweats, arthralgias, and myalgias (7). A history of back pain, rash, or dyspnea or a spectrum of neuropsychiatric symptoms is not uncommon in IE (7). Clinicians, however, seldom initially attribute these less-common symptoms to IE. Physicians should also be aware of patients at higher risk for IE such as patients with diabetes, immunocompromised patients, valvular cardiac disease patients, IVDUs, patients with indwelling cardiac devices (pacemakers and implanted defibrillators), and patients receiving chronic hemodialysis (1,3,7,9). Patients should be asked about recent dental, gastrointestinal, and urologic procedures. Elderly patients, in particular, may not volunteer or may forget to relate these high-risk procedures. Young patients who are being evaluated “for the flu” or other febrile illnesses seldom provide information about IV drug use unless specifically questioned.

Physical findings suggestive of endocarditis are listed in Table 88.2. Patients with IE may appear acutely or chronically ill. Nearly all nonimmunocompromised patients have fever. The presence of unexplained fever for more than 1 week should raise the clinician’s suspicion for endocarditis (17). Other abnormal vital signs, especially tachycardia, are relatively common. It is important for the clinician to be vigilant because many of the symptoms of endocarditis are nonspecific and many of the classic findings of endocarditis are not commonly seen.

A careful cardiac examination is critical in patients suspected of having IE. The majority of patients with IE will have a murmur and many of these will be pre-existing (7). Patients most likely to lack murmurs are those with acute IE. Therefore, lack of a murmur in an IVDU should never decrease the suspicion for IE. On the other hand, a new aortic or mitral regurgitant murmur in a febrile patient is very strong evidence for the disease (17). The cardiac examination should also seek any findings suggestive of heart failure. Findings of new-onset heart failure, especially in younger patients without a history of cardiac disease, should prompt a high index of suspicion for endocarditis. Rarely, a large (usually fungal) vegetation may block the outflow tract, resulting in a new stenotic murmur.

A variety of skin lesions are considered classic for IE, but these are relatively uncommon. Petechial lesions may be found in different locations. Splinter hemorrhages are tiny red, purple, brown, or black splinter-like lesions that appear under the fingernails. They are seen in up to 20% of patients with IE, but they are also found in approximately 8% of all hospitalized patients. Osler nodes are small, painful, tender erythematous nodules that are most commonly seen in the distal finger pads; they occur in 5% to 20% of patients. Janeway lesions are small, flat, nontender red spots on the palms and soles; they occur in only about 10% of patients with IE. Conjunctival petechiae may occur in approximately 10% of patients. Roth spots are retinal petechial hemorrhages with central pallor, which may be seen in 10% to 25% of patients with IE. The remainder of the physical examination may reveal abnormal abdominal or neurologic findings. Splenomegaly is a common finding, and a tender, enlarged liver is often noted. The presence of a splenic abscess should raise a high suspicion for IE (19). Neurologic examination may reveal signs consistent with meningitis, encephalitis, embolic stroke, or a leaking aneurysm. Some patients present with subtle mental status changes or behavioral symptoms that appear to be psychiatric in nature (17).

There are numerous nonspecific laboratory findings in IE (Table 88.3). Normochromic, normocytic anemia occurs in up to 75% of patients and microscopic hematuria occurs in nearly 50%.

Leukocytosis is seen in about 50% of cases and, thus, its absence should not be used to rule out the diagnosis. Studies differ in regard to the value of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in patients ultimately diagnosed with IE. Both tests lack specificity and neither test has perfect sensitivity to rule-out a diagnosis of IE.

TABLE 88.3
Laboratory and Diagnostic Findings in Endocarditis

Blood	**Echocardiogram**
Positive blood cultures	Vegetations
Anemia	Valve dysfunction
Microscopic or gross hematuria	Perivalvular abscess
Leukocytosis	Aortic Root aneurysm
Uremia	Chamber enlargement
Elevated ESR or CRP	Pericardial effusion
Chest Radiograph	**V/Q Scan**
Cardiomegaly	Multiple pulmonary infarcts
Congestive heart failure	**Cerebrospinal Fluid**
Pulmonary infiltrates	Purulent meningitis
Pulmonary infarcts	Aseptic meningitis
Pulmonary effusions	Bloody leaking aneurysm
Chamber enlargement	**Computed Tomography**
Abnormal movement of prosthetic valve	Lung abscess
Stimson sign	Cerebral abscess
Electrocardiogram	Splenic Abscess
Conduction defect	Subarachnoid hemorrhage
Acute myocardial infarction	Pulmonary Emboli
Pericarditis	Mycotic aneurysm

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; V/Q, ventilation/perfusion.

The most important part of the laboratory evaluation is the blood culture, as precise identification of the organism is critical in tailoring appropriate antibiotic therapy. Approximately 20 mL of blood (not 5 to 10 mL) should be drawn for each set of blood cultures and sent for aerobic and anaerobic cultures. The diagnosis

of possible endocarditis should appear on the specimen label so that the laboratory will hold the specimen for at least 3 weeks to ensure detection of slow-growing organisms. Whenever possible, a minimum of three blood cultures should be performed from three separate sites and should be drawn over a period of approximately 1 hour.

Blood cultures may be positive in the majority of patients with IE. Even in cases wherein the blood cultures are negative, other tests can be obtained that may aid in a definitive diagnosis. If the cultures are sterile in cases of proven endocarditis, *Coxiella, Bartonella,* and *Chlamydia* species may be identified by the use of serology, immunohistochemical staining, and PCR (7). To maximize the chances of a positive culture and to minimize the confusion caused by contaminant, multiple cultures are recommended as described above in the IE work-up. Recent antibiotic use by the patient and infection with fastidious or slow-growing organisms are the two major reasons for negative cultures in the context of IE. The patients who most commonly have negative cultures are drug users, patients with prosthetic valves, and those who have recently received antibiotics.

Although usually normal, the ECG should always be carefully examined for evidence of pericarditis, ischemia, infarction, conduction delay, or any degree of heart block. These changes may be indirect evidence for the coexistence of myocarditis, myocardial abscess, pericarditis, or coronary artery embolism (16).

The chest radiograph of patients with IE is usually normal. Signs of CHF, including cardiomegaly, isolated chamber enlargement, and abnormal vascular patterns, provide valuable information regarding abnormal valvular or cardiac function. The chest radiograph may also reveal pneumonia, especially in patients who are IVDUs. Multiple pulmonary infarcts or nodular infiltrates suggest right-sided disease, usually tricuspid valve endocarditis. In PVIE, a double shadow of a mechanical valve, known as Stimson sign, indicates movement of a valve that has undergone partial dehiscence.

Echocardiograms are almost always performed in patients who are suspected of having IE. The finding of vegetation is a very strong

evidence for the diagnosis of IE. However, a negative echocardiogram should never be used as the definitive test to rule out IE, as up to one-third of patients with IE have nondiagnostic echocardiograms (20). Although it is probably more appropriate to begin with transthoracic echocardiography (TTE), TEE should be performed in all patients in whom there is strong suspicion for IE (20). The greater value of TEE lies in its ability to provide greater spatial resolution of cardiac anatomy and the fact that by placing the probe in the esophagus, limitations from overlying structures and chest wall structures are eliminated (20). Various studies have shown sensitivities for TTE in diagnosing IE at between 18% and 63%. This compares to 48% to 100% sensitivity for TEE in diagnosing IE. Furthermore, TEE is far more sensitive in diagnosing accompanying pathology such as perivalvular abscess. Because of their anterior location, aortic root abscesses may be better visualized with TTE (20). Echocardiographic detection of valve malfunction, chamber enlargement, or an associated pericardial effusion may also be helpful in the clinical management of IE. Mechanical valves are too echo-dense for TTE to be of significant value, and valvular function should instead be evaluated by either TEE or cinefluoroscopy (20,21).

KEY TESTING

- Obtain at least three sets of high-volume blood cultures from separate sites over a period of 1 hour in stable patients suspected of having endocarditis.
- Obtain a transthoracic echocardiogram (TTE) to evaluate for vegetations and valvular insufficiency, followed by a TEE in conjunction with cardiology consultation based on the TTE results.
- Obtain an ECG and chest X-ray to evaluate for conduction disease and signs of heart failure or secondary infectious processes such as pneumonia.
- Laboratory studies such as ESR, CRP, and white count may influence the probability of a diagnosis but are never sufficient

to rule-in or rule-out a diagnosis of IE.

ED MANAGEMENT

Definitive therapy for IE is guided by the infecting organism's sensitivity to specific antimicrobial agents. If a stable patient presents to the ED with the possibility of IE, it is best to obtain at least three sets of blood cultures from three separate sites over a period of 1 hour. Administration of antibiotics reduces the positive blood culture rate by as much as 40% (21). The patient should be admitted to an inpatient area, and subsequent care and additional culturing should be provided at the direction of the patient's physician or infectious diseases consultant. Antibiotics should, however, be started in the ED if the patient appears septic, is elderly, is debilitated, is immunocompromised, has concomitant pneumonia, is in heart failure, or is hemodynamically unstable. Once blood culture and sensitivity data are available, optimal therapy should follow the most recent AHA guidelines (21). The choice of optimal empiric therapy for presumed IE in a specific patient type is guided by the most commonly suspected organism and the organism's antibiotic sensitivities.

Empiric Antibiotic Coverage

There is no universal agreement on optimal empiric antibiotic therapy. However, ED physicians can begin therapy by choosing an antibiotic regimen that provides broad-spectrum bactericidal coverage for the most common organisms causing IE. The authors' specific recommendations for empiric therapy for use in the ED appear in Table 88.4.

TABLE 88.4
Empiric Emergency Department Therapy for Presumed Endocarditis Prior to Culture Results

Patients with Native Valves (Including Intravenous Drug Users)		Patients with Prosthetic Valves	
Nafcillin[a]	2 g IV q4h	Rifampin	300 mg PO q8h
and		and	
Gentamicin[b]	3 mg/kg IV q24h	Gentamicin[b]	3 mg/kg IV q24h
and		and	
Vancomycin	1 g IV q12h (or 30 mg/kg per 24 hrs in equally divided doses)	Vancomycin	1 g IV q12h (or 30 mg/kg per 24 hrs in equally divided doses)

[a]Consider ceftriaxone 2 g IV in penicillin-allergic patients.
[b]Use q8h dosing and not single daily dosing in infective endocarditis.

The recommendations attempt to provide broad coverage divided into two regimens: one for presumed IE in a seriously ill patient with native valves and a second for presumed IE in a patient with one or more prosthetic valves. The regimens are designed to be easily remembered and do not address whether the patient may have developed IE in association with IV drug abuse or how long ago the prosthetic valve was implanted. In addition, with the increasing frequency of all types of IE from *S. aureus* and the increasing frequency of MRSA, empiric therapy must cover MRSA until culture data prove otherwise. Consequently, patients with the possibility of IE should receive nafcillin, gentamicin, and vancomycin. Patients with prosthetic valves who require that therapy be initiated on an emergent basis should receive rifampin, gentamicin, and vancomycin. The regimen should be adjusted after the patient is admitted to the hospital, on the basis of inpatient physician preference and culture and sensitivity data. Consultation with an infectious disease physician should be accomplished at the earliest possible time.

Antibiotics Based on Known Organism

The rapid changes in the epidemiology and antibiotic susceptibilities in all of the major bacterial organisms causing IE make specific recommendations for precise therapy beyond the scope of this

chapter. The most recent AHA guidelines give precise details on appropriate antibiotic therapy once organism and antibiotic susceptibilities are known (21). The clinician should be aware of these guidelines as well as the possibilities that empiric therapy will need to be altered, as increasing cases of high level resistance to vancomycin are being reported in both *S. aureus* and enterococci (21).

Anticoagulants

Anticoagulation is contraindicated in patients with native-valve IE because of the greatly increased risk of intracranial bleeding that occurs in patients with IE who have cerebral emboli. Anticoagulants confer no protection against cerebral or peripheral embolization in native-valve IE, although many experts recommend their continued use. The exception is the patient who develops massive life-threatening pulmonary emboli. Patients with PVIE who are already maintained on anticoagulation should probably continue the medication and be closely monitored for complications related to the prosthetic valve unless there has been a recent central nervous system embolic event (21).

Surgery

Valve replacement has become much more widely accepted as a therapy for complicated IE (22). Surgery is required in 25% to 50% of all cases of acute endocarditis (23). Although there is agreement on the indications for surgery, the timing and specific details are being debated. The following are general indications for valve replacement: heart failure as a result of new valve malfunction, acute valvular insufficiency, major embolic complications, continued bacteremia despite administration of appropriate antibiotics, dysrhythmia or new conduction defect, or a fungal cause (2,21–23). Indications for emergent surgical intervention include acute aortic regurgitation with early closure of the mitral valve, rupture of the pericardium, and rupture of a sinus of Valsalva aneurysm into the right heart chamber (16,23). Furthermore,

certain infections such as those caused by *Brucella* species, *Coxiella burnetii, Pseudomonas aeruginosa, Staphylococcus lugdunensis,* and Candida species are difficult to manage medically and are best managed by surgery (7).

Traditionally, surgical management has been considered superior to medical management alone with regard to the treatment of PVIE. This continues to be true in the case of patients with hemodynamic instability, heart failure, or perivalvular abscess. Persistent infection, advanced age, and the development of renal failure are associated with an increased postsurgical mortality (21,22). There is emerging evidence that in a subset of stable patients medical management with antibiotics alone may suffice (21). It is not clear to what extent the size of the vegetations seen on the echocardiogram determines the prognosis and need for valve replacement.

CRITICAL INTERVENTIONS

- Obtain at least three sets of high-volume blood cultures from separate sites over a period of 1 hour in stable patients suspected of having endocarditis.
- Initiate antibiotics if the patient appears septic, is elderly, is debilitated, is immunocompromised, has concomitant pneumonia, is in heart failure, or is unstable.
- Administer prophylactic antibiotics to at-risk patients undergoing dental procedures, upper-respiratory tract procedures, or procedures involving infected skin or musculoskeletal tissue.

DISPOSITION

Because of the frequency of serious complications and the need for parenteral antibiotic therapy, all patients who are strongly suspected of having IE should be admitted to the hospital. Patients with overwhelming sepsis, serious embolic complications, or any degree of heart failure or conduction block require admission to an intensive care setting. In addition, intensive care unit admission is mandatory for PVIE patients with any evidence of perivalvular leak.

Blood cultures (20 mL of blood for each set) should be obtained in patients suspected of having IE but in whom the diagnosis is thought to be unlikely. Outpatient follow-up for these patients is appropriate if the patient is reliable and can be readily contacted and if the patient's private physician agrees.

When IE is strongly suspected, a cardiologist should be consulted for possible echocardiographic examination. TEE must be done as soon as possible in any patient with a prosthetic valve in whom the possibility of IE is considered. Patients with PVIE or those who may need valve replacement should have a cardiac surgeon involved early to ensure that the timing of surgery is optimal. For patients with possible brain abscess or aneurysm, appropriate imaging studies should be performed, and a neurosurgeon should be consulted promptly.

ANTIBIOTIC PROPHYLAXIS AGAINST INFECTIVE ENDOCARDITIS

The aim of antibiotic prophylaxis is to prevent bacteremia from occurring during procedures in patients who have conditions that may predispose them to IE. Prophylactic antibiotics may, in fact, not confer any significant protection from IE and there is no good evidence that prophylactic antibiotics prevent IE caused by dental, GI, or GU procedures (2,24,25). As a result, the AHA has implemented major revisions in its 2007 guidelines that eliminate the antibiotic prophylaxis recommendations for GI and GU procedures and significantly alter the recommendations for dental procedures, respiratory procedures, and those involving infected skin and musculoskeletal structures (Table 88.5). According to current recommendations, only those at the highest risk for IE should receive prophylaxis (24). These include patients with prosthetic heart valves, previous endocarditis or certain types of congenital heart disease, and cardiac transplant recipients with cardiac valvular disease (2,24). Specific antibiotic recommendations and dosages are listed in Table 88.6.

TABLE 88.5
Cardiac Conditions Warranting Antibiotic Prophylaxis for Dental Procedures,[a] Respiratory Procedures, or Procedures Involving Infected Skin or Musculoskeletal Tissue

Prosthetic cardiac valve

Previous endocarditis

Congenital heart disease only in the following categories:

- Unrepaired cyanotic congenital heart disease, including palliative shunts and conduits
- Completely repaired congenital heart disease with prosthetic material or device, whether placed by surgery or catheter intervention, during the first 6 mos after the procedure[b]
- Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)

Cardiac transplantation recipients with cardiac valvular disease

[a]All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth, or perforation of the oral mucosa.

[b]Prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 months after the procedure.

From Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: Guidelines from the American Heart Association. A Guideline From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007;116(15):1736–1754.

TABLE 88.6
Antibiotic Prophylaxis for Dental Procedures, Respiratory Procedures, or Procedures Involving Infected Skin or Musculoskeletal Tissue

Situation	Agent	Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	OR		
	Cefazolin or Ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—able to take oral medications	Cephalexin[a,b]	2 g	50 mg/kg
	OR		
	Clindamycin	600 mg	20 mg/kg
	OR		
	Azithromycin or Clarithromycin	500 mg	15 mg/kg
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin and unable to take oral medication	OR		
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

IM, intramuscular; IV, intravenous.
[a]Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
[b]Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.
Note: Regimen: single dose 30 to 60 minutes before procedure.
From Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: Guidelines from the American Heart Association. A Guideline From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007;116(15):1736–1754.

Common Pitfalls

- Not asking about risk factors in patients who present with nonspecific symptoms consistent with IE.
- Missing the diagnosis in the elderly by attributing a cardiac murmur to chronic heart disease.
- Not asking specifically about IV drug use in patients who present with nonspecific symptoms consistent with endocarditis.
- Failing to consider the embolic and immune-mediated complications of IE as the underlying cause of stroke, meningitis, myocardial infarction, septic arthritis, or renal failure.

- Not asking about risk factors for IE in patients about to undergo a procedure prone to cause bacteremia.

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CHAPTER 89

Acute Pericarditis and Cardiac Tamponade

Richard Byyny and Howard A. Bessen

Pericarditis is present in approximately 5% of chest pain patients presenting to the ED without myocardial infarction (MI) (1) and can complicate nearly any class of disease, including infectious, neoplastic, rheumatologic, and metabolic diseases, as well as trauma. In the majority of cases the cause remains unclear despite testing (i.e., idiopathic pericarditis) (2,3). Many of these cases are thought to be viral in origin.

However, pericarditis may also occur as a complication of a systemic or intrathoracic infection. It is the most prominent cardiac complication of neoplastic disease, and nontraumatic pericardial tamponade is usually of metastatic origin (4,5). In addition, patients receiving radiation treatment as therapy for their cancer may develop postirradiation pericarditis. Pericarditis may occur as a complication of chronic renal failure or of connective tissue diseases such as systemic lupus erythematosus, scleroderma, or rheumatoid arthritis. Medications may also be implicated.

Pericarditis frequently occurs during the first few days after acute MI (6,7) and may also present as late-onset postinfarction pericarditis (Dressler syndrome). Aortic dissection, cardiac trauma, invasive procedures that involve the great vessels and the heart (central venous catheter insertion and cardiac catheterization), and thoracic surgery may also cause pericarditis and pericardial tamponade within hours to weeks. The common causes of acute pericarditis are listed in Table 89.1.

TABLE 89.1
Causes of Acute Pericarditis

Idiopathic	Systemic lupus erythematosus
Infectious	Scleroderma
Viral	Drug-related
Bacterial	Anticoagulants
Tuberculosis	Procainamide
Fungal	Hydralazine
Parasitic	Methyldopa
Malignancy	Cardiac Injury
Metastatic disease	Postmyocardial infarction
Radiation-induced	Postsurgical
Uremia	Postinstrumentation
Connective Tissue Disease	Cardiac trauma
Rheumatoid arthritis	Aortic dissection

From Khandaker MH, Espinosa RE, Nishimura RA, et al. Pericardial disease: Diagnosis and management, Mayo Clinic proceedings. *Mayo Clinic*. 2010;85(6):572–593.

Acute pericarditis is a diagnostic challenge because its presentation is similar to that of several other disorders and because it may have life-threatening complications. Management ranges from symptomatic treatment to lifesaving invasive procedures.

CLINICAL PRESENTATION

There are no predefined diagnostic criteria for pericarditis. However, presence of two of the following four criteria is highly suggestive: (1) characteristic chest pain, (2) pericardial friction rub, (3) suggestive ECG changes, and (4) new or worsening pericardial effusion (1,8–10). The prevalence of symptoms is presented in Table 89.2.

TABLE 89.2
Symptom Prevalence with Acute Pericarditis

Symptom	%
Chest pain	95.5
Character of chest pain	
Pleuritic pain	66.5
Retrosternal pain	59.2
Sharp	50.0
Dull or other	50.0
Postural change in pain	46.4
Radiation	
Left shoulder	45.3
No radiation	23.5
Multiple regions	14.5
Neck/jaw/throat	8.4
Back	6.7
Arm	4.5
Abdomen	1.7
Across chest	1.1
Associated Symptoms	
Shortness of Breath	33.5
Recent infection	27.4
Nausea/vomiting	11.7
Light-headedness	7.8
Dysphagia	1.1

Hooper AJ, Celenza A. A descriptive analysis of patients with an emergency department diagnosis of acute pericarditis. *Emerg Med J*. 2013;30(12):1003–1008.

Chest pain is the most common presenting complaint with acute pericarditis. The pain is usually sharp, substernal, and often pleuritic, but it may also be dull, constrictive, or aching. Pain may radiate to any part of the chest and back as well as to the ridge of the trapezius (11). Typically, the chest discomfort is described as being positional with the pain being eased by sitting up and leaning forward and increased with recumbency. The pain may be associated with shortness of breath, which may be caused by coexisting pleuritis or by cardiac tamponade. Patients may also present with hypotension and other signs and symptoms of tamponade.

The classic diagnostic physical finding is the pericardial friction rub, which may consist of one, two, or three components (1). An audio file can be found in the work by Carlson et al. (12). It is

important to recognize that the rub is often transient and may not be heard at all times. However, it is present at some point in up to 85% of patients. The rub is often described as being high-pitched like leather squeaking or scratching. It is typically heard best along the left sternal border and is increased by having the patient sit or lean forward. The rub may be confused with a heart murmur or a pleural friction rub. However, having the patient hold their breath helps distinguish a pleural friction rub from a pericardial rub.

The major complications of acute pericarditis are pericardial effusion (potentially leading to cardiac tamponade), recurrent pericarditis, and chronic constrictive pericarditis. Dysrhythmias are unusual in pericarditis but may occur in patients with associated myocarditis or other underlying heart disease.

Cardiac tamponade is an acute life-threatening complication resulting from the accumulation of fluid within the pericardial space. The pericardium is poorly distensible; therefore, the fluid can cause an impairment of cardiac filling and thus a decrease in cardiac output. Beck's triad (jugular venous distension [JVD], hypotension, and distant heart sounds) has been taught as the classic presentation, but the sensitivity of these findings is poor (Table 89.3). The presentation may be subtle, potentially leading to a delayed or missed diagnosis and a poor outcome. Close attention to physical findings is essential to make the diagnosis. Clinical decompensation can be rapid. Tamponade is often mistaken for congestive heart failure (CHF) because patients present with dyspnea, orthopnea, JVD, and hepatic enlargement.

TABLE 89.3
Sensitivity of Presenting Signs and Symptoms of Cardiac Tamponade

Sign or Symptom	Sensitivity (%) (95% CI)
Tachycardia	77 (69–85%)
Hypotension	26 (16–36%)
Diminished heart sounds	28 (21–35%)
Jugular venous distension	76 (62–90%)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes other conditions that cause chest pain and dyspnea, such as acute MI, CHF, pulmonary embolism, pneumonia, pneumothorax, pneumomediastinum, pleuritis, and aortic dissection. Cardiac tamponade may be confused with CHF, cardiogenic shock, or massive pulmonary embolism.

Acute pericarditis has many overlapping features with acute MI. Both cause chest pain, cause electrocardiographic abnormalities, and can cause elevations of cardiac markers (13). In contrast to patients with MI, patients with pericarditis may describe a viral prodrome, may present with fever, and typically have sharper pain that increases with body motion and varies with position. ECG findings may be useful in distinguishing MI from pericarditis (see section "ED Evaluation"). Patients with pericarditis (even with tamponade) have clear lung fields, unlike patients with CHF with pulmonary edema or those with pneumonia.

ED EVALUATION

Initial assessment and therapy consists of measures appropriate for any patient who presents with shortness of breath and chest pain: supplemental oxygen administration, intravenous access placement, cardiac monitoring, and a 12-lead ECG.

The ECG can be diagnostic. The most common ECG finding is concave-upward ST-segment elevation seen in most of the leads; PR-segment depression may also be seen (Fig. 89.1). Although the ECG is usually abnormal, diagnostic changes may be absent in patients with clinically evident pericarditis, particularly in patients with post-MI pericarditis.

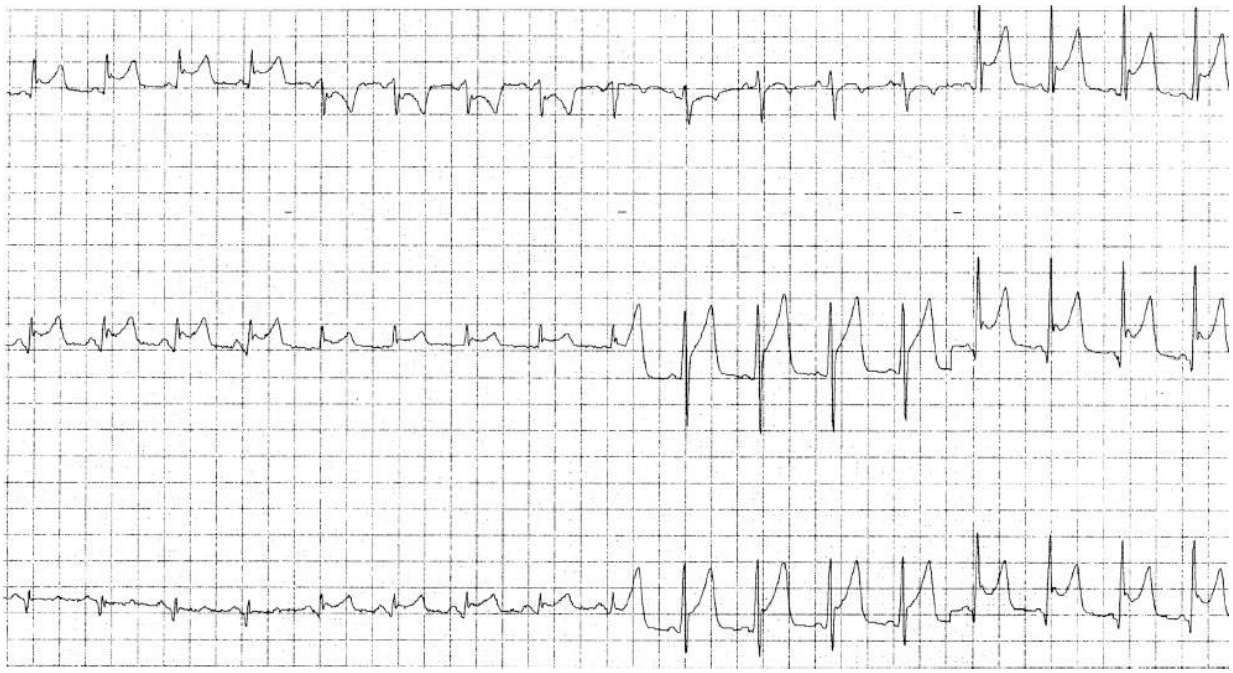

FIGURE 89.1 Electrocardiogram of a 35-year-old man with acute (stage 1) pericarditis. Note the diffuse, concave upward ST-segment elevation.

Early repolarization, a normal electrocardiographic variant characterized by ST-segment elevation, can be difficult to distinguish from pericarditis (1,14–16). If the clinical presentation suggests pericarditis, serial ECGs may be required to differentiate pericarditis from the benign early repolarization variant. On a single ECG, an ST/T ratio (the amount of ST-segment elevation divided by the height of the T wave) of 0.25 or more in lead V_6 is suggestive of pericarditis.

MI and pericarditis may be difficult to differentiate. In pericarditis, ST-segment elevation is more diffuse, usually is upward sloping and is without reciprocal ST depression (16), and the Q waves that evolve in acute infarction do not develop. Pericarditis is also more likely to have associated PR depression. Having PR depression in both limb and precordial leads has a positive predictive value of 96.7% and a negative predictive value of 90% (17). Additionally ST-segment elevation in patients with acute MI is typically focal (in the distribution of a coronary artery), usually is convex or downward

sloping and may be associated with ST-segment depression in reciprocal leads.

The chest radiograph is often normal. The cardiac silhouette may be enlarged secondary to a pericardial effusion, but the heart size may be normal even if an effusion is present (18).

The white blood cell count can range from normal to markedly elevated and is usually not helpful in making or excluding the diagnosis. Similarly, the erythrocyte sedimentation rate is usually elevated, but this is a nonspecific finding. Cardiac marker levels may be significantly elevated because of associated myocarditis (13,19,20).

Echocardiography can provide useful information in suspected pericarditis. In the absence of significant associated myocarditis, most patients with pericarditis have normal cardiac wall motion. In contrast, patients with chest pain caused by cardiac ischemia often have focal wall motion abnormalities. Echocardiography is also the best method for detecting and monitoring pericardial effusions (discussion follows).

Cardiac Tamponade

The classic findings of cardiac tamponade are muffled heart sounds, diminished arterial pressure, and JVD. However, these findings are seen only with fully developed tamponade and are much more likely to occur when pericardial fluid accumulates quickly, precluding pericardial distension (5,21). The most common presenting signs and symptoms associated with tamponade are summarized in Table 89.3 (22).

An important clue to the diagnosis is the presence of pulsus paradoxus, an inspiratory decrease in systolic blood pressure of >10 mm Hg (23). Other clinical entities associated with pulsus paradoxus include emphysema, asthma, obesity, pulmonary embolism, cardiogenic shock, right ventricular infarction, and restrictive cardiomyopathy. Patients with acute traumatic tamponade may not have a pulsus paradoxus.

Patients with tamponade may have relatively normal ECGs. With large effusions, reduction of the QRS amplitude or electrical alternans

(alternating beat-to-beat variation in QRS amplitude) may be seen. Central venous pressure measurements reveal an elevation of right-sided pressures and can help confirm the diagnosis, although this may also be present in patients with pulmonary embolism or CHF.

A definitive diagnosis can be made with cardiac ultrasound. Echocardiography can detect small amounts of pericardial fluid; in cardiac tamponade, it may demonstrate diffuse hypokinesis, right atrial collapse, and right ventricular diastolic collapse (21,24). If possible, echocardiography should be performed emergently in any patient with suspected tamponade, because delays in evaluating the presence and size of a pericardial effusion can be disastrous (4).

The diagnosis of tamponade can also be definitively established by measuring pressures in the cardiac chambers. Right atrial, right ventricular diastolic, pulmonary artery diastolic, and pulmonary capillary wedge pressures are equalized in this condition.

Recurrent Pericarditis

After recovering from acute pericarditis, patients may have one or several episodes of recurrent pericarditis, weeks to months after the initial episode (25–28). Evaluation and management of recurrences are, for the most part, the same as for a first presentation of acute pericarditis. Choice of initial therapy may affect the frequency of recurrence (see the ED management section of this chapter).

Constrictive Pericarditis

Constrictive pericarditis, an uncommon complication of acute pericarditis, results when healing of acute pericarditis leads to encasement of the heart in fibrous tissue, impeding ventricular filling (1,9). Patients often present with dyspnea on exertion, ascites, peripheral edema, and hepatic enlargement. The lung fields are clear in these patients, in contrast to patients with CHF. The presence of distended neck veins in constrictive pericarditis helps to separate these patients from those with severe liver disease, who may appear clinically similar. Pericardial calcification on the chest radiograph and pericardial thickening on echocardiography may also provide

clues to this diagnosis. The definitive treatment is resection of the pericardium.

KEY TESTING

Test	Indication	Supports Pericarditis	Does Not Support Pericarditis
EKG	Chest Pain	Diffuse ST elevation	Focal ST elevation
	Auscultated rub	Diffuse PR depression	Reciprocal ST depression
		ST-segment elevation to T-wave height ratio >0.25 in V6	
Troponin	Suspected coexisting myocarditis Suspected myocardial infarction	Troponin may be positive or negative in simple pericarditis but is usually only mildly elevated or indeterminate	Very high troponin implies either coexisting myocarditis or myocardial infarction
Bedside ultrasound	Suspected pericarditis Suspected tamponade	Pericardial effusion	Absence of pericardial effusion does not rule out pericarditis
	Suspected myocardial infarction		Regional wall motion abnormality
Consultative ultrasound	Suspected tamponade Large effusion on bedside ultrasound	Pericardial effusion	Absence of pericardial effusion does not rule out pericarditis
	Suspected coexisting myocarditis Suspected myocardial infarction		Regional wall motion abnormality

ED MANAGEMENT

The treatment of uncomplicated pericarditis is largely symptomatic, but specific therapy is available for a few causes of pericarditis. Most studies have evaluated either aspirin at moderate to high doses or other nonsteroidal anti-inflammatory drugs in particular ibuprofen (29). There is no standard duration of therapy but many studies suggest a course of several weeks with a gradually tapering dose during that time period. Because of the high doses recommended, physicians should consider giving a proton pump inhibitor as prophylaxis against gastrointestinal discomfort or hemorrhage. In patients with suspected coronary artery disease indomethacin should be avoided because it can decrease coronary blood flow (1,30). In patients with post-MI pericarditis nonsteroidal anti-inflammatory drugs in general should be avoided because they impair myocardial remodeling and it is recommended that patients should be on aspirin therapy at baseline (31).

Colchicine can also be used to treat patients with idiopathic, viral, or autoimmune pericarditis. In a randomized trial of aspirin alone versus aspirin plus colchicine, patients who received both drugs had both a faster resolution of symptoms (36.7% of patients in the aspirin group were still symptomatic at 72 hours versus only 11.7% in the

combination group) and a lower rate of recurrence (32.3% in the aspirin only group versus 10.7% in the combination group) (9). The most common reason for discontinuation of colchicine is diarrhea. Colchicine is generally safe but should be avoided in severe liver or kidney disease.

Bacterial pericarditis must be treated with drainage and appropriate antimicrobial therapy. Uremic pericarditis is usually an indication for dialysis. Corticosteroids should be avoided in most patients, because steroids have been associated with an increased rate of recurrence of pericarditis (28). The exception to this contraindication are patients in whom pericarditis is secondary to rheumatologic causes, where treating the underlying rheumatologic etiology with steroids may be indicated.

The definitive treatment for pericardial tamponade is pericardiocentesis. However, to “buy time” until pericardiocentesis can be performed, volume infusion is the treatment of choice. Ideally, pericardiocentesis should be done with echocardiographic or fluoroscopic guidance (often in the cardiac catheterization laboratory), but emergent “blind” pericardiocentesis may be necessary for hypotensive patients who do not respond to volume infusion.

The pericardium may be accessed by a left parasternal or subxiphoid puncture. In the parasternal approach, the needle is inserted perpendicular to the skin in the fifth intercostal space, just lateral to the sternum. In the subxiphoid approach, the puncture is made about 2 cm below and 1 cm to the left of the xiphoid process; the needle enters the skin at a 30° to 45° angle and is aimed toward the sternal notch or the left shoulder. The needle is advanced with constant syringe aspiration. As much fluid is aspirated as is needed to improve the clinical condition or to obtain specimens for diagnostic use.

After completing the procedure, a chest radiograph should be obtained to look for complications such as pneumothorax or pleural effusion secondary to laceration of the lung or myocardium. Serial physical examinations and central venous pressure monitoring are critical to detect reaccumulation of fluid. The admitting consultant

may choose to observe the patient for fluid reaccumulation, may place a soft catheter in the pericardial space for continued drainage, or may perform surgical drainage in the operating room.

CRITICAL INTERVENTIONS

- Perform pericardiocentesis (with echocardiographic or fluoroscopic guidance if possible) to treat pericardial tamponade.
- Obtain an echocardiogram to exclude pericardial effusion before discharging patients with pericarditis.

DISPOSITION

Many patients with pericarditis can be successfully treated on an outpatient basis. Patients should be considered for admission if they exhibit any high-risk features (Table 89.4) (32,33). Before making a decision for outpatient therapy, it is prudent to obtain an echocardiogram to rule out a large effusion, tamponade, or myocarditis. Patients without high-risk clinical features on history, physical examination, or echocardiogram can be treated as outpatients if close follow-up can be assured; otherwise, they should be admitted with a cardiology consultation.

TABLE 89.4
High-Risk Features of Pericarditis

Fever >38°C
Subacute onset
Anticoagulated
Immunocompromised
Trauma
Tamponade
Severe pericardial effusion (an echo-free space >20 mm)

Common Pitfalls

- Failing to consider pericarditis in the differential diagnosis of chest pain.

- Mistakenly diagnosing pericarditis in patients with other causes of chest pain, such as MI, pulmonary embolism, or aortic dissection.
- Misdiagnosing acute pericarditis as acute MI, potentially leading to the inappropriate administration of thrombolytics or activation of the catheterization laboratory.
- Failing to consider the etiology of pericarditis. Many of the causes require specific therapy.
- Failing to consider cardiac tamponade in the differential diagnosis of hypotension, especially in patients with cancer.

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CHAPTER 90

Hypertension

Philip Shayne and Edward Stettner

When does an elevated blood pressure become an emergency? The World Health Organization has established that hypertension contributes to one in every eight deaths worldwide. One-quarter of all Americans have hypertension, yet only one-half of those individuals receive treatment, and less than one-third of cases are adequately controlled (6). National treatment guidelines exist based on large studies involving tens of thousands of patients (3); however, there is a dearth of evidence available to guide the acute management of severely elevated blood pressure (1–4,8,14,18,19,21,22). As many as one-third of all patients in the emergency department (ED) with markedly elevated blood pressure have been referred there for blood pressure evaluation from some other clinical setting, making the emergency physician the recognized expert. Yet few of these patients are in crisis or require immediate intervention. In most cases, this requires the emergency physician to determine what to do with the incidental finding of an elevated blood pressure in the patient with no symptoms or with nonspecific complaints. The broad spectrum of disease, from the asymptomatic to the critically ill patient, creates the dilemma for the emergency physician in deciding how and when in the process to intervene.

A hypertensive emergency involves rapid and progressive decompensation or damage of vital-organ function resulting from severely elevated blood pressure. These patients need careful evaluation and monitoring; many, but not all, need immediate parenteral blood pressure control. There is no evidence to suggest

that the severe, but asymptomatic, hypertensive patient requires any emergent care. Each patient does require a careful and specific evaluation for signs of critical organ compromise. A rational approach to the elevated blood pressure should be formulated on the basis of the patient's history and presentation.

CLINICAL PRESENTATION

The presence or risk of target-organ deterioration determines the urgency with which a patient with elevated blood pressure must be treated. A hypertensive emergency is defined as the acute and progressive decompensation or damage of vital organ function caused by an elevated blood pressure. The major organs affected by hypertension are primarily the brain, kidney, heart, and vascular system. Patients determined to have a hypertensive emergency need to be carefully evaluated, be monitored, and usually need to have their blood pressure controlled. The treatment should be dictated by the clinical situation, not the severity of blood pressure elevation. No degree of hypertension by itself defines an emergency.

Many patients present with an elevated blood pressure and with nonspecific symptoms. The emergency physician needs to make a decision as to the etiology of the symptoms to determine how the blood pressure must be managed. If a hypertensive patient's chest pain is possibly angina, immediate parenteral control might be necessary. However, if that pain is determined not to be cardiovascular in origin, the same patient might need no immediate treatment for the blood pressure. The assessment of the patient determines the need to treat.

The concept of the hypertensive urgency, usually referring to markedly elevated, asymptomatic blood pressures requiring rapid intervention, is no longer widely used. Most patients without acute and progressive target-organ disease can have their severely elevated blood pressure managed on an outpatient basis (19). This approach de-emphasizes the degree to which the blood pressure is elevated. However, the clinician should be aware that certain patients are at higher risk of near-term complications from their uncontrolled

hypertension, especially those patients with a history of previous end-organ disease. These patients do require increased vigilance.

Hypertensive Encephalopathy

The triad of severe hypertension, altered mental status, and, often, papilledema characterizes hypertensive encephalopathy. This encephalopathy may be accompanied by the acute or subacute onset of lethargy, confusion, headache, visual disturbances, and seizures. Retinopathy may or may not be present. The diagnosis is confirmed if cerebral function improves with lowering of the blood pressure. The mechanism is cerebral overperfusion; in effect, the pressure overwhelms the brain's ability to autoregulate cerebral blood flow (CBF). Overperfusion results in vasodilation and increased permeability of cerebral blood vessels, leading in turn to the development of cerebral edema. If not adequately treated, hypertensive encephalopathy can progress to cerebral hemorrhage, coma, and death (1).

Hypertensive encephalopathy is most likely to occur in previously normotensive individuals who experience a rapid rise in blood pressure, such as children with acute glomerulonephritis and young women with preeclampsia or eclampsia. Patients with chronic hypertension usually experience a more gradual rise in blood pressure and therefore develop a right shift in their pressure perfusion autoregulation curve that makes cerebral decompensation less likely. Hypertensive encephalopathy produces characteristic findings on computed tomography (CT), a posterior leukoencephalopathy that predominantly affects the white matter of the parieto-occipital regions bilaterally (17). CT is useful in excluding other causes of altered mental status such as intracranial bleeding.

Accelerated Malignant Hypertension

Accelerated malignant hypertension occurs most commonly in young African American men with underlying renal parenchymal disease or renovascular disease. When endothelial-vasodilator responses are

overwhelmed, endothelial decompensation causes further hypertension and endothelial damage, resulting in an inflammatory vasculopathy (22). The diagnosis is based on marked elevation of blood pressure and characteristic eye-ground findings. Flame-shaped hemorrhages occur around the optic disk because of high intravascular pressures, and "soft" exudates are caused by ischemic infarction of the nerve fibers secondary to occlusion of supplying arterioles. Papilledema is considered by many to be the sine qua non of "malignant hypertension." For this reason, the term "accelerated hypertension" has been used to describe the same condition (hemorrhages and exudates) without papilledema. Because absence of papilledema does not connote different clinical features or a better prognosis, the term "accelerated malignant hypertension" is now recommended (9).

Common symptoms include headache (85%), visual blurring (55%), nocturia (38%), and weakness (30%). Laboratory evidence includes azotemia, proteinuria, hematuria, hypokalemia, and metabolic alkalosis. Accelerated malignant hypertension is most commonly found in patients with long-standing hypertension and usually occurs without encephalopathy. Since the 1950s, the long-term prognosis of accelerated malignant hypertension has improved from a 1-year survival rate of 10% to a 5-year survival rate of >75% (10).

Cerebrovascular Crisis

Hypertension frequently complicates the presentation of cerebrovascular ischemia and hemorrhage (7). An understanding of cerebrovascular physiology is helpful in determining the best treatment strategy (1,9). CBF is a function of the cerebral perfusion pressure (CPP), which is equal to the mean arterial pressure (MAP) minus the intracranial pressure (ICP): CPP = MAP – ICP. CBF is maintained by vasoconstriction and vasodilation of the cerebral vasculature. However, cerebral autoregulation fails at about 25% more or less than the MAP. In addition, changes in ICP or brain injury can result in loss of the brain's ability to autoregulate blood flow. Increased ICP, commonly seen with hemorrhage or edema,

decreases the CPP, making the brain more vulnerable to changes in MAP.

Cardiovascular Crisis

Hypertensive emergencies involving the heart and great vessels include congestive heart failure (CHF), acute coronary syndromes, and dissecting aortic aneurysm. Blood pressure is frequently elevated in patients with acute pulmonary edema, particularly when a high output state is the cause, as in volume-overloaded patients with renal failure, patients with thyrotoxicosis, or those with severe anemia. Acute pulmonary edema with hypertension and CHF may be caused by transient diastolic dysfunction, which may or may not be a direct result of the elevated blood pressure.

Acute coronary syndromes are also frequently accompanied by hypertension. The reduction of myocardial work by lowering the blood pressure and heart rate has been demonstrated to reduce infarct size in patients not receiving thrombolytic therapy. However, Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study trial demonstrated an increased incidence of cardiogenic shock with the administration of intravenous metoprolol in patients with suspected myocardial infarction. This effect was greatest in patients >70 years of age, with systolic blood pressure (SBP) <120 mm Hg, a heart rate >110 beats/min, or with evidence of CHF (Killip class greater than one). American Heart Association (AHA) guidelines for the treatment of acute coronary syndrome recommend the administration of oral β-blockers within 24 hours for patients without signs of heart failure, evidence of a low-output state, or other relative contraindications to β-blockers (13). Nitroglycerin remains the agent of choice in patients with ST-elevation myocardial infarction; intravenous β-blockers should be considered only in those patients who are not at risk of developing CHF or hypotension.

Acute aortic dissection is thought to occur via aortic dilatation or high blood pressures superimposed on a structural weakness of the arterial wall. The result is a tear of the intimal layer of the aorta. Pulsatile pressure extends the dissection by separating the layers of

the arterial wall. Historical series report a mortality of 1% to 2% per hour. The stresses that extend the dissection are related as much to the pulse pressure (d*p*/d*t* or difference between SBP and diastolic blood pressure [DBP] throughout time) as it is to MAP. Factors that contribute to increased pulse pressure include the heart rate, myocardial contractility, and the MAP (15).

Renovascular Crisis

The kidney is unique in being both a target organ as well as the cause of many hypertensive emergencies. Chronic hypertension causes 30% of cases of end-stage renal disease, making it the second most common cause after diabetes. Chronic hypertensive patients may develop nephrosclerosis after 10 to 15 years, which is manifested by damage to the medial layer of capillaries, reduced kidney size, and nonnephrotic levels of proteinuria without hematuria. In contrast, malignant hypertension damages the intimal layer of the renal capillary bed and may result in enlarged kidneys, a cellular urinary sediment, hematuria, and severe proteinuria.

Severe hypertension in a young patient should raise the possibility of intrinsic acute renal disease, such as glomerulonephritis. Immunoglobulin (Ig) A nephropathy has surpassed poststreptococcal glomerulonephritis in frequency, and Henoch–Schönlein purpura is the most likely cause of acute glomerular disease among children.

Stenosis of the renal arteries is present in only 1% of unselected patients with hypertension, but it is present in 4% of blacks and 32% of whites who have severe hypertension (DBP >125 with retinopathy). It is also more common among patients who have a rapidly progressive course. Most patients have atherosclerosis, but a minority of these patients are young women with medial fibroplasia of the renal arteries. An abdominal bruit is present in 46% of patients, and these patients are more likely to have the onset of hypertension after age 50.

Occasionally, a rare but devastating acute renal failure may occur because of intrarenal vasculitis. This disorder is common in the setting of scleroderma and may be responsive to angiotensin-converting enzyme inhibitors (ACEIs).

Catecholamine Excess

The most familiar drugs that cause hypertension in EDs today are sympathomimetic drugs such as phenylephrine, cocaine, and methamphetamine. Tyramine can induce a hypertensive crisis in patients who are taking a monoamine oxidase inhibitor drug, and hypertension can complicate withdrawal syndromes from alcohol, clonidine, and, less frequently, β-blockers.

Pheochromocytomas can cause intermittent hypertensive crises, usually accompanied by headache. Patients with pheochromocytoma can secrete a bewildering variety of catecholamines and even peptide hormones in either a constant or wildly intermittent pattern. Patients can produce many clinical findings other than hypertension, such as headache, sweating, palpitations, pallor, nausea, and, rarely, seizures. Some patients with pheochromocytomas have paroxysms of low blood pressure rather than high blood pressure.

Hypertension in Pregnancy

Hypertension in pregnancy is addressed separately in Chapter 140. Emergencies include eclampsia and preeclampsia. Pregnant women between 20 weeks of gestation and 2 weeks postpartum who have any degree of hypertension ($\geq$140/90 mm Hg) or an increase of more than 30/15 mm Hg above their baseline, accompanied by peripheral edema and proteinuria, should be considered to have preeclampsia. Hypertension is important mainly as a symptom of the underlying disorder rather than a cause. Preeclampsia is important to recognize, because it can progress suddenly to eclampsia, which is defined by the occurrence of convulsions and can rapidly progress to coma or death. Magnesium infusion is more effective than other anticonvulsants in this setting (11). Definitive treatment consists of delivery of the fetus, so the emergency physician usually collaborates with an obstetrician early in the patient's progress through the department.

Asymptomatic Hypertension

Many ED patients are found to have incidentally elevated blood pressure without active symptoms of target-organ injury. Many of these patients will have a spontaneous decrease in their blood pressure without intervention, though some will remain persistently hypertensive. These patients present a diagnostic and therapeutic challenge to the clinician as there is a dearth of evidence concerning how best to manage them acutely. In general, workup for these patients should be focused on their presenting complaints and symptoms, with therapy directed toward any identified active medical emergencies. There is little evidence to support routine testing in patients with asymptomatic hypertension.

DIFFERENTIAL DIAGNOSIS

Blood pressure elevation may be primary or secondary to underlying causes (pain, anxiety, drugs). A hypertensive emergency exists if the elevated blood pressure is causing progressive target-organ damage. Two of the entities described above are specific complications of uncontrolled hypertension: hypertensive encephalopathy and malignant accelerated hypertension (9). The other hypertensive emergencies are primary crises of the brain, heart, kidneys, or vasculature that are precipitated or exacerbated by the stress of an elevated blood pressure (Table 90.1). For example, a myocardial infarction may occur in a normotensive as well as hypertensive patient. If the blood pressure is elevated in the setting of an infarct, then it must be managed, but the therapy must be decided primarily in the context of treating the coronary ischemia.

TABLE 90.1
Hypertensive Emergencies

- Primary
  - Hypertensive encephalopathy
  - Accelerated malignant hypertension
- Secondary
  - Cerebrovascular accidents
    - Thromboembolic stroke
    - Hemorrhagic stroke
    - Subarachnoid hemorrhage
  - Cardiovascular crises
    - Myocardial infarction
    - Acute coronary syndromes
    - Cardiogenic pulmonary edema
    - Aortic dissection
    - Uncontrollable arterial bleeding
  - Renal crises
    - Acute renal failure
    - Glomerular nephritis
    - Severe hypertension after kidney transplant
  - Other emergencies
    - Preeclampsia/eclampsia
    - Perioperative hypertension
    - Catecholamine excess

ED EVALUATION

The clinical evaluation should determine the nature, severity, and management of patients in hypertensive crisis. When a patient with markedly elevated blood pressure presents to the ED, attention should first be given to assessing the patient's airway, breathing, and circulation. This includes accurate measurement of blood pressure. Initially, elevated ED blood pressures frequently decrease spontaneously by the time a second reading is obtained (14). For this reason alone, interventions should be based on the composite of several, separate blood pressure determinations in the ED. To obtain an accurate measurement, the patient should be seated with the arm at the level of the heart and the cuff bladder should cover at least 80% of the arm circumference. Blood pressure should be evaluated in both arms. Blood pressure measurement with an automated cuff is inaccurate in patients with atrial fibrillation and other heart rhythm

irregularities, especially tachydysrhythmias. Appropriate pain management and relief of underlying causes (e.g., hypoxia, bladder distention) may resolve hypertension (3). Other medications, over-the-counter preparations, or illicit drugs may exacerbate or mitigate blood pressure (Table 90.2).

TABLE 90.2
Drugs that Can Elevate Blood Pressure or Interfere with the Effectiveness of Antihypertensive Agents

Oral contraceptives
Steroids
NSAIDs
Nasal decongestants
Cold remedies
Appetite suppressants
Tricyclic antidepressants
Monoamine oxidase inhibitors

NSAIDs, nonsteroidal anti-inflammatory drugs.

If the patient's blood pressure is persistently elevated, the history should start with an assessment of symptoms that might be consistent with target-organ compromise. Physicians should ask about specific symptoms such as dyspnea, chest pain, neurologic complaints, and visual changes. Additional important historical details include the duration and severity of pre-existing hypertension, the degree of previous success with blood pressure control, and the presence of target-organ disease (cardiovascular, cerebrovascular, renovascular, and great vessel). The physical examination should be directed toward identifying signs of target-organ damage. A fundoscopic examination demonstrating retinal hemorrhage or papilledema is sufficient to diagnose accelerated malignant hypertension. The cardiovascular examination should focus on identifying signs of heart failure (e.g., increased jugular venous pressure, pulmonary rales, and an S_3) and asymmetric pulses. The neurologic examination should assess the level of consciousness, visual fields, and the presence of focal motor and sensory deficits.

Diagnostic studies should be based primarily on the patient's symptoms. A chest radiograph is indicated for patients with dyspnea and a head CT scan for abnormal neurologic findings. Few studies have assessed the prognostic value of abnormal laboratory findings in patients with severe asymptomatic hypertension (17). If a patient's blood pressure remains persistently >180/110 mm Hg after treatment of any aggravating symptoms, practitioners should consider a brief assessment of target-organ function. According to the 2013 American College of Emergency Physicians clinical policy, there is no definite role for screening for end-organ damage in adults with markedly elevated blood pressure, though high-risk populations may benefit from a limited evaluation (23). Because renal failure is silent, the measurement of the serum creatinine and/or a urinalysis is used to detect evidence of renal failure or glomerular disease. An ECG is useful in assessing the baseline level of left ventricular hypertrophy, which carries a poor prognosis and should prompt more vigilant follow-up. When renovascular disease or hypercortisolism are suspected causes of hypertension, a serum tube for plasma renin activity and aldosterone should be drawn before medications are administered. A urine screen for cocaine and amphetamines may help confirm common causes of hypertension. The incremental value of obtaining a chest radiograph or complete blood count in the ED patient without relevant symptoms is generally likely to be low.

KEY TESTING

- Base diagnostic evaluation on individual patient presentation and symptoms.
- Consider urinalysis and chemistry panel to assess renal function in patients with markedly elevated blood pressure.
- Patients with suspected cerebrovascular crisis or hypertensive encephalopathy should receive immediate CT of the head.
- Patients with suspected cardiovascular crisis should receive immediate ECG, cardiac enzyme, and chest radiography.

ED MANAGEMENT

The goal of therapy in a hypertensive crisis is a reduction in the mean MAP by 20% to 25% in 1 to 2 hours. Although not well evidence based, this therapeutic guideline is supported by shared practice experience in patients who have done poorly with more aggressive blood pressure reduction. The ideal drug for treating hypertensive emergencies has a rapid onset, rapid maximal effect, and rapid offset for easy titration of blood pressure. These characteristics are found only in parenteral agents. The most common drugs of this group are summarized in Table 90.3 from the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII) (8).

TABLE 90.3
Parenteral Drugs for Treatment of Hypertensive Emergencies

Drug	Dose[a]	Onset of Action	Duration of Action	Adverse Effects[b]	Special Indications
Vasodilators					
Sodium nitroprusside	0.25–10 µg/kg/min as IV infusion (maximal dose for 10 min only)	Immediate	1–2 min	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Most hypertensive emergencies; caution with high intracranial pressure or azotemia
Nicardipine hydrochloride	5–15 mg/hr IV	5–10 min	1–4 hrs	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies except acute heart failure; caution with coronary ischemia
Fenoldopam mesylate	0.1–0.3 µg/kg/min IV infusion	<5 min	30 min	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma
Nitroglycerin	5–100 µg/min as IV infusion[c]	2–5 min	3–5 min	Headache, vomiting methemoglobinemia, tolerance with prolonged use	Coronary ischemia
Enalaprilat	1.25–5 mg q6 h IV	15–30 min	6 hrs	Precipitous fall in pressure in high-renin states; response variable	Acute left-ventricular failure; avoid in acute myocardial infarction
Hydralazine hydrochloride	10–20 mg IV 10–50 mg IM	10–20 min 20–30 min	3–8 hrs	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia
Diazoxide	50–100 mg IV bolus repeated or 15–30 mg/min infusion	2–4 min	6–12 hrs	Nausea, flushing, tachycardia, chest pain	Now obsolete; when no intensive monitoring available
Adrenergic Inhibitors					
Labetalol hydrochloride	20–80 mg IV bolus every 10 min 0.5–2 mg/min IV infusion	5–10 min	3–6 hrs	Vomiting, scalp tingling, burning in throat, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure
Esmolol hydrochloride	250–500 µg/kg/min IV for 1 min, then 50–100 µg/kg/min for 4 min; may repeat sequence	1–2 min	10–20 min	Hypotension, nausea	Aortic dissection, perioperative
Phentolamine	5–15 mg IV	1–2 min	3–10 min	Tachycardia, flushing, headache	Catecholamine excess

These doses may vary from those in the *Physicians' Desk Reference* (51st edition).
[a]IV, intravenous; IM, intramuscular.
[b]Hypotension may occur with all agents.
[c]Requires special delivery system.
From the National High Blood Pressure Education Program (JNC-VII) (8).

Nitroprusside remains the classic treatment for patients with hypertensive emergencies (8). Nitroprusside is a direct arteriovenous vasodilator that decreases both preload and afterload without significant reflex tachycardia. It is quick in onset of action, and its effect lasts for only 2 to 5 minutes after the drug is discontinued. Nitroprusside should be given with close hemodynamic monitoring to prevent inadvertent hypotension. Thiocyanate toxicity may occur if the drug is used for a period of days, particularly in patients with renal failure. Although not strictly contraindicated in pregnancy, nitroprusside does cross the placental barrier and causes elevated fetal cyanide levels. Because there is no oral form, the patient must be switched to another antihypertensive once control is achieved. Despite the many benefits of nitroprusside, there are often agents better suited for individual hypertensive crises.

Nicardipine is a rapid-acting parenteral calcium channel blocker. Nicardipine has a predictable and smooth onset of action but is relatively long acting. Esmolol is a β-blocking agent that is both rapid in onset and of short duration, making it easy to titrate. Labetalol is a combined α- and β-blocker that is more potent than esmolol and is perhaps better at maintaining a consistent CPP. Unlike esmolol, labetalol has a long half-life, making it possible to administer in miniboluses rather than a constant perfusion, but it is more difficult to titrate down. β-Blockers should not be used in patients with asthma, chronic obstructive pulmonary disease, acute CHF, cocaine abuse, or other contraindications to β-blockade. Fenoldopam is a parenteral dopaminergic receptor-blocking agent with an excellent efficacy and safety profile. Fenoldopam holds some promise as being equivalent to nitroprusside in efficacy, without the rare side effects associated with the nitroprusside cyanide moiety and perhaps with less overshoot hypotension. Enalaprilat is a parenteral ACEI, and phentolamine is a pure α-blocking agent.

Cerebrovascular Crisis

Blood pressure control in cerebrovascular hypertensive emergencies should be undertaken with parenteral drugs that have a short half-life and that are easily titrated with minimal effect on cerebral

vasculature. Because labetalol does not dilate cerebral capacitance vessels, it is theoretically attractive for use in intracerebral disorders. Direct vasodilators, such as nitroprusside, should be used with caution in the setting of focal brain injury, as they can extend the area of ischemia. Nitroprusside has also been implicated in raising ICP and should be avoided in patients with suspected elevated ICP. Some calcium channel blockers have been linked to this rise as well and therefore are not favored in patients with brain injury, although nicardipine is safe and widely used (20).

The treatment of elevated blood pressure in the setting of ischemic cerebrovascular accidents is controversial. When systemic blood pressure is reduced, cerebral autoregulation may fail, thereby producing an ischemic penumbra surrounding the infarct, leading to stroke extension (7). Alternatively, infarction can lead to edema, which will elevate ICP and reduce CBF further. The current AHA guidelines recommend lowering the blood pressure with stroke only when the DBP is >120 mm Hg or the SBP is >220 mm Hg (12). The guidelines further suggest that for patients deemed to be eligible for thrombolytic therapy, blood pressure should be controlled to a systolic <185 mm Hg and diastolic <110 mm Hg. Recommended agents include intravenous labetalol, intravenous nicardipine, or transdermal nitroglycerin paste. Although no study has examined the use of thrombolytics after acutely lowering arterial hypertension, failure to achieve this level of control is considered an absolute contraindication to the administration of systemic thrombolytic therapy. The AHA guidelines are based on consensus opinion, as there is currently no definitive data that establish the clinical benefit of rapidly lowering blood pressure in patients with ischemic stroke. When the decision is made to lower arterial hypertension, the current guidelines recommend a drop of 15% to 25% in the first 24 hours (12).

The role of antihypertensive therapy in hemorrhagic cerebrovascular accidents and subarachnoid hemorrhage is similarly unclear. Theoretically, treatment for elevated blood pressure in intracranial hemorrhage should be more aggressive than for patients with ischemic stroke. The rationale is to decrease the risk of ongoing

bleeding from ruptured small arteries and arterioles; however, the relationship between rebleeding and systemic blood pressure is unproven. As with an ischemic cardiovascular accident, overly aggressive treatment of hypertension may worsen brain injury by decreasing CPP, especially when ICP is increased. There is some evidence to suggest that the tissue immediately surrounding the hemorrhage may be particularly sensitive to changes in the CPP and aggressive lowering of blood pressure may cause tissue ischemia. The most recent AHA guidelines for blood pressure control with hemorrhagic stroke advocate a three-tiered approach. For an SBP >200 mm Hg or MAP >150 mm Hg, it is recommended that clinicians consider aggressive parenteral blood pressure control. The guidelines further suggest that when the SBP is >180 mm Hg or the MAP is >130 mm Hg and there is the possibility of elevated ICP, clinicians should consider using antihypertensive therapy in conjunction with ICP monitoring to maintain a CPP between 60 and 80 mm Hg. Finally, in patients with an SBP >180 mm Hg or a MAP >130 mm Hg and in which elevated ICP is not a concern, the guidelines suggest a modest reduction in blood pressure to a MAP of 110 mm Hg or a blood pressure of 160/90 (12). Nimodipine may be given to decrease the incidence of vasospasm and rebleeding after subarachnoid hemorrhage, but the drug is not recommended for blood pressure control (20).

Cardiovascular Crisis

Nitroglycerin is favored in the treatment of severe hypertension complicating cardiac ischemia. *Nitroglycerin* is a direct vasodilator that affects the venous vasculature more than the arterial. Nitroglycerin dilates the coronary arteries and, in contrast to nitroprusside, promotes a favorable redistribution of blood flow to ischemic areas. As previously discussed, the role of β-blockers in acute coronary syndromes has changed, and intravenous β-blockers are no longer considered first-line therapy in the ED. Oral β-blockers should be given within 24 hours to patients with acute coronary syndrome who are not at high risk for developing heart failure. The goal of treatment for patients with acute coronary syndromes is

reduction of blood pressure to normal or even lower if evidence of ischemia persists. However, this reduction should occur carefully with the patient monitored intensively. Overly vigorous blood pressure lowering may worsen ischemia, because coronary perfusion depends on DBP.

Most critical cases of CHF are treated with a combination of nitroglycerin, furosemide, and an ACEI. For patients with pulmonary edema and hypertension, initiate sublingual nitroglycerin while preparing intravenous nitroglycerin. An ACEI is helpful whenever there is pulmonary congestion and hypertension; captopril may be given orally or sublingually, or enalaprilat can be given intravenously if the patient cannot take oral medications. If systemic fluid overload is present, then administer intravenous furosemide. However, some patients with CHF will not have signs of right-sided heart failure (e.g., jugular venous congestion, peripheral edema, and hepatomegaly) and will in fact be volume depleted because of a pressure diuresis despite the presence of pulmonary edema. In these patients with "dry failure," diuresis may initially exacerbate the underlying pressure natriuresis and further stimulate the renin–angiotensin axis, leading to hypotension. The decision is based on a clinical judgment of whole-body fluid status. β-Blockers have been found to improve survival in patients with chronic CHF; however, this observation should not be extended to patients with acute pulmonary edema because the negative inotropic effects and bradycardia of β-blockade may precipitate immediate worsening.

In aortic dissection, unlike many presentations of hypertensive emergencies, immediate and aggressive blood pressure control is required. Most guidelines recommend targeting an SBP between 100 and 120 mm Hg, as long as tissue perfusion can be maintained (5). Additionally, it is important to control heart rates in patients with aortic dissection, as tachycardia can increase shearing forces on the damaged aorta, therefore increasing the size of the dissection. β-Blockers should be initiated before starting nitroprusside to avoid the potential adverse effects of reflex tachycardia. As an alternative, labetalol is a unique parenteral agent that achieves its maximal effect within minutes and then remains effective for several hours. This

quality allows titration with small boluses, thereby avoiding the constant monitoring required and increased cost incurred with use of nitroprusside (15). Labetalol can also be administered as a parenteral infusion rather than as individual boluses, but careful monitoring is required with this strategy.

Renovascular Crisis

Although malignant hypertension may precipitate acute renal failure by injuring the kidney's microvasculature, this causal chain is often reversed with hypertension being a manifestation, rather than a cause, of the renal failure. Because this distinction cannot be made in the ED, these patients should have their blood pressure lowered. Both nitroprusside and labetalol are excellent choices in this setting. ACEI drugs definitely improve prognosis among chronic hypertensive patients with mild proteinuria; however, they should be used cautiously in hyperkalemic patients with renal failure. Nitroprusside can cause thiocyanate poisoning in several days in patients with renal failure and should be used only briefly or if the patient is to have dialysis soon.

Treatment with an ACEI may reverse high blood pressure dramatically in patients with unilateral stenosis, but it may provoke acute renal failure and severe hyperkalemia in patients with bilateral stenosis, particularly if these patients are taking supplemental potassium or a potassium-sparing diuretic. This complication can be completely reversed by discontinuing the ACEI (16).

Catecholamine Excess

Patients with severe hypertension resulting from pheochromocytoma are commonly treated with the pure α-blocker phentolamine, given intravenously. This drug may be accompanied by a β-blocker if needed for tachycardia. Administration of β-blockers alone in the setting of any sympathomimetic (e.g., cocaine) may leave the α-receptors "open," with subsequent worsening of hypertension. Therefore, an attractive alternative to β-blockers is labetalol, a β-blocker with some α-antagonist properties. However, the α- and β-

blockade with labetalol may not be equally effective. Although several studies report reductions in blood pressure and heart rate when labetalol is given to patients with cocaine toxicity, case reports indicate that some individuals may get worse. The clinical importance of the "unopposed α" effect of labetalol increasing blood pressure requires further investigation.

Benzodiazepine therapy is considered by some to be the first-line treatment for hypertension caused by catecholamine excess, especially in the setting of sympathomimetic (e.g., cocaine or methamphetamine) toxicity. It is believed that the central nervous sedation may blunt the sympathomimetic effects caused by central stimulation, therefore lowering blood pressure. Regardless of which benzodiazepine is selected as the therapeutic agent, it is important to titrate the dose to clinical efficacy while carefully observing for respiratory depression.

Hypertension in Pregnancy

The mainstay of antihypertensive treatment for hypertensive crisis in pregnancy in many institutions is hydralazine administered intravenously in boluses of 5 to 10 mg every 20 to 30 minutes. This dose is in addition to magnesium therapy for seizure control. If treatment is refractory to hydralazine, second-line agents are diazoxide and β-blockers. Calcium channel blockers have been studied in chronic hypertension among pregnant patients, but they may not be effective with proteinuric hypertension.

Asymptomatic Hypertension

In patients with asymptomatic elevations in blood pressure and no evidence of target-organ damage, there is no role for immediate lowering of blood pressure. The 2013 American College of Emergency Physicians clinical policy states explicitly that routine intervention is not required, though clinicians can consider beginning therapy in selected high-risk populations, and all patients should be referred for follow-up (level C recommendation).

CRITICAL INTERVENTIONS

- Base clinical decisions on correctly measured and repeated blood pressure.
- Search for and correct underlying causes of an elevated blood pressure (e.g., pain, hypoxia, bladder distention, ingestion, or withdrawal).
- Investigate complaints carefully for evidence of target-organ disease.
- Treat the blood pressure according to specific indications (e.g., ischemia).
- Avoid relative hypotension or dropping blood pressure in the absence of an indication.

DISPOSITION

All hypertensive emergencies require admission to a monitored setting. These patients generally require emergent involvement of an appropriate specialist for management of a neurologic, cardiovascular, or renovascular crisis. Close blood pressure monitoring, preferably with an arterial line, is indicated. Patients with preeclampsia/eclampsia require emergent obstetric consultation.

Most patients presenting with elevated blood pressures are not in crisis. In patients with asymptomatic elevated blood pressure with no evidence of target-organ disease, the most important intervention is to ensure proper follow-up (3,18). The goal should be life-long control of the blood pressure. When the elevated blood pressure may be the artifact of a systemic process such as pain or infection, the best strategy is to refer the patient for reevaluation of the blood pressure once the primary problem has resolved. If the patient has discontinued their blood pressure medications, the regimen should be restarted, barriers to compliance evaluated, and a primary care physician contacted to ensure reevaluation in a week. The JNC-VII guidelines recommend a thiazide-type diuretic as an initial agent, usually in combination with drugs from other classes (3). The second agent may be from a number of categories and is best chosen in

relation to any compelling indications in the patient's history (Table 90.4).

TABLE 90.4
Compelling Indications for Individual Drug Classes for Hypertension Therapy

Compelling Indication[a]	*Recommended Drugs*[b]					
	Diuretic	BB	ACEI	ARB	CCB	Aldo ANT
Heart failure	X	X	X	X		X
Postmyocardial infarction		X	X			X
High coronary disease risk	X	X	X		X	
Diabetes	X	X	X	X	X	
Chronic kidney disease			X	X		
Recurrent stroke prevention	X		X			

[a]Compelling indications for antihypertensive drugs are based on benefits from outcomes, studies, or existing clinical guidelines; the compelling indication is managed in parallel with the blood pressure.
[b]Drug abbreviations: BB, β-blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CCB, calcium channel blocker; Aldo ANT, aldosterone antagonist.
From the National High Blood Pressure Education Program (JNC-VII) (3).

In principle, if there has never been a previous measurement of elevated blood pressure, the blood pressure needs to be rechecked during another visit before the diagnosis of hypertension can be made. However, in individuals with readings persistently >180/110 mm Hg in the ED, the latest national guidelines recommend starting a combination therapy immediately (3). Ideally, the physician who will provide ongoing supervision should be the one to pick the initial agents with which they are comfortable. The best role of the emergency physician is to identify a primary physician for the patient, encourage that physician to select an initial antihypertensive agent, and provide a follow-up appointment within the week.

There is an intermediate group of patients with a severely elevated blood pressure and with known target-organ disease but without

active decompensation. Examples include a severely hypertensive patient with a previous history of myocardial infarction or stroke. The immediacy arises because the patient with known target-organ disease may be considered at higher risk for a hypertension-related adverse event in the short term. There is no good evidence basis for how these patients should best be managed. These patients should have a treatment strategy initiated from the ED although the blood pressure does not necessarily need to be lowered during the visit. These patients do require an increased level of vigilance. It may be reasonable to treat these patients as outpatients, although some may need to be held for short-term observation if there is question as to medication compliance or blood pressure monitoring. The decision depends on the clinical judgment of the physician.

Common Pitfalls

- Diagnosing a hypertensive emergency when one does not exist. Patients with hypertensive emergencies have evidence of acute end-organ dysfunction.
- Reducing the blood pressure too quickly or to too low a level. In patients with chronic hypertension whose autoregulation curve has been reset, this reduction can lead to cerebral or cardiac ischemia.
- Lowering a patient's blood pressure acutely without an urgent indication.
- Failing to diagnose hypertension or preeclampsia in pregnant patients with blood pressures >140/90 mm Hg or with an increase in blood pressure of more than 30/15 mm Hg.
- Neglecting to match the antihypertensive agent to the clinical scenario.

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SECTION IX
Vascular Emergencies

Section Editor: GREGORY W. HENDEY

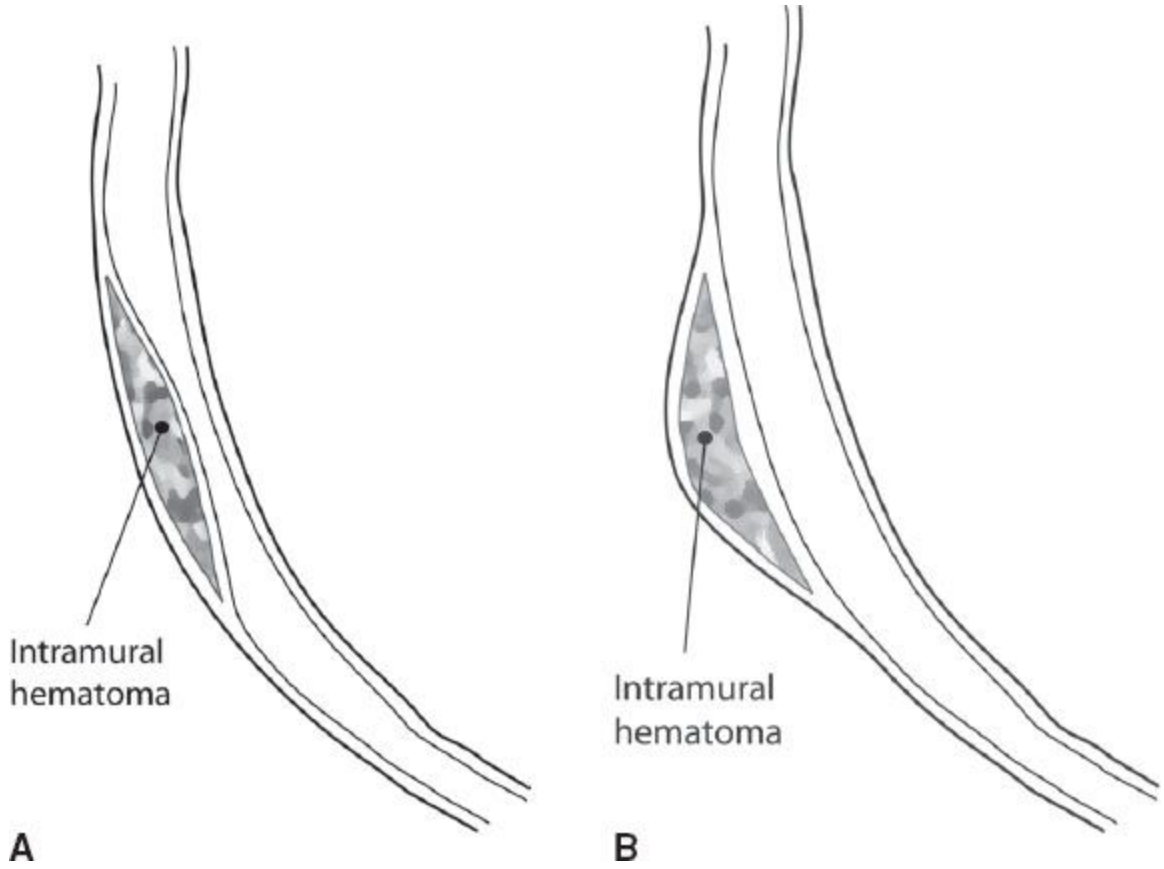
CHAPTER 91

Nontraumatic Carotid and Vertebral Artery Disorders

Brian Chinnock

PART 1: DISSECTION

Internal carotid artery (ICA) or vertebral artery (VA) dissection results from an intimal tear. Following the tear, blood under pressure enters the wall of the artery within the tunica media, forming an intramural hematoma. The hematoma, while contained within the tunica media, may press toward either the intima causing vessel stenosis (eFig. 91.1A), or toward the adventitia (eFig. 91.1B) causing aneurysmal dilation. Neurologic sequelae may result from either decreased blood flow, or more often from distal embolization of clots formed in this thrombogenic environment, causing CVA or TIA. In the intracranial portion of the artery, dissection may result in subarachnoid hemorrhage.



eFIGURE 91.1 A: Intramural hematoma producing vessel stenosis. B: Intramural hematoma causing aneurysmal dilation without vessel stenosis.

The extracranial ICA and VA are much more vulnerable to dissection than are the intracranial segments, probably due to increased mobility. Thus, the origin of the ICA dissection is typically just distal to the carotid bulb. VA dissection most commonly begins at its exit point from the transverse foramen between the first and second cervical vertebrae.

Together, ICA and VA dissections cause about 20% of strokes in patients younger than 45 years of age (1). ICA dissection is twice as common as VA dissection.

Spontaneous (atraumatic) dissections are thought to be the result of structural defects and connective tissue disorders, such as Ehlers–Danlos syndrome type IV, osteogenesis imperfecta, Marfan syndrome, and autosomal dominant polycystic kidney disease (2). Family history is important because 5% of patients with a spontaneous ICA or VA dissection will have a family member with an arterial dissection. Risk factors for the development of carotid and VA stenosis, such as hypertension, hypercholesterolemia, diabetes, or tobacco use, have not been found to be risk factors for dissection.

Spontaneous dissection of the ICA or VA is often associated with commonplace events that cause sudden neck movement or sustained positioning of the neck in a position that may predispose to vessel damage. Some of the reported events include forceful flexion–extension movements of the neck (coughing, sneezing, roller-coaster riding), prolonged neck extension (painting a ceiling or "beauty-parlor" syndrome where the neck is extended over the sink), or prolonged lateral bending (propping a phone between the neck and shoulder) (3–5). Chiropractic treatment is more commonly associated with VA than ICA dissection (6), probably because of the rapid rotation of C1 on C2 stretching the VA as it exits the foramen.

CLINICAL PRESENTATION

The median ages of patients presenting with extracranial ICA or VA dissection are 44 and 41 years, respectively (7). Intracranial dissection of either artery reportedly occurs in younger patients, 20

to 30 years of age (3). The clinical effects from arterial dissection generally result from the local effects of the dissection causing pain, and the distal embolization from the dissection site causing ischemic symptoms.

ICA Dissection

Table 91.1 illustrates the differences in the clinical presentation of ICA versus VA dissection. Headache is the most prominent initial complaint of the patient with ICA dissection. The headache is typically frontotemporal and unilateral. The onset is usually gradual, but "thunderclap" headaches have been described. Facial, eye, or ear pain, without headache, is described in 10% of patients (7). The unilateral neck pain is typically over the area of the carotid artery itself and has also been mistaken for a peritonsillar abscess. Oculosympathetic palsy (ipsilateral miosis and ptosis) is classically associated with ICA dissection, but only half of patients will have it. Oculosympathetic palsy can be differentiated from Horner syndrome in that there is no facial anhidrosis, because facial sweat glands are innervated by the sympathetic plexus surrounding the external, not internal, carotid artery. The focal cerebral and retinal ischemic symptoms of extracranial ICA dissection begin a median of four days after the onset of pain and are similar to those described for ICA-territory strokes (see Chapter 151) (7). In intracranial ICA dissection, the neurologic symptoms begin only a few hours after the onset of pain (8). The lower cranial nerves are commonly affected, particularly the hypoglossal nerve, and is thought to be caused by either compression or stretching of the nerve by the enlarged ICA or by interruption of nutrient vessels of the nerves (3–5).

TABLE 91.1
ICA Versus VA Dissection

Clinical Presentation (% Incidence of Finding)	
Carotid	**Vertebral**
Unilateral headache (67–90)	Occipital headache (66–83)
Unilateral facial/orbital pain (50)	Posterior neck pain (50)
Unilateral anterior neck pain (25)	Unilateral arm pain
Oculosympathetic palsy (50)	Isolated cervical cord ischemia
Pulsatile tinnitus (25)	Nausea, vomiting
Syncope	
Cerebral or retinal ischemic symptoms (50–95)	Vertebrobasilar ischemic symptoms (70–90)
Cranial nerve palsies (12)	Wallenberg syndrome
More likely to have preceding TIA	Less likely to have preceding TIA
Neurologic findings begin days after headache	Neurologic findings begin hours after headache

ICA, interval carotid artery; VA, vertebral artery; TIA, transient ischemic syndrome.

Vertebral Artery Dissection

As with ICA dissection, headache is the most common presenting complaint. The headache is almost always occipital, may involve the frontal area and may be intermittent. Neck pain is more commonly noted in VA dissection than in ICA dissection and is more commonly described as posterior. Unilateral arm pain may be noted when the dissection occurs within the cervical spine and compresses a cervical nerve root most commonly at the C5 to C6 level (4,9).

The focal ischemic neurologic symptoms are typically those of vertebrobasilar insufficiency, as described in Chapter 155. The classic finding is involvement of the posterolateral medulla and cerebellum, termed Wallenberg syndrome. The thalamus and cerebral hemispheres may also be affected, although less commonly than the cerebellum and brainstem. Importantly, neck pain has been described as beginning a median of about 2 weeks before the development of neurologic findings, but headache may precede neurologic symptoms by a matter of hours (10).

DIFFERENTIAL DIAGNOSIS

The main differential diagnoses for carotid and VA dissection before the development of focal neurologic symptoms are meningitis, subarachnoid hemorrhage, subdural or epidural hematoma, migraine or tension headache, and cervical strain, fracture, or radiculopathy. Once neurologic symptoms appear, the differential is similar to that of ischemic stroke. One of the main ways to differentiate ICA or VA dissection from these other disorders is the history of head or neck pain, followed hours to days later by ICA or VA-territory neurologic symptoms. The ideal situation is to diagnose and treat dissection before the development of neurologic symptoms. This is why it is important to consider ICA and VA dissection in the differential for headache and neck pain.

ED EVALUATION

When ICA or VA dissection is suspected by history and physical examination findings, the most important consideration is the imaging modality. The gold standard by which other radiologic tests are measured is four-vessel contrast digital subtraction angiography (DSA). The disadvantages of this procedure include its invasiveness and the need to have access to a specialist to perform the procedure. The most commonly used alternative radiologic tests are duplex ultrasound (DUS), magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and computed tomography angiography (CTA).

Duplex Ultrasound

Extracranial DUS can identify intimal defects and aneurysmal dilation. In addition, color flow DUS is useful for identifying the true and false lumens seen in dissection. The true lumen typically has antegrade flow, and the false lumen has high-resistance flow that is forward, reversed, or bidirectional. DUS is limited by its inability to visualize intracranial dissection.

Two prospective studies have compared DUS to the gold standard of DSA or MRA in the evaluation of ICA dissection. The sensitivity of Doppler to detect flow abnormalities was 93% to 96%. Standard

DUS had a sensitivity of 72% to 79%, and color flow scanning had a sensitivity of 82% (11,12). The sensitivity of DUS has improved in the last decade owing to technologic improvements.

The use of DUS in the diagnosis of VA dissection is less clear because it is technically more difficult. Most VA dissections show abnormal flow patterns, but no finding is characteristic. Small case series have shown promise, but it is not currently the study of choice for suspected VA dissection.

Magnetic Resonance Imaging/Magnetic Resonance Angiography

MRI allows visualization of the intramural hematoma itself, as well as aneurysmal dilation. Contrast-enhanced MRA shows luminal irregularities and stenosis. The combination of MRI with MRA demonstrates a sensitivity of 84% to 100% and specificity of 95% to 100% when compared against DSA in small studies (13). One study that examined ICA dissection demonstrated a better sensitivity of the MRI/MRA combination than with DSA (14). DSA is unable to detect an abnormality if there is no luminal irregularity (eFig. 91.1B). MRI can also show cerebral parenchymal abnormalities in the affected vascular area, including acute ischemic lesions with diffusion-weighted MRI.

Computed Tomography Angiography

Multislice CTA gives excellent visualization of vessels because of the contrast difference between the enhanced lumen and surrounding structures. Postprocessing of the data in multiplanar formats can also provide three-dimensional images that closely approximate DSA but also show the surrounding soft tissues. Two studies examining CTA showed sensitivities near 100% for the diagnosis of ICA and VA dissection (15).

MRI/MRA VERSUS CT/CTA

Studies comparing MRI/MRA, CTA, and conventional angiography have shown similar high sensitivities and specificities (16). Small

studies have reported that CT/CTA has better ability to visualize specific anatomic features of the dissection, such as pseudoaneurysm, intimal flaps, and high-grade stenoses than MRI/MRA. However, MRI/MRA has the advantage of being able to detect ischemic lesions. The decision of which test is more appropriate should be guided by local protocol and resources. Whether CT or MRI is chosen, it is important to include both the standard and angiographic components.

KEY TESTING

- For suspected ICA or VA dissection, perform MRI/MRA or CT/CTA

ED MANAGEMENT

The treatment for an extracranial ICA or VA dissection is anticoagulation with heparin followed by coumadin. The goal is to reduce the risk of distal embolization, the most common cause of neurologic insult. Anticoagulation is contraindicated if there is intracranial dissection because of its theoretical risk of hemorrhagic transformation, or pseudoaneurysm. Despite the wide acceptance of anticoagulation, there is no controlled study comparing anticoagulation to placebo in the treatment of dissection. Antiplatelet agents such as aspirin, and, less commonly, ticlopidine and clopidogrel have been described as treatment options. There are no randomized trials comparing anticoagulant with antiplatelet drugs, and nonrandomized studies did not demonstrate any difference. Antiplatelet agents are often considered as first-line treatment in patients who are poor candidates for anticoagulation and in those patients who have a dissection with no ischemic symptoms. Thrombolytics have been used safely in one small study, but in 9 of 11 treated patients the vessel remained occluded (17). Blood pressure control to a normotensive level has a theoretical benefit in preventing extension of the dissection, but no studies have examined this treatment.

Surgery or endovascular treatment for ICA or VA dissection is used for those not responding to conservative measures. This includes patients with neurologic deterioration or ischemic insult despite adequate anticoagulation, or a persistent or worsening aneurysm after 6 months of anticoagulation. Intradural VA dissections are treated aggressively with endovascular therapy, as the rate of subarachnoid hemorrhage is high (15).

CRITICAL INTERVENTIONS

- Anticoagulation is the most common treatment option for extracranial ICA or VA dissection.

DISPOSITION

Patients with ICA or VA dissection should be admitted to the hospital to monitor for further progression of neurologic injury and to establish anticoagulation. Either neurology, neurosurgery, or vascular surgery should be consulted, depending on institutional arrangements.

The prognosis for neurologic recovery is good. Approximately 70% of extracranial ICA dissection patients have full neurologic recovery, 14% have a mild deficit, and 16% have a moderate to severe deficit or death (5). One long-term follow-up study of extracranial VA dissection patients showed 88% with good or excellent recovery and 12% with moderate or severe disability (18). Intracranial dissection patients and bilateral extracranial dissection patients have significantly higher morbidity and mortality rates.

Common Pitfalls

- Failure to consider the diagnosis in a patient with headache or neck pain associated with minor trauma, particularly if neurologic symptoms are present.
- Failure to consider the diagnosis in a relatively young patient with stroke symptoms.
- Failure to perform a CT or MRI in addition to the contrast angiography component of each of these examinations, as some

dissections will not be detectable on angiography

PART 2: STENOSIS

Stenosis or occlusion of the ICA or VA is most commonly caused by atherosclerosis. There is a 2% to 5% annual ipsilateral stroke risk for people with ICA stenosis of >50%. Although less is known about VA stenosis, symptomatic patients with >50% stenosis have a 1-year stroke risk of as high as 22% (19). ICA stenosis is responsible for approximately 30% of all anterior circulation strokes and transient ischemic attacks (TIAs). Cerebral ischemia may result directly from decreased blood flow, or more commonly, from distal embolization from the plaque.

The risk factors are those of atherosclerosis, and include hypertension, tobacco use, hypercholesterolemia, and obesity. Other less common causes of stenosis include fibromuscular dysplasia, radiation, and arteritis (i.e., Takayasu arteritis).

The most common location for extracranial ICA stenosis is at the carotid bulb, and for extracranial VA stenosis, at its origin from the aorta or brachiocephalic trunk.

ICA kinking and VA occlusion resulting from rotation (bow hunter syndrome) deserve special mention as they are causes of vessel occlusion without stenosis or dissection (20). ICA tortuosity with kinking is a common incidental finding on ultrasound or angiography. In some patients, the site of kinking can be caused by atherosclerosis and stenosis, and this is a source of potential embolization. It may also cause reversible cerebral ischemia during head or neck rotation.

The VA may also be occluded because of head or neck rotation. *Os odontoideum,* a condition in which the dens is hypoplastic, absent, or incompletely fused to the body of C2 with subsequent atlantoaxial instability and bony impingement on the VA during movement, is described as a cause. Other causes include impingement by nerve fibers of the stellate ganglion, or lateral cervical disk herniation.

CLINICAL PRESENTATION

The patient with symptomatic ICA or VA stenosis will usually present to the ED with symptoms related to stroke or TIA of the affected vascular area (see Chapter 155). Table 91.2 contrasts the neurologic findings associated with ICA versus VA stenosis, although there can be considerable overlap between the two.

TABLE 91.2
ICA- Versus VA-Territory Stroke or TIA

ICA Territory	VA Territory
Weakness and/or numbness contralateral face and extremities	Weakness and/or numbness ipsilateral face, contralateral extremities
Vision loss ipsilateral, monocular (amaurosis fugax)	Vision loss bilateral homonymous hemianopia
Aphasia	Ataxia
	Vertigo
	Diplopia

ICA, internal carotid artery; VA, vertebral artery; TIA, transient ischemic attack.

DIFFERENTIAL DIAGNOSIS

As noted previously, TIA and stroke are the most common events bringing the patient with ICA or VA stenosis to the ED.

ED EVALUATION

In addition to evaluating the patients for history and physical examination findings of stroke, imaging can be an important part of the evaluation for ICA or VA stenosis.

Internal Carotid Artery Stenosis

The degree of extracranial ICA stenosis can be used to predict which patients are at the highest risk for stroke and will get the most benefit from surgery. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) demonstrated that in patients with 70% to 99% stenosis demonstrated on DUS, carotid endarterectomy is superior to medical therapy in preventing stroke (21). A systematic review of trials done between 1994 and 2001 compared

imaging modalities to the gold standard of DSA in detecting 70% to 99% stenosis and gave the following pooled test characteristics: DUS, sensitivity 86% and specificity 87%; MRI/MRA, 95% and 90%, respectively; and the combination of MRA + DUS, 95% and 95%, respectively (22). More recently, CTA has shown good agreement with DSA, and may be especially helpful in evaluating the ICA in a patient with complete obstruction, as CTA can better show a small residual lumen, which may influence the decision of medical versus procedural management (23). DUS is highly operator dependent, and it is often used as the sole test in determining degree of stenosis at centers with expertise.

Vertebral Artery Stenosis

The degree of VA stenosis that is most clinically important is not well defined, although 50% to 99% is the range usually cited. A systematic literature review comparing DUS, MRI, MRA, and CTA to the reference standard of DSA demonstrated little high quality data directly comparing these modalities. However, using this data, MRA and CTA had the best sensitivity for detection of VA stenosis (24).

KEY TESTING

- Extracranial ICA stenosis is most commonly evaluated with DUS. MRA or CTA may be used if there is continued diagnostic uncertainty.
- Extracranial VA stenosis is evaluated with MRA or CTA.

ED MANAGEMENT

Acute treatment of stroke caused by ICA or VA stenosis is described in detail in Chapter 155 and includes prevention of hyperglycemia and hyperthermia and monitoring of volume status and blood pressure. An important intervention is to start the patient on antiplatelet therapy after ruling out hemorrhagic stroke with a CT scan. Aspirin, at a dose of 160 to 300 mg, has been shown to significantly decrease death and disability in acute ischemic stroke.

Clopidogrel and ticlopidine are alternatives for patients unable to take aspirin.

Patients with 70% to 99% symptomatic ICA stenosis as demonstrated on ultrasound are likely to benefit from carotid endarterectomy, but in patients with 50% to 69% stenosis, only certain subgroups, such as those with large hemispheric TIAs, may benefit from surgery (21). The CREST study compared carotid stenting to endarterectomy in an RCT of 2,502 patients and found no difference in combined stroke, MI, or death rate in a 2.5-year follow-up (25). Current practice is to stabilize the symptomatic patient medically prior to either procedure, but future studies may challenge this practice. Patients with 100% occlusion are treated medically.

The optimal treatment strategies for extracranial VA stenosis are more poorly understood. No RCT has shown an advantage of medical management, surgery, or endovascular stenting. Case series have demonstrated drug-eluting stent placement to have a low rate of periprocedural complications and restenosis rates comparable to non-drug-eluting stenting. Surgical options include endarterectomy or reconstruction (often done by transposing the VA to the common carotid artery). Surgery is recommended for patients with symptomatic ICA kinking. Correction of the process that causes extrinsic VA compression during neck rotation (i.e., atlantoaxial stability or cervical disk protrusion) is also necessary to prevent further cerebral ischemia.

CRITICAL INTERVENTIONS

- Aspirin (160 to 325 mg) is recommended for patients with symptomatic ICA or VA stenosis, or clopidogrel or ticlopidine for those patients who cannot take aspirin.
- Obtain imaging studies of patients with stroke or TIA to determine whether they may be candidates for carotid stenting or endarterectomy.

DISPOSITION

Stroke resulting from significant ICA or VA stenosis mandates admission to the hospital to monitor for deterioration, cerebral edema, or hemorrhagic transformation. Cardiac monitoring, swallowing studies, and aggressive rehabilitation are also commonly needed.

Patients with TIAs that are not crescendo or recurrent and are unlikely to have an embolic source may be candidates for outpatient care with urgent imaging and rapid follow-up. However, 5% of patients presenting to an ED with a TIA will have a stroke within 2 days after presentation. Consultation should involve the patient's primary care doctor and/or a neurologist. Patients who are found to have significant ICA or VA stenosis as an acute cause of TIA or stroke are candidates for inpatient evaluation for endarterectomy or angioplasty.

Common Pitfalls

- Failure to recognize the difference between ICA and VA territory neurologic symptoms. A normal carotid DUS study is irrelevant when the symptomatology suggests VA stenosis.
- Failure to consider ICA kinking or "bow hunter syndrome" in the patient with stroke or TIA symptoms with head or neck rotation.

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CHAPTER 92

Thoracic Aortic Dissection and Aneurysm

Shawna J. Perry

THORACIC AORTIC DISSECTION

Aortic dissection is the most frequently occurring catastrophic event involving the aorta. First recognized postmortem by Morgagni in 1761, aortic dissection remains a diagnostic challenge to the emergency medicine physician because of its nonspecific presentation, diverse population at risk, and time pressure for diagnosis. Delays or misdiagnosis can have devastating consequences.

Dissection of the aorta begins with a tear in the innermost layer of the vessel, the intima. This tear occurs most commonly in the proximal ascending portion of the thoracic aorta. The tear may begin in the aortic root or between the origin of the left subclavian artery and the ligamentum arteriosum. These areas of the aorta are relatively fixed, and it is believed that a tear can be initiated when maximum stress is applied to these areas during systole. An intimal tear can then allow blood to penetrate into the media layer of the aorta (middle layer of a blood vessel), separating the intimal layer from the outermost layer of the vessel, the adventitia. The length of time required to dissect the entire aorta can be seconds, with the dissection continuing either distally or proximally. Reentry tears occur distal to the initial site, creating a false lumen which provides an alternate path for aortic blood flow. An intramural hematoma can develop within this false lumen, minimizing flow and occasionally causing dilation. The dissection may dilate as the flow of blood increases through the false lumen or as an intramural hematoma organizes. The term *dissecting aneurysm* is frequently used because of this pathologic finding of dilation, but the term is inaccurate, because this is not a true aneurysm. Spontaneous rupture is common, occurring most often into the pericardium. A small number of patients develop an intramural hematoma within the dissection with no evidence of a reentry tear. A dissection that begins with a tear high in the aorta that is associated with an open false lumen, has a very poor prognosis.

The exact causes of the intimal tear and other structural defects of the aortic wall remain unclear. The classic pathologic model is based on histologic changes found in patients with Marfan syndrome that demonstrate recurrent injury and repair to the aorta associated with cystic medial necrosis. This model is expanding to include a variety of molecular derangements that result in collagen and elastin degradation within the aorta (1). The result is a weakening of the aortic wall that may then make it more susceptible to injury from another insult, such as chronic hypertension.

Hypertension is the most common predisposing factor to dissection. It is not yet known why one hypertensive person undergoes dissection and another does not. Aortic dissection is likely a multifactorial disease, with hypertension as the principal risk factor. Marfan syndrome is a widely recognized risk factor that carries a mortality rate over 90% in the event of acute dissection or rupture. Connective tissue diseases such as Ehlers–Danlos syndrome, systemic lupus erythematous, and Turner syndrome, have all been associated with aortic dissection. Cigarette smoking and dyslipidemia may be contributing factors, although aortic dissection does not occur secondary to atherosclerotic disease. Congenital abnormalities of the aorta, such as bicuspid valve and coarctation, are also risk factors. Dissection has also been reported in the third trimester of pregnancy, during the postpartum period and in association with cocaine and methamphetamine use, blunt trauma, and weightlifting. Most of these patients have evidence of systemic hypertension or connective tissue abnormalities similar to those of Marfan syndrome (2,3). Iatrogenic aortic dissection can result from invasive vascular procedures (i.e., cardiac catheterization) or nonaortic cardiac surgery such as a valve replacement or coronary artery bypass graft (CABG) (4).

CLASSIFICATION

DeBakey originally classified aortic dissection into three categories according to the origin of the dissection: Type I, involving the entire length of the aorta; Type II, beginning in the ascending aorta (the aortic root to the left subclavian); and Type III, originating from the

area distal to the left subclavian (5). The Stanford classification, a simpler and more widely used nomenclature, divides dissections into type A, involving the ascending aorta, and type B, beginning after the left subclavian artery and confined to the descending aorta (Fig. 92.1).

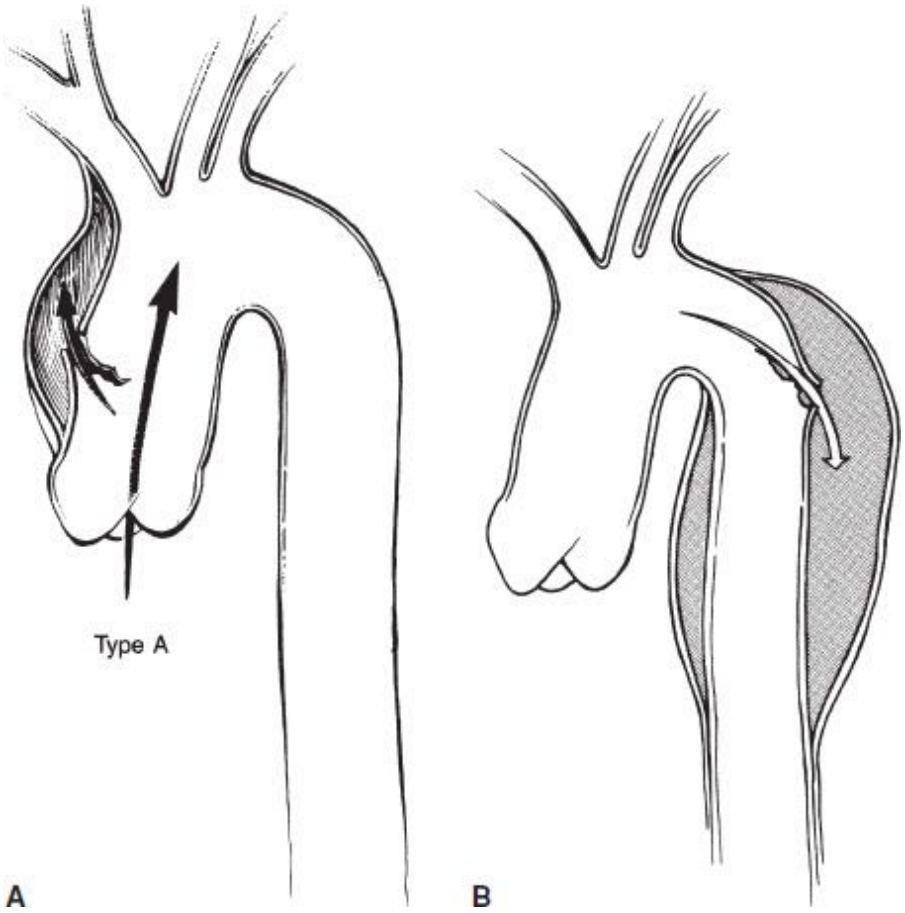

FIGURE 92.1 Classification of aortic dissections. **A:** Dissection of ascending aorta. **B:** Dissection of descending aorta.

Type A dissections are the most common (80%) and considered surgical emergencies. Potential complications include aortic rupture, cardiac tamponade, aortic valve insufficiency, shock, stroke, and involvement of coronary arteries resulting in acute cardiac ischemia and arrhythmias (e.g., atrial fibrillation from direct compression of atrium) (6). Type B dissections are predominantly managed medically, but up to one-fourth of patients require urgent operation because of hemorrhage, limb or organ ischemia, intractable pain,

progression of dissection, expansion, or impending rupture. Women tend to present with dissection at a later than men (over 70 vs. 61 years of age).

The most common cause of death for untreated type A dissections is rupture of the aortic wall into the pericardial sac. This rupture usually occurs along the right lateral wall of the aorta where the adventitia is thinnest. Rupture may also occur into the mediastinum, pleural space, abdomen depending upon how far the dissection extends. Death may result from associated pericardial tamponade, myocardial infarction, hemorrhagic shock, acute congestive heart failure, or cerebrovascular accident. Patients with painless acute aortic dissection have a very high mortality rate, especially when it is type B, and are more likely to have associated congestive heart failure, syncope, and a history of previous cardiovascular surgery (7).

The mortality rate for patients with untreated or medically managed type A dissection ranges from 52% to 75%. Risk factors for death include age over 70 years, hypertension, preoperative cardiopulmonary resuscitation or shock, lack of cerebral perfusion, syncope with residual neurologic dysfunction, cardiac tamponade, migrating pain, pulse deficit, or ECG findings of myocardial ischemia (8). Of note, women with Type A dissections tend to be diagnosed 24 hours later than men, and are more likely to present with gradual onset, altered mental status, and complications (myocardial infarction, pericardial effusion) (9). The in-hospital postsurgical mortality for all patients with type A dissection averages 26%, but is higher for women (32%) (9,10). Because mortality rates for uncomplicated type-B dissections are the same with either medical or surgical treatment, medical therapy is preferred. The use of β-blockers and afterload-reducing medications appears to decrease the risk of extension or dilation of the dissection. Medical treatment does not stop the progression of the disease indefinitely, and aortic replacement is eventually needed. With aggressive medical management the early mortality rate of uncomplicated acute type B dissection is 8% to 10%, and with continued pharmacologic therapy 1-year and 4-year mortality of 72% and 81%, respectively (11,12). Emergent surgery is indicated in type B dissections that are

complicated by rupture, leak, ischemia, intractable pain, uncontrollable hypertension, or aneurysm, but with generally poor results (11). Death is almost certain in the presence of mesenteric, renal, or peripheral vascular ischemia. Newer treatment options include percutaneous stent-graft placement, also known as thoracic endovascular aortic repair (TEVAR), which may provide better results than open surgical repair of Type B dissections (10,13).

CLINICAL PRESENTATION

To make the diagnosis of aortic dissection, the emergency medicine physician must include it in the differential diagnosis at patient presentation. The pain of aortic dissection is classically described as "ripping" or "tearing"; however, this can also be associated with a number of other entities. A study of 464 patients with aortic dissection found that the classic tearing or ripping sensation was reported in only 51% of cases (12). The majority reported the abrupt onset of severe pain, either sharp or dull, located in the anterior or posterior chest (73%). Back pain was experienced in 53% of patients, with 30% reporting abdominal pain and a few experiencing pain across the chest, back, or abdomen (12,14). Type A aortic dissection in the elderly is less likely to be associated with abrupt back and chest pain or to manifest findings such as aortic regurgitation or pulse deficit (10). The nonspecific and variable presentation of aortic dissection makes the identification of risk factors important for early diagnosis; these include a history of hypertension, Marfan syndrome, connective tissue or autoimmune disorder, cocaine or methamphetamine use, and prior cardiac surgery (i.e., valve replacement, cardiac catheterization).

In addition to pain in the chest and back, discomfort may also be localized to the neck, throat, mandible, abdomen, and leg. Patients may also complain of pain in the lower back, pelvis, or a lower extremity of dissection extends beyond the diaphragm. One emergency department (ED) study found that dissection was more likely to be suspected in patients with dissection who presented with both chest and back pain (86%) but less likely to be considered in patients who had only chest pain (45%) or abdominal pain (8%)

(15). Fifteen percent to 20% of dissections are associated with no pain at all. Patients with sudden onset of pain, followed by a pain-free interval, appear to be especially likely to be missed (8).

The patient may appear to be in shock, exhibiting cool and diaphoretic skin, yet with paradoxically normal or elevated blood pressure. Although most patients present this way, nearly one-fourth present with hypotension, presumably due to leaking or rupture. A variety of signs and symptoms are caused by vascular compromise from the dissection. The majority are neurologic and include syncope, altered mental status (especially in women), stroke, seizure, visual disturbances, or paraplegia. Syncope is the initial complaint in 13% of patients, but decreased level of consciousness occurs more frequently. Syncope may be associated with the development of hemopericardium or stroke, and is associated with increased mortality (16).

Cardiovascular collapse is seen most often with Type A dissection. A developing hematoma can cause hoarseness (laryngeal nerve compression), dyspnea, stridor with wheezing (tracheal compression), or dysphagia (esophageal compression). The presence of hypotension in the presence of chest and back pain strongly suggests either a Type A dissection, a rupture of either type of dissection, or a dissection into the mesenteric or brachiocephalic artery. Gastrointestinal symptoms of midepigastric pain, melena, or frank hemorrhage can occur secondary to splanchnic vessel infarctions and are frequently misdiagnosed. Dissection into the renal artery may lead to hematuria, flank pain, oliguria, or uncontrollable hypertension because of excess renin release. Unusual presentations of aortic dissection have included hemoptysis, superior vena cava syndrome, acute arterial occlusion, right atrial or ventricular rupture, testicular pain, and deep-vein thrombosis.

DIFFERENTIAL DIAGNOSIS

Chest pain with associated back pain is the most prevalent symptom of aortic dissection; however, the differential diagnosis of this constellation is broad and contains numerous other life-threatening conditions. Myocardial infarction is the principal diagnosis of

exclusion as well as cerebrovascular accident in patients with neurologic symptoms. In fact both MI and stroke may result from thoracic aortic dissection. Misdiagnosis of either could result in the use of thrombolytic therapy and therein an increased risk of death from exsanguination. Other diagnoses to be considered are hypertensive crisis, pulmonary embolism, thoracic aneurysm, pneumothorax, multilobar pneumonia, mediastinal cyst or tumor, pericarditis, pancreatitis, cholelithiasis, cholecystitis, perforated viscus, esophagitis, peptic ulcer disease, gastritis, and peripheral vascular disease.

The diagnosis of aortic dissection should be considered in the presence of the following: history of hypertension, connective tissue disease, congenital aortic abnormalities, aortic insufficiency, atypical chest or back pain, acute neurologic symptoms, diminished or absent peripheral pulses (especially if they reappear), syncope, chest pain in pregnancy (third trimester and postpartum), chest trauma, flank pain and hematuria without an obvious source, evidence of multiple sites of ischemia, and chest pain following the use of cocaine or methamphetamine.

ED EVALUATION

Patients suspected of aortic dissection should be evaluated quickly and managed aggressively in anticipation of impending leak or rupture. On physical examination, initial hypertension is very common (systolic >150 mm Hg), but the patient may still appear clinically to be in shock. Jugular venous distention should be assessed, as it may signify cardiac tamponade, an expanding hematoma around the aorta with outflow obstruction, or congestive heart failure. Aortic insufficiency murmurs occur in 16% to 20% of patients as a result of proximal dissection causing dilation of the aortic valve ring.

Abdominal examination may reveal decreased or absent bowel sounds, tenderness, or rigidity secondary to ischemia. Rarely, a pulsatile mass is palpable. Examination of the limbs may reveal unequal, decreased, or absent peripheral pulses in 50% of cases, with these findings less likely to be present in the elderly (17). A complete

deficit of pulse is found in only 8% to 10% of patients. A pulse deficit can be easily assessed at the bedside by comparing the measured blood pressure between both arms, or between the arms and legs. Cranial nerve deficits secondary to dissection into the carotid arteries or motor deficits secondary to distal dissection of spinal arteries have also been reported.

Initial laboratory studies should include a complete blood cell count with differential, serum electrolytes, troponin, coagulation studies, lactate, urinalysis, and a 12-lead ECG. A specimen should be sent for type and crossmatch. Lipase and liver function tests should be considered if there is suspicion of intra-abdominal pathology.

Although routine laboratory studies are not usually helpful in the diagnosis of aortic dissection, they may rule out other causes and help guide resuscitation. The hematocrit may be low if there is leakage, rupture, or if a sufficient amount of blood has accumulated in the false lumen. Renal artery involvement may result in increased blood urea nitrogen and creatinine levels as well as hematuria, indicating ischemia or infarction of the kidney. An elevated lactate level may suggest shock or ischemic bowel. A small number of patients dissect proximally into the right coronary artery and suffer a myocardial infarction. Normal troponin levels may help distinguish dissection from MI, but it must be kept in mind that dissection and MI coexist in some cases. EKG changes can be found in 50% of patients with dissection, with approximately 25% demonstrating ECG changes compatible with myocardial infarction or pericarditis (6). In some cases, testing the urine for drugs of abuse may be appropriate. D-dimer has shown promise, in that it is elevated in most patients with aortic dissection. Whether it can reliably exclude this lethal disorder has not been established.

The most readily available radiologic study to assist in the diagnosis of aortic dissection is the chest radiograph. In 65% to 85% of cases, the chest radiograph demonstrates some abnormality. A widened mediastinum is the most common finding, but a left-sided pleural effusion or an indistinct aortic knob may also be seen (Fig. 92.2). The deviation of a calcified aortic intima by >6 mm from the outer wall of the aorta is considered pathognomonic of dissection.

Other findings suggestive of dissection are the double density sign (a false lumen that is less radiopaque than the true lumen), tracheal deviation, and an irregular aortic contour. Unfortunately, a normal chest radiograph does not exclude the diagnosis. If suspicious for dissection, radiographic confirmation is required by either computed tomography (CT) or transesophageal echocardiography (TEE).

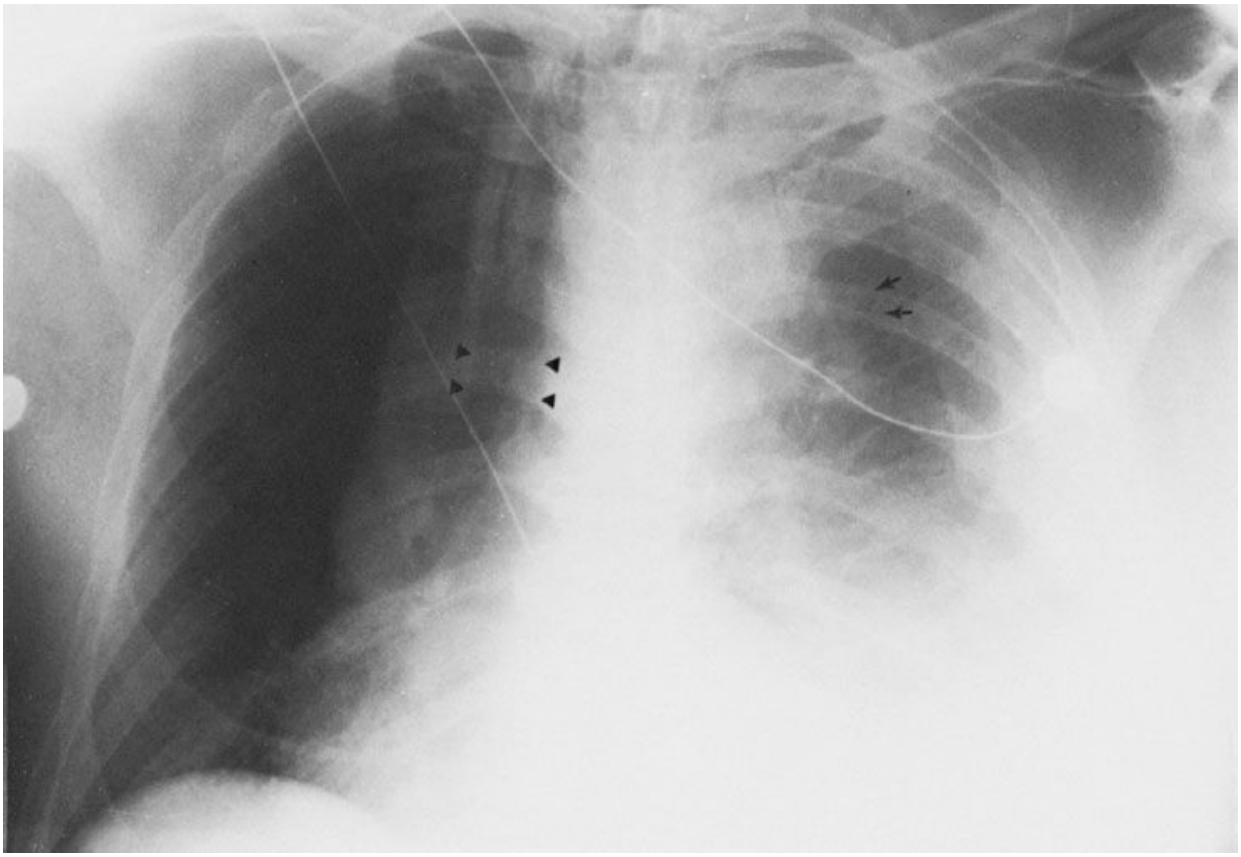

FIGURE 92.2 Chest x-ray film of a 65-year-old woman with type-A dissection. Note the widened mediastinum, indistinct aortic knob (*arrows*), tracheal deviation (*triangles*), and left pleural effusion.

In most institutions, CT angiography (CTA) has supplanted aortography for making the diagnosis of dissection. The advantages of CT include superior visualization of intimal flaps and fluid collection in the pericardium, pleura, and mediastinum; demonstration of distal aortic patency; noninvasiveness; and sensitivity and specificity equal to aortography. Three-dimensional reconstruction of CT images provides delineation of the intimal tear

and assessment of the great vessels, with sensitivity and specificity similar to that of TEE and magnetic resonance imaging (MRI). The main disadvantages of CT include the exposure to contrast material and radiation.

TEE, if readily available, can be used as the initial diagnostic study in suspected dissection, especially for unstable patients who cannot be moved to CT scan. TEE has a sensitivity and specificity of 99% and 98%, respectively. The goals of TEE in aortic dissection are to confirm the diagnosis, differentiate true and false lumens, localize the intimal tear, evaluate left ventricular wall motion, determine the presence of fluid collections, and to detect aortic insufficiency. TEE has a reported diagnostic accuracy of 100% for aortic insufficiency and cardiac tamponade but has limited ability to evaluate the great vessels and coronary vessels. Complications of transient atrioventricular (AV) block, bradycardia, and asthma can occur during introduction of the probe (18). Images may be limited in obese or emphysematous patients. TEE can be combined with CTA.

MRI has high sensitivity and specificity, but it is seldom used in the emergent setting because of cost, length of time needed for the study, and relative unavailability. Emergency physician–performed bedside ultrasound should not supplant more definitive assessment by CTA and/or TEE.

KEY TESTING

- Basic laboratory studies, troponin, EKG
- Advanced imaging with CT angiogram or TEE

ED MANAGEMENT

The patient should be placed in a high acuity area, on a cardiac monitor, with intravascular access established with at least *two* large-bore catheters (16 gauge or larger). The goals of ED management are to reduce the arterial blood pressure and to decrease the forceful contractility of the left ventricle, in an attempt to limit the propagation of the dissection. Systolic blood pressure control is important because the rate of dissection is directly proportional to

the rate of rise of arterial blood pressure. The systolic blood pressure should be maintained at 100 to 110 mm Hg (mean arterial pressure of 60 to 80 mm Hg) or the lowest level compatible with adequate renal and cerebral perfusion. This is best achieved by titrating intravenous (IV) medications. Direct arterial blood pressure monitoring (e.g., through a radial arterial catheter) can aid management but should not delay treatment. If suspicion for dissection is high, treatment should be initiated rapidly and before confirmatory tests are performed.

β-blockers are first line for controlling blood pressure in aortic dissection but are relatively contraindicated with known or suspected cocaine toxicity. Esmolol IV is the drug of choice (0.5 mg/kg loading dose in 1 minute, infusion rate of 0.05 mg/kg/min). Propranolol IV may also be used (0.5 to 1 mg increments at 5-minute intervals) as well as metoprolol or labetalol. Acute congestive heart failure, heart block, and bradycardia are contraindications to β-blocker use. Nitroprusside IV at an initial rate of 0.5 to 1 μg/kg/min or nicardipine IV (5 mg/hr initially) can be added or additional blood pressure control *after* β-blockers have been initiated. Fenoldopam IV (0.1 μg/kg/min initially) is a dopamine-1 agonist that can be used as an alternative to nitroprusside in patients with renal impairment, but it has a longer half-life (5 to 9 minutes) and may cause reflex tachycardia and ECG changes. Verapamil IV or diltiazem IV may also be used if β-blockers are contraindicated. Morphine IV can also assist in reduction of blood pressure by treating pain associated with the dissection. Oral agents should *never* be used in the emergency setting for patients with suspected or confirmed aortic dissection.

CRITICAL INTERVENTIONS

- Aggressive blood pressure control with short-acting agents such as β-blockers IV
- Expedient consultation with a thoracic surgeon for early operative management

DISPOSITION

Management of the patient with aortic dissection requires a multispecialty approach. The radiologist should be consulted emergently to obtain and read the appropriate diagnostic procedures. The cardiothoracic surgeon should also be notified as quickly as possible. Cardiology may need to be consulted to obtain an emergent TEE. Once the diagnosis of dissection has been made, an internist or intensivist may also need to be consulted for medical management, especially if a stable type B dissection is found. Patients with acute aortic dissection should be admitted to an intensive care unit.

Indications for transfer include inadequate facilities or personnel to definitively make the diagnosis or to treat the condition. If transfer is indicated, a unit that can provide the appropriate speed and level of care during transport is highly recommended, such as air transport or critical care transport.

Common Pitfalls

- Failure to consider the diagnosis of aortic dissection. Unexplained, severe, and sustained chest pain (especially with associated back pain) must be evaluated with CT or TEE to definitively rule out dissection.
- Failure to obtain early consultation with a radiologist and cardiothoracic surgeon.
- Failure to arrange rapid transfer to the nearest appropriate hospital, if presenting facility has inadequate resources for diagnosis or management of dissection.

THORACIC AORTIC ANEURYSM

Thoracic aortic aneurysm (TAA) is insidious in onset and presentation. Defined as a localized or diffuse dilation of the aorta, surgical intervention is needed at a diameter of 5.5 cm or greater, except for patients with Marfan or bicuspid aortic valve in which the critical diameter is 5 cm or greater. Dilation is the result of an undermining of the overall strength of the aortic wall by direct loss of supportive proteins such as elastin and collagen. Once the wall of the aorta is weakened, there is progressive alteration in anatomy,

with a growing diameter and thinning of the aortic wall that leads to dilation and rupture. Turbulent flow can lead to thrombus formation. The risk of rupture, dissection, or death increases exponentially when the diameter is >6 cm^3, known as the "hinge point" upon which the tensile strength of the tissue is overcome. Causes for the undermining of the aortic wall are listed in Table 92.1.

TABLE 92.1
Diseases Contributing to Thoracic Aortic Aneurysms

Atherosclerosis
Coarctation of the aorta
Cystic medial necrosis
Giant cell arteritis
Marfan syndrome
Mycotic aneurysms
Seronegative spondyloarthropathies
Syphilis
Tuberculosis
Takayasu arteritis

The incidence of TAA is 10.4 per 100,000 with 3.5 per 100,000 developing dissection or rupture (14). It affects men and women equally and is more common with advancing age. Risk factors are hypertension, advanced atherosclerotic disease, and smoking. The natural history of TAA is one of progressive dilation and rupture, with a 76% mortality rate at 2 years in untreated patients (19). Aneurysm diameter is a significant risk factor for rupture. The median size at time of rupture is 6 cm for ascending aneurysms and 7 cm for descending aneurysms. The average increase in diameter is 0.1 cm per year (0.7 cm ascending and 0.19 cm descending), and the risk of rupture increases dramatically as the diameter increases (19). Rupture occurs at smaller diameters in patients with connective tissue disorders such as Marfan syndrome. Surgical intervention is planned according to the patient's stability at the time of diagnosis and the diameter of the aneurysm as monitored through time, with an annual calculation of risk of rupture (20). Five-year survival from

elective TAA repair is 87%, but only 37% after emergent surgical intervention (21).

The clinical presentation of TAA in the ED is often that of an incidental finding on chest x-ray. Occasionally, patients will present with aortic regurgitation murmurs or with symptoms directly related to impingement of thoracic structures by the aneurysm (e.g., hoarse voice from compression of the recurrent laryngeal nerve or atrial fibrillation from left atrium compression). The rare patient with rupture or impending rupture may present with deep, aching or throbbing chest or back pain with or without hypotension. A sudden escalation of pain and sudden onset of hypotension are signs of aneurysm rupture. Rupture may also present as cardiopulmonary arrest secondary to intrathoracic or intra-abdominal hemorrhage, if the aneurysm extends beyond the diaphragm.

The ED evaluation should focus on imaging to define the aneurysm. CTA and TEE can be used to evaluate suspected aneurysms, depending upon the stability of the patient. If the diagnosis has not been made previously, aneurysms suspected in the ED should be evaluated at the time of presentation, even if they are asymptomatic. Consultation with a thoracic surgeon is imperative for determination of a treatment plan, even if asymptomatic. Patients who do not need immediate surgical repair may need medical consultation for blood pressure control and should have periodic outpatient diagnostic tests to monitor the aneurysm diameter. First-order relatives of patients with known thoracic aneurysms should be screened, because approximately 20% may be found to have aneurysms.

The ED management of the symptomatic patient with rupture or impending rupture requires immediate aggressive resuscitative measures, including close cardiac monitoring including EKG, two large-bore IV access, and resuscitation with fluids and blood. Bedside ultrasound can be of assistance in locating collections of fluid in the chest, abdomen, or pericardium. Emergent involvement of the thoracic surgeon is imperative if surgical repair is a possibility, with prompt transfer to another facility if the necessary imaging, critical care, and surgical expertise are not readily available.

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CHAPTER 93

Abdominal Aortic Aneurysm

Matthew R. Lewin and Stephen P. Samuel

The timely recognition of an abdominal aortic aneurysm (AAA or "triple A") is a major challenge to the emergency physician. The presentation may be confusing, diagnosis difficult, and the cost of delayed or missed diagnosis devastating (1). AAA is one of the most common causes of unexpected death after discharge from the emergency department (ED) (2) and is one of the highest risk areas for medical malpractice litigation in emergency medicine (3).

AAA is defined as a 50% or greater increase in aortic diameter or an infrarenal aortic diameter ≥ 3 cm (4). Two percent to 5% of elderly patients have an AAA (5). The majority of patients are male, but the prevalence of AAA increases with age in both sexes (6). As the population continues to age, emergency physicians can expect to encounter patients with AAAs more frequently.

Despite a clear link to atherosclerosis, the etiology of AAA remains incompletely understood. Smoking is the strongest independent risk factor for AAA (7), but familial, biochemical, and hemodynamic factors have been implicated as well and are overtaking smoking as associated causes (8). Evidence suggests that up to 20% of AAAs have a dominant genetic component with incomplete penetrance, highlighting the importance of family history when examining patients with abdominal or back pain (9). Recently, matrix metalloproteinases and localized chronic inflammation are thought to play key role in the pathophysiology of AAA (9).

The natural history of the AAA is one of gradual expansion (although sudden changes in size may occur) followed by rupture, exsanguination, and death. Most AAAs are asymptomatic until rapid expansion or leakage occurs. The appearance of symptoms is associated with an 80% 1-year mortality in untreated patients (33% in 1 month and 74% in 6 months) (10).

The risk of rupture and death depends primarily on aneurysm size. Small aneurysms (3 to 5.4 cm) are at low risk for rupture; between 5.5 and 6.9 cm, the incidence of rupture at 1 year is 9.4% to 10.2%; and for aneurysms measuring $\geq$7 cm, the 1-year rate of rupture climbs to 32.5% (11). Early detection and elective repair of AAAs, now primarily done by interventional radiologists, leads to increased life expectancy, even for elderly patients. Thirty-day mortality after elective surgery ranges from 1% to 7% (12). However, given that rupture of an AAA is inevitable given enough time and that mortality in the setting of rupture exceeds 80%, elective resection is generally recommended for aneurysms of 5.5 cm or more in men and aneurysms $>$5 cm in women (8). Four major trials to date demonstrate no advantage to immediate repair (via open or endovascular surgery) for small AAA (4 to 5.5 cm) and favors image-based surveillance (13).

CLINICAL PRESENTATION

AAAs typically present in three ways: asymptomatic; symptomatic but hemodynamically stable; and ruptured. The latter two are immediately life-threatening complications of AAA for which delayed or missed diagnosis is likely to be catastrophic.

Asymptomatic Aneurysm

Occasionally, an AAA is discovered on routine examination for another, unrelated problem. Frequently, the aneurysm is noted on abdominal plain films, CT scan or other imaging study. The emergency physician's task in this setting is to confirm that the aneurysm is truly asymptomatic and to refer the patient to primary care or outpatient surgical consultation.

Symptomatic Aneurysm

Patients who are hemodynamically stable but who have symptoms potentially referable to an AAA can present in a variety of ways, and are therefore easily misdiagnosed. In fact, almost one half of all symptomatic AAAs are misdiagnosed at their initial presentation (1). The cardinal symptoms of AAA—abdominal, low back, or flank pain—are highly nonspecific (14). Discomfort occasionally radiates to the testis or leg, causing the symptoms to be misattributed to renal colic, inguinal hernia, or lumbar spine disease. The pain is usually not much affected by movement and can vary considerably in location. Radicular findings, isolated hip pain or hematuria may be present, misleading the physician. Of note, the pain of AAA may be associated with syncope at the time of onset (15).

Less common presentations of symptomatic AAA include hydronephrosis or leg swelling (usually left), new onset or worsening of hypertension (secondary to renal artery compression), testicular swelling, or evidence of peripheral embolization. Aortovenous or aortocaval fistulas are uncommon and usually present as high-output failure with marked distention of the lower abdominal and leg veins, accompanied by more typical evidence of AAA, such as abdominal mass and back pain (15).

About 10% of patients with symptomatic AAAs present with severe pain and marked abdominal tenderness (10). Because these patients have the appearance of an acute abdomen, recognizing the urgency of the situation is straightforward, even though the presumptive diagnosis may be erroneous (e.g., perforated viscus). Symptomatic AAA may present acutely as complete aortic occlusion with a clinical picture similar to that of a saddle embolus or acute Leriche syndrome (impotence due to aortoiliac compression). Even with prompt operative intervention, this complication carries an approximate 50% mortality (10).

An uncommon acute presentation of a symptomatic AAA is gastrointestinal bleeding secondary to an aortoenteric fistula, most commonly in a patient who has had previous AAA repair. Such bleeding may be massive and can distract the emergency physician

from suspecting vascular disease. In particular, aortoenteric fistula should be assumed whenever a patient who has had a previous repair of an AAA presents with gastrointestinal bleeding. Emergency physicians should be familiar with identification and management of such postoperative complications of both conventional and endovascular AAA repair. Fortunately, with the increasing utilization of endovascular techniques, postoperative abdominal complications have declined. Nevertheless, aneurysm remodeling and shortening can cause stent-graft dislodgment or kinking, and progression of underlying atherosclerotic disease can cause compression of the lower limbs of the graft (16). Post-AAA endograft complications include pelvic ischemia, impotence, buttock claudication, and colonic ischemia (17).

Ruptured Aneurysm

The classic triad of findings in ruptured AAA is back pain, hypotension, and a pulsatile abdominal mass, but only about one-half of patients who survive to reach the ED manifest all three findings (7). Therefore, the presence of any one of these findings in a patient with a known AAA is sufficient to make the presumptive diagnosis of rupture without confirmatory testing (18). Unfortunately, most patients presenting with a ruptured AAA have no prior knowledge of their aneurysm, thus increasing the need for emergency physicians to be alert to the possibility of ruptured AAA in the presence of any of these presenting findings (19).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of AAA includes the large number of causes of shock, abdominal pain, and back pain. If shock is present, it is important to consider AAA along with myocardial infarction, hemorrhagic pancreatitis, perforated viscous, mesenteric infarction, and infection alone or in conjunction with ruptured AAA. In patients whose presentation is less severe, renal or biliary colic, diverticulitis, and lumbosacral disc disease also need to be considered. Because these conditions are much more common than

AAA, aneurysm is often low on the differential. Nevertheless, with its potentially catastrophic outcome, ruptured AAA should always be given due consideration.

ED EVALUATION

Symptoms and signs of AAA are varied and nonspecific. Physical examination is important in early recognition, because about one-half of asymptomatic AAAs are palpable (19). Only 30% to 50% of acute AAA patients present with the classic triad of hypotension, pulsatile mass, and abdominal or low back pain and 30% are misdiagnosed with renal colic, diverticulitis, or GI bleed (20). Most palpable aneurysms are found in the epigastrium, extending to the paraumbilical areas on both sides of the midline. The sensitivity of physical examination depends on the size of the aneurysm, ranging from about 60% for aneurysms between 3 and 4 cm to 82% for those >5 cm (12). Unfortunately, this sensitivity is not sufficient to confidently rule out an aneurysm based on a negative physical examination. *False-positive* physical findings are also common, illustrating the difficulty of the diagnosis (17).

Laboratory studies are rarely helpful in the diagnosis of AAA but should be obtained in the symptomatic patient to evaluate the status of other comorbid conditions (diabetes and renal insufficiency, among others), to investigate other possibilities in the differential, or to guide resuscitation. Blood cell counts and coagulation studies should be evaluated in patients with suspected hemorrhage or coagulopathy, and blood should be made available in the blood bank in such cases, including O type blood for STAT administration if needed.

Radiographic Imaging

Plain films of the abdomen are occasionally helpful in the diagnosis of AAA, in that calcified walls sometimes provide a visible contour of a dilated aorta (12) and is also implicated as a risk factor for rupture of aneurysm (21). Though such fusiform calcifications indicate the presence of an AAA, they do not distinguish enlarging

or leaking aneurysms. Absent or “normal” aortic calcifications are of no value in ruling out the diagnosis. Therefore, plain films should not be routinely ordered to evaluate the presence of an AAA or its complications.

Abdominal ultrasonography is useful in quickly and accurately establishing the presence of an aneurysm with almost 100% sensitivity (Fig. 93.1) (22). Indeed, bedside ultrasonography is a reliable tool for AAA screening in ED (23,24). However, this technique is *not* reliable in determining whether rupture has occurred or in estimating the proximal and distal extent of the aneurysm. Its role in the ED lies in rapidly establishing the presence of AAA at the bedside. Recently, 3D ultrasound imaging was found clinically reliable in quantification of AAA (23,24). Detection of a saccular aneurysm of any size warrants the immediate attention of a vascular surgeon. It is also useful to remember that AAA compressing a ureter can cause hydronephrosis, mimicking urolithiasis.

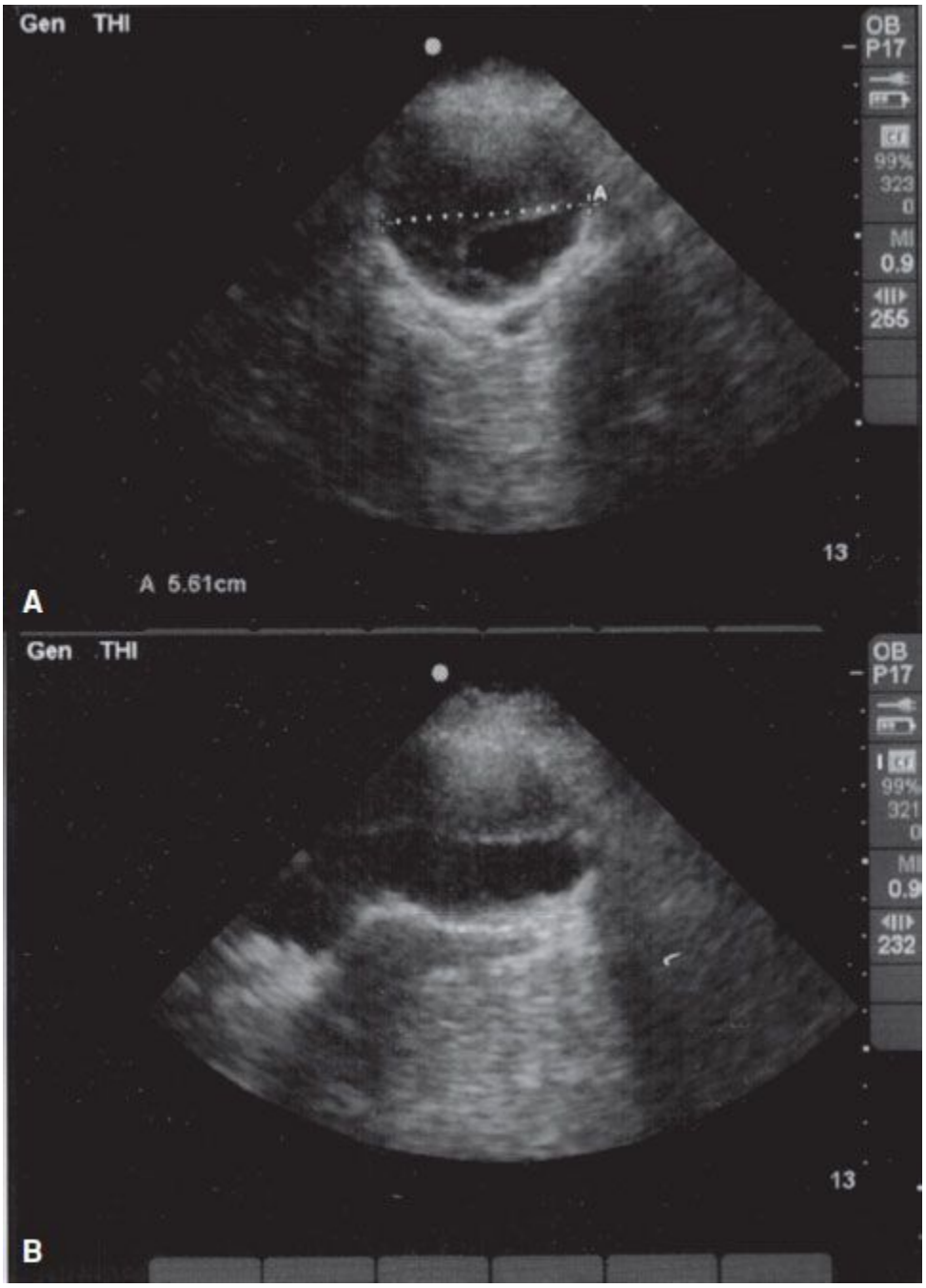

FIGURE 93.1 **A:** Cross-sectional view of large (5.6 cm) AAA with extensive intraluminal clot visualized by ED ultrasound. **B:** The same aneurysm seen in sagittal section. This was an incidental finding in the examination of an elderly patient with an unrelated complaint. *(Courtesy of Dr. Matthew R. Lewin, San Francisco, California)*

CT provides greater detail and more accurate measurements than does ultrasound. It is particularly useful in identifying leakage or rupture, assessing the thickness of mural thrombus, and visualizing blood within the thrombus. This “crescent sign” is thought by some to be a harbinger of imminent rupture (12). In fact, multislice CT has become an integral part of evaluation of AAA due to its ability to assess impending rupture, contained rupture, aortocaval fistula, aorto-left renal vein fistula, aortoenteric fistula, and infection (25). Because CT takes more time, involves intravenous contrast, and requires removal of the patient from the ED, it should be limited to stable patients in whom precise information is necessary, but the speed of CT has increased rapidly and is becoming more routine even in emergency situations. Many hospitals have a CT scanner in or near the ED, making this modality increasingly useful. CT can reliably detect aortic rupture with or without contrast enhancement. The main advantage of contrast is identifying entry and exit points of rupture with greater definition, including information about renal or iliofemoral involvement, mesenteric artery stenosis, or suspected visceral lesions (e.g., horseshoe kidney). Magnetic resonance imaging (MRI) also provides detailed images but is expensive, time consuming, and not universally available. MRI is also contraindicated in patients with pacemakers or ferromagnetic implants or clips, and thus it currently offers no substantive advantage over CT (18). Aortography is useful in selected cases in planning the operative repair of AAAs, but should not be used for the initial diagnosis. CT angiography is highly accurate in the diagnosis and characterization of suspected ruptured AAA (26).

High-speed MRI, 3D reconstruction vascular CTs, and sensitive and specific biochemical markers of aneurysm and dissection are exciting and promising areas of vascular research. Soon, rapid visualization techniques and proteomic approaches may be able to diagnose and track the progression of aneurysms and dissection, even in the ED setting.

KEY TESTING

- Bedside ultrasonography is useful in quickly identifying AAA.
- CT scan accurately defines size and whether rupture has occurred.
- CBC, chemistries, and blood typing and crossmatching should be sent if there is a reasonable suspicion of symptomatic AAA.

ED MANAGEMENT

The ED management of a patient with a suspected AAA must be tailored to the patient's presentation which ranges from asymptomatic to frank shock. The use of fluid resuscitation and appropriate blood pressure maintenance is controversial (27,28). Large volumes of blood or crystalloid may dislodge a metastable clot or result in dilutional coagulopathy. Conversely, older patients (the demographic most commonly presenting with symptomatic AAA) do not tolerate hypotension and its sequelae well, especially in the setting of comorbidities. All patients with suspected ruptured or symptomatic AAA should be placed on cardiac monitoring and receive supplemental oxygen, have at least two large-bore intravenous catheters securely in place, and have packed red blood cells, fresh frozen plasma, and platelets available for emergency transfusion. However, studies have suggested that early transfusion of platelets or fresh frozen plasma is unlikely to improve clinical outcome, and aggressive volume resuscitation should be delayed until proximal aortic control of bleeding is achieved (29–31). The use of medical antishock trousers and aortic cross-clamping has been reported in the setting of profound hypotension. The goals of resuscitation should be established as early as possible in the patient's course and discussed with the surgical and interventional radiology consultants when indicated. There are gender differences in presentation, and women experience more perioperative complications (32). Some patients may wish to decline intervention. A notable example was Albert Einstein, whose original diagnosis was "cholecystitis" and who refused a second surgery after becoming symptomatic after the first repair.

Asymptomatic Aneurysm

If the AAA is clearly unrelated to the patient's presenting complaint, the patient should be referred promptly to a vascular surgeon for further evaluation. An abdominal ultrasound may be useful in establishing the presence or absence of AAA, but it *cannot* rule out aneurysm rupture, leak, or expansion. Again, family history should be obtained for clues to possible syndromic and nonsyndromic causes of AAA.

Symptomatic Aneurysm

An aneurysm producing symptoms should be assumed to be ruptured, rapidly expanding, or otherwise complicated (infected, dissecting). Even when the patient is hemodynamically stable, prompt surgical consultation should be obtained, and preparations for fluid resuscitation and operative repair should be made. Elevated blood pressure should be controlled early, and fluid resuscitation confined to the volume needed to maintain patient's consciousness and systolic blood pressure of 50 to 100 mm of Hg (permissive hypotension) (33). Patients presenting with an acute abdomen or with known AAA accompanied by acute back pain or hypotension require immediate surgery. Operative repair should proceed without the usual preoperative evaluation and preparation, as rupture is either imminent or has already occurred and is temporarily confined to the retroperitoneum (18). In less acute presentations, radiologic imaging may be helpful but should be ordered with caution.

Patients with a history of previous AAA repair, whether open or endovascular, are still at risk for rupture, infection, occlusion, and other vascular catastrophes such as aortoenteric fistula. Graft clots may require thrombolysis, thrombectomy, or emergent surgical revision. As such, an emergency physician should have a low threshold for vascular surgery consultation, even long after AAA repair.

Ruptured Aneurysm

Patients in shock from a ruptured AAA need rapid resuscitation and emergent surgical intervention. Except in unusual circumstances, these patients should be transported to the operating room as quickly as possible without waiting for diagnostic testing or stabilization. A policy of immediate operation in such circumstances maximizes the patient's chances of survival. Even if it is discovered that a ruptured AAA is not present, many of these patients will have another surgical condition requiring operation, so the risk of unnecessary laparotomy is not great.

CRITICAL INTERVENTIONS

- Rapid diagnosis of a patient with a symptomatic or ruptured AAA, with emergent surgical consultation for operative repair.
- Resuscitation of shock with fluids and blood products as necessary. Permissive hypotension should be considered as a strategy to buy time and aid in stabilization.

DISPOSITION

Asymptomatic patients with an aortic diameter of 3 cm or more should be referred to a vascular surgeon for evaluation for elective repair. Recent reports suggest elective repair as first-line treatment even in patients >85 years of age (34). Patients with a symptomatic AAA, regardless of size, should be admitted for surgical evaluation and close observation. These patients will require prompt surgery if it becomes clear that the aneurysm is the source of their symptoms.

Patients who present with rupture of their AAA require emergent surgical consultation and should proceed to the operating room as quickly as possible. If the initial hospital does not have sufficient surgical and critical care resources to treat an AAA, transfer to a more appropriate institution is indicated. The local capabilities, anticipated transport time, likelihood of survival, and patient and family wishes must all be taken into consideration.

Common Pitfalls

- Falsely attributing the referred back pain of an AAA to musculoskeletal causes or another diagnosis. The combination of flank pain and hematuria may be mistaken for renal colic, while left lower quadrant pain and guaiac-positive stool may be mistaken for diverticulitis. Acute low back pain may be mistaken for vertebral or disk disease.
- Failing to diagnose AAA in an obese patient in whom physical examination may be more difficult.
- Assuming that an aneurysm discovered on physical examination is incidental and not the source of the patient's symptoms. Back or abdominal pain in the presence of a pulsatile abdominal mass must be considered a symptomatic AAA until proven otherwise.

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CHAPTER 94

Mesenteric Ischemia

Stephanie A. Taft

Mesenteric ischemia occurs when the blood supply to the small and large intestine is compromised, resulting in insufficient oxygen delivery. While there are different mechanisms for the interruption of normal blood flow, the end result is inadequate perfusion and subsequent cell damage and death. In acute mesenteric ischemia (AMI), delay to diagnosis is the rule rather than the exception (1), resulting in persistently high mortality rates of 40% to 70% despite advances in diagnosis and treatment (2). Other factors affecting mortality are old age, signs of peritonitis, and delays in surgical intervention (3). The clinical presentation is highly variable due to the different vessels involved, the location of the affected bowel, and the different levels of illness severity (4). The most common form of bowel ischemia is ischemic colitis (4), which is a distinct entity described below. Mesenteric ischemia can be acute or chronic and can be further categorized as arterial occlusion, venous occlusion, and arterial nonocclusive disease.

ACUTE MESENTERIC ISCHEMIA

Around 40% to 50% cases of AMI are caused by arterial occlusion due to embolism from the heart or a proximal arterial source (3,5). Thrombosis of atherosclerotic arteries accounts for about 25% of cases (3). Mesenteric venous thrombosis (MVT) is less common, accounting for only 10% to 15% of cases (3) while nonocclusive mesenteric ischemia (NOMI) comprises the remaining 20% to 30% of cases (3,4).

CHRONIC MESENTERIC ISCHEMIA

Chronic mesenteric ischemia (CMI) is commonly caused by the progressive stenosis of multiple atherosclerotic mesenteric blood vessels (5).

CLINICAL PRESENTATION

Acute Mesenteric Ischemia

Patients with AMI secondary to arterial embolism often present with *severe abdominal pain with minimal physical signs* and usually have a history of cardiovascular disease (5). Nausea, vomiting, and diarrhea are common complaints (1), and stools may be bloody (6). Unfortunately, key findings in AMI are inconsistently present (1), and the nature, location, and duration of the abdominal pain are variable (5), contributing to the delay in diagnosis. As ischemia progresses, peritoneal irritation gives rise to abdominal tenderness (5). Distension, rigidity, and systemic symptoms may take days to develop and correlate with intestinal perforation (5). Later signs also include confusion, tachycardia, tachypnea, and ultimately circulatory collapse due to dehydration and fluid third-spacing (6). Approximately two-thirds of patients with AMI are women, with a median age of 70 (5).

The clinical presentation of patients with AMI secondary to acute thrombosis is similar to that of arterial embolism. However, patients frequently report preceding symptoms of chronic insufficiency such as postprandial abdominal pain, nausea, and weight loss (6). Arterial thrombosis is almost always seen in the setting of severe atherosclerotic mesenteric arterial disease, most commonly near the origin of the superior mesenteric artery (SMA) (5,6). Gradual development of atherosclerotic disease allows development of collaterals, so significant arterial obstruction is often well-tolerated (6). Acute symptoms occur after rupture of a plaque and subsequent occlusion of a normally patent artery or occlusion of an important collateral (6). Ischemia due to acute thrombosis tends to involve larger portions of both small and large intestines, so the extent of bowel ischemia or infarction is greater than that with embolism (6).

Ischemia due to acute thrombosis also has higher perioperative mortality due to delays in diagnosis, a greater amount of bowel involved, and the need for more complex revascularization (6).

Patients with acute mesenteric venous thrombosis present with acute, severe midabdominal pain that is out of proportion to physical examination (7). Those with subacute or chronic MVT often present with complications of portal hypertension such as variceal bleeding, and the symptoms may evolve over days to weeks (7). Other symptoms such as nausea, vomiting, and constipation or diarrhea may also occur (7). Ascites in a patient with abdominal pain should heighten suspicion for MVT (7). Causes of MVT include any condition that leads to thrombosis. Examples include inherited or acquired hypercoagulable states (such as Factor V Leiden deficiency, polycythemia vera, malignancy, or oral contraceptive use), or local blood vessel injury (from inflammatory conditions such as pancreatitis or surgery), or from stasis due to conditions such as cirrhosis (7).

NOMI should be suspected in patients who develop abdominal pain or distension in the context of low-flow states or shock, particularly cardiogenic shock, or in patients receiving vasopressors or other vasoconstricting substances, such as cocaine or ergotamine (5). Ischemia occurs without identifiable blood vessel occlusion (3), usually as a result of low-flow states and subsequent severe prolonged vasospasm (5). NOMI is seen most commonly in elderly, critically ill patients. These patients are often intubated and sedated, so the only clue is deterioration of clinical status (6).

Chronic Mesenteric Ischemia

CMI is characterized by postprandial abdominal pain and weight loss which occurs over months to years (5). Patients with CMI often have a history of cardiovascular disease or vascular surgery (5). Because many people who have atherosclerosis of the mesenteric vessels are actually asymptomatic due to collateral circulation (5,9), CMI is diagnosed by demonstration of arterial lesions in the context of abdominal pain, weight loss, history of cardiovascular disease,

and no other obvious cause of symptoms (5). Other GI symptoms such as vomiting and diarrhea are uncommon (5). Rare causes include Buerger's disease, fibromuscular dysplasia, or dissection (5). Some cases progress to AMI while the remainder have progressive weight loss and ultimately die (5).

Ischemic Colitis

Ischemic colitis (IC) is actually the most common form of mesenteric ischemia (4). It is characterized by a sudden onset of mild left lower quadrant abdominal pain followed by mild hematochezia (4). It is most often due to an acute, self-limited compromise of blood flow which is inadequate to meet the metabolic demands of part of the colon. It can be seen in conditions such as congestive heart failure, hypotension, hypovolemia, sepsis, vascular occlusion, vasculitis, or drug use (4,17). The most susceptible areas are the splenic flexure, descending and sigmoid colon, but right-sided (ascending colon) IC is usually associated with more severe colitis and worse outcome (4,18).

DIFFERENTIAL DIAGNOSIS

Mesenteric ischemia is a diagnostic challenge, partly because the differential is extensive and includes nearly any disorder that causes abdominal pain (see Chapter 10), and the physical signs may be nonspecific. While many other conditions are more common than acute ischemia, the incidence of mesenteric ischemia increases with advancing age (10).

ED EVALUATION

Laboratory Testing

There is no sufficiently sensitive or specific serum marker that can identify AMI early (11). The classic findings of elevated lactate, leukocytosis, and acidosis are all insensitive and nonspecific (12). There are also no diagnostic laboratory tests for CMI (5).

Imaging

Contrast-Enhanced Multidetector Computed Tomography

Computed tomography (CT) is the imaging modality of choice in both AMI and CMI (9). CT is able to evaluate the vascular system and the bowel wall and may also identify an alternative etiology (13). In AMI, CT demonstrates a progression of findings, starting with mildly dilated loops of bowel, and a normal or slightly thinned bowel wall (8,13). This is followed by further bowel dilation and progressive thinning of the bowel wall with poor contrast enhancement (13). If reperfusion occurs, the bowel wall thickens due to edema and hemorrhage; however, the bowel wall can still perforate (13). Pneumatosis intestinalis with portomesenteric venous gas often indicates transmural infarction but can also be seen in other conditions, such as inflammatory bowel disease or connective tissue disorders (13). These findings must be interpreted in the correct clinical context and in association with the previously mentioned CT findings suggesting mesenteric ischemia (13). In the absence of other findings of AMI, isolated pneumatosis intestinalis does not necessarily indicate acute ischemia (13). While intravenous (IV) contrast is necessary for CT, oral contrast is neither necessary nor often feasible (13).

In the case of acute MVT, bowel wall thickening is the most common finding, and mesenteric haziness and ascites are also present in most patients (13). In the case of NOMI, CT findings are similar to that of acute arterial occlusive disease but no focal occlusion can be found (13).

Plain Abdominal X-Rays

Plain films are usually nonspecific and do not contribute to diagnosis (5).

Duplex Ultrasound

Ultrasound may be useful in supporting the diagnosis of CMI but has no role in AMI (5). It may be able to identify proximal occlusive lesions but cannot directly diagnose mesenteric ischemia. It also

requires ideal exam conditions which include fasting prior to the exam and absence of significant abdominal distension (5,14).

Magnetic Resonance Angiography with Gadolinium

Magnetic resonance angiography is sensitive and specific but generally not readily available and takes too long to perform in a critically ill patient (4,9). It is more useful in diagnosing CMI (5,9,14).

Angiography

Traditional angiography is often diagnostic and may be therapeutic if coupled with endovascular therapy (see below), but it is resource-intensive and not always readily available. Angiography is no longer the gold standard (15).

For patients with ischemic colitis, CT is usually nonspecific but suggestive (4,17). Colonoscopy is the test of choice (17) but is not performed on an emergent basis. Angiography is not indicated (4).

KEY TESTING

- Contrast-enhanced CT.
- Lactate and other basic studies often ordered in the evaluation of abdominal pain.

ED MANAGEMENT

Management in the ED is focused upon resuscitation and basic supportive care. The goal is to minimize the amount of bowel that progresses from ischemia to infarction (5). Appropriate care may include some or all of the following measures depending upon the degree of shock.

Intubation may be necessary for airway protection, oxygenation, or ventilation. Fluid resuscitation should be aggressive, beginning with a bolus of crystalloid. Bedside ultrasound may be useful early on to exclude other pathology such as abdominal aortic aneurysm and to help evaluate the hydration status of the patient. Broad-spectrum IV antibiotics should be administered early, due to the high risk of bacterial translocation across bowel wall (14). If

vasopressors are required, pure alpha-adrenergic agents such as phenylephrine should be avoided because they may produce mesenteric vasoconstriction and worsening ischemia (3). Treatment of the underlying shock state is the most important treatment principle in cases of NOMI (5). CT scanning should be accomplished as soon as reasonably possible, given the patient's condition. Emergent surgical consultation should be obtained, even prior to a definitive diagnosis if the index of suspicion is high or if there are peritoneal findings (3). Anticoagulation should be initiated if there are no contraindications, but this should be done in consultation with the surgeon. In the case of MVT, hematology consultation may be useful to initiate appropriate thrombophilia screening prior to starting anticoagulation (7).

Most patients with ischemic colitis respond within 1 to 2 days to basic supportive care (i.e., bowel rest, IV fluids, empiric antibiotics) (17). In 20% of cases, surgery is required because of deterioration or peritonitis (17).

For patients with *chronic ischemia,* timely treatment is key for the prevention of acute ischemia (10). Percutaneous endovascular treatment or surgery may be appropriate, depending on the clinical presentation. Recurrence is more common after angioplasty than surgery, but these recurrences can also be treated percutaneously (5). Surgical treatment or revascularization may be accomplished by endarterectomy or bypass grafting (5). Surgery has a good success rate with lower recurrence than percutaneous intervention but has its own associated morbidity and mortality (5).

Beyond the diagnostic and resuscitation issues in the ED, there are several important options and considerations for more definitive care in patients with mesenteric ischemia.

Percutaneous Endovascular Treatment (Angiography)

Angiography may be used for directed lytic therapy, vasodilator (papaverine) therapy, angioplasty, and/or stenting. This modality is evolving into first-line treatment in select patients (1). It is noteworthy that angiography carries a higher risk of reperfusion

syndrome than with surgery. Reperfusion syndrome occurs due to the sudden release of endotoxins, resulting in disseminated intravascular coagulation, adult respiratory distress syndrome, and cardiovascular collapse (5).

Surgical Treatment

Laparotomy allows direct visualization and assessment of bowel viability, revascularization (balloon catheter thromboembolectomy or bypass grafting), and resection of infarcted bowel (10). A second operation is often scheduled to re-assess the viability of bowel, avoiding resection of potentially viable bowel during the first operation while allowing further resection of nonviable bowel (5).

CRITICAL INTERVENTIONS

- Fluid resuscitation, may need up to 100 mL/kg (16).
- Broad spectrum IV antibiotics.
- Anticoagulation (in selected cases).
- Surgical consultation.

DISPOSITION

Patients with AMI should be admitted to the hospital and may require surgery. Because the diagnosis is often delayed, these patients are often very sick and require intensive care.

Common Pitfalls

- Allowing a benign abdominal examination to direct the management of a patient with risk factors for AMI. Intervention is most effective when there are few findings on examination.
- Failing to recognize that acute abdominal pain in a patient with a previous diagnosis of CMI is AMI until proven otherwise.
- Relying on a blood gas or serum lactate to rule out mesenteric ischemia. Both are insensitive and become abnormal late in the disease (1).
- Allowing elevation of serum biomarkers to lead to misdiagnosis: elevation of troponin, amylase, lipase, and liver transaminases

have all been seen relatively commonly in AMI (1).

- Failing to interpret CT results correctly in the context of a clinical presentation suggestive of AMI. Early mesenteric ischemia can look similar to adynamic ileus on CT (13).

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CHAPTER 95

Peripheral Arterial Disease

Dusadee Sarangarm and Darren Braude

Peripheral arterial disease (PAD) is usually secondary to atherosclerosis and occurs most frequently in the lower extremities. PAD is analogous in many ways to coronary artery disease (CAD). Like CAD, PAD is often asymptomatic in patients with known cardiovascular disease or risk factors. Stable angina corresponds to noncritical ischemia and presents as predictable claudication. Unstable angina corresponds to the progression of chronic PAD to critical limb ischemia and presents as rest pain, ulceration, or gangrene. Myocardial infarction corresponds to acute, critical limb ischemia caused by thrombus or embolism. Irreversible damage to nerves and muscle may develop within 6 hours and up to 20% of patients may die (1).

CLINICAL PRESENTATION

PAD may be categorized as acute or chronic, critical or noncritical, and limb-threatening or not. Acute ischemia most often occurs secondary to in situ expansion of an atherosclerotic thrombus or less commonly due to an embolus from a more proximal source. Chronic, *noncritical* ischemia can present as intermittent claudication (IC) and asymptomatic arterial insufficiency. Chronic, *critical* ischemia can present as rest pain and/or skin ulcerations, infections, or necrosis. Limb-threatening ischemia can be caused by

both acute ischemia of an extremity and chronic, critical ischemia (Table 95.1).

TABLE 95.1
Classification of Peripheral Arterial Disease

Limb-Threatening Ischemia
Acute ischemia: thrombus, embolism
Chronic critical ischemia: thrombus, rest pain
Ischemic skin changes: ulcers, gangrene
Non-Limb-Threatening Ischemia
Chronic noncritical ischemia: intermittent claudication

Because most PAD in developed countries is related to underlying atherosclerosis, the typical patient has known atherosclerotic disease or risk factors including diabetes, obesity, smoking history, hypertension, hyperlipidemia, renal insufficiency, and hyperhomocysteinemia; other risk factors include advanced age, male sex, and non-White ethnicity (1,2,3).

Acute Ischemia

Patients with acute ischemia usually present to the ED because of severe pain in a lower extremity. Pain is usually not well defined and in most cases extends above the ankle, depending on the location of the obstruction and degree of collateral flow. Patients with coexisting diabetic neuropathy, however, may not have typical pain. Patients may also complain of paresthesias, weakness, numbness, and/or a cold, white, or discolored extremity.

Acute ischemia is usually caused by an arterial embolism or thrombus of a native artery or bypass graft. Thrombosis is much more common than embolism. Patients with an arterial thrombosis become symptomatic from thrombus extension and subsequent arterial occlusion. Most patients will have prior chronic arterial insufficiency with claudication, rest pain, typical trophic skin changes, and/or prior bypass grafting. Because long-standing disease has led to the development of collateral circulation, symptoms and

physical findings in thrombosis are typically not as dramatic as with embolism.

Arterial embolism arises from the heart in most cases, often from ventricular thrombus such as in postmyocardial infarction ventricular aneurysm or from atrial thrombus in the setting of mitral valve disease or atrial fibrillation. Unless the patient has significant coexisting lower extremity atherosclerosis, there typically is no established collateral circulation to deliver blood distally. Thus, arterial embolism usually presents in a more dramatic fashion than thrombosis. The hallmarks of acute ischemia are sudden onset of symptoms without preceding symptoms of chronic PAD, an identifiable embolic source, and a normal circulatory examination of the unaffected leg.

Chronic Critical Ischemia

Patients with chronic, critical ischemia usually present to the ED due to new or worsening rest pain or skin changes. As circulation is affected by gravity, rest pain typically occurs as the patient is sleeping or when the patient is supine. Pain occurs distally in the forefoot or toes but not usually in the calves. Because the pain is exacerbated by leg elevation and improved with dependency, many patients will sleep in a chair or prefer to hang the affected leg over the side of the bed. Symptoms worsen in the cold and the pain is often severe. Associated ischemic peripheral neuropathy may cause sharp shooting pains and sensations of heat and cold.

Chronic Noncritical Ischemia

Patients with chronic, noncritical ischemia usually present to the ED because of new or worsening claudication, which is essentially angina of the lower extremities. Patients classically report calf cramping or aching after a predictable amount of activity. This prompts the patient to stop activity, thereby relieving the pain. Depending on the site of the occlusion, claudication may occur in the calf, hip, buttock, or thigh. In general, foot claudication is rare with atherosclerosis.

DIFFERENTIAL DIAGNOSIS

Acute Thrombus or Embolus

If there is involvement of both legs, the clinician should consider a low cardiac output state or an aortic dissection tracking into the bilateral iliac arteries. If only one lower extremity is involved, the differential diagnosis includes conditions that mimic ischemia, such as phlegmasia cerulea dolens and acute compressive neuropathy, as well as nonatherosclerotic causes of true ischemia, such as phlegmasia alba dolens, arterial trauma, aortic dissection, arteritis, hypercoagulable states, and vasospasm.

Intermittent Claudication

Calf claudication in patients with atherosclerotic risk factors may be confused with venous claudication, compressive neuropathy, calf spasms, or symptomatic Baker's cyst. Venous claudication follows treatment for deep venous thrombosis, resolves slowly when exercise stops, improves with limb elevation, and is usually associated with edema. Compressive spinal neuropathy usually produces distinctly dermatomal sharp pain, is associated with back pain, and does not resolve immediately when activity stops. The discomfort from a Baker's cyst persists at rest.

Hip, thigh, or buttock claudication may be confused with arthritis of the hip and spinal stenosis. Pain from arthritis is not consistently reproduced with activity, often present at rest, and not relieved quickly with rest. Spinal stenosis symptoms are dermatomal, usually associated with back pain, and more typically relieved by bending forward than by stopping activity.

Rest Pain

Any distal sensory neuropathy may present with pain primarily at night. This pain tends to be symmetric, foot-based, shooting pains that are neither exacerbated by elevation nor relieved with dependency; an exception is in the case of ischemic neuropathy associated with chronic arterial ischemia. Other important causes of neuropathy include diabetes, vitamin deficiency, and alcohol abuse. Additionally, gout may cause extremity pain at rest, although this

pain persists despite dependency, is localized to a joint, and is almost always associated with visible findings. Disc herniation of the lumbosacral nerve roots may also produce extremity pain at rest. This pain usually persists with dependency, follows a dermatomal pattern, is associated with back complaints, and presents with a normal vascular examination. Some confusion may arise with the straight-leg raise examination maneuver as it can cause pain in patients with rest pain, as well as in nerve root compression. Reflex sympathetic dystrophy can present with burning pain and skin changes though the pain is not exacerbated by elevation and pulses should be normal. Finally, simple night cramps cause calf rather than foot pain that is relieved with massage, not exacerbated by elevation, and is not associated with pulse deficits.

Ulcers and Gangrene

Ulcers secondary to arterial ischemia must be differentiated from ulcers secondary to other causes, such as venous stasis and diabetes. Ulcers related to venous insufficiency are the most common, tend to occur more proximally, produce less pain, are relieved with elevation, coexist with edema and stasis dermatitis, and have a wet base with copious granulation tissue. The ulcers of diabetes may occur in the same distal pressure point locations as PAD-associated ulcers but tend to be painless, deep, and surrounded by significant callus and/or inflammation. The primary differential of dry gangrene is frostbite. Wet gangrene may originate in other skin ulcers or wounds.

ED EVALUATION

Acute, critical PAD is primarily a clinical diagnosis based upon history and physical examination, including the ankle-brachial pressure index (ABI). The 2011 American College of Cardiology Foundation and American Heart Association guideline update defines patients with suspected lower extremity PAD as individuals with one or more of the following signs or symptoms: exertional leg symptoms, nonhealing wounds, age 70 and older, or 50 years and

older with a history of smoking or diabetes (10). In patients with clinical evidence of acute ischemia, vascular surgery consultation should precede diagnostic studies and may require immediate transfer in some settings. In cases of diagnostic uncertainty, or when an alternative emergent diagnosis such as aortic dissection is highly likely, the ED physician may order imaging studies prior to consultation in the patient with previously undiagnosed PAD and no evidence of critical ischemia. However, diagnostic tests should not delay consultation or transfer if acute, critical PAD is suspected. Definitive diagnostic testing should ideally be at the discretion of the vascular surgery consultant given individual practitioner preference, institutional resources, associated delays, and potential adverse effects.

Examination of the lower extremities should include bilateral inspection for sores, edema, dermatitis, gangrene, and signs of infection; palpation of skin temperature; assessment of capillary refill time; palpation of the femoral, popliteal, dorsalis pedis, and posterior tibial pulses; auscultation of the femoral artery; and motor and sensory examinations. The abdomen should be examined for masses or bruits suggestive of abdominal aortic aneurysm. Capillary refill has not been found to be useful in assessing chronic peripheral vascular disease while the most useful findings to confirm PAD are pulse deficit, bruit, and cool skin (4,5).

The signs and symptoms in acute arterial occlusion resulting from an embolus can be dramatic and reflect the “six Ps” of ischemia: pain, pallor, pulselessness, poikilothermia, paralysis, and paresthesia.

If acute ischemia is embolic in nature, without pre-existing PAD, the unaffected extremity tends to be normal on examination. The affected extremity is white or cyanotic, cool to the touch, and pulseless without appreciable new swelling. There will usually be some component of neuropathy with weakness and sensory deficits. Sensory deficits begin with diminished light touch, two-point discrimination, and proprioception. Loss of deep-pain, pressure sensation, and motor deficits reflect advanced ischemia and possibly irreversible ischemia. The intrinsic muscles of the feet are the most

sensitive to ischemia and are tested by having the patient spread their toes.

In arterial thrombosis, findings are usually more subtle than with embolus owing to collateral blood flow and/or slower onset, although the major pulses distal to the obstruction will typically be absent. Unfortunately, there is variability in the presence of peripheral pulses and their detection. Comparison with the unaffected extremity and use of a Doppler are very helpful. The presence of pulses detected on Doppler indicates blood flow but does not necessarily exclude ischemia. Both the affected and the unaffected extremity should show findings of chronic PAD including atrophy of calf muscles, loss of hair over the dorsum of the foot, thickened toenails, shiny skin, diminished pulses, and possibly skin ulcers. Edema may be present as patients prefer to keep their extremities dependent.

Patients with IC will usually have a normal examination at rest, although they may have some subtle findings of chronic ischemia. Further in the disease process, patients with rest pain will show many of the changes noted previously for chronic PAD. These patients do not have complete occlusion; so capillary refill should be present, although delayed, and pulses will be present, at least by Doppler. Another clinical finding of severe ischemia frequently cited is Buerger's sign. A positive test is the observation of pallor with foot elevation and exaggerated delayed erythema with subsequent dependency (5). This sign is not well validated (4).

Skin ulcerations from arterial insufficiency tend to occur distally at pressure points, such as at the tips of the toes, between the toes, or on the heel. These ulcers often have an irregular border with a pale base and may show signs of infection. Plain radiography is appropriate to screen for underlying osteomyelitis when the ulcer appears sufficiently deep or infected. Gangrene is rarely missed when the distal extremities are examined. Uninfected gangrene is dry while discharge, weeping, crepitance, lymphangitis, and cellulitis suggest infection.

Ankle-Brachial Pressure Index

The ABI is a rapid, objective screening measurement of arterial insufficiency and should be assessed in any patient in whom arterial insufficiency is suspected. If the ABI can be measured, the limb is not immediately threatened, but may still be ischemic. If arterial signals are absent, limb loss is probable without emergent revascularization. Absent venous pulsations indicate severe ischemia. It is helpful to check the ABI in the unaffected leg to ascertain whether the patient has underlying arterial disease or noncompressible vessels. The technique and interpretation of ABI measurement are summarized in **Tables 95.2** and **95.3** (6,7). While the typically used ABI cut-off of 0.9 maximizes sensitivity and specificity, any value <1.0 in a symptomatic patient should be considered sufficient evidence of arterial insufficiency (6,7).

TABLE 95.2
Technique for the Measurement of Ankle-Brachial Pressure Index

Place patient supine
Measure systolic blood pressure at brachial artery of both arms by using Doppler
Select higher value of the two pressures
Measure systolic blood pressure at the posterior tibial and dorsalis pedis arteries of affected leg by using Doppler
If neither is obtainable, limb is immediately threatened, otherwise select higher value of the two pressures
Divide higher ankle pressure by higher brachial pressure

TABLE 95.3
Interpretation of Ankle-Brachial Pressure Index Results

ABI	Interpretation
≥1.4	Abnormal (increased risk for PAD, noncompressible vessels)
1.0–1.39	Normal
0.91–0.99	Borderline
≤0.9	Abnormal (increased risk for PAD)
0.41–0.89	Mild to moderate disease
≤0.4	Severe disease

Imaging Studies

While catheter angiogram remains the gold standard, noninvasive studies are being increasingly used. According to the American College of Radiology 2012 guideline, lower extremity magnetic resonance angiography (MRA) and computed tomography angiography (CTA) have a higher level appropriateness rating than catheter arteriography as the initial radiologic examination for patients with suspected PAD (9). The increased availability of CTA has likely contributed to its increasing use, while MRA has been shown to be more cost-effective and safer than the gold standard of angiography. In addition, these noninvasive diagnostic modalities have been shown to have high sensitivity and specificity (90% to 100%) for the detection of stenosis >50% diameter when compared to catheter angiogram (9). Ultrasound is preferred in patients with moderate to severe renal insufficiency, as both CT contrast and gadolinium are associated with complications in these patients (8).

KEY TESTING

- Determination of ABI
- Doppler of extremity pulses
- Angiography, MRA, or CTA in consultation with a vascular surgeon

ED MANAGEMENT

Supportive care for patients with PAD includes keeping the affected limb dependent and warm, providing analgesia as needed, and maximizing cardiac output. Aspirin or clopidogrel is indicated in all

patients with symptomatic PAD to reduce risk of further vascular injury such as MI and ischemic CVA although the role of these drugs in the acute setting has not been adequately investigated (1,7,10,11).

Acute Ischemia

In the absence of contraindications, patients with acute critical ischemia should receive anticoagulation with unfractionated heparin despite little objective evidence (1,7,11). Supplemental oxygen may be helpful and should be provided when acute ischemia is considered. Options for definitive therapy include surgical or interventional procedures at the discretion of the vascular surgeon. Considerations include degree and duration of ischemia, contraindications, local resources, and results of imaging studies. In patients with severe ischemia, angiography may be performed intraoperatively to minimize delay in care. Surgical options include direct removal of the occlusion (most common with established thrombus), bypass grafting, primary amputation, and Fogarty catheter embolectomy (most common with embolus or suspected new thrombus). Interventional options include direct intra-arterial administration of thrombolytics, mechanical thrombectomy, thromboaspiration, and angioplasty. There is currently no accepted role for intravenous thrombolytics, although this treatment merits discussion with a vascular surgeon if definitive care is expected to be significantly delayed (7,10).

Chronic Critical Ischemia and Rest Pain

Patients with rest pain in the dependent position should be treated as for acute ischemia. Patients experiencing rest pain only when the foot is elevated represent an intermediate group and definitive therapy for this group may involve pharmacotherapy, endovascular procedures, or surgery though these measures may not need to be started emergently. At a minimum, telephone consultation with the patient's primary care physician and/or vascular surgeon is appropriate. After consultation, these patients may be discharged

home on aspirin 75 to 100 mg per day with an adequate follow-up plan and return precautions (11). Should the patient have an allergy to aspirin, clopidogrel 75 mg per day has been found to be a safe and effective alternative (11).

Chronic Ischemia with Ulcerations or Infection

Patients with uninfected ulcerations require wound debridement and dressing, close monitoring for the development of infection, analgesia, and at a minimum, telephone consultation with a vascular surgeon. Admission should be considered but is not mandatory when adequate follow-up is assured.

Patients with infected ulcerations need supportive care, aggressive wound management, systemic antibiotics, admission, and vascular surgery consultation for possible revascularization. Appropriate empiric antibiotic choices should take into account risk factors for gram-negative infections such as diabetes, recent hospitalization, local epidemiology, resistance patterns, and the rising incidence of methicillin-resistant *Staphylococcus aureus.* A reasonable choice for intravenous therapy is ampicillin- sulbactam (1.5 to 3 g q6 h) plus clindamycin (900 mg q8 h) plus ciprofloxacin (400 mg q12 h) (12). If there is a high suspicion for hospital-acquired methicillin-resistant *Staphylococcus aureus,* vancomycin (dosing dependent on renal function) may be substituted for clindamycin.

Patients with dry gangrene require supportive care and timely surgery consultation. Patients with evidence of necrotizing infections (gas gangrene, wet gangrene, or sepsis) require intensive care unit admission, immediate surgical consultation, and broad-spectrum antibiotics to cover gram-negative infection, *Staphylococcus aureus, Streptococcus* sp, and *Clostridium* sp.

Chronic Noncritical Ischemia and Intermittent Claudication

Although this is a nonemergent condition, these patients require close follow-up with their primary care physician and/or vascular surgeon. In the meantime, they should be reassured that walking,

despite causing pain, is not harmful. Pharmacotherapy may be deferred to follow-up, though it is reasonable to start patients without contraindications on 75 to 100 mg per day of aspirin (1,7,10).

CRITICAL INTERVENTIONS

- Aspirin and weight-based heparin (80 units/kg bolus followed by 18 units/kg/hr continuous infusion) for acute ischemia and rest pain that persists in the dependent position.
- Emergent vascular surgery consultation, including transfer as necessary, for limb-threatening ischemia or infection.
- Supportive care, keeping affected extremity warm and dependent, maximizing cardiac output, and providing supplemental oxygen.
- Early initiation of antibiotics for patients with signs of infection.

DISPOSITION

All patients with PAD require vascular surgery consultation. The emergency physician must decide according to the acuity of the situation whether that consultation must take place emergently in the ED or on an outpatient basis. In some situations, the patient may be admitted to their primary care provider or hospitalist with inpatient vascular surgery consultation.

Emergent vascular surgery consultation is appropriate for patients with acute ischemia or evidence of serious infection in an ischemic extremity. If vascular surgery consultation is not available, the patient should be transferred expeditiously. Patients with chronic critical ischemia require emergent vascular surgery consultation in most cases. Patients with rest pain that is well controlled with supportive measures, and patients with uninfected ulcers without gangrene, may be candidates for admission with urgent vascular surgery consultation as an inpatient.

Patients with noncritical ischemia may be discharged home with close outpatient follow-up. Consultation with a vascular surgeon before discharge is recommended when possible.

Common Pitfalls

- Delaying consultation or transfer for testing and definitive diagnosis.
- Failing to consider diabetic neuropathy masking the pain of an ischemic extremity.
- Failing to elicit a history of claudication because the patient's baseline activity is limited.
- Failing to recognize IC can occur in the hip, buttock, or thigh.

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CHAPTER 96

Deep Venous Thrombosis and Thrombophlebitis

Carolyn Chooljian

Deep venous thrombosis (DVT) of the lower extremity is a relatively common diagnosis made in the emergency department (ED), with an annual incidence of 67 per 100 000 in the United States. Two million patients are diagnosed with DVT and 600 000 have pulmonary embolism (PE) each year. Thromboembolic disease is responsible for an estimated 200 000 deaths annually and ranks third only to myocardial infarction and stroke as a life-threatening cardiovascular disease in the United States (1). Millions more experience sequelae such as stasis dermatitis and venous ulcers. The risk for development of DVT as described by Virchow is the triad of stasis, hypercoagulability, and endothelial injury. Additional conditions that either cross categories or separately place patients at risk are listed in Table 96.1. These risk factors are additive in nature and have been used to develop a prediction tool to establish likelihood of the disease in patients.

TABLE 96.1
Risk Factors for Deep Venous Thrombosis

Stasis	Coagulation disorders
Immobility	Protein S deficiency or resistance
Bed rest (≥3 d)	Protein C deficiency
Prolonged sitting owing to long rides (plane, car, or train)	Antithrombin III deficiency
Paralysis	Factor V Leiden
CNS injury	Increased estrogen
Cast	Pregnancy
Endothelial Injury	Postpartum <3 mo
Intravenous drug abuse	Oral contraceptives
Vascular trauma	Disorders of fibrinogen or plasminogen
Recent surgery	Antiphospholipid antibodies (lupus anticoagulant and anticardiolipin)
Central lines	**Multifactorial**
Hypercoagulability	Recent trauma
Malignancy	Recent surgery
Previous thromboembolic disease	Age >60 yr
Inflammatory conditions (e.g., SLE)	Cardiac disease (especially CHF)
Nephrotic syndrome (loss of antithrombin III)	Obesity
	Venous insufficiency
	Smoking

CNS, central nervous system; SLE, systemic lupus erythematosus; CHF, congestive heart failure.

The initiating stimulus for thrombus formation is often an intimal defect. The dynamic interplay of coagulation and fibrinolytic forces then results in clot propagation or dissolution. Conditions affecting the balance of these forces are what place patients at increased risk for symptomatic thrombus formation. If the process is of sufficient severity or duration, the associated vein can become inflamed; the condition is then referred to as thrombophlebitis.

It is useful to divide DVT of the lower extremities into two categories: distal and proximal. Distal DVT is confined to the calf veins and proximal DVT involves the popliteal, femoral, and/or iliac veins. Most DVTs start in the calf. Isolated calf DVT is usually silent and rarely causes clinically significant PE. About 25% of untreated symptomatic calf DVT progresses to the proximal veins within 1 week (2). Up to 40% of patients with DVT have clinically silent PE (3). PE occurs in 50% of proximal vein DVTs, which are the source of most fatal emboli, and over 90% of acute PE are from proximal

lower extremity DVT (4). Although isolated superficial thrombophlebitis generally does not pose a significant risk for embolization, 23% of patients with symptoms of superficial thrombophlebitis have been shown to have involvement of the deep system as well (5).

Superficial thrombophlebitis involving the proximal saphenous vein or saphenous–femoral junction has a much higher risk of progression to DVT (6). In addition, patients with a first episode of DVT complicated by superficial thrombophlebitis have a 2-fold increased risk of recurrent DVT compared to patients without superficial thrombophlebitis (7). Although embolization to the lung is the most serious complication of DVT, it can also result in other complicating conditions. Venous hypertension and persistent clot can destroy valves, thereby leading to a postthrombotic syndrome (chronic leg pain and venous stasis) that occurs in 28% of patients after symptomatic DVT. Other patients develop only recurrent edema. Occasionally, acute cases can develop a compartment syndrome of the thigh or lower leg.

CLINICAL PRESENTATION

Patients with DVT can present with a symptom complex that ranges from completely occult to obvious. Most commonly, they present with lower extremity pain and swelling that may worsen with standing or walking. Manifestations are almost always unilateral, except in the rare life-threatening case of inferior vena cava (IVC) involvement. Generally, DVT symptoms develop over a period of several days, whereas sudden severe pain is more likely related to an injury. Associated symptoms, such as chest pain or dyspnea, may also be present, particularly as they relate to the presence of PE. Risk factors can be identified in the majority of patients.

DIFFERENTIAL DIAGNOSIS

Several medical conditions can present with symptoms suggestive of DVT (Table 96.2).

TABLE 96.2
Differential Diagnosis of Deep Venous Thrombosis

Postthrombotic syndrome
Leg swelling in paralyzed limb
Cellulitis/abscess
Muscle injury/hematoma
Popliteal cyst (Baker cyst)
Superficial thrombophlebitis
Septic thrombophlebitis
Congestive heart failure
Lymphedema
Malignancy (obstructive)
Capillary leak syndrome
Fracture
Sciatica
Acute arthritis
Myositis
Pregnancy
Superior vena cava syndrome (upper extremity DVT)

DVT, deep venous thrombosis.

Many of these conditions generally cause bilateral leg swelling resulting from either increased production of edema fluid or an IVC obstructive process. However, if prior DVT has resulted in damage to the venous valves, these conditions can exacerbate asymmetric swelling. In addition, abdominal masses (e.g., a gravid uterus) can occasionally compress a single iliac vein, resulting in unilateral venous stasis. One of the most difficult conditions to distinguish from DVT is the postthrombotic syndrome. Recurrent DVT in the same leg predisposes to postthrombotic syndrome. Patients with prior DVT can develop recurrent unilateral pain and swelling that is clinically indistinguishable from acute DVT. Other conditions that are most often confused with DVT are cellulitis, *superficial thrombophlebitis,* and *septic thrombophlebitis.* There is much clinical overlap among these conditions, and a low threshold for objective diagnostic testing is required.

ED EVALUATION

The clinical evaluation of the patient with possible DVT focuses both on identifying findings consistent with DVT and on diagnosing alternative conditions that may explain the patient's presentation. It is important to question the patient about risk factors for DVT (Table 96.1) including a family history. As many as one-fourth of patients with acute DVT have a history of prior DVT. The physical examination can provide useful findings but must be interpreted with caution. Although patients with cellulitis and other infections usually have a fever, DVT can also result in an elevated temperature, although often only low grade. Unilateral warmth and erythema are common with both DVT and cellulitis. The presence of an abscess, enlarged lymph nodes, and ulcerations can be important clues for distinguishing an infectious etiology. A difference of 3 cm in the circumference of the calves, measured 10 cm below the tibial tuberosity, or 3 cm in the circumference of the thighs, measured equally from the patella, is clinically significant and one of the most specific findings for DVT. The presence of palpable "cords" in the thigh is considered fairly specific but quite insensitive for thrombosis. In the popliteal fossa, they can easily be confused with a Baker cyst. Homan sign was classically taught as being important in the evaluation of DVT, but it is now well known that its sensitivity and specificity are only about 50%.

The assessment for DVT begins with an estimation of the probability of disease based on the presence of patient-based clinical variables. This can be combined with the measurement of a derivative of cross-linked fibrin, the D-dimer. D-Dimer levels are nonspecific, being elevated in DVT as well as infection, cancer, trauma, and other inflammatory states. Different D-dimer assays exist and can be divided into high-sensitivity (ELISA, second-generation latex agglutination-immunoturbidometric) and moderate-sensitivity (non-ELISA) forms (8,9).

Wells et al. described a clinical predictive model with a relatively simple scoring system that accurately identified patients at low, intermediate, or high risk of DVT (10). This model was subsequently

combined with D-dimer testing to further stratify patients' risk of DVT (11,12). A simplification of the Wells model divided the probability estimate into two categories: DVT likely or DVT unlikely (see Table 96.3) (13). A meta-analysis showed that the combination of a low-probability clinical estimate and a negative high- or moderate-sensitivity D-dimer was sufficient to exclude DVT without further testing. In cases where the D-dimer assay used had high sensitivity, a negative result also reduced the probability of DVT to $\leq$1% in moderate-risk patients. No D-dimer assay was adequate to eliminate DVT in high-risk patients to this level of probability and therefore it is not recommended to use D-dimer alone in assessing these patients (10,14).

TABLE 96.3
Clinical Model for Predicting Pretest Probability of Deep Venous Thrombosis

Clinical Feature	Score
Active cancer (treatment within 6 mo)	1
Paralysis, paresis, or recent cast immobilization of lower extremity	1
Recent bedridden (>3 d) or major surgery within previous 12 wk requiring general or regional anesthesia	1
Localized tenderness along deep venous system	1
Entire leg swollen	1
Calf swelling >3 cm compared to unaffected extremity (measured 10 cm below tibial tuberosity)	1
Greater pitting edema in the affected leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented DVT	1
Alternative diagnosis as likely or more than that of DVT	–2
A score of ≥2 indicates that the probability of deep-vein thrombosis is likely	
A score of <2 indicates that the probability of deep vein thrombosis is unlikely	
In patients with symptoms in both legs, the more symptomatic leg is used	

Adapted from Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep vein thrombosis. *N Engl J Med*. 2003;349(13):1227–1235; Carpenter JP, Holland GA, Baum RA, et al. Magnetic resonance venography for the detection of deep venous thrombosis: Comparison with contrast venography and duplex Doppler ultrasonography. *J Vasc Surg*. 1993;18:734–741.

Diagnostic studies for DVT include ultrasonography, contrast venography, impedance plethysmography, magnetic resonance venography (MRV), and computerized tomography venography (CTV). The primary imaging study to identify patients with DVT is ultrasonography. Lack of vein compressibility is highly sensitive (>95%) and specific (>95%) for proximal DVT. Ultrasound does not detect isolated thrombi in the iliac or femoral veins in the adductor canal. Ultrasound can also occasionally identify other conditions such as tumors, cysts, or aneurysms. In addition, the test is less accurate in the second half of pregnancy and for pelvic vein thrombus, for which the Doppler mode of the duplex ultrasound scan can be helpful. In these situations, or in patients felt to be at very high risk for DVT, it is recommended to use additional tests such as venography or close outpatient follow-up with serial ultrasound examinations within 5 to 7 days (14).

Patients with high clinical probability for DVT who have been evaluated and found to have a negative D-dimer and negative duplex ultrasound have a <1% probability of DVT and do not require serial ultrasound studies (10,15). However, if the initial ultrasound study is negative in a high-probability patient and the D-dimer is elevated, a repeat ultrasound should be obtained on day 5 to 7. MRV has a sensitivity of 100% and specificity 98% to 99% for pelvic and proximal DVTs, as well as 68% for calf DVTs. Advantages of MRV include the ability to distinguish between acute and chronic DVT, evaluate the pelvis and is the test of choice in pregnancy (16,17). CTV evaluates pelvis, thighs, and calves and has similar sensitivity and specificity to US for proximal DVT. It can be done with CT angiography for PE. CTV can diagnose pelvic and calf DVTs. Disadvantages of CT include radiation exposure and cost (18). DVT can also develop in the upper extremities, usually in the subclavian or axillary veins (19). Ultrasound may not be as sensitive as in the lower extremity, but it is still recommended as the first-line diagnostic test. Inadequate or negative examinations in high-risk patients may be followed with contrast venography.

KEY TESTING

- D-dimer
- Ultrasonography

ED MANAGEMENT

Patients with isolated DVT rarely require immediate lifesaving interventions. Treatment is important to prevent clot extension, acute PE, thrombosis recurrence, postthrombotic syndrome and chronic thromboembolic pulmonary hypertension. Many of these patients have occult PEs and all are at risk for new emboli. When a PE is strongly suspected, starting heparin prior to imaging studies is appropriate. In addition, occasional patients can present with complete venous obstruction, a condition referred to as “phlegmasia dolens.” These patients should also undergo immediate heparinization and fluid resuscitation prior to imaging studies when

the diagnosis is suspected. They may also require thrombolytics and occasionally, urgent thrombectomy.

For most patients, the initial treatment for DVT is anticoagulation with a non-vitamin-K-dependent anticoagulant, usually a form of heparin for a short time, in addition to a vitamin K antagonist, for example, coumadin. Combination therapy was shown to be superior by a randomized controlled trial in which recurrent DVT had three times greater incidence if only a vitamin K antagonist was used (20). Heparin blocks extension of thrombus and reduces the risk of further emboli. It does not actively lyse clot but allows the body's own fibrinolytic mechanism to operate over a period of several days to weeks. Heparin can be given in the unfractionated form, which is usually delivered by intravenous infusion or subcutaneously with one of the low-molecular-weight forms. *Unfractionated heparin* (UFH) is best dosed on a weight-based regimen. One of the most commonly used regimens is an 80-U/kg bolus followed by an 18-U/kg per hour infusion (21). Complex nomograms are reliable at attaining therapeutic anticoagulation adjustment while monitoring the aPTT. The efficacy of heparin therapy depends on achieving a critical therapeutic level of 1.5 to 2.5 above the normal aPTT (22).

Low-molecular-weight heparins (LMWHs) are fractionated versions of standard heparin that have a more predictable effect and have fewer side effects or complications. Compared to controls treated with UFH in the inpatient setting, these outpatient protocols have demonstrated very favorable outcomes with respect to short-term (2 weeks) events such as PEs, propagation of thrombus, and minor bleeding (23). Advantages over UFH include greater bioavailability, once or twice a day dosing, lack of need for laboratory monitoring except in certain circumstances (severe renal failure, pregnancy—which may require monitoring Factor anti-Xa levels), and lower risk of heparin-induced thrombocytopenia (HIT). Enoxaparin and dalteparin are two LMWHs used in the treatment of venous thromboembolism. The recommended dosing for these medications is as follows: enoxaparin, 1 mg/kg/dose every 12 hours or 1.5 mg/kg once daily subQ for inpatient treatment and 1 mg/kg/dose subQ every 12 hours for outpatient treatment. Dalteparin dosing is

200 U/kg once daily subQ or 100 units/kg twice daily subQ. These medications are predominantly eliminated by the kidneys. In patients with renal impairment and creatinine clearance >30 mL/min no specific adjustment is recommended, but in patients with severe renal failure lower doses should be used and anti-Xa levels monitored. Enoxaparin is not approved by the FDA for use in dialysis patients.

Fondaparinux is a synthetic heparin pentasaccharide analogue that binds to antithrombin and is given subcutaneously. It has been found to be effective in the treatment of venous thromboembolism (24). Dosing is weight based: <50 kg, 5 mg once daily; 50 to 100 kg, 7.5 mg once daily; >100 kg, 10 mg once daily. It should be adjusted in renal insufficiency and is contraindicated in severe renal failure. In patients with HIT, direct thrombin inhibitors (DTIs) should be used. Two direct thrombin inhibitors approved in the United States for use in patients with HIT are lepirudin and argatroban (25). Thrombolytic therapy has a role in treating limb-threatening thrombosis of the iliofemoral system, and can be considered in this setting, but is otherwise discouraged in the treatment of DVT (26).

Once a non-vitamin K anticoagulant has been initiated, warfarin (5 to 10 mg orally) may be begun, although this is generally not administered in the ED.

Those patients with absolute contraindications to anticoagulation require inferior vena caval interruption with an IVC filter (27). These devices are approximately 95% effective in preventing further PEs but have a 10% complication rate on insertion. However, this rate is not appreciably higher than that of full anticoagulation.

DVT below the knee should be managed in the same way as proximal DVTs. Similarly, there has been controversy regarding the ideal treatment of *superficial thrombophlebitis* of the leg. Though the danger of acute embolism may be less than that of calf DVT, propagation to the deep system must be ruled out at the time of the ED visit and close follow-up must be arranged. Compression bandages, anti-inflammatory drugs, and elevation are standard recommendations but anticoagulation should be considered in

patients with a prior history of DVT. If the patient is an intravenous drug user or appears toxic, *septic thrombophlebitis* must be ruled out. Septic thrombophlebitis most commonly occurs at a site of intravenous catheter placement, and because the most common causative organism is *Staphylococcus aureus,* appropriate antibiotic therapy should be administered.

Postthrombotic syndrome occurs in 20% to 50% of patients with lower extremity DVT, usually within the first 2 years but has been seen as late as 8 years out (28). Endovascular interventions to reduce the thrombus burden have been shown reduce the incidence and severity of postthrombotic syndrome (29,30). Endovascular interventions may include catheter-directed thrombolysis and thrombosuction to prevent postthrombotic syndrome. The American College of Chest Physicians recommend consideration of catheter-directed thrombolysis or pharmacomechanical thrombolysis if appropriate expertise and resources are available for patients who have iliofemoral DVT, symptoms less than 14 days, good functional status, life expectancy $>$ 1 year, and low risk of bleeding (31).

Patients referred for endovascular intervention consultation should be started on anticoagulation therapy in the ED.

CRITICAL INTERVENTIONS

- Anticoagulation with UFH, LMWH, or fondaparinux should be initiated in the ED.
- Traditional loading doses of heparin result in inconsistent anticoagulation of many patients. Weight-based dosing is more effective.
- LMWHs or fondaparinux are effective and allow outpatient therapy in appropriate cases.
- Isolated DVT distal to the knee is not as benign as previously thought. It should be treated more like proximal DVT in terms of therapeutic aggressiveness.
- Early consultation to consider catheter-directed thrombolysis or pharmacomechanical thrombolysis in appropriate patients with

extensive acute proximal DVT in addition to anticoagulant therapy.

DISPOSITION

Historically, all patients with proximal lower extremity or upper extremity DVT required admission to the hospital. However, many institutions now have protocols by which a select subset of patients is discharged directly home from the ED on subcutaneous LMWH with close outpatient follow-up. This practice is supported by the American College of Physicians and American Academy of Family Physician guidelines if the required support systems are in place (17). Referral for possible endovascular intervention to prevent postthrombotic syndrome should be made early in the course. Outpatient treatment is not appropriate in cases of massive DVT (e.g., iliofemoral DVT), symptomatic PE, patients at high risk of bleeding, and those with other conditions who would require hospitalization. Conversely, the treatment of patients with DVT distal to the knee was historically similar to that of superficial thrombophlebitis. Now, with increasing concerns that these patients have risks for embolization that are only modestly lower than those patients with proximal DVT, it is recommended they be treated as those with proximal DVT or entered into a close outpatient follow-up protocol. Patients with *phlegmasia dolens* require more aggressive therapy. Emergent vascular surgery consultation and intensive care admission is indicated. Transport to a higher level of care should be considered if vascular surgery is unavailable.

Common Pitfalls

- Patients with a painful or swollen leg should be considered to have DVT until proven otherwise. Clinical evaluation alone is not sufficient to rule out the diagnosis.
- The traditional physical examination findings of DVT are notoriously inaccurate. The Homan test should be abandoned, and the presence of a palpable cord is not reliable.

- A negative highly sensitive D-dimer (ELISA, second generation latex agglutination-immunoturbidometric) test is useful only in patients with a low and intermediate clinical risk of DVT. It should not be used to exclude the diagnosis in high-risk patients. Moderate-sensitivity (non-ELISA) D-dimers are only adequate in assessing low clinical risk patients.
- A negative ultrasound combined with a negative moderate or high-sensitivity D-dimer leaves a $<1\%$ probability of DVT even in a high clinical probability patient. In these patients further ultrasound testing may not be needed (18).

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CHAPTER 97

Vascular Graft Complications

Hoori Hovanessian

Vascular disease is a progressive, degenerative condition that disproportionately affects a subset of patients with other comorbid conditions, such as diabetes and hypertension. When vascular disease progresses despite medical management, surgical treatment often becomes necessary. Although surgery significantly improves quality of life, it is important to realize that the underlying disease continues to progress. These patients are frequent consumers of health care due to disease progression, early or late postoperative complications, or other illness. Knowledge of the pathologic processes that affect the vascular system as well as potential postoperative complications is essential for emergency physicians (EPs).

VASCULAR GRAFTS

Vascular pathology can be subdivided into aneurysmal and occlusive diseases. Aortic aneurysm and aortic dissection have potentially life-threatening consequences. When an aortic aneurysm becomes symptomatic or reaches a predetermined size, aneurysm repair is undertaken with graft replacement. Conventional treatment of aortic dissection involves resection of the damaged segment of the aorta and closure of the entrance into the false lumen. Closure of the lumen can be accomplished by placing sutures or by using biologic glue to seal the layers of the dissected part of the aortic

wall. The diseased section of the aorta that is removed is replaced by a prosthetic graft.

Patients with occlusive disease of the vasculature may undergo extra-anatomic and infrainguinal procedures. Extra-anatomic procedures do not conform to the pre-existing anatomy and include femoral–femoral, axillofemoral, and iliofemoral bypasses. Prosthetic grafts are preferred in extra-anatomic reconstruction. Infrainguinal arterial occlusive disease can affect the femoral, popliteal, or tibial arteries. In these cases, autogenous veins are used in below-the-knee reconstructions, whereas both autogenous and prosthetic grafts are used in above-the-knee repairs (1). Polytetrafluoroethylene (PTFE) is the most commonly used synthetic graft. Tissue can grow through the interstices of the graft, incorporating the graft into tissue, theoretically decreasing the chance of thrombosis and infection.

With the advent of endovascular repair techniques, the treatment of aneurysms, dissection and aortoiliac obstructive disease has been undergoing rapid evolution, with endovascular procedures supplanting conventional surgery in many cases. Endovascular aortic aneurysm repair is performed much more frequently than open repair. Thoracic endovascular aortic repair (TEVAR) is now recommended as first-line therapy for thoracic aortic aneurysms (1). TEVAR has been gaining popularity due to decreased perioperative morbidity and mortality compared to open surgical repair (2). Originally utilized as a treatment for aneurysms, its use has expanded to include the treatment of aortic dissections, transections, and penetrating aortic ulcers. Endovascular procedures also outnumber surgical procedures in the treatment of select types of aortoiliac occlusive lesions (3).

It is also important for the EP to be familiar with complications associated with dialysis shunts. Vascular access for dialysis can be obtained through the formation of an arteriovenous fistula (AVF), whereby an artery and vein are anastomosed. Alternatively, a prosthetic graft can be used to join an artery and vein. Common locations for the creation of both native fistula and graft are the radiocephalic (wrist) and brachiocephalic (upper arm) regions. AVFs are currently preferred over prosthetic grafts because of their lower

complication rates (less potential for thrombosis and lower infection rate) as well as their overall longevity. Prosthetic grafts may be the only option for patients with failed AVFs and those with poor peripheral veins.

GRAFT COMPLICATIONS

The complications of vascular grafts range in presentation from relatively straightforward to subtle and complex. They can be divided into the following categories: (i) stenosis, thrombosis, and occlusion, (ii) infection, (iii) erosion into contiguous structures with fistulization, (iv) pseudoaneurysm formation, (v) hemodynamic complications (dialysis access grafts), and (f) complications associated with endovascular grafts.

Stenosis, Thrombosis, and Occlusion

Early failure of vein grafts generally indicates a technical problem such as a kink or twist within the graft or incompletely lysed valves when autogenous grafts are used. Later failures are usually a result of intimal hyperplasia at the anastomotic sites (1). Failures that occur beyond 2 years are generally a result of progressive atherosclerosis. Graft thrombosis is the most common complication associated with permanent vascular access. Stenosis is the leading cause of thrombosis, accounting for up to 85% of thromboses. Graft thrombosis may result in a relatively sudden return of the patient's previous symptoms. These may include claudication or ischemic rest pain that is localized to the forefoot. Pain caused by arterial insufficiency is usually severe unless it is masked by neuropathy. Signs may include skin breakdown with the formation of nonhealing ulcers. Such ulcers may also form between adjacent toes as a result of mild friction. Superinfection of these ulcers as well as osteomyelitis is a well-documented resultant complication. Painful toes that have a cyanotic appearance are suggestive of microemboli.

Dialysis access graft thrombosis is common despite the fact that heparin is used routinely and uremic patients already have an increased bleeding tendency. Complication-free graft use of 51% at

2 years and 39% at 3 years has been reported with polytetrafluoroethylene grafts (4). Thrombosis and occlusion occur secondary to intimal hyperplasia and can be accelerated by hypotension, dehydration, and by excess pressure applied to the graft site (e.g., by bandages or perigraft hematomas). Patients may complain of a sensation of coldness, tingling, or numbness and weakness of the involved extremity.

Because the signs and symptoms associated with vascular graft complications overlap with other more common medical problems, the differential diagnosis is vast. Limb weakness may result from a cerebrovascular accident or a nerve compression syndrome. Embolic events may be caused by atrial fibrillation or endocarditis.

The ED evaluation of the patient with suspected graft occlusion should include a careful examination of distal pulses by palpation, hand-held Doppler, and duplex ultrasonography. Neurosensory examination is less useful in patients with neuropathy but should be attempted. Skin temperature and the color of the affected limb should also be evaluated. The limb may become pale on elevation with a dusky or cyanotic rubor with dependency. Findings in the affected extremity should be compared to findings on the contralateral side. An ankle-brachial index (ABI) measurement can also provide important information. (The technique and interpretation are described in Tables 95.2 and 95.3.) The loss of a previously palpable pulse or a change of 0.15 from a previous ABI requires further evaluation with duplex ultrasonography or angiography. Finally, low cardiac output (hypovolemic or cardiogenic) may enhance thrombosis and accelerate occlusion, resulting in acute limb ischemia. The patient should be evaluated for evidence of volume depletion (blood loss, dehydration), sepsis, or cardiac insufficiency.

The ED management should include optimization of the patient's volume status. Heparinization to prevent further thrombosis should be counterbalanced against the timing of angiography and the possible use of thrombolytic agents. This decision should be made in conjunction with the vascular surgeon, so consultation should be obtained early. Treatment options include percutaneous or surgical

thrombectomy; thrombolytic agents or mechanical dissolution in the case of thrombosis; and angioplasty, endovascular stent placement, or surgical revision in cases of stenosis. Angioplasty has a higher success rate in stenoses involving less than 60% of the lumen. Surgical revision and repair are preferred in cases of high-grade stenosis.

Infection

The incidence of infection after arterial reconstructive surgery with the use of synthetic grafts ranges from 1% (aortic and iliac artery repair) to as high as 5% (in situations wherein the graft is placed in the inguinal area) (5). Infection is a significant problem in patients with prosthetic dialysis access grafts, with an incidence of 3% to 6% (6,7). Risk factors for vascular graft infections include diabetes, renal failure, obesity, use of prosthetic (vs. native) grafts as well as infrainguinal procedures and surgical revisions (especially if done within 30 days of the original operation). The incidence is higher in patients with acquired immunodeficiency syndrome or a history of intravenous drug abuse.

Intraoperative contamination is likely the most common mechanism for early graft infection. Spread of pathogens from contiguous infected or colonized tissue may explain the relatively higher rate of infection in the groin. Other mechanisms may include hematogenous spread of microorganisms as well as erosion of the graft into contiguous bowel lumen, resulting in direct graft contamination.

Patients with graft infections may present with frank sepsis, an infected wound, or overlying cellulitis. More subtle presentations may include low-grade fever, vague abdominal discomfort, or malaise. Still more complicated presentations may include bleeding, evidence of distal emboli, or the presence of an abdominal mass as a consequence of a false aneurysm. Aortoenteric fistula (AEF) may be the presenting sign in approximately 30% of aortic graft infections (8).

In the ED evaluation of a patient with any type of suspected graft complication, the physician should consider an infectious source, because it may be the underlying cause of graft thrombosis, AEF, or false aneurysm formation. The most common responsible organism is *Staphylococcus aureus* (with methicillin-resistant staphylococcus aureus (MRSA) becoming increasingly common). Other implicated agents include coagulase-negative staphylococci, enterococci, *Pseudomonas aeruginosa, Enterobacteriaceae,* and *Bacteroides* species. Polymicrobial infections occur in 12% to 37% of patients (5). Blood cultures should be obtained, although they may be negative if the lumen is not involved. Computed tomography (CT) scanning may reveal perigraft inflammation or fluid collection, or air adjacent to the graft. Sterile perigraft fluid can be seen on a CT for up to 3 months following graft placement. However, an increase in the volume of the perigraft fluid or persistence of the fluid beyond 90 days may be indicative of infection (9). In the case of grafts that are located close to the skin, the diagnosis is relatively easy in the presence of cellulitic changes, fluctuance, or obvious drainage of pus from the vicinity of the graft site. However, local signs of infection may be absent initially. Graft infection should be considered in any febrile patient, even in the absence of any local findings. Finally, occult infection may be present in old, nonfunctioning dialysis access grafts. The graft may have become seeded from a previous episode of bacteremia or may have become directly inoculated from needle puncture at the time the graft was in use. This source of potential infection should be considered in dialysis patients, as well as in renal transplantation patients, with fever of unclear etiology (10). The diagnosis can be established on an inpatient basis by using indium-111 scanning, which has a sensitivity and specificity over 90% (10).

As with graft thrombosis, the ED management should include optimization of the patient's fluid status to prevent accelerated graft thrombosis and occlusion secondary to poor perfusion through the graft site. Incision and drainage of suspected abscesses in the vicinity of a graft should not be attempted in the ED, as it can result in catastrophic hemorrhage. Empiric antibiotic therapy should be

initiated early. Definitive treatment by a surgeon ranges from local incision and drainage to complete graft removal with debridement of the surrounding infected tissues. Infection in native fistulas can usually be treated with intravenous antibiotics, requiring surgical drainage only in select cases. Therapy should be guided by results obtained from the culture of the infected tissue at surgery following surgical repair. Infections with MRSA and *Pseudomonas* are associated with higher rates of treatment failure (11,12). Therefore appropriate broad-spectrum antibiotic therapy (such as vancomycin or linezolid for gram-positive coverage and ceftazidime, cefepime, piperacillin-tazobactam, or ticarcillin-clavulanate for gram-negative coverage) should be initiated pending blood culture results.

The rate of endograft infections is low (0.2% to 0.7%) (13). Patients have presented with signs and symptoms of severe sepsis, AEFs, as well as nonspecific symptoms such as malaise (13). Because of the low rates of infection with this relatively new procedure, experience is limited and clear-cut management guidelines are not available. These patients have been managed both conservatively as well as with surgery. Consultation with the vascular surgeon is of paramount importance.

Erosion into Contiguous Structures with Fistulization

Erosions of the prosthetic graft into the bowel can result in the formation of an AEF. Most commonly these occur between an aortic prosthetic graft and the distal duodenum. However, such fistulization has been reported after aortoiliac and aortofemoral procedures as well as after renal vascular graft placement. Fistulization to the bowel at sites other than the duodenum may also occur. Mechanical trauma, prosthetic graft or perigraft infection, and pressure necrosis all contribute to fistulization.

The time frame for AEF development is wide. Fistulization may occur several days to many years after the initial surgery (14). Clinical presentation is commonly that of gastrointestinal bleeding: hematemesis, hematochezia, melena, or occult blood loss. Patients may present with self-limited herald bleeding several hours to days

before exsanguinating hemorrhage ensues. Some patients may have nonspecific symptoms of back or abdominal pain. Because fistulization may be secondary to graft infection, other signs and symptoms may include fatigue and malaise, low-grade fevers, and leukocytosis.

AEF should be considered in the ED evaluation of any patient with gastrointestinal bleeding and a history of aortic repair with graft placement. In the stable patient, workup for other sources of bleeding should be initiated, as other sources of bleeding are more common than AEF. Laboratory studies should include a complete blood count, type and cross, coagulation studies, electrolytes, blood urea nitrogen (BUN), creatinine, and glucose. Endoscopy (upper and lower) is important primarily in evaluating other, more common causes of gastrointestinal bleeding. If endoscopy does not yield a clear-cut answer, abdominal CT with oral and intravenous contrast should be obtained to evaluate for inflammatory changes around the anastomotic sites (14,15).

The ED management should initially focus on stabilization and resuscitation. Unstable patients with suspected AEF require emergency laparotomy to control the bleeding. The patient's hemodynamic status should be evaluated and blood loss replaced before surgery. Even in stable patients with an AEF, surgical consultation should be obtained early as the treatment is invariably surgical. Occasionally, grafts erode through the skin. These grafts should be considered infected, and the patient should receive antibiotics. A vascular surgeon should be consulted for urgent repair.

Pseudoaneurysm

Disruption of the suture line (dehiscence) at the site of an anastomotic junction may give rise to a false aneurysm (pseudoaneurysm). False aneurysms most commonly occur in femoral artery graft anastomoses. Leaking blood is contained by the adjoining tissues as well as by fibrous scar formation. Infection is an important cause of pseudoaneurysm formation.

Patients with pseudoaneurysms may complain of pain in the groin, back, or abdomen. They may harbor a pulsatile mass in these locations. Other presentations may include hemorrhage (ranging from occult to life-threatening) caused by rupture of the false aneurysm or signs and symptoms associated with distal emboli. False aneurysms occur most commonly in the groin.

Repeated needle puncture for dialysis access can weaken the vessel wall, thereby leading to aneurysm formation. Pseudoaneurysms can form when the graft material is lacerated with the dialysis needle. In both cases, a pulsatile mass may be present. Pseudoaneurysms may expand and eventually rupture, resulting in significant hemorrhage. Pseudoaneurysm expansion can also threaten the viability of the overlying skin, thereby exposing the underlying graft to infection.

The ED evaluation of the patient with a suspected pseudoaneurysm should include imaging by duplex ultrasound, CT, magnetic resonance imaging, or angiography. Ultrasonography can gauge the size of a pseudoaneurysm and determine the presence of any hematoma and the status of the surrounding vasculature.

Surgical consultation is essential, although other management options such as thrombin injection and embolization procedures are currently being evaluated. In addition, antibiotics should be considered if the pseudoaneurysm is thought to have an infectious etiology. Treatment of vascular access graft aneurysms and pseudoaneurysms involves surgical repair.

Hemodynamic Complications of Vascular Access Grafts

Patients with borderline cardiac reserve and an excessive flow rate through their shunt (>500 mL/min) may exhibit signs and symptoms of congestive heart failure. An arterial steal syndrome with resultant distal ischemia may occur in patients with shunts. The incidence is somewhat higher in patients with proximal than those with distal access sites. The steal syndrome occurs when the blood flows from the artery into the low-resistance vein with less arterial blood available distal to the site of the shunt (1). Though

surgical correction may be required in severe cases, milder symptoms of paresthesias and coolness to touch can improve gradually with development of collateral blood flow. An alternate complication can occur with high-pressure arterial flow into the low-pressure venous system: Venous hypertension distal to the shunt ensues with swelling of the distal tissue and eventual skin induration and hyperpigmentation (1). Shunt repair may be necessary if the steal syndrome and venous hypertension cause clinical symptoms.

Neurovascular problems associated with vascular access include pain, weakness, muscle atrophy, and paresthesias. These hemodynamic and neurovascular complications are more problematic with fistulas but do occur with prosthetic grafts as well.

Complications Associated with Endovascular Grafts

Several early complications have been described in this emerging area of vascular repair. Limb ischemia or occlusion may require subsequent extra-anatomic (femoral–femoral) bypass, thrombectomy and angioplasty, or thrombolysis. These complications may occur intraoperatively (during endovascular graft placement) or over a year later (16). These complications are a result of vascular trauma as well as underlying peripheral vascular disease. Endoleaks, which complicate 10% to 20% of repairs, are defined as incomplete exclusion of the aneurysm with persistent leakage of blood into the aneurysmal sac (17). This can result in enlargement of the sac and/or increased pressure in the sac, ultimately leading to aneurysmal rupture. Several types of endoleaks have been defined including those that occur at the site of attachment of the graft to the aorta (from incomplete seal of the endograft) or through the stent graft itself (via a tear or fracture) (18). Other potential complications include distal embolization, graft occlusion, kinking, migration or prolapse into the aneurysm, and infection. Device migration may occur intraoperatively or over time. Device manufacturers are addressing this problem. Migration of the stent graft may present as an endoleak. Stent graft erosion into the

esophagus has also been reported (19). More commonly observed complications of TEVAR include spinal cord ischemia and stroke. The incidence of paraplegia or paraparesis after TEVAR with stent grafts varies from 0% to 8% and typically extends from the lumbosacral to the high thoracic cord levels (20). The incidence of stroke due to embolization of atheroma or thrombus formation after instrumentation and disruption of plaques varies from 2.3% to 8.2% (21).

Endovascular repair continues to evolve with advances in the design of endografts. Research is also ongoing in the design of more complex endografts, intended for situations where aortic pathology involves branch vessels. Long-term complications remain unknown given the relative infancy of this field. In general, however, endovascular procedures have been associated with lower complication rates, shorter hospital stays, as well as lower costs.

CRITICAL INTERVENTIONS

- The patient's hemodynamic status should be evaluated and fluid losses replaced.
- In patients with massive gastrointestinal hemorrhage and an intra-abdominal graft, emergent vascular consultation should be obtained and the patient readied for surgery.
- Empiric antibiotic therapy should be initiated in any febrile or septic-appearing patient with a fever of unknown etiology and the presence of a vascular graft, whether functioning or nonfunctioning. Given the higher complication rates with MRSA and *Pseudomonas* infections, antibiotic coverage should be provided for these organisms.

DISPOSITION

Most graft complications require surgical consultation and management in a hospital setting. After diagnosis and initial measures such as the initiation of antibiotic therapy and replenishment of fluid and blood loss, stable patients should be

admitted and managed by a vascular surgeon. Unstable patients require resuscitation prior to emergent surgical intervention.

Diagnostic and management decisions should ideally be made in conjunction with a vascular surgeon as well as an interventional radiologist skilled in these relatively novel procedures.

Common Pitfalls

- Failure to consider graft thrombosis when a patient with a vascular graft has a recurrence of claudication, rest pain, skin breakdown, or nonhealing ulcers
- Failure to exclude infection when evaluating patients for any type of graft complication
- Failure to evaluate the ABI and compare it to the previously obtained values
- Failure to consider AEF in any patient with gastrointestinal bleeding and a history of aortic repair
- Failure to consider a pseudoaneurysm in patients with a history of vascular repair and complaints of abdominal or groin pain, hemorrhage, or pulsatile mass
- Failure to appreciate that low-flow states may contribute to vascular access thrombosis

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SECTION X
Gastrointestinal Emergencies

Section Editor: GREGORY W. HENDEY

CHAPTER 98

Esophageal Disorders

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Esophageal disorders encompass a large differential in the emergency department with some life-threatening presentations as well as many benign disorders that require outpatient work up. Complicating matters further are significant overlap in symptoms with many life-threatening disorders including cardiac, vascular, and respiratory pathologies.

ESOPHAGITIS

Clinical Presentation

Patients may present with pain on swallowing (odynophagia), with or without difficulty in swallowing (dysphagia). Pain may be described as a retrosternal ache, a burning sensation, or a stabbing pain with radiation to the back. Patients with severe cases may present with anorexia or weight loss.

Patients with a history of immunosuppression are at increased risk of infectious esophagitis. Candida or herpes esophagitis may present with lesions present in the oropharynx as well. However, approximately 25% of patients with candidal esophagitis do not have oral thrush, so its absence does not rule out this entity (1). While immunocompetent patients usually report recent upper respiratory infection and have visible herpetic lesions, these lesions can be absent in immunocompromised patients. Herpes esophagitis should be suspected when symptoms do not improve with typical antifungal medications in immunocompromised patients (2). In esophageal candidiasis, odynophagia is usually mild. If symptoms

are so severe that the patient consciously limits oral intake, ulcerative esophagitis of some other etiology is likely. Patients with AIDS often have coinfection with more than one infectious source (3).

Most important immediate consequences of esophagitis are local pain and impaired oral intake. Rarely, the initial manifestation of esophageal disease is GI bleeding. Complications of candidal or viral esophagitis are uncommon and include hemorrhage, perforation, esophageal narrowing with stricture formation, and dissemination of infection.

Patients with pill esophagitis may give history of taking a new medication, with common offending agents including doxycycline, potassium chloride, quinidine, alendronate, ferrous sulfate, aspirin, and nonsteroidal anti-inflammatory agents. In all, more than 70 medications have been reported to cause esophageal injury (4). The elderly are at increased risk for pill esophagitis. Patients typically report retrosternal pain, odynophagia, and dysphagia that are temporally related to ingestion of medication. They may give a history of taking the medication with little or no water.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of esophagitis includes gastroesophageal reflux disease (GERD), esophageal dysmotility disorders, esophageal perforation, gallbladder disease, pharyngitis, abscesses, food impaction, or esophageal foreign body. Coronary artery disease, aortic pathology, and pulmonary embolism can present with similar symptoms and must be considered.

ED EVALUATION

The initial history should first focus on the duration and severity of the symptoms and on the patient's ability to maintain normal oral intake. The patient should be questioned about human immunodeficiency virus infection, malignancy, or other sources of immunosuppression. Other relevant questions include whether there is an association of symptoms with pill ingestion, food bolus, foreign

bodies, or symptoms suggestive of esophageal reflux. Myocardial ischemia should be considered.

Physical examination should concentrate initially on the patient's state of hydration. Vital signs should be noted, as well as skin turgor and the condition of the mucous membranes. One clue to the severity of the patient's symptoms may be the ability to swallow their own saliva. The oropharynx should be examined for candidal or herpetic lesions. A soft-tissue lateral neck radiograph or neck computed tomography (CT) scan should be obtained if mass or abscess is a consideration. Other life threats including cardiac causes of the patient's symptoms should be excluded.

KEY TESTING

- Chest X-ray to evaluate for evidence of esophageal perforation or foreign body
- EKG to evaluate for cardiac ischemia
- Cardiac markers, D-dimer, and advanced imaging as appropriate depending on suspicion of other pathology

ED MANAGEMENT

A number of antifungal agents have been used to treat oral and esophageal candidiasis. Fluconazole is currently the drug of choice (5,6). Other antifungal options exist, but they are generally tolerated less well and have more undesirable side effects. Patients requiring IV therapy or with resistance to azoles may benefit from use of echinocandins such as caspofungin (7). All systemic antifungal prescriptions should be written with care and checked against the patient's other medications, for many can cause potentially serious drug–drug interactions.

Foscarnet and ganciclovir appear to be similarly effective and safe in the treatment of AIDS-related CMV esophagitis (8). Herpes simplex virus (HSV) esophagitis may be self-limited in the immunocompetent host, but therapy with oral or IV acyclovir should be instituted in immunocompromised patients.

In patients presenting with mild esophageal symptoms that do not limit oral intake, an empiric trial of antifungal therapy with fluconazole is reasonable regardless of the presence or absence of oral candidiasis. If symptoms improve a presumptive diagnosis of esophageal candidiasis may be made. If a patient does not respond within 72 hours, endoscopy should be considered.

Pill esophagitis is easily treated by discontinuing the offending medication or changing to liquid or tablet (as opposed to gelatin) form when possible. Patients should be instructed to avoid taking pills before bedtime, take pills with plenty of water, and avoid lying down after taking pills. The condition usually resolves within 3 to 4 days without any intervention (4), provided the medication is discontinued, but complete resolution may take several weeks. The most common complication is stricture formation.

CRITICAL INTERVENTIONS

- Admit patients with dehydration due to severe odynophagia for IV rehydration.
- Treat patients with suspected candidal esophagitis with fluconazole.
- Admit immunocompromised patients for further evaluation and treatment.

DISPOSITION

Immunocompetent patients with mild symptoms may be treated as outpatients. Referral to a gastroenterologist and follow-up are appropriate for these patients, as well as for those who do not respond to initial therapy.

Patients who are experiencing severe difficulty with swallowing and are unable to maintain hydration require hospital admission. Immunocompromised patients should be strongly considered for IV antiviral or antifungal therapy and admission.

Patients with pill esophagitis should be referred to their primary care physician to ensure that timely resolution of symptoms occurs.

ESOPHAGEAL DYSMOTILITY

Clinical Presentation

Motility disorders including achalasia, diffuse esophageal spasm, nutcracker esophagus as well as obstructive causes including esophageal web, rings, strictures, and tumors comprise the second group of esophageal disorders which can present as chest pain as well as dysphagia, regurgitation, and heart burn. Weight loss is also a feature of the motility disorders due to decreased oral intake and fear of dysphagia and chest pain (9). Patients may also develop esophageal dysfunction secondary to other conditions, most notably scleroderma.

Achalasia is a motility disorder with deficient peristalsis and poor relaxation of the lower esophageal sphincter. Chest pain is the most common symptom in about half of patients followed by dysphagia, notably to both liquids and solids. Symptoms generally begin intermittently but become more persistent. Warm drinks may improve symptoms, whereas cold carbonated beverages produce more symptoms (9,10). The site of obstruction is often correctly located by the patient in the xiphoid area. Patients with achalasia learn maneuvers to assist esophageal emptying, such as throwing the shoulders back, extending the neck, or performing a Valsalva maneuver (1). Patients may report regurgitation of undigested food. Regurgitation occurs most commonly at night because of the recumbent position, and vomitus may be noted on the pillow on awakening in the morning. Aspiration is a common complication of achalasia and may present as cough, pneumonia, or lung abscess.

Diffuse esophageal spasm and nutcracker esophagus are characterized by increased simultaneous esophageal spasm and increased esophageal pressures, respectively. Patients may present with dysphagia or with chest pain that is triggered by the ingestion of very hot or cold liquids.

Obstructive dysphagia may be due to structural lesions of the esophagus, including esophageal webs and rings, as well as tumors. Esophageal carcinoma is a very important cause of dysphagia and is important to recognize early in its course. The prognosis is dismal

by the time a patient presents with progressive dysphagia. Heavy alcohol intake and smoking significantly increase the likelihood of squamous cell carcinoma of the esophagus, and adenocarcinoma tends to occur in patients with a long history of GERD or Barrett's esophagus. Food impaction is further discussed in Chapter 114, but food obstruction may be the first indication or presentation of an obstructive lesion.

DIFFERENTIAL DIAGNOSIS

In addition to those listed above, the differential diagnosis includes oropharyngeal dysphagia, or difficulty passing food from the mouth to the esophagus. This is often secondary to a CVA or other neurologic condition. Other conditions to be considered include cardiac, respiratory, and vascular causes of chest pain, as well as esophageal foreign bodies, GERD, and gastritis.

ED EVALUATION

The evaluation of dysmotility should begin, as always, with attention to the airway, breathing, circulation, and particularly to hydration status. A cardiac cause of chest pain should first be considered before implicating the esophagus. A chest X-ray to evaluate for evidence of esophageal perforation should be performed; this may also offer clues to other causes of dysmotility such as visualization of a mass, or evidence of achalasia with the presence of an air–fluid level in the posterior mediastinum (caused by the dilated, fluid-filled esophagus), and the absence of a gastric air bubble (because swallowed air cannot get into the stomach).

KEY TESTING

- Chest X-ray to evaluate for evidence of esophageal perforation

ED MANAGEMENT

Patients who are adequately hydrated, are able to eat and drink, and who have been ruled out for life-threatening causes of their symptoms can be referred for further work up as outpatients. If

patients have a known history of achalasia they should be encouraged to maintain an upright position after eating for several hours. Drinking hot liquids may also be helpful.

CRITICAL INTERVENTIONS

- Carefully differentiate esophageal chest pain from that of cardiac origin.

DISPOSITION

If cardiac causes have been excluded and the patient tolerates oral intake, follow up with the primary care physician or gastroenterologist is appropriate. Outpatient work up of dysmotility disorders may include Barium swallow, esophagogastroduodenoscopy (EGD), and esophageal manometry. Endoscopy is indicated in all patients suffering from food impaction, whether the food bolus is eventually passed or not. Food impaction may be the first sign of an obstructive lesion.

GASTROESOPHAGEAL REFLUX DISEASE

Clinical Presentation

GERD is defined as reflux of the stomach contents into the esophagus causing troubling symptoms or complications (11). Symptomatic GERD is common. Prevalence is significantly higher in developed countries. About 40% of US adults have monthly heartburn symptoms, about 20% have weekly symptoms, and about 7% have daily symptoms (12).

Risk factors for GERD include advanced age, male sex, white race, smoking, obesity, high-fat diet, and intake of alcohol, chocolate, citrus drinks, soda and coffee. Medications such as theophylline, nitrates, calcium channel blockers, meperidine, nonsteroidal anti-inflammatory drugs, and oral contraceptives may aggravate GERD. Stress and exercise have also been found to exacerbate symptoms. GERD is associated with several medical conditions including pregnancy, diabetes, hiatal hernia, scleroderma, cerebral palsy, and

Down's syndrome. Procedure-related conditions such as nasogastric tube insertion and gastrostomy feedings may lead to GERD (12).

The most common presenting symptoms include heartburn or a retrosternal burning sensation rising from the stomach to the throat, regurgitation or bitter taste, and dysphagia. Nausea may also be present (13). Symptoms are usually worse after eating, at night, with exercise, or with bending or lying supine. There may be radiation of the discomfort to the back, neck, or left arm. The intensity is variable, and the duration may be minutes or hours. Symptoms may improve after taking antacids.

DIFFERENTIAL DIAGNOSIS

A cardiac etiology must always be excluded when a patient presents with burning substernal chest pain, and the differential is the same as that of cardiac ischemia. Chest pain of esophageal origin may be impossible to distinguish from angina by history or physical examination alone. Both cardiac causes of chest pain as well as GERD can respond to either antacid/ "GI cocktail" or nitroglycerin; thus response to these medications is not diagnostic (14).

Unfortunately, there are no characteristic features of chest pain that are pathognomonic of esophageal disorders, including response to medications. Other considerations include pancreatitis, gallbladder disease, peptic ulcer disease, esophagitis, and esophageal dysmotility disorders.

ED EVALUATION

The ED evaluation should focus on ruling out cardiac ischemia as well as aortic and pulmonary pathology as the origin of chest pain. If these causes can be excluded and the patient gives a history of heartburn without dysphagia, fever, weight loss, or GI bleeding, no further studies are required in the ED and referral to a gastroenterologist may be appropriate. The most useful tests for diagnosing reflux are barium swallow, endoscopy, and 24-hour gastric pH monitoring, all of which are performed on an outpatient basis.

KEY TESTING

- Chest X-ray to evaluate for evidence of esophageal perforation
- EKG to evaluate for cardiac ischemia
- Cardiac markers, D-dimer, and advanced imaging as appropriate depending on suspicion of other pathologies

ED MANAGEMENT

ED management should begin with symptom control, including antacids, "GI cocktail," H_2 blockers, or proton pump inhibitors (PPIs). Gaviscon is a viscous solution containing antacids that float above the gastric pool to mechanically block reflux fluid and has been used for immediate relief (12).

Long-term management is typically with H_2 receptor antagonists or PPIs. For mild or intermittent symptoms, a trial of H_2 receptor antagonists has been considered traditional therapy. H_2 receptor antagonists can be used as premedication by patients who are able to predict symptom recurrence, such as before a large meal. They may also be used to prevent nocturnal acid production.

For moderate to severe symptoms and for those in whom there has not been adequate improvement with H_2 blockers, a 6-week trial of empiric acid suppressive therapy is often attempted. A meta-analysis suggests that PPIs are more effective at treating GERD when compared to H_2 blockers. Complete relief of symptoms with PPIs occurs at a rate of 11.5% per week versus 6.4% with H_2 blockers (15,16). PPIs have become standard therapy for GERD because they result in healing of about 80% of moderate to severe reflux esophagitis (12). Symptoms usually improve in 1 to 2 weeks. If symptoms disappear with therapy, then reappear when the medication is discontinued, a presumptive diagnosis of GERD is made (sensitivity 75%, specificity 80%) (17). If the diagnosis of GERD is established and symptoms still persist, physicians may elect to try twice daily dosing or switching to a different PPI (17).

Education at time of discharge regarding lifestyle modifications including dietary changes, remaining upright for 3 hours after

meals, elevation of head of bed, and cessation of smoking and alcohol intake is an important adjunct to pharmacologic treatment (18).

Patients whose symptoms persist for more than 6 weeks should be referred for outpatient GI workup including EGD. EGD is highly sensitive and specific for diagnosing reflux esophagitis and GERD complications such as Barrett's esophagus, bleeding, and strictures because the mucosa is observed directly. Biopsies can be performed and cultures obtained. Patients who should undergo initial EGD before a therapeutic trial include all patients older than 55 years, young patients with severe comorbidities; patients with severe symptoms, involuntary weight loss, or GI bleeding; patients using nonsteroidal anti-inflammatory drugs or aspirin; and native Japanese patients (12).

CRITICAL INTERVENTIONS

- Carefully differentiate GERD symptoms from those of cardiac origin.

DISPOSITION

If other life-threatening causes of patient symptoms have been excluded the patient can be discharged and referred to the primary care physician. ED physicians may elect to initiate acid suppressive therapy with a H_2 blocker or PPI. For severe or resistant symptoms or suspected complications of reflux esophagitis, the patient may be referred to a gastroenterologist for further evaluation.

ESOPHAGEAL PERFORATION

Esophageal perforation can be spontaneous, traumatic, or iatrogenic, with iatrogenic being the most common (19). Esophageal perforations have a very high morbidity and mortality. Traumatic esophageal ruptures are discussed further in Chapter 27. Esophageal foreign bodies can contribute to esophageal perforation, these are discussed further in Chapter 115. Caustic ingestions can also cause severe damage to the esophagus and represents a true emergency.

CLINICAL PRESENTATION

Patients with spontaneous esophageal perforations or Boorhave's syndrome present with chest pain radiating to the back, often following prolonged vomiting or coughing. A history of previous ingested foreign body, eating disorders, alcoholism, history of peptic ulcer disease, or pregnancy with hyperemesis may be obtained. Patients with iatrogenic perforations present with history of recent EGD or other esophageal procedures such as esophageal dilation. Nonbloody emesis followed acutely by chest pain, often radiating to the back, dominates the clinical picture. Patients with perforations appear more toxic and may also present with dyspnea or shock and their condition can deteriorate rapidly (19).

DIFFERENTIAL DIAGNOSIS

Again differential diagnosis includes other causes of chest pain including cardiac, aortic dissection, pulmonary causes including pneumonia or pneumothorax, as well as sepsis.

ED EVALUATION

Initial evaluation should include evaluation of airway, breathing, and circulation. IV access should be obtained and IV fluids started as indicated by the patient's hemodynamic status. A chest X-ray should quickly be obtained. Chest X-ray will usually demonstrate mediastinal air or free air under the diaphragm giving you the diagnosis. Other findings may include pleural effusion, pneumothorax, or widened mediastinum. If diagnosis is unclear after chest X-ray a CT scan of the chest should be pursued. Esophagram can also be performed but has a false negative rate of as high as 10% (20). Gastrografin should be used rather than barium as if perforation is present. Barium extravasation into the mediastinum can cause further complications (21).

KEY TESTING

- Chest X-ray. If chest X-ray is nondiagnostic, proceed to CT of the chest.

ED MANAGEMENT

ED management should include broad spectrum antibiotics, aggressive supportive care, and consultation with a thoracic surgeon for likely surgical repair.

CRITICAL INTERVENTIONS

- Identify perforation with chest X-ray, CT scan, or esophagram
- Early broad-spectrum antibiotics
- Early consultation with a thoracic surgeon

DISPOSITION

Patients with esophageal perforation require admission to the hospital.

Common Pitfalls

- Mistakenly attributing pain on swallowing to pharyngitis. Severe and potentially life-threatening conditions including epiglottitis and retropharyngeal abscesses should be excluded.
- Failing to consider an immunosuppressed state and susceptibility to infectious esophagitis.
- Failing to consider esophageal foreign bodies and food impaction, especially in the elderly and the alcoholic. Pill esophagitis is likewise underappreciated.
- Mistakenly attributing chest pain caused by coronary artery disease as GI in origin, especially when substernal burning or atypical chest pain appears to be relieved by antacids or a "GI cocktail."
- Failing to evaluate and refer patients with mild dysphagia when a potentially treatable obstructive lesion may be the cause.

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CHAPTER 99

Upper Gastrointestinal Bleeding

Michael A. Cole and Sukhjit S. Takhar

Gastrointestinal (GI) bleeding is a common emergency, with a prevalence of 170 cases per 100,000 adults per year in America. In the majority of cases, the source is the upper GI tract, and the mortality from upper GI bleeding (UGIB) has remained at approximately 6% to 8% for three decades (1). Patients with GI hemorrhage often have coexisting serious illnesses, making their care even more challenging. The site of bleeding is usually predictable from the history and physical examination and is often confirmed and treated by endoscopy. Although there have been many advances in care, the fundamental goals of resuscitation and hemostasis remain the same.

UGIB is defined as a source of bleeding originating between the upper esophageal sphincter and the ligament of Treitz. Although peptic ulcer disease is the cause of more than 60% of UGIB cases, the highest mortality rates are associated with variceal bleeding. Due to the potential severity and unique pathophysiology and treatment of variceal bleeding, it is useful to divide UGIB into variceal and nonvariceal bleeding (1,2).

Causes of UGIB are listed in Table 99.1. UGIB may occur at any age but has a higher incidence in patients older than 40 years. It is more common in males than females. Elderly patients have less ability to compensate for acute hemorrhage and the majority of deaths occur in this subgroup. Mortality is also higher in those with multiple comorbidities (3,4).

TABLE 99.1
Causes of Upper Gastrointestinal Tract Bleeding

Most Common	
Peptic ulcer	35–66%
Gastroduodenal erosions	8–15%
Esophagitis	8–15%
Varices (esophageal and gastric)	5–10%
Mallory–Weiss tear	5%
Less Common	
Epistaxis, hemoptysis	
Aortoenteric fistula	
Boerhaave syndrome	
Carcinoma	
Vascular anomalies	
Caustic ingestion	
Anastomotic ulcer	

CLINICAL PRESENTATION

Patients present with a variety of GI symptoms, such as nausea, vomiting, and abdominal pain, as well as symptoms of acute blood loss, such as lightheadedness or syncope. UGIB classically presents with hematemesis and melena. Bright-red emesis suggests fresh blood with significant, ongoing hemorrhage. Both coffee-ground emesis and melenic stools signify a more subacute to chronic UGIB. Experienced clinicians sometimes make a presumptive diagnosis of UGIB based on the unique odor of melenic stool. Hematochezia is usually a result of lower GI hemorrhage but may occur in those with a massive UGIB and rapid GI transit (2,5,6). Furthermore, some patients with melena may have a lower GI source for their bleeding (7).

UGIB can result in varying degrees of blood loss, ranging from trivial, occult bleeding to fatal exsanguination. Patients may have underlying comorbid conditions that can complicate the interpretation of the vital signs. Hypovolemic patients often complain of thirst, apprehension, weakness, or lightheadedness. When reflex mechanisms can no longer fully compensate for volume

loss, hypotension develops and organ perfusion is impaired. This can result in oliguria, altered mentation, metabolic acidosis, and dyspnea. Some patients may not recognize that a black stool is a sign of bleeding. Melena must also be differentiated from black stools due to iron or bismuth, which do not have the tarry consistency and are guaiac-negative.

DIFFERENTIAL DIAGNOSIS

If the clinician can appropriately categorize the bleeding as having an upper or lower source, the differential may be more focused. However, it is not always possible to establish the location of bleeding in the ED. The appearance of the stool is often helpful but is sometimes misleading. In one study, the ingestion of 1000 mL of blood led to hematochezia, demonstrating that an upper rather than lower source may be the cause of hematochezia (8). Conversely, melena may be produced by as little as 50 mL of blood from an upper GI source (9).

The most frequent cause of UGIB is *peptic ulcer disease.* Hemorrhage results from erosion into an underlying vascular structure. Predisposing factors for peptic ulcers include cigarette smoking, ingestion of alcohol, nonsteroidal anti-inflammatory (NSAID) use, hereditary factors, and colonization with *Helicobacter pylori* (10,11). The rate of hemorrhage from peptic ulcer disease appears to be decreasing in the United States, possibly due to increased use of proton pump inhibitors (PPIs) and treatment for *H. pylori* (11).

Erosive gastritis is also a common cause of UGIB. The resultant bleeding can range from minimal to life-threatening, and the clinical presentation is often indistinguishable from that of a peptic ulcer. The most common predisposing factor is the use of NSAIDs. Other risk factors include use of alcohol, prolonged corticosteroid use, age, major trauma, burns, or head injury.

Esophageal and gastric *varices* are two of the most dangerous causes of UGIB. Varices should be suspected in patients with a history of cirrhosis or with other stigmata of liver disease. The

presence of hepatic dysfunction and other comorbidities further worsens the prognosis. Bleeding can be sudden and massive and is associated with an acute mortality rate between 15% and 53%. Patients with variceal hemorrhage also have a poor long-term prognosis, with a projected 1-year mortality of 70% (12).

Mallory–Weiss tears are longitudinal, *nontransmural* tears that occur at the gastroesophageal junction and are usually caused by recurrent forceful vomiting or retching. The history of sudden vomiting of bright-red blood after retching is characteristic, but this history is present in only one-half of patients with Mallory–Weiss tears. Risk factors include alcohol abuse, hiatal hernia, and underlying esophagitis. Bleeding usually stops spontaneously, and intervention is rarely required. Mallory–Weiss tears are differentiated from Boerhaave syndrome, which is a *transmural* tear of the esophagus that typically presents as chest pain, odynophagia, and pneumomediastinum *without* GI bleeding.

Other, less common conditions account for the remaining 10% of episodes of UGIB (see Table 99.1). *Aortoenteric fistula* occurs when an aortic aneurysm or a synthetic graft erodes into the small intestine, producing massive hemorrhage. Aortoenteric fistulas can occur within weeks to many years after the initial aneurysm repair, with one study reporting an average of 2.8 years (13).

Patients with small intestinal angiodysplasias may present with melena. This diagnosis is usually made on a small bowel examination after upper and lower endoscopies are negative.

ED EVALUATION

The first priority should be to identify and treat patients who are hemodynamically unstable. This assessment should start with the initial triage or in the prehospital setting. The goal is to rapidly assess the severity and location of bleeding and to determine whether the patient may have variceal bleeding.

Medications and allergies should be noted, with an emphasis on NSAIDs, acetylsalicylic acid, and anticoagulants. Patients who are anticoagulated have more severe bleeding and a higher mortality

(3,11,14,15). Use of iron products or bismuth (Pepto-Bismol) should be noted, as their use may mimic melena. Severe abdominal pain is unusual, as many causes of UGIB are painless. The review of systems should include symptoms consistent with hypovolemia (e.g., chest pain, dyspnea, light-headedness, or syncope). Those with a history of cirrhosis or alcoholism should be assumed to have variceal bleeding (14,16).

The physical examination should focus on finding evidence of bleeding and attempting to localize and quantify the blood loss. Hypotension may not be present until 30% to 40% of the circulating blood volume has been lost, though orthostatic changes occur with more modest losses. In an adult, a supine systolic blood pressure of $<$100 mm Hg, or an orthostatic pulse increase of $>$20 to 30 beats per minute, suggests an acute blood loss of at least 1 L. However, orthostatic vital signs are not reliable, especially at the extremes of age. Although tachycardia is usually present after acute blood loss, it is not a reliable finding. Flat neck veins; cold, mottled extremities; altered mental status; or pallor are all suggestive of significant acute blood loss.

The nose and oropharynx should also be examined for potential bleeding sources. Stigmata of chronic liver disease (jaundice, ascites, and spider angiomata) are concerning for variceal bleeding. Ecchymosis, gingival bleeding, and epistaxis suggest a coagulopathy or platelet deficit.

Digital rectal examination and stool appearance are important parts of the early evaluation. The presence of gross blood should be noted. Not all black stool is melena, so it should be tested to confirm the presence of blood. Abdominal tenderness can be associated with perforated peptic ulcer or gastritis.

Initial laboratory evaluation should include a complete blood count, electrolyte panel, blood urea nitrogen (BUN), creatinine levels, liver function tests, and coagulation studies. Unless the bleeding seems minimal, patients should also have a type and screen or crossmatch for blood. An elevated BUN is often seen in the setting of a UGIB, and a BUN-to-creatinine ratio of $>$30 increases the likelihood of UGIB (17,18). The hemoglobin and hematocrit can

be normal immediately after massive blood loss. Elderly patients should be evaluated for myocardial ischemia. A chest radiograph is indicated if aspiration, esophageal rupture, or cardiopulmonary complications are suspected. Abdominal films may be helpful in the subset of patients with suspected perforation or bowel obstruction, but computed tomography scan is more definitive.

The placement of a nasogastric (NG) tube may be considered in select patients with UGIB; however, routine placement is controversial (1,11,19). NG tube placement has been reported to be one of the most painful procedures performed in the ED (20). More importantly, a negative aspirate does not rule out a significant source of bleeding. NG placement may provoke vomiting, and aspiration and a recent study demonstrates that NG tube placement does not decrease mortality or the length of stay in a hospital (17,21,22). The poor sensitivity and specificity of an NG tube aspirate has been well described (1). In patients with melena but no hematemesis, the finding of fresh blood may be useful, but this information comes at the expense of significant discomfort to the patient (19). The early use of endoscopy can provide much more information. NG aspiration also misses up to 25% of bleeding duodenal ulcers, because it does not reliably sample material past the pylorus. Thus, making disposition decisions based on a negative aspirate is risky. Of note, varices are not a contraindication to NG tube placement.

KEY TESTING

- CBC, platelets, coagulation studies, type, and screen
- Stool guaiac test

ED MANAGEMENT

Initial resuscitation efforts should be guided by the estimated severity of bleeding. Patients with significant bleeding should be placed on a cardiac monitor, receive supplemental oxygen, and have intravenous access established with two large-bore catheters. Close attention to airway, breathing, and circulation is paramount.

Critically ill patients, those with massive bleeding or altered mental status, usually need endotracheal intubation (2,5).

Intravenous fluid resuscitation to maintain blood pressure is essential. If the patient's condition has not substantially improved after IV fluids and ongoing hemorrhage is suspected, blood transfusion is indicated. Crossmatched blood is preferred, but those in extremis may require type-specific or type O blood. The appropriate transfusion thresholds and targets during emergency care have not been established, and in acute hemorrhage, hemoglobin values can be misleading since compensatory hemodilution may lag by several hours. A normal hemoglobin concentration thus does not exclude an acute massive hemorrhage. After admission, a restrictive approach involving blood transfusion below hemoglobin levels of 7 g per dL improves clinical outcomes, although this benefit has not been demonstrated in the emergency setting (23). The decision to transfuse should also take into account the patient's symptoms and hemodynamics, and the physician's estimate of ongoing blood loss. Warmed blood should be used in patients who require massive transfusion, and if a large number of packed red blood cells (PRBCs) have been transfused one may consider initiating a "massive transfusion protocol" involving administration of blood, platelets, and fresh frozen plasma (FFP) in a 1:1:1 ratio. Massive transfusion protocols may help prevent the dilutional coagulopathy that results from the administration of large quantities of packed red blood cells, although evidence for improved outcomes in UGIB is lacking.

Coagulopathy and thrombocytopenia should be corrected as needed. Current recommendations are to resuscitate with FFP until the patient reaches an INR < 2.7 and to maintain the platelet count above 50×10^9/L (24,25). Platelet transfusion may also be considered in the presence of qualitative platelet defects due to NSAID or aspirin use. There is no current evidence to justify the routine use of factor VII or tranexamic acid (TXA) in UGIB (25–27). In a *stable,* coagulopathic UGIB patient the decision to use plasma or vitamin K should be based on the medical cause of coagulopathy (e.g., warfarin for chronic atrial fibrillation versus cirrhosis) (28).

An ongoing assessment of vital signs, general clinical status, and urine output will help to guide resuscitative efforts. In patients with massive bleeding, early consultation with a gastroenterologist, an intensivist, and possibly a surgeon or an interventional radiologist should be arranged. Further treatment of UGIB depends on whether the bleeding is nonvariceal or variceal.

Nonvariceal Bleeding

Pharmacologic therapy in nonvariceal UGIB centers on acid suppression. Gastric acid impairs clot formation, and many common causes of UGIB (e.g., ulcers, gastritis, esophagitis, and duodenitis) respond well to PPIs. High-dose intravenous PPIs decrease the need for endoscopic therapy, and consensus guidelines recommend starting high-dose PPI therapy prior to endoscopy (1). Nevertheless, no current evidence demonstrates that PPIs decrease mortality, risk of rebleeding at 30 days, or risk of surgery in patients with UGIB (29). A commonly recommended regimen is omeprazole 80 mg as an IV bolus, followed by 8 mg/hr for 3 days (11). H_2 blockers have no role in the treatment of acute UGIB since they do not consistently raise the pH, and studies have failed to show any benefits (1).

Endoscopy is the most important diagnostic and therapeutic tool in UGIB. Endoscopy can identify the cause of bleeding, may provide prognostic information, and allows for the administration of endoscopic therapy (3,5,30,31). Patients with high-risk endoscopic findings such as active bleeding or a visible vessel require emergent endoscopic therapy (1), the main techniques being thermocoagulation and injection therapy. Patients with low-risk endoscopic findings (e.g., flat-based ulcer) do not require endoscopic treatment or high-dose PPI therapy but may benefit from standard oral PPI therapy as outpatients. Occasionally, endoscopy and pharmacologic therapy fail to stop the bleeding, and emergent surgery or angiography must then be considered (1,4). Angiographic therapy is gaining popularity for high-risk patients who cannot tolerate a major surgical procedure.

Variceal Bleeding

Variceal bleeding occurs mainly in patients with advanced cirrhosis and is associated with complications related to hepatic dysfunction such as coagulopathy, sepsis, renal failure, and hepatic encephalopathy. Overresuscitation is also a concern, as this increases portal pressure and may increase the risk of rebleeding.

Early endoscopy is critical in these high-risk patients since it may enable definitive therapy. However, endoscopy is often delayed due to logistical issues or patient instability. Pharmacologic therapy is utilized to decrease portal pressures. Octreotide, a synthetic analog of somatostatin, reduces portal hypertension. Although no mortality benefit has been established, octreotide improves endoscopic visualization and hemostasis (32,33). It has largely replaced vasopressin due to its better safety profile (32). The dose is 25 to 50 μg/hr by infusion.

Patients with variceal hemorrhage are also susceptible to bacteremia and infections such as pneumonia, spontaneous bacterial peritonitis, and urinary tract infection. Empiric treatment with a third-generation cephalosporin or a fluoroquinolone improves outcomes (34,35).

Endoscopic therapy for varices is divided into two types: sclerotherapy and band ligation. In the former, sclerosing agents are injected into the esophageal vessels, causing thrombosis and eventual necrosis. Band ligation involves endoscopic placement of a rubber band around the varix, inducing obstruction and eventual tissue necrosis that obliterates the varix. This is the preferred endoscopic approach, though it is technically more difficult (14,16). Gastric varices are deeper and more difficult to treat. The direct injection of tissue adhesive is becoming more widely used.

When endoscopy and pharmacologic therapy have been unsuccessful or unavailable, balloon tamponade can be a lifesaving measure. The *Sengstaken-Blakemore tube,* the *Minnesota tube,* and the *Linton tube* are specialized inflatable NG tubes that apply direct pressure to the bleeding varix. However, the use of these tubes is associated with a number of complications, including esophageal

rupture, pulmonary aspiration, and airway compromise. The tubes come with an explicit list of instructions that should be reviewed prior to their use, and they are best placed by an experienced practitioner. The Linton tube does not have an esophageal balloon, but it may be better at controlling gastric varices. Endotracheal intubation is recommended prior to placement (12,16).

More drastic measures are sometimes needed to reduce portal pressure. Transjugular intrahepatic portosystemic shunt is extremely effective at controlling refractory variceal bleeding. This involves the placement, by an interventional radiologist, of an expandable metal stent across a tract between a hepatic vein and a hepatic branch of the portal vein. Surgical treatment of variceal bleeding is much less common since the advent of transjugular intrahepatic portosystemic shunt and is now typically limited to portocaval shunts in patients with very-well-compensated stable liver disease. Orthotopic liver transplantation is considered in selected patients (12,14,16).

CRITICAL INTERVENTIONS

- Aggressively volume resuscitate patients with UGIB and clinical signs of shock.
- Consider early blood transfusion.
- Reverse coagulopathy as needed (platelets, FFP, and vitamin K).

DISPOSITION

Risk scores have been designed to predict rebleeding and mortality in UGIB. Commonly used scores include the Rockall score and the Glasgow–Blatchford Bleeding Score (GBS). The GBS has been more extensively used (Table 99.2). An advantage of the GBS is that it does not require NG aspirate or endoscopy (17). A GBS of 0 is seen in up to 22% of UGIB patients and predicts that emergent medical care is not required; outpatient evaluation may thus be considered (17,36,37). Most other risk stratification models rely on the endoscopic appearance of the culprit lesion, which typically cannot be obtained in the ED.

TABLE 99.2
Glasgow–Blatchford Score

	Score
Blood Urea	
6.5–7.9	2
8.0–9.9	3
10.0–24.9	4
≥25	6
Hemoglobin (g/L) for Men	
12–12.9	1
10–11.9	3
<10.0	6
Hemoglobin (g/L) for Women	
10–12	1
<10.0	6
Systolic Blood Pressure (mm Hg)	
100–109	1
90–99	2
<90	3
Other Markers	
Pulse ≥100 (per min)	1
Presence of melena	1
Syncope	2
Hepatic disease	2
Congestive heart failure	2

Nonvariceal Bleeding

Most patients with UGIB due to a nonvariceal source should be admitted to the hospital, but carefully selected, stable patients with minimal blood loss may be safely discharged from the ED with close follow-up (Table 99.2). Endoscopic criteria can help to identify patients who can be safely managed as outpatients, since the risk of rebleeding is associated with certain endoscopic findings (Table 99.3) (38). This approach has the potential to identify a large subset of patients who may be discharged. Candidates for outpatient management must have reliable access to close outpatient follow-up

and a demonstrated history of compliance with medical instructions. They should receive an oral PPI, should be told to avoid NSAIDs, and should be given clear instructions on reasons to return immediately for further medical attention.

TABLE 99.3
Endoscopic Appearance of Ulcers and Risk of Rebleeding (5)

Endoscopic Finding	Risk Stratification	Risk of Rebleed (%)
Clean base	Low risk	3
Flat spot	Low risk	7
Adherent clot	High risk	33
Visible vessel	High risk	50
Active bleeding	Highest risk	80

Patients who are unstable or have multiple adverse prognostic factors should be admitted to the ICU (Table 99.4). Although UGIB will stop spontaneously in many cases, up to 20% of patients may have continued or recurrent bleeding, with the risk of rebleeding being highest in the first 72 hours (1,38).

TABLE 99.4
Intensive Care Unit Admission Guidelines for Patients with Upper GI Bleed

Unstable vital signs in the ED
Persistent bleeding that does not clear with lavage
Advanced age (older than 75 years)
Presence of coagulopathy
Portal hypertension or ascites
Severe anemia (e.g., hematocrit <20%)
Large drop in hematocrit (>8%)
Unstable comorbid disease (e.g., unstable coronary artery disease, chronic obstructive pulmonary disease, renal insufficiency, peripheral vascular disease, cerebrovascular disease)
Endoscopic findings of a "visible vessel" or an "overlying clot" or a variceal source
Use of esophageal tamponade balloon

UGIB, upper gastrointestinal bleeding; ED, emergency department.

Variceal Bleeding

The prognosis of patients with variceal bleeding is usually related to the severity of associated liver disease, and all such patients should be admitted. These patients frequently require critical care services. Early consultation with a gastroenterologist is imperative (12,14,16).

If the necessary critical care and consultant services are not readily available, the UGIB patient should be transferred to a facility with the necessary resources.

Common Pitfalls

- Underestimation of blood loss. Some patients can lose up to 20% to 30% of their blood volume and yet maintain a relatively normal blood pressure in the supine position. Moreover, patients with significant bleeding can have a normal initial hematocrit.
- Overreliance on a negative NG aspirate.
- Failure to recognize aortoenteric fistula as a cause of sudden massive hematemesis.
- Failure to involve a surgeon and/or interventional radiology in cases of massive hemorrhage with failed endoscopy.
- Treatment of hypovolemic shock with vasopressors instead of volume resuscitation.

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CHAPTER 100

Lower Gastrointestinal Bleeding

Kenny V. Banh

Lower gastrointestinal bleeding (LGIB) is a common complaint of patients who present to the emergency department (ED), but is less significantly less common than upper gastrointestinal bleeding (UGIB), with an estimated annual incidence of 20 to 27 cases per 100,000 adults, compared to 100 to 200 cases per 100,000 for UGIB (1). The mortality rate for LGIB ranges from 2% to 4% (1).

The spectrum of illness is clinically broad, ranging from minor anorectal disorders to severe and life-threatening bleeding that results in hypovolemic shock and death. Depending upon the volume and rate of bleeding, patients can rapidly deteriorate in the ED. Therefore the clinician and ED staff must remain vigilant in the monitoring and care of these patients.

CLINICAL PRESENTATION

LGIB is defined as arising distal to the ligament of Treitz, which is the suspensory muscle of the duodenum. This includes bleeding from the distal one-fourth of the duodenum and from the jejunum, ileum, colon, rectum, and anus.

The appearance of the stool may provide a suggestion as to the location of the bleed, but is not an absolute indicator of the anatomic origin of the bleed. The terms *melena* and *hematochezia* are common descriptors of gastrointestinal bleeding. Melena appears as black, tarry stool and usually reflects the presence of blood that has

remained in the gastrointestinal tract for longer than 8 hours. Melena is approximately four times more likely to reflect an UGIB (2). *Hematochezia,* described as bright red or maroon stool, usually indicates an LGIB. It is about six times more likely to be caused by a lower gastrointestinal source than an upper source (2). However, 10% to 15% of patients with UGIB present with bright red blood coming from the rectum, as may occur with brisk bleeding and rapid transit of blood (3). Small amounts of bright red blood may come from minor anorectal sources and may be noticed on the outside of the stool or toilet paper following a bowel movement. Drops of blood from an anorectal source, when diffused in the toilet water, may cause patients to overestimate the volume and severity of the bleeding (4).

Because patients are not always aware of GI bleeding, clinicians should consider this diagnosis in patients who present with other concerning symptoms and signs such as hypotension, tachycardia, angina, syncope, weakness, confusion, stroke, myocardial infarction (MI), shock, or cardiac arrest.

DIFFERENTIAL DIAGNOSIS

Hemorrhoids and anal fissures are common, but rarely result in massive hemorrhage. Hemorrhoids are associated with chronic constipation, straining, low-fiber diet, and pregnancy. Patients may describe small amounts of bright red blood, pruritus ani, a protruding mass, pain with defecation, or pain when sitting on a hard surface. Hemorrhoids are divided into two major types. External hemorrhoids are found below the dentate line in well-innervated squamous epithelium and present with pain. Internal hemorrhoids originate above the dentate line and are classically seen at 2, 5, and 9 o'clock on anoscopy. *Anal fissures* are usually associated with hard stools but may also be seen with diarrhea. They present with extremely painful defecation; 90% are located in the posterior midline (5).

Anorectal varices are caused by portal hypertension of chronic liver disease and appear as discrete, bluish-gray submucosal veins.

They are usually more compressible and serpiginous than internal hemorrhoids and extend below the dentate line (5). Anorectal varices may cause severe rectal bleeding.

Rectal foreign bodies that cause tears need immediate surgical consultation. Improper technique or delay in removal of a retained rectal foreign body may cause perforation with subsequent infection and bleeding. Broken glass and other sharp retained foreign bodies pose the greatest risk for rectal tears and bleeding (6).

Ulcerative colitis affects the colon and rectum and presents with bloody stools, crampy abdominal pain, and tenesmus. Lesions involve both the mucosa and the submucosa. Distal disease is usually more severe. *Crohn disease* has a bimodal distribution of age of onset with peaks occurring in the 20s and at around age 70. The disease involves all layers of the bowel wall and lymph nodes. Any section of the gastrointestinal tract is vulnerable, but the distal ileum is the most commonly affected site. When present, colonic involvement is usually patchy with rectal sparing (5). During flares, patients describe bloody diarrhea, abdominal pain, fever, and weight loss.

Pseudomembranous colitis usually presents after the patient has been taking broad-spectrum antibiotics and is caused by the subsequent overgrowth of *Clostridium difficile.* Patients present with fever, crampy abdominal pain, and watery or bloody diarrhea, usually 7 to 10 days after a course of antibiotics but sometimes more remote. Pseudomembranous colitis rarely causes severe bleeding. The diagnosis can be confirmed by sending stool for *C. difficile* toxin or by finding the characteristic pseudomembranes on colonoscopy (7).

Infectious diarrhea, most commonly bacterial, may be associated with a significant inflammatory response and blood and mucus in the stool ("dysentery"). There is typically an abrupt onset with cramping abdominal pain. *Human immunodeficiency virus* (HIV)–related causes of gastrointestinal bleeding include cytomegalovirus colitis, Kaposi sarcoma, and gastrointestinal lymphoma (7).

Radiation colitis or *proctitis* most commonly occurs after radiation for cervical or prostate cancer. The onset of bleeding usually occurs

between 9 and 15 months following radiotherapy, but it may occur as far out as 41 months (1). Acute radiation colitis presents with rectal pain, diarrhea, and rectal bleeding.

Diverticulosis is described as the most common cause of severe LGIB in adults. In adults, diverticulosis and angiodysplasia together account for nearly 80% of significant lower gastrointestinal bleeds (8). Patients usually present with painless bleeding, which may be of a large volume. Diverticula are sac-like herniations (2 to 5 mm in greatest dimension) of the colonic mucosa and are most common in the sigmoid colon. The diagnosis should be considered in all patients older than 40 years of age. The prevalence increases with each decade of life, and more than 50% of patients have diverticula by age 60 (5). Other risk factors include living in industrialized countries and a diet that is deficient in fiber, high in fat, and high in red meat.

Angiodysplasias often bleed chronically and may present with occult fecal blood or iron-deficiency anemia. Angiodysplasias may also present as acute bleeding with hematochezia. This disease is more common in the elderly, in patients with renal failure, and in those with hereditary hemorrhagic telangiectasia (*Osler–Weber–Rendu* syndrome) (7).

Mesenteric ischemia most commonly presents in patients older than 50 years of age, especially in those with underlying cardiovascular disease. It is an uncommon but dangerous cause of LGIB. Risk factors also include atrial fibrillation, coronary artery disease (CAD), congestive heart failure (CHF), recent MI, valvular heart disease, hypercoagulable states, and hypotension. Specific causes include arterial embolus, venous thrombosis, atherosclerosis, external compression of vessels, and low flow states. The sudden onset of abdominal pain that is out of proportion to examination findings, especially with heme-positive stools, is suggestive of mesenteric ischemia.

Colonic polyps may cause LGIB and can be diagnosed and removed at colonoscopy. Postpolypectomy bleeding, although not common (up to 0.4%) (9), may be quite severe. Early bleeding most likely occurs because there is inadequate hemostasis of the blood vessel in

the stalk of the polyp. Later bleeding (up to 15 days following the procedure) may occur as a result of sloughing of the clot (1).

Colon cancer accounts for approximately 10% of major intestinal bleeding and 20% of minor bleeding in the elderly (1). Advanced colon cancer presents with altered bowel patterns, abdominal pain, involuntary weight loss, rectal bleeding, and anemia. Distal colon or rectal cancer may also cause a change in the caliber of the stools.

Aortoenteric fistula must be considered in patients who have abdominal aortic grafts and develop gastrointestinal bleeding.

ED EVALUATION

The initial assessment should include the patient's general appearance, vital signs, and mental status. Relevant questions include a history of colonic polyps, cancer, inflammatory bowel disease, or recent travel with bloody diarrhea. Medication use is also important, because there is an association between aspirin or nonsteroidal anti-inflammatory drug (NSAID) use and LGIB (1).

Orthostatic vital signs may be helpful in patients with significant blood loss without overt hemodynamic instability, but they are neither sensitive nor specific. Blood loss estimates per patient history are frequently inaccurate. Other clues that may be helpful in establishing a diagnosis include skin lesions such as telangiectasia, bruises, or petechiae. Hyperpigmentation of the lower abdomen may suggest previous radiation therapy. Diverticulosis, angiodysplasia, and cancer are unusual before the age of 40. Likewise, Meckel diverticulum rarely presents after adolescence (2). Stigmata of liver disease (ascites, jaundice, spider angiomata, and caput medusae) suggest the possibility of anorectal varices.

Abdominal tenderness may indicate an inflammatory condition or ischemic colitis (10). The perianal region and rectum should be carefully examined, both externally and by digital rectal examination, to check for masses, strictures, hemorrhoids, and blood. Stool should be tested for the presence of occult blood using the guaiac test. False-positive results may be seen with ingestion of red fruits, meat, iron, and bismuth.

Laboratory testing may be helpful, including measurement of hemoglobin, hematocrit, platelets, prothrombin (international normalized ratio [INR]), and partial thromboplastin time (PTT). A routine type-and-screen is recommended unless blood loss is significant or ongoing, demonstrating the need to crossmatch blood. Other laboratory studies that may be useful include a liver profile, blood urea nitrogen (BUN), creatinine, and electrolytes. Lactate and anion gap should be measured if mesenteric ischemia is suspected, but these tests may be normal early in the course of the disease. Likewise, the initial hematocrit may not accurately reflect the amount of acute blood loss. Cardiac ischemia can occur in gastrointestinal bleeding because of decreased oxygen delivery; therefore, an electrocardiogram should be performed, and supplemental oxygen should be administered if ischemia is suspected.

It is important to determine whether the bleeding is a result of LGIB or UGIB. Aspiration of the gastric contents with a nasogastric tube may be helpful if the source is unclear, though the value of this procedure is controversial. Gastric lavage may be falsely positive if the nasogastric tube insertion was traumatic (causing nasal trauma). Conversely, lavage is often negative in the presence of an UGIB when the source is distal to the pylorus.

Anoscopy may reveal an anorectal source of bleeding or may show bleeding from above the reach of the anoscope, suggesting a more proximal cause of bleeding. To perform this examination, place the patient in the lateral decubitus or knee–chest position. Lubricate the anoscope, insert it (with obturator) until the flange rests at the anal verge, and remove the obturator. Shine a bright light (e.g., an otoscope, penlight, or flashlight) into the center of the anoscope and visualize the rectal mucosa and stool above the opening to look for bleeding coming from above the anoscope. Finally, withdraw the anoscope slowly to look for anorectal disorders such as bleeding hemorrhoids, proctitis, or fissures. Although the presence of blood proximal to the anoscope may be seen with retrograde passage of blood, it usually indicates a more proximal bleed and should be further investigated.

Abdominal x-rays are rarely indicated in LGIBs unless perforation or bowel obstruction is suspected. Multidetector computed tomography should only be considered for the evaluation for tumor, mesenteric ischemia, or perforation.

Radionuclide scintigraphy (i.e., technetium-labeled red cell scan) remains controversial and is rarely applicable to the ED setting. The test localizes bleeding, and it can detect bleeding rates as low as 0.05 to 0.1 mL/min, therefore appearing to be more sensitive than angiography. However, it has variable accuracy and often does not change management (11).

Colonoscopy, in addition to identifying anorectal disorders, can diagnose many causes of lower gastrointestinal hemorrhage, including diverticulosis and angiodysplasia. Unfortunately, in emergent cases, the bowel is not adequately prepared, and the presence of stool can obscure lesions. Emergency colonoscopy in acute LGIB can miss the diagnosis in 40% of cases, especially in small bowel bleeding below the ligament of Treitz (12). Whether the best initial diagnostic procedure is colonoscopy or angiography (discussed below) is controversial (13). These decisions are commonly dependent upon the institution and consultant preferences.

KEY TESTING

- Test stool for gross or occult blood
- Serum hemoglobin and basic laboratory studies
- Anoscopy may help identify a distal bleeding source

ED MANAGEMENT

Adherence to a systematic approach to LGIB will help the clinician to be adequately prepared for sudden clinical deterioration. With any suspicion of significant blood loss, the patient should be placed on a monitor, oxygen should be administered, and intravenous access should be obtained with two large-bore intravenous catheters. Crystalloid solutions should be administered, and the fluid status should be evaluated frequently. While a restrictive transfusion

strategy has recently been supported for UGIB, this practice is not well studied in LGIB (14). Of critical importance is the generous use of blood products including packed red blood cells, platelets, and fresh frozen plasma in symptomatic, hypotensive, or hemodynamically unstable patients.

Surgical consultation should be considered when the patient is persistently unstable despite treatment, when there has been massive bleeding or when perforation is strongly suspected. Older patients usually need more aggressive surgical management (15). Patients presenting with gastrointestinal bleeding who have abdominal aortic grafts should have urgent vascular surgery consultation because of the possibility of an aortoenteric fistula.

Angiography has both diagnostic and therapeutic value. It is more commonly used in the evaluation of LGIB than UGIB, but should be considered in consultation with a surgeon and an interventional radiologist. A fairly brisk bleeding rate of at least 1 mL/min is required for angiography to be diagnostic (16). Although angiography rarely identifies the specific cause of the bleeding, it can help to identify the location, which can facilitate limited bowel resection during surgery (12). Available catheter-based interventional angiography techniques include intra-arterial infusion of vasopressin and arterial embolization. Unfortunately, when the infusion is stopped, the vasoconstrictive effects of vasopressin dissipate rapidly, so a stable clot must be formed and retained to prevent rebleeding. Recurrent hemorrhage is common occurring in 36% to 43% (17).

Arterial embolization used to be reserved for UGIB, because bowel infarction was a frequent complication of embolization in LGIB. However, with modern embolization techniques, clinically significant bowel ischemia has become an uncommon complication (17). Angiography is associated with a combined complication rate of 2% to 9%. These include hematomas, arterial dissection, renal failure, contrast allergy, and bowel ischemia and infarction.

Colonoscopy, besides its diagnostic value, may also be used therapeutically to ablate bleeding sites, but it fails to stop the bleeding in about 20% of cases (12).

Thrombosed external hemorrhoids can be excised under local anesthesia if pain is severe. Hemorrhoids and anal fissures are best treated with stool softeners, increased fiber, sitz baths, and external analgesics (see Chapter 114).

Treatment for ulcerative colitis and Crohn disease include analgesia, corticosteroids, sulfasalazine, and metronidazole (see Chapter 111). Pseudomembranous colitis is treated with oral vancomycin or metronidazole. Infectious diarrhea is treated with appropriate antibiotics to which the pathogen is sensitive (see Chapter 112).

CRITICAL INTERVENTIONS

- Initiate aggressive resuscitation in hypovolemic patients with LGIB, using crystalloid and blood as needed.
- Obtain emergent surgical consultation for unstable patients.

DISPOSITION

Optimizing the management of patients with gastrointestinal bleeding involves stratification of the risk of rebleeding and mortality. Evaluating these criteria can help the clinician to make management decisions such as (i) hospitalization versus outpatient treatment; (ii) admission to an unmonitored bed, a monitored bed, or an intensive care unit bed; (iii) emergency versus elective endoscopy; (iv) timing and number of packed red blood cell transfusions; and (v) diagnostic angiography versus conservative therapy (18).

Factors predicting rebleeding and mortality include age older than 60 years, comorbidity (particularly liver disease, renal disease, pulmonary disease, encephalopathy, cancer, recent major surgery, trauma, or coexisting disease in three-organ systems), low hematocrit, melena, hematochezia, or prolonged PT. Other factors include requiring more than 5 U of packed red blood cells, tachycardia, hypotension, shock, elevated serum transaminases, and elevated serum creatinine (18). Mortality in elderly patients has been shown to be 16% to 25% higher than in younger patients.

Mortality increases by 25% to 70% in patients who require transfusion of more than 5 U of packed red blood cells. Patients with high-risk criteria should be admitted to the intensive care unit. Patients who are at low risk can be admitted to the floor and have arrangements made for colonoscopy.

If the cause of LGIB is determined to be hemorrhoids, proctitis, or fissures and there is no evidence of portal hypertension, the stable patient may be discharged home with treatment and follow-up.

Common Pitfalls

- Failure to appreciate the significance and volume of LGIB or to anticipate the possibility of rapid clinical deterioration.
- Failure to adequately resuscitate the patient with crystalloid fluids and blood.
- Failure to consider gastrointestinal bleeding in patients who present with other seemingly unrelated complaints such as syncope, angina, MI, weakness, dyspnea, altered mental status, or shock.

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CHAPTER 101 Peptic Ulcer

Dale S. Birenbaum and Justin D. Britton

Peptic ulcer disease (PUD) affects almost 1 in 10 Americans. There are approximately 500 000 new cases of PUD and four million recurrent cases in the United States each year (1). Over the past three decades the incidence and prevalence of PUD has been on the decline (2). The decline is largely due to the discovery and treatment of *Helicobacter pylori* (*H. pylori*) in the 1980s. Despite this great advance in PUD management, it still remains a significant problem with the increasing use of nonsteroidal anti-inflammatory drugs (NSAIDs) and Aspirin in the aging population with coronary artery disease and arthropathy.

The estimated annual cost of PUD is about $10 billion in direct and indirect costs (1). The management of PUD has significantly changed over the last half century. Initially, PUD was thought to be due to stress and diet, but in the 1950s, it was found that gastric acid plays an important role in the development of an ulcer. Treatment of PUD evolved from dietary modifications, vagotomy, and acid suppression with H2 receptor antagonist to more potent proton pump inhibitors (PPIs) in the late 1980s. Elective peptic ulcer surgery declined between 80% and 97% in the 1980s with the development of acid-suppressive therapy (3). The discovery of *H. pylori*'s role in PUD has reshaped modern management and changed PUD from a chronic reoccurring disease to a potentially curable one. Antimicrobial therapy has since been tailored to *H. pylori* eradication and has thus decreased hospitalization, complication rates, and ulcer recurrences (4).

PATHOPHYSIOLOGY

The mechanisms leading to gastric and duodenal ulcers are due to an imbalance between the mucosal protective barrier and destructive acidic environment. Healthy gastric or duodenal mucosa provides an impressive barrier to the diffusion of hydrogen ions and can maintain a gradient of 3 million to 1 between the lumen and blood. It also secretes bicarbonate and mucus, which form a buffering gel over the mucosa. Mucosal gel thickness is increased by the E-prostaglandins and diminished by Aspirin and NSAIDs.

H. pylori is a small microaerophilic gram-negative spiral bacterium which was associated with up to 90% of duodenal and 80% of gastric ulcers in the 1980s, but more recent studies have shown that the prevalence has declined (5). *H. pylori* is uniquely adapted to survive in the acidic environment of the stomach. It does so by producing a large amount of urease, an enzyme that catalyzes the breakdown of urea to alkaline ammonia and carbon dioxide, which allows the bacteria to be protected in this alkaline milieu (6). *H. pylori* induces chronic inflammation, abnormal acid output, decreased bicarbonate secretion, and causes gastric metaplasia which all contribute to ulcer formation. Eradication of *H. pylori* has been shown to greatly reduce the incidence of ulcer recurrence from 67% to 6% in duodenal ulcers and 59% to 4% in gastric ulcers (7). Its eradication from the gastrointestinal (GI) tract on first detection has been routinely advocated; this treatment strategy has been associated with accelerated ulcer healing, a reduced rate of ulcer recurrence, and cure of the disease (8).

Several factors have a role in the pathogenesis of stress-related mucosal disease (SRMD), including mechanical ventilation longer than 48 hours, burns, coagulopathy, moderate to severe trauma, head or spinal cord injury, liver failure, and organ transplantation. Endoscopic signs of SRMD include multiple subepithelial petechiae progressing to superficial erosions and in some cases discrete ulceration in the gastric fundus. Because of their diffuse nature these ulcers are generally not amendable to endoscopic therapy (9). H2

blockers, PPIs, and early enteral nutrition have all been shown to decrease the risk of obtaining a SRMD (10).

Many factors predispose to the development of ulcers (Table 101.1).

TABLE 101.1
Risk Factors for Peptic Ulcer Disease

Helicobacter pylori
Nonsteroidal anti-inflammatory drugs
Aspirin
Acid hypersecretory conditions (Zollinger–Ellison)
Family history
History of prior ulcers
Associated disease (COPD, cirrhosis, chronic renal failure)
Male gender
Advanced age
Smoking

COMPLICATIONS

In the United States, hemorrhage is the most common complication and accounts for 73%, followed by perforation 9% and obstruction 3% (11). The demographics of *H. pylori* prevalence and PUD complications have been shifting toward the later years of life, and there has been a significant decrease in the hospitalization rate over the last decade (11).

Hemorrhage occurs in 10% to 20% of patients. The bleeding from peptic ulcers is usually self-limited, but occasionally massive and life-threatening with mortality between 5% and 10%.

Perforation continues to occur in peptic ulcer patients despite the availability of reasonably effective medical treatment (12). Perforation can present with sudden or gradual symptoms, but either way this is a surgical emergency.

Gastric outlet obstruction is usually the result of fibrous tissue from chronic scarring or edema from an active ulcer, and is more common in duodenal ulcer. Massive distention of the stomach can

occur; volume depletion and electrolyte disturbances may be dramatic. However, almost 70% of cases resolve without surgery.

Penetration is similar to perforation, but rather than the ulcer eroding into the peritoneal cavity, it erodes into an adjacent organ. Penetration can occur into the pancreas, omentum, biliary tract, liver, colon, and vascular structures.

Malignancy can be characterized by a chronic nonhealing ulcer that continues to give problems despite acid-suppressive therapy or *H. pylori* eradication. *H. pylori*-positive patients are at a higher risk of gastric carcinoma, and *H. pylori* is considered to be a carcinogen.

CLINICAL PRESENTATION

PUD has a classic symptomatology, but these features are not always specific in ulcer localization. Gastric ulcers cause pain shortly after eating when acid production is high. This has led to anorexia and weight loss in up to 50% of patients with gastric ulcers. Duodenal ulcers are painful 2 to 5 hours after a meal or between 2 and 3 AM when there is no bicarbonate or food to buffer the ulcer from the acid. Symptoms are often relieved with antacids, thus many patients do not seek medical attention.

Most patients present to the emergency department (ED) because of constant burning, gnawing, or aching pain. The pain of PUD is primarily epigastric, but it can be localized anywhere in the upper abdomen.

Asymptomatic peptic ulcers are not uncommon and abdominal pain may be absent in up to 30% of elderly patients (13). Uncomplicated PUD does not produce remarkable physical findings. Epigastric tenderness may be noted, but guarding and rebound are not present. Bowel sounds are usually normal, and there is no organomegaly. Rectal examination may show guaiac-positive stool if there has been unrecognized bleeding.

Guarding, rebound, and a tense abdomen signal perforation of an ulcer. Patients with perforation usually lie perfectly still, because the slightest movement produces intense peritoneal pain. In the

elderly, findings may be minimal or absent, which tends to delay the diagnosis.

Hemorrhage from PUD may cause surprisingly few physical findings on examination. A history of melenic stools should be sought, and orthostatic vital signs may help uncover clinically important but nonobvious bleeding. Many patients present with hematemesis, but nearly a third with ulcer perforation and a fifth of those with upper GI hemorrhage have no previous symptoms of ulcer disease.

Gastric outlet obstruction usually produces some degree of nausea, vomiting, and a distended abdomen. The patient may get some relief with vomiting or nasogastric suctioning.

DIFFERENTIAL DIAGNOSIS

Cardiac disease is one of the more serious diagnoses to consider in a patient with pain anywhere from the chest to epigastrium. Acute coronary syndrome may present atypically with epigastric pain, nausea, bloating, and burning sensation similar to those of PUD. A careful history and electrocardiographic (ECG) examination can help differentiate heart disease.

Many medical conditions of the GI track can present with pain or burning in the epigastrium: functional dyspepsia, gastroesophageal reflux disease (GERD), gastritis, gastric carcinoma, biliary tract disease, and acute pancreatitis. History, physical examination, laboratory test, and imaging when indicated can help rule out many of these disorders.

ED EVALUATION

PUD is a clinical diagnosis based on adequate history and physical examination. The diagnosis is confirmed by direct visualization through endoscopy, which is not typically performed in the ED. Management in the ED focuses on ruling out life-threatening problems and complications. Specific studies to diagnose *H. pylori* take time and therefore are not routinely ordered in the ED.

Bleeding is a common complication of PUD; so a complete blood count is typically used to assess for significant blood loss. Type and screen is also necessary if the patient will need blood products. Red cell indices may indicate a more chronic source. The white cell count is usually normal in uncomplicated PUD but can rise with any stressful event like perforation. Serum lipase is helpful if pancreatitis is in the differential. Electrolytes, blood urea nitrogen, and serum creatinine are useful if the patient is critically ill, has significant vomiting, or has a gastric outlet obstruction. Liver function tests, including alkaline phosphatase and bilirubin levels, may be useful to delineate hepatobiliary disease.

A nasogastric tube should be placed in the presence of gastric outlet obstruction. The need for a nasogastric tube for upper GI bleeding has questionable value. Aspiration of bloody fluid through a nasogastric tube that does not clear with gastric irrigation may help the gastroenterologist decide whether emergent endoscopy is needed. Tests for the presence of occult gastric blood are available, but their value is questionable because clinically insignificant iatrogenic bleeding often accompanies nasogastric tube insertion.

Chest X-rays are a useful adjunct for detecting free air under the diaphragm giving suspicion for perforation. Unfortunately, pneumoperitoneum is only seen in 50% of patients with perforation, and the absence of this finding is often associated with delayed diagnosis and increased mortality. In cases where there is still a high clinical suspicion for perforation, CT scan is more sensitive and specific for detecting the perforation.

With *H. pylori* being the most common cause of PUD, testing has become standard (Table 101.2). Patients usually have these tests performed on an outpatient basis for uncomplicated PUD. Noninvasive testing is usually recommended for those under 55 years without alarming signs, and endoscopy is usually recommended for any alarming symptoms or patients over 55 years.

TABLE 101.2
***Helicobacter Pylori* Testing (Outpatient Workup)**

Noninvasive
- Urea breath test
- Stool antigen test
- ELISA for *H. Pylori* (only for initial diagnosis)

Invasive (endoscopy)
- Biopsy and culture
- Histological stain of tissue sample
- Rapid urease test on biopsy specimen

KEY TESTING

- Laboratory studies: complete blood count, electrolytes, blood urea nitrogen, creatinine, liver function test, lipase, coagulation studies, type and Screen (if transfusion considered)
- EKG
- CXR and/or CT scan (if perforation or obstruction suspected)

ED MANAGEMENT

Uncomplicated Peptic Ulcer Disease

Most patients that present with PUD have normal vital signs and only have mild abdominal discomfort. ED management usually focuses on symptomatic relief with antacids. These patients are usually discharged from the ED with instruction for primary care physician follow-up for further workup and acid-suppressive therapy with a H2 blocker or PPI. If they take salicylates or NSAIDs they are discouraged from using them unless necessary for another medical condition like coronary artery disease.

All patients with suspected PUD need to be tested for *H. pylori.* If *H. pylori* testing results come back negative, then therapy focuses on acid-suppressive therapy and risk-factor modifications. If results are positive, treatment for *H. pylori* eradication is initiated, consisting of antimicrobials and acid-suppressive therapy (see Table 101.3).

TABLE 101.3
***Helicobacter Pylori* Eradication Regimens**

	Regimens	Duration (d)	Indications
First-line therapy	Amoxicillin 1000 mg bid, Clarithromycin 500 mg bid, and PPI[a]	10–14	Standard regimen
	Metronidazole 500 mg bid, Clarithromycin 500 mg bid, and PPI[a]	10–14	Penicillin allergy
	Bismuth subsalicylate 525 mg qid, Metronidazole 500 mg qid, Tetracycline 500 mg qid, and PPI[a]	10–14	High clarithromycin resistance area or penicillin allergy
	Days 1–5 Amoxicillin 1000 mg bid and PPI[a] Days 6–10 Clarithromycin 500 mg bid, Tinidazole 500 mg bid, and PPI[a]	10	
2nd line therapy	Bismuth subsalicylate 525 mg qid, Metronidazole 500 mg qid, Tetracycline 500 mg qid, and PPI[a]	14	1st line treatment failure
	Levofloxacin 250 mg bid, Amoxicillin 1000 mg bid, and PPI[a]	10–14	
	Rifabutin 150 mg bid, Amoxicillin 1000 mg bid, and PPI[a]	14	

[a]PPI at standard bid dosing; esomeprazole can be dosed once daily.
Adapted from Feldman M, Friedman L, Brandt LJ, et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th ed. Philadelphia, PA: Saunder; 2010.

- H2-receptor antagonists inhibit the action of histamine on H2 receptors located in gastric parietal cells resulting in reduced acid secretion. They are generally safe and effective.
- PPIs, such as omeprazole, effectively reduce gastric acid secretion and are effective in the treatment of PUD (7). The use of a PPI is relatively safe, but is not without risk. Patients on PPIs have an increased risk of pneumonia and *Clostridium difficile* colitis.

- Sucralfate is an aluminum salt of sucrose that forms a polymer in the acid environment of the stomach. This polymer adheres selectively to the ulcer, forming a barrier between the acid environment and the damaged mucosa.
- Prostaglandins, such as misoprostol, increase the cytoprotective properties of the gastric mucosa; they stimulate mucus production, bicarbonate production, and stimulate vascular blood flow to gastric mucosa.
- Bismuth, aka Pepto-Bismol, coats ulcer craters and has ulcer-healing properties. It increases mucosal prostaglandins, bicarbonate secretion, and has some antimicrobial properties against *H. pylori.*

Hemorrhage

Prompt assessment, resuscitation, and hemostasis are essential. Hemostasis is generally attempted through endoscopic management with injection of vasopressor agents at bleeding site, ablative therapy, or placing a clip. Early intravenous PPI therapy has been shown to decrease risk of rebleeding and need for surgical intervention (14). Upper GI bleeding from PUD will resolve spontaneously in up to 80% of patients. Inability to control bleeding or recurrent bleeding despite endoscopy attempts is an indication for surgery; radiologic intervention with embolization may be an alternative to surgery.

Penetration/Perforation

Rapid diagnosis and resuscitation prior to surgical repair are essential. Resuscitation with IV fluids, sometimes blood, pain medication, and broad-spectrum antibiotics are indicated in this circumstance. Resection of the ulcer along with simple closure and patch repair with open versus endoscopic surgery, and sometimes bowel resection, are the treatment alternatives for this condition (6,15).

Gastric Outlet Obstruction

Patients with gastric outlet obstructions are often markedly dehydrated and require urgent fluid resuscitation along with a nasogastric tube set to suction for decompression. The majority of these patients will improve with these measures; when combined with endoscopic balloon dilation, they produce a nice result in patients with acute inflammatory edema versus those with chronic scarring and fibrosis (6,15).

CRITICAL INTERVENTIONS

- Aggressive resuscitation for patients with serious complications of PUD
  - Hemorrhage: IV fluids (up to 2 L), blood products (if indicated), PPI, GI and/or surgical consultation
  - Penetration/perforation: IV fluids and surgical consultation
  - Gastric outlet obstruction: nasogastric tube, IV fluids, GI and/or surgical consultation.
- Rule out acute coronary syndrome when patients come with epigastric pain with symptoms similar to PUD.

DISPOSITION

Patients who are stable with no signs of PUD complications or abnormal laboratory work can be discharged home with a H2 blocker or PPI. The patient will need follow up with a primary care provider or GI physician for further evaluation and possible endoscopy.

Patients that are unstable or showing symptoms of a possible complication from PUD required immediate resuscitation, stabilization, specialist consultation, and admission.

Common Pitfalls

- Failure to consider other life-threatening etiologies for epigastric pain, such as, acute myocardial infarction or abdominal aortic aneurysm
- Failure to recognize signs and symptoms of a serious PUD complication

- Failure to place a nasogastric tube for a gastric outlet obstruction
- Failure to refer the patient to an appropriate specialist for further evaluation and management

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CHAPTER 102
Jaundice

Gus M. Garmel and Tobias D. Barker

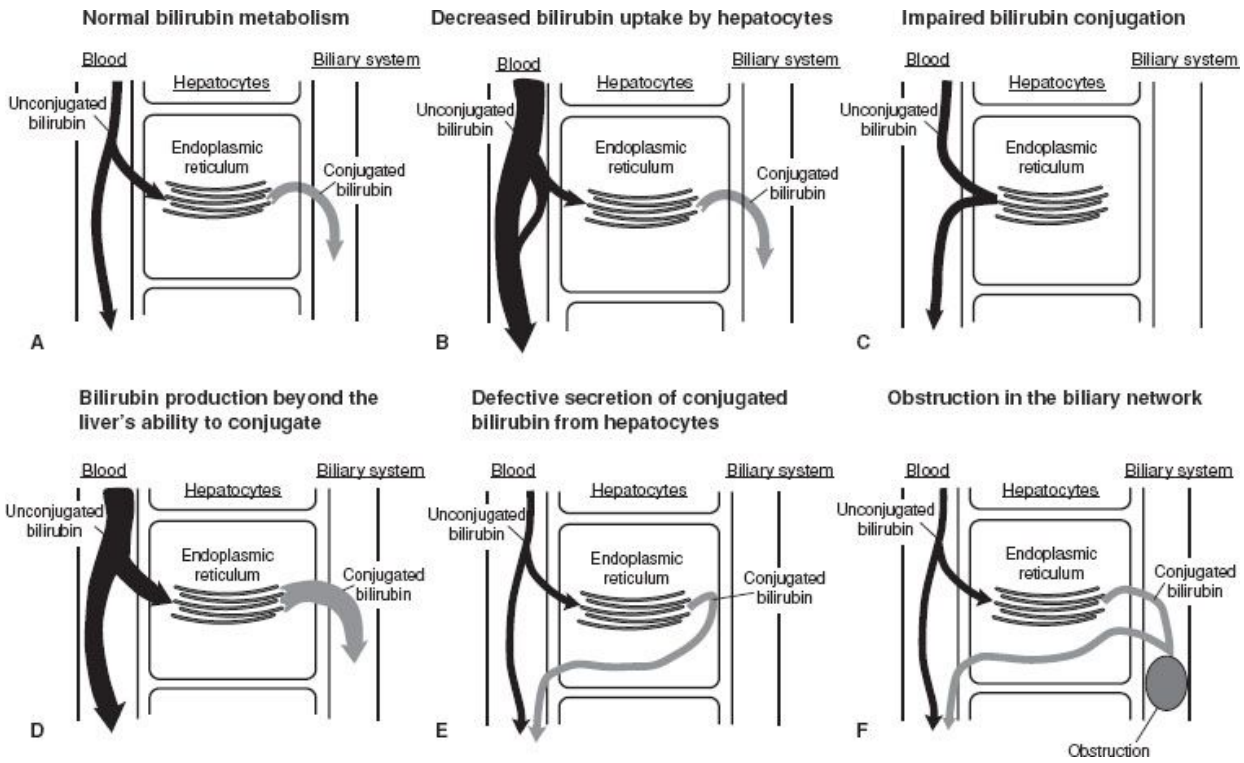
JAUNDICE, APPROACH TO JAUNDICE, ICTERUS, BILIRUBIN METABOLISM, BILIRUBIN CONJUGATION

Jaundice may be defined as the yellowing of skin, sclera, and other tissues owing to deposition of excess circulating bilirubin. The clinical challenge is not the identification of jaundice but with the workup to delineate the responsible pathologic process, typically liver disease or a hemolytic condition. This chapter describes an approach to the jaundiced patient, with particular attention to understanding bilirubin metabolism. It includes historical, physical examination, laboratory, and imaging findings that should help clinicians establish an etiology. This chapter also discusses diagnostic and management strategies based on findings associated with the presentation of jaundice.

BILIRUBIN METABOLISM

Bilirubin is an end product of heme metabolism. Approximately 75% of bilirubin is derived from the hemoglobin of senescent red blood cells; the remainder comes from myoglobin, cytochromes, and respiratory enzymes with structures similar to that of heme (1,2). Initially, bilirubin produced in the body is unconjugated. Physiological jaundice in newborns is due to the relatively low activity of glucuronosyltransferase, an enzyme responsible for the conversion of unconjugated bilirubin to conjugated bilirubin. Unconjugated bilirubin is able to cross the placenta, which prevents fetal accumulation. Unconjugated bilirubin is actively transported from albumin into liver cells. Here, bilirubin is combined with

glucuronic acid in the smooth endoplasmic reticulum, where it becomes conjugated. Conjugated bilirubin is then excreted from the hepatocyte to the biliary tract, where it eventually reaches the intestines and is excreted from the body (eFig. 102.1A).



eFIGURE 102.1 Mechanisms of hyperbilirubinemia. A: Normal bilirubin metabolism. B: Gilbert disease and certain drugs: defective bilirubin uptake from the blood, resulting in unconjugated hyperbilirubinemia. C: Physiologic jaundice of the newborn and Crigler–Najjar syndrome, inability to conjugate bilirubin. D: Hemolytic anemia, the capacity of the hepatocytes is overwhelmed, resulting in unconjugated hyperbilirubinemia. E: Dubin–Johnson syndrome: Hepatocytes are unable to secrete conjugated bilirubin into the biliary system. F: Obstruction in the biliary outflow tract (e.g., gallstones, tumor, mass) results in backup and reabsorption of conjugated bilirubin. (Baggott J, Dennis SE. Diseases associated with hyperbilirubinemia. Available at: http://library.med.utah.edu/NetBiochem/hi7d.htm. Accessed 9 June, 2014. Modified and used with permission.)

CLINICAL PRESENTATION

Sir William Osler stated, “Jaundice is the disease your friends diagnose” (3). Regardless of who identifies the color changes associated with jaundice (also known as *icterus*), patients are likely to be concerned about the underlying cause. Skin color changes may occur in isolation or with nausea, vomiting, abdominal pain, pruritus, and/or fever. Patients may notice darkening or discoloration of their urine (often described as “tea” or “cola” in color). Although rarely a true medical emergency in itself, physicians must quickly assess for and begin treating any concomitant life-threatening conditions, such as hypotension, sepsis, or alterations in mental status.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of jaundice is extensive. Jaundice has many possible etiologies, including biliary obstruction, hepatocellular dysfunction, hemolysis, and hereditary disorders of bilirubin metabolism. Certain epidemiologic factors may provide clues to the cause of a patient’s jaundice. In general, younger patients are more likely to have parenchymal liver disease, whereas older patients are more likely to have biliary stones or malignancy. Jaundice in the newborn (neonatal jaundice) is discussed in Chapter 221. Worldwide, the most common cause of hepatocellular disease-causing jaundice is viral hepatitis, whereas in the developed world, alcoholic hepatitis is increasingly prevalent. Liver injury may be the result of sepsis or ischemia (4), in addition to toxic effects of drugs, alcohol, or pathogens. Zoonotic infections have been reported as a rare cause of jaundice (5). Table 102.1 suggests common causes of jaundice grouped by age.

TABLE 102.1
Common Causes of Jaundice According to Age

Neonates
Physiologic jaundice
Biliary atresia
Infections (TORCHES)
Metabolic
Adolescents
Gilbert syndrome
Viral hepatitis
Pregnant patients
Hyperemesis gravidarum
Intrahepatic cholestasis of pregnancy
Adults
Viral hepatitis
Biliary tract disease
Alcoholic liver disease
Ischemic liver disease
Sepsis
Drug-induced liver disease
Elderly
Malignant disease
Biliary tract disease
Sepsis
Ischemic liver disease
Drug toxicity

TORCHES: *toxoplasma gondii*, rubella, cytomegalovirus, herpes simplex, syphilis.

Causes of yellow skin in the absence of hyperbilirubinemia include carotenemia (carotenoderma), quinacrine ingestion, and occupational exposure to phenols (6). One feature that differentiates jaundice from other causes of yellow skin is that bilirubin stains the sclera. Other areas where jaundice may be identified are those regions relatively free of melanin, such as the palms, soles, and the undersurface of the tongue.

ED EVALUATION

The underlying pathology behind a patient's jaundice can often be discovered after a thorough history, physical examination, selected laboratory tests, and focused imaging studies. The cause of jaundice was successfully identified as either obstructive or nonobstructive in

75% of cases in one study (7). A diagnostic approach to the jaundiced patient is provided in Figure 102.1 (8).

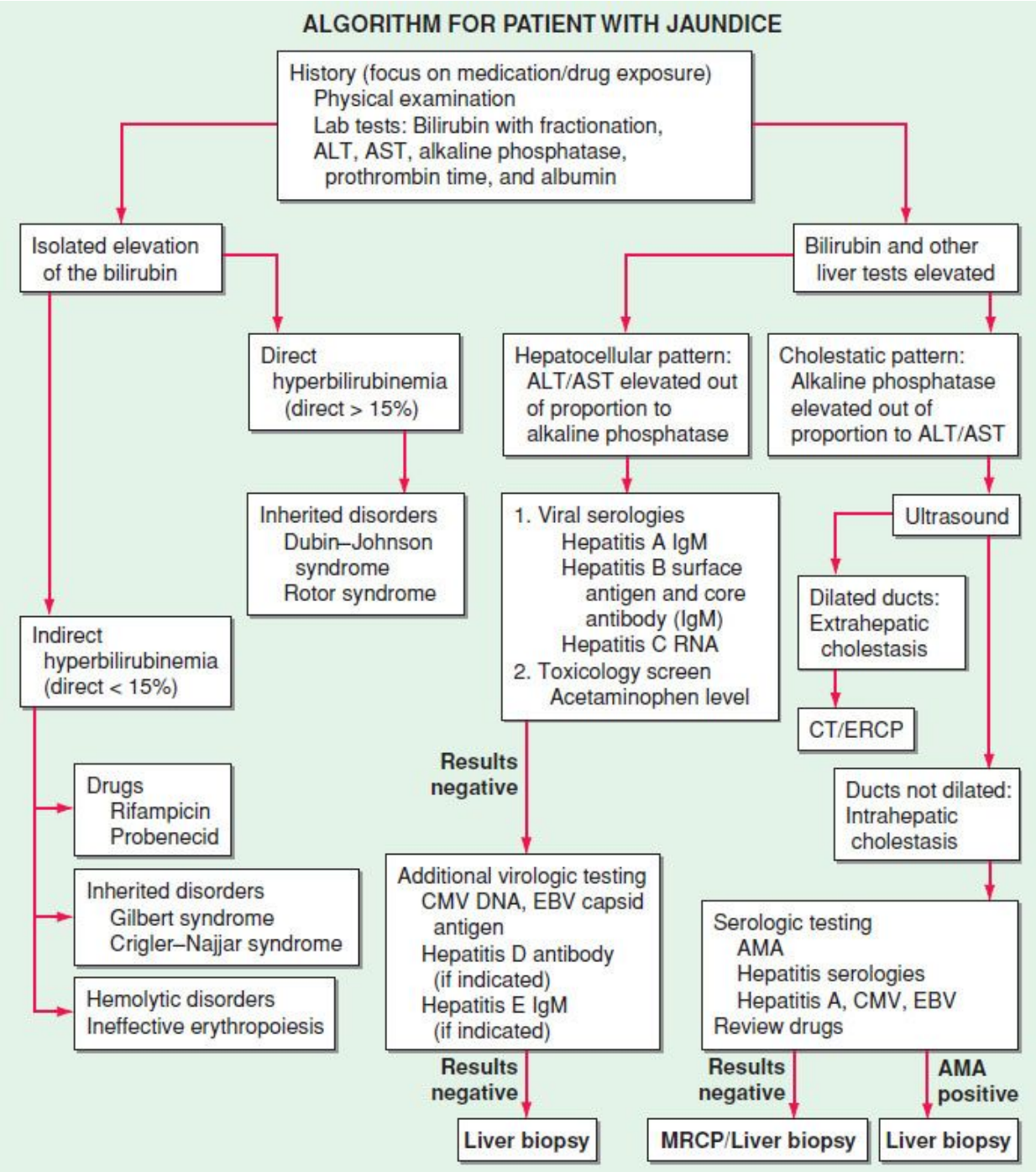


FIGURE 102.1 Algorithm for patient with jaundice (8). (Modified from Pratt DS, Kaplan MM. Jaundice. In: Longo DL, Fauci AS, Kasper DL, et al., eds. *Access Medicine, Harrison's Principles of Internal*

Medicine, Harrison's Online. 18th ed. McGraw Hill Professional; 2011). Accessed June 9, 2014 through www.AccessMed.com. Used with permission.)

History

As always, a good history can help delineate possible etiologies responsible for any patient's presentation. Important historical points in a jaundiced patient include the following:

New-onset dark urine indicates conjugated hyperbilirubinemia, as unconjugated bilirubin is bound to albumin in the serum and is not filtered into the urine. Patients often notice dark urine before skin discoloration, which may be the first indication of hyperbilirubinemia.

Clay-colored stool indicates that bilirubin is not leaving the biliary ducts due to an obstruction, resulting in conjugated hyperbilirubinemia.

Medications, alcohol, and *environmental hepatotoxins* (such as phosphorus, petrochemicals, organic solvents, or toxic mushrooms) may result in jaundice. Medications such as acetaminophen, anabolic steroids, and sulfonamides can cause jaundice through direct cellular damage or by interfering with biliary secretion. Idiosyncratic drug-induced liver injury may result in jaundice (9).

Nausea and vomiting preceding jaundice most often indicate acute hepatitis or obstruction of the common biliary duct by a gallstone. Abdominal pain, fever, chills, or rigors favor the latter. Recent flu-like symptoms and aspirin use raise the possibility of Reye syndrome in younger patients. Anorexia and malaise, especially long-standing, suggest alcoholic liver disease, chronic hepatitis, or pancreatic cancer.

Infectious exposures, intravenous drug use, or blood transfusions increase the possibility of viral hepatitis.

Pregnancy suggests benign recurrent cholestasis or acute fatty liver of pregnancy.

Family history of jaundice or liver disease increases the likelihood of a hereditary cause of hyperbilirubinemia, such as Gilbert, Crigler–

Najjar, Dubin–Johnson, or Rotor syndrome.

Physical Examination

Jaundice is best seen in natural light and is usually detectable when serum bilirubin exceeds 2.5 mg/dL (about twice the upper limit of normal) (10). The identification of jaundice may be more difficult in artificial light, especially in the fluorescent lights found in many emergency departments (EDs). Jaundice may also be more difficult to identify depending on the patient's skin color, age, or hydration status. The greater the bilirubin level, the more easily jaundice is recognized. One study calculated the clinical sensitivity of diagnosing jaundice in patients with a bilirubin level >3.0 mg/dL at 78.4%, reaching a sensitivity of 100% with a bilirubin level >15 mg/dL (11).

Other useful physical examination findings include the following:

Signs of cirrhosis include ascites (serous fluid accumulation in the abdominal cavity resulting from salt and water retention in patients with cirrhosis); spider hemangiomas (red tufts of fine blood vessels which blanch with pressure, oriented in a spider-like pattern on the trunk, face, forearms and hands, thought to be a result of increased levels of circulating estrogens); or caput medusae (dilated veins in the abdominal wall, radiating from the umbilicus, which develop as portosystemic collateral vessels secondary to portal hypertension).

Right upper quadrant (RUQ) *tenderness* and inspiratory arrest on palpation of the gallbladder (Murphy sign) suggest cholecystitis. *Charcot triad* (RUQ pain, jaundice, and fever) and *Reynold pentad* (RUQ pain, jaundice, fever, hypotension, and mental status changes) are indicative of cholangitis.

Fetor hepaticus (a musty, sweetish breath odor) may develop in patients with advanced liver disease or hepatic encephalopathy.

Diffuse lymphadenopathy is suggestive of infectious mononucleosis in acute jaundice, and lymphoma or leukemia in chronic illness with jaundice. Specific lymph node enlargement, such as an enlarged left supraclavicular (Virchow) node or periumbilical (Sister Mary Joseph) node, increases the likelihood of abdominal malignancy.

Hepatosplenomegaly without other signs of chronic liver disease may be the result of an infiltrative disorder, such as lymphoma or amyloidosis. Nodularity or a small liver may suggest cirrhosis. A palpable mass suggests an abscess or malignancy.

Temporal and proximal muscle wasting suggest long-standing diseases, such as cirrhosis or malignancy.

Asterixis and altered mentation are ominous findings that indicate fulminant hepatic failure.

Kayser–Fleischer rings are seen in Wilson disease (a rare, progressive, autosomal recessive disease due to a defect in copper metabolism), which may result in cirrhosis.

Skin pigmentation (often bronze in nature) is seen in hemochromatosis, a condition resulting in liver dysfunction due to abnormal deposits of hemosiderin in the liver.

Laboratory Evaluation

Laboratory testing is important in the evaluation of a patient with jaundice, as the results may identify a specific etiology or assist in the next stage of the evaluation, such as imaging or consultation. The minimum laboratory tests needed in these patients include bilirubin level with fractionation, aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), alkaline phosphatase, prothrombin time, and complete blood count. The first step in the decision analysis is to determine whether hyperbilirubinemia is isolated or associated with liver function abnormalities (see Fig. 102.1).

Hyperbilirubinemia Without Other Laboratory Abnormalities

In a patient with isolated hyperbilirubinemia, it is important to determine whether the bilirubin is unconjugated or conjugated. Isolated *unconjugated (indirect) hyperbilirubinemia* is due to either a hemolytic process or impaired hepatic function. Therefore, isolated unconjugated (indirect) hyperbilirubinemia is caused either by decreased uptake (see eFig. 102.1B), decreased conjugation (see eFig. 102.1C), or overproduction of bilirubin (see eFig. 102.1D). The drugs rifampin, probenecid, and ribavirin can decrease bilirubin uptake

into the hepatocyte. *Gilbert syndrome* is a hereditary disorder resulting in abnormal bilirubin metabolism, in part through decreased bilirubin uptake (12,13). It is the most common hereditary cause of isolated unconjugated hyperbilirubinemia, occurring in approximately 9% of Caucasians (14). This benign condition is usually noted as an incidental laboratory finding and is not responsible for liver damage or hematologic abnormalities.

Decreased bilirubin conjugation may be the result of decreased levels or inactivity of UDP-glucuronosyltransferase (UGT), the enzyme necessary for the formation of conjugated bilirubin. *Crigler–Najjar syndrome* is a more serious condition than Gilbert syndrome and has varying degrees of jaundice directly related to the degree of UGT available. In type I Crigler–Najjar syndrome, UGT is absent; these patients often die in the neonatal period. In type II disease, there is reduced but variable UGT activity, so the diagnosis may not be established until later in childhood. These patients may have a normal life expectancy and usually take phenobarbital, which increases UGT activity. *Physiologic jaundice of the newborn* is thought to be secondary to decreased conjugation as a result of delayed expression of UGT during the newborn period (see Chapter 221).

Disorders resulting in overproduction of bilirubin cause jaundice by overwhelming the capacity of hepatocytes to conjugate bilirubin (eFig. 102.1D). One cause is *hemolysis,* which may occur from mechanical shearing (disseminated intravascular coagulation, artificial valves). Other causes include hereditary red cell fragility (G6PD deficiency, sickle cell anemia, paroxysmal nocturnal hemoglobinuria), environmental stressors (heat, envenomation), or reactions following blood transfusion. Hemolysis due to vitamin B12 deficiency from pernicious anemia has been reported as an underlying cause of jaundice (15). Increased bilirubin that occurs from the resorption of hematoma following trauma is a more benign cause. A complete blood count in these patients may reveal anemia or an abnormal red blood cell morphology implicating an underlying pathologic cause for the anemia.

Isolated *conjugated (direct) hyperbilirubinemia* is usually caused by one of two inherited disorders. *Dubin–Johnson syndrome* (rare except

in Jews of Middle Eastern descent) and *Rotor syndrome* both have fairly benign clinical courses. These are the result of an inability to secrete conjugated bilirubin through the canalicular membrane into the biliary system (eFig. 102.1E).

ED imaging is not generally required in the primary diagnosis of isolated hyperbilirubinemia. However, one may find secondary signs of the underlying pathology responsible for the hyperbilirubinemia (paravertebral masses seen in extramedullary hematopoiesis, avascular necrosis of the femoral head seen in sickle cell disease). In such cases, focused imaging directed at a potential etiology is appropriate, although this may occur in the outpatient setting based on the patient's medical condition and the availability of follow-up care.

Hyperbilirubinemia With Other Laboratory Abnormalities

In patients with jaundice due to hyperbilirubinemia and other laboratory abnormalities, it is important to determine whether a hepatocellular condition or cholestasis is responsible. This can be determined by identifying which laboratory abnormalities predominate—elevated transaminases or an elevated alkaline phosphatase.

If **elevated transaminases predominate,** direct hepatocellular damage in *hepatitis* is likely (16,17). There are two common transaminase enzymes: AST (found primarily in the liver, although it is also in several other tissues) and ALT (found predominantly in hepatocytes). AST activity is increased in alcoholics; therefore, an AST:ALT ratio $>2:1$ suggests alcohol toxicity (18,19). AST levels >400 IU/mL indicate hepatocellular injury, whereas higher levels may be associated with liver ischemia, viral infection, or toxins. Imaging for these intrahepatic causes of jaundice often reveal no specific findings. The liver parenchyma often has diffuse interstitial edema and infiltration of inflammatory cells that causes diffuse decreased parenchymal echogenicity on ultrasound. This gives rise to the "starry sky" appearance of the relatively bright portal triads against the background of dark parenchyma (20).

If **elevated alkaline phosphatase predominates,** clinicians must be concerned about *biliary obstruction.* Whether the cause of obstruction is intrahepatic or extrahepatic, the synthesis and release of alkaline phosphatase into the serum is increased (eFig. 102.1F). However, extrahepatic tissues also synthesize and release alkaline phosphatase. To confirm the hepatic origin for the elevated alkaline phosphatase, enzymes such as γ-glutamyl transferase may be tested. In a jaundiced patient, however, an increased alkaline phosphatase with normal transaminases strongly suggests biliary tract obstruction. Patients in this category should have their gallbladder and liver evaluated with abdominal ultrasound. This test is noninvasive and has a sensitivity of 77% and a specificity of 83% to 95% for bile duct obstruction (21).

The goal of imaging jaundiced patients is to identify which patients have an obstructive (and therefore perhaps correctable) cause of their jaundice. Ultrasound is particularly suited to this purpose because of its ability to visualize the intra- and extrahepatic biliary tree in detail. If dilated ducts are present, one must determine whether sonographic signs consistent with *cholecystitis* or *cholangitis* are present. Ultrasound findings consistent with cholecystitis include the sonographic Murphy sign, calculi in the gallbladder, gallbladder wall thickening of >3 mm, distention of the gallbladder, and pericholecystic fluid. Any of these findings warrant antibiotics and surgical consultation. A gastroenterology consultation to discuss whether a computed tomography (CT) scan or endoscopic retrograde cholangiopancreatography (ERCP) is prudent if these findings are absent should occur in a patient with dilated ducts, as extrinsic compression of the bile duct must be excluded. Magnetic resonance cholangiopancreatography (MRCP) is gaining favor among specialists as a diagnostic examination for a jaundiced patient without or with borderline common biliary duct dilatation if choledocholithiasis is a possible etiology. If available, MRCP has fewer risks than ERCP, although it does not provide the option for therapeutic maneuvers. Endoscopic ultrasound may serve as the standard for identifying gallbladder and bile duct stones in some institutions (22). If dilated ducts are not seen on ultrasound, further workup should focus on

sources of intrahepatic cholestasis, such as viral infection (hepatitis, Epstein–Barr virus, cytomegalovirus), toxin damage (alcohol, steroids), or disorders such as primary biliary cirrhosis and primary sclerosing cholangitis. This workup can generally be performed on an outpatient basis if the patient does not appear ill, can tolerate oral intake, and has reliable follow-up.

KEY TESTING

- Bilirubin (fractionated), transaminases, alkaline phosphatase, CBC, PT
- Biliary ultrasound if laboratory tests suggest biliary obstruction

ED MANAGEMENT

When evaluating a patient with jaundice, emergency physicians must quickly determine whether a life-threatening condition is present. During assessment of the airway, breathing, and circulation (ABCs), history, and physical examination, patients should be given oxygen, placed on a cardiac monitor, and intravenous access should be obtained. Caution is advised during invasive procedures, as hepatitis transmission through occupational exposures is a concern. Patients may require aggressive intravenous fluid resuscitation, as they may be dehydrated, hypotensive, or in shock due to decreased oral intake, vomiting, infection, sepsis, or third-space losses (such as occurs with ascites). Antiemetics should be given as needed. Patients with ascending cholangitis are often critically ill and require aggressive resuscitation. Airway intervention, cardiovascular support (including pressors after aggressive fluid resuscitation), early antibiotics, and emergent surgical consultation are all important measures in reducing morbidity and mortality.

Depending on the cause of jaundice and the toxicity of the patient, surgical, gastroenterologic, or radiologic intervention may be necessary to relieve an obstruction or address the cause of underlying infection. A general surgeon may need to perform an open or laparoscopic cholecystectomy depending on the patient's condition, the underlying pathology, and their skill set. A

gastroenterologist (or a surgeon at some institutions) may do an ERCP to stent an obstruction, to remove an obstructing gallstone from the common bile duct, or to perform a sphincterotomy. An interventional radiologist may execute a percutaneous transhepatic cholangiogram (PTC), a diagnostic and therapeutic procedure that may allow drainage of an obstructed bile duct with or without cholangitis. Further information about the evaluation and management of ascending cholangitis may be found in Chapter 103.

Fortunately, most patients with jaundice are not acutely ill. Pruritus may be their most troublesome symptom. Drugs such as cholestyramine (4 g PO qd-tid) and rifampin (300 to 450 mg PO qd) improve pruritus in patients with cholestasis, although these do not act immediately. Of note, long-term administration of rifampin for refractory pruritus has been associated with occasional hepatotoxicity (23). Oral naltrexone (50 mg qd) has also been shown to significantly decrease symptoms in patients with pruritus (24). Antihistamines should be used with caution, as they may precipitate hepatic encephalopathy. Additional treatment options depend on the underlying pathology.

CRITICAL INTERVENTIONS

- When a serious infection is likely, aggressive fluid administration, broad-spectrum parenteral antibiotics, and emergent consultation are mandatory.
- Aggressive fluid resuscitation and blood transfusion may be necessary in patients presenting in acute hemolytic crisis. Administration of folic acid is useful because hemolysis depletes folate.
- Patients with jaundice presenting in fulminant liver failure and confusion may require emergent airway management. Fluids, broad-spectrum antibiotics, and lactulose and/or neomycin should be administered, and any critical electrolyte abnormalities should be aggressively corrected.

DISPOSITION

Acute hemolysis must be ruled out in patients with *isolated unconjugated hyperbilirubinemia.* If hemolysis is present, the patient should be admitted and a diligent search for the underlying cause (either inherited or acquired) must occur in consultation with hematology. If hemolysis or resorption of a hematoma do not appear to be the cause of the unconjugated hyperbilirubinemia, hereditary problems of bilirubin metabolism are likely. Affected patients may be candidates for outpatient follow-up with gastroenterology consultation.

In patients with *isolated conjugated hyperbilirubinemia,* hereditary metabolic problems are most likely. These patients may need gastroenterology consultation, although they can usually be followed on an outpatient basis as long as critical laboratory abnormalities do not exist, reliable follow-up arrangements can be made, and symptoms are controlled.

Patients with *hyperbilirubinemia and elevated transaminases* to a degree greater than the alkaline phosphatase require medical evaluation for causes of hepatocellular injury, often in the inpatient setting if these are not known to be chronic. Treatment may include cessation of offending toxins (e.g., alcohol, acetaminophen, isoniazid, other drugs), antiviral treatment for hepatitis, or treatment for autoimmune or metabolic causes (e.g., Wilson disease, hemochromatosis).

Patients with *hyperbilirubinemia and an elevated alkaline phosphatase* to an extent greater than the transaminases require urgent abdominal ultrasound to search for obstructive causes. Those patients *with dilated ducts* and fever, leukocytosis, bandemia, or toxic appearance should be aggressively hydrated, started on broad-spectrum antibiotics in the ED, and admitted to the hospital. It is prudent to keep these patients nil per os, provide analgesia and antiemetics as needed, as well as antipyretics if fever is present and no signs of acute hepatotoxicity exist. Prompt consultation with surgery (for possible laparotomy or laparoscopy, depending on the condition of the patient and the skills of the surgeon) or gastroenterology (for possible ERCP) is essential. Further workup of these patients is discussed in Chapter 103. Afebrile patients with dilated ducts who

are less acutely ill may have extrinsic compression of the biliary tree from such sources as pancreatic cancer, nearby arterial aneurysms, or other abdominal masses. These patients may benefit from abdominal CT scan, MRCP, or PTC. Patients *without dilated ducts* require a medical workup for causes of intrahepatic jaundice, such as infiltrative disorders, drugs or toxins, primary biliary cirrhosis, primary sclerosing cholangitis, or complications of pregnancy. The disposition of these patients depends on their clinical status and degree of laboratory abnormalities. Patients with chronic alcoholism who present with jaundice, especially of new onset, should be carefully managed and observed prior to release from the ED. This is extremely important for those who are unreliable, have uncertain follow-up care, or live in suboptimal conditions.

Common Pitfalls

- Delayed fluid intervention, broad-spectrum antibiotic administration, and emergent consultation in an acutely ill patient with jaundice and signs of cholangitis, such as Charcot triad (RUQ pain, jaundice, fever) or Reynold pentad (RUQ pain, jaundice, fever, hypotension, mental status changes).
- Failure to recognize signs and symptoms of fulminant liver failure (e.g., confusion, asterixis, abnormal vital signs), as well as predict associated problems related to the airway, cardiovascular status, glucose, and electrolytes.
- Failure to order appropriate imaging studies for patients with hyperbilirubinemia and an elevated alkaline phosphatase, suggestive of biliary obstruction requiring intervention.
- Failure to arrange or ensure reliable follow-up care for patients with unclear etiologies of their jaundice, as these patients will likely require serial evaluations and repeat testing before a diagnosis is confirmed.

ACKNOWLEDGMENTS

Drs. Garmel and Barker would like to thank Elaine Barnes from the Kaiser Santa Clara Health Sciences Library for her research assistance

and Dr. Timothy Steck from the Department of Gastroenterology at Kaiser Santa Clara Medical Center for his thoughtful review.

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CHAPTER 103

Acute Diseases of the Biliary Tract

Boris Garber and Lance D. Wilson

Biliary disease is a common problem in emergency department patients, primarily because of the high prevalence of gallstones, which are present in as many as 25% of women and 15% of men over the age of 50. In the United States, over 120,000 cholecystectomies are performed yearly for acute cholecystitis, contributing to the $6.3 billion annual cost of gallbladder disease (1). Emergency physicians are confronted with a wide range of biliary pathology and must be familiar with the natural history of biliary disease to understand the variable presentations of acute disease and acute complications of chronic disease.

PATHOPHYSIOLOGY

The gallbladder is a reservoir off the common bile duct (CBD) that receives, concentrates, and secretes bile to assist in intestinal absorption of fat and fat-soluble vitamins. Gallstones form when cholesterol is supersaturated in the bile, leaves solution, and crystallizes on a matrix of calcium and other bile constituents. In Western countries, 75% to 80% of gallstones are cholesterol or mixed cholesterol stones (2). Once formed, gallstones may dissolve, remain unchanged, or grow larger.

Risk factors for gallstones are features that predispose to increased concentrations of cholesterol in the bile, including increased age, obesity, female sex, ethnicity, and hyperlipidemia. Family history is increasingly recognized as an important risk factor for biliary disease

(3). Crohn disease, ileal resection, total parenteral nutrition, and rapid weight loss, particularly in the setting of bariatric surgery, also predispose patients to gallstone formation (3). Approximately 10% to 20% of gallstones are formed of calcium bilirubinate (pigment stones); these are associated with hemolytic anemias, cirrhosis, biliary tract anomalies, and biliary infections.

Although gallbladder pathology is secondary to gallstones, as much as 10% of acute cholecystitis is acalculous. Acalculous cholecystitis classically occurs in patients after major surgery, burns, trauma, or sepsis, where after a major insult, bile stasis and low arterial inflow lead to gallbladder inflammation, infection, and eventually necrosis (4); however, patients clearly present to the emergency department with acalculous cholecystitis. These patients are typically elderly men with significant atherosclerotic disease; however, other risk factors include diabetes, abdominal vasculitis, renal failure, congestive heart failure (CHF), and resuscitation from shock or arrest. Importantly, acalculous cholecystitis represents 50% to 70% of all acute cholecystitis in children (5). Acalculous cholecystitis must be considered in patients with acquired immunodeficiency syndrome (AIDS), who may present with cholecystitis and cholangitis secondary to cytomegalovirus and *Cryptosporidium* infection; however, the incidence of these infections is decreasing with highly active antiretroviral treatment (5). Gangrene or perforation of the gallbladder complicate a significant percentage of acalculous cholecystitis cases. Diagnosis is challenging as clinical and laboratory findings are nonspecific, so a high index of suspicion and imaging studies are necessary though the imaging criteria are complex. Definite therapy is cholecystectomy; rarely gallbladder drainage can be used (4). Acute acalculous cholecystitis is associated with a mortality rate of greater than 30% (5).

Gallbladder cancer also must be considered in the approach to patients with presumed biliary disease. It is the most common biliary tract tumor, is highly lethal, and early on lacks any specific symptoms or signs. When localized, surgery offers the hope for cure, so early diagnosis is crucial. Chronically inflamed gallbladders can become calcified, thereby leading to the radiographic finding of a

porcelain gallbladder. These patients have as much as a 21% risk of developing gallbladder cancer, which normally occurs in less than 1% of patients with chronic cholelithiasis (6). Additional risk factors are asymptomatic gall stones 3 cm in diameter or larger (although surgery for asymptomatic gall stones is controversial) (6) and gallbladder polyps larger than 10 mm in diameter. Therefore, when these are discovered incidently during abdominal imaging, this mandates a discussion with the patient and a referral. Differentiating between benign and malignant gallbladder lesions based on imaging is difficult. Color Doppler study of polyps has been proposed to distinguish benign from malignant lesions (7).

CLINICAL PRESENTATION

It is helpful to view cholelithiasis in three categories: asymptomatic, symptomatic, and complicated. Clinical features of biliary emergencies are summarized in Table 103.1 (3,5,8–10).

TABLE 103.1
Diagnostic Features in Diseases of the Gallbladder

Cholelithiasis	Acute Cholecystitis	Choledocholithiasis	Cholangitis	Acalculous Cholecystitis
Presentation				
Usually asymptomatic, if not: biliary pain either RUQ or epigastric, persistent, associated nausea and vomiting, classically associated with meals	Pain in RUQ (sensitivity 81%, specificity 67%), severe, nausea, vomiting most common symptom in children (60%)	May be asymptomatic; usually persistent pain in RUQ	Usually elderly patients with biliary tract disease; recent biliary instrumentation, intermittent RUQ pain, typically more mild, fever, chills	Suspected in patients with recent critical illness or other risk factors who have unexplained sepsis, abdominal pain, jaundice, fever
Physical Examination				
Asymptomatic—normal examination, biliary colic—tenderness (RUQ and/or epigastrium)	Fever (sensitivity 35%, specificity 80%), tachycardia, tenderness in RUQ (sensitivity 77%, specificity 54%) + Murphy sign (sensitivity 65%, specificity 89%); palpable mass in RUQ + 1/3 of patients; clinical jaundice: unusual, although most common symptom in children younger than 1 yr (90%)	May have normal examination, or if common duct obstruction; clinical jaundice, RUQ tenderness	RUQ tenderness, clinical jaundice (mild); fever, sometimes shock, and sepsis; typical clinical picture in only 50%	Similar to calculous cholecystitis, but may be unreliable
Laboratory				
Typically normal	Leukocytosis (sensitivity 63%, specificity 57%); liver chemistries—typically slight elevation total bilirubin, AST, alkaline phosphatase (sensitivity 34%, specificity 80% for all three, for any one sensitivity 70%, specificity 42%)	If CBD obstruction; elevated bilirubin, alkaline phosphatase, LFTs, pancreatitis	Leukocytosis with left shift; hyperbilirubinemia elevated alkaline phosphatase level	Leukocytosis and hyperbilirubinemia common
Diagnostic Imaging				
Ultrasonography → gallstones (sensitivity 88%; specificity, 99%, both >95% for stones >3 mm)	Ultrasonography—(sensitivity 88%; specificity 80%) for cholecystitis. Tc99-HIDA scans somewhat better test characteristics but more inconvenient	Ultrasonography—stones in CBD (sensitivity 25–68%, specificity 97–100%), dilation of CBD (75%)	Similar ultrasound findings to those with choledocholithiasis	Ultrasonography—sensitivity 80%; specificity 98% for gallbladder wall thickness >5 mm, although controversial. Tc-HIDA scans 98% accuracy, but high false-negative rates reported
Differential Diagnosis				
Gastric/duodenal ulcer, pancreatitis, hepatitis, renal colic, gastroesophageal reflux, angina, hiatal hernia	Appendicitis, pancreatitis, hepatitis, RLL pneumonia, gastric/duodenal ulcer, renal colic, cardiac pain, hiatal hernia	Other causes of obstructive jaundice: Mirizzi syndrome, tumor in CBD, hepatic duct, head of pancreas	Nonsuppurative cholangitis; amoebic/pyogenic hepatic abscess, choledocholithiasis, cholangiocarcinoma, biliary stricture or fistula, extrinsic bile-duct obstruction, primary sclerosing cholangitis	Similar to calculous cholecystitis, other causes of sepsis

RUQ, right upper quadrant; LFT, liver function test; AST, aspartate aminotransferase; CBD, common bile duct; RLL, right lower lobe.

Asymptomatic Cholelithiasis

Most people with asymptomatic gallstones remain asymptomatic with only about 1% to 4% developing symptoms every year (1). When patients become symptomatic, nearly all initially develop pain, rather than cholecystitis or other acute complications, so they can be managed expectantly. The incidental discovery of gall stones when using ultrasound (US) or other imaging can be problematic and care should be taken not to attribute all the presenting symptoms to potentially incidental gallstones (6).

Symptomatic Cholelithiasis

Many people present to the emergency department with symptomatic gallstones. Pain is caused by distention of the gallbladder as it contracts against stones obstructing the gallbladder neck or cystic duct. Typically, biliary pain is a vague epigastric or right upper quadrant (RUQ) discomfort, usually associated with nausea. The term *biliary colic* is a misnomer, as biliary pain is constant, typically lasting longer than 30 minutes but less than 4 to 6 hours. Pain typically occurs in the evening and is usually postprandial (10). The vague nature and nonspecific location of the discomfort makes it easily mistaken for gastritis, reflux disease, or other benign abdominal pathologies. If the process continues, pain may become more severe, become localized to the epigastrium or the RUQ, radiates to the back or scapula, and may be associated with vomiting.

Complicated Cholelithiasis

Complicated cholelithiasis includes conditions such as acute cholecystitis and its complications, choledocholithiasis (stones in the CBD), cholangitis, and the acute complications of chronic gallstones. All are potentially life-threatening and require prompt recognition and treatment.

Acute Cholecystitis

In acute cholecystitis, the gallbladder neck or cystic duct is obstructed, and persistently increased intraluminal pressure along with irritation from bile and stones leads to mucosal damage, inflammation of the gallbladder wall, and eventually ischemia. Bacterial suprainfection (usually enteric gram-negative bacteria and occasionally anaerobes) plays a role in majority of the cases (1). In acute cholecystitis, pain is typically more severe and more often localized to the RUQ, with variable radiation to the epigastrium or back. Nausea and vomiting are common. Low-grade fever and tachycardia are typically present. *Murphy's sign* (inspiratory arrest during palpation of the RUQ) or localized peritonitis may be elicited.

In up to one-third of cases, a swollen, tender gallbladder is palpated. Typically, a leukocytosis with left shift is present, and mild increases in liver function tests, alkaline phosphatase, and bilirubin are seen in 30% to 40% of patients. Laboratory tests are frequently normal and fever can be absent, especially in the diabetic or chronically debilitated patient and must not be relied on to make the diagnosis. In acute cholecystitis, patients are rarely septic. If sepsis is present, consider more complicated conditions, particularly ascending cholangitis.

Complications of Acute Cholecystitis

Gallbladder perforation usually occurs in the setting of acute or chronic cholecystitis, typically in the elderly, debilitated, or diabetic patients. The gallbladder becomes gangrenous, perforates, and normally walls off to form an empyema, but occasionally a bile leak occurs, leading to bile peritonitis. Gallbladder wall gangrene may lead to diminishing pain and tenderness and absence of Murphy sign as nerve endings necrose (11). Rarely, acute cholecystitis is complicated by infection with a gas-forming organism, leading to *emphysematous cholecystitis*. This typically occurs in diabetics and elderly men with vascular disease. Emphysematous cholecystitis is a disease with mortality much higher than uncomplicated acute cholecystitis (11).

Choledocholithiasis

Gallstones in the CBD are termed *choledocholithiasis*. Stones usually form in the gallbladder and migrate from the cystic duct, but they can form primarily in the biliary tree. Presentation is usually similar to that of acute cholecystitis but can be variable and more subtle. Patients may have jaundice (3). Choledocholithiasis usually causes an elevation in alkaline phosphatase and conjugated bilirubin, consistent with extrahepatic obstruction. Increases in amylase and lipase are variable. A small proportion of patients with gallstones develop acute *gallstone pancreatitis*. *Mirizzi syndrome* is caused by extrinsic compression of the common hepatic duct by a gallstone

impacted in the cystic duct or neck of gallbladder and presents in similar fashion to choledocholithiasis (3).

Ascending Cholangitis

Ascending cholangitis must be considered in any septic patient who presents with signs and symptoms of acute biliary tract disease, especially if the patient is diabetic, elderly, or debilitated. Ascending cholangitis is a bacterial infection of the biliary system, most frequently associated with CBD stones and obstruction from any cause. Various bacteria have been isolated from bile in patients with cholangitis; polymicrobial isolation is not unusual and blood cultures are positive in approximately 50% of patients. Endoscopic retrograde cholangiopancreatography (ERCP) in patients with biliary obstruction is the most common iatrogenic way of introducing bacteria into the biliary system, and cholangitis after biliary manipulation has a poor prognosis (12). Classically, it presents with *Charcot triad* of RUQ pain, jaundice, and fever; if mental status changes and shock occurs, this is considered *Reynold pentad.* Ascending cholangitis seldom presents classically, so it must be considered in any septic patient without a source. Mortality approaches 40%. To investigate the etiology of cholangitis, endoscopic ultrasonography is the most sensitive study to detect small stones, but ERCP is the only method which may also be therapeutic. Computed tomography (CT) and MRCP are also useful diagnostically. Tokyo criteria defines mild, moderate, and severe diseases. Treatment requires aggressive supportive measures, admission to ICU for patients with severe disease, intravenous antibiotics as soon as the diagnosis is suspected, followed by prompt biliary drainage. The more severe the presentation, the more urgently biliary decompression should be performed. A landmark study (13) showed that endoscopic therapy results in much lower mortality when compared to surgery. ERCP can be done at bedside, but it should be recognized that if contrast injection increases intrabiliary pressure, the patient may acutely decompensate from worsening septicemia (12).

Complications of Chronic Cholelithiasis

In chronic and occasionally in acute cholecystitis, gallbladder–enteric fistulas may form, causing pain, aerobilia, or infection. Rarely, a gallstone may pass through a fistula into the small bowel and lodge in the ileocecal valve, causing a small bowel obstruction (*gallstone ileus*) (3). Fistulas between the gallbladder and the duodenum, stomach, colon, pleura, and other organs have also been described. Presentation for gallstone ileus is typically abdominal distention, pain, vomiting, usually in an elderly patient with multiple medical problems. Patients will appear acutely ill and dehydrated, and have signs of intestinal obstruction, but clinical jaundice is unusual. Abdominal films are useful for showing evidence of mechanical bowel obstruction, pneumobilia, or a stone in the gastrointestinal tract.

DIFFERENTIAL DIAGNOSIS

When patients present with complaints attributable to gallbladder disease, a wide range of both intra-abdominal and extra-abdominal processes must be considered (Table 103.2). Failing to consider biliary tract pathology in the differential diagnosis of nonspecific abdominal pain, fever, or sepsis in special populations can be problematic. The elderly can have very subtle presentations with only food intolerance or altered mental status (14). Elderly, diabetic, or debilitated patients are often difficult to assess and require ancillary studies to rule out life-threatening disease. Because pregnancy is associated with increased incidence of biliary sludge and cholesterol stone formation (14), biliary disease must be considered in the differential diagnosis of the pregnant patient with abdominal pain. Signs and symptoms of acute cholecystitis in pregnant and nonpregnant patients are similar. Although advancing age is a primary risk factor for gallstones, gallbladder disease and cholecystectomies are increasing among children, potentially related to increasing obesity (15). Acquired gall bladder pathology in infants is associated with prematurity, total parenteral nutrition status, and generalized severe illness, particularly in neonates, dehydration, and

sepsis (16). Children with cholelithiasis typically have underlying risk factors for the development of stones and biliary disease, such as sickle cell disease or other hemolytic anemias. Hispanic race and female gender appear to be important risk factors (15).

TABLE 103.2
Differential Diagnosis of Acute Diseases of the Gallbladder

Complications of gallstones
Acute cholecystitis
Hepatitis
Pancreatitis
Peptic ulcer disease
Esophageal disease, with or without perforation
Appendicitis
Bowel obstruction
Colonic pathology
Pelvic inflammatory disease
Fitz–Hugh–Curtis syndrome/perihepatitis
Renal colic
Pyelonephritis
Pneumonia
Pulmonary embolism
Acute myocardial infarction
Aortic dissection
HELLP syndrome

HELLP, hemolytic anemia, elevated liver enzymes, low platelet count.

ED EVALUATION

Despite the diversity in acute gallbladder pathology, evaluation should follow a relatively straightforward sequence based on the patient's clinical status (Table 103.1). The emergency physician's goal is to rule out life-threatening problems and if gallbladder pathology is suspected, acute cholecystitis and other complicated acute biliary diseases should be ruled out. If the patient presents with symptoms attributable to gallstones without complications, referral for outpatient ultrasound and follow-up is appropriate. No further emergency department workup is necessary. In the patient with more

severe symptoms or dehydration, further workup is indicated, including a complete blood count, electrolytes, liver function tests, bilirubin, amylase, lipase, urinalysis, and possibly diagnostic imaging. A summary of the clinical features and test characteristics in acute biliary diseases are shown in Table 103.2 (5,8,10,16). As no single clinical or laboratory finding is sufficient for diagnosing acute cholecystitis or acute biliary pathology, the physician's overall impression of the likelihood of the disease determines whether the diagnosis is pursed and diagnostic imaging is initiated (10).

Diagnostic Imaging

Plain radiographs are helpful only for diagnosing associated bowel obstruction or ileus, although gallstones are visible on plain radiographs in approximately 10% of cases. US and cholescintigraphy (commonly referred to as HIDA scans) both have excellent positive and negative predictive values when done appropriately; HIDA is considered to have higher accuracy, but because of its accessibility and ease of use, US is typically the initial study of choice. Sonographic evaluation for gallstones and acute cholecystitis by emergency physicians is now an accepted part of routine practice, reduces length of stay, and has test characteristics similar to US performed in the radiology department (7,17). However, as with other radiographic studies, ED physicians must use caution when interpreting bed-side US and avoid premature diagnostic closure. Gallstones alone do not establish the diagnosis of acute cholecystitis. To establish US diagnosis of cholecystitis secondary signs such as pericholecystic fluid, sonographic Murphy sign, and thickened Gallbladder wall need to be present in addition to gall stones. Presence of stones together with either positive sonographic Murphy sign or Gallbladder wall thickening of 5 mm or greater has positive predictive value of greater than 90%, alternatively absence of the above results in negative predictive value of 95% (1). Gallbladder wall thickening is nonspecific and can occur in chronic cholecystitis, CHF, cirrhosis, hepatitis, and other conditions (9). Other relevant findings include sludge in the gallbladder, gallbladder distention, and pericholecystic fluid. US is

also helpful in making the diagnosis of complications of acute cholecystitis where free fluid suggests gallbladder perforation.

CT scanning is reserved for patients with atypical presentations in whom other intra-abdominal pathology is a consideration and where a wide differential diagnosis persists (18). Ultrasound is superior to CT in ruling out acute cholecystitis and a CT diagnosis of cholecystitis should usually be confirmed with US. Only ~2/3 of gall stones will be visible on CT. Normal CT examination of gallbladder makes acute cholecystitis unlikely but if high suspicion persists US should still be done. CT is most useful in evaluating complications such as gallbladder perforation, pericholecystic abscess, and gangrenous and emphysematous cholecystitis (9). Intraluminal gas, membranes, or irregular or absent wall on CT or US are indicative of gangrenous cholecystitis (11).

A dilated CBD or intraluminal stone is diagnostic of choledocholithiasis. However, these findings are not present in all cases, and if CBD stones are suspected, they may be evaluated by ERCP or MRI with cholangiography. Ultrasound can also assess other extrabiliary causes of RUQ pain involving liver, kidney, or pancreas. HIDA scans test the patency of the cystic duct. Failure to visualize the gallbladder is highly sensitive for acute cholecystitis. The main indication for HIDA is a high suspicion for acute cholecystitis, with an equivocal or negative ultrasound examination, particularly if acalculous cholecystitis is suspected (1).

KEY TESTING

- Although laboratory testing lacks sensitivity and specificity, liver function tests and lipase may be useful in identifying patients with biliary obstruction.
- Ultrasound is the most useful initial imaging study.

ED MANAGEMENT

Emergency department management of symptomatic cholelithiasis includes hydration, antiemetics, and analgesia. These patients can usually be sent home with appropriate follow-up. If acute

cholecystitis or another complicated presentation of gallbladder disease is suspected, prompt consultation with a general surgeon is mandatory. Attention to the patient's volume and electrolyte status, antiemetics, and analgesia, typically with nonsteroidal anti-inflammatory drugs or narcotics, is appropriate (3). For acute cholecystitis, antibiotics are indicated and should be discussed with the consultant. The patient who is septic or suspected of having ascending cholangitis, perforation, or emphysematous cholecystitis should be given antibiotics promptly. Typical biliary pathogens include enteric gram-negative bacteria and gram-positive species such as *enterococcus* or *streptococci.* Anaerobic species, particularly *Clostridium* and *Bacteroides fragilis,* occur in approximately 10% to 15% of cases, usually in the elderly or in patients with biliary obstruction. Appropriate coverage includes a parenteral antipseudomonal penicillin such as ticarcillin/clavulanate 3.1 g q6 h or piperacillin/tazobactam 3.375 g q6 h. Alternative regimens, especially if anaerobes are suspected, include a second- or third-generation cephalosporin or a quinolone plus clindamycin or metronidazole (1).

Treatment for symptomatic gallstones is surgical, almost exclusively with laparoscopic cholecystectomy (1,19). In acute cholecystitis, urgent cholecystectomy, optimally performed within 48 to 96 hours of presentation, is preferred over delayed surgery for mild disease as defined by Tokyo criteria (1,19,20). Patients with moderate disease can have either early or delayed surgical intervention while those with severe disease should be stabilized in the ICU first (1). Early cholecystectomy is safe and appropriate in elderly patients as well (21). In patients who present with pain, fever, or jaundice after laparoscopic cholecystectomy, one must consider the recognized complications of the procedure, including biliary injury and fistulas, wound infections, and intra-abdominal abscesses, which may present weeks to months after surgery (19). Newer techniques, such as endoscopic surgery through natural orifices, which do not require a skin incision and routine open cholecystectomies via minilaparotomies are currently being tested (3). Percutaneous urgent cholecystostomy followed by elective

cholecystectomy is an option for patients with significant comorbidities who are at high operative risk (1,19). Oral dissolution therapy for gallstones, occasionally in conjunction with extracorporeal shock-wave lithotripsy, is used in patients who are substantial surgical risks or do not want surgery.

In patients with CBD stones, endoscopic sphincterotomy or dilatation to relieve obstruction followed by elective cholecystectomy is typically performed, rather than open cholecystectomy with CBD exploration. Almost all patients with ascending cholangitis require urgent biliary decompression. Typically this is performed by using endoscopic sphincterotomy rather than surgical approaches (12). All patients with gallbladder perforation, emphysematous cholecystitis, or gallbladder empyema need emergent surgery. Pregnant patients with biliary colic should be admitted and if symptoms persist more than 12 hours, antibiotics should be administered. Whether early surgical intervention is warranted in pregnancy is still a controversy (14). Children with biliary colic should also be admitted.

CRITICAL INTERVENTIONS

- Surgical consultation in all cases of acute cholecystitis or acute biliary disease
- Early surgical or gastroenterology consultation for ERCP when prompt biliary decompression is indicated
- Antibiotics in suspected acute cholecystitis or cholangitis

DISPOSITION

Most patients with symptomatic cholelithiasis may be managed as outpatients, with analgesics, antiemetics, and follow-up with a general surgeon. Those with more severe symptoms refractory to emergency department treatment should be admitted. Patients with acute cholecystitis, choledocholithiasis, gallstone pancreatitis, ascending cholangitis, or complications of chronic cholelithiasis such as gallstone ileus must be admitted to the hospital for antibiotics and/or surgical care.

Common Pitfalls

- Acute complications of gallstone disease must be considered and recognized, particularly in the elderly and debilitated who typically have subtle presentations.
- Remember to consider cholecystitis or cholangitis in the elderly, diabetic, or debilitated patient who presents with fever of unknown origin, change in mental status, or other nonspecific complaints.
- Symptomatic gallstones should be considered in patients with mild or atypical presentations, such as nausea, dyspepsia, or vague abdominal pain.
- Always consider acute gallbladder disease in pregnant women and children with abdominal pain.
- Always obtain timely surgical consultation when complications of gallstone disease are considered and arrange for urgent biliary decompression in cases of cholangitis.

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CHAPTER 104
Hepatitis

Mark J. Ault and Joel M. Geiderman

Viruses are responsible for the majority of cases of acute hepatitis. The primary hepatotropic viruses include hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus, also called the delta agent (HDV), hepatitis E virus (HEV), and the non-A through E hepatitis viruses. In addition, Epstein–Barr virus (EBV), cytomegalovirus (CMV), and other viruses are known to cause hepatitis as part of a systemic infection, as are a variety of bacteria, rickettsiae, and protozoal organisms (Table 104.1). A similar clinical and histopathologic picture can result from a variety of toxic and metabolic processes.

TABLE 104.1
Infectious Agents Known to Cause Hepatitis

- Primary hepatitis viruses
  - Hepatitis A (HAV)
  - Hepatitis B (HBV)
  - Hepatitis C (HCV)
  - Hepatitis D (HDV)
  - Hepatitis E (HEV)
  - Non-A through E
- Secondary hepatitis viruses
  - Epstein–Barr
  - Cytomegalovirus
  - Herpes simplex
  - Varicella-zoster
  - Rubella
  - Rubeola
  - Mumps
  - Adenovirus
  - Coxsackievirus B
  - Yellow fever
- Nonviral infectious agents
  - Brucellosis
  - Ehrlichiosis
  - Gram-negative sepsis
  - Gram-positive toxic shock syndromes
  - Legionellosis
  - Leptospirosis
  - Malaria
  - Mycoplasma disease
  - Plague
  - Q fever
  - Salmonellosis
  - Syphilis
  - Toxoplasmosis
  - Tularemia
  - Tuberculosis

CLINICAL PRESENTATION

The clinical manifestations of hepatitis, regardless of cause, are protean and vary from individual to individual with respect to the severity of symptoms, duration of illness, and outcome. The ultimate

course of the illness is thought to depend on the nature of the etiologic agent, the extent of pre-existing or underlying liver disease, and, with infectious causes, the interaction between host factors, and the pathogen.

In its classic presentation, viral hepatitis has a highly characteristic clinical picture that is easily recognizable in its various stages. After a variable incubation period, a *prodromal phase* of illness occurs, with symptoms such as anorexia, low-grade fever, malaise, and lassitude. Often characterized as flu-like symptoms, they are nonspecific constitutional complaints typical of a variety of viral illnesses. Gastrointestinal symptoms may predominate, particularly in the adult patient, and abdominal discomfort representing hepatic, and occasionally splenic, enlargement may be reported. Within days to weeks after the onset of symptoms, the patient who enters the *icteric phase* of the illness first notes discoloration of the urine, representing the early rise of direct-reacting bilirubin and the spillage of bilirubin pigment into the urine. Subsequently, light (clay-colored) stools develop, scleral icterus may be noted, and clinical jaundice may become evident both to the patient and to the clinician as the serum bilirubin level exceeds 3 to 4 mg/dL. At this point, particularly in hepatitis A, symptoms may begin to resolve, heralding the *convalescent phase* of the illness.

Physical findings are highly variable in that the examination findings may be completely normal or may reveal frank jaundice and evidence of hepatic dysfunction. Liver enlargement and tenderness are common, and splenomegaly and lymphadenopathy may be present in 15% to 20% of cases.

Hepatitis may not be recognized when it does not present as the classic textbook picture because the history may be nonspecific or even misleading. This may occur, for example, when surreptitious toxin ingestion is involved or when the patient is reluctant to reveal specific risk factors for viral hepatitis.

If the patient is frankly jaundiced, hepatitis is usually readily considered. Recognition of more subtle findings such as scleral

discoloration, sublingual yellowing, or excoriations, which may only be evident on careful examination, may also be informative.

When frank jaundice is absent, a higher index of suspicion is necessary. Constitutional symptoms alone are not at all specific for hepatitis but nonetheless are usually a sensitive trigger for initial laboratory screening which may reveal viral hepatitis.

Extrahepatic manifestations are particularly prevalent in hepatitis B and are generally considered to result from the deposition of immune complexes in various extrahepatic sites. They include urticaria and morbilliform rashes, arthralgias and frank arthritis, hematuria and proteinuria, and, less commonly, vasculitis of the mixed cryoglobulinemia or polyarteritis nodosa types (7). Other extrahepatic manifestations are not believed to be immunologically mediated. Pancreatitis, pneumonitis, and myocarditis are thought to be caused by direct viral involvement.

Occasionally, a patient presents with advanced hepatic failure and no history of hepatitis. This may occur in the context of progressive chronic hepatitis, a toxic insult, or acute-on-chronic hepatitis. Unexplained encephalopathy, personality change, coagulopathy, hypoglycemia, or respiratory alkalosis should prompt consideration of hepatic disease, including hepatitis. The following is a discussion of the myriad causes of hepatitis.

Viral Hepatitis

During the incubation period, there are no clinical manifestations of disease, but viral replication is occurring and serologic and chemical markers of this activity and the host response to it can be detected. Clinical manifestations appear only if and when enough hepatocytes are invaded. The etiologic agent causing hepatitis cannot be determined from the clinical presentation. Therefore, in evaluating the patient with presumed viral hepatitis, one must be familiar with the serologic markers associated with the various types.

HAV is spread primarily by the fecal–oral route, although the virus can be found in the blood as well as in the liver, bile, and stool during the latter part of the incubation period. The 2-week period

before the onset of jaundice is the time of greatest infectivity; viremia, fecal shedding in the stool, and infectivity diminishes markedly by the time the icteric phase begins (Fig. 104.1). Source outbreaks are usually the result of fecal contamination of water supplies (e.g., with poor sanitation or during disasters) or food contamination, or occasionally by oral–anal contact. The incubation period is short: 2 to 7 weeks. The *preicteric* phase of hepatitis A usually lasts 4 to 14 days, presenting with nonspecific weakness, malaise, anorexia, nausea, and vomiting. There may be pain in the right upper quadrant and a characteristic loss of taste for cigarettes. Rash, urticaria, and joint pain occur infrequently, but the diagnosis of acute hepatitis should be considered in patients with these complaints. The term *preicteric* is presumptive (and often retrospective), because not all patients infected at this stage go on to have clinically evident jaundice. Children with hepatitis A typically manifest with gastroenteritis and commonly do not develop jaundice.

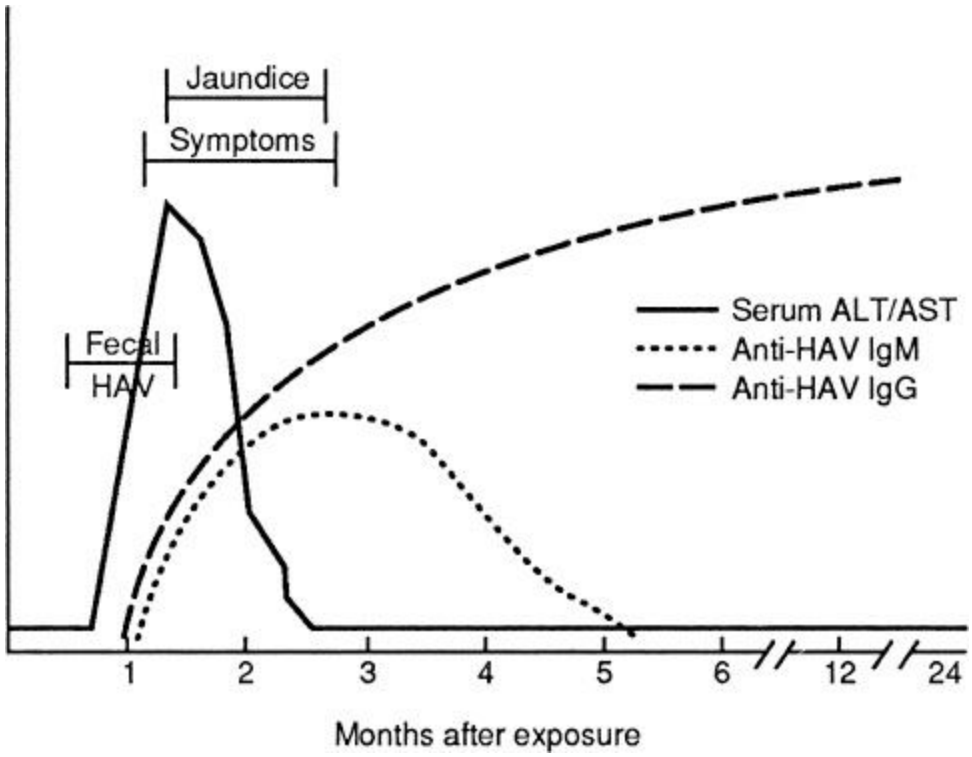

FIGURE 104.1 Serologic course of viral hepatitis A. Children usually have only mild symptoms with no jaundice. Adults more

often develop jaundice. (Adapted from Hoofnagle JH. Serologic diagnosis of acute and chronic hepatitis. In: Hepatology update/portal hypertension: viral hepatitis [postgraduate course of the American Association for the Study of Liver Diseases]. *Hosp Med.* 1988;6:26.)

The presence of dark urine frequently heralds the onset of the icteric phase and is often what prompts the patient to seek medical attention. Most of the other symptoms, with the exception of malaise, resolve shortly after the appearance of jaundice, which may persist for up to a month. However, jaundice appears in the minority of patients infected with HAV. The convalescent period is variable; weakness and malaise may last for months. The onset of hepatitis A is usually more abrupt than that of the other types of viral hepatitis, but this observation is not useful in the individual case. Figure 104.1 depicts the usual serologic and biochemical course of hepatitis A. The alanine aminotransferase (ALT) level begins to rise late in the incubation phase, just before the onset of symptoms. Fecal shedding has peaked before this time and is abating. During the symptomatic period, about 4 to 5 weeks after exposure, immunoglobulin M (IgM) antibodies to HAV (anti-HAV IgM) begin to rise. Because this antibody usually becomes undetectable after 4 to 5 months, its presence implies recent infection. IgG antibodies rise later and remain detectable for life. The presence of such antibodies in the serum of at least 50% of adults reflects the high incidence of asymptomatic or unrecognized prior infection.

HBV is spread by exposure to blood, contaminated needles, infected secretions, sexual contact, and perinatal contact. Its prevalence is high among homosexual men, intravenous drug abusers, dialysis patients, patients and staff of institutions for the mentally retarded, and in certain endemic regions of the world. HBV has an incubation period of 45 to 160 days, during which the virus is actively replicating and is present not only in the hepatocyte but in virtually all body fluids. Patients are contagious during this

asymptomatic period, and diagnostic serologic markers become positive. Immunoprophylaxis given before the onset of symptoms may prevent or attenuate the disease.

The acute clinical course of hepatitis B is similar to that of hepatitis A. Jaundice is more likely to occur in hepatitis B than A but still occurs in a minority of cases. About 85% of cases resolve completely, leaving the patient immune to hepatitis B; 1% to 3% of cases evolve into fulminant hepatitis, which has a mortality rate of 90%, and the remainder develop chronic hepatitis.

The serologic and biochemical courses of acute hepatitis B are depicted in Figure 104.2. The first marker to appear in the serum is the hepatitis B surface antigen (HBsAg), indicating infection with hepatitis B. Next, DNA polymerase, HBV DNA, and the hepatitis B e antigen (HBeAg) appear in the serum. These reflect active HBV replication and infectivity and appear well before the onset of biochemical damage to the liver. Of this group, only HBeAg can be measured easily; the presence of antibody to the HBeAg (anti-HBe) suggests low infectivity. In patients who become symptomatic, the ALT level rises and, in some, jaundice appears. It is important to understand the significance of the next immunologic event—the appearance of antibodies to the hepatitis B core antigen (anti-HBc), initially IgM, then IgG. This rise precedes the appearance of antibodies to the surface antigen (anti-HBs). In Figure 104.2, the gap between *HBsAg* and the rise of *anti-HBs* is called the “window,” when the sole specific marker of recent infection with HBV is the presence of anti-HBc IgM.

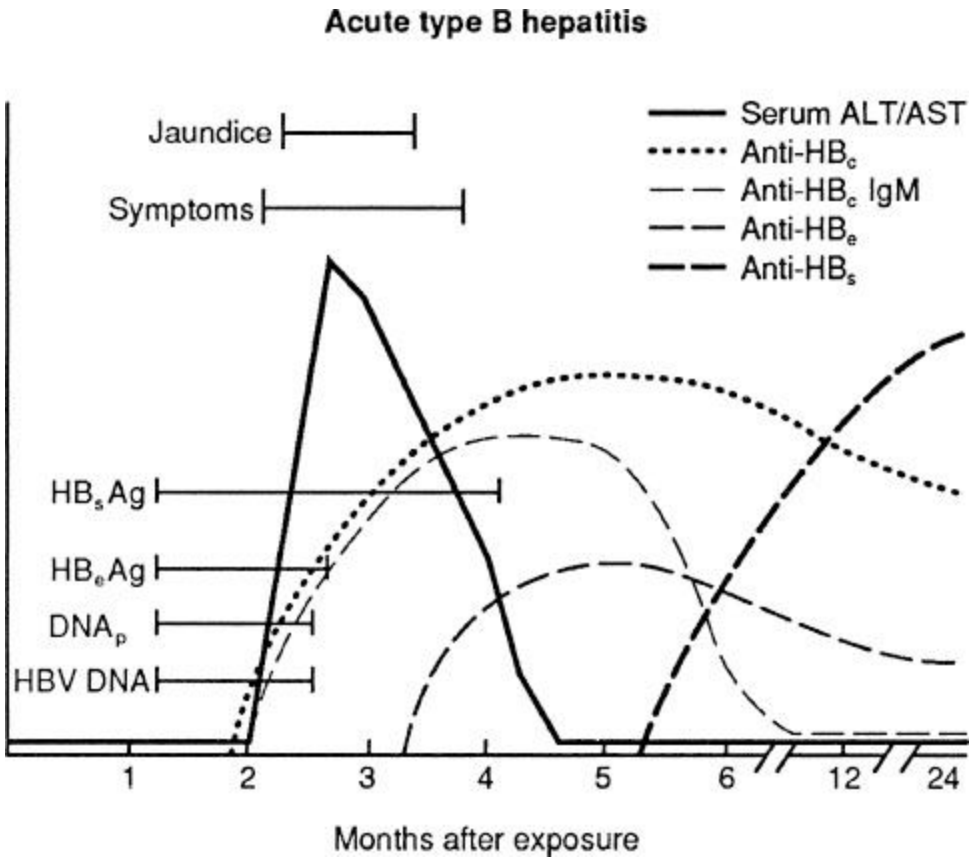

FIGURE 104.2 Serologic course of acute hepatitis B. This is more likely to cause jaundice than type A or non-A/non-B types. (Adapted from Hoofnagle JH. Serologic diagnosis of acute and chronic hepatitis. In: Hepatology update/portal hypertension: viral hepatitis [postgraduate course of the American Association for the Study of Liver Diseases]. *Hosp Med.* 1988;6:33.)

The rise of anti-HBsAg signifies immunity to HBV and corresponds to the abatement of symptoms and the return of ALT to normal levels. When hepatitis B fails to resolve, a chronic carrier state occurs. This is characterized by the persistence of HBsAg for a period exceeding 6 months and may be associated with the presence of either HBeAg or the antibodies to HBeAg. The carriage rate in United States is only 0.1% to 0.5% but may be as high as 5% to 20% in some demographic groups. Figure 104.3 depicts the typical serologic course of chronic HBV disease. Note that the HBsAg remains positive, anti-HBs is lacking, and the patient remains

susceptible to further liver damage or to superinfection with hepatitis D.

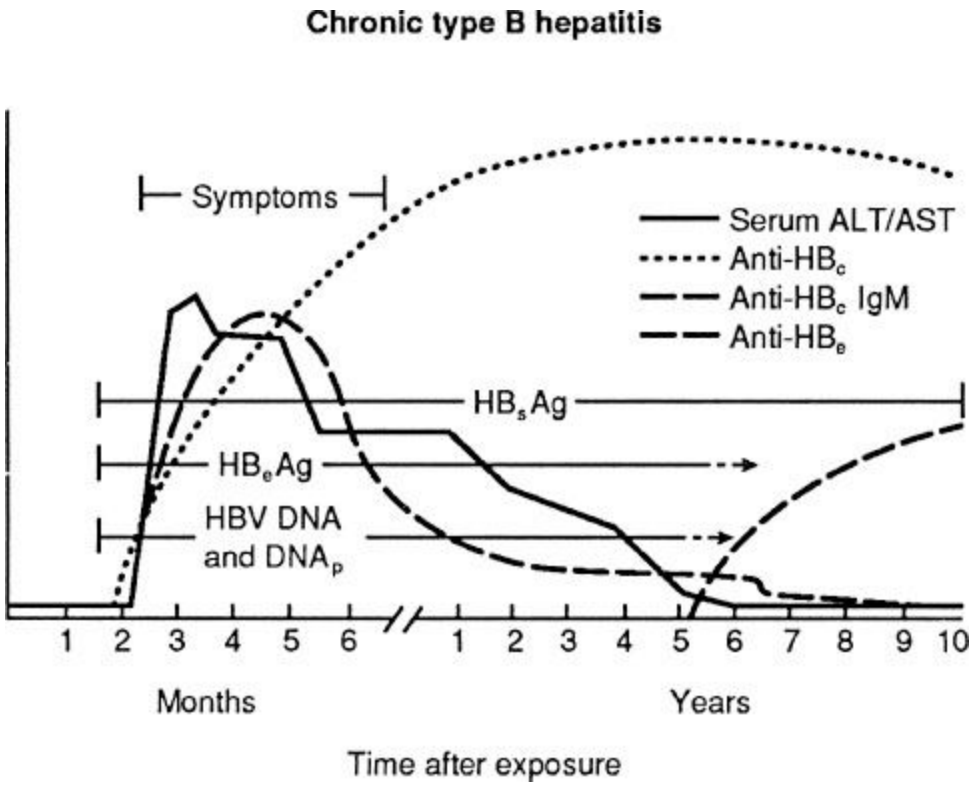

FIGURE 104.3 Serologic course of chronic hepatitis B virus (HBV) disease. (Adapted from Hoofnagle JH. Serologic diagnosis of acute and chronic hepatitis. In: Hepatology update/portal hypertension: viral hepatitis [postgraduate course of the American Association for the Study of Liver Diseases]. *Hosp Med.* 1988;6:33.)

HCV is an RNA virus of the Flaviviridae family. After the introduction of donor screening for HBV infection, posttransfusion hepatitis continued to be a significant problem. This led to the conclusion that most of the posttransfusion hepatitis was caused by another blood-borne pathogen, which was designated non-A, non-B (NANB) hepatitis. After the discovery of HCV in 1989 and the routine screening of the blood supply in the United States since 1990, it became clear that 80% to 90% of parenterally transmitted NANB hepatitis was caused by HCV. Currently, since the advent of genomic testing, the risk of transfusion-related hepatitis C is in the

range of 1 in 1,000,000 units transfused. Aside from blood transfusion, other parenteral sources of HCV infection include intravenous drug use, hemodialysis, organ transplantation, and occupational exposure. Low levels of transmission occur in sexual and household contacts and perinatally (i.e., vertical transmission) (1). There is no evidence that breast feeding transmits HCV from mother to baby. Sporadic cases also occur.

Hepatitis C viral RNA can be detected in blood within 1 to 3 weeks of exposure. Anti-HCV can be detected in 50% to 70% of patients at the onset of symptoms and in approximately 90% of patients 3 months after the onset of infection. However, the majority of infected patients are asymptomatic and anicteric. The symptoms of HCV—malaise, weakness, and anorexia—are similar to those seen with other types of hepatitis. However, compared with hepatitis B, the acute disease is usually milder. Acute HCV infection rarely causes fulminant disease.

Chronic disease, with persistent although sometimes intermittent viremia, occurs in 85% of infected patients (10). Most patients with chronic disease are clinically well (12). Unfortunately, although the natural history of HCV infection is somewhat unclear, most researchers would agree that the disease ultimately causes progression to clinically significant liver disease in a large portion of infected patients. Important factors leading to more accelerated progression of hepatic fibrosis include coinfection with HIV, infection with other hepatotropic viruses, alcohol use, and young age of acquisition. Hepatitis C is the leading reason for liver transplantation in the United States, owing to the high prevalence rate, estimated to be approximately 4 million (3).

Chronic HCV infection also leads to hepatocellular carcinoma in up to 5% of patients after 20 years. Once cirrhosis develops, the rate of acquiring hepatocellular carcinoma rises to 1% to 4% per year.

There are several different tests for hepatitis C, including anti-HCV by enzyme immunoassay (EIA), recombinant immunoblot assay (RIBA), HCV-RNA, viral load, and genotyping. Anti-HCV is positive in approximately 90% of infected patients, usually within 5 to 6 weeks after the onset of clinical hepatitis. However, it does not

distinguish among acute, chronic, and past infection, and positive tests are frequently falsely positive in populations with a low prevalence of infection. The HCV-RNA test identifies the presence of the virus in the blood. A reasonable testing strategy would be to order an anti-HCV and HCV-RNA. If both are negative, it is unlikely that the patient has acute hepatitis C. A positive anti-HCV and negative HCV-RNA generally represents remote infection. If both tests are positive, it may represent acute hepatitis C or an acute exacerbation of chronic hepatitis C. Finally, a positive HCV-RNA and negative anti-HCV is strongly suggestive of acute hepatitis C infection.

It appears that passive immunization with immune serum globulin derived from patients with previous HCV infection is unlikely to prevent disease, and no active vaccine is presently on the horizon. The Centre for Disease Control (CDC) recommends no postexposure prophylaxis. Until recently, treatment of chronic function has included combination therapy with recombinant α-interferon and ribavirin with the possible addition of boceprevir or telapravir, both protease inhibitors, for HCV genotype 1 infection (14). This resulted in a two- to threefold improvement in virologic response rates over the prior α-interferon monotherapy regimens. It is not known whether combination treatment can prevent the development of cirrhosis and hepatocellular carcinoma. Side effects of therapy are frequent and may prompt emergency department evaluation. Side effects of interferon include fever, nausea, irritability, and depression. Hemolytic anemia with subsequent decrease in the hematocrit is a common side effect of ribavirin and may require dose reduction.

In late 2013, the Food and Drug Administration approved 2 new direct acting antiviral agents, Sovaldi and Simeprivir, both oral agents, that can be effective in treating certain patients with chronic HCV infection. Treatment is tailored depending on viral genotype (14). A full discussion of the treatment of chronic HCV disease is beyond the scope of this text.

Hepatitis D, or delta hepatitis, is caused by a defective virus, the replication of which is dependent on the presence of HBsAg

synthesis. The virus consists of the delta-antigen–bearing core encapsulated by an HBsAg coat. It should not be surprising that a virus that requires HBV for its replication follows a similar transmission pattern. The clinical course of HDV infection depends on whether the virus is acquired at the same time as HBV (coinfection) or whether HDV infects a patient with chronic HBV infection (superinfection).

In coinfection, the fate of HDV parallels that of HBV. The clinical course is similar to that described for hepatitis B, although it is often more severe. Because patients with HDV superinfection, by definition, have not been able to mount an immunologic response sufficient to clear their HBV infection, these individuals are prone to unchecked HDV replication and fulminant hepatitis.

Hepatitis E, formerly called *enterically transmitted NANB hepatitis,* is responsible for more than 50% of acute viral hepatitis occurring in some developing countries (5). Caused by an RNA virus of the genus *Hepevirus,* this organism was originally discovered during electron microscopy of feces contaminated with enteric NANB hepatitis. More recently, isolation and sequencing of the hepatitis E viral genome has revealed four genotypes that fall into two major groups. Genotypes 1 and 2 cause epidemic hepatitis. Genotypes 3 and 4 cause a sporadic (autochthonous) form of hepatitis. These two variants have distinct clinical and epidemiologic characteristics.

The epidemic form, as its name implies, can have a fairly widespread distribution particularly in developing countries. Large outbreaks have occurred in Sudan and Iraq. It is generally of little concern in the United States, although imported cases have occurred in patients who have traveled to endemic areas such as India, Nepal, Pakistan, and parts of the former Soviet Union and Mexico. Clinically, the presentation is very similar to hepatitis A. Transmission is largely by the fecal–oral route and can result from contamination of the water supply, with human feces a frequent source of epidemic outbreaks. Secondary spread is uncommon. The clinical course is very similar to that of hepatitis A, with an incubation period of 2 to 9 weeks and an anicteric phase lasting 3 to 8 weeks. As in hepatitis A, nausea, vomiting, and diarrhea are

frequent and usually resolve with the onset of jaundice. Overall, the case fatality rate is approximately 5% but can be as high as 20% for pregnant women. No chronic hepatitis has been described for these genotypes.

While genotypically similar, autochthonous hepatitis E has a distinct clinical presentation from the more common epidemic form. Acquisition is generally attributed to food exposure, particularly undercooked pork and sausage. Autochthonous hepatitis E tends to present in an older age group. The disease is usually subclinical and mild, with icterus occurring in only 20% of cases. On the other hand, autochthonous hepatitis E is also associated with a striking spectrum of unique and serious extrahepatic complications which include acute-on-chronic liver failure, neurologic disorders, and chronic hepatitis. Patients with mild or unsuspected hepatitis from other etiologies may experience a fairly rapid appearance of ascites, encephalopathy, or overt liver failure, with secondary infection by hepatitis E. The extrahepatic manifestations may be striking and may be the predominant presentation. Neurologic symptomatology in particular, such as Guillain–Barré syndrome, Bell palsy, ataxia, confusion, or peripheral neuropathy, may be so striking as to obscure the primary diagnosis of hepatitis. Nonneurologic extrahepatic manifestations such as aplastic anemia, pancreatitis, or arthritis can present a similarly distracting clinical picture. While not common, autochthonous hepatitis E has been associated with chronic infection, predominantly in immunocompromised individuals. Liver transplantation patients, HIV-infected patients, and cancer patients receiving chemotherapy seem to be particularly susceptible. Although hepatitis E is not commonly diagnosed in the United States, exposure to the virus may be fairly common. Studies have found that up to 21% of adults in United States had anti-HEV antibodies, making it more common than hepatitis B (5.7%) or C (2%), and only slightly less common than hepatitis A (38.3%). Tests for anti-hepatitis E antibody are available commercially, but their sensitivity and specificity vary widely and at present do not have Food and Drug Administration approval. As with other forms of the viral hepatitis, treatment options are generally limited to supportive

care. Limited reports describing the use of ribavirin and peginterferon suggest a potential for viral clearance and a sustained response with treatment of chronic hepatitis E. This combination therapy has also been used in the treatment of severe, acute hepatitis E, although neither agent has been approved for this use. Hepatitis E infection is potentially preventable by vaccination, though at present this is more applicable to endemic areas. The most effective form of prevention at this time is for travelers to endemic areas to use strict enteric precautions, avoid exposure to raw shellfish, and ensure that pork has been cooked at 260˚F for at least 20 minutes.

Non-A through E hepatitis refers to the small population of patients with clinical hepatitis in whom all serologic studies on both the donor and the recipient patients are negative. With the discovery of new viruses and the development of new serologic tests, these patients will undoubtedly be further differentiated. One of these, independently discovered and named hepatitis G virus and hepatitis Gallbladder virus C, is an RNA virus of the Flaviviridae family (2). It appears to be blood-borne and has been found in as many as 10% of patients with non-A through E hepatitis. Its role has been questioned, and its definition as a true hepatotropic cause of acute or chronic hepatitis is yet to be determined (6). Similarly, hepatitis F virus has been isolated from the stool of a patient with hepatitis and transmitted to primates. As with hepatitis G, the role of this virus as a significant cause of non-A through E hepatitis is unclear.

Infectious, Nonviral Hepatitis

Although uncommon, hepatitis can accompany a wide variety of bacterial, rickettsial, and protozoal diseases. Included in this list are legionellosis, salmonellosis, tularemia, leptospirosis, brucellosis, plague, syphilis, gram-negative sepsis, gram-positive toxic shock syndromes, Q fever, mycoplasmal disease, tuberculosis, toxoplasmosis, ehrlichiosis, and malaria (see Table 104.1).

Autoimmune Hepatitis

Autoimmune hepatitis is a chronic inflammatory liver disorder of uncertain etiology. A standardized definition and diagnostic criteria have been developed (8). The diagnosis relies heavily on the exclusion of viral etiologies, lack of exposure to alcohol and other hepatotoxic agents, and hypergammaglobulinemia with gamma globulin levels >1.5 times the upper limits of normal. A scoring system for the quantitative diagnosis of autoimmune hepatitis has been proposed by the International Autoimmune Hepatitis Group. With a sensitivity of 97% to 100% and a specificity of 66% to 92%, it has utility in clinical practice especially for atypical or overlapping cases. Liver biopsy remains essential to the diagnosis and evaluation of disease severity in patients with autoimmune hepatitis. Compounding the diagnostic clarity of this illness is the recognition that the overlap syndrome, the simultaneous presence of autoimmune hepatitis and another liver disease, seems to occur more frequently than expected (9).

Clinically, the presentation may be extremely variable and difficult to differentiate from viral hepatitis. Two types have been described based on the presence of circulating autoantibodies. Type I (classic) autoimmune hepatitis has been associated with antinuclear and anti–smooth-muscle antibodies, and type II has been characterized by the presence of autoantibodies against liver–kidney microsome type I (anti-L K M-1). Both types are more prevalent in young females, and appropriate diagnosis is crucial, as they may be treated with prednisone and immunosuppressive therapy.

Toxic Hepatitis

Liver injury may result from direct hepatocellular toxicity or from idiosyncratic injury caused by a hypersensitivity-type reaction (10). Toxic exposures also may manifest as cholestasis, in which elevations of alkaline phosphatase and bilirubin levels predominate. Pharmacologic and chemical agents produce a diverse spectrum of hepatic insults, including both acute and chronic liver disease (Table 104.2). Drug-induced hepatic injury is the most frequent reason cited for withdrawal a drug approved by the U.S. Food and Drug

Administration (FDA) from the market, and it accounts for more than 50% of cases of acute liver failure in the United States. Although any evidence of hepatic dysfunction should prompt a diligent search for both intentional and inadvertent exposure to any of a number of chemical agents, several agents deserve specific mention because of the inherent likelihood of hepatocellular injury, because of their widespread use, or because of their particular relevance to the practice of emergency medicine.

TABLE 104.2
Drug-Induced Hepatitis

Clinical/Morphologic Presentation	Examples
Hepatitis (acute)	α-Methyldopa
	Isoniazid
	Phenytoin
	Chlorothiazide
	Nonsteroidal anti-inflammatory agents
	Statins
Cholestasis	Anabolic steroids
	Flutamide
	Oral contraceptive agents
	Erythromycin estolate
	Methimazole
	Chlorpropamide
	Chlorpromazine
Hepatic necrosis	Carbon tetrachloride
	Amanita phalloides mushrooms
	Acetaminophen
	Yellow phosphorus
Hepatitis (chronic)	α-Methyldopa
	Arsenic
	Isoniazid
	Halothane

Acetaminophen is one of the most common agents encountered in the acute setting that is responsible for striking liver enzyme elevations (see Chapter 285). Toxicity is dose-dependent, but several factors have been shown to contribute in a synergistic way to toxicity at even relatively low doses. These include concomitant alcohol ingestion, chronic phenobarbital use, or chronic exposure to moderately large doses of acetaminophen.

Hepatitis caused by *isoniazid* clinically resembles acute viral hepatitis and may occur in as many as 20% of patients taking the drug, with the risk and severity of injury increasing with the age of the patient. Clinical toxicity generally occurs in the first few months of therapy, but transaminase elevations greater than two to three times normal at any time must be considered potentially serious, because progression to fulminant hepatitis may occur.

Statins are generally well tolerated but have been associated with severe hepatocellular injury. Moreover, there is concern that concomitant use of nicotinic acid for the treatment of hypercholesterolemia may promote additional toxicity.

Although overt hepatotoxicity to *phenytoin* is unusual, use of the drug is particularly common, and prevention of serious toxicity requires an awareness of the nature and mechanisms of injury. Hepatic injury is believed to be caused by toxic metabolites; current evidence has implicated a heritable metabolic defect that may predispose to a viral hepatitis-like hypersensitivity reaction within weeks of starting therapy at usual therapeutic doses. Like the other toxic exposures, early detection and interruption of therapy can result in complete resolution and the avoidance of serious hepatic injury.

Troglitazone (Rezulin) was the first of a new class of oral agents used for the treatment of type II diabetes. The agent was originally approved by the FDA in 1997, and the recognition of significant hepatotoxicity appeared to outweigh the benefits of therapy, thereby leading to the withdrawal of *troglitazone* from the market. Two new agents of the same class have been available since 1999, *rosiglitazone (Avandia)* and *pioglitazone (Actos)*. They do not appear to have the same degree of hepatic toxicity, although liver injury

has been reported. Recognition of potential severe liver injury, monitoring of liver enzymes, and early discontinuation of therapy are important to maintain the safety of these agents (11).

Flutamide is an antiandrogen drug used in the treatment of metastatic prostate cancer. Well-documented cases of serious hepatotoxicity have been reported. Although the toxicity appeared to be reversible, several patients have died of massive hepatic necrosis, emphasizing the need for prompt consideration and diagnosis.

Hepatitis has been reported to be associated with the use of several of the *nonsteroidal anti-inflammatory drugs* (NSAIDs). Because of the frequency with which NSAIDs are used, emergency physicians should be aware of their potential for causing hepatic toxicity. *Sulindac* has received special attention because it has been well established as a cause of hepatitis, including fatal hepatic necrosis. Similarly, *bromfenac* was introduced for short-term use for the treatment of orthopedic pain. Reports of severe liver injury led to withdrawal of this agent.

In the past, the inhalational anesthetics *halothane* and *methoxyflurane* were well-known causes of fulminant hepatitis. Halothane has been superseded by newer agents, and methoxyflurane is no longer marketed in the United States.

Recently, reports have implicated *clopidogrel* as a cause of mixed hepatocellular and cholestatic liver damage. The true incidence of this complication is unknown, but *clopidogrel* is virtually universally used for patients undergoing percutaneous coronary intervention and in those with acute coronary syndromes. Additionally, treatment courses are generally protracted, thus resulting in more prolonged exposure. Routine liver enzyme testing is not currently recommended; however, given the wide use of this drug, clinical suspicion is reasonable in appropriate clinical settings.

A careful medication history should include an inventory of complementary and alternative medications. Studies have demonstrated that use of these modalities is common but volunteer reporting of their use to the physician is limited. Often referred to as simply “Chinese herbs,” specific compounds of interest include

germander, chaparral leaf, and weight loss preparations containing usnic acid.

It is worth mentioning that alcohol is probably the most common chemical to result in liver injury; this is covered in depth in Chapter 281 on Ethanol and its complications.

Metabolic Causes of Hepatitis

Although the metabolic causes of liver disease are numerous, several are notable for the potential for acute presentations. *Wilson disease* is a disorder of copper excretion. Patients generally present in adolescence when copper has had sufficient time to accumulate in excess. Liver involvement is common but, occasionally in younger patients, the illness will present as fulminant hepatitis. Prompt recognition and treatment are necessary to limit end-organ damage (13).

Acute fatty liver of pregnancy is a life-threatening condition that occurs late in pregnancy. Histologically, it is described as microvesicular fatty liver and is believed to be caused by disordered metabolism of fatty acids. Pregnant patients, usually in the 35th week or later, present with jaundice and hepatic failure frequently accompanied by disseminated vascular coagulation. The condition resolves with termination of pregnancy, although the mother must first be stabilized.

Reye's syndrome presents almost exclusively in children younger than 15 years. Though an association with salicylate use has been noted, it can occur in the absence of salicylates. It is generally seen after upper-respiratory illness, especially influenza and chickenpox, and is characterized by hepatic injury, hypoglycemia, and encephalopathy. Care is supportive, and chronic liver disease has not been reported when recovery occurs.

Another cause of elevated transaminase levels (transaminitis) that should be considered in the differential diagnosis is *hepatobiliary disease.* Elevated ALT and aspartate amino transferase (AST) levels should not lead one on a fruitless search for infection or toxic causes of hepatitis when the chemistry patterns suggest hepatobiliary

obstruction (i.e., elevated serum bilirubin, alkaline phosphatase, and γ-glutamyl transpeptidase levels [GGTP]).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for the patient with right upper quadrant abdominal pain is extensive and includes hepatitis, biliary colic, cholecystitis, peptic ulcer disease, pyelonephritis, renal colic, cardiac ischemia, and right lower lobe pneumonia. The differential diagnosis for jaundice includes many other possibilities, and is discussed further in Chapter 101. Once the differential has been narrowed to hepatitis, the next task is to determine the specific etiologic agent, whether infectious, toxic, metabolic, or autoimmune. Eliciting a history of risk factors, medications, exposures, and clinical course as described previously, combined with laboratory testing, will help in determining the specific cause.

ED EVALUATION

Evaluation of suspected hepatitis may be divided into several steps. The first step is to make the diagnosis, which, in light of the previous discussion, may not be entirely straightforward. Clearly, a reasonable index of suspicion is necessary in most cases, and the physician must consider the relative likelihood of illness in each patient compared with the risk of excessive testing in the many patients with nonspecific symptomatology.

If the likelihood of hepatitis is present but low, a reasonable approach initially is to order a serum AST level as a preliminary screen. Although nonspecific, this is a sensitive screen, and a normal AST value virtually excludes hepatocellular disease.

In patients in whom hepatic disease is believed to be more likely or who has an abnormal AST level on the preliminary screen, more extensive laboratory testing is necessary. This should consist of indices of necrosis (AST and ALT) as well as indices of cholestasis (alkaline phosphatase, total bilirubin, or GGTP). Although these values lack diagnostic specificity, certain patterns may be helpful in limiting the differential diagnosis and in directing further

evaluation. For instance, a transaminase elevation >10 times normal strongly suggests acute viral or toxic injury and essentially excludes chronic hepatitis. Elevation of alkaline phosphatase and bilirubin values suggests intrahepatic or extrahepatic obstruction. Transaminase elevations of two to three times normal, with the AST higher than the ALT, suggest alcoholic injury.

In the second step of the evaluation, specific tests of hepatic synthetic function are necessary. Serum protein, albumin, and glucose levels should be used in conjunction with the serum bilirubin level to assess the extent of hepatocellular dysfunction. If there is indication of central nervous system involvement, with lethargy or confusion, a serum ammonia level may serve as a useful baseline for serial evaluations.

Further evaluation should focus on defining the specific cause of the illness. If hepatocellular necrosis is the dominant picture, detailed serologic studies (anti-HAV IgM, HBsAg, anti-HBs, anti-HBc, anti-HCV by enzyme immunoassay (EIA), HCV-RNA and Monospot test) are warranted, as well as a diligent historical search for foreign travel to HEV-endemic regions and for drug or toxic exposures. If cholestasis is the dominant picture, ultrasound examination should be performed to exclude mechanical obstruction.

KEY TESTING

- Consider the diagnosis of hepatitis and the risk profile. If risk is low, consider screening with an AST. If high, test more extensively for hepatic necrosis and obstructive etiologies.
- If hepatitis is confirmed, stage the severity of disease and seek evidence of clinically significant hepatic dysfunction: serum protein, albumin, glucose, and bilirubin, and ammonia levels if altered mental status is noted.
- Begin a search for a definitive diagnosis. Send acute hepatitis serologies and consider drug exposures (especially acetaminophen and alcohol) and travel history.

ED MANAGEMENT

Patients with acute viral hepatitis may present to the emergency department because of signs and symptoms typical of a viral syndrome that may include prostration, nausea, vomiting, and dehydration. Treatment for these patients is symptomatic and is usually limited to intravenous fluids, acetaminophen, and antiemetics. Metoclopramide (Reglan) or ondansetron (Zofran) are the antiemetic agents of choice, because phenothiazines can impair hepatic excretory function and may produce cholestasis. Patients who present without symptoms or present because they have noticed jaundice require no specific therapy.

For patients with diagnosed viral hepatitis, there is no specific therapy indicated beyond supportive care and symptomatic treatment. If the prothrombin time is prolonged, the patient should receive vitamin K. Immune globulin is of no use for the patient who has already contracted hepatitis. Corticosteroids are probably harmful rather than beneficial.

Patients who present because they have been exposed, or think they have been exposed, to hepatitis present a different management problem (see Chapter 194). Immunoprophylaxis is highly effective if given under the proper circumstances. Because this treatment should be guided in part by serologic studies, it is often not initiated in the emergency department.

If results of serologic testing are not available in a timely fashion, therapy must be empiric. The discussion that follows and Table 104.3 should help guide immunoprophylactic therapy.

TABLE 104.3
Immunoprophylaxis of Viral Hepatitis

Type	Persons at Risk	Immunoprophylaxis
A	Household and sexual contacts[a] Staff and attendees of daycare centers Staff and residents of custodial institutions	Immune globulin, 0.02 mL/kg IM
B	Sexual contacts	Hepatitis B immune globulin, 0.06 mg/kg IM
	Percutaneous or transmucosal exposure	Begin active immunization (Heptavax or Recombivax)
C	Intravenous drug abusers, intranasal cocaine abusers, homosexuals, multiple sexual partners, perinatal exposure, household contacts	None
D	Same as B	Protection against hepatitis B
E	Travelers to endemic areas	None in serum pooled from US donors
Non-A through E	Percutaneous exposure to blood or certain products of patients with no serologic evidence or HAV, HBV, or HCV	None

HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.
[a]Residents of dormitories and barracks are frequently included in this group.

Patients considered at risk for contracting hepatitis A include household and sexual contacts of persons with hepatitis A, staff and attendees at daycare centers, and staff and residents in close contact at custodial care institutions. Immune globulin, which is derived from pooled human serum but treated so as not to be capable of transmitting HIV infection or other diseases, is given as a single intramuscular dose of 0.02 mL/kg as soon as possible within the first 2 weeks after exposure. Casual contacts need not be treated.

Postexposure prophylaxis for hepatitis B is indicated for sexual contacts of persons with hepatitis B or after percutaneous or transmucosal exposure to HBsAg-positive blood. For nonimmunized patients, treatment is with hepatitis B immune globulin, 0.06 mL/kg intramuscularly. Active immunization should be started at the same time. If information about the source patient is unknown but can be

obtained within 5 to 7 days, it is reasonable to wait. If not, one must make a decision based on risk factors such as sexual contacts and intravenous drug use. See Chapter 191 for more information on postexposure prophylaxis.

Immunoprophylaxis has not proven useful in patients who have been exposed to hepatitis C or in those suspected of being exposed to non-A through E hepatitis.

CRITICAL INTERVENTIONS

- Hospitalize patients with evidence of fulminant hepatitis (e.g., significantly impaired synthetic function, encephalopathy).

DISPOSITION

Most patients with hepatitis do not require hospital admission, but it is recommended in circumstances such as intractable nausea and vomiting, dehydration, or severe electrolyte imbalance or for signs of hepatic deterioration, as evidenced by changes in sensorium or increased international normalized ratio. Patients with signs or symptoms suggesting a fulminant course of hepatic failure require admission. The absolute levels of serum transaminase values should not be a criterion for admission.

Patients with acute viral hepatitis who are discharged should be prescribed antiemetic agents and instructed to ensure adequate caloric intake. It is best to allow patients to eat small meals of their choice rather than insist they follow some of the high-calorie or high-protein dietary regimens that have been proposed. Prolonged bed rest, once a staple of care, has been shown to be of no value and has its own risks (6). Alcohol consumption should be avoided during the acute illness. After recovery, alcohol consumption has not been shown to be any more harmful for these patients than for the general population (4). Estrogen-based oral contraceptives may be continued during hepatitis.

Patients with acute hepatitis should be seen by an internist or gastroenterologist for follow-up within a few days, after the results of serologic tests. Patients with any prolongation of the prothrombin

time are often admitted to the hospital, but others should probably be seen the next day. Instructions should include an admonition to return if food and fluids cannot be kept down or if there is any change in sensorium.

Finally, it is the duty of the emergency physician in many locales to notify public health authorities of cases of acute hepatitis. Patients and their close contacts should be counseled with regard to preventing the spread of hepatitis.

Common Pitfalls

- Missed toxic ingestion or exposure, with continued exposure.
- Failure to recognize hepatitis B or hepatitis C by performing serologic tests during "window periods" between infection and seroconversion.
- Missed hepatobiliary disease, with failure to diagnose surgically correctable lesions.
- Failure to recognize the distinction between liver tests and liver function (e.g., patients with cirrhosis may have nearly normal enzyme levels; patients with "sky high" transaminase levels may have reasonably intact synthetic capability).
- Inappropriate admission of patients with uncomplicated hepatitis and markedly elevated ALT or AST levels without consideration of synthetic factors or clinical status.
- Inappropriate discharge of patients with early evidence of synthetic failure.
- Failure to follow-up contacts for recommended prophylaxis.
- Inappropriate restrictions: Patients with hepatitis need not be excluded from school or work; education regarding precautions is indicated.
- Failure to consider the effects of hepatitis on drugs with hepatic clearance, resulting in high serum levels or long duration of action.

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CHAPTER 105 Hepatic Failure and Cirrhosis

Stacie Zelman

Acute hepatic failure (AHF) differs clinically, therapeutically, and prognostically from hepatic cirrhosis, but priorities for the management of both entities have similar features. AHF is relatively rare with approximately 2,000 cases per year in the United States but is associated with a high mortality rate (1). The majority of cases are due to acetaminophen overdose and drug reactions, followed by viral illness (2). Hepatic cirrhosis is a more common condition in the United States and also has a high mortality rate accounting for approximately 25,000 deaths in 2000 (3). Cirrhosis is most commonly caused by alcoholism or hepatitis C. The presence of ascites in combination with cirrhosis has an association with poor long-term survival (3).

CLINICAL PRESENTATION

The presentation of AHF is, to some degree, dependent on the specific etiologic agent, but the basic definition is altered mental status (encephalopathy) with coagulopathy (INR >1.5) in a patient without previously known liver pathology (1,4). Other symptoms that may be present are jaundice, motor dysfunction, and fetor hepaticus (a sweetish, musty, or pungent odor on the breath). In severe cases, a patient may present with signs indistinguishable from septic shock including tachycardia, hypotension, and multiorgan failure (5).

The manifestations of hepatic encephalopathy in both AHF and cirrhosis are similar, but the onset is generally slower with cirrhosis. Encephalopathy may present anywhere on a continuum of mild confusion to frank coma. Encephalopathic patients with cirrhosis commonly present with euphoria, depression, or muscular incoordination or may demonstrate more obvious mental status changes. Symptoms such as malaise, lethargy, fluid retention, loss of libido, and pruritus are common, and typical physical findings include hepatomegaly, spider angioma, ascites, and jaundice (Fig. 105.1). Asterixis, a flapping tremor best seen with the patient's arms outstretched and wrists hyperextended, is a classic symptom that is absent in many cases. The factors most commonly precipitating hepatic encephalopathy in patients with cirrhosis are infection, gastrointestinal bleeding, use of tranquilizing drugs or alcohol, and overuse of diuretics.

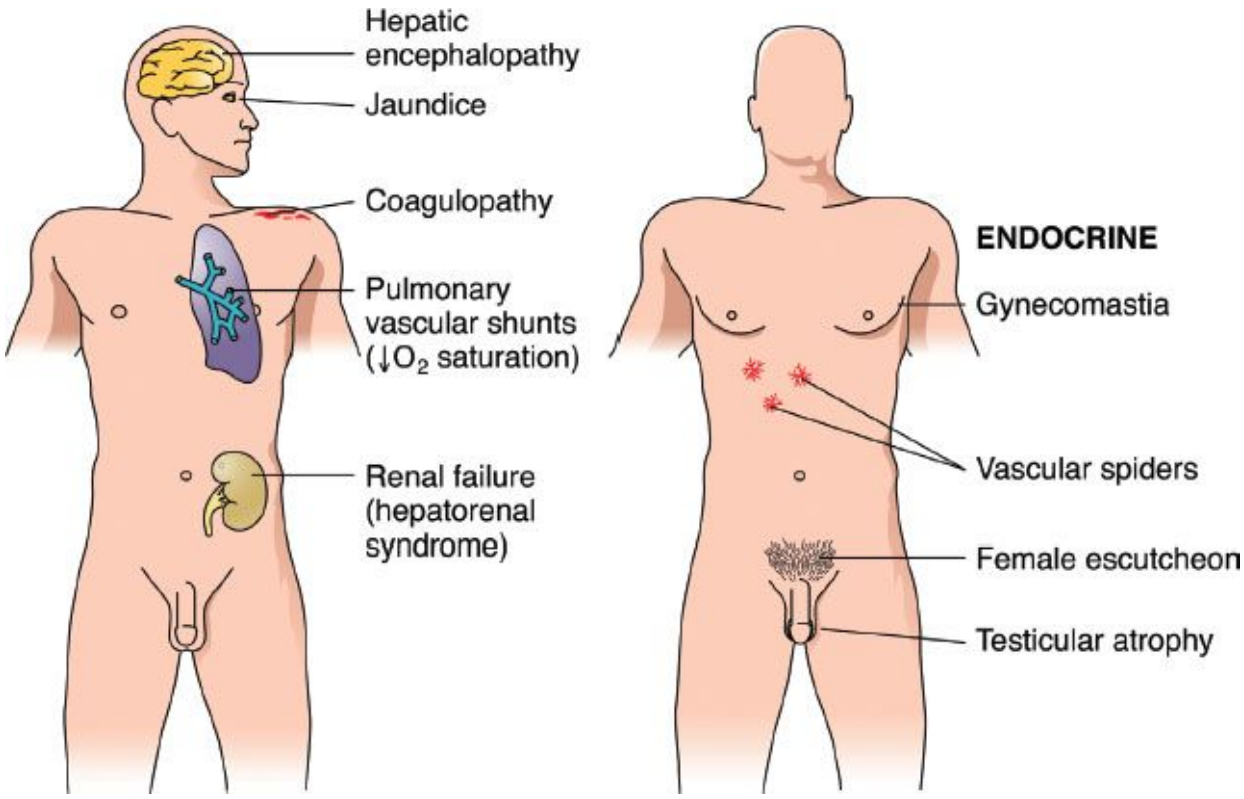

FIGURE 105.1 Complications of hepatic failure. (Image from Rubin E, Farber JL. *Pathology.* 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.)

Most patients with hepatic disease are, at baseline, immunocompromised. Thus, any infection, such as spontaneous bacterial peritonitis (SBP), pneumonia, urinary tract infection, and systemic inflammatory response syndrome (SIRS), are serious complications. Infection is a prominent precipitant of acute chronic liver failure and can advance to multisystem organ failure (6,17). Febrile patients with cirrhosis, ascites, and abdominal pain should be considered to have SBP until proven otherwise, as SBP complicates up to 33% of these patients (7,8). Patients admitted with SBP and septic shock have a mortality rate greater than 70% (9). While typical signs of infection may not always be apparent in this population, rapid treatment at first suspicion should be a priority.

Because of portal hypertension and secondary esophageal varices, death from gastrointestinal bleeding is more common with cirrhosis than with AHF. In the later stages of cirrhosis, ascites may become markedly symptomatic with abdominal pain and shortness of breath (3). The hepatorenal syndrome, or functional renal failure, occurs in advanced cirrhosis and is commonly fatal.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of cirrhosis and AHF varies, depending on presenting symptoms and precipitating causes. The differential diagnosis of cirrhosis presenting with jaundice includes hemolysis, biliary tract obstruction, viral hepatitis, hepatotoxic ingestions, septicemia, and numerous minor causes. The association of mental status changes with jaundice should alert the emergency physician to the possibility of hepatic encephalopathy. In the patient without known chronic liver disease, the differential diagnosis of hepatic encephalopathy includes viral hepatitis, fatty degeneration of pregnancy, Reye syndrome, and hepatotoxic ingestions such as acetaminophen, isoniazid, rifampin, *Amanita phalloides* mushrooms, carbon tetrachloride, or ecstasy. Historical information, such as preillness activity, previous suicidal behavior, and the presence of fever or malaise, may help to differentiate among potential causes.

Patients with hepatic cirrhosis may have chronic jaundice and may sustain acute mental status changes for reasons other than hepatic

encephalopathy. Because alcoholic patients are at greater risk for bleeding after a traumatic event, subdural hematoma or other form of ICH must be considered in cirrhotic patients with altered sensorium. Patients with renal failure also may present with features suggestive of severe liver disease—altered sensorium, fluid retention, and coagulopathy. Alcoholics may develop pancreatitis or alcoholic hepatitis, with severe dehydration and associated mental status changes that may mimic hepatic encephalopathy.

ED EVALUATION

Current and past medical information should be sought from the patient, prehospital personnel, family, previous medical records, and the patient's private physician to differentiate acute from chronic abnormalities. ABCs need to be addressed before secondary evaluation may begin.

Key points of the physical examination include the following:

- Examination of the conjunctiva and skin for the presence of jaundice (Fig. 105.2)

FIGURE 105.2 Jaundice. A patient in hepatic failure displays a yellow sclera. (Image from Rubin E, Farber JL. *Pathology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.)

- Abdominal examination for the presence of ascites and liver size
- Rectal examination for evidence of gastrointestinal bleeding
- Careful neurologic examination with attention to subtle changes in mental status. Asterixis, alterations in motor tone, or abnormal posturing should be noted.

Appropriate laboratory testing includes blood counts and electrolytes, as well as serum ammonia, coagulation studies (PT/INR), and in some cases toxicologic studies or acetaminophen level. It is important to keep in mind that encephalopathy may precede an elevated ammonia level. Chest radiography may be indicated if pulmonary edema or pleural effusion is suspected. Abdominal imaging with CT or ultrasound may be useful in the evaluation of abdominal pain, excluding biliary tract disease, or localizing ascites. If SBP is suspected or ascites is excessive, paracentesis is indicated, with subsequent laboratory evaluation for cell counts, Gram stain, and culture. The diagnosis of SPB is determined on the basis of positive culture or ascitic fluid with a absolute neutrophil count >250 cells/mL (3).

KEY TESTING

- **Lab Studies:** complete blood count (CBC), electrolytes, ammonia, INR, and acetaminophen level
- **Imaging:** chest x-ray (CXR), abdominal ultrasound, and CT of abdomen/pelvis
- **Paracentesis**

ED MANAGEMENT

The treatment of hepatic encephalopathy in patients with AHF requires a more aggressive approach than in those with an exacerbation of chronic liver disease. Hepatic encephalopathy in AHF develops rapidly and is almost always complicated by cerebral edema, with possible central herniation of the brain (5).

Immediate attention should be given to securing a patent airway and initiating artificial ventilation if the patient is comatose or lacks an active gag reflex. Supplemental oxygen should be given, even in

the absence of pulmonary edema. Fluid resuscitation should be aggressive in hypotensive or bleeding patients and should be undertaken despite the possibility of pulmonary edema (5,10). Persistent hypotension signals the need for vasopressors with the preferred drug of choice being norepinephrine (10).

Patients should be placed on a cardiac monitor and quickly assessed for dysrhythmias. Blood glucose should be monitored closely, as impaired glucogenesis and reduced glycogen stores predispose these patients to hypoglycemia (11). Patients who demonstrate clinical signs of significant, increased intracranial pressure, such as abnormal posturing or unreactive pupils, should receive mannitol 0.5 g/kg intravenously over 10 minutes (after head CT) (12). Fresh-frozen plasma (2 to 4 U) should be given when the prothrombin time is >1.5 times normal and there is evidence of active bleeding (12). Platelet infusions (5 to 10 U) are recommended when thrombocytopenia is severe ($<10{,}000$ or $<50{,}000$ in the presence of active bleeding) (12). Severe variceal bleeding when present should be treated with blood, antibiotics (a quinolone or third-generation cephalosporin), endoscopy within 12 hours, and vasoactive therapy (such as octreotide 25 to 50 μg/hr) (13).

Proven or suspected infection should be treated promptly. Cultures may be used to modify therapy, but if SIRS or septic shock is evident, empiric antibiotics should be started immediately. Responsible organisms are both gram-positive and gram-negative, but gram-negative organisms may have an increased association with worsening encephalopathy (14). Empiric broad-spectrum coverage such as piperacillin–tazobactam (3.375 g intravenously) or cefotaxime (1 to 2 g intravenously) is recommended. Care should be taken not to use nephrotoxic or hepatotoxic antibiotics unless there is a favorable risk/benefit ratio. In addition, aspiration pneumonia should be considered in these patients, and if suspected, it should be treated with pulmonary toilet, ventilatory support, and broad-spectrum antibiotics. Prophylactic antibiotics in AHF are controversial.

Lactulose may decrease the severity of hepatic encephalopathy in cirrhosis, but its benefits in AHF are unproven (5). *N*-acetylcysteine

improves survival from acetaminophen overdose, even late in its course (12).

Decisions concerning potential transplantation for AHF should be made early by a gastroenterologist (12,15). In many cases of severe AHF, transplantation is the only means of increasing the chance of survival (15). Survival after transplantation is nearly 70% (15). Artificial liver support is helpful for acute-on-chronic liver failure (16), but in general is not recommended outside clinical trials (12).

For the management of symptomatic recurrent ascites in cirrhotic patients, large-volume paracentesis is recommended as having fewer side effects than diuretics and a comparable rate of fluid reaccumulation (3,16). Hypovolemia may occur 3 to 6 hours later when volumes of >5 L are removed. Administration of albumin, 8 g/L of ascites removed, is recommended in some cases. Other plasma volume expanders are available, but albumin is thought to have greater circulatory protection (7). Ultrasound-guided paracentesis may lower needle-related intra-abdominal complications.

When patients with hepatic cirrhosis present to the emergency department with nonlife-threatening conditions, care must be taken to avoid interventions (e.g., medications) that may cause clinical deterioration. Sedatives may trigger clinical hepatic encephalopathy. Nonsteroidal anti-inflammatory drugs may induce renal failure in cirrhotic patients and should be used with caution and at appropriate doses.

CRITICAL INTERVENTIONS

- Airway control for obtunded liver failure patients
- Fluid resuscitation and pressor support as indicated for patients in shock
- Fresh-frozen plasma and platelets in patients with bleeding or undergoing invasive procedures
- Appropriate cultures and intravenous antibiotics for suspected or proven infection
- Oral or rectal lactulose for patients with cirrhosis and hepatic encephalopathy

DISPOSITION

Patients with gastrointestinal bleeding, SBP, and hepatic encephalopathy should be admitted to the hospital. Those with severe presentations often require an intensive care setting, and immediate consultation with a gastroenterologist is indicated. For severe cases, consideration should be given to transporting the patient to a facility capable of critical care and liver transplantation (15).

Because patients with chronic liver disease commonly respond poorly to illness or other stresses, indications for admission to the hospital are generally less stringent than for other patients. Thus admission for intravenous antibiotic treatment should be considered for most infections.

Common Pitfalls

- Failure to consider a hepatotoxic drug as the cause of the patient's symptoms. Patients who have ingested a hepatotoxic drug may be unwilling to give an adequate history and may present early in the course of their illness, before there is obvious clinical evidence of hepatic failure.
- Ruling out the diagnosis of hepatic encephalopathy on the basis of a normal serum ammonia level.
- Failure to adequately treat hypoglycemia. One bolus of 50% dextrose may not be adequate therapy because of depleted glycogen stores; in this case, maintenance infusions of D_{10} or D_{20} should be administered.
- Failure to identify causes of coma other than hepatic encephalopathy in patients with cirrhosis. In particular, subdural hematoma/Intracerebral hemorrhage, drug overdose, and meningitis/encephalitis should be ruled out.

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CHAPTER 106 The Liver Transplant Patient

Douglas W. Lowery-North and Scott R. Votey

Since the first human orthotopic liver transplant (OLT) in 1963, more than 120,000 transplants have been performed in the United States. Three-year survival rates for both patients and grafts of nearly 70% to 80% are the result of utilization of multidisciplinary care teams, increased availability of organs, improved organ allocation systems, newer operative techniques, safer immunosuppressive regimens, and improved management of postoperative complications (1–3). More than 120 US centers perform approximately 6000 OLT operations each year. As of 2011, more than 62,000 liver transplant recipients were living in the United States, and the number of OLT recipients presenting to the emergency department (ED) continues to rise. To provide effective care, ED physicians must be aware of the particular OLT-related problems these patients may experience.

TRANSPLANT SURGERY

Surgical innovations have resulted in several transplant technique variants. A whole cadaveric liver can be transplanted, or the organ can be surgically split to provide two transplantable segments, or reduced for transplant into a single smaller recipient. Alternately, a portion of the liver, usually the right lobe, can be transplanted from an adult living donor into a child or an adult (2,4–6). Regardless of the technique used, the liver is transplanted without a gallbladder.

Transplantation of the donor organ into the recipient has three major phases. First, the recipient undergoes hepatectomy. Typically, a bilateral subcostal incision is made, which is extended cephalad in the midline. The recipient may be placed on femoral to axillary venovenous bypass, and the recipient portal vein and inferior vena cava (IVC) are clamped. After vascular clamping, hepatectomy is performed. In the second phase the donor graft is inserted, and the vascular anastomoses are performed, beginning with the suprahepatic and infrahepatic IVC, followed by the portal vein, and finally the hepatic artery. Vascular clamps are released, and reperfusion of the graft occurs. In the third phase, the biliary anastomosis is performed. Most adult recipients have an end-to-end re-anastomosis (choledochocholedochostomy) with or without T-tube placement. T-tube placement affords direct monitoring of bile production as well as access for evaluation of the biliary system by T-tube cholangiography. Despite these advantages, T-tube use has declined owing to a high rate of postoperative complications (7,8). Alternately, a Roux-en-Y loop with a choledochojejunostomy can be performed. This technique is used in patients having intrinsic biliary system disease, such as biliary atresia or primary sclerosing cholangitis, or who are undergoing repeat transplantation. Pneumobilia is a normal result of choledochojejunostomy.

Typical Posttransplant Course

After surgery, OLT recipients spend several days in an intensive care unit (ICU), during which time their liver function indices are closely monitored. Recipients continue on an aggressive immunosuppressive regimen, begun intraoperatively, designed to minimize immune-mediated graft rejection. Immunosuppressive regimens continue to evolve and vary between institutions, but currently the most common initial “tolerance-friendly” regimen consists of three drugs: tacrolimus (TAC), mycophenolate (MMF/MPA), and prednisone (9,10). Alternate regimens include two drug regimens consisting of TAC combined with MMF/MPA, and TAC combined with prednisone.

Early postoperative complications of transplantation include bleeding and primary nonfunction (PNF) of the graft. Systemic coagulopathy, thrombocytopenia, and portal hypertension-induced abdominal venous collaterals render OLT candidates susceptible to bleeding complications. Postoperative bleeding is usually the result of dehiscence of a vascular anastomosis, and patients present with intraperitoneal hemorrhage before discharge from the hospital (11). Emergency physicians are much more likely to encounter OLT patients with upper gastrointestinal tract bleeding from peptic ulcer disease. Upper and lower gastrointestinal tract bleeding in OLT patients is managed in the standard fashion.

PNF occurs in 4% to 10% of adult OLT recipients. The pathophysiology is multifactorial. Graft harvest technique, ischemia time, reperfusion injury, and graft size all influence graft viability (4). Early bile production, restoration of normal clotting function, and the absence of lactic acidosis are signs of good graft function. Profound hypoglycemia, progressive coagulopathy, metabolic acidosis, progressive encephalopathy, and hemodynamic instability clinically characterize graft failure. The only therapy for PNF is prompt retransplantation.

In the absence of complications, OLT recipients are transferred from the to a surgical ward for additional days. Close outpatient care at the transplant center continues for an additional 1 to 2 months, during which time patients undergo careful adjustments of their immunosuppressive regimens. Recipients are then followed up on a monthly basis for the remainder of the first year after transplantation. The progressive withdrawal of corticosteroids now begins during the first 3 months but may be delayed. The follow-up interval after 1 year is decided on a case-by-case basis.

CLINICAL PRESENTATION

OLT patients present to the ED with a wide variety of illnesses. Emergency physicians encounter vascular and biliary anastomotic complications, rejection, infections, and medication-related adverse effects in these patients.

Vascular Complications

Typically, there are one arterial and several venous anastomoses performed at the time of transplantation. However, up to 25% of transplant recipients have normal anatomic variants of their arterial circulation that require additional anastomoses (12). Each anastomosis is vulnerable to leakage, thrombosis, stenosis, and pseudoaneurysm. The most common vascular complications after liver transplantation are hepatic artery thrombosis (HAT), hepatic vein thrombosis (HVT), and portal vein thrombosis (PVT) (11,13). Together they account for about 10% of graft failure in adults and 40% of graft failure in children. The mortality of HAT ranges from 15% to 55% in adults, with death being more common if thrombosis occurs soon after transplantation. Fortunately, the incidence of HAT has been declining owing to improved surgical technique, from rates as high as 26% in the 1980s to $<10\%$ currently. Nevertheless, HAT continues to account for the majority of post-OLT vascular complications. The vascular supply to the donor common bile duct endothelium is entirely dependent on the newly reconstructed hepatic artery. The graft, in contrast to the native liver, has no collateral arterial blood supply, and any disruption to hepatic artery blood flow rapidly leads to bile duct necrosis, with resultant bile duct leaks, graft dysfunction, abscess formation, and sepsis. Although HAT tends to occur within the first month and most often within the first week after transplantation, it may occur months or even years later. The clinical presentation of HAT varies. Patients typically have fever and jaundice and may have right upper quadrant abdominal pain. Some present acutely ill with peritonitis or sepsis. Laboratory evidence of graft dysfunction (elevated transaminases and bilirubin levels) is present. Rapid deterioration of graft function is common, and patients often require retransplantation. Patients with HVT and PVT have similar presentations but are often less acutely ill and typically have better outcomes.

Biliary Complications

With an incidence of 17% to 28%, biliary complications—bile leaks and obstructions to bile flow from strictures, stones, or ampullary dysfunction—are the most common anastomotic complications of OLT (8,14–16). Biliary complications are typically the result of technical complications or ischemic injury to the bile ducts. Biliary leaks and strictures occur with both choledochocholedochostomy and Roux-en-Y choledochojejunostomy anastomoses. T-tubes are also associated with biliary leaks. Although biliary leaks tend to occur in the first month postoperatively and biliary obstructions are usually a later complication, the presentations are similar. Patients typically complain of abdominal pain, jaundice, or fever. In some cases evidence of cholangitis or peritonitis may be present. Unfortunately, some patients with biliary complications present with isolated fever, rigors, or elevated liver enzymes without jaundice or abdominal pain. The abdomen may even be soft and nontender. Emergency physicians should strongly consider the possibility of a biliary complication whenever faced with an OLT patient presenting with any combination of abdominal complaints, fever, or evidence of graft dysfunction.

Rejection

Immune-mediated disease in OLT recipients includes hyperacute, acute, and chronic forms of rejection, as well as graft-versus-host disease. Acute and chronic rejections are most clinically relevant to emergency physicians. The liver is relatively resistant to hyperacute rejection, and graft-versus-host disease is uncommon in liver transplantation (17). Acute and chronic rejections are classified on the basis of time of occurrence and histology. Between 60% and 80% of OLT patients in some published series have at least one episode of acute rejection (18). With current immunosuppressive regimens, the incidence of chronic allograft rejection has declined to approximately 5% of OLT recipients. Owing to the development of tolerance after liver transplantation, it is possible for some OLT recipients to be successfully weaned from immunosuppressive drug therapy (19–21).

Acute rejection commonly manifests as malaise, generalized weakness, progressive jaundice, right upper quadrant pain, and often fever. Alternately, acute rejection may be clinically asymptomatic, with elevation of liver enzymes as the only clue to the diagnosis. A pattern of early alkaline phosphatase and bilirubin elevation, followed shortly by a rise in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, is typical of acute rejection. Although suggestive, this pattern is not specific for acute rejection and may occur with cholestasis, cholangitis, drug toxicity, and other states of hepatic dysfunction. Acute rejection occurs most commonly in the first 3 months after transplant and generally has a good prognosis (18). Most episodes respond to increased immunosuppression, commonly a corticosteroid pulse. Patients who are infected with hepatitis C may not be treated for mild episodes of acute rejection as treatment appears to worsen outcomes (22). Steroid-resistant episodes are often treated with antilymphocyte antibody preparations. Late acute rejection is more commonly associated with noncompliance, may be less responsive to steroids, and carries a higher risk of progression to chronic rejection.

The clinical presentation of chronic rejection is similar to that of acute rejection. Patients may report low-grade fever, fatigue, progressive jaundice, right upper quadrant pain, clay-colored stools, and dark urine. Patients with chronic rejection usually experience a more gradual clinical deterioration compared with patients suffering from acute rejection. Laboratory findings of chronic rejection are persistently elevated transaminase levels, increasing cholestasis, and declining hepatic synthetic function. Chronic rejection is resistant to therapy and often results in eventual graft loss.

Infection

Infection continues to be a major source of morbidity and mortality in OLT patients (23–25). Sepsis is the most common cause of death in the first year after transplantation, and up to 67% of recipients have at least one serious infection after OLT. Approximately 50% to 60% of these infections are bacterial, 15% are fungal, 5% to 15%

are viral, and <10% are caused by other organisms, such as *Pneumocystis jiroveci* or *Toxoplasma* species. Most infections occur during times of peak immunosuppression. Specifically, the risk of serious acute infection is greatest during the first month after transplantation but remains high throughout the first 6 to 12 months.

Infections occur during three distinct periods. In the month immediately after transplantation, patients are susceptible to the typical nosocomial pathogens. During the second through sixth month, the patients are susceptible to a variety of opportunistic infections, and after 6 months, the patients are susceptible to the typical community-acquired pathogens, although opportunistic infections may still occur if the patient has chronic viral infections or requires persistently elevated levels of immunosuppression. OLT recipients maintained on high levels of immunosuppressive medications after acute rejection episodes, recipients with indwelling central lines, and recipients with biliary complications (e.g., biliary strictures) also remain at high risk for serious acute infections irrespective of the duration of posttransplantation. Emergency physicians should bear in mind that OLT recipients are immunocompromised. They may present to the ED appearing well and complaining only of isolated fever, only to deteriorate rapidly during their subsequent hospital course.

Medication-Related Adverse Effects

The immunosuppressive regimens that make graft survival possible are a frequent source of adverse effects. In addition to promoting infection and malignancy, immunosuppressive medications may result in metabolic, renal, neurologic, hematologic, dermatologic, and bone disorders. Each agent has a characteristic pattern of adverse effects (Table 106.1), many of which are clinically important and may result in ED visits (18). Drug–drug interactions may precipitate these events, and the potential for adverse drug interactions should always be considered (Table 106.2).

TABLE 106.1
Immunosuppressive Medications and Associated Adverse Effects

Drug	Indications	Adverse Effects
Corticosteroids	Adjuvant prophylaxis for rejection Primary therapy for acute rejection	Hypertension, increased appetite, Cushing syndrome, acne, gastritis, hyperglycemia, delayed wound healing, osteoporosis
Cyclosporine (Gengraf, Neoral, Sandimmune)	Primary prophylaxis for rejection	Hypertension, infection, hyperglycemia, chronic renal failure, hirsutism, gingival hyperplasia, PTLD
Mycophenolate Mofetil (Cellcept)	Adjuvant prophylaxis for rejection Adjuvant therapy for acute and chronic rejection	Intestinal hypermotility, vomiting, cramping, diarrhea, infection, anemia, leukopenia, PTLD
Sirolimus (Rapamune)	Primary prophylaxis for rejection Primary therapy for chronic rejection	Hypercholesterolemia, infection, edema, PTLD
Tacrolimus (Prograf)	Primary prophylaxis for rejection Primary therapy for chronic rejection	Hypertension, headache, infection, hyperglycemia, tremor, chronic renal failure, PTLD

PTLD, posttransplant lymphoproliferative disorder.
Adapted from Rand EB, Olthoff KM. Overview of pediatric liver transplantation. *Gastroenterol Clin North Am.* 2003;32:913–929.

TABLE 106.2
Significant Drug Interactions

Some substances that *lower* tacrolimus, cyclosporine, and sirolimus levels

Carbamazepine
Nafcillin
Phenobarbital
Phenytoin
Rifampin
Valproic acid
Garlic
St. John's wort

Some substances that *elevate* tacrolimus, cyclosporine, and sirolimus levels

Amiodarone
Bromocriptine
Cimetidine
Diltiazem, nicardipine, nifedipine, verapamil
Efavirenz
Erythromycin, clarithromycin
Fluconazole, itraconazole, ketoconazole
Imipenem
Metoclopramide
Methylprednisolone
Grapefruit juice

Avoid nonsteroidal anti-inflammatory drugs, as they may further compromise renal function in patients taking either tacrolimus or cyclosporine.

Oral contraceptives are contraindicated, due to the increased risk of a thrombotic event (e.g., hepatic artery thrombosis).

No live virus vaccinations should be administered to OLT recipients or any of their close household contacts.

Corticosteroids that OLT patients receive result in all of the typical complications of chronic steroid excess, including adrenal suppression, hypertension, insulin resistance, Cushing syndrome, delayed wound healing, and osteoporosis. Osteoporosis-related fractures, especially vertebral body compression fractures, are a common problem in OLT patients because of pre-existing hepatic osteodystrophies coupled with the osteopenic effects of corticosteroids and other immunosuppressives.

Dose-dependent TAC or cyclosporine nephrotoxicity is common (26). The initial presentation may be occult, with a rise in creatinine occurring with minimal, nonspecific symptoms. Corticosteroids, TAC, and cyclosporine all induce insulin resistance, and OLT recipients may develop diabetes mellitus with hyperglycemic symptoms (27). Additionally, the immunosuppressive regimens OLT patients require have been associated with a variety of neurologic (tremors, headaches, altered mental status, and seizures) and gastrointestinal symptoms (nausea, vomiting, and diarrhea) (28,29).

Late Complications

Late complications are defined as those that occur more than 1 year after transplantation. The most common causes of late deaths are chronic rejection and malignancies (2). Late complications can be categorized as related to the allograft itself or extrahepatic. The differential diagnosis of late graft dysfunction is broad. Noncompliance is an unfortunately common cause of chronic rejection. Biliary strictures may occur. Reactivation of hepatitis B and C, for which transplantation may have been performed, may occur and lead to graft failure. Although reactivation of hepatitis C remains common, advances in the use of antiviral agents have reduced the recurrence of hepatitis B to low levels. Autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cirrhosis may all recur in OLT recipients though autoimmune hepatitis is also increasingly being diagnosed in recipients without a history of autoimmune disease (30).

The extrahepatic late complications of liver transplantation are commonly due to the long-term use of immunosuppressive agents. Infections remain a concern. Nephrotoxicity is the most serious complication of the long-term use of TAC and cyclosporine. Dehydration may precipitate further deterioration in renal function, and any illness resulting in dehydration in patients on these agents should be taken seriously and be treated with intravenous fluids.

Malignancies are an important late complication of transplantation and chronic immunosuppressive therapy.

Recurrence is common among patients who have undergone transplantation for hepatocellular carcinomas. The most common new neoplasms are the Epstein–Barr virus-mediated posttransplantation lymphoproliferative disorders, including true lymphomas, which may occur within the first several months to many years after transplantation. Skin cancers and other solid organ malignancies are also increased in adult OLT recipients.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses for some of the more common presenting complaints are provided in Table 106.3. The frequently nonspecific presentations of the major complications usually preclude making a specific diagnosis on clinical findings alone (31). In addition, multiple diagnoses are common, owing to the interrelationship between many of the complications (e.g., HAT causing bile duct necrosis, leading to bile leakage, and abscess formation). A convenient mnemonic for the common problems in the OLT patient that may have unusual or vague presentations is ARID: *A*nastomoses, *R*ejection, *I*nfection, and *D*rug toxicity.

TABLE 106.3
Final Diagnoses for Common Presenting Complaints[a]

Complaint	Percentage
Fever	
Bacterial illness	38
Viral illness	21
Fever of unclear origin	16
Immune-mediated illness	8
Nausea/Vomiting	
Gastroenteritis	14
Nausea/vomiting of unclear etiology	13
Bacteremia	11
Gastroesophageal reflux/ gastritis	10
Biliary obstruction/leak	10
Medication effect	8
Immune-mediated illness	8
Pneumonia	6
Pancreatitis	5
Abdominal Pain	
Abdominal pain of unclear etiology	30
Biliary obstruction/leak	20
Gastroenteritis/colitis	9
Pancreatitis	9
Bowel obstruction	6
Lethargy	
Bacterial illness	31
Hepatic dysfunction	14
Medication effect	11
Jaundice	
Immune-mediated illness	36
Biliary obstruction	29
Altered Mental Status	
Medication effect	46
Hepatic encephalopathy	36

[a]Because only the most common final diagnoses are included in this table, the listed percentages for each presenting-complaint subset do not add up to 100%.

Adapted from Savitsky EA, Votey SR, Mebust D, et al. A descriptive analysis of 290 liver transplant patient visits to an emergency department. *Acad Emerg Med*. 2000;7:898–905.

ED EVALUATION

ED evaluation of OLT patient begins with an extensive history and physical examination. Important historic factors include the etiology of liver failure, date of transplantation, history of postoperative complications, recent diagnostic studies, recent changes in medications, and current medications. A review of systems should determine the presence of fever, nausea, vomiting, abdominal pain, jaundice, acholic stools, and dark urine. Emergency physicians should bear in mind that serious OLT complications may present with deceptively nonspecific symptoms and normal initial physical examinations.

Because the presentations of many important complications of OLT are nonspecific, patients presenting to the ED generally require extensive laboratory testing. Laboratory tests should include a complete blood count and platelet count to screen for leukopenia or thrombocytopenia related to medications. Electrolytes and serum creatinine concentrations are useful to detect the nephrotoxic effects of TAC and cyclosporine. Total bilirubin, AST, ALT, alkaline phosphatase, and prothrombin time or international normalized ratio (INR) are used to evaluate graft function. Patients presenting with fever should have blood and urine cultures, chest radiography, and urinalysis (Table 106.4).

TABLE 106.4
Time of Occurrence and Management of Infections in OLT Recipients

Infectious Disease	Time of Presentation after OLT	Diagnostic Evaluation	Treatment[a]
Bacterial	Peak in months 1–2, progressive decline in incidence. Rare after 12 months, unless patient is still taking high-dose immunosuppressive regimen or has indwelling venous catheter	Blood, urine, and sputum cultures.[b] Culture all indwelling venous catheter and biliary tube fluid if T-tube present	Empiric broad-spectrum antibiotic coverage pending culture results (e.g., piperacillin/tazobactam 3.375 g IV q6h)
Fungal	Peak in months 1–2. Rare after 2 mos, unless patient is still taking high-dose immunosuppressive regimen	Blood, urine, and indwelling venous catheter cultures	Amphotericin B or fluconazole[c]
Viral	Most common in month 2 after OLT, rare after 2 mos. Cytomegalovirus is the most common infection	Blood, urine, and indwelling venous catheter cultures[d]	Ganciclovir or foscarnet
Protozoal	Rare, but occasionally occur months 1–6. *Pneumocystis jiroveci* pneumonia is the most common pathogen	Chest radiograph and sputum culture. Most require bronchoalveolar lavage; diagnosis is not usually made in ED	Trimethoprim-sulfamethoxazole, 20 mg/kg IV divided qid for 14–21 d

[a]Medication dosages must be adjusted on the basis of patient's renal function.
[b]Obtain sputum cultures and chest radiograph when clinically appropriate (e.g., patient with fever and cough). Consider stool cultures and Clostridium difficile toxin assay if infectious colitis is suspected.
[c]Antifungal and antiviral therapy are not routinely indicated in the emergency department. They are usually reserved for the hospital course of patients with orthotopic liver transplant when fungal infection has been documented or the patient's condition fails to improve with antibacterial therapy.
[d]Definitive diagnosis of clinically significant viral disease is difficult. Further diagnostic testing, such as polymerase chain reaction, serologic studies, and tissue histologic analysis, is performed later in the hospital course and is not an immediate priority during the emergency department visit.

When suspicion of vascular complications arises, several diagnostic modalities may be useful. Duplex ultrasonography has a reported sensitivity of more than 90% for detecting vascular complications and is often the initial imaging modality. Computed tomographic angiography (CTA) scanning has a similar sensitivity and may be used as the initial imaging study or employed to confirm or elucidate ultrasound findings. Angiography may be helpful diagnostically in equivocal cases or may be employed for a therapeutic intervention. Emergency physicians should have a low threshold for using ultrasonography or CT to evaluate OLT patients for vascular complications in the presence of abdominal complaints or laboratory evidence of graft dysfunction.

Although ultrasound or CT imaging may suggest biliary complications, definitive diagnosis is made by visualization of the biliary tract with T-tube cholangiography, endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography, or operative exploration.

Rejection is definitively diagnosed by liver biopsy. The histologic triad of portal tract inflammation and mononuclear cell involvement of portal vein branches and small bile ducts is diagnostic for acute rejection. Liver biopsy in chronic rejection reveals destruction and loss of interlobular bile ducts, mononuclear portal inflammation, arteriopathy, centrilobular cholestasis, and varying degrees of hepatocellular damage.

KEY TESTING

- Basic laboratory studies, plus liver function tests and INR
- Ultrasound or CT angiogram to assess vascular patency

ED MANAGEMENT

Emergency physicians should remember that rapid deterioration may occur in stable-appearing OLT patients with acute infections, particularly during times of peak immunosuppression. High-risk OLT patients presenting with fever, including recipients within 6

months of transplantation, should receive empiric broad-spectrum antibiotic therapy pending definitive culture results. Antibiotic coverage should include gram-positive organisms, gram-negative organisms (including *Pseudomonas aeruginosa*), and anaerobic organisms. Specific therapy against fungal, viral, and protozoal pathogens is rarely instituted in the ED.

A majority of OLT patients with vascular complications require surgical intervention for definitive therapy, and management of their cases should be done in concert with the liver transplantation team. Advances in nonsurgical techniques, including thrombectomy, thrombolysis, and angioplasty, have provided alternatives to open treatment of some of the less severe vascular complications. Utilization of these modalities is still center-specific.

Patients diagnosed with bile leaks require parenteral antibiotics, percutaneous drainage of any abscess, and, occasionally, surgical intervention for refractory cases. Bile leaks occurring earlier in the post-OLT period tend to be more severe and are often unresponsive to conventional therapy, probably because the higher initial level of immunosuppression renders patients incapable of eradicating infection. Infections tend to be polymicrobial and include the typical biliary tract bacterial pathogens (*Enterobacter, Enterococcus, Bacteroides,* and *Clostridium* species). Broad-spectrum gram-positive, gram-negative (including *P. aeruginosa*), and anaerobic coverage is recommended pending culture results. Many patients diagnosed with biliary strictures may be nonoperatively managed with stents or balloon dilation of their strictures.

Treatment of acute rejection involves the administration of high-dose intravenous methylprednisolone. Therapy is rarely initiated in the ED, because the definitive diagnosis of rejection is usually made later in the patient's hospital course by liver biopsy. Corticosteroids are effective in reversing 65% to 80% of acute rejection episodes. Patients who do not respond to glucocorticosteroids are treated with regimens using muromonab-CD3 (Orthoclone OKT3), with an 85% salvage rate. Chronic rejection does not respond to immunosuppressive regimens as uniformly as do acute rejection episodes. OLT recipients in whom chronic rejection is suspected

should be referred to a liver transplantation center for evaluation, because many patients with chronic rejection will suffer eventual graft failure and require retransplantation.

CRITICAL INTERVENTIONS

- Initiate broad spectrum antibiotic coverage for febrile, immunocompromised OLT patients
- Involve the liver transplantation team early in the care of OLT patients

DISPOSITION

Serious illness is common in OLT patients presenting to the ED. Not surprisingly, OLT recipients typically undergo extensive diagnostic evaluations and are frequently hospitalized. Much of the definitive diagnostic testing that patients with OLT require is beyond the scope of typical emergency medicine practice. Appropriate ED goals are assessing the severity and possible causes of an acute illness, stabilization, and transfer of care to the multidisciplinary liver transplantation team. Emergency physicians should involve the liver transplantation team early in the decision-making process to help coordinate the timing and location of the evaluation, especially if transfer to a tertiary care center is necessary.

New-onset graft failure mandates admission. The causes of graft failure are diverse, and their evaluation is best performed in the inpatient setting.

In general, febrile OLT patients who are $<$1-year posttransplantation and are without an obvious source of infection are admitted. Febrile patients who are $>$1-year posttransplantation but are still maintained at a high level of immunosuppression (e.g., chronic rejection patients) should also be hospitalized. Well-appearing, febrile patients who are $>$1-year posttransplant with an uncomplicated post-OLT course and whose immunosuppressives have been tapered may be managed as outpatients on an individual basis. Because maintaining a desired level of immunosuppression is vital in preventing rejection episodes, admission is mandatory if

compliance with the immunosuppressive regimen is in doubt (e.g., because of intractable vomiting).

Common Pitfalls

- Failure to consider the diagnoses that uniquely apply to the patient with OLT (ARID: *A*nastomoses, *R*ejection, *I*nfection, *D*rug toxicity) and that may have unusual or vague presentations.
- Failure to coordinate the ED evaluation and follow-up of OLT recipients with the multidisciplinary liver transplant team.
- Failure to manage infection aggressively in OLT recipients, especially early in the posttransplantation period when immunosuppression is at its peak.
- Using the leukocyte count as a marker for severity of infection. More than 50% of OLT patients with serious bacterial infections have a normal leukocyte count.
- Assuming that a soft and nontender abdomen excludes hepatobiliary complications.
- Prescribing *any* medication to OLT patients without carefully investigating potential drug interactions or adverse effects.

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CHAPTER 107 Pancreatitis

Anuj A. Parikh and David C. Seaberg

Pancreatitis is a disease that is commonly encountered by the emergency physician and is challenging to diagnose and treat, as the symptoms can range from mild to potentially life-threatening. The pancreas is a retroperitoneal organ located in the epigastric region. It is divided histologically into two parts, endocrine and exocrine. The endocrine pancreas is housed in the Islets of Langerhans and its alpha, beta, and delta cells produce and are responsible for insulin, glucagon, and somatostatin homeostasis. The acinar, or exocrine, pancreas is responsible for production of lipase, amylase, and other proteolytic enzymes. The products of the exocrine pancreas are secreted into the pancreatic duct and ultimately into the duodenum. Insult to the pancreas that can occur for a variety of reasons or blockage of its duct causes leakage of pancreatic products into the pancreas and the surrounding tissue. This leakage can potentially cause damage to the pancreas and nearby organs. Pancreatic damage and the resulting pain and clinical manifestations can occur either acutely or chronically and thus, pancreatitis has been divided into two types, acute and chronic.

The incidence of pancreatitis varies with patient population and geographic location, but it has been estimated to affect up to 50 to 80 per 100,000 patients worldwide with the highest incidences in the United States and Finland (1). The overall mortality observed with acute pancreatitis has been estimated to be approximately 5% to 15% with approximately 20,000 patients dying annually from pancreatitis (2). Chronic pancreatitis, typically manifested by recurrent episodes of acute pancreatitis superimposed on a

chronically damaged pancreas, is rarely fatal. The incidence of pancreatitis has been noted to be on the rise and this coincides with increased incidence of alcohol abuse and cholecystitis (3). The incidence of pancreatitis in the pediatric population is rare, but should certainly be considered in patients with inheritable disorders like hereditary pancreatitis and cystic fibrosis. In fact, acute pancreatitis can be the first symptom of otherwise undiagnosed cystic fibrosis in a child (4).

The causes of acute pancreatitis are listed in Table 107.1. The most common cause is gallstone and biliary tract–related obstructive disease. As noted above, as the incidence of alcohol abuse is on the rise and so is the incidence of alcohol-related pancreatitis. Drugs, particularly in elderly patients or those on immunomodulating agents are also responsible for disease. Endoscopic retrograde cholangiopancreatography (ERCP) in the hands of an inexperienced endoscopist can be a potential cause of pancreatitis. Elevated triglyceride levels of greater than 1,000 mg/dL can trigger acute pancreatitis. In the setting of hyperparathyroidism or cancer, hypercalcemia can trigger the activation of trypsinogen thereby leading to trypsin-mediated pancreatic necrosis. Genetic mutations have been found more and more often to be associated with both acute and chronic pancreatitis. Autoimmune and tropical pancreatitis remain elusive in their mechanism of disease propagation. Multiple infectious causes have been identified including mumps, coxsackievirus, cytomegalovirus, varicella, herpes simplex virus, HIV, Mycoplasma, Legionella, Leptospira, Salmonella, Toxoplasma, Cryptosporidium, Ascaris, and Aspergillus. Idiopathic causes followed by the less common causes are also listed in Table 107.1 and account for the majority of causes of acute pancreatitis (5–7). Scorpion venom–induced pancreatitis is frequently cited as a cause of pancreatitis but it is, however, exceedingly rare and should be considered only in the face of an acute or subacute envenomation (2).

TABLE 107.1
Causes of Acute Pancreatitis

More Common	Less Common
Gallbladder disease	Cystic pancreatic lesions
Alcohol related	Cystic fibrosis
Drug related	Pancreas divisum
ERCP	Pancreatic cancer
Hyperlipidemia	Peptic ulcer
Hypercalcemia/hyperparathyroidism	Postsurgical
Genetic	Tropical pancreatitis
Autoimmune	Vasculitis
Infectious	
Idiopathic	
Abdominal trauma	
Hypotension	

Adapted from Taichman, Turner, Williams, Gupta, Wu. In the Clinic: Acute Pancreatitis. *Ann of Intern Med*. 2010;153(9):ITC51–ITC55 & Cappell, MS. Acute Pancreatitis: Etiology, Clinical Presentation, Diagnosis, and Therapy. *Med Clin N Am* 2008;92:889–923.

CLINICAL PRESENTATION

Acute Pancreatitis

Although no clinical finding is pathognomonic of acute pancreatitis, abdominal pain is the most striking clinical feature. The classic pain pattern is described as acute onset epigastric abdominal pain with radiation to the back though there is great variation to this presentation (5). The pain is usually severe and constant; it may be diffuse but is commonly localized to the epigastrium or left upper quadrant and often radiates through to the back. The pain is typically exacerbated by recumbency and relieved by sitting up and flexing forward. Nausea and vomiting are noted in the majority of cases. On physical examination, there is usually abdominal tenderness and guarding, often with signs of peritoneal irritation. Fever, hypotension, tachycardia, abdominal guarding, respiratory distress, and diaphoresis may also be noted, depending on the severity of the case (8).

Necrotizing acute pancreatitis is a potentially life-threatening disease. Pancreatic inflammation from necrosis results in shunting of blood from other organs causing hypovolemia, hypotension, vasospasm, and hemoconcentration (9). At worst, patients with acute necrotizing pancreatitis present with severe abdominal pain, in hypovolemic shock, with fever, renal failure, hypoxemia, and GI bleed (10). Cullen sign (periumbilical bruising) and Grey Turner sign (flank bruising) are exceedingly rare in pancreatitis and can arise in any instance of retroperitoneal hemorrhage (11).

Chronic Pancreatitis

Patients with chronic pancreatitis often present to the emergency department (ED) with recurrent attacks of abdominal pain, although in some patients pain is overshadowed by weight loss and the effects of pancreatic endocrine or exocrine dysfunction (i.e., diabetes mellitus or malabsorption and steatorrhea). The pain is described as midepigastric postprandial pain that radiates to the back, relieved by sitting upright and leaning forward (12). Pancreatic endocrine dysfunction, with deficient insulin and glucagon secretion, may result in diabetes mellitus that is occasionally brittle and associated with frequent episodes of hypoglycemia. The source of epigastric abdominal pain in chronic pancreatitis is thought to be due to acute inflammation, neural inflammation, or increased intrapancreatic pressure due to pancreatic ductal dilatation or pancreatic pseudocyst (10).

DIFFERENTIAL DIAGNOSIS

Acute Pancreatitis

The differential diagnosis is listed in Table 107.2. A perforated viscus may be identified by the detection of free air under the diaphragm on a chest radiograph. Acute cholecystitis and biliary disease can be identified by ordering liver function tests and right upper quadrant ultrasonography. Intestinal obstruction can be identified on abdominal radiographs or computed tomography (CT) scan. Mesenteric vascular occlusion can be diagnosed with serum

lactate levels as well as CT angiography. Ultrasound can play a role in the diagnosis of mesenteric ischemia as well. Abdominal aortic pathology can be rapidly identified with ultrasound and with CT. Renal colic can be diagnosed with urinalysis along with ultrasound or CT. Acute myocardial infarction (AMI) should be included in the differential diagnosis of every patient with midepigastric pain and risk factors for AMI. Acute appendicitis can be detected with CT scan or ultrasound. Ectopic pregnancy can be identified by presence of urine or serum HCG and ultrasound. Pneumonia or pulmonary embolism in the right lower segments can mimic gallbladder and pancreatic disease and plain film or CT should be done in cases where other causes of epigastric pain cannot be found. Finally connective tissue disorders with vasculitis should be considered in the absence of other obvious causes of upper abdominal pain but its diagnosis in the ED may be limited (7).

TABLE 107.2
Differential Diagnosis for Pancreatitis

Perforated viscus
Acute cholecystitis or biliary disease
Intestinal obstruction
Vascular occlusion
Aortic dissection
Renal colic
Myocardial infarction
Vasculitis
Appendicitis
Ectopic Pregnancy
Pneumonia

Adapted from Taichman, Turner, Williams, Gupta, Wu. In the Clinic: Acute Pancreatitis. *Ann Inter Med*. 2010;153(9):ITC51–ITC55.

Chronic Pancreatitis

The diagnosis of chronic pancreatitis is primarily a clinical one, but Table 107.3 lists the common conditions that should be considered when evaluating a patient with known chronic pancreatitis who

presents to the ED with an acute exacerbation of their chronic epigastric abdominal pain. Note that a careful social and family history should be obtained from the patient with particular regard to a history of chronic alcohol use, cigarette smoking, and family history of pancreatitis. New research indicates that there is a genetic link to alcoholic pancreatitis and that several genetic mutations can predispose patients to the development of pancreatitis for no known reason (13). There is emerging, but limited, data to suggest that environmental tobacco smoke from cigarettes have linked smoking with chronic pancreatitis (4).

TABLE 107.3
Differential Diagnosis of Chronic Pancreatitis

More Common	Less Common
Acute cholecystitis	Acute appendicitis
Acute pancreatitis	Acute salpingitis
Intestinal ischemia/infarction	Crohn disease
Common bile duct obstruction	Ectopic pregnancy
Pancreatic tumors	Gastroparesis
Peptic ulcer disease	Intestinal obstruction
Renal insufficiency	Irritable bowel syndrome
	Malabsorption
	Ovarian cysts
	Ovarian adenocarcinoma
	Thoracic radiculopathy

Adapted from Nair RJ, Lawler L, Miller MR. Chronic Pancreatitis. *Am Fam Physician* 76(11); 2007:1679–1688.

ED EVALUATION

The diagnosis of pancreatitis requires the emergency physician to combine the findings of a thorough history and physical examination along with appropriate laboratory work-up and imaging. The challenge of the ED evaluation of suspected pancreatitis is to make the diagnosis and to exclude other causes of abdominal distress, keeping in mind that other serious illness may occur in combination with pancreatitis. Once the diagnosis is made,

one must assess the severity of the pancreatitis to make an appropriate disposition. The gold standard of diagnosis is direct inspection or pathologic examination of the pancreas; all other diagnostic modalities are indirect. Therefore, it is often stated that pancreatitis should remain a working diagnosis that one should feel free to modify in the face of a changing clinical picture.

The amylase and lipase have historically been the initial laboratory tests for diagnosing pancreatitis. An elevation of the serum *amylase* is often incorrectly considered to be diagnostic of acute pancreatitis. Because amylase is found in a variety of extrapancreatic locations (including the salivary glands, the small intestine, and the female genital tract), reliance on the amylase level alone may be misleading, especially since the amylase level can normalize several days into an acute attack. In addition, acute-on-chronic pancreatitis from alcohol abuse may only cause a mild elevation in the amylase due to pre-existing pancreatic injury. Serum amylase level is a very sensitive but nonspecific test so it should not be relied upon alone for the diagnosis of pancreatitis (2). Because of its availability and high specificity, the serum *lipase* level is the confirmatory test of choice for pancreatitis (7). Because the pancreas is the only major source of lipase, an increased level, particularly more than three times the upper limit of normal, is very specific for acute pancreatic inflammation. It is important to note that serum lipase may not be elevated in patients with acute-on-chronic pancreatitis. The clinician must use clinical judgment in these cases. Liver function tests are important in ruling out an obstructive cause of pancreatitis. Determination of the WBC count, hemoglobin, and basic metabolic panel are often helpful. An ionized calcium level should be obtained to ensure that elevated serum calcium is not the cause of inappropriate release of proteolytic pancreatic enzymes that can ultimately lead to trypsin-mediated necrosis. Finally, a triglyceride level should be obtained as highly elevated triglyceride levels can precipitate acute pancreatitis (7).

Imaging can help differentiate pancreatitis from other diagnoses and help to evaluate the complications caused by pancreatitis, especially in acute pancreatitis. Plain radiographs of the chest and

abdomen can be considered to rule out other entities, such as pneumoperitoneum or small bowel obstruction, but are not generally helpful in the evaluation of pancreatitis. CT is of particular importance, however, especially in evaluating pancreatitis and its complications. Patients presenting with mild episodes, especially chronic, alcohol-induced pancreatitis, usually do not require imaging. Balthazar et al. developed the CT severity index that combines pancreatic necrosis and local complications of fluid collection to create a predictive score. CT with intravenous contrast is the imaging gold standard for evaluating the presence and extent of pancreatic necrosis and other local anatomic sequelae of acute pancreatitis, and has become a routine part of the diagnostic evaluation (8).

Ultrasonography can identify pancreatic edema as well as such complications as pancreatic pseudocyst or abscess. It is also useful in identifying the presence of gallstones or dilatation of the biliary tree, findings that have important diagnostic and therapeutic implications (14). The American College of Gastroenterology's current clinical practice guidelines suggest ultrasonography within the first 24 to 48 hours of admission to essentially rule out surgical causes of acute pancreatitis (15).

Magnetic resonance imaging (MRI) has an emerging role in the evaluation and ultimate management of patients with pancreatitis. While it is not superior to CT diagnostically, MRI avoids ionizing radiation and nephrotoxic iodinated contrast. This makes MRI the study of choice for pregnant patients with suspected acute pancreatitis. The other major advantage of MRI is the use of magnetic resonance cholangiopancreatography (MRCP) that allows for noninvasive evaluation of the biliary system. The disadvantages include the lack of availability of MRI, inability to monitor a critically ill patient, and the increased time that it takes to complete the test (16).

KEY TESTING

- Lipase, CBC, basic metabolic panel, calcium, liver function tests, triglyceride level
- Ultrasound and/or CT
- Serum lactate, arterial blood gas (in severe cases)

ED MANAGEMENT

After establishing the diagnosis of acute pancreatitis, the second priority is to determine its severity. Top priority for the emergency specialist is airway, breathing, and circulation, all of which can be compromised in a patient afflicted with severe acute pancreatitis. 10% to 15% of patients with acute pancreatitis develop systemic inflammatory response syndrome (SIRS) leading to organ failure (including shock, pulmonary insufficiency, and renal failure) and/or the presence of local complications (especially pancreatic necrosis) (11). Predictors of severity within the first 48 hours of hospitalization, including Ranson criteria and the Acute Physiology and Chronic Health Evaluation (APACHE-II) score, which serve as an early warning sign that an episode is likely to be severe (15). The practice guideline for acute pancreatitis recommends that a formalized system of scoring should be generated for each patient. The APACHE-II and Ranson criteria score should be generated on the day of admission to help identify patients with severe pancreatitis. Furthermore, the Atlanta classification was created at an international symposium in 1992 to create a clinically based classification system for acute pancreatitis. According to the Atlanta Symposium, acute pancreatitis is defined as an acute inflammatory pancreatic process that may also involve peripancreatic tissues and/or remote organ systems. Criteria for severity included organ failure (shock, pulmonary insufficiency, and renal failure) and/or local complications (such as pancreatic necrosis but also including pancreatic abscess and pancreatic pseudocyst).

The Ranson criteria are used to predict the severity and mortality of disease. They are listed in Table 107.4. The APACHE-II score, which can be quickly and efficiently scored online (www.sfar.org/scores2/apache22.html#calcul) is based on 12

physiologic variables, the patient's age, and any history of severe organ-system insufficiency, or immunocompromised state. The value of the APACHE-II system is that it allows measurement of severity at presentation and can be measured daily, whereas other systems (including Ranson criteria) require data at 48 hours. In general, when the APACHE-II score is less than 8 during the first 24 to 48 hours, the patient usually survives.

TABLE 107.4
Ranson Criteria for Predicting the Severity of Acute Pancreatitis

On admission
Age >55 yr
WBC >16,000/mm^3
Blood glucose >200 mg/dL
Lactate dehydrogenase >350 IU/L
Aspartate transaminase >250 U/L
Within 48 hrs
BUN >5 mg/dL
PaO_2 <60 mm Hg
Serum calcium <8 mg/dL
Hematocrit decrease >10%
Base deficit >4 mEq/L
Fluid sequestration >6 L

WBC, white blood cell; BUN, blood urea nitrogen.
Note: Mortality is based on the number of prognostic signs as follows: 0–2, 1%; 3–4, 15%, 5–6, 40%; >6, 100%.
Adapted from Ranson JH Etiologic and prognostic factors in human acute pancreatitis: A review. *Am J Gastroenterol*. 1982;77:663–63.

Historically, antibiotics such as ceftriaxone have played a role in treatment of patients with necrotizing pancreatitis. First studied in 1976 with a randomized, double-blind study, ampicillin was administered to those with acute pancreatitis. The conclusion was that the role of prophylactic antibiotics needed further study. Nearly 40 years later, researchers from the US and the UK reached no clear consensus on the role of antibiotics for severe pancreatitis. A meta-analysis done in the late 1990s showed that there may be some mortality benefit to prophylactic antibiotics but a double-blind

placebo-controlled trial published afterward showed no benefit (17,18). The American Gastroenterology Association has no formal recommendation for antibiotic prophylaxis but notes that it should be considered in cases with 30% or more pancreatic necrosis on CT scan (19).

CRITICAL INTERVENTIONS

- Aggressive fluid resuscitation in patients with acute pancreatitis, who often have substantial retroperitoneal sequestration of fluids
- Adequate analgesia for patients with severe pain

DISPOSITION

Patients with mild symptoms and without biliary tract disease may be managed on an outpatient basis if they are able to tolerate clear liquids in the ED and have no evidence of systemic complications. For these individuals, a clear liquid diet and oral analgesics should be prescribed and close follow-up should be arranged. Patients with alcohol-associated pancreatitis should be encouraged to stop drinking and if they smoke, to stop smoking. For patients with chronic pancreatitis, indications for hospital admission include uncontrollable pain, intractable vomiting, severe nutritional deficiencies, or complications requiring surgery. Any adjustments in the regimen for analgesia or pancreatic enzyme supplementation should be carried out in consultation with the patient's primary care physician.

All other patients must be admitted to the hospital. If severe or necrotizing acute pancreatitis is suspected, admission to an intensive care unit is mandatory for critical care monitoring of cardiac, pulmonary, and renal function. Surgical consultation is indicated for patients with clinically severe pancreatitis or evidence of large peripancreatic fluid collections, abscess, or pancreatic necrosis on CT.

Common Pitfalls

- No clinical or laboratory finding is pathognomonic of pancreatitis. The serum amylase is not a specific test, and an elevated serum amylase level is not diagnostic.
- Underestimating the severity of an attack. Measurements of APACHE-II and/or Ranson criteria should be made to estimate severity.

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CHAPTER 108 Appendicitis

Brian K. Snyder

> "Acute appendicitis can mimic virtually any intra-abdominal process; therefore, to know acute appendicitis is to know well the diagnosis of acute abdominal pain."
>
> —Zachary Cope

Appendicitis is an acute inflammatory process of the appendix resulting from obstruction of the lumen with subsequent bacterial invasion, distention, ischemia, and ultimate rupture. As traditionally taught, appendicitis presents with initial periumbilical pain that later migrates to the right lower quadrant (RLQ). Anorexia, nausea, and vomiting are associated symptoms. Physical examination reveals a low-grade fever and RLQ tenderness, with guarding and rebound as the process progresses. Laboratory evaluation reveals a leukocytosis with neutrophilia. Unfortunately, this classic presentation occurs in only a minority of cases, and the diagnosis may be difficult to make. In one large series (before availability of CT), diagnostic accuracy averaged only 85%, with a 19% perforation rate. A percentage of the perforation rate surely results from delayed diagnosis. Incidence of perforation increases with the extremes of age, and perforation is associated with greater morbidity and mortality (1).

The lifetime risk of appendicitis is 8.6% for males and 6.7% for females, with an annual incidence of 1.1:1,000. The male-to-female ratio for appendicitis is 1.4:1, although females have a higher rate of negative appendectomies. The peak incidence for males is between 10 and 14 years and for females is between 14 and 19 years.

Appendicitis rates are 1.5 times higher for whites than for nonwhites and are higher in summer (1). The cause of these differences is unknown, but temporospatial clustering and outbreaks of appendicitis point to an infectious agent as a cause of some cases of appendicitis. A recent report found active infection with cytomegalovirus in a majority of examined appendicitis specimens from immunocompetent patients (2).

The normal, uninflamed appendix is a hollow visceral structure with a closed distal end arising from the cecum; on average, it is 9.5 to 10 cm in length. Although the density of immune cells in lymphoid follicles in the appendix suggests an immunologic role, the function of the appendix is unknown. Its anatomic position can be anterior (postilial, preilial, and pelvic) or posterior (retrocecal and subcecal), and many appendices are mobile or can be found outside the RLQ (Fig. 108.1). The traditional surface landmark for the location of the appendix is McBurney's point, which is located 1.5 to 2 in from the inferior aspect of a line drawn from the anterior superior iliac spine point to the umbilicus. However, barium and laparoscopic studies reveal that most appendices are pelvic and lie inferior to this point; therefore, making clinical decisions based on the presence or absence of pain or tenderness at exactly McBurney's point is unjustified (3).

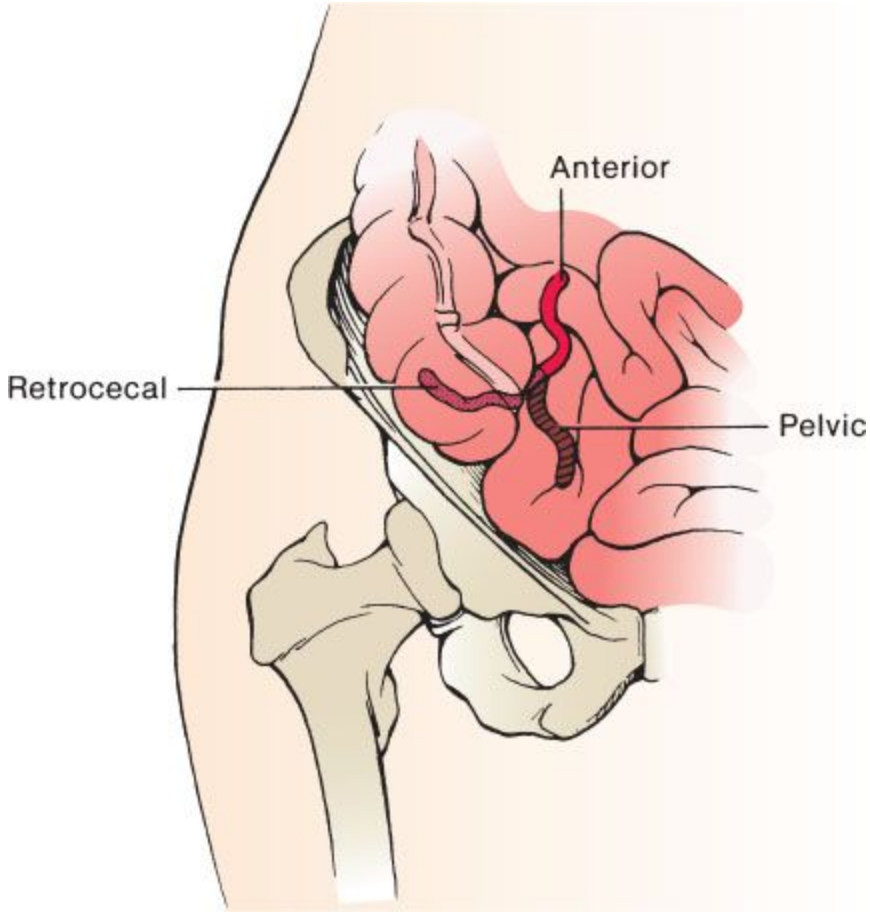

FIGURE 108.1 Various anatomic positions of acute appendix.

The common pathophysiologic event in appendicitis is obstruction of the lumen. Obstruction can be from lymphoid hyperplasia, intraluminal objects (fecaliths, foreign bodies, or parasites), or tumors (carcinoid, adenocarcinoma, or metastatic tumors). A variety of inflammatory conditions can result in hyperplasia of appendiceal lymphoid follicles that progresses until the appendiceal wall itself obstructs the lumen. Conditions noted for this process include respiratory infections, mumps, mononucleosis, amoebiasis, and bacterial gastroenteritis.

Crohn's disease can affect the appendix. Patients with the acquired immunodeficiency syndrome (AIDS) can have other processes of the appendix, including Kaposi sarcoma, lymphoma, or opportunistic infections (e.g., cytomegalovirus). Typhlitis can present similarly and occurs generally in neutropenic patients. Once

the appendiceal lumen is obstructed, secretion of mucus within the appendix raises intraluminal pressures until lymphatic and venous return is impaired. Ischemic injury to the mucosa results, followed by bacterial invasion of the appendiceal mucosa and submucosa. Continued inflammation and bacterial proliferation result in perforation of the appendix and spillage of inflammatory cells and bacteria into the peritoneum, resulting in peritonitis. At times, the peritoneal infection is contained by the omentum and a periappendiceal abscess forms.

CLINICAL PRESENTATION

History

The characteristic clinical presentation of acute appendicitis is abdominal pain in association with anorexia, nausea, and vomiting (see Table 108.1). Approximately 50% of patients present within 24 hours of the onset of symptoms, 33% between 24 and 48 hours, and the remainder thereafter. Abdominal pain occurs in nearly 100% of patients, is epigastric in onset in 74%, and migrates to the RLQ in 50%. Anorexia is present in 92% of patients, accompanied by nausea and vomiting in 78% and 54% of patients, respectively.

TABLE 108.1
Signs and Symptoms of Acute Appendicitis

	Nonperforated (%)	Perforated (%)	All Cases (%)
Symptoms			
Abdominal pain	99.6	99.3	99.6
Epigastric at onset	74.4	70.1	73.5
Constant RLQ	25.5	29.1	26
Anorexia		92	
Nausea	78	79.8	78.3
Vomiting	51.8	64.2	54.2
Migration of pain	52.3	38	49.6
Fever	16.3	39.6	20.8
Diarrhea	15	22.4	16.4
Constipation	8.3	14.2	9.4
Lucid interval[a]	3.2	11.2	4.8
Signs			
Abdominal tenderness			
Direct RLQ	99.6	99.3	99.6
Referred RLQ	26.3	18.6	24.9
Lower abdominal	7.8	21.6	10.6
Generalized	9.6	21.6	11.9
Right-sided rectal tenderness	48.7	41.8	47.4
Local rigidity over RLQ	26.3	45.5	30.1
Generalized rectal tenderness	11.4	19.4	12.9
Rebound tenderness	4.8	4.5	4.8
Positive psoas test	4.8	3.7	4.7
Generalized rigidity	0.7	12.7	3.1
Palpable mass in RLQ	0.5	3.7	1.2

RLQ, right lower quadrant.

[a]Lucid interval refers to a period after perforation in which pain is temporarily lessened; some authorities do not consider this a legitimate phenomenon.

Data from Lewis FH, Holcroft JW, Boey J, et al. Appendicitis: A critical review of diagnosis and treatment in 1,000 cases. *Arch Surg*. 1975;110:677; Pieper R, Kager L, Näsman P. Acute appendicitis: A clinical study of 1018 cases of emergency appendectomy. *Acta Chir Scand*. 1982;148:51.

Physical Examination

Although often regarded as a reliable clinical feature of appendicitis, fever is reported in only one-fifth of all cases and in only 16% of cases of appendicitis uncomplicated by perforation. The most

reliable sign of acute appendicitis is RLQ tenderness, present in nearly 100% of patients. Twenty-five percent of patients demonstrate referred RLQ tenderness under remote palpation (*Rovsing's sign*); rigidity in the RLQ is present in 30% of patients. Nearly one-half of patients demonstrate right-sided rectal tenderness.

The most significant complication of acute appendicitis is perforation, which either leads to generalized peritonitis and sepsis or is contained as an intra-abdominal abscess. The mortality rate of perforated appendicitis is 1.66%, seven times greater than that of patients undergoing appendectomy for simple, acute appendicitis (0.24%) and 12 times greater than that of appendectomy for a normal appendix (0.14%) (4). It is clear that the clinician must try to diagnose cases of simple acute appendicitis before perforation occurs.

There are few reliable clinical features that distinguish nonperforated from perforated appendicitis (Table 108.1). The duration of symptoms tends to be longer in patients with perforation (>48 hours). Signs that suggest perforation include lower or generalized abdominal tenderness, local or generalized rigidity over the RLQ, the presence of a palpable RLQ mass, and generalized rectal tenderness.

Pediatric, geriatric, and pregnant patients deserve special mention. Because diagnosis often is more difficult in these groups, their morbidity and mortality is greater.

Pediatric Patients

Appendices in children have a much thinner wall than those in the adult, allowing more rapid mucosal penetration and subsequent perforation. Besides higher perforation rates, the diagnosis can be more elusive given the inability of the very young to verbalize the symptoms, the difficulty sometimes encountered in examination, and the high prevalence of atypical features (e.g., diarrhea). See Chapter 269 covering pediatric appendicitis.

Geriatric Patients

Only 20% of patients older than age 60 years who are diagnosed with appendicitis present with the classic nausea, vomiting, RLQ tenderness, and elevated white blood cell count or shift. Consequently, the perforation rate is 67% to 90%. The mortality rate is 4.6%, 23 times greater than that of patients younger than age 60 years (1,5).

Pregnant Patients

The physiologic changes of pregnancy, especially during the second and third trimesters, impede the diagnosis and create a physiologic environment that suppresses the normal host response to inflammation. As the uterus enlarges, the appendix rotates in a counterclockwise direction out of the pelvis. In addition, as the expanding uterus lifts the abdominal wall away from the appendix, the omentum is less available to wall off the infectious process following perforation. Diffuse peritonitis develops preferentially over a periappendiceal abscess. The increase in serum steroids during pregnancy diminishes the inflammatory response and facilitates a more rapid and overwhelming peritonitis. These physiologic and anatomic processes result in a perforation rate of 43%. The maternal mortality rate remains low at 0.7%, but fetal mortality may approach 8.5% (6,7).

DIFFERENTIAL DIAGNOSIS

A variety of conditions mimic appendiceal inflammation (1) (see Table 108.2); the diagnostic accuracy of evaluation for suspected acute appendicitis may be as low as 85%. Disorders most commonly associated with removal of a normal appendix despite clinical suspicion of acute appendicitis include mesenteric lymphadenitis, other diseases of the appendix, and gynecologic processes. The greatest diagnostic difficulties are encountered in women of childbearing age. The overall diagnostic accuracy for females is 77%; in contrast, the diagnostic accuracy for males is 91% (1).

TABLE 108.2
Differential Diagnosis of Acute Appendicitis

Discharge Diagnoses Most Commonly Recorded after Negative Appendectomy	Percentage
Other diseases of the appendix (colic, concretion, Meckel diverticulum, fecalith, fistula, intussusception, mucocele)	19.4
Other appendicitis (chronic, recurrent, relapsing, or subacute)	16.5
Mesenteric lymphadenitis	22
Abdominal pain of unknown origin	12.2
Gastroenteritis, noninfectious	6.4
Cholelithiasis	4.1
Ovarian cyst	5.5
Uterine leiomyoma	4.3
Endometriosis	4
Lymphoid hyperplasia of the appendix	3.1
Cervicitis, endocervicitis	2.7

Other considerations in the differential diagnosis include regional enteritis, perforated peptic ulcer, diverticulitis, carcinoma of the bowel, ureteral calculi, pelvic inflammatory disease, and mittelschmerz.

Data from Addis DG, Shaffer N, Fowler S, et al. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol*. 1990;132:910.

In addition, patients with previous appendectomy, especially if done by the laparoscopic approach, may present with symptoms and signs consistent with acute appendicitis from inflammation of residual appendiceal tissue, the so-called stump appendicitis (8).

ED EVALUATION

Despite the widespread use of radiologic studies and other diagnostic aides in the evaluation of appendicitis, the diagnosis can still remain elusive. Appendicitis should be suspected on the basis of history and physical examination. The emergency physician should be particularly aggressive in evaluating the very young, the elderly, and the pregnant patient, as the morbidity and mortality rates of acute appendicitis in these subpopulations exceed those of others. No laboratory or radiographic study is completely reliable for acute appendicitis, but several are commonly used for their supportive value.

Laboratory Studies

Acute appendicitis is classically associated with leukocytosis with a left shift. In one large study, 88% of adult patients with acute appendicitis had a white blood cell count of >10,000 cells/μL, and 94% had a leukocytosis *or* a neutrophilia of >75%. Specificity was only 76% and 62%, respectively. Approximately 10% of patients with acute appendicitis have normal leukocyte and neutrophil counts (9,10). Unfortunately, an elevated leukocyte count is nonspecific, with the specificity being reported as low as 38%. Further complicating matters, the normal range for the leukocyte count changes with age. By calculating likelihood ratios, one finds that the leukocyte count has minimal effect on the probability of disease, except at extreme values that are very uncommon (11). Some authors advocate serial leukocyte counts. Studies regarding the clinical utility of sequential leukocyte counts are inconclusive, and it appears that utility, if any, is limited to a small percentage of the total patient population.

Other serum markers of inflammation, such as the C-reactive protein, have also been evaluated as an aid in diagnosis of acute appendicitis but generally demonstrate the same limitations as the leukocyte count.

Urinalysis, often obtained in the evaluation of abdominal pain, cannot be relied on to distinguish disease of the urinary tract from that of the appendix. In one study of patients with histologically confirmed acute appendicitis, 30% had an abnormal urinalysis regardless of the position of the appendix. In those patients with either a ruptured or an inflamed appendix in the retrocecal or pelvic position, abnormal urinalysis was detected in 50%. Diagnostic decisions should not be based solely on the presence of blood, pyuria, or bacteriuria (12).

Imaging Studies

Radiologic studies should be reserved for those with equivocal symptoms and physical findings. In cases of strongly suspected appendicitis, time-consuming diagnostic procedures should not be

ordered. Because the incidence of perforation is related to the interval between symptom onset and surgery, tests that may delay definitive therapy should be used cautiously.

The expanded use of helical computed tomographic (CT) scanning of the abdomen in the evaluation of appendicitis has changed practice in equivocal and low probability cases. Other radiologic modalities including plain radiographs, barium enema, and labeled WBC scan have little utility and are no longer commonly used (13).

Abdominal ultrasonography is often used in the evaluation of appendicitis, especially in pediatric and pregnant patients. When obstructed, the appendix appears as a blind-ended, immobile, noncompressible structure that cannot be displaced under direct pressure from the ultrasound probe. An appendix that is visualized on ultrasound examination is considered diagnostic of appendicitis. The test is negative if the appendix cannot be visualized. Unfortunately, ultrasonography is nondiagnostic in 3% to 11% of cases because of pain, guarding, obesity, or overlying gas. Sensitivity ranges from 75% to 89%, and specificity ranges from 86% to 100%. Worse results are obtained in early appendicitis, perforation, and retrocecal appendicitis. Ultrasound is the preferred initial modality in pregnant patients, because it does not involve contrast or radiation exposure (13). However, because of the risk of fetal wastage in cases of delayed diagnosis or negative appendectomy, magnetic resonance imaging (MRI) and CT (despite the radiation exposure) are being increasingly used in pregnant women for the evaluation of possible appendicitis (14). Factors that should be considered in this decision include the clinical suspicion, follow-up, test availability, and the radiation risk that must be balanced against the need to make a diagnosis.

Helical CT of the abdomen is fast and highly accurate in the evaluation of acute appendicitis. The sensitivity of unenhanced helical CT is approximately 90%; with the addition of oral, rectal, or intravenous contrast, the sensitivity increases up to 97% to 98% with low-dose CT having similar performance (15,16). Specificity is equally high at 94% to 97%. Findings include a fecalith, an inflamed appendix, stranding in the surrounding fat or periappendicular fluid,

phlegmon, or abscess (Fig. 108.2). Helical CT in the evaluation of appendicitis appears to be cost-effective, and its use may decrease the negative laparotomy and perforation rates (15). It is highly accurate, whether or not oral contrast is used (17). Furthermore, CT often provides an alternative diagnosis and may decrease the time to operative intervention for female patients (18). In addition, it is useful in the assessment of cases of suspected perforated appendicitis with periappendiceal abscess formation, which may be treated conservatively or with percutaneous drainage and interval appendectomy (19). Diagnostic laparoscopy has advocates, especially for women of childbearing age, and is highly accurate and safe (20).

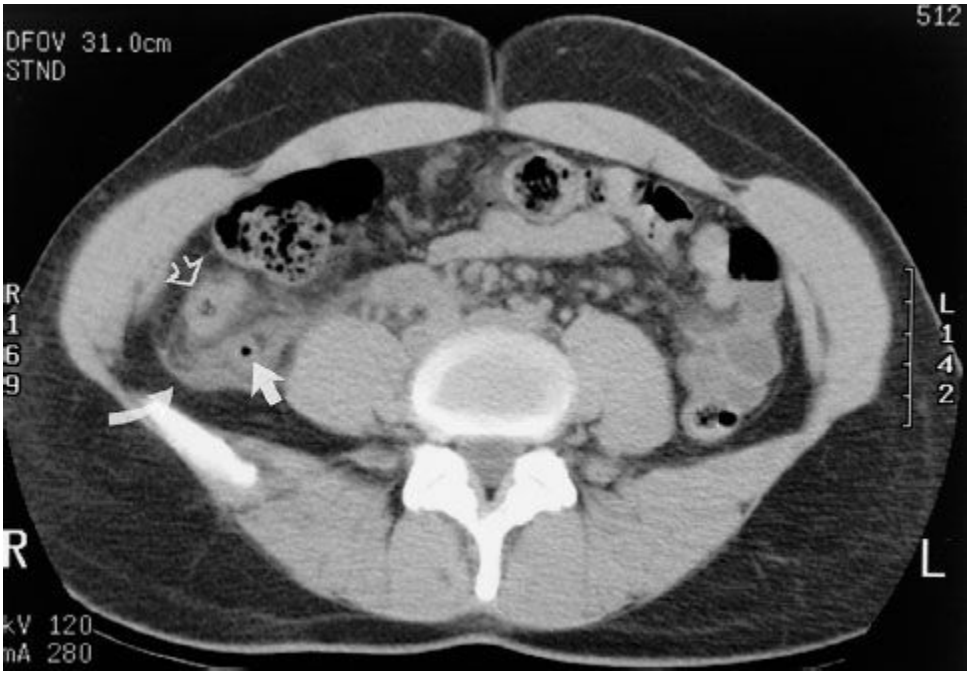

FIGURE 108.2 Computed tomographic appearance of appendicitis. Note the enlarged, thickened appendix (*open arrow*), surrounding fat stranding and inflammation (*curved arrow*), and extraluminal air, implying perforation (*closed arrow*).

KEY TESTING

- No laboratory or radiologic test is perfectly sensitive nor specific.

- Urinalysis, although urinary symptoms do not exclude appendicitis.
- Pregnancy test in women of child bearing age.
- Consider ultrasound in pregnancy and pediatric patients.
- Order CT scan when the diagnosis is uncertain.

ED MANAGEMENT

The patient suspected of having acute appendicitis should be given nothing by mouth except, perhaps, oral contrast. Intravenous fluid is indicated to ensure hydration. Surgical consultation should be obtained promptly, as timely appendectomy of an inflamed but nonperforated appendix is of paramount importance. If acute appendicitis is suspected but in doubt, radiologic study, ED observation, or admission for inpatient observation with serial examination are reasonable alternatives. Observation is a safe and effective way to distinguish patients with appendicitis from those without (21).

Although traditional teaching was that analgesia could obscure the diagnosis in acute abdominal pain, the use of narcotics has not been shown to increase the number of delayed or missed diagnoses (22). The judicious use of short-acting narcotics is reasonable in patients with acute abdominal pain while evaluation is in progress, especially those in which a radiologic procedure is to be performed or surgical consultation is delayed.

When perforation is highly suspected, intravenous antibiotics should be administered. Antibiotics that cover typical intestinal flora such as “triple antibiotics” (ampicillin 2 g, gentamicin 2 mg/kg, and metronidazole 500 mg), piperacillin/tazopactam, or a second-generation cephalosporin (cefotetan 1 to 2 g) or a quinolone (ciprofloxacin 500 mg or levofloxacin 500 mg) with metronidazole are appropriate.

There is increasing interest in treating uncomplicated appendicitis with antibiotics with or without later appendectomy (23).

CRITICAL INTERVENTIONS

- Obtain immediate surgical consultation for patients with a high likelihood of appendicitis, to reduce delay to the operating room and therefore the perforation rate.
- When in doubt, admit the patient to an observation area or surgical service for serial physical examinations.
- Administer intravenous antibiotics when perforation is highly suspected.

DISPOSITION

Patients in whom the clinical suspicion of appendicitis is moderate or high and those with a positive imaging study should be admitted to the hospital for further evaluation or surgery. For patients being discharged without a definitive diagnosis, who have low likelihood of appendicitis or other significant intra-abdominal process, it is important to provide clear, legible instructions explicitly detailing conditions meriting a return visit for further evaluation (e.g., continued or worsening pain, new symptoms). Advising a scheduled return visit in 12 to 24 hours for reassessment is good practice. In addition, when the diagnosis is uncertain, refrain from documenting a definitive diagnosis (e.g., gastroenteritis); rather refer to the process as “abdominal pain of undetermined origin.”

Common Pitfalls

- Caution is advised in evaluating the young, the elderly, pregnant women, and women of childbearing age. The diagnosis is often difficult, and many patients in these groups proceed to perforation.
- Reliance on the leukocyte count is unwarranted and usually leads to false reassurance.
- Overreliance on imaging studies may lead to a missed or delayed diagnosis. Imaging is most appropriate in patients with equivocal findings and moderate clinical suspicion.
- Failure to provide appropriate instructions and close follow-up for patients with abdominal pain without a clear diagnosis.

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CHAPTER 109

Bowel Obstruction

Philip L. Henneman and Susan P. Torrey

Intestinal obstruction is a common disorder that has been recognized by physicians for centuries. It accounts for approximately 4% of patients presenting to an emergency department (ED) with nontraumatic abdominal pain of <7 days' duration. The challenge for the emergency physician is to promptly identify the patients with bowel obstruction from many patients presenting to an ED with abdominal pain and vomiting, without excessive testing or delays in diagnosis, treatment, surgical consultation, and admission (1,2).

Intestinal obstruction was associated with a 60% mortality in 1900. This has decreased to approximately 5% owing to early recognition, aggressive stabilization with fluid resuscitation, simple nasogastric decompression and, in many cases, surgical intervention. Mortality can still result from strangulation leading to bowel infarction and subsequent sepsis. Early recognition and initiation of treatment are the only ways for the emergency physician to minimize major morbidity or mortality.

Intestinal obstruction accounts for about 20% of all acute surgical admissions. The obstruction most commonly affects the small intestine but involves the colon in up to 20% of patients. The vast majority of bowel obstructions are caused by postoperative adhesions, accounting for 50% of small-bowel obstructions. Other common causes include inflammatory bowel disease (especially Crohn disease), hernias and neoplasm in adults, and intussusception, hernias, and congenital abnormalities in children. Fecal impaction,

foreign bodies, strictures, abscesses, trauma, and volvulus are other less common causes (2,3).

The stomach, small bowel, biliary tract, and pancreas secrete 8 to 10 L of fluid daily. Almost all of this volume is reabsorbed in the large bowel. Obstruction prevents the flow of fluid and intraluminal contents to the colon, resulting in accumulation in the more proximal sections of the bowel. This causes a gradual distention of the bowel proximal to the obstruction and increasing intraluminal pressure. As pressure increases within the bowel, hypersecretion of fluid into the bowel develops, and absorption from the bowel is retarded. Volume losses into the intraluminal space are variable but can be up to 9 L in 24 hours, causing significant depletion of intravascular volume. Further increases in intraluminal pressure result in capillary and lymphatic obstruction and then edema of the bowel wall. Retrograde peristalsis eventually develops, resulting in emesis. If allowed to progress, venous and finally arterial obstruction will occur. Bacterial overgrowth occurs in the stagnant bowel contents. Hemorrhagic necrosis, gangrene of the bowel, and leakage of contaminated contents ensue, resulting in bacterial peritonitis and sepsis. It is the goal of therapy to prevent these life-threatening complications (1–3).

CLINICAL PRESENTATION

Bowel obstruction should be considered in all patients with abdominal pain and vomiting, especially if they have a history of previous abdominal surgery or colorectal cancer. Pain is the initial and primary complaint, although it may be poorly appreciated or communicated in some patients. The pain is usually intermittent and colicky, with cramps occurring every 3 to 10 minutes, depending on the location of obstruction. Vomiting generally follows the development of abdominal pain, and the more proximal the obstruction, the earlier the vomiting begins. In obstruction of the colon, vomiting may not develop for 24 to 48 hours. Although obstipation (i.e., no passage of feces or flatus) is the rule once obstruction is complete, the passage of stool and flatus may

continue until the distal bowel is evacuated. Diarrhea may even occur when there is partial obstruction. Late in the course, abdominal distention may develop.

The patient's vital signs, including postural changes, may reflect the degree of volume depletion and in general are only modestly altered until late in the disease process. Hypotension and tachycardia imply advanced disease. Gangrenous bowel, however, may be present without fever or tachycardia. A helpful sign in diagnosing early small-bowel obstruction is the auscultatory finding of crescendo–decrescendo rushes of high-pitched peristalsis sounds coincident with the patient's crampy abdominal pain. Bowel sounds eventually decrease and disappear with overdistention and infarction of the bowel.

Abdominal tenderness is present in most patients. The determination of rebound tenderness is often complicated by the presence of distended bowel, which may give a false-positive result of increased pain with rapid decompression of the abdominal wall. The absence of percussion tenderness (tapping on the abdomen) or pain with jostling of the patient's gurney or bed implies that peritoneal signs are not present. The absence of local tenderness or rebound, however, does not exclude the possibility of vascular compromise or infarction. It is important to evaluate for the presence of an external hernia. An incarcerated hernia may be easily reducible, with immediate relief of the intestinal obstruction.

DIFFERENTIAL DIAGNOSIS

There are multiple reasons for abdominal pain and vomiting, including cholecystitis, hepatitis, pancreatitis, peptic ulcer disease, appendicitis, myocardial infarction, nonspecific abdominal pain, and pregnancy, to name a few. The presence of right upper quadrant tenderness should help to differentiate hepatobiliary disease. Elevated lipase or amylase will identify pancreatitis. Patients with peptic ulcer disease may have heme-positive stool. Appendicitis usually presents with right lower quadrant tenderness. The absence of abdominal tenderness may imply cardiac etiology in an elderly

patient with risk factors. Patients with kidney stones may complain of abdominal pain but do not usually have abdominal tenderness. An electrocardiogram may help diagnose myocardial ischemia, and patients with kidney stones usually have hematuria. A pelvic examination and pregnancy test will identify the pregnant patient. Colicky pain can be associated with appendicitis, cholelithiasis, kidney stones, or gastroenteritis. Diarrhea occurs in all patients with gastroenteritis but is an uncommon complaint in patients with bowel obstruction. Uremia and hepatitis can be associated with abdominal distention (ascites) and vomiting. Ascites and peripheral edema do not occur with bowel obstruction. The presence of jaundice should direct the emergency physician to the diagnosis of liver disease. Finally, air–fluid levels on abdominal x-rays are a common finding in patients with gastroenteritis, but frequent diarrhea, lack of distended loops of bowel, or fecal leukocytes will help in making the correct diagnosis.

ED EVALUATION

The patient's general appearance often helps to determine the severity of illness. A complete history and physical examination are critical in making the diagnosis of bowel obstruction. Ill-appearing patients require supportive treatment (e.g., monitor, intravenous fluid) before a complete history can be obtained. Inspection of the patient's vital signs is critical to determine the patient's volume status and risk of infection. Tachycardia and hypotension should prompt the emergency physician to provide immediate fluid resuscitation. The presence of fever indicates an infectious etiology for the patient's symptoms and implies bowel infarction if bowel obstruction is diagnosed. Evaluation of the skin will help to identify jaundice in the patient with hepatobiliary disease or poor capillary refill in a patient in shock. Auscultation of the lungs may reveal a pulmonary cause of the patient's symptoms. Inspection of the abdomen may reveal distention or surgical scars. Auscultation of the abdomen may reveal crescendo–decrescendo, decreased, or absent bowel sounds. Gentle palpation of the abdomen demonstrates areas

of tenderness, the presence of ascites or a mass, and the presence of guarding or rebound tenderness. Gentle tapping of the patient's costovertebral angle should be undertaken to determine the presence or absence of tenderness, which would imply renal disease.

Pelvic examination is appropriate in women with abdominal pain, looking for discharge, cervical motion or adnexal tenderness, or masses—none of which are usually present in patients with bowel obstruction. Rectal examination and testing of stool for occult blood, although important in the evaluation of patients with abdominal pain, should be delayed until an upright abdominal x-ray is obtained in patients for whom there is a high clinical suspicion of bowel obstruction. Digital examination may introduce air into the rectum, confusing the determination of complete bowel obstruction. Inspection and examination for an external hernia may identify the cause of a patient's complaints and lead to early reduction and relief of an obstruction.

Traditionally, the most important diagnostic test for bowel obstruction has been the upright abdominal x-ray (4). Patients who are too ill to stand can undergo a left lateral decubitus abdominal x-ray, which will reveal the same findings. X-ray findings in bowel obstruction include dilated loops of bowel, air–fluid levels, and strings of air pockets called the "string of beads" sign (Figs. 109.1 and 109.2). In approximately 15% of patients with bowel obstruction, the abdominal x-ray is normal or nondiagnostic, and the experience of the reviewer affects the accuracy of plain film interpretation (5). In one study, looking at discordance between radiology and emergency physicians' interpretation of abdominal x-rays, the most common missed abnormality by emergency physicians was bowel obstruction (6). If the bowel lumen is completely filled with fluid, it will not show the characteristic interface of air and fluid. Absence of air in the rectum may be a sign of obstruction unless the rectal examination was performed before the abdominal x-ray. Air within more distal portions of the bowel may be seen if the obstruction is only partial, and air–fluid levels may not develop in early and partial obstruction.

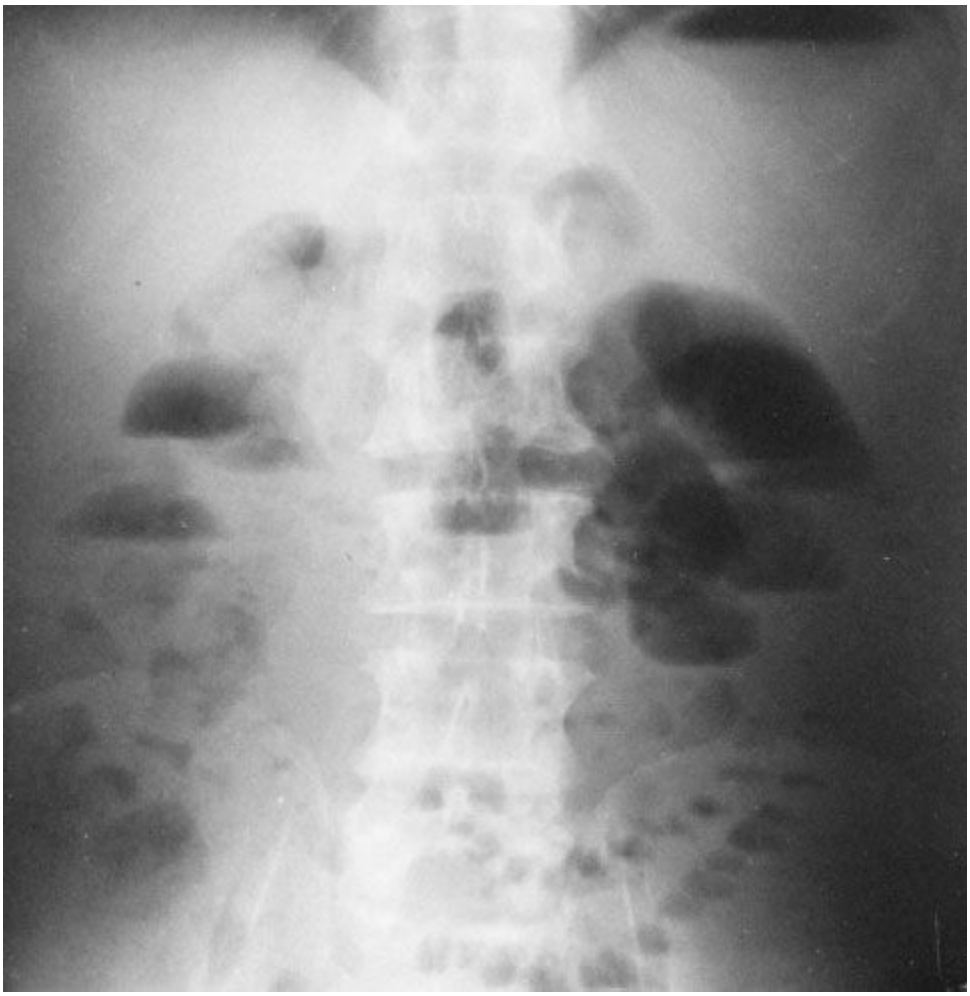

FIGURE 109.1 “Stepladder” pattern of air–fluid levels on upright view in patient with small bowel obstruction.

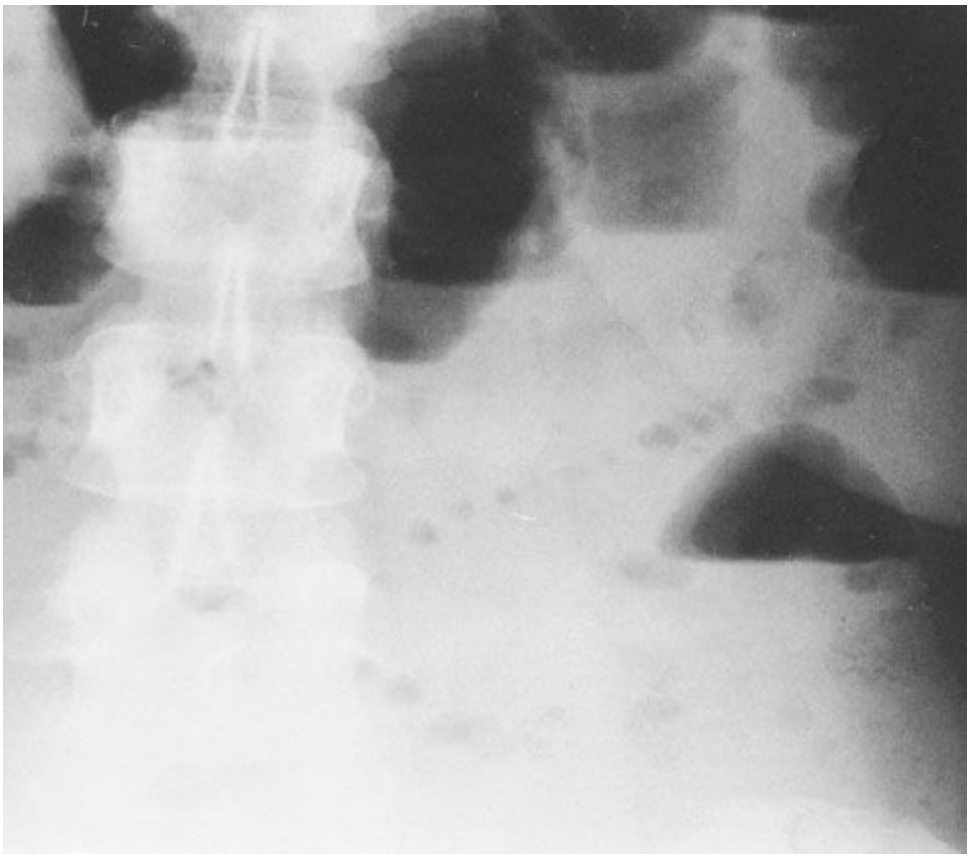

FIGURE 109.2 "String of pearls" sign on upright view in patient with small bowel obstruction.

Computed tomography (CT) has become an important tool in the diagnosis of bowel obstruction. Abdominal CT with water soluble contrast is superior to ultrasound and plain films in determining the presence, the level, and the cause of obstruction (1,4,7,8). Increasingly, the use of abdominal CT is advocated in determining the need for urgent surgery because of ischemic bowel or complete obstruction (1).

Patients with bowel obstruction may have metabolic abnormalities from profuse vomiting, third spacing of fluid into the lumen of the bowel, and resulting dehydration. Serum electrolytes, blood urea nitrogen, creatinine and glucose results should be obtained and abnormalities corrected. A lipase should be obtained if pancreatitis is being considered. An elevated lactate level may indicate bowel ischemia or a more toxic patient (9). A complete

blood count may reveal an elevated white blood cell count in an elderly patient without other signs of early sepsis, but this finding is nonspecific. A hemoglobin or hematocrit may be elevated from hemoconcentration or decreased from hemorrhagic complications of bowel necrosis or chronic blood loss from a malignancy. Clinical findings always trump laboratory results, which are nonspecific for bowel obstruction.

KEY TESTING

- Upright abdominal x-ray
- CT of the abdomen using water-soluble contrast.
- Complete blood count, electrolytes, BUN, creatinine, glucose, and lactic acid.

ED MANAGEMENT

An intravenous line should be started, and signs of hypovolemia should initiate prompt fluid resuscitation with normal saline. Several liters may be required for adults. Patients who are vomiting or nauseated should be treated with an antiemetic. Intravenous narcotic analgesia should be given early for relief of abdominal discomfort. Febrile patients or those with evidence of peritonitis should receive antibiotics active against bowel flora (2,7,10).

On confirmation of the diagnosis and after discussing the planned clinical course with the patient, a nasogastric tube should be inserted, after anesthetizing the nasal passage and posterior pharynx, and attached to intermittent suction. The gastric contents should be visualized to determine the presence or absence of blood. Surgical consultation should be obtained as soon as the diagnosis is made or immediately in patients with signs of peritonitis (2).

CRITICAL INTERVENTIONS

- Initiate fluid resuscitation, as many patients with bowel obstruction are hypovolemic.
- Administer antiemetics and narcotic analgesics for patient comfort.

- Place a nasogastric tube to allow decompression and reduce pain and distention.
- Facilitate surgical consultation and hospital admission.

DISPOSITION

Patients with bowel obstruction should be admitted to the hospital. Determining the appropriate hospital bed depends on the patient's condition and comorbid illnesses. Surgical consultation should be obtained promptly, with direct communication by the emergency physician. The challenge for the surgeon is to determine whether strangulation has occurred and whether the patient requires acute operative management or a 12- to 48-hour trial of observation and bowel rest (3,4,7,10).

Common Pitfalls

- Delay in promptly and aggressively treating hypovolemia.
- Delay or failure to treat a patient's symptoms with antiemetics and opioid analgesics.
- Extensive laboratory and radiographic testing that delays diagnosis and early consultation with a surgeon.
- Delay or failure to place a nasogastric tube after making the diagnosis of bowel obstruction.

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CHAPTER 110
Hernias

Sharon E. Mace

A hernia is the protrusion of a structure or organ through the tissues that normally contain it. External or abdominal wall hernias are far more common than internal hernias and are the focus of this chapter (Fig. 110.1). Herniorrhaphy is the most common general surgical procedure in the United States and worldwide, accounting for 10% to 15% of all general surgery operations (1–3). Inguinal hernias account for about 75% of herniorrhaphies (4). Inguinal hernia repair is also the most commonly performed pediatric surgical operation (5). It is estimated that 5% of the adult male population has a groin hernia (6), but the actual prevalence may be higher since many hernias are asymptomatic or have only mild symptoms and may be undiagnosed. Abdominal hernias are the second most common cause of small bowel obstruction (6,7).

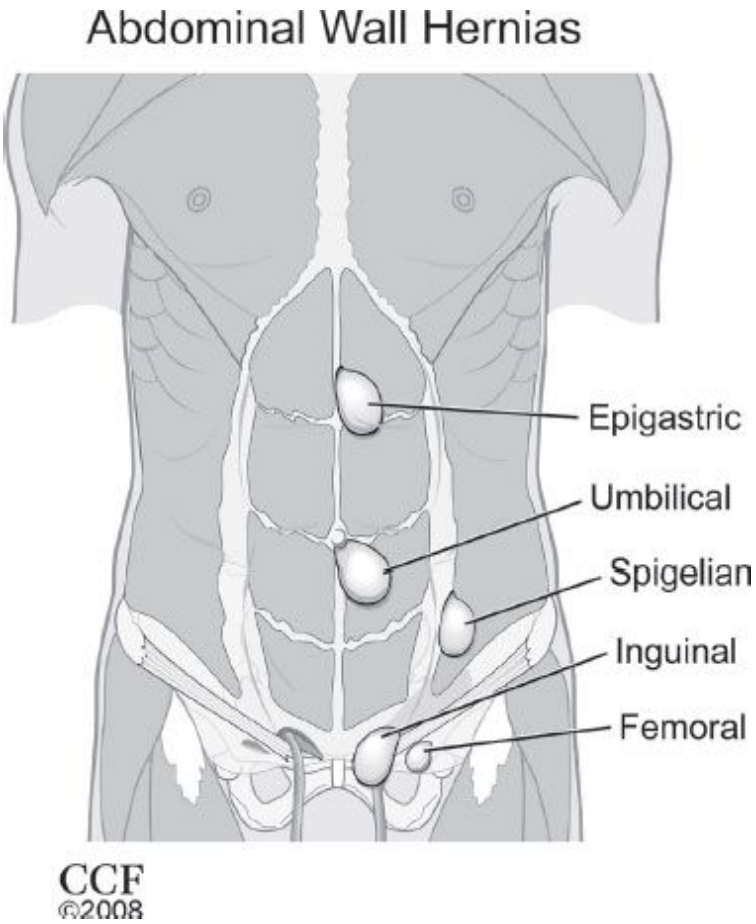

FIGURE 110.1 Abdominal wall hernias. (Reproduced with permission from Sharon E. Mace, MD, and Dave Schumick of the Cleveland Clinic Center for Art and Photography.)

Males are nine times more likely to have a groin hernia than females, while there is a marked female predilection (10:1) for femoral hernias. Femoral hernias are rare in men and direct hernias are rare in women. The most common hernia in either gender is an indirect inguinal hernia (Table 110.1).

TABLE 110.1
Relative Distribution of Hernias in Men and Women

Hernia Type	Men (%)	Women (%)
Indirect inguinal	53.6	32.9
Direct inguinal	27.4	1.5
Combination (direct and indirect)	7.6	3.1
Incisional	3.5	17.5
Femoral	2.8	11.1
Umbilical	2.3	16.6
Hiatal	2.2	14.8
Epigastric	0.66	2.5
Total	100	100

Percentages reproduced with permission from Ponka JL. *Hernias of the Abdominal Wall*. Philadelphia, PA: Saunders; 1980:85.

Age is also a factor affecting the incidence of hernia. For inguinal hernias, there is a bimodal distribution by age—those younger than 1 year and those older than 40 to 55, especially geriatric patients (7).

The cause of hernias is probably multifactorial: weak connective tissue with cellular and extracellular matrix defects, aging, and congenital defects; incisional and recurrent inguinal hernias may be due to surgical wound failure or technical limitations (8). Smoking and malnutrition can impair collagen structure (8). There is also a high prevalence of hernias in patients with connective tissue disorders such as Marfan syndrome, Ehlers–Danlos syndrome, Hurley–Hunter syndrome, and Down syndrome (8–10).

The “shutter mechanism” is a reflex contraction of the internal oblique and transversus abdominis muscles in response to increased abdominal pressure. It causes the inguinal ring to close like a sphincter around the spermatic cord, which protects against herniation. When the abdominal musculature is weakened (e.g., age, malnutrition, wasting, neuropathy), the protective shutter mechanism does not function optimally, and the risk of herniation is increased (11).

Increased intra-abdominal pressure (e.g., ascites, pregnancy, peritoneal dialysis) may also contribute to the development of a hernia. If the transversalis fascia is weakened or thinned or a patent processus vaginalis is present, a hernia may develop. Physical exertion precipitates the development of an inguinal hernia in $<10\%$

of patients, except when worker's compensation is a consideration (12). The fact that athletes such as weightlifters do not have a higher incidence of inguinal hernias supports the current view that a specific episode of physical exertion is not a major risk factor for a hernia.

A *reducible hernia* is defined as one in which the herniated structures can be returned through the abdominal wall defect back into the abdominal cavity. An *irreducible hernia* cannot be returned through the abdominal wall defect back into the abdominal cavity. Another term for an irreducible hernia is an *incarcerated hernia,* which is sometimes mistakenly used to imply an irreducible hernia about to become strangulated.

A *strangulated hernia* is one in which the blood supply to the herniated structures is compromised. Gangrene may occur if the vascular compromise is not relieved. A strangulated hernia is a life-threatening situation requiring emergency treatment and surgical intervention. Hernias with a small neck or opening and a large sac have a tendency to strangulate. All strangulated hernias are irreducible or incarcerated, but not all irreducible or incarcerated hernias are strangulated.

Hernias can be classified as an external, internal, or interparietal. An *external* hernia protrudes completely through the abdominal wall to the outside and, thus, can be seen and palpated. Examples include incisional, umbilical, inguinal, and femoral hernias. An *interparietal* hernia is a rare hernia in which the hernial sac is contained within the abdominal wall. An *internal* hernia is one in which the herniated part occurs within the confines of a body cavity. Internal hernias include diaphragmatic hernias, hernias through a tear in the mesentery or omentum, and hernias through the foramen of Winslow into the lesser sac. Internal hernias are much less common than external hernias and can be very difficult to diagnose.

Hernias occur where there is a weakness in the abdominal wall so that peritoneum and other internal abdominal structures or organs can protrude through the abdominal wall defect. Thus, hernias represent a failure of the abdominal wall to contain the abdominal structures or viscera. The intestines are the most common structure

undergoing herniation, but all intraperitoneal structures can herniate, from a tiny piece of omentum to an entire organ.

Groin hernias, which include *inguinal hernias* (both direct and indirect) and *femoral hernias,* are the most common, accounting for 85% of all hernias (80% groin, 5% femoral). Adding umbilical and incisional hernias to groin hernias would raise the total to 95% to 98% of all hernias.

Inguinal hernias are superior to the inguinal ligament, whereas the femoral hernia is inferior to the inguinal ligament (Fig. 110.2). The indirect inguinal hernia passes through the internal (or deep) inguinal ring and into the inguinal canal and lies lateral to the inferior epigastric vessels. The direct hernia lies medial to the inferior epigastric vessels and protrudes through Hesselbach triangle, which is bounded by the inferior epigastric artery, the lateral border of the rectus abdominis muscle, and the inguinal ligament. Of all inguinal hernias, about two-thirds are indirect.

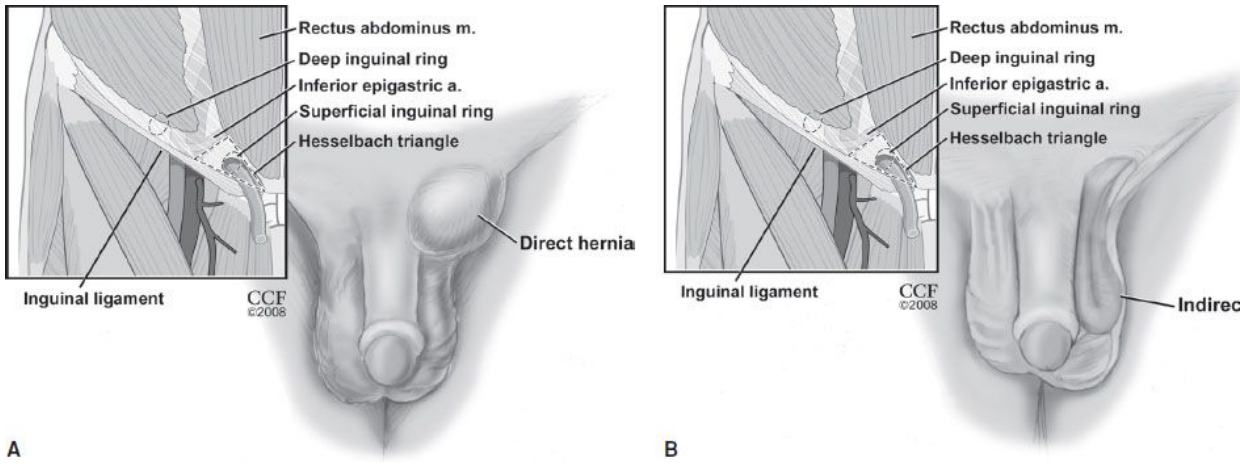

FIGURE 110.2 Inguinal hernias. **A:** Direct inguinal hernia. **B:** Indirect inguinal hernia. (Reproduced with permission from Sharon E. Mace, MD, and Dave Schumick of the Cleveland Clinic Center for Art and Photography.)

An indirect inguinal hernia follows the path of a patent processus vaginalis. The processus vaginalis is formed during fetal development to allow the descent of the testes in the male from their original retroperitoneal site into the scrotum (Fig. 110.3). If the processus

vaginalis fails to close off after birth, an indirect hernia may occur, allowing abdominal contents to progress down the inguinal canal into the scrotum.

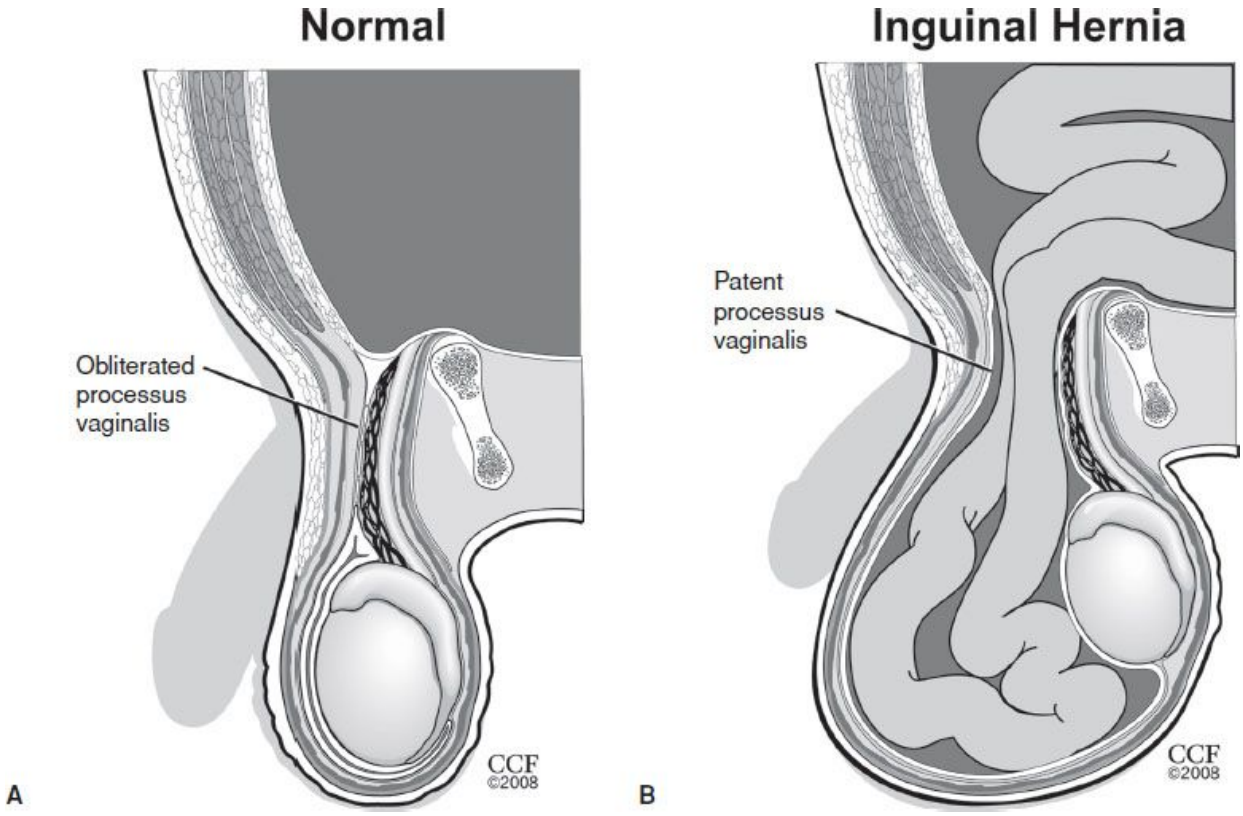

FIGURE 110.3 Processus vaginalis. **A:** Normal, fusion of processus vaginalis. **B:** Inguinal hernia, complete failure of fusion of processus vaginalis. (Reproduced with permission from Sharon E. Mace, MD, and Dave Schumick of the Cleveland Clinic Center for Art and Photography.)

A femoral hernia is the protrusion of abdominal contents between the femoral vessels (artery and vein) and the lacunar ligament in the femoral canal. Femoral hernias occur almost exclusively in women and, because of the narrow neck or opening, they frequently incarcerate.

Less common types of abdominal wall hernias include epigastric, pelvic, lumbar, and spigelian hernias. *Epigastric hernias* are hernias that occur in the midline of the abdominal wall between the umbilicus and the xiphoid. *Pelvic hernias* involve the protrusion of

abdominal contents through areas in the floor of the abdominal cavity. The *obturator hernia* involves herniation through the obturator foramen and generally occurs in elderly women. *Lumbar hernias* occur in the superior and inferior lumbar triangles, which are two naturally weak regions of the posterior abdominal wall. *Spigelian hernias* are protrusions of abdominal contents lateral to the rectus abdominis muscle through the external oblique fascia (Fig. 110.1).

Ventral hernias include umbilical, epigastric, and spigelian hernias. *Incisional hernias* constitute about 10% of all hernias and result from postincisional weakness of the anterior abdominal wall. Incisional hernias of the abdominal wall occur in up to 20% of postoperative patients and up to 35% to 50% of those with a postoperative wound infection or dehiscence. There is a 6% incidence of trocar site hernias following laparoscopic surgery. Parastomal hernias are reported in nearly half (50%) of ostomies (6).

Umbilical hernias in adults, unlike those in pediatric patients, result from an acquired rather than a congenital defect and are usually due to increased intra-abdominal pressure. Patients with increased intra-abdominal pressure, such as peritoneal dialysis, ascites, pregnancy, or obesity, have a higher incidence of umbilical hernias. Umbilical hernias occur in about 20% of patients with cirrhosis and ascites. Elective repair is often recommended for umbilical hernias in adults since there is a greater incidence of complications, including incarceration and spontaneous rupture than in children and infants (7). Ulceration and perforation are complications that are associated with high morbidity and mortality, especially in cirrhotic patients. Skin changes with maceration and ulceration usually occur before frank rupture occurs and so patients with these findings need referral for urgent repair (6). Strangulation of an umbilical hernia precipitated by rapid fluid removal during paracentesis has been reported. Therefore, before paracentesis is performed, an umbilical hernia should be reduced (6).

PEDIATRIC CONSIDERATIONS

In pediatric patients, the incidence of inguinal hernias is greatest in infancy (age 0 to 12 months) with a peak in the first month of life.

The overall incidence of pediatric inguinal hernia is 4%. There is an increased incidence in premature infants, with 30% of infants weighing <1,000 g having an inguinal hernia (9,13).

Inguinal hernia repair is the most common surgical procedure in children (5). As with adults, hernias are much more common in males than females, with a ratio of about 10:1 (5). Most children with an inguinal hernia are asymptomatic; the hernia is discovered by the parent changing the infant's diaper or by a physician during a routine examination. However, incarceration and strangulation can occur. It has been estimated that 70% of incarcerated hernias occur in infants younger than 1 year (14) and the rate of incarceration in premature infants with an inguinal hernia is as high as 31% (5). Most incarcerated hernias (90%) can be reduced outside the operating room (15). As with adults, if the hernia cannot be reduced, immediate surgery is warranted owing to the risk of subsequent strangulation (5).

Umbilical hernias are very common in infants, occurring in 10% of infants, with a higher incidence in African American infants (20%) versus white infants (3%) and in premature infants occurring in up to 75% of infants <1,500 g (10). The majority of umbilical hernias in infants close spontaneously by 2 years of age, and rarely incarcerate or strangulate. "Strapping" is not an effective treatment. Surgery is generally not recommended unless the hernia becomes strangulated, persists to age 5 years, becomes progressively larger after 1 to 2 years of age, or is symptomatic (9).

CLINICAL PRESENTATION

The most common presenting complaints of a symptomatic hernia are swelling and pain. If there is an acute incarceration, there may be the sudden onset of severe pain with nausea and vomiting. The pain occurring with an acute incarcerated hernia is caused by edema and inflammation of the herniated structures and the surrounding tissues. Incarcerated hernias are the second most common cause of bowel obstruction in the United States, with postoperative adhesions being first. If strangulation is present, the patient may present with pain, distention, peritonitis, vomiting, fever, or sepsis.

Occasionally, the initial symptoms may be somewhat misleading. In some patients, the pain from an incarcerated groin hernia may be located in the epigastrium because of traction on the abdominal contents from the hernia. In other patients, strangulation can occur without any symptoms and signs of bowel obstruction when only part of the bowel wall is herniated. This occurs with a *Richter hernia,* in which only one side of the intestinal wall is within the hernia sac.

Pain and/or hypesthesia located along the medial aspect of the thigh radiating to the knee owing to irritation of the obturator nerve (Howship–Romberg sign) occurs in half of patients with an obturator hernia.

DIFFERENTIAL DIAGNOSIS

The most common diagnoses to consider in a patient presenting with a groin mass are an inguinal hernia, enlarged inguinal lymph node(s), abscess, hydrocele, and testicular pathology such as torsion of an undescended testicle in an infant (Table 110.2).

TABLE 110.2
Differential Diagnosis of Groin and Scrotal Masses

- Groin hernias
  - Indirect inguinal (most common groin hernia in men and women)
  - Direct inguinal
  - Femoral
- Urologic
  - Hydrocele
  - Varicocele
  - Spermatocele
  - Testicular torsion
  - Torsion of appendix testis ("appendix epididymis")
  - Urologic tumors
    - Testicular tumor
    - Spermatic cord tumor
  - Undescended testes (especially in pediatric patients)
  - Retractile tests (especially in pediatric patients)
  - Epididymitis (also listed under infections)
  - Epididymal cyst
- Infectious
  - Lymph nodes (may be from infection or malignancy)
  - Epididymitis
  - Cellulitis of groin
  - Sexually transmitted disease (such as lymphogranuloma venereum)
  - Psoas abscess
- Vascular (involvement of femoral vein or artery)
  - Femoral artery aneurysm
  - Femoral thrombophlebitis
  - Femoral saphenous vein varices

ED EVALUATION

History should include questions about previous operations or hernia. Also noteworthy is whether the patient has noted variability in the size of the hernia related to activity or lying flat. Physical examination should include inspection and gentle palpation for any bulges or masses. Cooperative patients may be asked to cough or strain, which increases intra-abdominal pressure, in an attempt to demonstrate the hernia. Palpation of the external inguinal ring in a standing male patient may also be helpful in detecting an inguinal hernia.

Laboratory tests are generally not helpful unless the patient has developed an incarcerated or strangulated hernia. In such cases, leukocytosis with a left shift may be present, although these findings are not sensitive or specific. Dehydration with electrolyte abnormalities and an elevated BUN also occurs frequently in patients with incarceration or strangulation.

Acute abdominal series radiographs may be helpful if bowel obstruction is suspected. The upright chest roentgenogram can rule out free air under the diaphragm resulting from perforation or dead bowel. Computed tomography scan and ultrasound are also useful in demonstrating a hernia and whether it contains bowel, when the diagnosis is in doubt, or an acute complication is suspected. One study reported 100% sensitivity and specificity for the diagnosis of groin hernia by bedside emergency ultrasound (16).

KEY TESTING

- History and physical examination alone are adequate in most cases.
- CT scan and ultrasound are useful in equivocal cases or to evaluate for complications.

ED MANAGEMENT

Patients with hernias can be grouped into three categories: (a) asymptomatic or minimal symptoms (swelling or mild discomfort) with a reducible hernia, (b) irreducible but not strangulated hernia, and (c) strangulated hernia.

Although surgery is indicated for the majority of patients with complications or significant symptoms related to their hernia, a recent clinical trial comparing routine surgical repair versus observation for asymptomatic patients with inguinal hernias concluded that “watchful waiting” is an acceptable option for men with minimally symptomatic inguinal hernias (17). Although used in the past, trusses are generally not recommended (18) and may actually be harmful in some cases (19). If the irreducible hernia is acute (and there is no evidence for strangulation), nonsurgical

reduction should be performed. Cool compresses may be placed over the hernia site to diminish pain, edema, local blood flow, and decrease intraluminal gas pressure. Appropriate sedation should be given. If the patient has a groin hernia, he or she may be placed in the Trendelenburg position. The hernia may spontaneously reduce. If not, gentle manipulation (or taxis) may be attempted. Slow, steady compression should be used, not forceful attempts.

If the acute, incarcerated hernia cannot be reduced, emergency surgery should be performed as soon as fluid and electrolyte abnormalities are corrected. Complications of manual hernia reduction include partial reduction and hernia reduction en masse. Hernia reduction en masse is a rare complication in which the hernia sac is manipulated into the preperitoneal space. This gives the false impression that the hernia has been reduced although it is still incarcerated and at risk for strangulation.

The patient with a strangulated hernia requires aggressive resuscitation with fluids and blood as needed and emergent surgical consultation for operative intervention. Gastric decompression with a nasogastric tube is appropriate if bowel obstruction is present. Broad-spectrum antibiotics are also advised in the acutely ill or potentially septic patient.

CRITICAL INTERVENTIONS

- Reduction of an incarcerated hernia
- Aggressive resuscitation and early surgical consult for patients with a strangulated hernia

DISPOSITION

Patients with an asymptomatic or a reducible hernia should be given discharge instructions, which include the warning signs of incarceration and strangulation. They need referral to general surgery for evaluation for possible elective herniorrhaphy.

For patients with a hernia that has been reduced in the emergency department, urgent surgical referral for herniorrhaphy is recommended, as the incidence of recurrence is high.

Admission for surgical management is mandatory for acute, incarcerated hernias that cannot be reduced and for all strangulated hernias.

Common Pitfalls

- Failure to identify an incarcerated or strangulated hernia.
- Failure to diagnose a small hernia.
- Failure to make an appropriate referral to a surgeon.
- Failure to aggressively resuscitate a patient with a strangulated hernia.

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CHAPTER 111

Inflammatory Bowel Disease

Howard A. Werman, Sarah M. Greenberger, and Nicholas E. Kman

Inflammatory bowel disease (IBD) comprises two chronic intestinal disorders: *ulcerative colitis* (UC) and regional enteritis or *Crohn disease.* Both are characterized by recurrent episodes of gastrointestinal symptoms separated by periods of remission, and both are associated with a variety of systemic manifestations. Approximately 10% to 15% of patients with IBD have clinical features and endoscopic findings that do not allow clear classification. Emergency physicians must be familiar with IBD for two reasons. First, these disorders must be considered in the differential diagnosis of patients with chronic recurrent gastrointestinal complaints. Second, patients with established diagnoses of IBD may present to the emergency department (ED) for management of exacerbations and complications of their disease.

The cause of both disorders remains unknown. Immunologic, infectious, genetic, dietary, environmental, and psychological factors have been implicated. An abnormal immune response to enteric bacteria in genetically susceptible hosts appears to be the underlying disease mechanism (1). The role of steroids and immunosuppressive agents in treatment of UC and the efficacy of agents such as antitumor necrosis factor in treatment of Crohn disease further suggest that immunologic factors play a prominent role in IBD.

IBD affects approximately 1.4 million Americans (2). For both diseases, there is a bimodal age distribution at onset, with peaks at 15 to 25 years and at 55 to 60 years (3); 25% to 30% of patients with Crohn disease and 20% of patients with UC are younger than 20 years old. 10% to 15% of patients with IBD, particularly those with early onset of disease, have relatives who are also affected. The incidence and prevalence of Crohn disease is increasing in the United States for reasons that are unclear (4).

UC tends to remain localized to the colon; in the majority of patients, the disease is found in the rectum and left colon only. The entire colon is affected (pancolitis) in the most severe cases. UC usually is limited to the intestinal mucosa and submucosa and occurs in an uninterrupted pattern.

Crohn disease can be found along the entire gastrointestinal tract; involvement is often discontinuous ("skip areas"). In 30% of cases, only the terminal ileum is involved; 20% of patients have colonic disease only. Both small and large bowels are affected in the remaining 50%. Disease of the mouth, esophagus, and stomach is found in $<1\%$ of patients. The lesions of Crohn disease tend to involve all of the bowel wall layers and extend into the mesentery. Deep ulcerations, which often penetrate the bowel wall, are common and account for the development of fissures, fistulas, and abscesses; about 25% of patients with Crohn disease will manifest these perianal complications.

CLINICAL PRESENTATION

The most common signs and symptoms in patients with Crohn disease are chronic or nocturnal diarrhea, abdominal pain, fever, anorexia, rectal bleeding, and weight loss. This constellation of symptoms characterizes 75% to 80% of patients with this disorder. Presenting complaints in the ED vary, depending on the site of involvement of Crohn disease. Patients with primary ileal disease present with right lower quadrant abdominal pain associated with fever, abdominal distention, vomiting, and either profuse watery diarrhea or decreased output of stool and gas. Severe cases of

fulminant colitis in Crohn disease are characterized by abdominal pain associated with fever and massive diarrhea. Less common presentations include severe epigastric pain similar to peptic ulcer disease, acute pancreatitis, and large aphthous oral ulcers.

As in Crohn disease, the presentation of UC is quite variable and often depends on the anatomic distribution of disease. In fact, separation of the disorders on the basis of clinical findings alone can be very difficult. In mild cases, occasional constipation and rectal bleeding may be the only complaints. In more severe UC, patients have more than six to eight bloody diarrheal stools per day as well as crampy abdominal pain, tenesmus, fever, tachycardia, and anemia. UC is more commonly associated with rectal bleeding, whereas abdominal pain, abdominal masses, and perianal lesions are more common in patients with Crohn disease.

There is often a delay of several months from the onset of symptoms to the time the diagnosis is established. Therefore, failure to suspect IBD and refer patients appropriately is not uncommon; a high index of suspicion must be maintained in the ED for any patient with recurrent abdominal complaints. Patients with previous episodes of similar gastrointestinal symptoms, family history of IBD, perirectal disease, or any extraintestinal manifestations (rashes, back pain, arthritis, or iritis) that might suggest the diagnosis should be referred to an appropriate specialist for diagnostic workup.

A common reason for patients with well-established IBD to present to the ED is complications of their underlying disease. The major intestinal complications of Crohn disease and UC include intra-abdominal abscess formation, bowel perforation, massive hemorrhage, intestinal obstruction, dehydration, perianal complications (fissures, fistulas, and perirectal abscesses), and fulminant colitis with or without toxic megacolon (5). Massive hemorrhage, fulminant colitis, and toxic megacolon are more commonly seen in UC, whereas abscesses, obstruction, and perianal complications are more typical of Crohn disease. In addition to recognizing these complications, the emergency physician must also be aware that medications taken by patients with IBD, particularly corticosteroids and immunosuppressive agents, may mask the

findings typically associated with complications of IBD. Other drug-associated complications include leukopenia, thrombocytopenia, fever, infection, diarrhea, and pancreatitis, as well as renal and hepatic insufficiency (Table 111.1).

TABLE 111.1
Medication Side Effects in IBD

Medication	Side Effects
Corticosteroids	Acne, hirsutism, fluid retention, fat redistribution, hypertension, hyperglycemia, psychoneurologic disturbances, cataracts, growth failure in children, osteonecrosis
Mesalazine	Nausea, dyspepsia, rare nephritis, pulmonary infiltrates, rare idiosyncratic worsening of IBD
Sulfapyridine	Headache, nausea, vomiting, anorexia, epigastric pain, rare hypersensibility hepatitis, hemolytic anemia, pancreatitis, reversible sperm abnormalities, worsening of IBD
Azathioprine/mercaptopurine	Pancreatitis, bone marrow suppression, nausea, vomiting, hepatotoxicity
Methotrexate	Nausea, leucopenia, hepatic fibrosis, eosinophilic pneumonia
Cyclosporin	Nephrotoxicity, hypertension, headache, gingival hyperplasia, paresthesias
Tacrolimus	Headache, insomnia, nephrotoxicity
Infliximab	Infusion reactions, delayed hypersensitivity-like reactions, drug-induced lupus, tuberculosis reactivation, severe infections, cancer, non-Hodgkin lymphoma, demyelinating process
Metronidazole	Nausea, metallic taste, coating of tongue, peripheral neuropathy
Ciprofloxacin	Taste disturbance, gastrointestinal effects, tendonopathies

Modified from Danese S, Semeraro S, Papa A, et al. Extraintestinal manifestations in inflammatory bowel disease. *World J Gastroenterol*. 2005;11(46):7227–7236.

Toxic megacolon is perhaps the most significant complication seen in patients with IBD (6). This complication develops in 5% of adults with IBD but is rare in children. Toxic megacolon results from loss of muscular tone in the patient with advanced disease. It should

be suspected in patients with active colitis who report a decrease in stool output, particularly if they are on antidiarrheal agents, narcotics, or cathartics, or have undergone recent colonoscopy or barium enema. Affected patients demonstrate findings of fulminant colitis and appear toxic. The abdomen is distended, tender, and tympanitic. Fever, tachycardia, and signs of volume depletion are present. Other findings include mental status changes, leukocytosis, anemia, and electrolyte disturbances. With toxic megacolon, abdominal radiographs demonstrate a long, continuous dilated segment of bowel (>6 cm in width), loss of haustra, and "thumbprinting" as the result of bowel wall edema. Abdominal computed tomography (CT) findings in toxic megacolon include thinning of the colonic wall, distention of the bowel lumen, intramural gas (pneumatosis coli) and, in extreme cases, evidence of perforation. The mortality associated with this complication can be as high as 50% if perforation occurs, although with early recognition, mortality as low as 1% to 2% has been reported.

Twenty-one percent to 36% of patients with IBD have extraintestinal manifestations of their disease (7). Occasionally, these symptoms actually appear before gastrointestinal disease, particularly in children. Extraintestinal manifestations of IBD primarily affect the eyes, skin, joints, kidneys, liver, pancreas, biliary tract, lungs, and vasculature. The most common of these manifestations are arthritis (polyarthritis and ankylosing spondylitis), dermatologic complications (erythema nodosum and pyoderma gangrenosum), ocular inflammation (uveitis, episcleritis, or scleroconjunctivitis), and hepatobiliary disease (cholelithiasis, fatty liver, pericholangitis, chronic active hepatitis, and primary sclerosing cholangitis). In Crohn disease with small bowel involvement, malabsorption syndromes as well as fluid and electrolyte disturbances can occur. Gallstones are found in up to 33% of patients with Crohn disease. Calcium oxalate nephrolithiasis is also common. Patients with IBD may also develop a hypercoagulable state (8), even during periods of disease remission, resulting in deep venous thrombosis, pulmonary embolus and, occasionally, arterial occlusion. Rare involvement of portal veins,

cerebral and mesenteric vasculature, and retinal veins has been reported. Patients with thromboembolic complications have a mortality rate of approximately 25%. Pneumaturia and recurrent urinary tract infection occasionally occur with Crohn disease as the result of enterovesicular fistulas.

A long-term complication, particularly of patients with UC, is colon carcinoma. Patients with UC have had a reported 10- to 30-fold risk of developing colon cancer when compared with the general population, particularly with disease onset before age 25 years. Patients with Crohn disease have a five- to sixfold increase in risk. The incidence of colon cancer has been declining in recent years due to better surveillance and newer biologic therapies. Symptoms of colon cancer may overlap considerably with those of IBD, making diagnosis difficult.

DIFFERENTIAL DIAGNOSIS

The major challenge for the emergency physician is to differentiate IBD as a cause of diarrhea, vague abdominal pain, malaise, and low-grade fever from other treatable causes of these symptoms. Several other entities present with similar complaints. Acute infectious diarrheal illness due to *Shigella, Salmonella, Campylobacter jejuni,* cytomegalovirus, or *Yersinia* species must be considered. Parasitic disease such as amoebiasis can also masquerade as IBD. Cytomegalovirus can cause bloody diarrhea in the patient receiving immunosuppressive agents. When the symptoms primarily involve the rectum, anal intercourse–associated bowel syndrome should be considered. Methicillin-resistant staphylococcal abscesses are commonly found in the perineum and may mimic perianal disease. Symptoms of chronic diarrhea, low-grade fever, and cachexia also occur with HIV infection.

Antibiotic-induced colitis attributable to the overgrowth of *Clostridium difficile* must also be considered, particularly in patients with toxic megacolon. Ischemic colitis and diverticulitis, generally seen in older patients, and radiation colitis may present similarly to IBD.

When abdominal pain is the major complaint, IBD must be distinguished from other causes of the acute abdomen, including appendicitis, cholecystitis, intestinal obstruction, abdominal aortic aneurysm, and mesenteric ischemia. More chronic conditions such as celiac disease, irritable bowel syndrome, and acute intermittent porphyria should be considered in patients with recurrent symptoms. The emergency physician should consider IBD as a cause of abdominal complaints only after excluding other potentially serious causes of abdominal pain.

ED EVALUATION

The emergency physician's first priority is to identify patients with serious complications of IBD, particularly gastrointestinal hemorrhage, intestinal obstruction, bowel perforation, and toxic megacolon, for which aggressive resuscitation and surgical consultation may be required. These occur more commonly in elderly IBD patients (9). Patients may present to the ED with an acute or subacute exacerbation of IBD without evidence of an emergent complication requiring surgical intervention. A careful history should ascertain the frequency of bowel movements, associated symptoms, severity of abdominal pain, and history of hospitalizations. Crohn disease is suggested by such risk factors as a family history of IBD, nonsteroidal anti-inflammatory drug use, and cigarette smoking (10). Physical examination should assess signs of toxicity, dehydration, and metabolic imbalance and should include a careful abdominal examination. Abdominal fullness, mass or a perianal fissure, fistula, mass, or skin tags may be present in Crohn disease (11). Stool should be tested for the presence of blood.

Laboratory evaluation should include a complete blood cell count, blood chemistry profile, urinalysis, and type and screen if bleeding is significant. When liver involvement is suspected, liver function studies should be ordered. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum albumin may be followed to determine disease activity. Fecal calprotectin and lactoferrin are more sensitive in detecting intestinal inflammation, but, like ESR

and CRP, are nonspecific (12). Plain abdominal radiographs may detect clinically inapparent intestinal perforation, obstruction, or toxic megacolon. Abdominal CT scans differentiate complications of IBD from an acute exacerbation of the underlying disease. Abdominal CTs identify intra-abdominal abscesses, strictures, mesenteric inflammation, and fistulas. The role of abdominal ultrasound as well as CT and MR enterography in diagnosis of IBD complications is currently expanding (13), especially in light of concerns over radiation exposure (14).

KEY TESTING

- Most laboratory tests are nonspecific for the diagnosis of IBD.
- CT scan can help establish the diagnosis, location, and extent of disease, as well as major complications.

ED MANAGEMENT

Patients with significant hemorrhage, obstruction, or perforation as a result of IBD are managed in the same manner as other patients with these conditions. Aggressive fluid management, nasogastric decompression, blood product administration as necessary, and early surgical consultation are indicated. Antibiotic coverage of gram-negative and anaerobic bacteria is appropriate in cases of sepsis, intra-abdominal or perianal disease, or suspected perforation. In patients chronically maintained on corticosteroids, stress doses of intravenous corticosteroids (hydrocortisone 300 to 400 mg/d) also should be administered to prevent symptoms of adrenal insufficiency.

Less critically ill patients admitted to the hospital usually require intravenous fluids, corticosteroids, and sulfasalazine derivatives. A multidisciplinary approach involving gastroenterology, surgery, dietary services as well as nutritional support is needed to best manage these patients. Patients with fulminant colitis with or without toxic megacolon often are given a 24- to 48-hour trial of intensive medical therapy before surgical intervention is considered. Such medical therapy includes aggressive fluid and electrolyte

replacement, nasogastric decompression and bowel rest, and antibiotic coverage for bowel pathogens (enteric bacilli and anaerobes). Intravenous methylprednisolone (60 mg/d) or hydrocortisone (300 to 400 mg/d) is routinely administered. Cyclosporine 2 mg/kg/d has been advocated for severe cases of fulminant colitis (15). Intravenous metronidazole (10 to 20 mg/kg/d) and ciprofloxacin (1 g/d) may be added for intra-abdominal and perianal complications of Crohn disease (16). Should patients fail medical management, surgical consultation may be necessary, though drainage of intra-abdominal abscesses by interventional radiology has become an often-preferred initial option over open surgical procedures. Similarly, obstructions due to adhesions can usually be managed with nasogastric suction alone; however, fibrostenotic strictures cause obstructions that may transiently improve with bowel rest and steroids but often require further intervention including stricturoplasty or resection to prevent recurrence.

For those patients whose flares do not require hospital admission, medication adjustment and follow-up plans should be discussed with the patient's primary care physician or gastroenterologist. Systemic steroids (e.g., budesonide) are the mainstay of treatment for Crohn disease, with immunomodulators (azathioprine, methotrexate) and biologics (infliximab, natalizumab) used to maintain remission (17,18). UC is managed primarily with oral or topical sulfasalazine derivatives (e.g., mesalamine), with steroids, immunomodulators, and biologics reserved for more severe symptoms or extensive disease (19,20). Antidiarrheal agents such as loperamide (imodium) 4 to 16 mg/d or diphenoxylate (lomotil) 5 to 20 mg/d may be prescribed.

CRITICAL INTERVENTIONS

- Recognize serious complications of IBD, such as hemorrhage, obstruction, perforation, and toxic megacolon.
- Initiate aggressive supportive care (including fluid resuscitation, antibiotics, blood products, and steroids) for patients with

serious complications of IBD.

DISPOSITION

Fortunately, most patients with IBD can be managed as outpatients. Criteria for hospital admission include severe manifestations (more than six bowel movements daily, severe abdominal pain, or grossly bloody stool); systemic toxicity (fever, tachycardia, weight loss, and cachexia); those with dehydration or metabolic disturbances; acute complications (intestinal obstruction, bowel perforation, gastrointestinal hemorrhage, and toxic megacolon); and failure of outpatient therapy. Surgical consultation is indicated for complications of the disease, including intestinal obstruction or hemorrhage, perforation, intra-abdominal or perianal abscess or fistula formation, toxic megacolon, and perianal disease. Consultation with a rheumatologist, dermatologist, or ophthalmologist should be considered where extraintestinal manifestations of the disease predominate.

Common Pitfalls

- Mistaking one of the serious complications of IBD (such as abscess, perforation, obstruction, and toxic megacolon) with an exacerbation of chronic symptoms.
- Failure to refer a patient with recurrent abdominal symptoms suggestive of IBD for further diagnostic evaluation.
- Failure to administer intravenous fluids, analgesics, and steroids to patients with an acute exacerbation of IBD.

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CHAPTER 112
Diarrhea

Philip N. Salen and Lisa A. Spacek

"Diarrhea" is an alteration in a normal bowel movement characterized by an increase in the water content, volume, or frequency of stools. "Acute diarrhea" is an episode of diarrhea of <7 days in duration; persistent diarrhea lasts more than 7 days (1). Gastroenteritis refers to diarrheal disease associated with nausea, vomiting, and abdominal cramps. In the United States, an estimated 211 to 375 million episodes of diarrheal illness occur annually, resulting in 73 million physician consultations, 1.8 million hospitalizations, and 3,100 deaths (2). In developed nations, morbidity and mortality from diarrhea are rare and occur mainly in the young, the elderly, and the immunocompromised.

Acute diarrheal episodes and exacerbations of persistent diarrhea are common emergency department (ED) presenting complaints. The most common causes of acute diarrhea are infectious; however, there are many less commonly implicated causes, such as chemotherapies and toxins, radiation, food allergies, and inflammatory bowel disease. Among infectious causes of diarrhea, viruses account for 50% to 70%, bacteria for 15% to 20%, and parasites for 10% to 15%. Examples of groups with distinct epidemiologic exposures are: children in day care settings, travelers, individuals engaging in anal intercourse, immunocompromised individuals, people living in unhygienic environments, and those with exposure to contaminated water or foods (1).

Four basic pathophysiologic mechanisms induce diarrhea: alterations in ion secretion from the intestinal villi, alterations in mucosal morphology, alterations in intestinal motility, and osmotic

diarrhea. The majority of diarrheal illnesses are noninflammatory and secretory, usually arising in the proximal small intestine from the action of an enterotoxin or another process that specifically alters the absorptive function of the epithelial cells at the villus tip and results in excessive fluid production (3). Dysentery results from invasive pathogens that elicit inflammation, usually in the colon, and induce fever, abdominal cramps, and bloody diarrhea. In addition to implementing volume resuscitation and treating patients symptomatically, the goal of the emergency physician is to recognize invasive, inflammatory diarrhea, which can signify potential for systemic manifestations of illness, and to determine appropriate therapy.

CLINICAL PRESENTATION

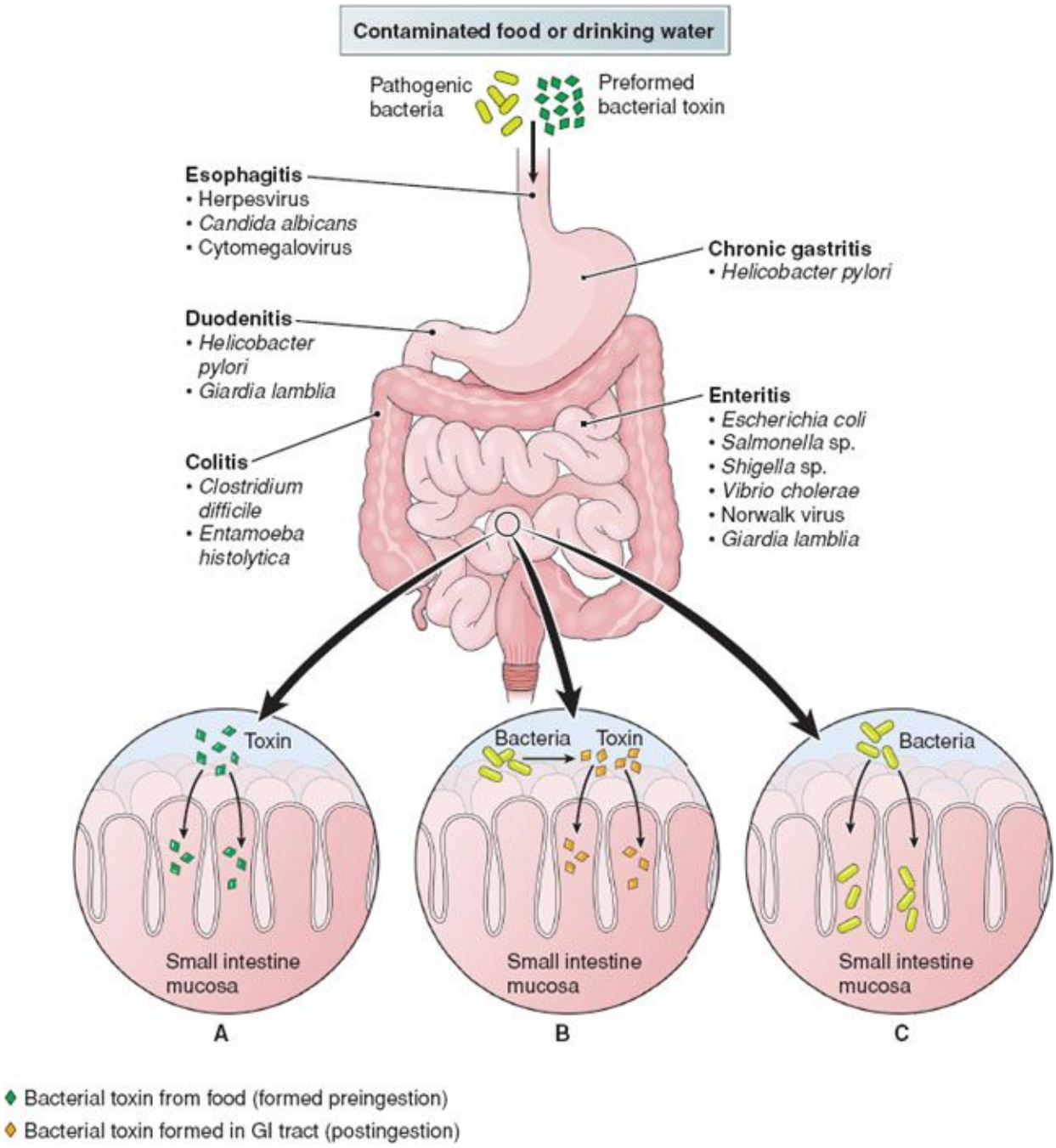
Diarrhea is an increase in stool frequency, an increase in stool volume, or a decrease in stool consistency. Associated gastrointestinal symptoms are nausea, vomiting, abdominal pain, abdominal cramps, bloating, tenesmus, perianal discomfort, intestinal flatus-related complaints, and incontinence. Depending on the etiology, the diarrhea may be: liquid, mucoid, or soft, nonsanguineous or sanguineous, voluminous or scant. Physical examination may reveal fever, tachycardia, dehydration, abdominal tenderness, pronounced borborygmi, and hematochezia. The combination of fever and bloody diarrhea is indicative of intestinal inflammation suggestive of an invasive bacterial colonic disease. From the standpoint of functional impairment caused by the illness, diarrhea may be categorized as mild–moderate, characterized by minimal change in activities of daily living and normal hydration status, or severe, characterized by systemic manifestations of illness and dehydration.

When evaluating complaints of diarrhea, the physician needs to establish whether the stool is truly diarrhea or nondiarrheal rectal discharge, rectal bleeding, or abnormally colored feces. Once the diagnosis of diarrhea is confirmed, the clinician must decide whether (a) there are signs of systemic illness, (b) diagnostic workup is necessary, (c) an etiology can be identified, (d) specific therapy is

warranted, and (e) there are social and community health implications (1). Generally, the severity of illness correlates to the fluid and electrolyte status of the patient and whether the diarrhea has an inflammatory component.

Acute Watery Diarrhea

Many nonbacterial and bacterial enteropathogens are noninflammatory, noninvasive, and act on the proximal small intestine to produce acute watery diarrhea (see eFig. 112.1) (4). Viruses are the most common cause of infectious diarrhea and are characterized by injury to the villus mucosa of the small intestine. Shortened villi decrease the intestinal surface area available for fluid absorption and alter ion secretion. Viral diarrhea is transmitted person to person by the fecal–oral route and by foodborne contamination. The CDC estimates that >50% of US foodborne gastroenteritis outbreaks are caused by the norovirus and rotavirus families (5). Hallmarks of viral enteritis are nausea, vomiting, nonbloody diarrhea, abdominal cramps, malaise, myalgias, chills, and fever in 50% of cases, though the fever is usually low grade. Cholera (eFig. 112.2), an important cause of morbidity and mortality in developing nations that also has low-level endemicity in US Gulf Coast states (4), induces a voluminous, watery, secretory diarrhea via its enterotoxin's effect on the small intestinal villus mucosa that can result in life-threatening dehydration (6). Many potentially important agents that cause watery diarrhea are not detectable by means of conventional stool culture; these pathogens include many types of enterotoxigenic *Escherichia coli,* noncholeraic vibrios, and noroviruses (4).



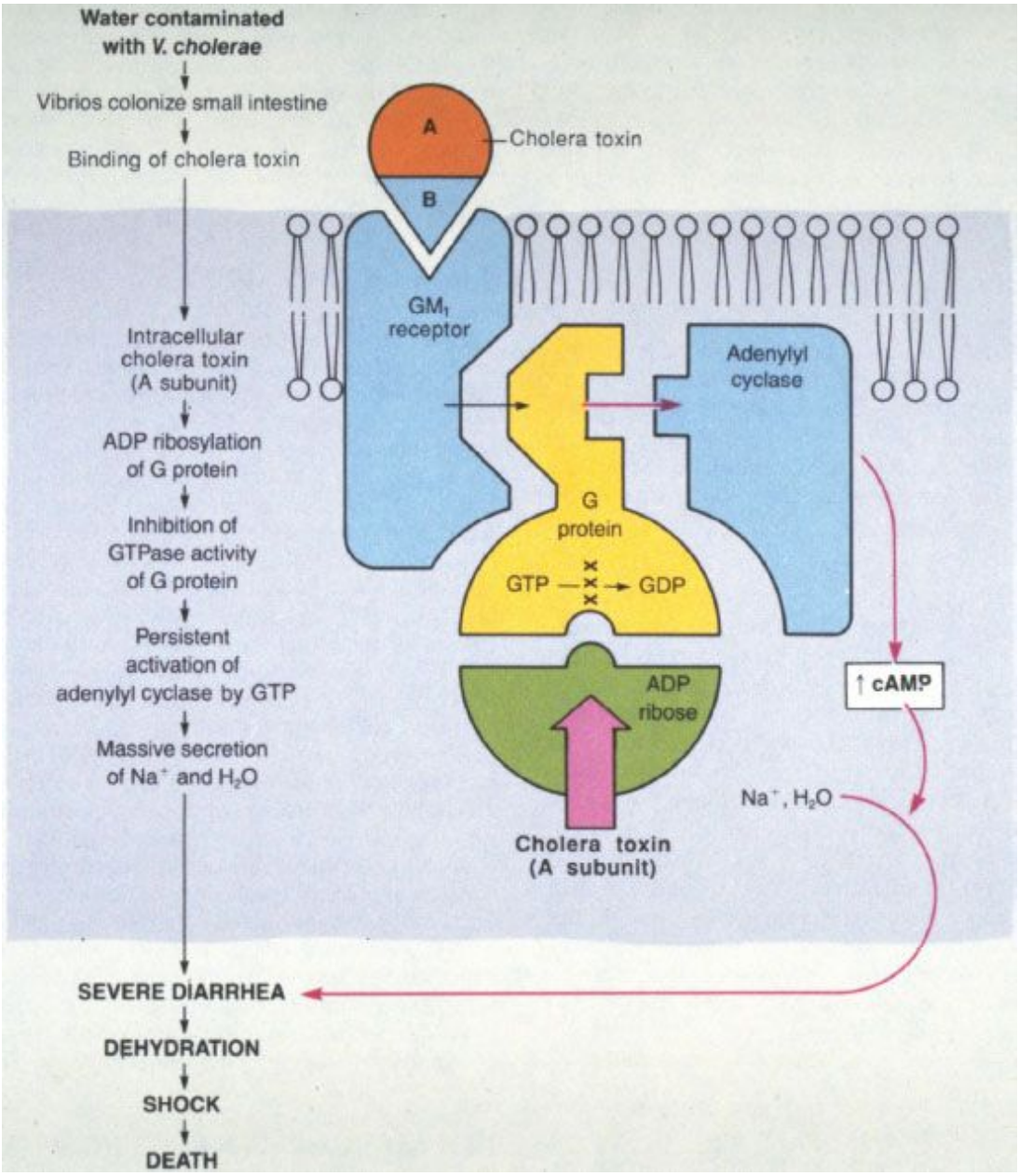
eFIGURE 112.1 Mechanisms of infectious enteritis. Note that pathogens can:

- Produce toxin in food prior to ingestion, which is discussed as food poisoning in this chapter
- Produce toxin in the intestines after ingestion, which can illicit nonbloody diarrhea (cholera is the classic example) or bloody

diarrhea (C. difficile is the classic example)

- Directly invade the bowel wall and cause inflammation (Shigella is the classic example).

McConnell TH. The Nature of Disease Pathology for the Health Professions, Philadelphia, PA: Lippincott Williams & Wilkins; 2007.



eFIGURE 112.2 Cholera. Infection comes from water contaminated with Vibrio cholerae or food prepared with contaminated water. The vibrios traverse the stomach, enter the small intestine, and

propagate. Although they do not invade the intestinal mucosa, the vibrios elaborate a potent toxin that induces a massive outpouring of water and electrolytes. Severe diarrhea ("ricewater stool") leads to dehydration and hypovolemic shock. (Image from Rubin E, Farber JL. Pathology. 3rd Ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.)

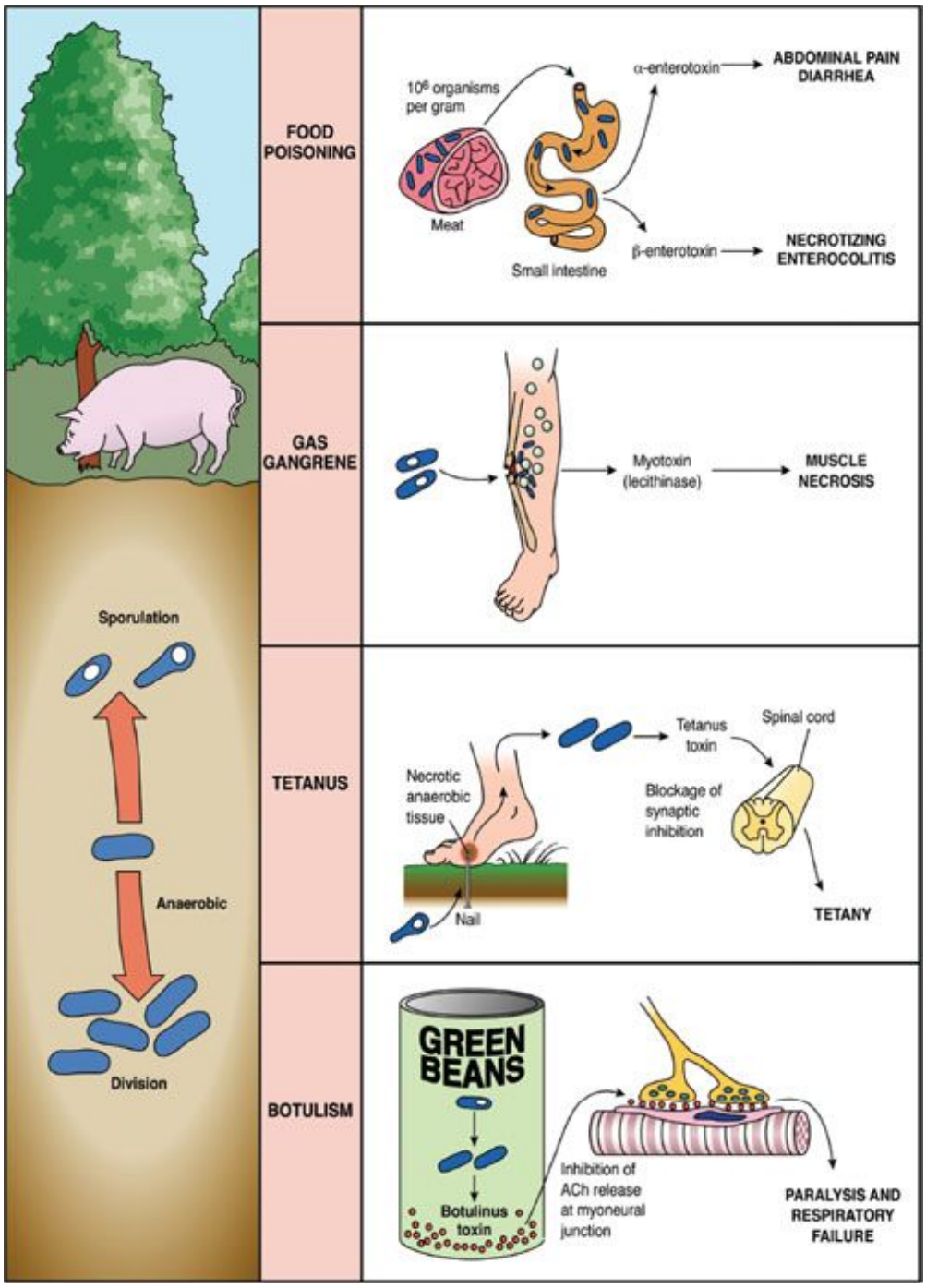
Dysentery

Profuse, explosive bloody diarrhea suggests invasive, bacterial ileocolitis (see eFig. 112.1) (4). Bacterial enteritis alters mucosal morphology by invasion of mucosa of the terminal ileum and colon and induces inflammation. Edema, bleeding, and leukocyte infiltration of the colonic wall manifest as blood and pus in the stool. Fever, which may be quite marked, is a characteristic feature of bacterial enteritis. The four most common causes of bloody diarrhea in the United States, in descending order of occurrence, are Shigella, Campylobacter, nontyphoid Salmonella, and Shiga toxin-producing *E. coli*. Other organisms may also cause dysentery, including *Aeromonas* spp., noncholeraic vibrios, and *Yersinia enterocolitica* (4). It is estimated that only 5% of organisms that cause bloody diarrhea in the United States and that are detectable by laboratory tests are identified (4). Special care must be taken when evaluating patients with suspected dysentery to eliminate the possibility that they may have an anatomic, noninfectious cause of diarrhea and its associated symptoms of abdominal pain and/or fever, such as ulcerative or ischemic colitis.

Food Poisoning

Food poisoning occurs when a preformed toxin in food is ingested resulting in an intoxication rather than an enteric infection (eFig. 112.1) (4). *Staphylococcus aureus* causes vomiting hours after ingestion of improperly cooked food containing a heat-stable preformed toxin. *Clostridium perfringens* causes watery diarrhea without vomiting within 14 hours after ingestion of contaminated meat (eFig. 112.3). Botulism occurs when improperly canned food is

contaminated by the vegetative form of *Clostridium botulinum,* which proliferates under anaerobic conditions and elaborates a neurotoxin. After the food is ingested, the neurotoxin is absorbed from the small intestine and eventually reaches the myoneural junction, where it inhibits the release of acetylcholine (eFig. 112.3). Scombroid food poisoning is caused by consumption of spoiled fish of the Scombroidiae family, for example, tuna, with high histamine levels and manifests as histamine toxicity (7). Symptoms include perioral tingling, headache, flushing, palpitations, truncal rash, abdominal cramps, and diarrhea; treatment with antihistamines is effective. Ciguatera food poisoning, caused by consumption of dinoflagellate toxins in tropical reef-dwelling fish, manifests as abdominal cramping and diarrhea manifest followed by neurologic manifestations, such as reversal of temperature perception (7).

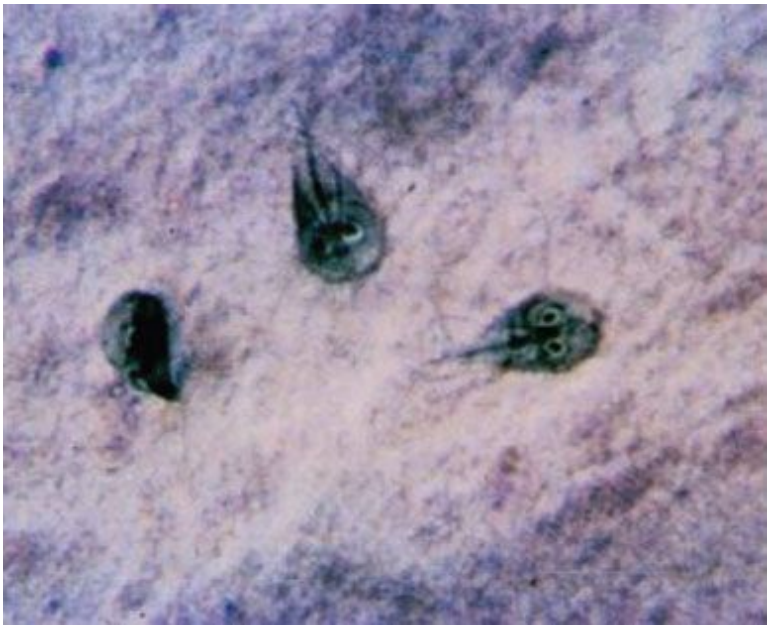


eFIGURE 112.3 Clostridial diarrheal infections meat dishes left to cool at room temperature grow large numbers of clostridia. When contaminated meat is ingested, C. perfringens types A and C produce alpha enterotoxin in the small intestine during sporulation, causing abdominal pain and diarrhea. Type C also produces beta-enterotoxin botulism. Improperly canned food is contaminated by the vegetative form of C. botulinum, which proliferates under aerobic conditions

and elaborates a neurotoxin. After the food is ingested, the neurotoxin is absorbed from the small intestine and eventually reaches the myoneural junction, where it inhibits the release of acetylcholine. (Image from Rubin E, Farber JL. *Pathology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.)

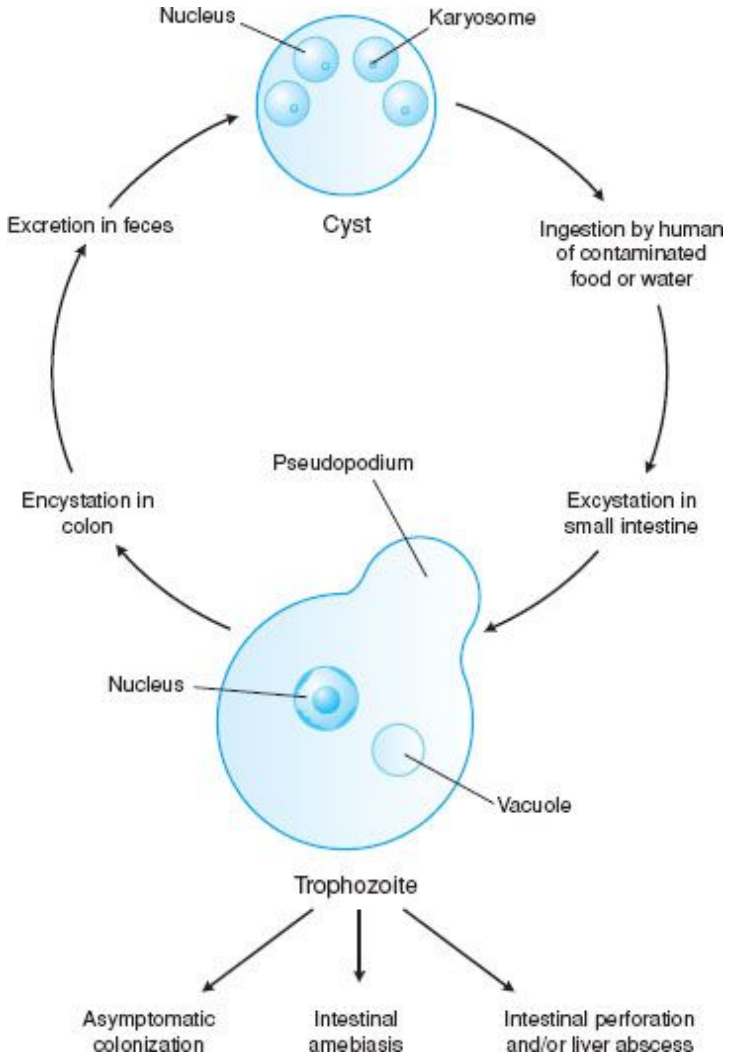
Protozoan Diarrhea

When evaluating patients suffering from persistent, nonspecific complaints of persistent diarrhea such as bloating and excessive flatulence, it is important to consider intestinal protozoa, which are common causes of persistent diarrhea, particularly in the traveler. Protozoan parasites are less common than viral and bacterial causes of traveler's diarrhea (TD), but should be considered in anyone with persistent diarrhea or when antibacterial therapy fails to shorten illness. The most commonly implicated parasites are giardiasis (eFig. 112.4), cryptosporidiosis, and amebiasis (8). *Giardia lamblia* and cryptosporidium-induced diarrhea is noninflammatory, without blood or pus. Giardia and cryptosporidium induce watery diarrhea, abdominal pain, and malabsorption that may last for weeks to months (9). International travel, hypochlorhydria, and ingestion of contaminated water are important risk factors; of note, Giardia is a common pathogen in the United States, particularly amongst campers drinking untreated lake or river water.



eFIGURE 112.4 Microscopic appearance of Giarda lamlia.

Bloody diarrhea in recent immigrants or travelers returning from tropical regions where *Entamoeba histolytica* (see eFig. 112.5) is endemic should prompt stool testing for protozoa (17). Ingestion of cysts of *E. histolytica* from fecally contaminated food or water initiates infection; in addition, infectious transmission is possible via genital–anal sexual contact. Infection with *E. histolytica* cysts ranges from asymptomatic excretion of the cysts to invasive intestinal disease. Invasive disease results when the parasite invades the intestinal epithelium. This invasion induces amebic dysentery, characterized by abdominal cramps and diarrhea, or, in its most severe manifestation, intestinal perforation. Intestinal amebiasis uncommonly causes fecal leukocytes, but commonly induces bloody diarrhea. Hepatic involvement occurs when *E. histolytica* ascends the portal venous system and induces hepatic necrosis from obstruction of portal vessels. Amebic liver abscess is 10 times as common in men as in women and is a rare disease in children. Approximately 80% of patients with amebic liver abscess present with symptoms that develop relatively quickly typically 2 to 4 weeks, which include fever, cough, and a constant, dull, aching abdominal pain in the right upper quadrant or epigastrium.



eFIGURE 112.5 Manifestations of amebiasis. Ingestion of E. histolytica cysts can result in several different clinical outcomes, ranging from asymptomatic excretion of the cysts to invasive disease. Asymptomatic infection occurs when the ingested cysts mature in the small intestine but do not invade the intestinal mucosa. These trophozoites then encyst in the colon, and excretion occurs in the feces. Invasive disease results when active trophozoites invade the intestinal epithelium. This invasion can result in asymptomatic colonization, intestinal amebiasis (amebic dysentery), which is characterized by diarrhea and abdominal cramps, or intestinal perforation. Spread of infection via the portal vein can cause liver abscesses. (Adapted with permission from Huston CD, Haque R, Petri WA. Molecular based diagnosis of Entamoeba histolytica infection. Expert Rev Mol Med. 1999;1999:1–11, Figure 112.1.)

Traveler's Diarrhea

TD frequently occurs in people traveling from developed nations to developing nations and has the potential for wrecking a meticulously planned vacation. TD results because travelers have low levels of immunity against the prevalent pathogens in the food and water in the visited countries (3). The most important and common causes of TD are bacterial with diarrhea-inducing *E. coli,* Shigella*,* Salmonella*,* and Campylobacter inducing the majority of significant illness (10).

Antibiotic-Associated Diarrhea

The spectrum of findings in antibiotic-associated diarrhea ranges from "nuisance diarrhea," frequent loose and watery stools, to life-threatening toxic megacolon. Antibiotic-associated diarrhea may be caused by enteric nosocomial pathogens, by the direct effects of antimicrobial and other chemotherapeutic agents on the intestinal mucosa, and by the metabolic consequences of reduced concentrations of fecal flora (11).

Clostridium difficile infection (CDI) is by far the most common cause of infectious diarrhea in hospitalized patients in North America and the incidence and severity of disease has increased alarmingly since 2000 (12). CDI results in increased morbidity, length of stay, and healthcare costs (11). Most cases of CDI present during or shortly after antimicrobial use. An overgrowth of pathogenic *C. difficile,* which occurs when native bowel flora is killed by antibiotics, produces exotoxins A and B that cause diarrhea (eFig. 112.1). While the majority of CDI results from antimicrobial use, other events may impair colonization resistance, including bowel preparation for colonoscopy or surgery, cytotoxic chemotherapy, and colitis caused by inflammatory bowel disease where colonization by *C. difficile* is common and may exacerbate the underlying inflammatory bowel disease (12). Other risk factors for CDI include age $\leq$65 years, immunosuppresion, and inhibition of gastric acid secretion, especially from proton pump inhibitors (11). Immunocompromised patients contract CDI more frequently and are at increased risk for resultant severe infection and complications. The

most severe manifestations of CDI will result in pseudomembranous colitis and toxic megacolon (eFig. 112.6). CDI relapse is common after therapeutic resolution, occurring in about 25% of cases. Prevention efforts against the nosocomial spread of *C. difficile* includes use of barrier precautions, isolation of infected patients, careful cleaning of fomites with dilute sodium hypochlorite solution, and fastidious hand hygiene. Specifically, hand washing with soap and water is required as a supplement to alcohol-based sanitizers, because such sanitizers do not eradicate *C. difficile* (11).

eFIGURE 112.6 Pseudomembranous plaques seen with colonoscopy in a patient with Clostridium difficile—associated pseudomembranous colitis. (Adapted from Gorbach SL, Bartlett JG, Blacklow NR, etal. Infectious Diseases. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

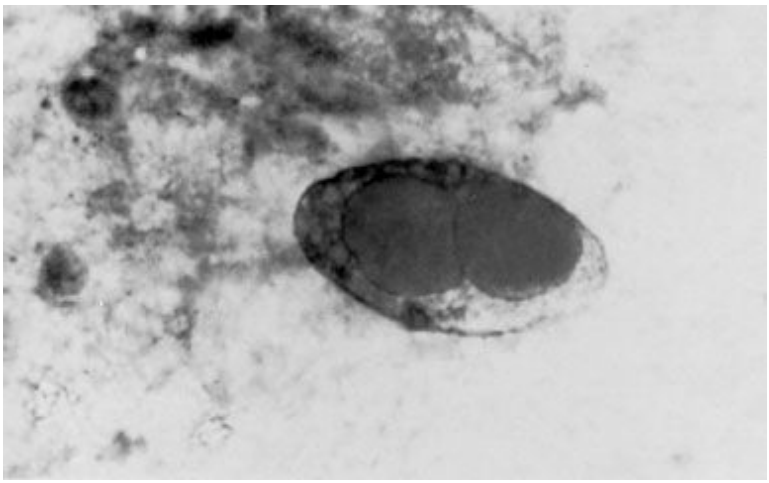
A newly identified hypervirulent strain of *C. difficile,* epidemic strain BI/NAP1 of toxinotype III, has been associated with more frequent and more severe disease, as indicated by higher rates of toxic megacolon, leukemoid reaction, shock, and death (13). This

strain is unique in that it produces substantially more toxin than most hospital strains (14). This emerging strain of *C. difficile* causes disease not only in the hospital setting in traditional at-risk patients but also in patients previously not considered at risk for the disease, specifically immunocompetent, community dwelling, young individuals without recent antibiotic exposure (13).

Diarrhea in Immunocompromised Hosts

Immunocompromised patients present frequently with severe and persistent diarrhea caused by a broad spectrum of infectious and noninfectious etiologies. Besides noninfectious causes, for example, lymphoma, Kaposi sarcoma, or drug-induced diarrhea from highly active antiretroviral therapy (HAART), diarrhea in HIV-infected patients is common and oftentimes caused by opportunistic infections owing to alterations in the mucosal immune system (15). The etiology of their diarrhea is linked to their degree of immunosuppression, which is measured by their CD4+ lymphocyte count. Opportunistic infections most often occur when their CD4+ cell count falls below 100 cells/uL.

Viral, ulcerative infections due to cytomegalovirus and less often herpes simplex virus (HSV) cause chronic inflammatory diarrhea. Cryptosporidium, *Cystoisospora belli* (eFig. 112.7), and microsporidium are opportunistic protozoan pathogens that require specialized diagnostic tests. *Mycobacterium avium intracellulare* infection is associated with fever, bacteremia, and weight loss. Fungal infection with histoplasmosis causes systemic illness that may present as a diffuse colitis. An emerging opportunistic fungus that is endemic in Southeast Asia, *Penicillium marneffei,* causes systemic illness and intestinal ulceration in HIV-infected individuals with CD4 <100 cells/uL, and disseminated disease manifesting with diarrhea and abdominal pain in solid organ transplant recipients (16). HIV-AIDS enteropathy, a pathogen-negative diarrhea that results from CD4+ lymphocyte depletion and failure to maintain the epithelial barrier function of the gut mucosa, is best treated by initiating, or ensuring compliance with HAART to promote recovery of the CD4 count (15).



eFIGURE 112.7 Acid-fast Cystoisospora belli oocyst in the stained smear of a fecal specimen from a patient with AIDS and diarrhea (450×). (Courtesy of Madeleine Boncy, Haitian Study Group on Kaposi's Sarcoma and Opportunistic Infection [GHESKIO], Port-au-Prince, Haiti.)

Diarrhea of Noninfectious Etiology

Consider noninfectious causes of diarrhea when the compendium of diagnostic evaluation has not identified a pathogen (1). Noninfectious and extraintestinal processes may present as acute, persistent, and chronic diarrhea. Some important noninfectious diarrheal diagnoses to contemplate include irritable bowel syndrome, ischemic bowel disease, bowel obstruction, celiac sprue, malabsorption syndromes, and medicinal adverse reactions (e.g., sorbitol, lactulose). Fecal evidence of inflammation in persistent diarrhea should arouse concern about inflammatory bowel disease, particularly if the presence of a treatable inflammatory pathogen, such as Shigella or *C. difficile,* has been ruled out (2).

Potential Complications from Diarrhea

Salmonella and Campylobacter are organisms that deeply penetrate the intestinal mucosa and are prone to cause bacteremia (4). Shiga toxin-producing *E. coli* is a common cause of sanguineous diarrhea that induces colonic vasculitis and allows inflammatory mediators to gain access to the systemic circulation initiating hemolytic-uremic

syndrome. Shiga toxin-producing *E. coli* is differentiated from other bacterial enteric diseases by the absence of fever in the setting of bloody diarrhea (2). Hemolytic uremic syndrome occurs usually within a week after onset of diarrhea and can affect people of any age. Clinical features of hemolytic uremic syndrome include hemolytic anemia, thrombocytopenia, and acute renal failure. Once an isolate has been identified, notify the local health department to identify the source and prevent spread (1). Immune-mediated extraintestinal manifestations such as reactive arthritis and iritis complicate diarrheal illness secondary to Shigella, Salmonella, Yersinia, and Campylobacter. Yersinia infection can induce an autoimmune-type thyroiditis, pericarditis, erythema nodosum, and glomerulonephritis. Guillain-Barré syndrome is an uncommon, late, deadly complication of Campylobacter infection (4).

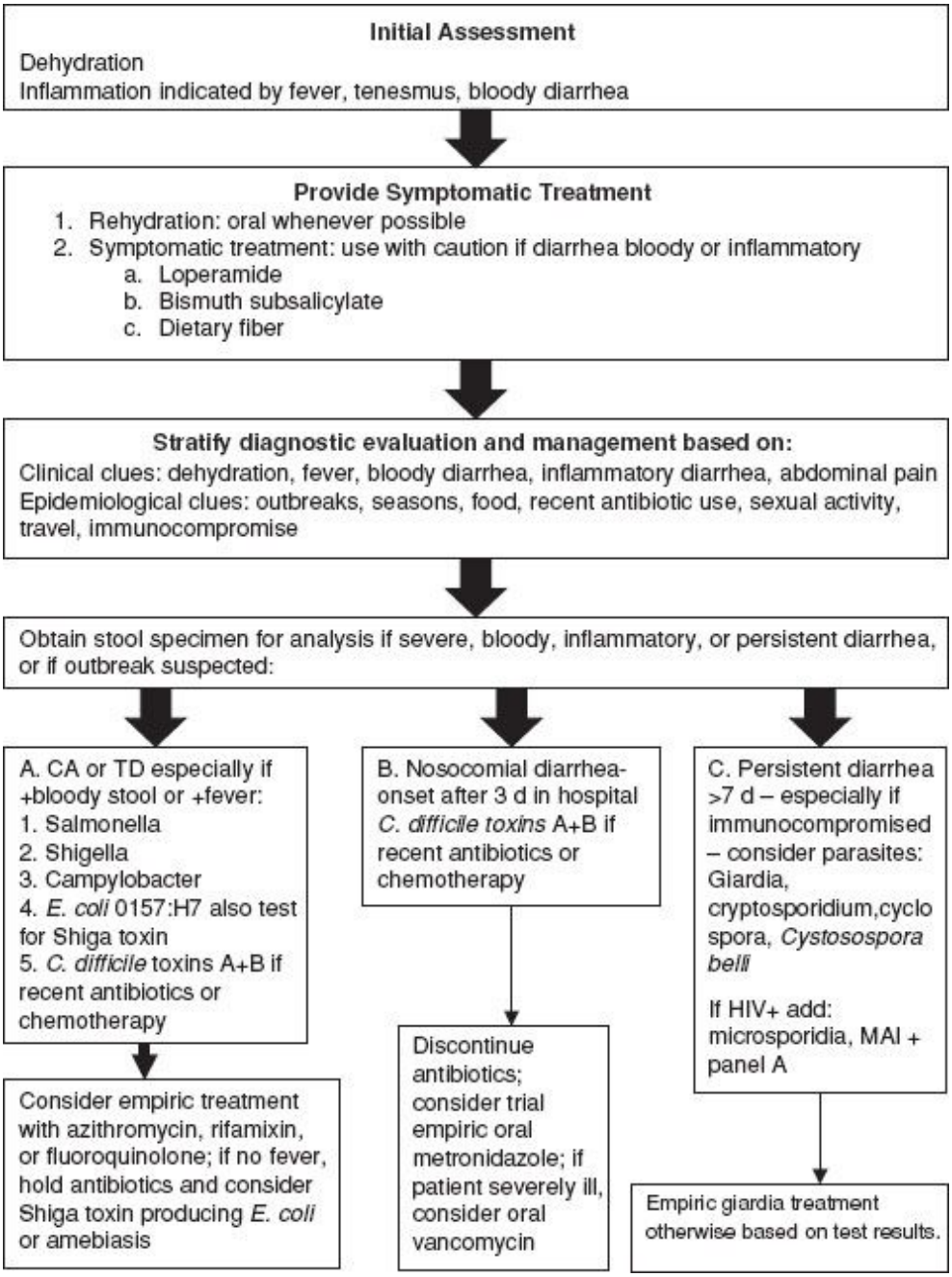
DIFFERENTIAL DIAGNOSIS

Although there are many causes of acute diarrhea, most cases presenting to the emergency physician will be infectious and are transmitted by ingestion of contaminated food or water laden with the organism. Most infectious diarrhea is nonbloody, viral in origin, and will resolve with supportive care. The differential diagnosis of an infectious diarrheal illness with occult or grossly bloody stools includes infection with Shigella, Salmonella, Campylobacter, Shiga toxin-producing *E. coli, E. histolytica* (if recent travel to the tropics), or *C. difficile* (if recent antibiotics or hospitalization) (17). Noninfectious etiologies of bloody diarrhea include inflammatory-bowel disease, ischemic colitis, diverticulitis, radiation colitis, celiac sprue, and malignancy.

ED EVALUATION

Assessment of the severity and duration of enteritis, the presence of dehydration, the character of the diarrhea, and the presence of fever, vomiting, or dysentery aid in identifying diarrheal illness with systemic manifestations. Diarrheal illness can be parsed into four broad categories: (1) community acquired or TD, (2) nosocomial (antibiotic or hospital associated) diarrhea, (3) persistent diarrhea,

and (4) diarrhea in immunocompromised hosts (eFig. 112.8). eTable 112.1 documents epidemiologic, symptomatic, and testing characteristics of important diarrheal pathogens. If there is bloody diarrhea in association with fever, entertain culturing diarrhea for: Salmonella, Shigella, Campylobacter*, E. coli 157:H7,* and *C. difficile.* Consider nosocomial diarrhea in the posthospitalization or postantibiotics patient. For persistent, nonbloody diarrhea, evaluate for parasites and elucidate the patient's immune status. Noninflammatory enteritis typically presents with emesis, mild or absent fever, mild crampy pain, and watery diarrhea, all of which reflect viral disease with small intestine involvement. Inflammatory enteritis presents with fever, significant abdominal pain, tenesmus, and bloody diarrhea, which suggest invasive colonic involvement. Focus physical examination on vital signs, that is, the presence of fever, tachycardia, and hypotension, and the abdomen, which may be tender to palpation and have hyperactive borborygmi, but should lack distension and peritoneal signs.



eFIGURE 112.8 Algorithm for Diarrheal Assessment and Management. CA, community acquired; TD, traveler's diarrhea; MAI, Mycobacterium avium intracellulare.

eTABLE 112.1
Epidemiology, Clinical Characteristics, and Treatment for Selected Pathogens

Infectious Agent	Epidemiology	F	AP	NV	BD	FL	Evaluation	Therapy[a]	Clinical Pearls
Norovirus (e.g., Norwalk virus)	Winter predilection, epidemic outbreaks; most common infectious diarrhea	+/–	+	+	–	–	Clinical	Symptomatic therapy	Hypochlorite 5,000 ppm provides effective surface decontamination (5)
Noncholeraic vibrios	Seafood and shellfish contaminant	+/–	+/–	+/–	+/–	+/–	Specialized stool culture	Doxycycline 100 mg PO BID	*V. vulnificus* most lethal; preexisting liver disease increases risk.
Campylobacter	Contamination of food or water, especially poultry	+	+	+	+	+	Standard stool culture	Azithromycin 500 mg PO QD × 3 d OR Erythromycin stearate 500 mg PO q12h × 5 d	Often resistant to fluoroquinolones; be wary for postinfectious complications
Yersinia	Foodborne contaminant; seen most commonly in northern countries (e.g., Canada, Sweden)	+	+	+/–	+/–	+/–	Specialized stool culture	Ciprofloxacin 500 mg PO bid × 3 d	Can mimic appendicitis symptoms
Shigella	Foodborne and person to person spread	+	+	+	+	+	Standard stool culture	Ciprofloxacin 500 mg PO bid × 3 d	Severe diarrhea; low inoculum required for infection
Salmonella	Primarily foodborne transmission, prevalent in poultry	+	+	+	+	+	Standard stool culture	Ciprofloxacin 500 mg PO bid × 3 d	Reserve antibiotics for systemically ill; antibiotic therapy may prolong fecal excretion
Shiga toxin-producing *E. coli*	Foodborne transmission; also farm animal contact and person to person transmission	–	+	+/–	+	–	Specialized stool culture + EIA for Shiga toxin	Supportive care; hydration	Antibiotic and antimotility therapy ⇑ risk of hemolytic uremic syndrome
Enterotoxigenic *E. coli*	Foodborne transmission	+/–	+	+	–	–	Stool culture for *E. coli*	Ciprofloxacin 500 mg PO bid × 3 d	Common cause of TD
Clostridium botulinum	Preformed toxin ingestion; infants more at risk	–	–	–	–	–	Anaerobic cultures and toxin assays of serum, stool, and implicated food	Supportive	Toxin induces cranial nerve palsies, weakness, and respiratory failure
Clostridium difficile	Nosocomial; postantibiotic complication	+	+	+–	+	+	EIA for toxins A+B	Metronidazole 500 mg PO q6; vancomycin 125 mg PO q6	Increasing virulence; consider adjuvant probiotic therapy
Vibrio cholerae 01 or 0139	Waterborne transmission	–	+/–	+/–	–	–	Specialized stool culture	Azithromycin 1,000 mg PO × 1 dose	Primary therapy is rehydration; without treatment case fatality rate 50%
Giardia lamblia	Contaminated food and water	–	+	+/–	–	–	EIA	Tinidazole 2 g PO once OR Nitazoxanide 500 mg PO bid × 3 d	Most common GI parasite in US
Entamoeba histolytica	Travel to tropics; fecal oral transmission	+	+	+/–	+	–	EIA	Metronidazole 750 mg PO TID × 10 d then paromycin 25 mg/kg/d in 3 doses × 7 d	Consider when TD patient has bloody diarrhea but no fecal leucocytes. Associated with liver abscess
Cryptosporidium	Contaminated water; immunocompromised hosts	+/–	+/–	+/–	–	–	EIA	Nitazoxanide 500 mg PO bid × 3 d	Highly active antiretroviral therapy sufficient to achieve immunologic reconstitution in AIDS patients and resolution of diarrhea
Cyclospora cayetanensis	Foodborne transmission	+/–	+/–	+	–	–	Microscopy	TMP/SMX DS 1 tab PO bid × 7–10 d	Fatigue, which may be profound, is present in ≥90% of patients with cyclosporiasis
Cystoisospora belli	Fecal–oral transmission, contaminated water	+/–	+/–	+/–	–	–	Microscopy	TMP/SMX DS 1 tab PO bid × 10 d	Prevalent in AIDS patients

+, common; –, not common; +/–, occasional; AP, abdominal pain; FL, fecal leukocytes; BD, bloody diarrhea; PO, by mouth; GI, gastrointestinal; EIA, enzyme immunoassay; TMP/SMX, trimethoprim-sulfamethoxazole; DS, double strength.

[a]Therapy. Only adult doses given. Please refer to pediatric diarrhea chapter for specific doses and therapies for children.

Adapted from Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis.* 2001;32:331–350; Thielman NM, Guerrant RL. Acute infectious diarrhea. *N Engl J Med.* 2004;350:38–47; DuPont HL. Bacterial diarrhea. *N Engl J Med.* 2009;361:1560–1569.

Documentation of fecal leukocytes, blood, or fecal lactoferrin aids in bedside identification of dysentery. Commonly identified bacterial pathogens in patients with fecal leukocytes include Shigella,

Salmonella, Campylobacter, *E. coli,* Yersinia, *Vibrio parahaemolyticus,* and *C. difficile.* When diarrhea is persistent or recurring, or if the history of fever or hematochezia is equivocal, fecal testing by means of microscopy for polymorphonuclear leukocytes or by means of immunoassay for the neutrophil marker, fecal lactoferrin, can quickly provide additional laboratory evidence to support a presumptive diagnosis of inflammatory diarrhea (2). Fecal leukocytes can also be seen in nonenteritis conditions, such as inflammatory bowel disease.

Relatively well-appearing patients presenting with signs and symptoms of bacterial enteritis can be treated empirically with antibiotics, and stool cultures need not be sent. Stool cultures are not routinely recommended in most cases of watery diarrhea or TD because of the low yield of identification of bacterial pathogens (4). Patients with symptoms of dehydration, severe dysentery, abnormal abdominal examination, or diagnostic uncertainty, warrant further investigation. Systemic illness, fever, or bloody diarrhea should prompt stool testing for Salmonella, Shigella, and Campylobacter; eTable 112.2 lists specific indications for diarrheal cultures. Patients presenting with acute onset of bloody diarrhea, especially if they have no fever, should have stool testing for Shiga toxin along with cultures for *E. coli* 0157:H7 (2). If the patient has been on antibiotics antecedent to diarrheal onset, consider *C. difficile* and test for toxins A and B. Assays for *C. difficile* toxin are not recommended after the completion of a course of therapy as the results may be misleading (2); many patients treated successfully for CDI will continue to shed *C. difficile* and toxins A and B in their stool for some weeks despite complete clinical recovery (12).

eTABLE 112.2
Indications for Stool Culture in Patients with Acute Diarrhea

Immunocompromised hosts
Travel history to developing countries
History of anal intercourse
Failure to respond to empiric antibiotic therapy
Individuals with close contact to others where fecal–oral spread can occur (day-care workers, health care workers, food handlers)
"Toxic" clinical appearance—fever or other abnormal vital signs
Significant abdominal pain
Persistent diarrhea (≥14 days) with suspicion of protozoan cause
Severe, bloody, inflammatory diarrheal illness
Suspicion of antibiotic-resistant bacterial dysentery
Recent antibiotic use
Bloody diarrhea with suspicion of hemolytic uremic syndrome

It is rarely necessary to send stool for ova and parasites during an episode of acute diarrhea. However, illnesses lasting longer than 14 days should prompt consideration of parasites, most notably *G. lamblia,* particularly in travelers who have returned from areas where untreated water is consumed and in immunocompromised patients. Testing of one or two specimens for giardia, cryptosporidium, and amebiasis by means of enzyme immunoassay has a sensitivity of more than 95% and is considerably better than older methods based on microscopical examinations (2). Direct immunofluorescent assays, immunochromatographic assays, and enzyme-linked immunoabsorbent assays are more sensitive and provide speedier results for diagnosis of giardia, cryptosporidia, and amebiasis infections than microscopic ova and parasite examination (9). Stool smear and stain for parasites for direct visualization by microscopy still has a role in the diagnostic evaluation of parasites because, while serology is highly sensitive for extraintestinal disease, it is only moderately sensitive for intestinal disease, and poorly sensitive for asymptomatic infection. In patients with advanced HIV disease, especially those who have fewer than 50 CD4+ lymphocytes per cubic millimeter, consider stool studies for cryptosporidia, microsporidia, cyclospora, and cystoisospora in addition to routine diarrheal cultures. If these stool studies are unrevealing, endoscopy and colonic biopsies for *Mycobacterium avium complex* and cytomegalovirus are indicated (2).

KEY TESTING

- Consider point of care testing for dysentery: fecal occult blood testing, fecal leukocytes, or fecal lactoferrin.
- If suspicion of dysentery, send stool for culture.
- If suspicious for antibiotic associated diarrhea, evaluate diarrhea by enzyme immunoassay for *C. difficile* toxins A and B.

ED MANAGEMENT

The main objectives of ED management of diarrhea are to: (a) provide fluid and electrolyte replacement, (b) prevent spread of the enteropathogens, (c) provide symptomatic relief, and (d) provide specific therapy if warranted.

Fluid and Electrolyte Therapy

Regardless of the causative agent, initial therapy for enteritis must address volume status and rehydration. Unless the patient is comatose or severely dehydrated, oral rehydration with a glucose-based electrolyte solution is preferred (18). The standard oral rehydration solution formulation is lifesaving in resource-poor regions and helpful in the industrialized world for clinically important dehydration.

Dietary Recommendations

Avoid carbonated beverages and fatty foods because both slow gastric emptying and worsens vomiting. Avoid sugary foods because sugar acts osmotically to draw water into the intestines worsening diarrhea. Consumption of small portions of easily digestible foods are recommended as soon as feeding is tolerated and are more effective than restricted or progressive diets in reducing duration of acute gastroenteritis because caloric intake facilitates enterocyte renewal during a bout of acute diarrhea (1). Fiber rich foods, for example, rice, potatoes, or corn, or fiber supplements, for example, psyllium or methylcellulose, are helpful because fiber absorbs water in the digestive tract and adds bulk to feces. Because transient lactase deficiency may occur, avoidance of milk products is commonly recommended (2).

Antimotility Agents

Loperamide, diphenoxylate with atropine, and dicyclomine are used to reduce urgency, bowel-movement frequency, and stool volume in diarrheal illness. Loperamide, the antimotility agent of choice for enteritis, slows peristalsis via its action on intestinal m-opiate receptors, but unlike other opiates such as diphenoxylate, it does not penetrate the central nervous system and has no potential for addiction (3). Loperamide administration with an antibiotic is safe for most causes of dysentery; it reduces diarrhea volume, and accelerates symptomatic recovery (3). Loperamide must be used in conjunction with antibiotics for dysentery, as it can inhibit clearance of the offending organism if used as solo therapy and worsen diarrheal illness (4).

Bismuth Subsalicylate

Although not as effective as loperamide in direct comparisons, bismuth subsalicylate can mitigate stool output and lessen the symptoms of diarrhea, nausea, and abdominal pain in patients with TD and other infectious causes of diarrhea, including dysentery (2). Bismuth subsalicylate's salicylate moiety has antibacterial and antisecretory effects that make it effective prophylaxis for TD. Instruct patients that bismuth subsalicylate turns the stool's color black. Administer bismuth subsalicylate with the caution to avoid inadvertent excessive ingestion and induction of salicylism.

Probiotics

Probiotics are live, nonpathogenic microorganisms, marketed for prevention and treatment of diarrhea. Yogurt is a readily available source of small amounts of probiotic bacteria such as *Lactobacillus bulgaricus* and *Streptococcus thermophilus.* Probiotics such as *Lactobacillus* GG and *Saccharomyces boulardii* are available as dietary supplements. Evidence suggests that probiotic prophylaxis results in a reduction in *C. difficile*-associated diarrhea (19). Infectious complications caused by probiotics, including sepsis with *Lactobacillus casei,* fungemia with *S. boulardii,* and liver abscesses

caused by *Lactobacillus* GG, limits probiotic use in immunosuppressed and in critically ill patients, particularly those with an indwelling vascular catheters (19).

Antibiotics

For patients with dysentery or severe TD, administration of empiric antimicrobial therapy is recommended (1), and fluoroquinolones or azithromycin are efficacious choices (eTable 112.1). For high fever, >39.4°C, or the passage of grossly bloody stools, azithromycin is recommended to treat presumed Campylobacter (4). While they should be withheld for salmonellosis because treatment prolongs carriage, administer antibiotics if the patient has risk factors for Salmonella bacteremia, which include age >65 years, immunosuppression, corticosteroid use, inflammatory bowel disease, sickle cell anemia, hemodialysis, abdominal aortic aneurysm, or prosthetic heart valve (4). The administration of antibiotics and antimotility agents is contraindicated for Shiga toxin-producing *E. coli* because antibiotics increase the risk of hemolytic uremic syndrome (2). Empiric treatment for persistent diarrhea without systemic symptoms secondary to presumed giardiasis with metronidazole is reasonable, especially if there is a history of recent travel or exposure to contaminated water because giardiasis is common and testing often fails to reveal the organism (1). Treatment of CDI can be stratified according to severity of illness, recurrence of disease, and host factors: mild-moderate, severe, or recurrent. Both oral metronidazole and vancomycin are effective for mild to moderate CDI, but vancomycin is a second-line agent because of its cost and propagation of vancomycin resistance (12). Metronidazole is less expensive, effective administered orally or intravenously, and avoids the risk of promoting vancomycin-resistant pathogens (2). Indications for using oral vancomycin to treat CDI include severe disease, metronidazole contraindications or intolerance, and inadequate response to metronidazole treatment (12). Severe CDI is defined as: intensive care unit admission, pseudomembranous colitis at endoscopy (eFig. 112.6), age >60 years, temperature >38.4°C, serum albumin <2.5 g/dL, and white blood cell count >15,000/μL

(12). Fidaxomicin, a newly available FDA approved oral antibiotic, may be superior to vancomycin in severe and recurrent CDI, but is still second line because of financial considerations (20).

Advice for Travelers

TD avoidance involves adherence to the axiom: "cook it, boil it, peel it—or forget it." In unhygienic locales, travelers must abstain from raw vegetables, fruit they have not personally peeled, unpasteurized dairy products, cooked food not served steaming hot, and tap water, including ice (21). Boiling water for 3 minutes kills most potential pathogens, which are destroyed at temperatures of 55 to 80°C, even at high altitudes (22). Oral fluid and electrolyte requirements in TD can be met in nearly all cases in otherwise healthy patients by increasing fluids and salt-containing foods in the diet (1). Bismuth subsalicylate, fluoroquinolone antibiotics, and possibly probiotics are effective prophylactic pharmacologic self-therapy of TD (21).

CRITICAL INTERVENTIONS

- Treat dehydration with appropriate fluid, salt, and caloric repletion.
- Initiate appropriate empiric antibiotic therapy for patients with dysentery.
- Appropriate dietary advice advocates early refeeding with high fiber, low fat and sugar, and nondairy diets to facilitate early enterocyte recovery and avoids exacerbating diarrheal illness.

- Antimotility agents, for example loperamide, are safe and appropriate in the setting of dysentery if administered in conjunction with appropriate antidysentery antibiotics.
- Probiotics aid in prevention of recurrent CDI.

DISPOSITION

Most ED diarrheal complaints can be managed on an outpatient basis. Consider admission if there is bloody diarrhea, severe dehydration, intractable vomiting, evidence systemic illness (e.g.,

septicemia or hemolytic uremic syndrome), and diagnostic uncertainty regarding the etiology of diarrhea, particularly if it is bloody, for consultation to rule out noninfectious, pathologic processes.

Common Pitfalls

- Anchoring diagnostic focus on viral gastroenteritis: Consider dysentery and *C. difficile* colitis if there are risk factors; also evaluate for noninfectious diarrheal etiologies, for example, inflammatory bowel disease, sprue, and small bowel obstruction.
- Ignoring examination of diarrhea: While stool cultures require laboratory processing time, point of care examination of stool for blood or leukocytes affects ED therapy and disposition.
- Omitting adjuvant diarrheal therapy: Oral rehydration solution, loperamide and bismuth subsalicylate have proven efficacy for diarrheal illness.
- Consider *C. difficile* not only in patients with colitis and diarrhea after antibiotic use but also after chemotherapy and in the community setting as well, especially if they have other risk factors for CDI (e.g., proton pump inhibitor therapy).

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CHAPTER 113

Diverticular Disease

Janak K. Acharya

In the industrialized world, the increasing prevalence of diverticular disease parallels the advancing age of the population. The prevalence of diverticular disease increases from 5% in persons younger than age 40 years to 30% in those older than age 50, to 50% in those older than age 70, and to 66% in those older than age 85 years (1). Diverticulosis is equally common among men and women. The disease has widely differing prevalence rates in various geographic areas and ethnic groups (1).

The key factor in the development of diverticulosis appears to be a reduction in dietary fiber content. The pathophysiology is related to a pressure gradient between the colonic lumen and the serosa and areas of relative weakness in the bowel wall. Very high intraluminal pressure can develop within short segments of the colon. According to the Laplace law of pressures within a cylinder, pressure equals tension divided by radius. Accordingly, the descending and sigmoid colons, which have narrow lumens, have the greatest intraluminal pressures. This pressure causes herniation of diverticula at the points where the intramural vessels penetrate the circular muscle layer, usually between the mesenteric and antimesenteric taenia. Increased fiber intake enlarges the lumen size, thereby decreasing the intraluminal pressure.

The sigmoid colon is involved in more than 90% of patients with the disease, and in approximately one-half of patients it is the only segment of the bowel involved. The cecum is involved in 2%, the ascending colon and rectum in 4% each, and the transverse colon in 10%. Most individuals with diverticulosis remain asymptomatic

throughout their lives. The longer a patient has diverticulosis, the greater is the probability of complications, primarily diverticulitis and bleeding. There is no relationship, however, between the number and size of diverticula and the incidence of complications or probability of recurrent disease. The use of aspirin and other nonsteroidal anti-inflammatory drugs is an etiologic factor in the development of diverticulitis (1,2). Diverticulitis results from inflammation of diverticula, resulting in microperforation or macroperforation (abscess, fistula, peritonitis, or obstruction). Diverticular bleeding results from an arterial lesion in the vasa recta, characterized by eccentric intimal thickening, altered internal elastic lamina, and focal medial thinning (3). There is a disproportionately high tendency for diverticula on the right side of the colon to hemorrhage. One theory holds that the wider necks and domes of right-sided diverticula cause greater exposure to injurious factors than in left-sided diverticula (4). Bleeding from diverticulosis is massive in about one-fourth of patients in whom it occurs, and mandates transfusion in approximately one-third (5). Fortunately, the vast bulk of diverticular bleeding ceases spontaneously.

CLINICAL PRESENTATION

Patients with diverticulosis present to the emergency physician with three common clinical presentations: (a) acute diverticulitis, (b) lower gastrointestinal (GI) bleeding, and (c) painful diverticular disease, with mild lower left quadrant pain.

Acute Diverticulitis

Patients with acute diverticulitis classically present with abrupt onset, severe, constant left lower quadrant pain; localized tenderness; and fever, leukocytosis, or other signs of systemic toxicity. Occasionally, the pain and tenderness occur in the left upper quadrant. Patients may present with a picture of a ruptured viscus with diffuse tenderness, rebound, guarding, and diminished or absent bowel sounds. Rarely, diverticulitis may present with signs of fistulization, such as pneumaturia and draining infections of the

lower abdomen or medial aspect of the upper thigh. Diverticulitis may present atypically in immunocompromised patients, such as those with acquired immunodeficiency syndrome, renal failure, or diabetes and those receiving immunosuppressive therapy. In these patients, fever, abdominal pain, or abdominal tenderness may be absent (6). The incidence of free perforation, a rare complication in the immunocompetent, is much higher among immunocompromised patients (6–8). Although recurrence rates are similar between immunocompromised and immunocompetent patients, mortality following surgery is twice as high in the immunocompromised (9).

Lower Gastrointestinal Bleeding

Patients with diverticulosis may present with painless, massive rectal bleeding. Such bleeding is characteristically sudden, often profuse from the onset, and more frequent in older persons. The blood is usually bright or dark red, and although the patient may feel faint, initial hypotension is not common.

Painful Diverticular Disease

Although most patients with diverticulosis are asymptomatic, some develop recurrent episodes of left lower quadrant abdominal pain. The pain is usually dull, crampy, and intermittent and is often alleviated by the passage of flatus or stool. Signs of infection are absent.

DIFFERENTIAL DIAGNOSIS

Painless diverticular bleeding must be distinguished from other causes of lower GI bleeding, such as angiodysplasia, ischemic colitis, ulcerative colitis, hemorrhoids, polyps, and colonic or rectal cancer. Upper GI hemorrhage may present with rectal bleeding.

When diverticulosis presents as mild, left lower quadrant pain, it must be differentiated from irritable bowel syndrome (IBS), Crohn disease, colon cancer, ovarian pathology, and nephrolithiasis, which may present with pain radiating to the left lower quadrant.

Acute diverticulitis must be distinguished from more severe presentations of Crohn disease, ulcerative colitis, and ischemic colitis, although diverticulitis and inflammatory bowel disease may coexist. Vascular catastrophes, such as aortic rupture or dissection or mesenteric ischemia, are generally distinguished by pain out of proportion to physical findings. In women, diverticulitis that presents as a left lower quadrant mass has been misdiagnosed as a gynecologic mass (6). High fever, leukocytosis, and left lower quadrant mass should suggest perforation and abscess. These findings may also be suggested by inflammatory bowel disease, colon cancer, sigmoid volvulus, iatrogenic perforation of the rectosigmoid, or a tubo-ovarian abscess (10). Right-sided diverticulitis, a rare disease seen primarily in Asian populations, may mimic acute appendicitis (11).

ED EVALUATION

Left Lower Quadrant Pain

Historical information should focus on GI symptoms, previous similar attacks, prior diagnostic studies, and change in bowel habits. The duration of the attack, characteristics of the pain, and history of fever should also be elicited. With diverticulitis, the pain may be intermittent, crampy, and associated with nausea and vomiting. The attack may be associated with either constipation or diarrhea.

The physical examination should take careful note of the patient's temperature, pulse rate, and blood pressure. Complete abdominal, pelvic, and rectal examinations are necessary. In rare cases, tenderness may be found only on rectal examination. Palpation may reveal the outline of the sigmoid colon as a ropelike mass. Minimal tenderness and mobility point to an irritable colon; a large, sausage-like, markedly tender, fixed mass points to diverticulitis. Signs of peritonitis and the presence of a mass on pelvic and rectal examinations are important to note. A complete blood cell count (CBC) may be helpful, in that leukocytosis with a left shift is often noted in patients with diverticulitis.

Although acute diverticulitis can be diagnosed solely on clinical grounds, confirmatory imaging is necessary for all but mild, recurrent cases. Abdominal and chest radiographs may show obstruction or free air, but computed tomography (CT) is the most cost-effective test (12). CT allows evaluation of vascular structures, estimates the extent of diverticulitis, allows possible percutaneous drainage, and is less invasive than traditional contrast enema evaluation (1) (Fig. 113.1). The method also has a greater sensitivity than contrast enema (13). If CT is unavailable, contrast enema remains a safe and effective option (5,8). A few centers have reported high accuracy in diagnosing diverticulitis with ultrasonography (5,8,14). Ultrasonographic findings seen in diverticulitis include the following: hypoechoic, tender, thickened colonic segment; visible diverticula; and increased echogenicity surrounding the diseased colon (12). Sigmoidoscopy should be avoided in patients with acute diverticulitis.

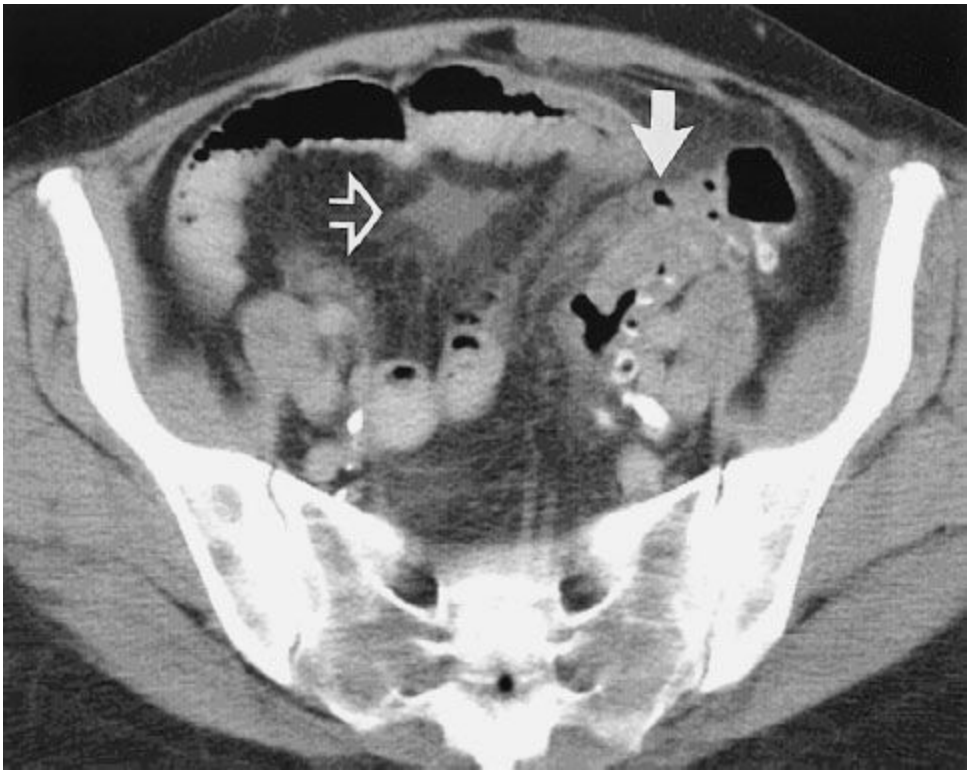

FIGURE 113.1 Sigmoid diverticulitis. CT scan shows multiple sigmoid diverticula, inflammatory stranding (*arrow*), and a small amount of free fluid (*open arrow*). (From Harris JH, Harris WH, eds.

The Radiology of Emergency Medicine, 4th ed. New York, NY: Lippincott; 2000:651.)

The Hinchey classification scheme was originally used to describe intraoperative findings associated with diverticulitis (15). Stage 1 and 2 represent confined pericolic or perimesenteric abscesses and carry a 5% mortality. Stage 3 disease presents with peritonitis secondary to rupture of a peridiverticular abscess and has a 13% mortality. Stage 4 diverticulitis or free rupture of an uninflamed diverticulum, causing fecal contamination of the peritoneum, is rare but carries a 43% mortality (16). CT scanning can be used to risk stratify patients according to their Hinchey classification and facilitate appropriate management and disposition.

Lower Gastrointestinal Bleeding

The history should focus on the onset, color, amount, and frequency of bloody bowel movements. A history of previous attacks, bleeding tendencies, and bowel habits is important. Hemodynamic instability should be assessed (blood pressure, pulse, and orthostatic changes). The abdominal examination should focus on areas of tenderness and the presence or absence of a mass. The rectum should be palpated for masses, and the color of the blood in the rectal vault should be examined. Nasogastric intubation may indicate upper GI hemorrhage, particularly if the source is proximal to the duodenum. If there is brisk and bright red bleeding, anoscopy can exclude anorectal causes such as internal hemorrhoids. Laboratory studies should include a CBC to help estimate the amount of blood loss, and a type and screen if transfusion is considered.

KEY TESTING

- Basic laboratory studies
- CT scan of the abdomen and pelvis with IV contrast

ED MANAGEMENT

Acute Diverticulitis

For the patient with acute diverticulitis, an intravenous line should be started, blood and urine specimens should be collected, and intravenous antibiotics begun. Antibiotics should target gram-negative rods and anaerobic bacteria. Effective single agents include imipenem/cilastatin (0.5 to 1 g), ampicillin/sulbactam (3 g), or piperacillin/tazobactam (3.375 g), and an effective traditional triple-therapy regimen consists of ampicillin (0.5 g), gentamycin (1.5 mg/kg), and metronidazole (0.5 to 1 g) (1,12). Outpatient management for mild cases may include a combination of metronidazole and either trimethoprim-sulfamethoxazole or ciprofloxacin, or monotherapy with amoxicillin-clavulanate. Supportive management of uncomplicated diverticulitis without antibiotics has been evaluated, with data showing similar recovery times and recurrence rates but with a higher rate of complications (17). Early surgical consultation is indicated in patients with peritonitis or radiographic evidence of large abscess or free rupture.

Diverticular Bleeding

For the patient with massive lower GI bleeding, two large-bore intravenous lines (16 gauge or larger) should be inserted. A blood specimen should be obtained and sent for type and crossmatch for 4 to 6 units of blood. A Foley catheter should be placed. Lactated Ringer solution or normal saline should then be infused in accordance with the patient's vital signs and cardiac status. If the patient remains hypovolemic after 2 L of crystalloid infusion, blood transfusion should be considered. Fluid resuscitation should be aimed at restoring urine output to a rate of approximately 1 mL/kg/h.

Painful Diverticular Disease

For the patient with left lower quadrant pain but without signs of acute diverticulitis or bleeding, institution of a high-fiber diet is effective in relieving pain. There is an increased incidence of IBS

following acute diverticulitis and an increased association of diverticular disease in patients with IBS (7). Anticholinergic agents have long been used, but their efficacy remains unproven. Routine colonoscopy following uncomplicated diverticulitis in the absence of other risk factors has not identified a higher incidence of malignancy than in the general population (11).

The use of probiotics such as *Lactobacillus casei,* alone or in combination with mesalamine, has been shown to prevent recurrence of uncomplicated diverticular disease (18). Mesalamine, in addition, has been shown to reduce the GI symptoms following an acute attack of diverticulitis as compared with placebo or a probiotic-mesalamine combination (19).

CRITICAL INTERVENTIONS

- Administer parenteral antibiotic therapy and analgesics for those with acute severe diverticulitis.
- Provide adequate fluid and blood component therapy for patients with significant lower GI bleeding.
- Obtain early surgical consultation in patients with peritonitis, abscess, or free rupture.

DISPOSITION

Patients with severe acute diverticulitis (Hinchey stage 2 or greater) and those with gross lower GI bleeding must be admitted. Patients with diverticulitis complicated by abscesses more than 4 cm in diameter that are not amenable to percutaneous drainage, as well as those with fistula formation, obstruction, or localized peritonitis, should be admitted to a surgical service. Patients with clinical or radiographic signs of free rupture, fecal contamination with generalized peritonitis (Hinchey stage 3 or 4), or massive lower GI hemorrhage warrant emergent surgical evaluation for operative management. Septic patients, those with significant comorbidities, and those with massive GI bleeding should be admitted to an intensive care unit.

Outpatient management should be limited to immunocompetent patients with mild uncomplicated diverticulitis (Hinchey stage 1), or with diverticulosis with minimal bleeding. Immunocompromised patients and renal-failure patients with diverticulitis should be admitted despite benign-appearing presentations.

Common Pitfalls

- Failure to appreciate the severity of illness in immunocompromised patients. These patients have a higher incidence of free perforation, failure of medical therapy, and postoperative morbidity and mortality (6,8).
- Although less frequently encountered in patients younger than age 40 years, diverticulitis is relatively more likely to be complicated and require surgery in younger patients than in older patients (20,21).

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CHAPTER 114 Anorectal Disorders

Wendy C. Coates

A variety of anorectal conditions can prompt a visit to the emergency department (ED). These conditions may be isolated and temporary or may signal an underlying systemic disease. Great sensitivity is required in dealing with patients who have problems in this area, as they may be embarrassed to share details with the healthcare provider.

The rectum originates at the end of the sigmoid colon and stores stool until a convenient time for defecation. The anal canal is the terminal portion of the digestive system and is approximately 4 cm in length. At the dentate line of the anal canal, the epithelium changes from the columnar epithelium of the intestine to a modified squamous epithelium. Several glands reside in this area to provide lubrication for the easy passage of stool. Fecal continence is maintained by a cooperation of both voluntary and involuntary muscle sphincters.

CLINICAL PRESENTATION

Patients with anorectal conditions may present with a variety of symptoms, including pain, itching, swelling, bleeding, fever, mass, or discharge, depending upon the specific condition (Fig. 114.1). Many patients present with a chief complaint of “hemorrhoids” to represent any anorectal condition. Careful questioning can elucidate the actual diagnosis.

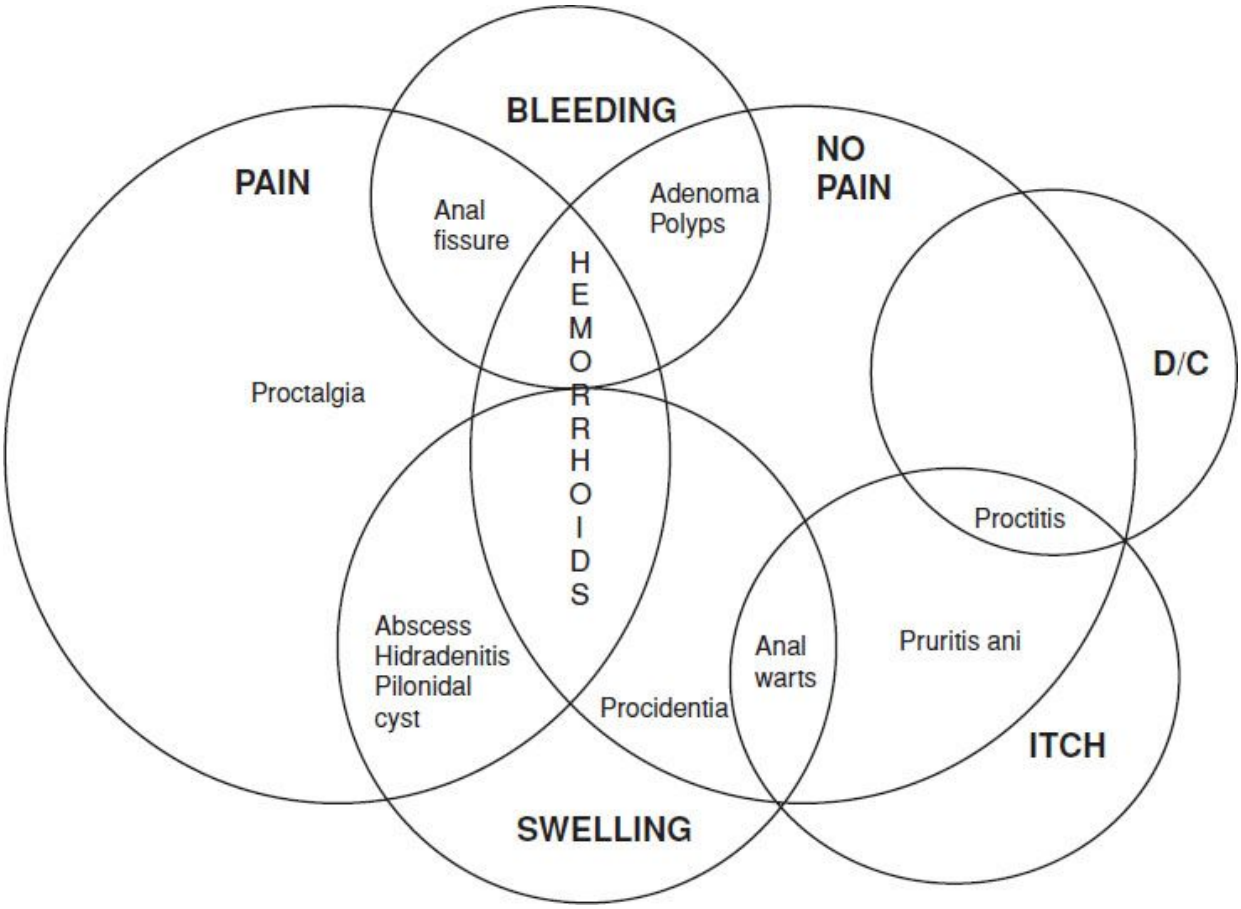

FIGURE 114.1 Anorectal complaints algorithm (Venn diagram).

Painful Swelling

Anorectal abscess is a common acute infection involving the anorectum. The etiology may be the entrapment of mucous and bacteria in the glands of the anal crypts. When deep abscesses rupture, a fistulous tract forms. A complex network of abscesses and fistulas may evolve if the acute condition goes untreated. Abscesses are named according to their location (Fig. 114.2).

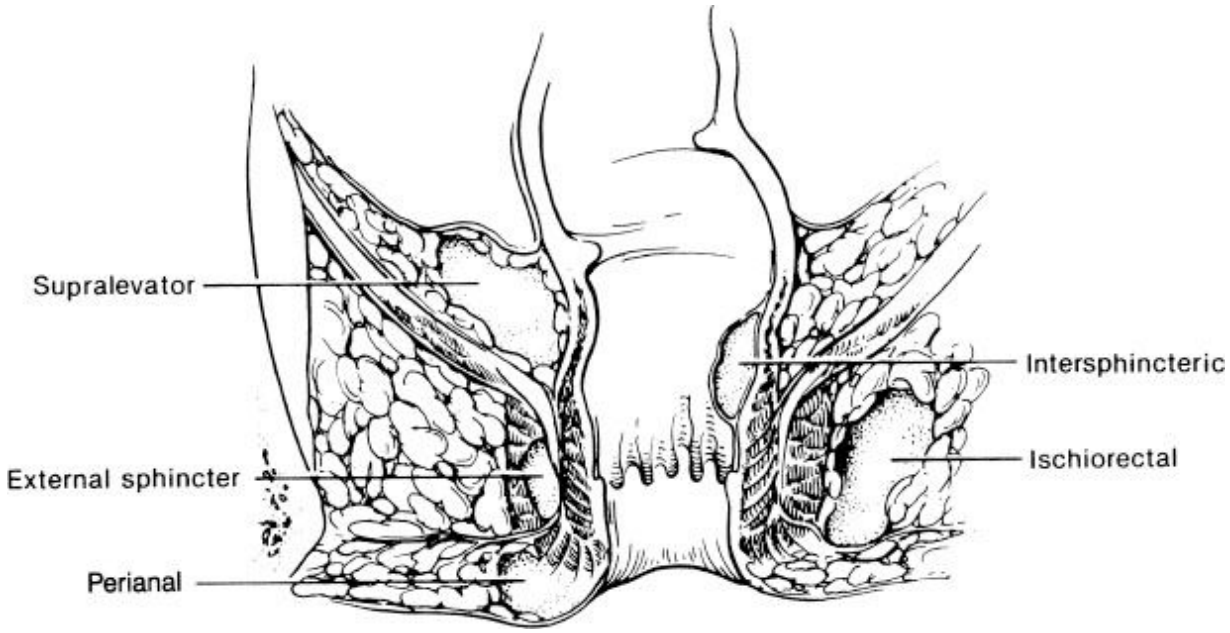

FIGURE 114.2 Anorectal abscesses.

Symptoms and sequelae vary depending on the depth and natural ability of the abscess to drain. The clinical presentation depends on the depth and location of the abscess. Superficial (*perianal*) abscesses usually present as tender swellings near the anus. Foul-smelling pus may drain from spontaneously ruptured abscesses. Deep abscesses may cause pain within the rectal cavity or pelvis and progress to a systemic infection. Fistulous tracts may develop and may open directly into the anorectum or through the skin of the buttocks (1,2).

A *pilonidal abscess* (cyst) is a painful, indurated swelling that occurs in the presacral midline (3). Sinus tracts may develop and open into the surrounding skin of the buttocks. Afflicted patients may also demonstrate hair in the midline in other locations of their bodies, such as the eyebrows.

Hidradenitis suppurativa is caused by an infection to the apocrine glands and is related to poor hygiene or an underlying disease, such as diabetes mellitus or predisposition to the condition. Patients frequently have fever and leukocytosis and may have similar lesions in the axilla or sternum (4).

Painful Bleeding

Anal fissures produce sudden, sharp, tearing pain at the anal orifice during defecation. The patient generally reports seeing bright-red blood on the tissue. Most fissures occur in the midline. Ectatic fissures often suggest underlying disease. Fissures are the most common pediatric anorectal complaint. *Hemorrhoids* can present in a variety of ways, but the classic presentation is painful bright-red blood that coats the stool. A variety of factors predispose patients to develop hemorrhoids. Most often, the condition is self-limited and is caused by frequent diarrhea, prolonged sitting, low-fiber diet, and pregnancy and may be exacerbated by underlying medical conditions such as obesity, portal hypertension, or bleeding disorders. Patients may complain of anorectal swelling with moist discharge or intense unbearable pain and swelling (1,5,6).

Without Bleeding or Swelling

Some patients have rectal pain that does not have any of the pathophysiologic mechanisms described. Their pain may be of sudden or gradual onset and takes on different characteristics depending on the cause. Before making a diagnosis of the two common entities, *levator syndrome* or *proctalgia fugax,* it is important to exclude other causes of pain.

Painless Conditions

Patients with *rectal prolapse* (*procidentia*) present with a large externally protruding mass. The presentation may be preceded by defecation, sneezing, or coughing. Most patients are in the extremes of age. A foul odor may be present (7).

Anal warts (*condylomata acuminata*) may also present as a painless swelling at the anal opening. Patients generally report concurrent itching and often have had contact with another individual with a similar condition. Genital warts are caused by the human papilloma virus. A sexual history highlighting the role of the anus in intercourse is essential. Children with genital warts may have contracted them as a result of sexual assault or simply by the

transmission of the virus on the hands of the person changing their diaper. Other causes of perianal itching (*pruritus ani*) range from dietary habits (caffeine, citrus, and spicy foods) or drugs (steroids, tetracycline, and colchicine) to hygiene and underlying skin conditions (pinworms and psoriasis). Patients frequently complain of an insurmountable urge to scratch, and the symptoms typically are worse in the warm months. Underlying anorectal disease (fistula, fissures, proctitis, and prolapsed hemorrhoids) may present as pruritus ani.

Patients who have proctitis, an inflammatory condition of the rectum, may present with a sensation of internal fullness accompanied by a change in bowel habits such as constipation or diarrhea. This can be caused by infections, sexually transmitted diseases (STDs), antibiotics, radiation, or inflammatory bowel disease. Occasionally, proctitis may present with pain or discharge.

Foreign Bodies

Rectal foreign bodies are covered more specifically in Chapter 115.

DIFFERENTIAL DIAGNOSIS

Painful swellings of the anorectum include hemorrhoids, abscesses, pilonidal disease, and hidradenitis suppurativa (Fig. 114.1). The presence of pus or fever suggests an abscess. For many patients with abscesses and fistulas, their problem is recurrent. A specialized abscess that is lined with epithelium and is found in the presacral area is a pilonidal cyst. This condition occurs more frequently in young men and reflects a midline defect in which debris from hair follicles and glandular secretions collects and becomes indurated.

Patients who present with painful bleeding are likely to have hemorrhoids or an anal fissure. Fissures tend to present as sudden, sharp, and tearing pain with subsequent burning, whereas hemorrhoids generally have a more gradual onset and a more varied course. Hemorrhoids can mimic any anorectal condition. A thorough history and physical examination can confirm an ultimate diagnosis of hemorrhoids.

Rectal pain that occurs from a cause other than those already mentioned may be of neuromuscular etiology. Levator ani syndrome is distinguished by its gradual onset and persistence as a dull pain that is exacerbated by defecation. Patients with sudden, intense spasmodic pain in the rectal area may have proctalgia fugax. This condition is frequently associated with the "type A" personality but may occur in any patient. Its onset is often during intercourse, urination, defecation, or sleep (8,9).

Patients who present with rectal bleeding that is unaccompanied by pain may have internal or external hemorrhoids that are neither thrombosed nor lodged in the sphincter to produce pain. These patients typically have intermittent bright-red blood that coats the stool. Patients with bright-red blood mixed in with the stool should be evaluated for brisk upper or lower gastrointestinal (GI) bleeding. Patients whose source of bleeding is of uncertain etiology should be evaluated for rectal cancer or polyps.

Procidentia may be complete (all layers of the rectum protrude) or incomplete (mucosal layer only). It is important to distinguish this from prolapsed internal hemorrhoids and rectal masses. In young children, the diagnosis of cystic fibrosis is suspected (7).

Patients with pruritus ani should be examined closely and questioned about potential sources of their condition. Other diseases to consider in the differential diagnosis of condylomata acuminata are squamous cell carcinoma or secondary syphilis (condyloma latum), which is flatter.

Proctitis should be considered in patients who have undergone radiotherapy or recent antibiotic therapy, who utilize the rectum for sexual gratification, who have introduced foreign objects or lubricants into the rectum, or who have underlying inflammatory bowel disease.

ED EVALUATION

A thorough history and physical examination are important in distinguishing common anorectal complaints (see Fig. 114.1) (9). Local symptoms such as pain, bleeding, discharge, and itching are the foundation for the history. Questions about underlying GI

conditions (e.g., Crohn disease, inflammatory bowel disease, and GI cancer); systemic illnesses (e.g., diabetes mellitus, AIDS, and cancer); and trauma provide clues about the etiology of the symptoms. Some individuals use the rectum during intercourse and others introduce foreign objects that they cannot retrieve.

The physical examination should begin with an observation of hygiene, structural integrity, and the presence of lesions, blood, or discharge. A digital rectal examination (DRE) can assess sphincter tone and can reveal masses in the anorectum or adjacent structures. Any stool remaining on the examiner's glove can be used to check for occult blood. Finally, anoscopy can be performed to visualize lesions in the anal canal.

Abscesses are defined by their location. *Perianal abscesses* are adjacent to the anal outlet and are superficial in nature. Most patients are afebrile. Visual inspection of the perianal area may reveal pus or a fluctuant mass with or without surrounding erythema. *Ischiorectal abscesses* are exterior to the sphincter muscles and are located in the buttocks. Patients frequently cite severe buttock pain. Deeper ischiorectal abscesses may cause fever and leukocytosis. *Intersphincteric abscesses* form above the external sphincter and below the levator ani muscles. They may appear as a protrusion into the rectum and may be confused with inflamed hemorrhoids upon anoscopy. *Supralevator abscesses* are uncommon and are located deep to the levator ani muscles. There is an increased predominance in patients who are immunocompromised and in those with associated conditions (e.g., Crohn disease, pelvic inflammatory disease, or diverticulitis). Diagnosis relies on a high index of suspicion in patients with pelvic pain, fever, and leukocytosis. DRE may reveal a fistulous outflow track in the anal canal that may be palpable (1,2). If the extent of the abscess cannot be determined by physical exam, CT scan may be helpful.

Patients with a painful swelling in the presacral area with associated openings from sinus tracts have pilonidal disease. They are usually fluctuant and tender and may spontaneously begin to drain hairy pus. Extension of the disease to the entire presacrum is possible (3). Multiple infected openings that are not limited to the

presacral area may indicate hidradenitis suppurativa. Local lymphadenopathy is a common finding, and many patients are febrile and have an elevated white blood cell count (4).

Anal fissures are suspected when there is a sudden pain near the anus and bright-red blood on the tissue. Most benign fissures are located in the anoderm at the posterior midline. Although women may have fissures in the anterior midline, fissures in other locations often herald a serious underlying disease (e.g., Crohn disease, leukemia, tuberculosis, or human immunodeficiency virus [HIV]). The acute appearance of the fissure is similar to that of a laceration of the anoderm. Chronic changes may occur if a fissure is left untreated and include the development of tissue edema, a sentinel pile (hypertrophic and edematous skin), and skin tags upon resolution (10).

Hemorrhoids may be classified as external or internal. External hemorrhoids are close to the anal orifice and are covered with anoderm. Careful inspection reveals a coloring of the epithelium that is similar to that of surrounding skin. Patients may have perianal skin tags that have resulted from prior episodes of external hemorrhoids. A hard, bluish mass in the location of an external hemorrhoid denotes a thrombosed external hemorrhoid (5,6).

Internal hemorrhoids originate superior to the dentate line and are supplied by the superior hemorrhoidal vessels. Their covering appears mucosal in nature and does not resemble surrounding skin at all. A classification system of four grades has been developed. Grade I internal hemorrhoids produce symptoms of fullness and pain with bleeding but do not exit the anus at any time. Grade II internal hemorrhoids prolapse during defecation but spontaneously retract when straining ceases. Grade III internal hemorrhoids prolapse during defecation and require manual replacement. Grade IV internal hemorrhoids prolapse at any time, cannot be reduced, and may thrombose or become gangrenous (5,6).

To delineate the cause of rectal pain that does not fit into one of the categories described previously, one must first rule out a serious underlying condition, including cauda equina syndrome, cancer, or endometriosis. The diagnosis of proctalgia fugax or levator ani

syndrome is typically based on historical findings. If the patient tolerates a rectal examination, the levator ani muscles may be tender to palpation in levator ani syndrome (11).

Evaluation of patients with painless rectal bleeding includes DRE with subsequent hemoccult testing. If desired, anoscopy can be performed to visualize hemorrhoids or potential erosions in the mucosal wall. Procidentia is identified by noting concentric rings of mucosal tissue that may be ulcerated and is associated with a mucoid discharge or is stained with stool. If all layers are involved in the prolapse, they can be identified as well (12).

Anal warts appear as papilliform lesions that often coalesce at the anus and may extend to the anal canal. Direct irritation to the warts may induce minimal bleeding. A detailed sexual history may reveal that the patient is HIV-positive or has concurrent STDs. Evaluation of pruritus ani begins with a detailed history and physical examination.

Proctitis of infectious etiology is most often caused by organisms responsible for STDs in persons who have receptive anal intercourse. Common organisms are herpes simplex (HSV), gonorrhea, and chlamydia. Patients may present with diarrhea or constipation and may have a mucopurulent discharge from the rectum. Occasionally, they may have manifestations of systemic disease, including fever, chills, and leukocytosis. These patients may also have a component of allergic proctitis that results from the introduction of foreign substances into the rectum. For example, lubricants, erotic objects, and soaps may irritate the mucosa or produce small tears, leading to inflammatory changes. Patients with underlying inflammatory bowel disease may experience periodic inflammation of the rectum and have a mucoid discharge, constipation, or diarrhea, indicative of proctitis. Radiation proctitis occurs most often in cancer patients who have undergone focused irradiation to the pelvic and lower GI systems and may present with diarrhea, pain, tenesmus, fistula-in-ano, or rectal strictures (13).

KEY TESTING

- Digital rectal examination
- Anoscopy as needed

ED MANAGEMENT

General treatment of most anorectal conditions focuses on maintaining good hygiene and producing stool that is easy to pass. This can be accomplished by following the WASH regimen (Fig. 114.3).

W	Warm water	Promotes anal sphincter relaxation and good hygiene
A	Analgesics	Provides symptomatic relief from pain
S	Stool softener	Makes stool easier to traverse anal opening
H	High-fiber diet	Produces stool with bulk and air and reduces transit time

FIGURE 114.3 The WASH regimen.

Perianal abscesses can usually be incised and drained in the ED with good local anesthesia. Exceptions include abscesses in children and in patients who are immunocompromised (14). Superficial ischiorectal abscesses may be incised and drained via a skin incision on the buttocks. However, deeper perirectal abscesses generally require drainage in the operating room (OR) under anesthesia. Antibiotics should be considered, especially if there is surrounding cellulitis, fever, or leukocytosis. Drainage of intersphincteric and supralevator abscesses takes place in the OR. If a fistula is palpated in the anorectum or along the surface of the buttocks, it should be left intact to prevent the inadvertent puncture and subsequent extension of the fistulous network. Definitive treatment is a fistulectomy in the OR, although fibrin glue has been tried successfully as a less-invasive management strategy (2,10). Patients with a fistula without evidence of an abscess may have Crohn disease, cancer, or tuberculosis. These patients should be referred appropriately when a fistula is detected.

The ED treatment of an isolated pilonidal cyst begins with its identification in the presacrum. Incision and drainage should be done vertically and lateral to the midline to prevent further scarring and inflammation. Antibiotics may be used as an adjunct to incision and

drainage in patients who have accompanying cellulitis. Patients with extensive spread of pilonidal disease may be referred to surgery to consider wide excision (3).

Treatment of hidradenitis suppurativa begins with attention to improved hygiene. Incision and drainage of pustules may provide symptomatic relief, but a broad-spectrum antibiotic may be necessary to diminish the severity of the exacerbation of this condition (4).

Anal fissures should be treated acutely by following the WASH regimen so that the stool is easier to pass. Application of topical nitroglycerin ointment (0.4%) twice daily may alleviate symptoms. Short-term application of topical nifedipine gel (0.2%) with lidocaine (1.5%) alleviates symptoms and may promote healing. Finally, the injection of botulinum toxin (2.5 to 5.0 million units) into the muscular anal sphincter produces rapid relief from the fissure but may cause temporary fecal incontinence (10). ED management of external hemorrhoids is to follow the WASH regimen. Topical creams available over the counter may provide symptomatic relief but do not alter the course of the disease. Prolonged use of local anesthetic or steroid creams can lead to local skin irritation and breakdown. Thrombosed external hemorrhoids may be excised in the ED by anesthetizing the skin and completely removing the clot and its overlying tissue. The use of excision rather than incision and drainage prevents the formation of perianal skin tags. It is critical to distinguish between external and internal thrombosed hemorrhoids before attempting an excision (15).

Internal hemorrhoids should be managed with the WASH regimen. Warm water may produce enough anal dilation to reduce prolapsed internal hemorrhoids. Pain medications may be administered, but care should be taken to prevent constipation. Thrombosed fourth-degree internal hemorrhoids are generally managed operatively. Gangrenous hemorrhoids require prompt surgical treatment (6). If a benign source of rectal bleeding (e.g., internal hemorrhoid) cannot be identified, the patient should be referred to a specialist for endoscopic evaluation of the rectum and colon (9).

Treatment of levator ani syndrome focuses on the relaxation of the involved muscles using benzodiazepines, topical nitrates, or warm water baths (8). In addition to these regimens, patients who have proctalgia fugax have reported relief when applying upward pressure with their fist against the anus.

Procidentia can be managed in the ED or the OR by attempting reduction. Gauze moistened with saline can be applied to the protruding rectum, which can be reinserted through the anal verge. In most cases, sedation is required. If the reduction is successful, conservative management using the WASH regimen may prevent recurrence, especially in children (7). However, it is likely that a more permanent cure is surgical to strengthen the muscles that enabled the rectum to prolapse through the anus (12).

Once anal warts have been diagnosed, the cause should be identified. A full sexual history should be taken, and the patient should be referred for HIV testing. Children should be referred for testing for sexual abuse if there is not a credible source for inadvertent transmission of the virus during routine care. Treatment can be done as an outpatient with 0.5% podofilox gel for isolated condylomas. Diffuse disease requires frequent visits to the physician for application of podophyllin resin, excision, or other removal techniques.

Treatment of pruritus ani is directed at the particular cause, if possible. It may include advice on how to maintain proper hygiene or alter the diet to reduce intake of the offending food or beverage. If an anorectal problem is the cause, treating the underlying condition is likely to improve the symptoms. Medical conditions, both dermatologic and systemic, should be treated appropriately. For idiopathic pruritus ani, symptoms may be alleviated by a short course of topical 1% hydrocortisone ointment (16).

ED treatment of proctitis is aimed at relieving symptoms and is often simply supportive. Infectious proctitis should be treated with a regimen that covers organisms commonly associated with STDs. At the time of evaluation, the identity of the offending organism is usually unknown, and it is helpful to obtain cultures to direct future therapy. The suggested empiric antibiotic regimen is a single dose of

ceftriaxone 125 mg intramuscularly, plus doxycycline 100 mg orally for 7 days. If ulcerative lesions are seen on anoscopy or in the perianal area, an infection with HSV is possible. In addition to the above regimen, treatment with acyclovir 800 mg orally for 7 to 10 days is indicated (17). These patients should be referred for HIV and syphilis testing.

Treatment for radiation proctitis is aimed at relieving symptoms. In addition to supportive therapy, patients can sometimes benefit from botulinum toxin injection, oral sucralfate, or hyperbaric oxygen therapy or may be referred to a proctologist for sclerosing therapy (18).

Some rectal foreign bodies may be removed with adequate sedation in the ED, as described in Chapter 115. Patients who have anorectal foreign bodies, trauma, or proctitis should be questioned about the possibility of sexual assault.

CRITICAL INTERVENTIONS

- Initiate antibiotics and surgical consultation for patients with a suspected deep perirectal abscess and systemic signs of infection.
- Stabilize patients with acute blood loss of anorectal origin.
- Search for signs of complications (hemorrhage and perforation) in patients with rectal foreign bodies. Consider sexual assault.

DISPOSITION

Most patients with limited anorectal complaints can be discharged safely from the ED and told to follow the WASH regimen (see Fig. 114.3). For abscesses that cannot be drained easily in the ED, operative management is indicated. Those who display signs of systemic infection, such as fever and leukocytosis, should receive prompt surgical intervention. Several surgical options are available for repair of hemorrhoids, and an appropriate referral should be made. Immediate surgical referral should be made for gangrenous fourth-degree internal hemorrhoids. For patients whose genital warts are widespread, referral for repetitive topical treatment or surgical management can be made. Patients with rectal foreign bodies can be

discharged if the removal was routine and uncomplicated. Many require admission for surgical intervention.

Common Pitfalls

- Do not assume that a patient complaining of "hemorrhoids" actually has them. Consider underlying disease with an anorectal component that may be described as "hemorrhoids" by the patient.
- Mistaking a thrombosed internal hemorrhoid for an external one and excising it.
- Probing anorectal fistulas in the ED.

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CHAPTER 115 Gastrointestinal Foreign Bodies

Valerie C. Norton

Gastrointestinal (GI) foreign bodies present a diverse set of challenges. Presentations range from the obvious to the occult and from the benign to the life-threatening. Management options range from watchful waiting to emergent endoscopy or surgery.

Children account for about 80% of cases of ingested foreign bodies (see Chapter 273) and tend to ingest coins, toys, and other small objects left within their reach. Adult patients at highest risk include:

- psychiatric patients (who may swallow unusual objects intentionally)
- prisoners (usually seeking secondary gain through release to a hospital)
- patients with mental disability or impairment
- intoxicated patients
- those with underlying esophageal abnormalities such as strictures
- denture wearers (due to reduced sensation of the palate) (1)

Ingested foreign bodies frequently become lodged in the esophagus, often requiring urgent removal. Much more rarely, objects fail to pass the pylorus or the ileocecal valve. More than 80% of ingested foreign bodies that pass into the stomach will traverse the rest of the gut uneventfully (2). Objects longer than 6 cm or wider than 2.5 are less likely to pass spontaneously and may have to be retrieved endoscopically if still in the stomach or

proximal duodenum. Objects that are more likely to cause perforation include sharp objects such as pins or toothpicks, animal bones, button batteries, and magnets. However, many of these will still pass without sequelae if they make it past the esophagus (1,3).

Of primary concern are objects lodged in the esophagus, because these are at highest risk for complications such as mucosal erosions, perforation, or airway compromise. Objects typically lodge at the level of the cricopharyngeus muscle, the level of the aortic arch, or the lower esophageal sphincter. High esophageal impactions are most common in children; adults most often have obstructions at the lower esophageal sphincter (2). Food boluses, particularly meat, are the most common cause of esophageal impaction in adults, and often result from underlying esophageal pathology, usually a stricture (1). Foreign bodies with toxic contents, such as button batteries and packages of cocaine, represent special cases (see Chapters 254 and 329). A button battery lodged in the esophagus is a true emergency requiring immediate endoscopic removal, whereas endoscopy is contraindicated for drug packets because of the risk of rupturing the packet (1,4).

Rectal foreign bodies are usually the result of sexual misadventure or assault, though occasionally a patient will present with an ingested foreign body, such as an animal bone or toothpick, that passes through the entire gut only to become lodged in the rectum (5,6). Men are at least 28 times more likely than women to present with rectal foreign bodies (2). Objects inserted into the rectum range from vibrators and vegetables to drugs or other contraband. Many objects are not visible on x-ray, though most are low-lying and palpable on rectal examination. Mucosal lacerations and rectal perforations are fairly common, especially in assault victims, and may result in life-threatening sepsis.

CLINICAL PRESENTATION

Healthy adults with ingested foreign bodies usually give a clear history of the inciting incident and may report a foreign body sensation if the object is lodged in the upper esophagus or

hypopharynx where somatic nerve endings are present. Scratches or abrasions to the hypopharynx cause a foreign body sensation as well, and endoscopy shows no pathology in about 75% of patients who think they have a foreign body in the throat (2). If a meat bolus or other object is impacted in the mid- to lower esophagus, patients usually complain of more visceral-type chest pain, odynophagia, and difficulty handling secretions. Objects that have passed into the stomach or beyond frequently cause no symptoms, unless obstruction or perforation has ensued.

Small children and adults with impaired mentation may not give a clear history of foreign body ingestion. Clinicians may have to rely on symptoms of obstruction, such as drooling if the object is in the esophagus, or vomiting and distension if it is impacted below the stomach. Patients may also present with GI bleeding or signs and symptoms of peritonitis due to perforation. Small children often display indirect symptoms such as gagging, choking, drooling, refusal to eat, irritability, blood-tinged saliva, stridor, wheezing, or respiratory distress. Esophageal foreign bodies can cause respiratory symptoms in small children because the object often compresses the adjacent trachea or causes aspiration of saliva.

Patients with rectal foreign bodies usually state clearly that something is in the rectum, though they may be reluctant to report how it got there. Patients or their partners have often made multiple attempts to remove the object (2). Some patients may be unaware of the object if intoxicated at the time of insertion, or may be too embarrassed to admit to it, complaining instead of rectal pain or bleeding. Patients with extraperitoneal rectal perforation may present with sepsis, whereas those with intraperitoneal perforation present with peritonitis.

DIFFERENTIAL DIAGNOSIS

In the absence of a history of ingestion or insertion of a foreign body, the differential diagnosis is broad. Other organ systems may initially be the focus of concern, because esophageal pain can mimic cardiac angina, and respiratory symptoms may be mistaken for

croup, asthma, or allergic reaction. The possibility of foreign body ingestion or aspiration should always be considered in small children with new-onset wheezing, especially if it does not respond to bronchodilators (4).

Subacute and chronic presentations do not rule out foreign bodies. There are many reports of patients with objects dwelling in the stomach or intestines for years before causing symptoms. Esophageal foreign bodies have been impacted for a month or more in some children without serious sequelae (7). Even when there is a clear-cut history of foreign body ingestion or insertion, other unsuspected pathology may be present, such as a second foreign body, a mucosal laceration, perforation of the esophagus or the rectum, or underlying esophageal disease (4,5).

ED EVALUATION

Initial assessment should aim at immediate detection and treatment of those with airway compromise, sepsis, or perforation. In more stable patients, the examiner should look for signs of esophageal obstruction such as drooling or the inability to swallow secretions, signs of lower intestinal obstruction, or evidence of GI bleeding. In the majority of patients with upper GI foreign bodies, the physical examination will be unrevealing. By contrast, rectal foreign bodies are usually palpable on rectal examination. Some authors advise against a digital rectal examination prior to obtaining radiographs, because the examiners may injure themselves if an unexpectedly sharp object is present (2).

Imaging studies are often helpful, though a negative study does not rule out a radiolucent foreign body. For small fish bones lodged in the hypopharynx, computerized tomography (CT) has been found to be more sensitive than plain films (8). Although chicken bones are often visible on plain films (2), some authors report poor sensitivity with plain films and recommend CT for any suspected animal bone above the diaphragm (1,2). For suspected esophageal foreign bodies, both anteroposterior and lateral radiographs of the neck and chest are recommended to avoid missing a second foreign

body located behind the first, or lower in the esophagus (1,2,9,10). Both views also help to rule out a tracheobronchial foreign body. Flat objects in the esophagus, such as coins, typically appear “en face” on anteroposterior view because the easily compressible esophagus typically lies somewhat flattened between the trachea and the spine. Tracheal coins, by contrast, typically appear “on end” on anteroposterior views, because the more rigid tracheal rings have their widest diameter in the sagittal plane (2). Radiographic evidence of esophageal edema on a lateral view indicates a prolonged impaction and the need for urgent endoscopic evaluation (4,7,9,11).

Imaging with oral contrast should not be done for suspected foreign bodies in the esophagus. In cases with negative imaging but high clinical suspicion, patients should go straight to endoscopy, as oral contrast material may increase the risk of aspiration or obscure endoscopic visualization of the object (1,12).

Some authors have advocated the use of a hand-held metal detector in lieu of plain films to evaluate the presence and location of metal foreign bodies (13,14). However, studies published to date indicate that hand-held metal detectors are not as sensitive as radiographs. Small objects with low metallic mass can be missed, and even coins are occasionally missed or incorrectly localized. More importantly, metal detectors cannot distinguish between sharp and blunt objects, and cannot reliably make the crucial distinction between the lower esophagus and the stomach when localizing an object (13,14).

Objects below the esophagus may be evaluated with standard plain films or contrast radiography if necessary. In most cases the primary reasons to obtain radiographs are to determine whether an ingested object has passed beyond the esophagus and whether the object has any physical characteristics that will make passage or extraction more difficult, such as a sharp edge.

KEY TESTING

- Plain films (AP and lateral) will identify most inorganic items likely to be ingested by children, such as coins, batteries, or toys.
- CT is more sensitive for fish bones in the hypopharynx and may be helpful for other smaller esophageal foreign bodies such as small chicken bones, glass, or plastic.
- Patients with suspected esophageal foreign body and persistent symptoms should undergo endoscopy even in the setting of negative imaging.

ED MANAGEMENT

Patients with signs of airway compromise require definitive airway management and emergent endoscopic consultation to remove the foreign body. Those with signs of hollow viscus perforation, massive bleeding, or sepsis require immediate resuscitation, intravenous antibiotics, and emergent surgical consultation.

The management of stable patients depends on the type, location, and duration of impaction of the foreign body. Management guidelines are summarized in Figure 115.1.

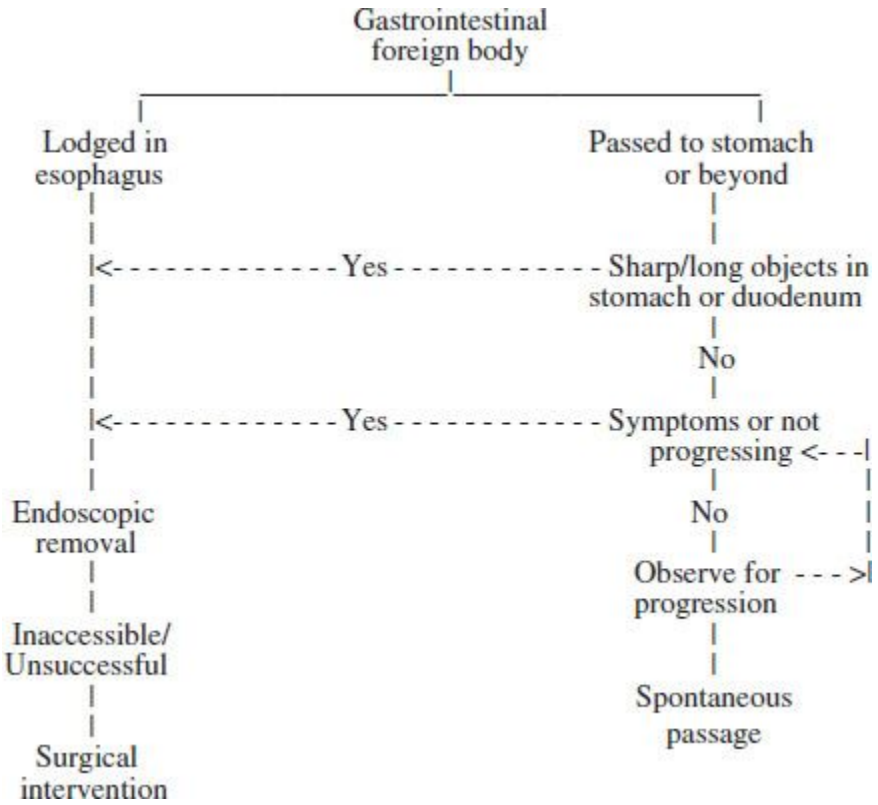

FIGURE 115.1 Management of the stable patient with a gastrointestinal foreign body.

Hypopharynx

The most common presentation is a sensation of a fish or chicken bone stuck in the throat, with distinct, well-localized pain in the throat. Well-appearing patients with negative imaging can be sent home with follow-up in 24 hours for endoscopy if still symptomatic, since most have only a mucosal abrasion. The vast majority with a mucosal abrasion will be asymptomatic at follow-up, whereas those with a true hypopharyngeal foreign body typically do not develop any complications from the delay (2). Highly symptomatic patients with severe pain and negative plain films should undergo CT, which is more sensitive for smaller bones and objects (2,8). If a bone or other impacted sharp object is identified in the hypopharynx, it should be removed promptly, typically by an otolaryngologist via nasopharyngoscopy (2).

Esophagus: Indications for Immediate Endoscopic Removal

Sharp objects in the esophagus need immediate endoscopic removal because of the risk of perforation (1). Button batteries in the esophagus are a true emergency and require immediate endoscopic removal, since serious mucosal burns and even perforation have been reported within as little as 2 hours (15). Patients with high-grade obstruction with inability to swallow secretions (usually from a meat bolus) require emergent endoscopy because of the risk of aspiration, particularly if the patient falls asleep (1,4).

All Other Blunt Esophageal Foreign Bodies

Objects in the upper half of the esophagus are unlikely to pass spontaneously, mandating intervention. The standard of care at most large institutions is prompt endoscopic removal (1,2,10,12). If the patient has a full stomach or if endoscopy is not readily

available, it may be postponed briefly as long as the patient is able to handle secretions. Most experts recommend removal within 12 to 24 hours (1,10,16).

Objects lodged at the lower esophageal sphincter are often managed with a trial of watchful waiting with or without measures to relax the sphincter, because up to 50% of these objects may pass spontaneously (16). Glucagon (1 to 2 mg IV) may be given to help relax the lower esophageal sphincter. This dose may be repeated once in 20 to 30 minutes if unsuccessful. However, its use is controversial and it may cause vomiting (2). Its efficacy has been questioned, with some authors reporting no better success than with watchful waiting (17). If passage has not occurred in 12 to 24 hours, most authors recommend endoscopic removal (1,10,16). A few small case reports and case series report success with the use of effervescent agents (such as carbonated beverages) to aid in break-up and passage of a meat bolus, but no prospective trials have validated the utility of this approach (18). Other medications such as nitroglycerin and calcium-channel blockers have been reported to be no better than glucagon (2). *Proteolytic enzymes (such as meat tenderizers) are contraindicated as they can cause severe damage to the esophageal mucosa.*

Although endoscopic removal of esophageal foreign bodies is standard at many institutions, the choice of technique is controversial in some areas because of concerns about cost or availability. A number of authors have advocated the alternative techniques of fluoroscopic Foley catheter extraction and esophageal bougienage (advancement of the foreign body with an esophageal dilator) (7,11,19). In experienced hands and in selected patients, these techniques have success and complication rates comparable to endoscopy. However, in patients with a history of prolonged impaction or a sharp-edged foreign body, the object may become embedded in the esophageal mucosa and be very difficult to remove (4). These alternative techniques should therefore be limited to patients with a blunt foreign body (usually a coin), impaction of $<$24 hours of duration, no history of esophageal disease, no

radiographic evidence of esophageal edema, and no signs of respiratory distress or airway compromise (7,9,11,19).

Advanced airway management should be immediately available at all times. The procedure should be terminated if resistance is met or multiple attempts are needed, as serious complications have occurred in these settings (11).

Cost has become less of an issue as flexible endoscopy with procedural sedation has increasingly replaced rigid endoscopy under general anesthesia in the operating room, resulting in lower charges and shorter recovery times. In many institutions, flexible endoscopy is now comparable to catheter extraction or bougienage in terms of cost and convenience.

Stomach and intestine: Objects below the diaphragm are much less problematic than those in the esophagus, because the vast majority will pass spontaneously. The exceptions are sharp objects, which may cause perforation in up to 35% of patients; these should be removed endoscopically if still in the stomach or duodenum (1,2,12). Some authors also recommend endoscopic removal of objects more than 6 cm long or 2.5 cm wide that are found in the stomach or duodenum (1), although one study of adults found that gastric foreign bodies as long as 17 cm passed into the stool without problem (3). Two special cases that usually require urgent removal by endoscopy or laparotomy are magnetic jewelry beads, which can trap bowel wall between them with resultant erosion and perforation (1,20), and objects with multiple sharp points, such that there is no blunt “leading edge” that can negotiate passage through the intestines—these are much more likely to cause perforation.

Small, blunt objects that pass into the stomach can be followed clinically, with repeat x-rays in 3 to 4 weeks if passage in the stool is not noted. A high-fiber diet may aid passage of the foreign body. Blunt objects should be given 3 to 6 weeks to pass out of the stomach before resorting to endoscopic removal (1,10). Objects may be given 2 to 3 weeks to traverse the rest of the gut. The development of symptoms or the failure of the object to progress mandates surgical consultation.

Rectum: Rectal foreign bodies frequently require surgical consultation to bring about removal, though various authors report being able to remove 20% to 75% of objects in the ED (5,6,21). Removal in the ED is dependent on the ability to achieve adequate relaxation of the anal sphincter and the ability to locate and retrieve the foreign body. Many patients with long histories of rectal stimulation will have lax anal tone and may only require lidocaine gel with or without conscious sedation to relax the sphincter. Other patients may require infiltrative local anesthesia, and some may only achieve adequate relaxation with spinal or general anesthesia in the operating room.

Soft, low-lying objects with an edge can often be grasped and removed manually or with forceps. Some objects create suction on the rectal mucosa with downward traction; this can be overcome by passing a Foley catheter beyond the object and insufflating air into the rectum (2,21,22). Sigmoidoscopy after removal is recommended to look for complications such as abscesses or mucosal lacerations, as these are very common (2,5,6,21). Hard, smooth-edged, or high-lying objects often cannot be removed manually and require surgical consultation for removal by flexible sigmoidoscopy in the operating room or endoscopy suite (6,21). Laparotomy is a last resort for foreign bodies in which sigmoidoscopy is unsuccessful.

CRITICAL INTERVENTIONS

- Immediate airway management and endoscopic intervention in patients with respiratory compromise due to an esophageal foreign body
- Immediate stabilization, antibiotics, and surgical consultation in patients with sepsis, massive GI bleeding, or perforation due to a foreign body anywhere in the GI tract
- Emergent endoscopic removal of all sharp objects, button batteries, and objects causing high-grade obstruction in the esophagus
- Prompt surgical consultation for rectal foreign bodies that are not amenable to removal in the ED

DISPOSITION

Asymptomatic patients with uncomplicated, blunt foreign bodies in the stomach or intestine can be discharged from the ED with observation of the stools or radiographic follow-up at appropriate intervals to ensure progress of the object through the gut. All others require consultation with an endoscopist or a surgeon, depending on the type and location of the foreign body and the presence of any complications. Following the uncomplicated removal of a foreign body in the ED, asymptomatic patients can be sent home with close follow-up by their primary care provider or an appropriate consultant. Patients who remain symptomatic or who develop complications after a procedure require admission.

Common Pitfalls

- Failure to consider an esophageal foreign body in patients without a foreign body history but with suggestive symptoms such as gagging, drooling, wheezing, repetitive vomiting, or refusal to eat.
- Failure to obtain immediate endoscopy for patients with high-grade esophageal obstruction, sharp esophageal foreign bodies, or button batteries in the esophagus.
- Inappropriate use of Foley catheter or other removal techniques in patients with sharp or irregularly shaped esophageal foreign bodies, prolonged impactions, esophageal edema, signs of respiratory compromise, or when initial attempts meet resistance —all of these may lead to serious complications.
- Inappropriate, repeated attempts to remove hard, smooth, or high-lying rectal foreign bodies in the ED—this may lead to further mucosal damage or even rectal perforation.
- Failure to evaluate the rectal mucosa (usually sigmoidoscopy) after removal of rectal foreign bodies to rule out mucosal lacerations.

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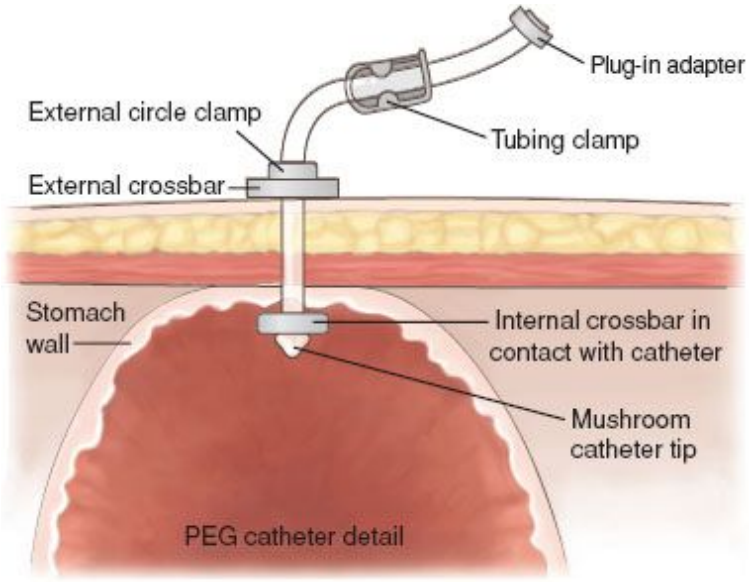
CHAPTER 116 Feeding Tubes

Philip Salen and Steven Solga

CLINICAL PRESENTATION

The assessment and management of a malfunctioning or displaced feeding tube in a debilitated, noncommunicative patient is a common clinical scenario for the ED physician. Even identifying the type of the original feeding tube, its proper placement, and the location of the ostomy may be difficult. Feeding tubes are best categorized by their site of insertion: (1) Nasal (nasogastric, nasoduodenal, and nasojejunal), (2) cervical (pharyngostomy and esophagostomy), (3) abdominal percutaneous (gastrostomy, duodenostomy, and jejunostomy) (1). For short-term enteral feeding, nasogastric tube feeding is recommended (1). Percutaneous endoscopic gastrostomy (PEG) (eFig. 116.1) is the most common device for establishing long-term enteral access in patients unable to take oral feedings because of its safety profile and low cost compared with surgically placed enterostomies (2).



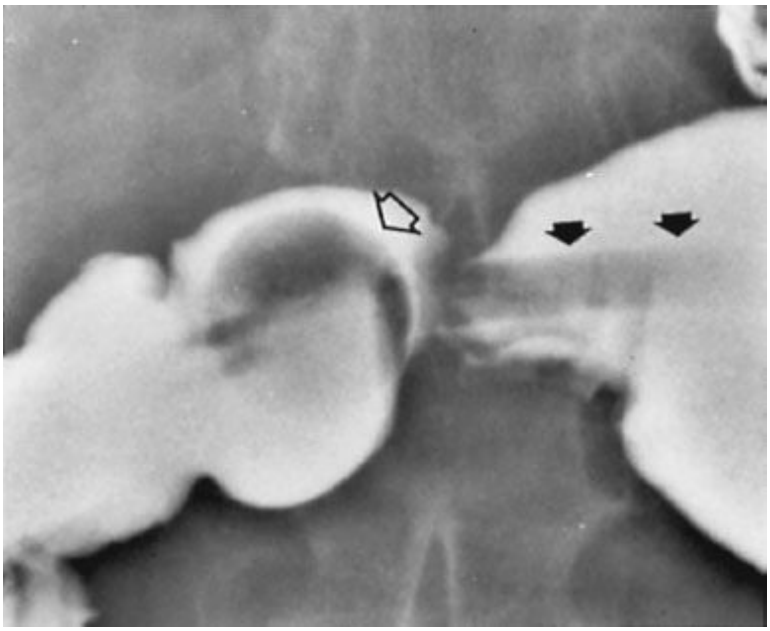
eFIGURE 116.1 Percutaneous endoscopic gastrostomy (PEG) tube in place in the stomach. Note that not all PEG devices have mushroom catheter tips nor internal crossbars; many will have balloon tips to anchor their positions. (From Smeltzer SC, Bare BG, Hinkle JH, et al. Brunner and Suddarth's Textbook of Medical Surgical Nursing. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:998.)

Of the many kinds of enteral feeding tubes, the PEG tube is most often encountered by the ED physician (2). There are many variants of the PEG, notably the percutaneous endoscopic jejunostomy and the percutaneous endoscopic gastrostomy/jejunostomy (PEG/J) tubes. Unlike the usual small-bore nasogastric feeding tube, PEG tubes come in different sizes ranging from 14# to 30# French. They are made of silicone, latex, or urethane, and are radio-opaque. Large-bore tubes, 20# and larger, are less likely to become occluded (3). Urinary catheters are occasionally used as PEG tube replacements, but not designed for this purpose and should only be placed temporarily in order to maintain the patency of the ostomy lumen, which can quickly shrink and close (1). PEG tubes have bumpers or balloons that aid in maintaining their positioning and come with or without external skin disks to secure their placement to the abdominal wall (see eFig. 116.1).

Jejunostomy, or J tubes, are placed surgically, endoscopically, via interventional radiology, or through the PEG. Feeding through gastrostomy tubes results in better digestion compared with intestinal feeding, whereas J tubes are less likely to result in reflux and aspiration (4). The PEG/J is a J tube that is inserted through the PEG past the pylorus with its tip in the proximal small intestine. The PEG/J allows for feeding through the J tube with less aspiration risk and for administration of medications through the PEG port with less risk of tube clogging.

ENTERAL TUBE FEEDING COMPLICATIONS

The annual incidence of enteral tube complication rate ranges from 8% to 70% (5). Enteral tube complications can be divided into mechanical, gastrointestinal, metabolic, and infectious (1). All tubes, whether nasogastric, cervical, or abdominal percutaneous, can have mechanical complications: malposition, migration, clogging, leaking, fracture, kinking, deterioration, or inadvertent removal (2). Accidental endotracheal or endobronchial nasoenteric tube insertion can result in pulmonary aspiration (1). Gastrostomy tube migration and malposition occurs when the outer bumper becomes too loose or too tight (see eFig. 116.1). Tube migration can lead to inward displacement of the internal bumper or balloon, resulting in obstruction of the pylorus with resultant vomiting, distension, or pain (see eFig. 116.2) (6). An outer bumper that is too tight can induce pressure necrosis and fasciitis, as well as a “buried bumper” where the internal bumper migrates from the stomach into the peritoneum (2).



eFIGURE 116.2 Small bowel obstruction secondary to gastrostomy tube. Feeding gastrostomy tube (open arrow) prolapsed into the duodenal bulb. The tube could be mistaken for a polyp on a large stalk (solid arrows). (From Eisenberg RL. An Atlas of Differential Diagnosis. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

A clogged PEG tube, a common ED presentation, occurs secondary to crushed medications, inadequate flushing, or precipitation of protein in the feedings administered (1). Saline flushes can crystallize within the tubing and cause obstruction. The best initial irrigant for unclogging PEG tubes is warm water (2). Clogged tubes may also be manually cleared with special "declogging" plastic brush devices, but not by wires, which can perforate the tube walls (2). The passage of water with gravity alone through the feeding tube is a good method for testing feeding tube patency (1).

Inadvertent PEG tube removal is a common complication usually occurring in combative or confused patients who pull on the tube. When PEG tubes are inadvertently removed within the first 4 weeks of placement, "blind" bedside replacement is contraindicated. The PEG tube tract may not have matured adequately resulting in gastric

and abdominal wall separation and may result in PEG placement in the peritoneal cavity or creation of a false tract (6).

Common gastrointestinal complaints associated with enteral tube feeding include nausea, abdominal cramps, and diarrhea. The diarrhea may result from drugs, antibiotics, sorbitol in the feedings, alterations in intestinal flora, fat malabsorption, contaminated feeds, and overly rapid administration of feeds (1). Enteral feed contamination by pathogenic bacteria can result in infectious diarrhea (1). Enteral feeding has the potential to cause metabolic complications, such as deficiency or excess of electrolytes, vitamins, trace elements, and hyponatremic hypervolemia as a result of excessive tube flushing with free water (2).

The ostomy site may become infected. This can be treated with oral antibiotics that cover skin flora unless the infection is severe or the patient is immunocompromised. Placement of a feeding tube does not eliminate the risk of aspiration and pneumonia. The risk of aspiration is reduced by elevating the head of the bed to 30 degrees for enteral feeding (1).

REMOVAL AND REPLACEMENT OF GASTROSTOMY TUBES

When evaluating a nonfunctioning feeding tube that is still in place, the clinician should weigh the risks and benefits of repositioning or unclogging the tube versus removing and replacing it in the ED. Other indications for PEG tube removal or replacement include progressive enlargement of the gastrostomy site, severe stomal infections, tube erosion into the gastric or abdominal wall, gastrocolocutaneous fistula, and deterioration of the tube resulting in leakage. Most tubes can be removed at the patient's bedside with gentle traction; however, the physician should investigate the timing and type of tube prior to attempting removal.

Bedside replacement of a percutaneous feeding tube carries the potential risk of inadvertent positioning into the peritoneum, with resultant peritonitis and catastrophic consequences (5). Characteristics that contribute to complications when replacing percutaneous feeding tubes include trauma to the tract during

dislodgement or replacement, tract immaturity, severe malnutrition, prolonged time interval between dislodgement and replacement, and chronic corticosteroid use.

If the tube has been removed less than 4 weeks after initial placement, the ED physician should not attempt bedside replacement. Instead, the patient should be returned to the endoscopy suite for repeat PEG placement through the same site because of the risk of site dehiscence (6). Tract site atrophy prior to replacement also mandates PEG endoscopic replacement (7). Replacement of tubes dislodged from mature fistulous tracts should be performed as soon as possible to prevent atrophy and closure of the gastrocutaneous tract. Figure 116.1 illustrates the placement of three different types of gastrostomy tubes done at the bedside. Anesthetic jelly or ointment can be placed at the stomal entrance to enhance patient comfort prior to tube placement. In most cases, tube replacement can be performed with minimal discomfort using gentle, persistent pressure of the tube through the stoma.

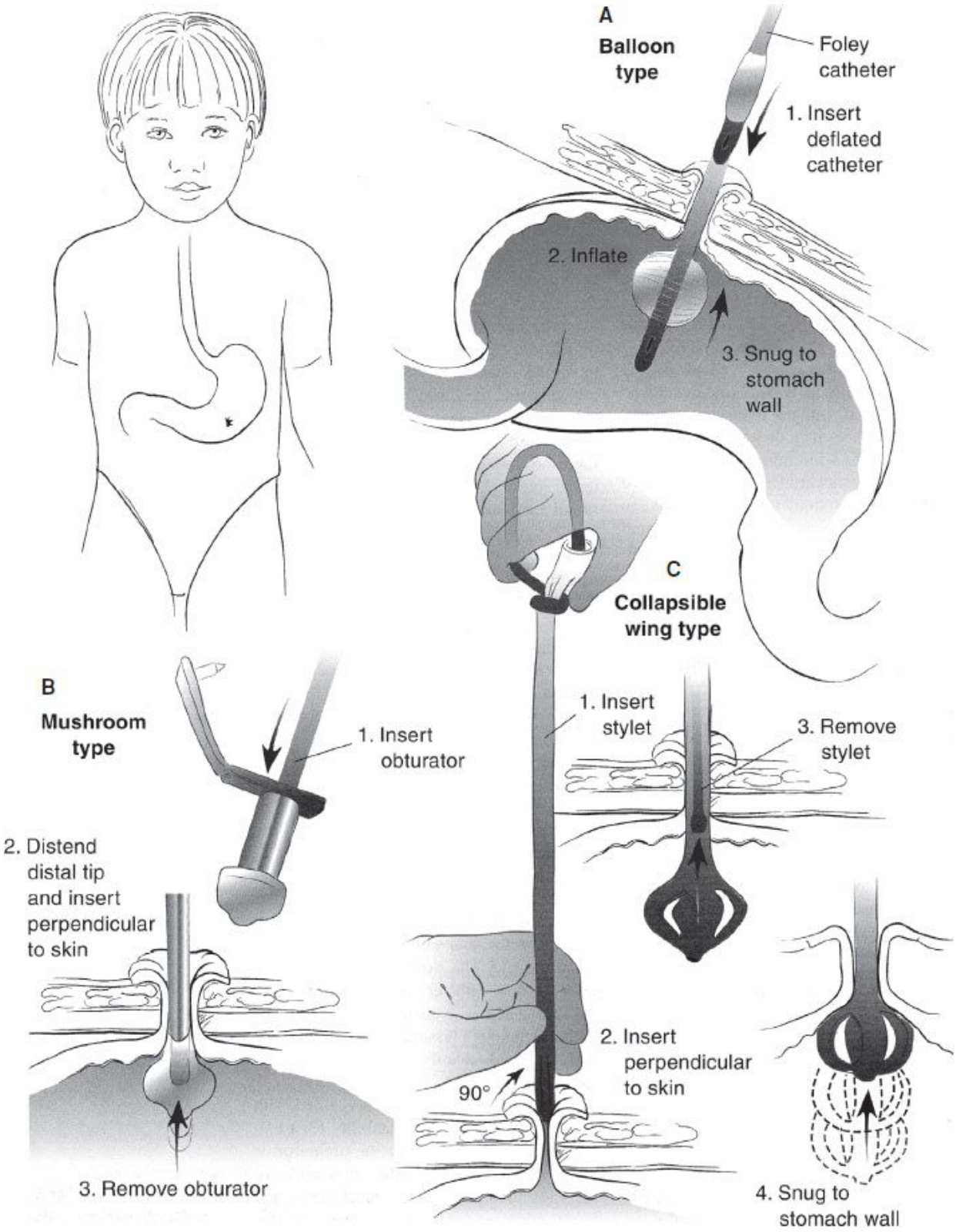


FIGURE 116.1 Three types of gastrostomy tube replacements: balloon-type **(A),** mushroom-type **(B),** and collapsible **(C)** wing-type

catheters. Note that both mushroom type and collapsible wing type catheters require stylets to distend the tip for replacement. (From Fleisher GR, Ludwig S, Henretig FM, et al. *Textbook of Pediatric Emergency Medicine.* 5th ed. Philadelphia, PA: Lippincott; 2005.)

Some advocate obtaining radiologic confirmation every time an enteric feeding tube is replaced. Others feel that radiologic confirmation is necessary only when there is a concern about tract integrity or the exact place of the tip of the feeding tube. If there is concern about the possibility of peritoneal placement of the gastrostomy tube, injecting 30 mL of water-soluble contrast solution through the gastrostomy tube followed by a supine abdominal radiograph confirms proper position prior to the initiation of feedings (6). A confirmatory contrast study is recommended following PEG replacement if the procedure is difficult, if it results in pain upon tube irrigation, or if bilious and gastric contents are not easily aspirated. The cost associated with routine radiographic confirmation pale in comparison to the cost of a single missed misplaced tube with complications (5). Other methods for confirmation of tube placement include post-insertion gastric liquid aspiration, pH testing of gastric aspirates, and auscultation for borborygmi after air insufflation into the tube (8). However, these nonradiologic methods are more liable to misinterpretation than radiologic confirmation (8). After confirmation of tube placement, the clinician must take care to adequately secure the tube, using the tube bolsters if present, to ensure that the tube is not accidentally removed and to inhibit migration. Finally, the type, size, and distance of insertion (most have markings imprinted on the side) should be recorded in the medical record, and the tube itself can be marked so that tube migration can be more easily detected (1).

CRITICAL INTERVENTIONS

- Acquire information about the enteral tube (type of tube, placement date, who placed the tube, and how it was secured) prior to removal or replacement.

- Replace a disloged PEG tube through a mature tract as soon as possible to prevent tract atrophy and closure.
- Do not attempt blind replacement of a recent tube through an immature tract (< 4 weeks).
- Confirm and document successful enteral tube replacement.

DISPOSITION

Most patients can be safely discharged from the ED after tube placement has been confirmed, and the tube may be used immediately.

Common Pitfalls

- Inadequate examination of the enteral tube ostomy site, which can suffer a myriad of complications including peristomal infection, leakage, buried bumper syndrome, and necrotizing fasciitis.
- Attempting replacement of a PEG tube into an immature gastrocutaneous tract, < 4 weeks old.
- Lack of radiographic confirmation with contrast of successful tube replacement, if the patient is at risk for complication (difficult placement, painful placement, or inability to aspirate gastric contents after placement).

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SECTION XI
Renal and Urologic Emergencies

Section Editor: GREGORY W. HENDEY

CHAPTER 117

Hematuria

H. Gene Hern Jr., Abigail R. Pease, and Nicholas Gavin

Nontraumatic hematuria is surprisingly common, with an estimated prevalence in the general population ranging from 3% to 4% (1). Hematuria may be even more common in older adults; studies using home screening urinalyses in men older than 50 years reported rates of 10% to 20% (2,3). The causes of hematuria, whether it is a chief complaint or an incidental finding, range from sources as benign as vigorous exercise to potentially serious underlying disorders such as infection, renal failure, or malignancy. The challenge for the emergency physician is to differentiate between the serious and nonserious etiologies and determine the appropriate evaluation, treatment, and disposition.

CLINICAL PRESENTATION

Hematuria is generally classified into two categories: gross hematuria and microscopic hematuria. Gross hematuria refers to visibly bloody urine and often presents as a chief complaint. Microscopic hematuria is blood in the urine visible only under the microscope and is often discovered incidentally on urinalysis.

Gross hematuria can be quite distressing to patients. However, in most cases (trauma being the notable exception), there is little correlation between the amount of blood and the seriousness of the cause. Also, the color of the urine does not correlate well with the amount of blood loss; as little as 1 mL of blood in 1 L of urine is enough to discolor the urine. Substances other than blood may discolor the urine red or brown. This condition is called

pseudohematuria and may be caused by a variety of conditions such as porphyria, rhabdomyolysis, ingestion of beets or berries, or medications such as phenazopyridine or rifampin (see Table 117.1). Microscopic examination of the centrifuged urine for red blood cells (RBCs) is useful in distinguishing true hematuria from pseudohematuria. The rare discolored specimen that is heme-negative on dipstick and has no RBCs on microscopy indicates a nonheme source. A discolored specimen that is heme-positive on dipstick but without RBCs on microscopy indicates the presence of hemoglobin or myoglobin in the urine.

TABLE 117.1
Causes of Hematuria

Pseudohematuria

Pigmenturia—myoglobinuria, hemoglobinuria, porphyria

Foods—beets, blackberries, rhubarb

Drugs—phenazopyridine, rifampin

Vaginal/perineal bleeding

Hematologic

Sickle cell disease

Coagulopathy—idiopathic thrombocytopenic purpura, hemophilia

Pharmacologic anticoagulation

Renal (Glomerular)

Glomerulonephritis—primary; poststreptococcal glomerulonephritis, IgA nephropathy, hereditary nephritis (Alport syndrome), other

—Multisystem; systemic lupus erythematosus, Goodpasture syndrome, vasculitis, other

Renal (Nonglomerular)

Pyelonephritis

Infarction

Trauma

Interstitial nephritis

Papillary necrosis

Malignancy

Vascular malformation

Postrenal

Infection—cystitis, prostatitis, urethritis

Stones/calculi

Trauma—blunt trauma, exercise, Foley catheter placement

Malignancy

Benign prostatic hypertrophy

Schistosoma haematobium

Miscellaneous

Eroding abdominal aortic aneurysm

Renal vein thrombosis

Exercise-induced hematuria

Malignant hypertension

Microscopic hematuria is defined by an abnormally high number of RBCs present in the urine on microscopy. The American Urological Association defines asymptomatic microscopic hematuria as three or more RBCs per high-powered field (HPF) on a properly

collected urine specimen (4). Although microscopy is the gold standard for diagnosis, the urine dipstick frequently replaces the time-intensive microscopic examination. Urine dipsticks accurately detect hemoglobin in very small quantities, with reported sensitivities from 91% to 100%; the specificity ranges from 65% to 99% (5,6). The high sensitivity results in more false-positive results but fewer false-negative results. A negative urine dipstick thus reliably excludes abnormal hematuria (7). A positive urine dipstick should be confirmed by microscopy to exclude hemoglobinuria or myoglobinuria.

DIFFERENTIAL DIAGNOSIS

The most common causes of nontraumatic hematuria include urinary tract infections, nephrolithiasis, glomerulonephritis, benign prostatic hypertrophy (BPH), and urologic malignancies (Table 117.1). The history and physical examination provide important clues to the underlying diagnosis.

Associated symptoms such as dysuria, urgency, and urinary frequency indicate cystitis as a likely cause. With flank pain, fever, and other systemic symptoms, pyelonephritis should be considered. Unilateral flank pain that radiates to the groin or testicle may indicate nephrolithiasis. Of note, about 15% of patients with renal calculi do not have hematuria, making it an unreliable predictor (8,9). Symptoms of BPH such as dribbling, hesitancy, and poor stream may also suggest the cause of hematuria; new vessels in the proliferating tissue may be fragile and prone to disruption. Some controversy exists as to whether there is a higher incidence of hematuria in patients with BPH than in controls (10,11). Regardless, the presence of BPH should not deter the clinician from further evaluating hematuria, because older men have a higher incidence of cancers of the genitourinary (GU) tract.

A history of a recent sore throat or skin infection should prompt consideration of poststreptococcal glomerulonephritis. Immunoglobulin A (IgA) nephropathy, often also associated with a previous upper respiratory tract infection or pharyngitis, may

present with gross hematuria as well. Concomitant hypertension and proteinuria also indicate potential glomerulonephritis. Glomerulonephritis can range in severity from mild asymptomatic hematuria to full-blown nephritic syndrome and renal failure. It is important to note that passage of clots typically excludes the presence of glomerular disease alone and should prompt further urologic evaluation for lower GU etiologies.

In asymptomatic patients, it is important to consider and assess risk factors for urologic malignancy. A number of screening studies in adults with asymptomatic hematuria show a significant risk of urinary tract malignancies, reporting rates of 3% to 5% in women and 7% to 13% in men (3,12,13). Known risk factors for malignancy include age, tobacco use, occupational exposures (e.g., aniline dyes or benzenes), pelvic irradiation, and cyclophosphamide use (5,14).

A family history of sickle cell disease, hemophilia, polycystic kidney disease, or hereditary nephritis can suggest a possible explanation of hematuria. Recent use of medications known to cause nephritis (e.g., penicillins, sulfonamides, cimetidine, and allopurinol) or anticoagulants also may be helpful in suggesting an etiology. It is important to note that hematuria in patients on anticoagulants may originate from a potentially serious lesion and should not be attributed to the anticoagulated state itself. Screening studies show similar rates of hematuria in patients on anticoagulants and in control patients, with rates of urologic cancer the same in both groups (15). A history of travel or residency in Africa or the Middle East should prompt consideration of *Schistosoma haematobium,* one of the most common causes of hematuria worldwide.

Hematuria in women that occurs during menstruation may be caused by contamination of the urine specimen during collection or by endometriosis of the urinary tract. If contamination by vaginal or perineal bleeding is suspected, obtaining a catheterized specimen after the area has been thoroughly cleaned is recommended. Urethral catheterization itself can produce small amounts of blood in the urine. Studies comparing pre- and postcatheterization

urinalyses suggest that more than three to four RBCs/HPF cannot be attributed to catheterization alone (16,17).

Finally, vigorous exercise occasionally produces hematuria (18). Whether from direct contact sports (football, boxing) or other aerobic exercise (biking, long-distance running), exercise-induced hematuria is usually short-lived and benign.

ED EVALUATION

Evaluation of hematuria begins with a urinalysis to confirm the diagnosis of true hematuria. The urinalysis is of further value in determining whether hematuria is glomerular or nonglomerular in origin. On urine microscopy, the presence of RBC casts or a multitude of dysmorphic RBCs is indicative of a glomerular source. Urinary-protein excretion >500 mg/d (on a specimen without gross blood) also indicates probable glomerular involvement. Although these signs are helpful if present, their absence does not rule out glomerular disease.

Coagulation studies should be considered in patients taking anticoagulants. A complete blood count is appropriate for the rare patient with sustained heavy bleeding or evidence of hemodynamic compromise. Electrolytes, blood urea nitrogen (BUN), and creatinine (Cr) should be ordered in patients with suspected glomerulonephritis or symptoms of renal failure. Computed tomography (CT) without contrast should be ordered to evaluate for suspected nephrolithiasis (19). CT also provides information about other potentially lethal causes of hematuria such as abdominal aortic aneurysm (20) and neoplasms of the kidney, ureter, or bladder. When CT is relatively or absolutely contraindicated, particularly in pregnant patients, ultrasound of the kidneys and bladder is the ideal first-line test to assess for nephrolithiasis.

KEY TESTING

- Urinalysis
- Blood urea nitrogen (BUN) and creatinine (if renal parenchymal disease suspected)

- Complete blood count (if significant bleeding or hemodynamic compromise are present)
- Urine culture (if symptoms of infection are present)
- CT scan of abdomen and pelvis without intravenous contrast (in patients with pain and no history of nephrolithiasis)

ED MANAGEMENT

The clinically stable patient with nontraumatic hematuria rarely requires urgent or emergent ED management (see Fig. 117.1). The rare patient with hemodynamic compromise caused by hematuria should be resuscitated with intravenous (IV) crystalloids and blood transfusion as necessary. As always, patients with significant pain and discomfort should receive appropriate analgesics.

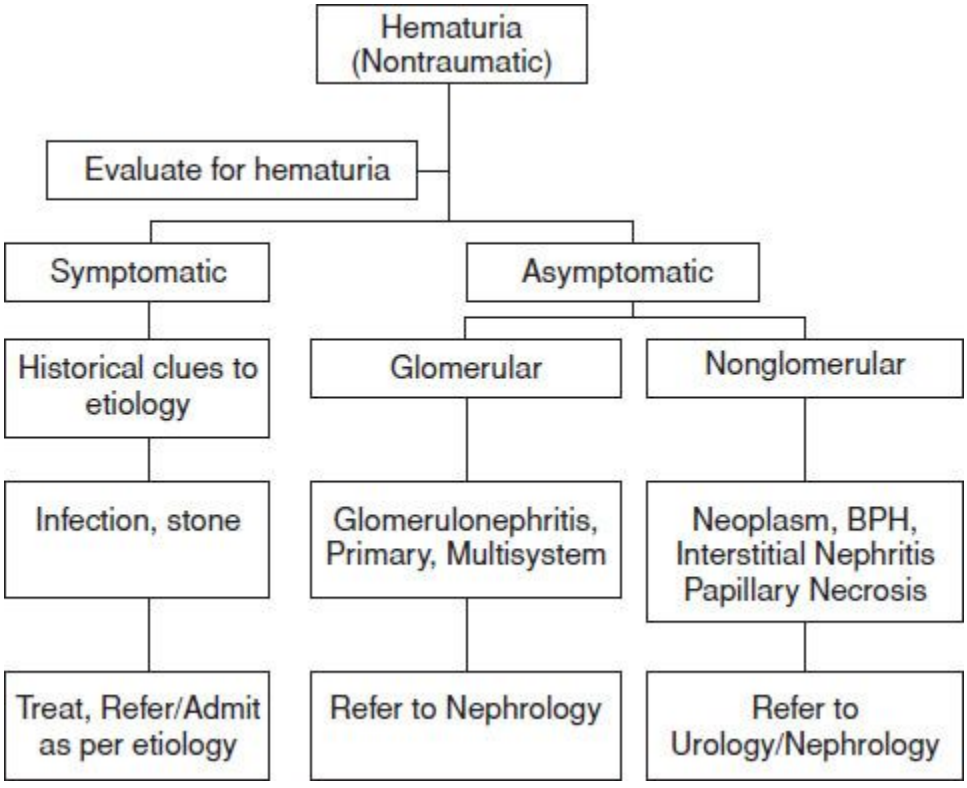

FIGURE 117.1 Approach to nontraumatic hematuria.

Further management of hematuria is directed at the cause. Urinary tract infections should be treated with appropriate antibiotics (see Chapter 123). Nephrolithiasis should be treated with

analgesics (see Chapter 126). The risk of complications associated with glomerulonephritis (e.g., volume overload, pulmonary edema, electrolyte imbalance, and oliguria) is significant, and thus consultation with a nephrologist is recommended.

With brisk bleeding, often in the postoperative setting, the formation of intravesicular clots can lead to bladder outlet obstruction. This obstruction is managed by placing a triple-lumen urinary catheter to relieve obstruction and then irrigating the bladder with normal saline until the effluent is pink or clear and free of clots.

CRITICAL INTERVENTIONS

- Volume resuscitation of any hemodynamic instability caused by severe hematuria
- Relieving obstruction and irrigating clots with a catheter as needed

DISPOSITION

Most patients with nontraumatic hematuria are managed as outpatients, regardless of cause. Patients with intractable nausea and vomiting, bladder outlet obstruction, renal failure, hemodynamic instability, or signs and symptoms of sepsis should be admitted.

Stable patients with a clear glomerular source of bleeding do not require further ED workup for a urologic source and may be referred to a nephrologist for further evaluation. Asymptomatic nonglomerular hematuria requires outpatient referral to a primary care physician, urologist, or nephrologist but not admission or emergent consultation. Patients older than 35 years, those with gross hematuria, or those with risk factors for malignancy require urgent referral to a urologist for cystoscopy and imaging of the upper urinary tract, typically CT urography. This age cut-off is lower than in past recommendations and is based on the 2012 AUA guidelines (4). Patients younger than 35 years with asymptomatic

microscopic hematuria can simply have a repeat urinalysis in 1 to 2 weeks to determine whether hematuria is persistent.

Common Pitfalls

- Failing to provide adequate follow-up for asymptomatic patients with hematuria, especially those who are older than 35 years or who have a high risk of malignancy.
- Eliminating the possibility of ureteral stone based on a negative urinalysis.

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CHAPTER 118 Acute Kidney Injury

Danielle D. Campagne

The kidney functions to excrete nitrogenous metabolites (urea, creatinine, and uric acid) and to maintain volume status and electrolyte balance. Normal kidney function depends on adequate renal perfusion, efficient filtration of plasma at the glomeruli, nearly complete reabsorption of filtered solutes by the renal tubules, and the unhampered passage of formed urine from the body.

Acute kidney injury (AKI) is the new consensus term for acute renal failure. AKI, defined as a recent (within 48 hours) decline in renal function, accounts for about 1.9% of hospital admissions (1,2). In the critically ill patients who are admitted to the intensive care unit with sepsis, the prevalence of AKI is greater than 40% (2). The hallmark of AKI is azotemia, in which nitrogenous wastes such as creatinine and urea accumulate in the blood. A decrease in urine output may or may not accompany AKI. Because about 400 to 600 mOsmol of solute is created by the body every 24 hours and because maximum urine osmolality is approximately 1,200 mOsmol/L, urine output must be at least 300 to 500 mL/d to maintain adequate solute clearance from the body. *Oliguria* is thus defined as urine output $<$400 mL/d and anuria as urine output $<$100 mL/d. The term AKI implies a continuum of injury representing the entire spectrum of acute renal failure. Studies show that even small increases in serum creatinine are associated with an increased mortality (3).

AKI is staged by two commonly accepted criteria: (1) RIFLE (risk, injury, failure, loss, end-stage renal disease), and (2) AKIN (Acute Kidney Injury Network) (4). The RIFLE criteria (Table 118.1) take

into account three graded levels of renal injury (risk, injury, and failure) and two outcome measurements (loss and end-stage renal disease). The AKIN staging system (Table 118.1) differs in some important ways: (1) diagnostic criteria are applied after volume optimization, and (2) urinary obstruction needs to be excluded if oliguria was used as the sole diagnostic criterion (4).

TABLE 118.1
RIFLE and AKIN Classification of AKI

RIFLE			AKIN
Risk	Cr 1.5 × baseline (or increase 0.3 mg/dL AKIN)	UO <0.5 mL/kg/hr for 6 hrs	Stage 1
Injury	Cr 2–3 × baseline	UO <0.5 mL/kg/hr for 12 hrs	Stage 2
Failure	Cr > 3 × baseline	UO <0.3 mL/kg/h for 24 hrs or anuria for 12 hrs	Stage 3
Loss	Complete loss of kidney function >4 wks		
ESRD	Complete loss of kidney function >3 mos		

ESRD, end-stage renal disease; UO, urine output; Cr, serum creatinine; AKIN, Acute Kidney Injury Network.

Renal function is most often measured by determining the clearance of creatinine (C_{cr}), a clinical estimate of the glomerular filtration rate (GFR). Creatinine is released continuously from skeletal muscle as a by-product of the metabolism of muscle and is completely filtered at the glomerulus. Blood creatinine concentration is proportional to muscle mass and inversely proportional to GFR (5). The Cockcroft–Gault formula provides an estimate of creatinine clearance from a single measurement of serum creatinine (S_{cr}) (4):

$$C_{cr}\ (mL/min) = (140 - age)\ (lean\ body\ weight\ in\ kg)/72 \times S_{cr}\ (mg/dL)$$

The result is multiplied by 0.85 in women to correct for approximately 15% less muscle mass in proportion to body weight. These calculated results are accurate only in the steady state. For example, sudden bilateral ureteral obstruction would cause true GFR to fall to zero, but GFR calculated from the previous equation would decline only slowly, as serum creatinine increased at the rate of 1 to 3 mg/dL per day, as expected from ongoing endogenous production. Changes in GFR are eventually reflected by changes in serum creatinine, and small changes in creatinine can indicate a significantly decreased GFR.

AKI can lead to life-threatening complications such as pulmonary edema, hyperkalemia, acidemia, severe hypertension, and uremic pericarditis with effusion or tamponade. The goal of the emergency physician is to recognize and treat these complications and to halt any further decline in renal function by correcting any reversible underlying cause.

CLINICAL PRESENTATION

There are no presenting signs or symptoms that are pathognomonic for AKI. Most often, AKI occurs in the setting of other illnesses (6). Patients may present in critical condition, or asymptomatic azotemia may be discovered on routine blood screening. Some nonspecific symptoms include fatigue, weakness, shortness of breath, and peripheral edema. The diagnosis is thus established only after laboratory studies are performed. Patients rarely present because of oliguria unless it is accompanied by pain from obstruction. However, bladder outlet obstruction may be suggested by complaints of urinary frequency, incontinence, and urgency. Volume overload eventually becomes apparent in oliguric patients, but the severity of symptoms depends significantly on the patient's prior cardiovascular status.

It may be difficult to distinguish clinically between acute and recently identified chronic renal failure. A careful history, as well as laboratory evaluation, can often help (7). Patients with chronic renal failure generally have anemia, hypocalcemia,

hyperphosphatemia, and small kidneys and increased parenchymal echogenicity on ultrasound examination (8).

Uremia refers to the clinical syndrome resulting from the adverse effects of renal failure on other organ systems. These include the cardiovascular (pericarditis with or without effusion), central nervous (somnolence, coma, and seizures), gastrointestinal (nausea, vomiting, and ileus), hematologic (anemia, coagulopathy, and platelet dysfunction), and immunologic (impaired defenses and response to infection) systems (6,9). Only a minority of patients with AKI present with full-blown uremia.

DIFFERENTIAL DIAGNOSIS

AKI is classically divided into three broad etiologic categories (Table 118.2): prerenal failure (inadequate renal perfusion), intrinsic renal failure (disorders of the renal parenchyma), and postrenal failure (obstructive uropathy). Prerenal failure is the most common in both adults and children, followed by acute tubular necrosis (ATN) in adults (6) and the hemolytic uremic syndrome (HUS) in children (10). Other causes of AKI are less frequently seen.

TABLE 118.2
Common Causes of AKI

- Prerenal azotemia (decreased renal perfusion)
- Hypovolemia
  - Hemorrhage
  - Excessive diuresis
  - Vomiting or diarrhea
  - Heat losses
  - Burns
- Decreased cardiac output
  - Myocardial diseases
  - Pulmonary hypertension
  - Congestive heart failure
- Altered systemic vascular resistance
  - Sepsis
  - Cirrhosis
  - General anesthesia
- Impaired renal autoregulation
  - NSAIDs
  - Angiotensin-converting enzyme inhibitors
  - Renal arterial stenosis (atherosclerotic, fibromuscular dysplasia)
- Intrinsic renal insufficiency
- Acute tubular necrosis
  - Ischemic injury secondary to shock, hemorrhage
  - Aminoglycosides
  - Intravenous contrast agents
  - Pigment nephropathy secondary to trauma
  - Ethylene glycol
- Acute interstitial nephritis
  - Drugs (β-lactam antibiotics)
  - Infections (Legionnaire disease, hantavirus)
  - Autoimmune diseases (SLE)
  - Infiltrative process (lymphoma, sarcoidosis)
- Acute glomerulonephritis
- Vascular disease
  - Malignant hypertension
  - Vascular occlusion
- Postrenal occlusion
- Urethral obstruction
  - Prostatic hypertrophy or carcinoma
  - Cervical carcinoma
  - Urethral stricture
  - Bladder stone
- Ureteral obstruction
  - Blood clots
  - Intra-abdominal tumor
  - Bilateral calculi
  - Retroperitoneal fibrosis
  - Retroperitoneal malignancy
  - Neurogenic bladder

NSAID, nonsteroidal anti-inflammatory drug; SLE, systemic lupus erythematosus.

Prerenal failure (azotemia) is characterized by decreased renal perfusion with intact tubular function. Hypoperfusion stimulates tubular reabsorption of sodium and free water and leads to the formation of concentrated urine, with a urinary sodium often <20 mEq/L (9). Because the kidneys are essentially normal, microscopic urinalysis is usually unremarkable (6). Prerenal azotemia is seen in conditions of hypovolemia, decreased cardiac output, and altered systemic or intrarenal vascular resistance. Nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors are increasingly common causes of prerenal azotemia, especially in the elderly, who are predisposed to this condition by decreased renal function and a high incidence of coexisting disease (11). If the underlying hemodynamic disorder can be corrected, prerenal failure is, by definition, reversible.

Intrinsic renal failure may be divided into disorders affecting the glomeruli (e.g., acute glomerulonephritis), the renal interstitium (e.g., acute interstitial nephritis [AIN]), the renal vasculature (e.g., malignant hypertension), or the tubules (e.g., ATN) (6).

ATN accounts for up to 85% of intrinsic renal failure in adults (6). It is frequently self-limited and often reversible. Etiologies include ischemic insults to the kidney (e.g., shock and hemorrhage), administration of drugs (e.g., aminoglycosides and intravenous contrast agents), and pigment nephropathy (e.g., myoglobinuria occurring secondary to limb ischemia, cocaine use, hyperthermia, or crush injuries). In ATN, the tubules lose the ability to concentrate urine and to reabsorb sodium. The urine tends to have a specific gravity similar to that of serum (1.010, isosthenuria), and the urinary sodium concentration tends to be >40 mEq/L (6). On microscopic urinalysis, granular casts and tubular epithelial cells are noted in about 80% of patients (9). ATN may be either oliguric or nonoliguric, the nonoliguric variety having a better prognosis (6).

ATN due to the administration of iodinated radiocontrast agents (contrast-induced nerphropathy [CIN]) usually occurs within the first 48 hours after the contrast study and is usually reversible. Its

reported incidence varies from zero to more than 50%, depending on risk factors (11). Important risk factors include diabetes, preexisting renal insufficiency (Cr > 1.5), age older than 60, volume depletion, multiple myeloma, and higher doses of contrast (as, e.g., with percutaneous coronary intervention) (11). Renal vasoconstriction, with a consequent decrease in medullary blood flow, and direct cytotoxic effects of contrast are the presumed pathogenesis (12). Strategies to prevent this complication center around IV hydration with isotonic saline. Sodium bicarbonate (13) and N-acetylcysteine have not consistently shown benefit and their use remains controversial (2). IV fluid hydration with isotonic fluids started prior to the contrast procedure has a more favorable impact on serum creatinine at 24 hours than hydration started after the procedure (2,14).

Attempting to avoid iodinated contrast in patients with AKI, some physicians turn to magnetic resonance imaging (MRI) for imaging. However, MRI with gadolinium should not be utilized in patients with AKI or with moderate-to-severe chronic kidney disease due to the risk of nephrogenic systemic fibrosis (NSF) (4). NSF is a rare but very serious condition that involves fibrosis of skin, joints, eyes, and internal organs.

New biomarkers (urinary interleukin-18 [IL-18], neutrophil gelatinase-associated lipocalin [NGAL], and kidney injury molecule 1 [KIM-1]) show promise in helping discriminate between prerenal azotemia and ATN (15). This information can help physicians in the future determine which patients with AKI are most likely to progress to chronic kidney disease (15,16).

AIN accounts for about 10% of intrinsic renal failure in adults (6). It is usually caused by a drug hypersensitivity reaction but can also result from infection, immune-mediated disease, or other causes (17). Many drugs have been implicated in AIN, including β-lactam antibiotics, sulfonamide drugs, and NSAIDs (17). Patients with AIN may present with fever, rash, arthralgias, eosinophilia, and eosinophiluria (the latter detectable by Hansel stain of the urine). However, these findings are frequently absent, making differentiation of AIN from other causes of AKI difficult (17).

Postrenal azotemia results from obstruction of the renal collecting system at the level of the ureters, bladder, or urethra. For renal failure to develop, ureteral obstruction must be bilateral (except in patients with a single functioning kidney). Among the common causes of obstruction are prostatic hypertrophy or carcinoma, cervical carcinoma, neurogenic bladder, and urethral stricture. Ureteral obstruction may also occur as a result of blood clots, tumors, calculi, retroperitoneal fibrosis, or malignancy (18). It is important to note that patients with obstructive, postrenal failure may present with anuria, oliguria, or normal urinary output. Because the renal parenchyma is unaffected, microscopic urinalysis may reveal hematuria but is otherwise essentially normal.

ED EVALUATION

The emergency department (ED) evaluation of the patient with ARF requires a two-step approach. First, the physician should immediately determine whether life-threatening complications exist and second, attempt to determine the cause of AKI so that potentially reversible causes can be corrected.

A detailed history should be obtained, including recent exposure to new medications (especially diuretics, NSAIDs, and ACE inhibitors), intravenous contrast material, chemicals, animal venoms, unusual plants or foods, or illicit drugs (6). A history of recent hospitalization, surgery, or other intercurrent illness that might be associated with renal hypoperfusion (e.g., cirrhosis, aortic or vascular disease, or congestive heart failure) should also be sought. A history of malignancy is especially important, as these patients are at risk of AKI from obstruction, radiation nephritis, or chemotherapy. Urinary retention in conjunction with back pain or neurologic symptoms should prompt immediate evaluation for spinal cord compression. Bone pain in the elderly should suggest multiple myeloma. Recent onset of paroxysmal nocturnal dyspnea or orthopnea may suggest volume overload.

Physical examination should begin with an assessment of volume status. Hypertension, rales, peripheral edema, or jugular venous

distention suggest fluid overload. Resting tachycardia, orthostatic hypotension, dry mucous membranes, or poor skin turgor point to hypovolemia. Signs of uremia should be sought, including asterixis, alteration in mental status, and pericardial friction rub. Skin examination may reveal a generalized rash in AIN, livedo reticularis in atheroembolic renal failure, or palpable purpura with vasculitis.

After immediately life-threatening complications are ruled out, the patient should be evaluated for evidence of urinary tract obstruction. A prostate examination in men and a pelvic examination in women are mandatory. Percussion of the suprapubic area, or bedside ED ultrasonography, may reveal an enlarged bladder. Costovertebral angle tenderness may suggest ureteral obstruction. A Foley catheter should be passed after the patient attempts to void to exclude bladder outlet obstruction and to monitor urine output, even in patients without oliguria.

Laboratory analysis should include a complete blood count, electrolytes, glucose, calcium, phosphorus, blood urea nitrogen (BUN), and creatinine. The urine should be sent for microscopic analysis and determination of specific gravity, osmolality, and sodium and creatinine concentrations. Urine specific gravity, rapidly available in the ED, is a reasonable estimate of urine osmolarity, except when solutes such as glucose or radiocontrast media are present. The detection of blood on urine dipstick may actually indicate the presence of myoglobin, and a serum myoglobin or serum creatine kinase should be ordered in cases in which rhabdomyolysis is suspected. Anemia and thrombocytopenia may suggest thrombotic thrombocytopenic purpura or HUS. A pregnancy test should be done in women of childbearing age because of the unusual but important causes of AKI that are associated with pregnancy, including preeclampsia and septic abortion (2), and because radiography may be used during the evaluation. A chest radiograph aids in the determination of volume status. An electrocardiogram (ECG) should be performed to evaluate for hyperkalemia. An arterial blood gas analysis may be helpful especially if acidosis, reflected in a low serum bicarbonate, is severe.

If bladder catheterization does not reveal evidence of distal obstruction and another etiology for AKI is not readily apparent, attention must be directed at ruling out bilateral ureteral obstruction. Renal ultrasound can detect hydronephrosis with a sensitivity of 98% to 99% and a specificity of 75% to 80% (13). Despite this high sensitivity, nondilated obstructive uropathy can occur early after obstruction in cases resulting from malignancy or retroperitoneal fibrosis and in patients who are severely dehydrated (9). Noncontrast computed tomography of the renal collecting system may be helpful if ultrasonography is inconclusive or if the etiology of the obstruction is unclear (19). MRI may also be used to assess for obstruction and hydronephrosis, with the additional benefit of visualizing abnormalities of the renal arteries and veins (20).

If obstruction is not the cause of AKI, urinary electrolytes should be evaluated to determine whether renal failure is prerenal or renal (7). As previously noted, urinary sodium is frequently <20 mEq/L in prerenal azotemia (9), whereas in intrinsic renal failure, tubular reabsorption of sodium is compromised, and the urinary sodium concentration often exceeds 40 mEq/L (6). In addition, in prerenal failure, enhanced sodium and water reabsorption results in increased passive reabsorption of urea, elevating the BUN out of proportion to the serum creatinine. Hence, a BUN–creatinine ratio >20:1 suggests prerenal azotemia. The most accurate index for differentiating between prerenal and renal failure is the fractional excretion of sodium (FE_{Na}) (7), which measures the percentage of sodium presented to the renal tubules that is not reabsorbed:

$$FE_{Na} = [U_{Na}/P_{Na}]/[U_{cr}/P_{cr}]$$

In prerenal azotemia, the FE_{Na} is usually much less than 1%, whereas in intrinsic causes such as ATN or AIN it is often elevated above 3%. Urinary sodium and FE_{Na} are increased in patients who have received diuretics.

Microscopic urinalysis provides further information (6). In prerenal azotemia, the urinalysis is unremarkable; occasional hyaline casts may be all that is noted. With intrinsic renal causes of AKI, one can expect to see a more "active sediment." In ATN, the urine contains granular casts and tubular epithelial cells, individually or in casts (9). In AIN, there is often eosinophiluria and white blood cell casts. Patients with acute glomerulonephritis often have dysmorphic red blood cells and red cell casts (6). Table 118.3 lists laboratory features useful in distinguishing between prerenal azotemia and ATN.

TABLE 118.3
Distinguishing Between Prerenal Azotemia and Acute Tubular Necrosis

	Prerenal Azotemia	Acute Tubular Necrosis
BUN–creatinine ratio	>20:1	<20:1
Urinary sodium	<20 mEq/L	>40 mEq/L
Urinary osmolarity	>500	<350
Urine specific gravity	>1.020	<1.010
FE_{Na}	<1%	>2%
Urinalysis	Normal sediment or hyaline casts	Granular casts, tubular epithelial cells

BUN, blood urea nitrogen; FE_{Na}, fractional excretion of sodium.

KEY TESTING

- Urinalysis
- Electrolytes, BUN, creatinine
- Renal ultrasound is a useful initial imaging study in newly diagnosed AKI

ED MANAGEMENT

Volume overload and hyperkalemia are the most common causes of early death in AKI patients. Fluid overload is best avoided by accurate initial assessment of volume status, judicious

administration of fluids, and constant reassessment of oliguric or anuric patients. Patients who present in pulmonary edema benefit from traditional therapies (i.e., oxygen, nitrates, diuretics, and CPAP) until hemodialysis is available (21).

Hyperkalemia is a life-threatening emergency that may manifest abruptly in AKI, particularly in patients whose renal failure is caused by rhabdomyolysis. The management of hyperkalemia is discussed in Chapter 211.

Hypertension requiring immediate treatment may be managed with intravenous nitrates or sodium nitroprusside (1). The latter agent should be used for only relatively brief periods in patients with renal failure, owing to the risk of thiocyanate toxicity. Other medications with a relatively rapid onset of action include labetalol, β-blockers, α_2-agonists, and calcium-channel blockers (1).

Once potentially life-threatening complications of renal failure have been addressed, the next priority is to identify the cause of renal dysfunction and to reverse it, if possible. If the etiology appears to be postrenal, prompt relief of the obstruction can prevent further renal injury. Bladder outlet obstruction is almost always relieved by passage of a Foley catheter. Clamping the Foley catheter when large volumes of urine are released from the bladder, once a common practice, is unnecessary, even if the patient develops gross hematuria (18). If obstruction persists after bladder catheterization or if a Foley catheter cannot be placed, urologic imaging and consultation are indicated.

If the cause of renal insufficiency appears to be prerenal, intravascular volume should be replenished with intravenous crystalloid or blood. If prerenal azotemia occurs in the face of normal or increased total body sodium (e.g., congestive heart failure), efforts must be made to correct the underlying disorder to improve renal perfusion. Invasive monitoring may be necessary to monitor volume status.

The efficacy of diuretics and dopamine in oliguric patients with AKI is the subject of controversy (1,6,9,22). There are no data to support the routine use of dopamine (which can cause

tachydysrhythmias, cardiac ischemia, and digital and gut necrosis) in patients with adequate cardiac output (1,6,22). The routine use of diuretics in the initial care of AKI patients poses a number of risks. Administering a diuretic to a patient who is already volume-contracted may precipitate ischemic ATN, and administering a diuretic to a patient with obstructive uropathy might increase hydrostatic damage to the kidneys. Administering mannitol to an anuric patient can cause intravascular volume expansion and pulmonary edema. For patients with myoglobinuric renal failure, however, mannitol is recommended, in combination with volume replacement and sodium bicarbonate (23).

A number of life-threatening emergencies associated with AKI may require emergent dialysis. Nevertheless, treatments or temporizing measures are available for each and should be instituted while arrangements are made for dialysis or transfer. The indications for acute dialysis can be remembered using the mnemonic AEIOU: *a*cidosis, *e*lectrolyte abnormalities (hyperkalemia), *i*ngestions (ethylene glycol, methanol, lithium, theophylline, salicylate), volume *o*verload, and *u*remia. Central venous access with a large-bore catheter is required for hemodialysis. Should emergent dialysis be necessary, direct consultation with a nephrologist is essential to coordinate timely intervention.

CRITICAL INTERVENTIONS

- Insert a urinary catheter to both diagnose and relieve bladder outlet obstruction.
- Quickly identify and treat patients with hyperkalemia or pulmonary edema.
- Arrange emergent dialysis for those with serious complications (severe acidosis, hyperkalemia, or volume overload).

DISPOSITION

Most patients presenting to the ED with AKI should be admitted to the hospital for further evaluation and treatment. If the etiology is

clearly postrenal, consultation with urology is mandatory, as emergent surgical decompression may be indicated. For metabolic or uremic complications of renal failure, whether acute or chronic, nephrology consultation in the ED is prudent.

Nonazotemic patients with acute urinary outflow tract obstruction corrected by bladder catheterization can, in many cases, be discharged with an indwelling catheter. In these cases, urine should be cultured and close urologic follow-up arranged.

Transfer to a tertiary care facility should be considered for any patient with renal failure if dialysis is not available at the primary facility. In rare cases, the patient must be transferred to an out-of-hospital dialysis unit. In these cases, the emergency physician must ensure that the accepting physician will be immediately available upon the patient's arrival. All available and appropriate treatment modalities should be instituted before transfer, and the patient should be transported by an advanced life support unit.

Common Pitfalls

Forgetting the simple things: a prostate examination in men and a pelvic examination in women, and insertion of a Foley catheter to rule out bladder outlet obstruction.

- Failing to recognize and promptly initiate therapy for life-threatening complications, most of which can be treated before emergency dialysis is initiated. An ECG should be obtained if hyperkalemia is suspected.
- Failing to assess volume status adequately; fluid replacement may be all that is necessary to reverse prerenal azotemia.
- Delaying appropriate transfer to a center where dialysis can be performed

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CHAPTER 119

Chronic Kidney Disease and Dialysis-Related Emergencies

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Although patients with *acute* kidney injury (AKI) have a relatively rapid loss of renal function and tend to develop clinical manifestations requiring prompt attention, patients with *chronic* renal disease have usually experienced a slow decrease in renal function over a period of months to years. They commonly present to the emergency department (ED) with subacute or chronic symptoms, often of a progressive nature, or with acute problems resulting from a superimposed illness or stress.

Standard terminology for this condition has changed over the past 10 years (1). *Chronic kidney disease* (CKD) is defined as kidney damage or decreased kidney function for 3 months or more. It is characterized by irreversible nephron loss and scarring. The term *chronic renal insufficiency,* denoting a condition in which renal function has been reduced to a moderate degree but not enough to require renal replacement therapy, has been replaced by this term (CKD) and a specification of the degree of decrease of the glomerular filtration rate (GFR) (CKD stages 1 to 5) (1). *Kidney failure,* also called *end-stage renal disease,* denotes a chronic condition in which the GFR is decreased to a low level at which clinical symptoms begin to be prominent; serious, life-threatening manifestations can be expected to develop in the absence of dialysis treatments or renal transplantation.

The causes of CKD are numerous and, as with acute renal failure, they can be classified as prerenal (vascular), intrinsic renal (glomerular and tubulointerstitial), and postrenal (obstructive) (Table 119.1). In the United States, about one-half of CKD is caused by glomerular disease, with diabetic nephropathy accounting for the largest single group. Hypertensive nephrosclerosis is another major cause, particularly among blacks. The history, physical examination, and laboratory and imaging studies may provide clues to other specific etiologies. Determining the exact etiology of CKD can allow the underlying cause to be treated and thereby slow the progression of kidney disease in some cases.

TABLE 119.1
Major Causes of Chronic Kidney Disease

Vascular	**Tubulointerstitial**
Renal arterial disease	Nephrotoxins
Hypertensive nephrosclerosis	Analgesic nephropathy
Glomerular	Hypercalcemia/nephrocalcinosis
Primary glomerulopathies	Multiple myeloma
Focal sclerosing glomerulonephritis	Sickle nephropathy
Membranoproliferative glomerulonephritis	Reflux nephropathy
Membranous glomerulonephritis	**Obstructive**
Crescentic glomerulonephritis	Nephrolithiasis
IgA nephropathy	Reflux nephropathy
Secondary glomerulopathies	Retroperitoneal fibrosis
Diabetic nephropathy	Retroperitoneal tumor
Collagen vascular disease	Prostatic obstruction
Amyloidosis	Congenital
Postinfectious	**Hereditary**
HIV nephropathy	Polycystic kidney disease
	Alport syndrome
	Medullary cystic disease

poorly defined substances appear to be responsible for many of the clinical manifestations of uremia.

Progressive loss of renal function eventually results in the syndrome of *uremia.* Uremia is associated with derangements in homeostasis and metabolism and results in specific defects in multiple organ systems (Table 119.2). Many of these manifestations are corrected or relieved by dialysis, but others are not. All tend to develop gradually in patients with CKD, although some may present acutely.

TABLE 119.2
Major Manifestations of Uremia

Derangements of Homeostasis
Sodium balance
Water balance
Hyperkalemia
Metabolic acidosis
Hypocalcemia
Hyperphosphatemia
Hypermagnesemia
Derangements of Metabolism
Azotemia
Decreased glucose tolerance
Hyperlipidemia
Specific Organ System Effects
Cardiovascular
Hypertension, volume overload, pericarditis
Pulmonary
Pulmonary edema, pleuritis
Neurologic
Lethargy, difficulty concentrating, altered mental status, seizures, myoclonic twitching, asterixis, hiccups, cramps, peripheral neuropathy
Gastrointestinal
Anorexia, nausea, vomiting, gastrointestinal ulceration, pancreatitis
Musculoskeletal
Secondary hyperparathyroidism, renal osteodystrophy, crystal-induced arthritis, myopathy, spontaneous tendon rupture, carpal tunnel syndrome
Hematologic
Anemia, altered immunity, qualitative platelet abnormality

Clinical manifestations are not always evident even when the GFR has decreased to approximately 25% of normal, especially in younger patients. Although laboratory abnormalities may be impressive, the remaining functioning nephrons may be able to compensate reasonably well. Beyond a certain point, however, significant amounts of metabolic by-products are retained. These poorly defined substances appear to be responsible for many of the clinical manifestations of uremia.

APPROACH TO THE PATIENT

Patients with untreated CKD most commonly present to the ED with nonspecific complaints such as generalized weakness, poor appetite, or increasing confusion. These are typically of insidious onset. The first clue to the diagnosis may be a laboratory finding of a reasonably well tolerated but rather severe anemia. Elevated blood urea nitrogen and serum creatinine levels can then confirm the diagnosis.

Once it has been ascertained that the patient is in no immediate danger (e.g., from life-threatening hyperkalemia), the next step is to establish the cause of renal dysfunction, determine whether it is chronic or acute, and identify any correctable cause such as volume depletion or obstruction (Table 119.3). A finding of bilaterally small kidneys on plain radiography or ultrasonography is good evidence for chronic disease, although the presence of normal-sized or large kidneys does not rule out CKD. A history of familial kidney disease, such as polycystic kidney disease or Alport syndrome, may also be helpful.

TABLE 119.3
Reversible Factors and Treatable Causes of Chronic Kidney Disease

Reversible Factors	Treatable Causes
Hypovolemia	Renal artery stenosis
Congestive heart failure	Malignant hypertension
Pericardial tamponade	Acute interstitial nephritis
Severe hypertension	Hypercalcemic nephropathy
Catabolic state/protein loads	Multiple myeloma
Nephrotoxic agents	Vasculitis (e.g., systemic lupus erythematosus, Wegener granulomatosis, periarteritis nodosa)
Obstructive disease	Obstructive nephropathy
Reflux disease	Reflux nephropathy

Laboratory abnormalities such as anemia, acidosis, hyperkalemia, hypocalcemia, and hyperphosphatemia can occur with *acute* renal failure as early as 10 days after its onset, but they tend to be better tolerated in patients with chronic renal disease. Findings on urinalysis are usually not helpful.

DIALYSIS

Patients with CKD are often sustained on chronic hemodialysis or peritoneal dialysis (PD). Nevertheless, they are subject to those complications of CKD that are not corrected by dialysis, to the manifestations of underlying systemic diseases, and to complications of the dialytic therapy itself (2–4).

There is a significant potential for iatrogenic illness owing to inappropriate fluid or drug administration. Even apparently innocuous agents, such as antacids and enemas, can cause serious problems. Physicians caring for patients with CKD should thus have ready access to a reference compendium containing guidelines for the adjustment of drug dosages in renal failure (5).

Several serious problems are commonly encountered both in dialysis patients and in those with CKD who have not yet undergone dialytic therapy, and the approach is similar in the two patient groups. The two major dialysis modalities, hemodialysis and PD, are themselves associated with specific complications with which the emergency physician should be familiar (6,7).

HEMODIALYSIS

In hemodialysis, the patient's heparinized blood passes through an extracorporeal dialyzer circuit in which it is in contact with an artificial dialysis membrane across which water and solutes from the blood diffuse. The high blood-flow rates that are necessary to make hemodialysis an efficient process necessitate special access to the patient's circulation, generally through a surgically created arteriovenous fistula or through an artificial vascular graft, both of which are usually placed in the arm, or a surgically placed tunneled catheter.

The vascular access must be treated with care to avoid causing thrombosis or bleeding or introducing infection. The blood pressure should never be taken in the involved arm, and a tourniquet should never be applied. One should avoid drawing blood from the access or placing an intravenous line in it, unless absolutely essential. Even in this case, a hemodialysis nurse should be called to access these sites whenever possible. Careful skin cleansing and sterile technique are mandatory, and firm but nonocclusive pressure should be applied to the site for 10 minutes after the puncture. The presence of a thrill both before and after the procedure should be documented.

If intravenous access is critical but otherwise impossible, an intravenous line may be placed in the access, with an automated infusion pump used to control the infusion rate.

Hemodialysis patients may present to the ED with a variety of complaints relating to the vascular access. Hemorrhage from a recent puncture site is usually easily managed with continuous, firm, but nonocclusive pressure over the site. Thrombosis, signaled by the loss of the thrill in the access, requires consultation with a vascular surgeon, who may elect to perform a radiocontrast fistulogram to infuse a thrombolytic agent, or to revise the access surgically. Forceful attempts to flush the access are inadvisable.

The most common access-related problem is access infection, which is a serious concern because of the associated risk of bacteremia and metastatic infection. Moreover, there is the risk that

the access may have to be removed because of persistent infection or poor flow.

Most access infections are staphylococcal; contamination with skin flora at the time of puncture is the most likely cause. The diagnosis of access infection is not always obvious. When there is warmth, redness, tenderness, or local induration over the area and the patient is febrile, there is little cause for confusion, but some patients lack local signs and may present with repeated episodes of bacteremia, or with fever and no obvious source of infection. In this situation, one should suspect access infection, draw blood cultures, and begin antibiotic therapy promptly.

A commonly used regimen is vancomycin 15 to 20 mg/kg given intravenously as a single loading dose. Vancomycin is minimally dialyzable and generally needs to be given only once every 4 to 7 days, making it an attractive choice for staphylococcal coverage. A third-generation cephalosporin or an aminoglycoside can be added for coverage of suspected gram-negative organism infection. Emergency physicians should be familiar with the regimens in common use in their own institutions.

Not all febrile dialysis patients need to be admitted to the hospital. After intravenous antibiotic loading, a reliable patient who otherwise feels and looks relatively well may be sent home with careful instructions to return if there is any clinical deterioration. This decision is best reached in conjunction with the consulting nephrologist.

PERITONEAL DIALYSIS

In PD, the patient's own peritoneum serves as the membrane across which diffusion of water and solutes occurs. Sterile dialysis fluid is infused into the peritoneal cavity through a surgically implanted Tenckhoff catheter. Osmotic forces generated by high concentrations of glucose in the dialysis fluid ensure adequate removal of fluid volume from the blood; this is in contrast to hemodialysis, in which the amount of fluid removed is controlled by adjusting the pressure gradient across the dialyzer membrane. PD offers several theoretical

advantages over hemodialysis: greater patient independence, smoother control of excess volume and hypertension, and avoidance of rapid solute shifts and intermittent anticoagulation.

As with hemodialysis, many of the emergency problems encountered by the patient on PD are related to access devices, in this case the peritoneal catheter. By far the most common problem is peritonitis, caused by inadvertent contamination of the peritoneal cavity when fluid exchanges are performed or by direct invasion of organisms from an infected catheter exit site. Peritonitis in these patients is as a rule less severe than other types of peritonitis. In fact, many of these infections can be treated on an outpatient basis, despite the fact that they involve the presence of a foreign body. If infection cannot be eradicated with antibiotic therapy, the catheter must be removed surgically, and the patient must be sustained on hemodialysis until placement of a new catheter once the infection has cleared.

About 60% of episodes of peritonitis are caused by gram-positive organisms, predominantly staphylococci. In most of the remainder, assorted gram-negative organisms are responsible. A small percentage is caused by fungal infection, which is usually considered an indication for catheter removal. Polymicrobial infection suggests a communication with the bowel or genitourinary tract. Approximately 15% of episodes of peritonitis are culture-negative.

The diagnosis of peritonitis is usually based on the patient's observation of cloudiness in the dialysate effluent at the time an exchange is performed. This is generally the earliest sign of peritonitis, and therefore patients are instructed to seek medical attention immediately when they notice it. Abdominal pain and fever often develop if treatment is not initiated promptly.

In the ED, the diagnosis of peritonitis is confirmed by the finding of organisms on Gram stain of the peritoneal fluid or a cell count of more than 100 white blood cells per microliter (with $>50\%$ neutrophils). This cell count corresponds approximately to the level at which cloudiness begins to be grossly detectable. The fluid is obtained using meticulous sterile technique, preferably by a dialysis

nurse when possible; a sample is also sent for culture (using blood culture bottles to increase the yield). Even in patients without cloudiness of the peritoneal effluent but who have fever, abdominal pain, or vague malaise, it is advisable to obtain a sample of fluid for examination, as the presentation of peritonitis can initially be subtle.

PD-related peritonitis can usually be treated on an outpatient basis (8,9). Treatment decisions should be made in conjunction with the patient's nephrologist or the PD nurse specialist, because these individuals are usually aware of the patient's overall medical condition, the types of infection recently experienced, and any psychosocial considerations that might affect outpatient management. Hospital admission is necessary if there is high fever, hypotension, severe abdominal pain, or nausea and vomiting or if the patient cannot continue to carry out exchanges at home.

A common empiric treatment regimen is vancomycin 15 to 30 mg/kg intraperitoneally (IP) plus ceftazidime or cefepime 1 g IP (or alternatively gentamicin) at the time of diagnosis. Further antibiotic treatment is based upon Gram stain and culture results. Additional vancomycin dosing is generally not required for 4 to 7 days, whereas the initial loading dose of ceftazidime, cefepime, or gentamicin is typically followed by a once-daily intraperitoneal maintenance dose. All antibiotics should be allowed to dwell IP for at least 6 hours. Heparin 500 to 1,000 U may be added to each bag for the first few days of treatment in an effort to decrease the risk of fibrin obstructing the catheter. Adequate analgesia should be provided as well, and arrangements should be made for the patient to be seen in 1 to 2 days to make sure the infection is responding to treatment and to check culture results and adjust therapy accordingly. Again, emergency physicians should be familiar with the regimens in common use in their own institutions.

There are several important caveats regarding the diagnosis of peritonitis. A similar clinical picture can be presented by other acute abdominal processes such as pancreatitis, diverticulitis, or ruptured viscus. To confuse the picture further, the finding of intra-abdominal free air on radiographs is often the result of its inadvertent

introduction during dialysis exchanges and does not necessarily indicate perforation (10). The finding of brownish or fecal material in the dialysate, however, mandates immediate surgical consultation.

Several other problems related to the peritoneal dialysis procedure occasionally bring the PD patient to the ED. An exit site infection or an infection of the subcutaneous catheter tunnel may present as tenderness, warmth, or induration or simply as a painless purulent exudate. Any exudate should be Gram-stained and cultured. Treatment can be started with an oral antibiotic active against skin flora, but intensive local cleansing and skin care are also a critical part of management. Closed infections of the subcutaneous tunnel may be difficult to appreciate and they respond poorly to medical therapy unless they are drained. If the patient should develop a leak of dialysis fluid from the tubing, bag, or catheter, or from around the catheter, evaluation and treatment should proceed as with peritonitis. The leaking elements must be replaced, if possible. A switch to low-volume exchanges may be helpful for leaks around the catheter, but surgical intervention may be necessary.

Difficulties with inflow or outflow of the dialysis fluid also occur occasionally. After ruling out straightforward problems such as kinked tubing or a closed clamp, the physician must consider more troublesome mechanical causes, including malposition of the catheter or obstruction of the catheter lumen; in the latter case, surgical or nephrology consultation is necessary. A common cause of poor inflow or outflow is constipation. Catheter position is usually evaluated with plain abdominal x-rays, and a contrast catheterogram may help to direct specific intervention.

CLINICAL PRESENTATION

Infection

Infections are a major cause of death in dialysis patients, and vascular access infection and peritonitis are the most common infections in hemodialysis patients and patients with PD,

respectively (6,7). Most infections are caused by the usual pathogens rather than by opportunistic organisms. The challenge for the clinician arises from the fact that classic findings may not be obvious.

Dialysis patients commonly do not present with high fever in response to infection. Rather, they are likely to have nonspecific complaints such as fatigue, malaise, decreased appetite, or generalized weakness. Some manifestations of infections may be attributed to CKD per se, to the effects of dialysis, or to other underlying medical illness. For instance, pneumonia may present as dyspnea alone, which is easily attributed to volume overload or to the effects of chronic anemia. Urinary tract infection can occur even in patients who are essentially anuric (11); upper urinary tract infection, presenting as renal colic or with symptoms typical of pyelonephritis, is most common in patients with polycystic kidney disease. These and other infections are generally treated as in any other patient, but antibiotic doses must be adjusted for CKD and the type of dialysis being used.

Hypotension

Hypotension commonly occurs in hemodialysis patients during or immediately after the dialysis procedure, but it often resolves spontaneously or responds readily to fluid infusion. It is usually the result of rapid fluid and electrolyte shifts. Patients with PD are not subject to this cause of hypotension, but they too can become volume depleted if intake does not keep up with fluid losses that occur through dialysis. Other potentially lethal causes of hypotension must also be considered; sepsis, drug effects, myocardial dysfunction, dysrhythmia, myocardial infarction, and pericardial tamponade are important considerations in patients treated by either dialysis modality. Acute electrolyte disturbances, vascular instability, anaphylactoid reaction, and air embolism are considerations primarily in hemodialysis patients.

Pericardial tamponade may develop acutely when there is bleeding into the pericardial sac or when volume depletion allows a

previously subclinical effusion to compromise cardiac filling. Tamponade in this setting generally presents with the expected physical findings, but coexisting cardiac or pulmonary disease may make the diagnosis difficult. The size of an effusion does not correlate well with the presence of tamponade. Echocardiography is useful in detecting pericardial fluid, however, and in demonstrating right ventricular collapse, which is the best indicator of tamponade. Emergency pericardiocentesis may be necessary if the patient's condition deteriorates rapidly and tamponade is thought likely; it can establish the diagnosis and buy time until definitive surgical therapy can be undertaken. Another temporizing measure, which is useful when tamponade has been precipitated by volume depletion, is intravenous saline infusion to raise filling pressures.

Dyspnea and Volume Overload

Dyspnea in the dialysis patient is most commonly caused by volume overload. In the hemodialysis patient, it usually develops during the interval between dialyses. Physical examination is not always reliable in detecting volume overload in these patients, and even chest radiographic findings may be misleading (12). The most reliable clue is a history of recent weight gain.

The definitive treatment of volume overload is dialysis, but several temporizing measures are available (Table 119.4) (13). Oxygen should be administered and the patient kept in the sitting position. Sublingual nitroglycerin can be administered quickly, does not require intravenous access, and often provides very rapid relief by reducing preload and afterload. Obviously, it should not be used if the patient is hypotensive. Intravenous nitroglycerin is an additional useful option and can be titrated to blood pressure and clinical effect.

TABLE 119.4
Treatment of Pulmonary Edema in Renal Failure

Dialysis
- Hemodialysis
- Hemofiltration
- Peritoneal dialysis

Oxygen
Nitroglycerin (sublingual or intravenous)
Intravenous opioids (but may increase the need for intubation)
Loop diuretics (if there is residual renal function)

Intravenous opioids such as hydromorphone can be given acutely, as in nondialysis patients, but may increase the need for intubation. Intravenous furosemide has a minimal diuretic effect in most dialysis patients, unless they retain significant residual renal function. Finally, the use of continuous positive airway pressure devices may make it possible to avoid intubation in some patients who would otherwise require it.

Although volume overload is the most likely cause of shortness of breath in the dialysis patient, dyspnea can also be the result of cardiac impairment of any cause, hypotension, infection, pleural or pericardial effusion, or any of the other causes of dyspnea in nondialysis patients.

Another potentially adverse effect of volume overload is severe hypertension, because blood pressure is often volume-dependent in dialysis patients. For hypertensive crisis (i.e., hypertension, usually severe, with evidence of acute end-organ dysfunction), therapy should include not only intravenous nicardipine or labetalol, but also prompt initiation or intensification of dialysis to lower blood volume.

Chest Pain

Chest pain in a dialysis patient should always suggest coronary artery disease. The leading cause of death in dialysis patients is cardiovascular disease (14,15). CKD itself appears to be a risk factor (16–19), and most patients have other risk factors such as hypertension, hyperlipidemia, and carbohydrate intolerance. Added to this are the effects of chronic anemia, intermittent or chronic

volume overload, and calcium and phosphorus disturbances. The hemodialysis procedure itself is often the occasion for additional ischemic stress to the myocardium because of transient hypoxemia and hypotension.

Initial interventions for suspected ischemic chest pain are similar to those for other patients, but particular attention should be directed toward such correctable factors as volume overload, hypertension, and anemia. The diagnosis of myocardial infarction by standard electrocardiographic (ECG) and enzyme criteria is generally not affected by the abnormalities of kidney failure (20,21). Although baseline cardiac enzyme levels may be somewhat higher than in the nondialysis population, when infarction occurs the pattern of enzyme changes is not affected. Troponin appears to be the most reliable serum marker of infarction in these patients (20–23). Decisions as to the most appropriate reperfusion therapy for dialysis patients with acute coronary syndromes should be made in concert with a cardiologist and the patient's nephrologist.

Chest pain may, of course, result from any of the other commonly incriminated causes, but in dialysis patients pericarditis should always be a consideration once myocardial ischemia has been excluded. Pericarditis (and tamponade) may occur even in well-dialyzed patients. The signs and symptoms are the same as those noted in nondialysis patients. Based on experience in undialyzed uremic patients, it has traditionally been taught that increased or intensified dialysis, without heparin anticoagulation, hastens resolution of pericarditis or prevents the development of tamponade or pericardial constriction. This remains an open question, however. For many patients with pericarditis, indomethacin can provide prompt pain relief. For others, intrapericardial instillation of corticosteroids, or pericardial stripping, is ultimately necessary.

Bleeding

Bleeding is relatively common in dialysis patients. It is at least in part related to platelet dysfunction (which is not completely corrected by dialysis) and, in hemodialysis patients, to transient

anticoagulation. It is important to ascertain the patient's usual or baseline hemoglobin level. Epoetin or darbepoetin are now administered routinely to almost all dialysis patients, but in untreated patients, the baseline hemoglobin level may be 6 to 7 g/dL. Moderately severe anemia may present with increased angina or dyspnea. Other symptoms, sometimes life-threatening ones, may be caused by occult bleeding into particular anatomic sites. Spontaneous intracranial, intraocular, pericardial, and retroperitoneal bleeding have been reported.

Treatment of acute bleeding episodes follows standard principles. Because correction of severe anemia (hematocrit $<25\%$) improves bleeding time (probably by a rheologic effect), red blood cell transfusion should be considered, and additional acute treatment with desmopressin (0.3 μg/kg intravenously or subcutaneously) or conjugated estrogens (0.6 mg/kg intravenously) should be begun. For life-threatening bleeding, cryoprecipitate infusion and platelet transfusions are recommended (6).

Neurologic Dysfunction

Neurologic dysfunction in the form of *disequilibrium syndrome* can occur during and just after the hemodialysis procedure, although usually only in patients with high blood urea nitrogen who are just initiating dialytic therapy. Typical mild manifestations are headache, nausea, and muscle cramps, whereas more severe cases may cause altered mental status and grand mal seizures. Disequilibrium is presumed to be caused by the rapid changes in intracellular composition and osmolality that occur with the removal of large volumes of fluid or the rapid correction of marked metabolic and electrolyte abnormalities. It usually resolves within a few hours after the hemodialysis treatment is completed. During dialysis, symptoms often respond promptly to intravenous infusion of mannitol or hypertonic saline. The syndrome does not occur with PD.

Because there are many other potential causes for neurologic dysfunction in these patients, however, it is unwise to attribute any

acute neurologic abnormality to the disequilibrium syndrome without carefully considering other causes, including intracranial hemorrhage, hypertensive encephalopathy, infection, and untoward drug effects. If findings are focal, appear suddenly, or fluctuate or become worse after a reasonable period of observation, attention should be directed to all of the other potential causes. Similarly, the presence of fever, papilledema, or severe hypertension should suggest more serious etiologies.

Electrolyte Abnormalities

Hyperkalemia is a common life-threatening emergency in undialyzed patients with AKI or CKD. It is also seen in dialyzed patients as a result of noncompliance with dietary restrictions or dialysis treatments or of vascular access dysfunction. On occasion, it may develop because of intercurrent disorders such as rhabdomyolysis, sepsis, or severe acidosis. Hyperkalemia is particularly dangerous because it is generally completely asymptomatic until dangerous cardiac effects develop. Although many dialysis patients chronically tolerate moderate hyperkalemia (6 to 7 mEq/L) with no apparent problem, a potassium level in this range must still be considered potentially dangerous because severe effects can develop fairly rapidly. Moreover, the ECG is occasionally completely normal even when hyperkalemia is severe, and it cannot be relied on to exclude any danger of serious hyperkalemic complications developing. Thus, the serum potassium level should always be checked.

The treatment of hyperkalemia is outlined in Chapter 211. The guidelines for treatment in dialysis patients follow those for treatment in other patients, but particular attention must be directed to avoiding volume overload, symptomatic hypocalcemia, or other potential complications of therapy. These interventions are temporizing measures only, and dialysis should be instituted (or reinstituted) as promptly as possible. A particularly convenient and effective method of decreasing the serum potassium level is by the administration of nebulized albuterol in a dose of 10 to 20 mg over

an hour, four to eight times the dose used in the typical patient with asthma. This intervention provides rapid improvement in the serum potassium concentration which is sustained for at least several hours, and appears to be associated with few side effects.

A dialysis patient in cardiac arrest should be presumed to be hyperkalemic and should receive intravenous calcium. This is one group of patients in whom this drug should still be administered routinely, as emphasized in the most recent advance cardiac life support (ACLS) guidelines.

Other electrolyte abnormalities can occur in patients with kidney failure under a variety of conditions, but the most important and the most common are hypocalcemia and hypermagnesemia. Although hypocalcemic symptoms are uncommon in dialyzed patients, they may occur in those who have not been treated with vitamin D and calcium supplementation, particularly when intravenous bicarbonate is given to treat hyperkalemia or severe acidosis. Symptomatic hypocalcemia should be treated with intravenous calcium gluconate or calcium chloride.

Mild hypermagnesemia is common in chronic kidney failure, but symptoms do not usually occur until magnesium levels are high (generally ≤ 4 mg/dL). Symptomatic hypermagnesemia is almost always a result of inadvertent ingestion of magnesium-containing antacids or laxatives. Intravenous calcium acts as a direct antagonist to the neuromuscular effects of hypermagnesemia, but is a temporizing measure. In the absence of the renal route of excretion, removal of excess magnesium from the body requires emergent dialysis.

KEY TESTING

- ECG and stat serum potassium, if suspicion for hyperkalemia
- Chest x-ray, if dyspnea and/or suspicion for volume overload
- CBC, blood chemistries including electrolytes, calcium, and magnesium
- ECG and chest x-ray as otherwise indicated
- Head CT, if suspicion for intracranial hemorrhage

- Blood cultures for suspected bacteremia or vascular access infection
- Peritoneal fluid cell count, Gram stain, and culture, if suspicion for PD-associated peritonitis

CRITICAL INTERVENTIONS

- Quickly diagnose and initiate treatment for severe complications of CKD such as hyperkalemia, fluid overload, and pericardial tamponade.
- Promptly initiate antibiotic treatment for patients with infected dialysis catheters or peritonitis.

DISPOSITION

A critical decision commonly facing the emergency physician is whether emergency dialysis is necessary for patients presenting to the ED with acute clinical problems. Some patients may have deteriorated between hemodialysis treatments or despite continuing PD. Others may have failed to undergo scheduled dialyses. The most common indication for emergency dialysis (Table 119.5) is severe volume overload or pulmonary edema; the available temporizing measures should be instituted and maintained until dialysis can be initiated. Temporizing measures may also be employed to manage malignant hypertension, severe electrolyte disturbances, or severe acidosis while awaiting the definitive treatment afforded by dialysis.

TABLE 119.5
Indications for Emergency Dialysis

Pulmonary edema
Severe uncontrollable hypertension with volume overload
Severe or uncontrolled hyperkalemia
Other severe electrolyte or acid–base disturbances
Some overdoses
Pericarditis

Uremic symptoms such as lethargy, confusion, asterixis, nausea, and vomiting indicate that dialysis is needed but are not, in and of themselves, indications for *emergency* dialysis unless they are severe. Similarly, serum creatinine and blood urea nitrogen levels correlate only roughly with uremic symptoms or life-threatening metabolic disturbances and do not by themselves indicate an urgent need for dialysis. The appearance of pericarditis, with or without pericardial tamponade, is often considered an indication for urgent or intensified dialysis, but pericarditis can occur even in well-dialyzed patients, and it is not clear that there is an increased risk of clinical deterioration if it is not treated with aggressive dialysis.

A key component of the ED management of all types of problems in the dialysis patient must always be consultation with the patient's nephrologist or dialysis nurse, both to take advantage of their expertise in caring for these patients' complicated problems and to ensure optimal continuity of care. The emergency physician nevertheless must be familiar with the evaluation and treatment of acute problems in dialysis patients so that needed emergency interventions can be initiated promptly.

Common Pitfalls

- Failing to identify treatable factors in patients who may have a reversible component of their CKD (particularly obstruction or volume depletion).
- Causing iatrogenic illness through inappropriate fluid or drug administration.
- Allowing the vascular access to be used for measuring blood pressure or drawing blood or for intravenous infusion.
- Failing to consider vascular access infection in hemodialysis patients, or peritonitis in PD patients, because of lack of specific findings on history and physical examination.
- Failing to consider the diagnosis of tamponade because the patient does not demonstrate all the classic signs and symptoms.
- Failing to treat volume overload because of a lack of specific findings.

- Overlooking anemia as a cause of increased angina or shortness of breath.
- Inappropriately attributing any neurologic dysfunction to disequilibrium syndrome.
- Failing to seek evidence of hyperkalemia by blood test or ECG.
- Inducing symptomatic hypocalcemia by ill-advised bicarbonate therapy.

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CHAPTER 120 The Renal Transplant Patient

Louis G. Graff

The kidney is the most commonly transplanted organ in the United States. More than 17,000 are transplanted each year (1). Kidneys have been successfully transplanted for more than 60 years (2,3). In contrast to dialysis, transplantation allows the patient to live a normal life. Transplant patients do not need a treatment (dialysis) three times a week, do not need to restrict their diets (potassium, sodium, and fluid intake), and can have children (4,5). Therefore, transplantation is the preferred treatment for patients with end-stage renal disease.

The unique aspects of caring for the patient with a transplanted kidney must be considered when such a patient presents to the emergency department (ED). Evaluation and management of even minor problems is often complicated by the patient's immunosuppressed state and the presence of a transplant. Transplant patients often have a limited ability to tolerate illness, trauma, or other physiologic stresses. Moreover, chronic immunosuppression places them at increased risk for severe infections and often makes it difficult to evaluate emergent problems such as abdominal pain or fever. The status of the transplanted kidney must always be a concern as well. Patients may present with complications of the transplant surgery or with signs and symptoms of graft rejection.

MEDICATIONS

Treatment is often more complicated in the transplant patient because certain medications may have adverse effects or be frankly contraindicated in these patients (Table 120.1). For example, potassium-sparing diuretics can cause severe hyperkalemia in patients who are taking cyclosporine. Nephrotoxic drugs can act synergistically with cyclosporine and contribute to renal dysfunction. Lovastatin can cause a severe myopathy in patients taking cyclosporine. Also, a number of medications can increase or decrease cyclosporine, tacrolimus, and sirolimus levels (6) and thus affect drug effectiveness and toxicity (Table 120.2). Killed and antigen-based vaccines as well as immunoglobulin can be safely used in patients who have undergone transplantation. In contrast, live or attenuated vaccines are contraindicated in the immunosuppressed patient, as they can cause serious infection.

TABLE 120.1
Some Drugs to Avoid in the Renal Transplant Patient

Nephrotoxins

Gentamicin, tobramycin, vancomycin, cimetidine, ranitidine, diclofenac, amphotericin B, ketoconazole, melphalan, trimethoprim-sulfamethoxazole, azapropazone

Drugs that Decrease Cyclosporine, Tacrolimus, Sirolimus, Everolimus, or Tofacitinib Levels

Rifampin, phenobarbital, phenytoin, carbamazepine, isoniazid, nafcillin, octreotide, ticlopidine, rifabutin, valproic acid, rifapentine, St. John's wort

Drugs that Increase Cyclosporine, Tacrolimus, Sirolimus, Everolimus, or Tofacitinib Levels

Diltiazem, nifedipine, nicardipine, verapamil, danazol, bromocriptine, metoclopramide, ketoconazole, fluconazole, itraconazole, clotrimazole, erythromycin, clarithromycin, imipenem, doxycycline, methylprednisolone, oral contraceptives, allopurinol, cisapride, metoclopramide, bromocriptine, cimetidine, danazol, protease inhibitors, nephrotoxins (aminoglycosides, amphotericin B, cisplatin), troleandomycin, furanocoumarins (grapefruit)

Drugs that Inhibit Azathioprine Metabolism

Allopurinol

Potassium-Sparing Diuretics

Amiloride, spironolactone, triamterene

Lovastatin

May cause myopathy

Live or Attenuated Vaccines

Measles, mumps, rubella, oral polio, bacille Calmette–Guérin (BCG), yellow fever, and typhoid

TABLE 120.2
Adverse Effects of Renal Transplant Medications

Induction Agents

Antilymphocyte antibody (category C in pregnancy, may be excreted in milk)—fever, chills, leukopenia, dizziness

Basiliximab (category B in pregnancy, may be excreted in milk)—nausea, vomiting, headache, dizziness, bleeding, leukopenia

Daclizumab (category C in pregnancy, may be excreted in milk)—nausea, vomiting, headache, dizziness, bleeding, leukopenia

Alemtuzumab (category C in pregnancy, may be excreted in milk)—neutropenia, pancytopenia, ITP, hemolytic anemia, serious infections, fever, nausea, vomiting, headache, diarrhea, autoimmune disease

Rituximab (category C in pregnancy, excreted in milk)—serious infection, progressive multifocal leukoencephalopathy, mucocutaneous reaction, fever, headache, angioedema, glucose intolerance

Maintenance Immunosuppressive Agents

Azathioprine (category D in pregnancy, some excretion in milk)—serious infections, leukopenia, thrombocytopenia, lymphoma, skin malignancies, alopecia, nausea and vomiting, hepatotoxicity, gingival hyperplasia

Tacrolimus (category C in pregnancy, excreted in milk)—precipitation of diabetes mellitus, hypertension, lymphoma, skin malignancies, nephrotoxicity, neurotoxicity (tremor, headache, mental status change, sensory function change, insomnia), hepatotoxicity, hyperkalemia, serious infections

Cyclosporine (category C in pregnancy, excreted in milk)—serious infections, nephrotoxicity, hyperkalemia, neurotoxicity (tremor, seizure, headaches), hypertension, lymphoma, hepatotoxicity, hyperuricemia, cosmetic side effects (gingival hyperplasia, hypertrichosis)

Sirolimus (category C in pregnancy, may be excreted in milk)—anemia, leukopenia, thrombocytopenia, hypokalemia, hyperlipidemia, nephrotoxicity, hepatotoxicity

Everolimus (category D in pregnancy, may be excreted in milk)—anemia, leukopenia, thrombocytopenia, hypokalemia, hyperlipidemia, proteinuria, nephrotoxicity, hepatotoxicity, diarrhea, edema

Tofacitinib (category C in pregnancy, may be excreted in milk)—serious infection, lymphoma, nephrotoxicity, gastrointestinal perforation, headache, diarrhea, hyperlipidemia, hepatotoxicity, angioedema, arterial thrombosis (kidney, liver)

Belatacept (category C in pregnancy, excreted in milk)—serious infection, anemia, leukopenia, thrombocytopenia, hypokalemia, hyperlipidemia, proteinuria, nephrotoxicity, hepatotoxicity, diarrhea, edema, progressive multifocal leukoencephalopathy

Mycophenolate mofetil (category C in pregnancy, may be excreted in milk)—serious infections, neutropenia, gastrointestinal hemorrhage, pulmonary edema, lymphoma, hypertension

Corticosteroids—adrenal insufficiency, osteoporosis, hypertension, hyperglycemia, cataracts, avascular necrosis, peptic ulcer disease, Cushing syndrome, congestive heart failure, seizure, headaches, papilledema, glaucoma, growth suppression

Immunosuppressive induction agents such as antilymphocyte antibodies or daclizumab cause leukopenia and thrombocytopenia and may lead to infection or bleeding. Maintenance agents such as cyclosporine, tacrolimus, and azathioprine increase the patient's susceptibility to infection, particularly by opportunistic organisms. The patient's risk of cancer (especially lymphoma, cervical cancer, and skin cancer) is 3% or 4% (7). Because azathioprine causes leukopenia in >50% of patients, close monitoring of the blood count is necessary. These drugs can also cause hepatotoxicity, so liver enzymes should be checked in patients with symptoms consistent with hepatitis. In addition, liver failure can decrease the metabolism of cyclosporine and cause cyclosporine nephrotoxicity. Corticosteroids can contribute to the development of peptic ulcer disease, hypertension, accelerated coronary artery disease, diabetes, osteoporosis, aseptic necrosis of the hip, impaired healing, cataract, hemorrhagic pancreatitis, and candida pharyngitis. Newer agents such as mycophenolate mofetil and sirolimus are more costly but have lower rates of side effects than older medications (8).

In addition, the physician needs to consider whether the patient's illness might be caused by failure to take prescribed medications and the resulting complications from such noncompliance. Approximately 6% of renal transplant patients are not compliant with their medicines (9). Patients who are at higher risk for noncompliance are older, have had a longer time since transplantation, are male, and are nonwhite (9).

EARLY COMPLICATIONS OF TRANSPLANT SURGERY

Early after transplantation, postsurgical complications may cause patients to return to the ED. Acute tubular necrosis may occur if the graft preservation time before surgery was prolonged. Vascular complications such as renal artery stenosis or thrombosis or renal vein thrombosis can cause graft dysfunction or localized pain. Ureteral stenosis can cause decreased graft function as well. The cause of the patient's problem may become evident with

examination of the urinalysis, computed tomography (CT) imaging of the kidney, or evaluation of renal artery flow with Doppler ultrasound (10).

Local hematoma or lymphocele can cause pain or compromise graft function by mass effect. The immunosuppressive drugs given to prevent graft rejection also inhibit wound healing and the normal response to infection. At least 20% of patients develop a wound infection, and many others develop other infections. Most patients with surgical complications present within days or weeks of transplantation, although some complications (e.g., ureteral stenosis and smoldering infection) may have a delayed presentation.

RENAL DYSFUNCTION

Evidence of renal dysfunction should always be sought in the patient with a renal transplant, and any reversible cause of renal failure must be identified and treated promptly (Table 120.3). Small changes in the serum creatinine level may indicate important changes in renal function. For example, an increase in the serum creatinine level from 1 to 2 mg/dL represents a 50% decrease in renal function. During the first days after transplant surgery, the most common causes of renal failure are acute tubular necrosis, hyperacute rejection, urinary tract obstruction, urine leak, compression of the graft or renal artery by hematoma, and hypovolemia. During the first 12 weeks after transplant surgery, the patient may experience acute rejection, renal artery stenosis, or urinary tract obstruction. Renal failure more than 3 months after surgery is usually a result of acute rejection, chronic rejection, recurrence of underlying renal disease, or new renal disease.

TABLE 120.3
Differential Diagnosis of Renal Failure in the Renal Transplant Patient

Prerenal	Cyclosporine toxicity
Hypovolemia	Recurrence of chronic kidney disease
Renal artery stenosis	**Postrenal (Obstruction)**
Renal artery thrombosis	Prostate
Renal vein thrombosis	Abscess
Renal (Intrinsic Disease)	Urinoma
Acute rejection	Lymphocele
Chronic rejection	Ureteral stenosis at the anastomosis
Acute tubular necrosis	

All patients with renal dysfunction must be evaluated for obstruction. There are often no clues to this obstruction; the urinalysis may be normal, and urine output unchanged. Ultrasound can show hydronephrosis and confirm the diagnosis of obstruction.

Prerenal causes are often responsible for decreased renal function in transplant patients (Table 120.3). The patient may be volume-depleted or have widespread arteriosclerotic disease.

The anastomosis to the native artery may be a site of particular vulnerability to stenosis. A high blood urea nitrogen (BUN)–creatinine ratio and low urine sodium are consistent with this cause of renal failure. If the stenosis is not severe, the only sign or symptom may be severe hypertension. If the artery is completely thrombosed, the patient will have anuria. Percutaneous transluminal angioplasty with or without stent placement is the preferred approach in reversing hypertension and renal failure (11), but surgical reconstruction may be necessary. Radioisotope scanning using technetium or hippuran or Doppler ultrasound evaluation (10) can identify renal artery stenosis; complete occlusion can result in irreversible infarction unless blood flow is restored within 2 hours.

Renal vein thrombosis can also occur. Patients may present with graft pain and tenderness, fever, hypertension, hematuria, and proteinuria. The treatment is surgical intervention and/or long-term anticoagulation.

Clues to the presence of intrinsic renal disease (Table 120.3) may be found in the urinalysis. Red blood cell casts or proteinuria is seen in glomerulonephritis and vasculitis. Consideration should be given

to recurrence of the disease that originally caused renal failure, especially with systemic diseases such as diabetes mellitus or vasculitis. Glomerulonephritis may recur in the graft if the disease is still active in the original kidneys at the time of transplantation.

REJECTION

Patients with kidney transplants are always at risk for transplant rejection. Acute rejection usually occurs within 4 weeks of transplantation but can occur many months later and can result in complete loss of graft function. The precipitant is usually unknown, but the clinician should be circumspect in exposing the transplant patient to antigens, whether in the form of drugs or blood transfusions (12). The laboratory findings are often those of prerenal or intrinsic renal disease (i.e., low urine sodium level and high BUN–creatinine ratio). The kidney is enlarged and tender, and there may be fever, hypertension, or oliguria. An increased serum level of β_2-microglobulin supports the diagnosis of acute rejection, but the diagnosis is usually confirmed by percutaneous renal biopsy (11). The prognosis is poor when acute rejection occurs >6 months after transplantation or shows evidence of increased severity (by histologic grade or change in the serum creatinine) (14).

Treatment is hospitalization and administration of a combination of immunosuppressive drugs, including high-dose corticosteroids (e.g., methylprednisolone 500 to 1,000 mg/d). Chronic rejection, which cannot be treated, occurs months to years after transplantation and is manifested by a gradual deterioration of renal function.

Cyclosporine and tacrolimus are low-molecular-weight fungal metabolites that are very effective at preventing transplant rejection by depleting circulating T lymphocytes. Unfortunately, cyclosporine and tacrolimus produce nephrotoxicity (8), which usually occurs >6 weeks after transplantation. Some centers use newer agents such as belatacept to lower the risk of nephrotoxicity. In patients with drug nephrotoxicity, the BUN–creatinine ratio tends to reflect a prerenal process. The graft is not tender or swollen, and ultrasound

examination is normal. A reduction in the dose of immunosuppressives can lead to return of renal function. In practice, the question often is whether a decrease in renal function is caused by transplant rejection, thereby requiring an increase in the dose of drug, or to drug nephrotoxicity, requiring a decrease in the dose. Assays for serum drug levels can help differentiate rejection from drug nephrotoxicity.

FEVER OR INFECTION

Organ transplantation became possible because of the development of immunosuppressive agents to prevent organ rejection but at the cost of greatly increased infectious complications. An aggressive approach to identifying and treating infection has been the primary factor responsible for today's high survival rates for transplant patients.

Because the signs and symptoms of serious infection may be masked with the immunosuppression, blood cultures should be obtained for any transplant patient with fever, and hospital admission should be considered even when the source of infection cannot be identified. Uncomplicated urinary tract infections and wound infections may be treated with conventional antibiotics on an outpatient basis (15).

Renal transplant patients can develop cytomegalovirus (CMV) infection, which includes symptoms of fever, adenopathy, leukopenia, and myalgias. Complications include retinitis, pneumonitis, hepatitis, fungal and parasitic superinfection, and transplant rejection. Preoperative administration of valganciclovir, or ganciclovir and then postoperative valacyclovir, valganciclovir, or ganciclovir significantly reduces the risk of postoperative CMV infection (16). Active infection can be treated with ganciclovir or valganciclovir.

Meningitis can present very subtly in the transplant patient. Classic signs of meningitis (e.g., fever or meningismus) may not be present, and opportunistic organisms are likely to be involved. Headache is the most common symptom. The emergency physician

must have a high level of suspicion and a low threshold for performing a diagnostic lumbar puncture.

Trimethoprim-sulfamethoxazole prophylaxis has become the standard treatment in renal transplant patients because of the high risk of infections (17). *Pneumocystis carinii* pneumonia ordinarily develops in up to 12% of patients, but it is eliminated with prophylaxis. In addition, prophylaxis reduces the risk of urinary tract infection in the first 6 months from >50% to 5% (17).

ABDOMINAL PAIN

Evaluation of abdominal pain in the transplant patient is challenging because immunosuppressive medications can mask the signs and symptoms of disease. Most patients do not have fever or leukocytosis. Because of the subtle presentation and difficulty in diagnosis, delays before surgery often are substantial and correlate with increased risk of perforation and mortality (18).

The most common causes of an acute abdomen in transplant patients are similar to those in the general population: gastroduodenal bleeding or perforation, colonic bleeding or perforation, bowel obstruction, appendicitis, cholecystitis, volvulus, and ovarian torsion (18). Patients with polycystic kidney disease may have abdominal pain because of hemorrhage or infection in the cysts, if their own kidneys have not been removed. Ultrasonography can be used to evaluate these patients. Because both azathioprine and cyclosporine can cause hepatitis with abdominal pain, liver enzymes should be measured in transplant patients with abdominal pain. The transplant patient has an increased risk of developing lymphoma, probably because of chronic immunosuppression. Abdominal CT scanning can identify enlarged retroperitoneal nodes or tumor mass. Pancreatitis occurs infrequently (1%) in renal transplant patients. When pancreatitis does occur, it is often quite serious, with 80% to 100% mortality (19).

KEY TESTING

- Basic laboratory studies including BUN, creatinine, liver function tests, and urinalysis
- Renal ultrasound

CRITICAL INTERVENTIONS

- Aggressively seek the source of fever in immunosuppressed patients.
- Order an ultrasound to rule out obstruction in patients with renal dysfunction.
- Recognize and admit patients with acute rejection to the hospital.

DISPOSITION

The threshold for hospitalizing the transplant patient should be very low. One must always suspect a pathologic process, even in patients who seem to have only minor complaints. When a transplant-related problem is identified, the emergency physician should not hesitate to seek appropriate consultation or to arrange transfer of the patient to a facility with the resources to manage transplant patients. Nevertheless, the emergency physician can manage most acute problems in renal transplant patients if a thorough and meticulous approach is used.

Common Pitfalls

- Prescribing potentially nephrotoxic drugs in the renal transplant patient.
- Failing to realize that a small rise in the transplant patient's serum creatinine level may represent a relatively large decrement in renal function.
- Assuming that a normal urine output excludes obstruction as the cause of acute renal failure.
- Failing to remember that the immunosuppressed transplant patient often does not show classic signs of infection.
- Failing to remember that certain drugs may decrease cyclosporine or tacrolimus levels and lead to transplant rejection;

likewise, certain drugs may increase these drug levels and lead to toxicity.

- Failing to provide increased doses of steroids when transplant patients taking corticosteroids undergo major stress, such as surgery, myocardial infarction, major trauma, or sepsis.
- Giving a blood transfusion without a clear indication, because stimulation by exogenous antigens may lead to rejection.

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CHAPTER 121 Acute Scrotal Pain

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The acute scrotum is defined as an acute painful swelling of the scrotum or its contents, accompanied by local signs or general symptoms (1). The three most common diagnoses are torsion of the testis and spermatic cord, acute epididymitis, and torsion of the appendix testis or appendix epididymis. Other causes include orchitis, acute hydrocele, varicocele, inguinal hernia, and necrotizing fasciitis of the perineum (Fournier gangrene). The ischemic insult from testicular torsion makes acute scrotal pain a true surgical emergency. The evaluation may be challenging, and time is of the essence.

Testicular torsion can occur at any age but is most common in neonates or adolescents (2). Testes predisposed to torsion lack posterior fixation to the scrotal wall and have an abnormally high attachment of a voluminous tunica vaginalis (Fig. 121.1). The tunica vaginalis normally fixes the testis and epididymis to the posterolateral surface of the scrotum (Fig. 121.2). However, complete envelopment of the testis by the tunica vaginalis permits rotation of the testis (clapper) within the tunica (bell), resulting in the classic “bell clapper” deformity. The testis and cord twist within the tunica vaginalis, thereby causing occlusion of the venous system (3). Arterial flow is decreased by both the twisting mechanism and by the edema secondary to venous occlusion. The likelihood of testicular necrosis is related to the duration of ischemia. Partial arterial flow may occur with as little as 180 degrees of rotation, and associated edema may result in complete occlusion. A median of 360 degrees of torsion—one complete rotation of the spermatic cord—has

been documented in cases of testicular salvage, with a median of 540 degrees of torsion in nonsalvageable cases (3). The variable degree of testicular ischemia makes the absolute window for testicular viability unknown. A history of continuous pain for 24 hours is usually associated with testicular loss. A salvage rate approaching 100% following manual or surgical detorsion within 6 hours of ischemic onset is often quoted (4). However, following acute detorsion, nearly half of the involved testes atrophy by more than 20% (5). An atrophic testicle may have impaired fertility, and decreased fertility of the contralateral testicle is likely.

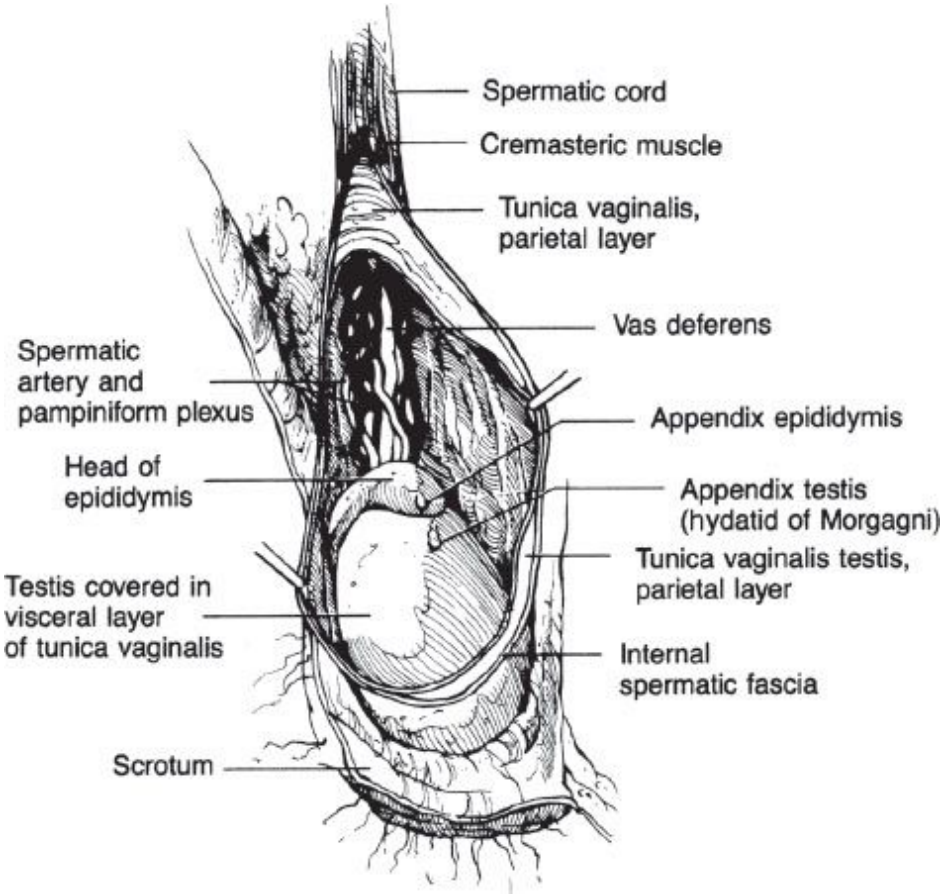

FIGURE 121.1 Bell clapper deformity.

Acute epididymitis is defined as inflammation or infection limited to the epididymis, causing acute pain and swelling of gradual onset (6). Epididymoorchitis implies extension of the inflammation or infection to the adjacent testis. Overall, epididymitis is the most common

cause of an acute scrotum (7). It is primarily a disease of adults and seldom occurs before puberty unless there is an associated anatomic abnormality that promotes urinary tract infection. Epididymitis most often results from retrograde spread of infected urine down the vas deferens into the globus minor, or tail, of the epididymis. Occasionally, reflux of sterile urine causes an inflammatory process (i.e., chemical epididymitis) (8).

In men younger than age 35, the most likely infectious agents are *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (9). In men older than age 35, bacteriuria caused by obstructive urinary disease is more common, and *Escherichia coli,* enterococcus, *Pseudomonas,* and *Proteus* predominate. However, this age distinction is arbitrary. Any organism may invade the epididymis in association with a systemic infection, such as blastomycosis, tuberculosis, or meningococcus. *Candida* and *E. coli* epididymitis have been seen in patients with acquired immune deficiency syndrome (AIDS). Amiodarone (Cordarone) has been associated with drug-induced epididymitis confined to the globus major, or head, of the epididymis. In the prepubertal patient, coliform bacteria predominate. Nongonococcal bacterial epididymitis in a boy younger than age 10 should prompt a thorough diagnostic evaluation for genitourinary anomalies or neurogenic bladder disease, as underlying urogenital abnormalities exist in up to 50% of prepubertal patients with bacterial epididymitis (8,10).

Acute orchitis is an uncommon primary infection of the testis. Most often, however, orchitis is associated with a primary epididymal infection. Orchitis may occur during a systemic illness in which systemic seeding of the testis occurs with *E. coli, Klebsiella, Pseudomonas, Staphylococcus,* or *Streptococcus* species. Influenza, infectious mononucleosis, tuberculosis, syphilis, and amoebiasis may cause orchitis. The latter pathogens occur most often in immunocompromised patients. Mumps orchitis occurs in males who are systemically infected with the virus but seldom occurs before puberty. About 15% to 20% of postpubertal males with mumps develop orchitis. The onset of the testicular swelling normally occurs 3 to 7 days after the development of parotitis. One-third of men with

mumps orchitis, however, do not have parotitis. One-third of cases may be bilateral. Atrophy results in about 50% of involved testes.

Hydrocele is the most common cause of nonacute scrotal swelling. It is an accumulation of serous fluid in the potential space between the visceral and parietal layers of the tunica vaginalis that normally envelops and fixes the testis and epididymis to the posterior scrotal wall. Most hydroceles are found in older patients, and an underlying cause is not identified. A sudden onset of a symptomatic hydrocele can occur secondary to epididymitis, epididymoorchitis, trauma, or tumor. Approximately 10% of testicular tumors present with a reactive hydrocele (11). In pediatric hydroceles, congenital failure of the tunica vaginalis to be obliterated after birth allows communication between the scrotum and the peritoneum, creating a hydrocele or hernia. These "communicating hydroceles" acutely enlarge and shrink depending on patient activity, as peritoneal fluid and occasionally a loop of intestine fill the scrotum when the patient is in the upright position and spontaneously decompress when the patient is supine. This is the classic history of scrotal swelling that vanishes when the child sleeps.

CLINICAL PRESENTATION

Sudden onset of testicular pain and swelling in an adolescent is the classic presentation for testicular torsion. However, many of the other causes of an acute scrotum present in a similar manner: a male patient complaining of an acute, painful, swollen, and tender hemiscrotum. Differentiating testicular torsion from epididymitis is often challenging, particularly in cases of severe swelling and pain (eTable 121.1).

eTABLE 121.1
Differentiating Characteristics of Testicular Torsion, Epididymitis, and Appendage Torsion

	Testicular Torsion	Epididymitis	Appendage Torsion
Historical Features			
Age	Incidence peaks in neonatal and adolescent groups, but may occur at any age	Primarily adolescents and adults, but may occur at any age	Typically prepubertal males
Risk factors	Undescended testicle (neonate), rapid increase in testicular size (adolescent), failure of prior orchiopexy	Sexual activity/promiscuity, GU anomalies, GU instrumentation	Presence of appendages
Pain onset	Sudden	Gradual	Gradual or sudden
Prior episodes of similar pain	Possible (spontaneous detorsion)	Unlikely (unless prior epididymitis)	Occasional
History of trauma	Possible	Possible	Possible
Nausea/vomiting	More likely	Less likely	Less likely
Dysuria	Less likely	More likely	Less likely
Physical Findings			
Fever	Less likely	More likely, particularly in advanced disease (epididymoorchitis)	Less likely
Location of swelling/tenderness	Testicle, progressing to diffuse hemiscrotal involvement	Epididymis, progressing to diffuse hemiscrotal involvement	Localized to head of affected testicle or epididymis
Cremasteric reflex	Testicular torsion less likely if present	May be present or absent	May be present or absent
Testicle position	High-riding testicle, transverse alignment	Normal position, vertical alignment	Normal position, vertical alignment
Pyuria	Less likely	More likely	Less likely

Often, the pain is abdominal and may mimic acute gastroenteritis. In one study, scrotal pain with radiation to the abdomen or inguinal region occurred in 50% of patients with testicular torsion, whereas abdominal or inguinal pain without scrotal pain occurred in 12.5% (11). A history of a similar event can be elicited in one-half of the patients and results from previous episodes of torsion followed by spontaneous detorsion. Approximately one-half of patients report the onset of pain during sleep. Cold weather, sexual arousal, and scrotal trauma are often important inciting events. Nausea, vomiting, and low-grade fever are common clinical findings. The presence of vomiting help to heighten the suspicion for testicular torsion (12). Voiding symptoms such as dysuria, urgency, and hesitancy, although nonspecific, are typically more consistent with epididymitis.

Patients with acute epididymitis may report a gradual onset of scrotal pain and swelling that peaks over a period of 3 to 24 hours. The pain can be sharp and often radiates to the groin and either lower abdominal quadrant, simulating appendicitis or diverticulitis, but, commonly, the only complaint is a dull ache in the scrotum. Initially, the pain is felt in the tail of the epididymis. This is usually disclosed as a firm, hard mass at the inferior portion of the normally smooth testis. Over time the process extends into the body, then to the head of the epididymis, producing the large sausage-shaped mass often found on the posterior surface of the testis. A history of fever is not common in uncomplicated epididymitis, whereas patients with

more advanced degrees of infection (epididymoorchitis) may exhibit systemic signs and symptoms (13). Occasionally, a debilitated or immunocompromised patient may present with bacteremia. A history of recent cystoscopy, an indwelling urethral catheter, urinary tract infection, or genitourinary surgery should be sought, especially in older men. Similarly, a thorough history of sexually transmitted disease, exercise routines, and job-related duties should be evaluated. Activities that promote a Valsalva maneuver or increase intrapelvic pressure may promote retrograde flow of sterile or infected urine. Body builders who lift excessive weight and construction workers who climb and do heavy lifting are prototypes for the development of epididymitis. Bilateral epididymal involvement may occur infrequently. Rarely, abdominal pain attributed to infection involving the vas deferens and spermatic cord is the sole presenting symptom, and has the potential to be mistaken for appendicitis or diverticulitis.

Most hydroceles in adults develop gradually and are asymptomatic. A chronically enlarging hydrocele may present as scrotal enlargement associated with a heavy sensation, occasionally radiating to the groin. An acute hydrocele may present with pain, depending on the inciting event. The classic hydrocele is a cystic, pear-shaped mass located anterior to the testis and epididymis. It often obscures definitive palpation of the testis. A hydrocele should be confined to the scrotum, with a normal spermatic cord above it. Rarely, a hydrocele of the spermatic cord can be palpated in the region of the external inguinal canal.

DIFFERENTIAL DIAGNOSIS

In an adolescent, acute scrotal swelling is *testicular torsion* until proven otherwise. The differential diagnosis includes acute epididymitis, torsion of the testicular or epididymal appendices, orchitis, testicular tumor, inguinal hernia, and traumatic hydrocele or hematocele (eTable 121.2). Age does not preclude the diagnosis of testicular torsion. A series of 243 patients with testicular torsion revealed that 31% were prepubertal, 60% were 12 to 18 years old, 5% were older than 30 years, and isolated case reports of men into their 60s continue to be reported (14).

eTABLE 121.2
Differential Diagnosis of Scrotal Pain

Diagnosis	Symptoms	Signs	Evaluation
Appendage torsion	Typically a more indolent onset of symptoms compared with testicular torsion; less likely to present with nausea or vomiting	Tender nodule typically at head of testicle or epididymis; blue-dot sign pathognomonic	US examination may demonstrate infracted appendage
Epididymitis	Typically a more indolent onset of symptoms compared with testicular torsion; less likely to present with nausea or vomiting	*Early:* firmness and nodularity isolated to epididymis. *Late:* with progression, inflammation may become contiguous with testicle (termed epididymoorchitis)	US examination may reveal increased intratesticular blood flow, although this is a nonspecific finding
Epididymoorchitis	More likely to present with systemic findings, including nausea, vomiting, fever	Large, swollen scrotal mass typically with indistinct border between testicle and epididymis	US examination may reveal increased intratesticular blood flow, although this is a nonspecific finding
Fournier disease	Perineal pain, swelling, redness; fever, vomiting, lethargy	May present with an absence of visible local findings on skin inspection in early stages (pain out of proportion to examination); ecchymosis, crepitus, necrotic eschar may be present in more advanced disease	Emergent surgical consultation for debridement, broad-spectrum antimicrobials
Hematocele	Large, painful scrotal mass; often antecedent history of trauma	Ecchymoses of scrotal skin; testicular tenderness or firmness	US examination may reveal fluid-filled tunica vaginalis
Hernia	Unilateral inguinal or scrotal swelling and pain	Reducible, incarcerated and strangulated forms; incarcerated/strangulated hernia may be particularly tender on examination	Emergent surgical consultation when incarcerated or strangulated, outpatient surgical referral reasonable if readily reducible
Hydrocele	Typically a gradual progression of swelling	Scrotal transillumination may be helpful	US examination may reveal fluid-filled tunica vaginalis
Idiopathic scrotal edema	Typically unilateral scrotal swelling and edema; primarily seen in children less than 10 years old	Scrotal, perineal, inguinal erythema and edema; may be difficult to distinguish from an acute skin–soft tissue infection	US examination
Orchitis	Typically gradual onset of unilateral (or bilateral) testicular swelling and pain	Swelling and tenderness isolated to testis/testes without epididymal involvement	US examination; often seen in conjunction with other systemic diseases (viral, other), treatment is disease-specific
Scrotal skin infection	Variable depending on cause	Must distinguish between lesions localized to scrotal wall and those contiguous with deeper scrotal structures	US or CT imaging may be helpful in determining the depth and extent of involvement if invasive process suspected
Testicular torsion	Typically a sudden and severe onset of pain; more likely to be associated with nausea or emesis	Classic findings include an elevated testis with a transverse lie	Emergent surgery consultation in high-probability cases
Trauma	History of blunt or penetrating mechanism of injury	Variable depending on mechanism	US examination, low threshold for surgical consultation in all but the most minor injuries
Tumor	Typically a gradually progressive testicular mass, may be painless or painful in case of acute intra-tumor hemorrhage	May palpate testicular mass, firmness, or induration	US examination
Varicocele	Typically a gradual onset of unilateral swelling, often painless	Abnormally enlarged spermatic cord (pampiniform) venous plexus (often described as a "bag of worms")	US examination
Vasculitis (e.g., HSP)	Testicular swelling and pain	Associated vasculitis findings (such as buttock/lower extremity purpura and renal involvement in HSP)	US examination, other diagnostic testing guided by suspected cause (e.g., complete blood count, serum electrolytes with renal function in HSP)

CT, computed tomography; HSP, Henoch–Schonlein purpura; US, ultrasound.

Acute epididymitis, the most common entity mistaken for testicular torsion, is rare before puberty. Sixty percent of patients with epididymitis are older than 30 years. A history of urinary tract infection, painful voiding, urethral discharge, or an indwelling urethral catheter suggest the diagnosis of epididymitis. A history of previous episodes of testicular pain suggests testicular torsion. Nausea with vomiting is more common in torsion.

Primary *orchitis* seldom occurs unless it represents contiguous spread of infection from the epididymis to the testis (epididymoorchitis).

Torsion of a testicular or *epididymal appendage* can cause venous engorgement with subsequent arterial occlusion and infarction. The appendix testis is the most common appendage to twist (11). It is usually located anteriorly, near the upper pole of the testis. Appendiceal torsion occurs most frequently in the prepubertal age group (2). The onset of pain may not be as rapid as that of testicular torsion and may occur intermittently and then progress over 3 to 5 days, with less severity than testicular torsion.

Carcinoma of the testis is the most common cancer in adolescent and younger adult-aged males, a similar age range for the occurrence of testicular torsion. The initial diagnosis may be incorrect; a common misdiagnosis is epididymitis. Symptoms from testicular tumors normally have a more gradual onset, with minimal pain.

An *inguinal hernia* may present with acute scrotal swelling. An incarcerated inguinal hernia may mimic testicular torsion with an acute onset of pain, swelling, and vomiting. Most hernias may be palpated in the superior scrotal and inguinal regions (11). Uncomplicated reduction of bowel through the inguinal defect into the abdominal cavity confirms the diagnosis.

Hydrocele usually presents as a chronic, painless mass. A *hematocele* is blood or a blood clot within the potential space between the two leaves of the tunica vaginalis. It occurs most often after needle aspiration of a hydrocele, but it can accompany testicular torsion or trauma. A *varicocele* is a chronic dilatation of the testicular pampiniform venous plexus. Varicoceles are often referred to as a “bag of worms” because of the multiple torturous vessels imprinting the scrotal skin. Nearly 20% of men have a left varicocele of some degree. The left side predominates because the left testicular vein drains perpendicularly into the left renal vein without valves to reduce hydrostatic pressure, as compared with the right testicular vein, which drains obliquely into the inferior vena cava.

ED EVALUATION

A rapid presumptive diagnosis of testicular torsion should be suspected on the basis of the history and physical examination findings. Because the acute scrotum has many possible causes, testicular torsion must be the primary consideration for any scrotal complaint in any age group, but particularly in young and adolescent males.

Physical examination of the male external genitalia should be done systematically in both the supine and standing positions. After assessing the penis and foreskin, both testes are compared for size and consistency. The testes normally are oriented vertically with a slight and forward tilt. The rubbery consistency should be homogeneous and the surface is smooth. The testes should be freely mobile within the scrotum (Fig. 121.2).

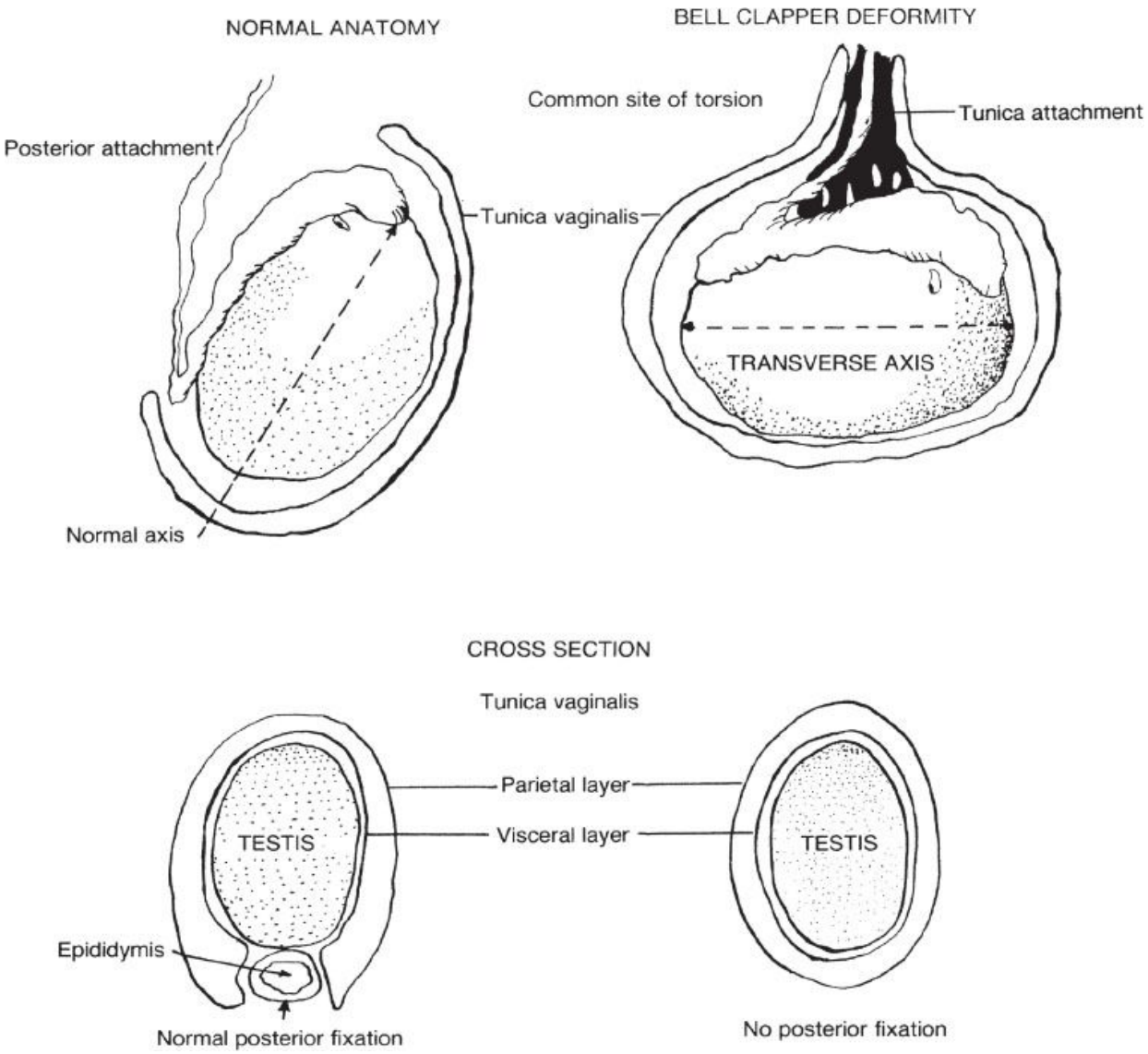

FIGURE 121.2 Normal anatomy of the scrotum.

The epididymis is a 1-cm thick, discrete, sausage-shaped structure, usually located on and firmly attached to the posterior wall of the testicle. Rarely, it is anteriorly oriented. The epididymal head is the thickest portion and lies on the top of the testis. The body of the epididymis is a continuation of the head and tapers to the tail, which is contiguous with the vas deferens. The 1- × 3-mm testicular and epididymal appendages are not normally palpable but are most commonly located anteriorly, near the upper pole of the testis and the head of the epididymis.

From the testis, the spermatic cord can be palpated ascending into the fascial cleft of the subcutaneous external inguinal ring. The vas deferens is a firm tubular structure lying within the cord. The spermatic arteries are not palpable, and the veins are palpable only when enlarged (varicocele). With the patient in a standing position, a cough or Valsalva maneuver may elicit a hernia, or may accentuate a varicocele.

The patient with testicular torsion may have a painful or nonpalpable testis that has elevated in the hemiscrotum due to the twisting and shortening of the spermatic cord. Engorgement of the testicle and secondary swelling of the scrotum are usually present. Instead of lying in the usual vertical orientation, the affected testis is often found lying horizontally in the scrotum because of its abnormal mobility within the tunica vaginalis. The spermatic cord tends to become thickened in the area of torsion.

In epididymititis, a localized, indurated, tender portion of the epididymis may be palpated inferiorly and separate from a less painful testis. Eventually, the entire epididymis becomes involved, and the distinction between the testis and epididymis is less evident (epididymoorchitis). The involved testis hangs low in an erythematous and edematous scrotum. Often the entire hemiscrotum is swollen, tender, and firm. The overlying scrotal skin rapidly develops redness and edema, and within a few hours, the testis and epididymis are no longer anatomically separable. In a series of 206 patients with torsion, 42% presented with swelling and precluded palpation of the intrascrotal contents (15).

The presence of an intact ipsilateral cremasteric reflex may be helpful in placing testicular torsion lower in the differential diagnosis, but a preserved reflex certainly does *not* exclude the diagnosis of testicular torsion (16,17). The cremasteric reflex is a superficial skin reflex mediated by spinal nerves T-12 to L-2, elicited by stroking the skin of the inner aspect of the ipsilateral thigh in an upward motion, resulting in contraction of the cremasteric muscle and elevation of the testis by at least 0.5 cm. This is best demonstrated with the patient in the supine, frogleg position and requires the absence of any inflammatory process in the overlying

scrotal skin. Certain individuals may lack the reflex altogether, particularly boys in the first 3 years of life (18).

The often-referenced “blue-dot” sign is pathognomonic for appendage torsion and refers to a small, tender, infarcted (blue), pea-like structure seen through the hormonally unstimulated thin and transparent prepubertal scrotal skin held taut over the head of the testis. This finding is very specific, yet insensitive (19).

Laboratory data are nonspecific and often not helpful. One-third of patients with torsion have a nonspecific leukocytosis of more than 10,000 white blood cells per cubic millimeter, and most patients have a normal urinalysis (11,15). A properly collected urinalysis shows pyuria or bacteriuria in 50% of patients with epididymitis, and a small number of patients have a urethral discharge that can be Gram-stained (20).

Diagnostic imaging tests such as color Doppler ultrasound or radionuclide testicular scintigraphy are always adjunctive and should never delay urologic consultation, attempted manual detorsion, or scrotal exploration. These adjunctive tests are not required to make the diagnosis. *Color Doppler ultrasound* yields the most information in the evaluation of the acute scrotum because it provides information about both anatomy and arterial perfusion. It is helpful, yet imperfect, in excluding testicular torsion (21). Color Doppler ultrasound evaluates for intratesticular blood flow. Gray-scale ultrasound is also helpful in evaluating the spermatic cord itself for twists or kinks consistent with cord torsion (22). Ultrasound evaluation can also determine whether a mass is intratesticular or extratesticular and is particularly applicable when swelling or a reactive hydrocele has made physical examination difficult or impossible. The normal testis has characteristic echoes that are homogeneous and finely granular, whereas the epididymis is distinguished by its coarser texture. A typical testicular tumor is detected as a hypoechoic, inhomogeneous mass within the testis. Epididymitis displays a thickened and enlarged epididymis. Abscess cavities may be apparent within both the testes and epididymis.

Although ultrasound studies are helpful, an aggregate clinical impression derived from a thorough history and physical

examination is more important. The imaging test used often depends on the consultant, the availability of the examination, the quality of the equipment, and the experience of the technician and radiologist reader. Adjunctive tests should never delay operative exploration. Imaging may be obtained while waiting for an operating suite, but it is imperative that the examining clinician remember that testicular torsion is definitively diagnosed at surgical exploration. Once the diagnosis of testicular torsion is suspected, immediate surgical consultation is initiated. Meticulous charting and documentation of the history and physical examination, the suspected diagnosis, and need for scrotal exploration, as well as the time course for all of these events, are imperative (23).

If the surgeon requests adjunctive testing, this must be documented in the ED record. The urologist should be informed that an attempt at manual detorsion will be made while awaiting the patient's transfer to the operating room or the radiology suite. If the urologist discourages or requests that detorsion not be attempted, this should be documented.

KEY TESTING

- Color Doppler Ultrasound in equivocal cases (must not delay surgical intervention)

ED MANAGEMENT

In patients with *testicular torsion,* manual detorsion is successful in 30% to 70% of patients (24,25). Spontaneous or successful manipulative preoperative testicular detorsion results in a high testicular salvage rate if accomplished quickly. Manual detorsion can be attempted with the patient standing or supine but most often is done with the patient supine, in bed, or on a stretcher, with the physician standing on the patient's right side. Classically, the patient is placed in the frogleg lithotomy position. Light sedation or spermatic cord block may be done to lessen the patient's discomfort. A spermatic cord block allows multiple detorsion attempts and experimentation with direction, but it eliminates pain relief as an

end point to judge successful detorsion. Documentation of return of intratesticular blood flow on color Doppler ultrasound imaging can be utilized as an alternative. About two-thirds of testes twist in a lateral-to-medial direction, so manual detorsion is initially attempted from medial to lateral, similar to opening a book; that is, the patient's right testis is detorsed in a counterclockwise direction, and the left testis in a clockwise direction (3). The testis is rotated 180 degrees in one direction and maintained in position. Further rotation is continued as necessary. If the initial detorsion increases the pain, the detorsion should be attempted in the opposite direction. Operating room data show that torsion may vary from 180 to 1,080 degrees, so continued detorsion should be guided by the patient's response (3). One to three turns are usually sufficient. The detorsion is stopped when either the anatomy is restored or the testicular pain is relieved. Both should occur promptly. Significant swelling makes the initial detorsion maneuver more difficult and there is much less chance of success. Manual detorsion should be followed by surgical exploration to confirm success and fixate both testes (orchiopexy), because torsion is an anatomic abnormality and tends to be bilateral.

The technique of spermatic cord block is straightforward. The spermatic cord is palpated and encircled with the nondominant hand at the scrotal inguinal junction. Three to four injections with 1% plain lidocaine are made at different angled approaches with a 25-gauge, 1.5-in needle. An alternative method can be instituted if the cord cannot be palpated because of severe pain or pronounced swelling. After palpating the pubic tubercle, a needle is inserted vertically downward, 1 cm below and medial to the pubic tubercle onto the anterior aspect of the pubic bone. Repeated slow injections should be made at different angles, attempting to infiltrate the area around the ilioinguinal nerve and genital branch of the genitofemoral nerve. The duration of a successful lidocaine spermatic cord block is about 1 to 3 hours.

Aggressive initial management of *acute epididymitis* is crucial to reduce the potential morbidity associated with this disease process. Bedrest, scrotal elevation with ice applied to the affected epididymis for 10 minutes three times per day, organism-specific antibiotic

therapy, nonsteroidal anti-inflammatory drugs, narcotic pain medication, and stool softeners are the initial treatment modalities recommended for acute epididymitis. Once pain-free in bed, patients may be ambulatory with a scrotal supporter and instructed not to lift or strain, as this may exacerbate the inflammatory process.

Antibiotics should be prescribed in all cases of epididymitis. Despite an infectious cause, cultures of the urine and urethral discharge may be negative. In younger patients with suspected sexually transmitted disease, a single 250-mg intramuscular dose of ceftriaxone should be administered in the ED, along with a 10-day course of doxycycline 100 mg orally every 12 hours. Because of high rates of resistance, both quinolones and oral cephalosporins are no longer recommended (26). Older men suspected of having a urinary source of infection caused by enteric gram-negative bacilli or *Pseudomonas* should be initially treated with ofloxacin 300 mg orally every 12 hours for 10 days, or levofloxacin 500 mg orally daily for 10 days. Urology follow-up is encouraged within 5 to 7 days.

CRITICAL INTERVENTIONS

- Consult a surgeon (urologist, pediatric surgeon, or general surgeon) immediately for a highly suspicious case of testicular torsion, without adding the delay of diagnostic studies.
- Perform manual detorsion while the patient awaits the operating room, in order to reduce the ischemic time to the testicle.
- Provide antibiotics and analgesics for patients with acute epididymitis.
- Neither the presence of an intact cremasteric reflex nor intratesticular blood flow on color Doppler ultrasound precludes the diagnosis of testicular torsion—if suspicion is high, specialty consultation is necessary.

DISPOSITION

The surgeon is obligated to establish a final diagnosis and perform definitive *orchiopexy* or *orchiectomy,* depending on the operative findings. Selected ancillary tests must not delay surgical exploration.

When securing written informed operative consent, the consultant should explain the need for bilateral orchiopexy, the possibility of orchiectomy, and the option for placement of a testicular prosthesis. An unequivocally infarcted testis is usually removed at exploration to lessen the chance for persistent pain and promote resolution of the inflammatory process. Bilateral orchiopexy is indicated, because the anatomic defect is present bilaterally.

All patients for whom testicular torsion is strongly suspected should be explored in the operating suite. Observation and serial examinations are not useful in the management of suspected testicular torsion. If preoperative manual detorsion successfully re-establishes testicular blood flow, arrangements for delayed orchiopexy can be made by the consultant, who is ultimately responsible for any planned delay in scrotal exploration and orchiopexy. The unavailability of a qualified surgeon, or immediate operating room facilities, warrants consideration of prompt transfer.

Outpatient management of epididymitis is appropriate in most cases. Urologic follow-up should be arranged for 5 to 7 days, unless worsening of the patient's condition necessitates an earlier visit. Pediatric cases of epididymitis require urologic consultation to evaluate the potential for lower urinary tract anomalies and urinary obstruction as the cause of the epididymitis. Adult patients with suspected bacteremia or severe constitutional symptoms, including intractable pain or nausea and vomiting, require hospitalization and parenteral antibiotics. Patients in whom the physical examination and ultrasonography are equivocal for abscess formation should also be admitted for antibiotic therapy and further evaluation.

Common Pitfalls

Delaying diagnosis, manual detorsion, or surgical intervention.

- Reliance on a single "classic" differentiating parameter, such as age, onset of pain, physical examination findings (including the cremasteric reflex); or imaging findings can erroneously convince the examiner that testicular torsion is not present.
- Delaying surgical consultation while awaiting ancillary testing.

- Accepting an alternative diagnosis by a consultant over the telephone.
- Misdiagnosis of epididymitis in cases of testicular tumor or testicular torsion.
- Dismissal of a newly developed hydrocele as a benign process may delay diagnosis of an underlying testicular malignancy.

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CHAPTER 122
Penile Disorders

Douglas L. McGee

Disorders of the penis, including balanoposthitis, phimosis, paraphimosis, and priapism, require expeditious evaluation and treatment.

BALANITIS, PHIMOSIS, AND PARAPHIMOSIS

Balanitis (inflammation of the glans penis) and *posthitis* (inflammation of the prepuce of the penis) usually occur together, and are referred to as *balanoposthitis* when they do. Balanitis is more common in uncircumcised men who exercise poor hygiene, but also affects young boys. Patients with balanoposthitis have an edematous, erythematous, fissured, and painful prepuce and glans. A variety of skin changes are possible, depending on the etiology (Table 122.1).

TABLE 122.1
Causes of Balanoposthitis

Infectious	Noninfectious
Fungal: *Candida albicans:* itching, burning, white discharge, discrete ulcerated papules, white, cheesy plaques	**Trauma**
Bacterial: group B streptococci, *Gardnerella vaginalis*, and mixed anaerobes	**Allergic:** latex allergy
STD-related: secondary syphilis, *Trichomonas vaginalis* genital herpes, condyloma lata, human papillomavirus	**Dermatologic:** psoriasis, lichen planus, erythema multiforme, premalignant, malignant lesions
Other: amoebiasis	

When the foreskin is not retractable behind the glans penis, the condition is termed *phimosis*. Physiologic phimosis is present until normal adhesions between the foreskin and glans have separated. Although most young boys are able to retract the foreskin by puberty, retraction is usually possible at an earlier age (1). As normal secretions accumulate and epithelial sloughing occurs, smegma is normally formed and assists in the separation of the foreskin from the glans. Parents may confuse smegma with infectious discharge if expressed from the penis. Pathologic phimosis, or simply phimosis, occurs when retraction of the foreskin is not possible after puberty or when the foreskin was previously retractable. When balanoposthitis is severe, phimosis may occur and precipitate urinary retention.

Paraphimosis occurs when the retracted foreskin is not replaced, usually after cleansing or catheter insertion. After foreskin retraction, the constricting phimotic ring causes progressive edema and impairs venous return, threatening the viability of the glans. Although most patients complain of pain and usually provide a history of foreskin retraction, debilitated uncircumcised patients may not provide this history. History of circumcision may be available from medical records or from a caregiver. Do not confuse paraphimosis with balanitis in these patients.

ED EVALUATION

The emergency department (ED) evaluation for patients with balanoposthitis, phimosis, or paraphimosis is usually limited to the history and physical examination. Measure the patient's blood glucose when there is infection with *Candida albicans,* and perform serologic testing if secondary syphilis is suspected. Acetic acid whitens the superficial epithelial skin layer when applied to lesions infected with human papillomavirus (HPV). Determine if the patient can urinate when severe phimosis or paraphimosis is diagnosed.

ED MANAGEMENT

The mainstay of ED management of balanoposthitis includes meticulous hygiene, including retraction of the foreskin and cleansing of the glans penis and prepuce, but the aggressive use of soap to clean under the prepuce is not advisable. Treatment of infectious balanoposthitis is directed against the offending organism. Fungal infections of the glans are treated with topical antifungal agents, and metronidazole is appropriate for *Gardnerella* sp, anaerobic infection, and *Trichomonas* sp. Secondary syphilis, if suspected, is treated according to established guidelines.

Asymptomatic phimosis does not require emergent treatment. Reassure concerned parents when physiologic phimosis is present, and discourage forceful retraction. Several studies demonstrate that medium- or high-potency topical steroids applied to the foreskin for 4 to 6 weeks are 85% to 90% effective when retraction is desired (2,3). However, several studies comparing steroid cream with placebo moisturizing showed resolution of phimosis in slightly more than half of the placebo group (4,5). When severe phimosis causes urinary retention or interferes with placement of a urinary catheter, a slit made in the dorsal aspect of the foreskin facilitates access to the urethral meatus (6). After providing local anesthesia of the penis with a dorsal nerve block or ring block placed at the base of the penis, gently separate adhesions between the foreskin and glans with a hemostat. Place one jaw of the hemostat inside the dorsal foreskin, taking care not to include the urethral meatus or glans. Close the hemostat to crush the foreskin for 3 to 5 minutes then

incise the crushed area with straight scissors. The crushed edges rarely bleed but may require absorbable suture for hemostasis if they separate. Although some patients are satisfied with the cosmetic appearance of the foreskin after the dorsal-slit procedure, a urologist may perform an elective circumcision at a later date. Always return the foreskin to the reduced position after urinary-catheter placement.

Paraphimosis requires emergent treatment. After adequate sedation or penile anesthesia, attempt manual reduction. A simple initial approach to paraphimosis is to wrap the edematous prepuce with an elastic bandage to provide gentle, nontraumatic compression that slowly forces edematous fluid under the phimotic ring (7). Self-adhering bandages facilitate continuous compression. Wrap the phallus, starting at the glans with 3 to 4 wraps of compression bandage and leave in place for 20 minutes. Marked reduction in edema has resulted in autoreduction or may facilitate other methods of manual reduction if paraphimosis persists after compression. Place the fingers of both hands distal to the phimotic ring and foreskin and apply gentle, steady pressure on the glans with the thumbs (6). Gauze placed under the fingers may improve traction on the foreskin while bringing it over the glans, but lubricants are rarely helpful. Several other techniques are described to treat paraphimosis; application of these techniques are guided by the physician's skill and training in the maneuvers. A 21-gauge needle may be used to puncture the edematous foreskin. Manual compression after puncture may allow the escape of enough edema fluid to facilitate reduction (7,8). Repeated punctures or blood aspirated from the engorged glans after a tourniquet is placed at the base of the penis may also allow reduction (9,10). Subdermal hyaluronidase (1 mL) injected into the edematous foreskin facilitates dispersion of edema fluid and may make reduction possible (11). Some recommend the application of granulated sugar to the edematous glans and foreskin to extract tissue water, reduce edema, and ease reduction (12). Gauze soaked in 20% mannitol wrapped around the edematous prepuce for 30 to 45 minutes may

also facilitate reduction (13). When less aggressive methods fail, incise the phimotic ring to facilitate foreskin reduction (6).

CRITICAL INTERVENTIONS

- Return the foreskin after urinary catheter insertion in uncircumcised males.
- Paraphimosis is a urologic emergency that must be relieved in the ED.

DISPOSITION

Most patients with balanoposthitis may be treated as outpatients. Some diabetics may require inpatient treatment if the infection is severe and the diabetes is poorly controlled.

When phimosis is present and causes urinary retention, consider urologic consultation to relieve phimosis and allow free drainage of urine if a urinary catheter cannot be placed.

Emergent urology consultation is necessary if paraphimosis cannot be successfully relieved in the ED. Patients in whom paraphimosis has been successfully relieved require follow-up with their primary physician and may benefit from future circumcision.

Refer patients with skin lesions suspicious for precancerous changes or malignancy to a dermatologist for further evaluation.

Common Pitfalls

- Phimosis is normal in young boys and does not require treatment in asymptomatic adults.
- Paraphimosis, a urologic emergency, can be confused with balanitis unless it is recognized that the foreskin is retracted.
- Always return the foreskin its anatomic location after retraction.

PRIAPISM

Priapism is characterized by a prolonged, painful, unwanted penile erection, usually in the absence of sexual stimulation. The physiologic balance achieved between venous outflow and arterial

dilatation of the corpora cavernosa controls erectile function. Priapism occurs when normal physiologic blood flow is altered disrupting this balance. Medications used to treat erectile dysfunction in men (sildenafil, papaverine, prostaglandin E1, etc.) are responsible for most cases of priapism (12). It is uncommon in boys, unless sickle cell disease is present, and it is rare in neonates (14). Henoch–Schönlein purpura is described as another cause of priapism (15). Patients with priapism complain of penile pain and persistent erection, even after ejaculation. The mean time to presentation in one series of 34 patients was 30 hours (16).

Priapism may be divided into "low-flow" and "high-flow" types (16). Low-flow priapism results from abnormal venous outflow, whereas high-flow priapism results from abnormally increased arterial inflow. Low-flow priapism is more common and is often caused by vasoactive drugs that cause engorgement of the corpora cavernosa. Impaired venous outflow causes sludging, thrombosis, acidosis, ischemia, and decreased oxygen tension within the corporal bodies. This pathophysiologic cascade causes the irreversible cellular damage and corporal fibrosis responsible for the long-term complications of low-flow priapism. Oral and intracavernosal agents used for erectile dysfunction, antihypertensive agents, psychotropic drugs, cocaine, and ethanol are among the drugs that have been implicated. Leukemia, sickle cell anemia, and a variety of neoplastic etiologies are also responsible for low-flow priapism (16). High-flow priapism is uncommon and usually results from trauma to the penis or perineum (17). Arterial fistula formation between the cavernosal artery and the corporal bodies increases arterial flow into the penis that exceeds venous outflow.

ED EVALUATION

The etiology of priapism can usually be ascertained with careful questioning. Determine the onset of erection and history of prior episodes of priapism. Pay careful attention to prescription or illicit drug use to help determine whether these agents are responsible.

Sickle cell disease may be causative in patients at risk or known to have this disease. The penis is erect and painful to palpation. The corpora cavernosa is engorged and tender to palpation, but in contrast to normal erections, the corpus spongiosum (erectile tissue surrounds the urethra) and glans penis are usually flaccid.

Some authors recommend blood-gas analysis of blood aspirated from the corporal bodies to assist in differentiating between low- and high-flow states (16,17). Low pH, low oxygen tension, and high carbon dioxide levels suggest low-flow priapism, caused by venous obstruction. Blood-gas parameters similar to arterial blood suggest high-flow priapism, a condition usually seen after trauma. Because nearly all cases of priapism are low flow, and trauma is usually associated with high-flow priapism, differentiating between the two is not difficult in most cases, making blood gas analysis unnecessary. Doppler flow ultrasonography of the penis and perineum can be used to document arteriovenous fistulas when high-flow priapism is suspected (17). However, treatment of low-flow priapism should *not* be delayed pending ultrasonography.

ED MANAGEMENT

The ED management of priapism includes both pharmacologic and mechanical treatment options. Untreated ischemic priapism may result in permanent erectile dysfunction. Consider analgesia and sedation to facilitate detumescence. There is conflicting literature describing the efficacy of terbutaline in priapism. Some small clinical trials demonstrate that oral terbutaline is more effective than placebo in achieving detumescence (18), but others have found no benefit (19). Because of its relative safety in patients without hypertension or coronary artery disease, a trial of subcutaneous terbutaline (0.25 to 0.5 mL injected subcutaneously, repeated in 20 minutes if needed) or oral terbutaline (5 mg repeated in 15 minutes) may be attempted (17).

When sedation, analgesia, or terbutaline do not result in detumescence, corporal aspiration and irrigation is indicated (16,17). The penis is anesthetized, and 30 to 60 mL of blood is

aspirated from a single corporal body at the 10 o'clock or 2 o'clock position after puncture with an 18- to 20-gauge needle; anastomoses between the corporal bodies obviate the need for bilateral aspiration. Do not puncture the glans. If the erection persists after aspiration, phenylephrine is carefully injected into the punctured corpus cavernosum. One milligram of phenylephrine is diluted in 9 mL of sterile saline to achieve a concentration of 100 μg/mL, and 100 to 200 μg aliquots of phenylephrine are injected up to three times to achieve detumescence. Monitor blood pressure and cardiac rhythm when repeated injections are required.

Sickle cell patients with priapism require analgesia, hydration, and supplemental oxygen but are also treated with the methods described above. Red blood cell exchange transfusion has been employed when traditional antisickling measures fail, but there is no evidence to support its efficacy (20,21). Emergent ED therapy is not required for high-flow priapism because it does not cause the ischemic injury seen in low-flow priapism.

CRITICAL INTERVENTIONS

- Treat patients with low-flow priapism with terbutaline, corporal aspiration, and/or phenylephrine injection.
- Priapism is a urologic emergency that requires ED treatment in coordination with the consulting urologist.

DISPOSITION

Patients with priapism may be discharged home to follow-up with an urologist after detumescence is accomplished in the ED. When ED treatment fails to relieve the erection or when high-flow priapism is suspected, urgent urologic evaluation is necessary.

Common Pitfalls

- Failure to obtain an adequate history to determine the etiology of priapism.
- Failure to achieve detumescence of priapism prior to discharge.

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CHAPTER 123 Urinary Tract Infection

Lara Kulchycki

Urinary tract infections (UTIs) are among the most common infections encountered by the emergency physician. Women younger than age 50 are affected disproportionately; young, sexually active women are 30 times more likely than their male contemporaries to have a UTI (1). Fifty percent to 70% of women will have a UTI at some time in their lives, placing the annual incidence between 3% and 10% (1,2). Although UTIs are reported in 15% of men prior to age 35 years, they are much more common later in life as disorders of the prostate become more prevalent (3). The incidence of UTI increases with age, affecting elderly men and women with nearly equal frequency.

UTI can be classified by the site of disease and risk of complications. Anatomically, they are divided into upper tract infections of the kidney (pyelonephritis) and lower tract infections of the bladder (cystitis). UTIs can be further classified as complicated when associated with conditions that increase the risk of infection, treatment failure, or morbidity. There are multiple factors associated with complicated infection, including urinary obstruction, indwelling bladder catheterization, ureterolithiasis, pre-existing renal disease, immunosuppression, and pregnancy (Table 123.1). Complicated UTIs can range in severity from simple cystitis to septic shock; it is the associated conditions, not disease severity, that make a UTI "complicated." It is generally held that all UTIs in men are complicated and that true uncomplicated infections occur only in nonpregnant, healthy adult women (4). These classifications have

clinical relevance, as the distinctions have important implications for treatment and disposition.

TABLE 123.1
Risk Factors for Development of Complicated UTI

Anatomic obstruction	Urinary retention/increased postvoid residual
Bladder diverticulum	Immunosuppression
Nephrolithiasis	Chronic renal failure
Other renal structural abnormality	Diabetes mellitus
Polycystic kidney disease	Drug or alcohol abuse
Prostatic hypertrophy	HIV/AIDS
Solitary kidney	Organ transplantation
Urethral/ureteric stricture	Sickle cell anemia and trait
Epidemiologic	Steroids/Immunosuppressant drugs
Age >55 years	Instrumentation
Childhood UTI (prior to age 12 yrs)	Indwelling catheter
Hospitalization	Intermittent catheterization
Male	Ureteric stent
Pregnancy	Other
Functional	Prolonged symptoms prior to treatment (>7 d)
Incontinence	Resistant etiologic organisms
Neurogenic bladder	Treatment failure

UTI, urinary tract infection; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.
Developed from information in articles by Bass PF 3rd, Jarvis JW, Mitchell CK. Urinary tract infections. *Prim Care.* 2003;30:41–61; Krieger JN. Urinary tract infections: What's new? *J Urol.* 2002;168:2351–2358.

The vast majority of UTIs, approximately 95%, result from ascending infection by enteric bacteria (1). The urinary tract is normally an enclosed, sterile system. Bacterial washout by urine flow is the primary host defense against infection, and any interference with this process predisposes an individual to UTI. The remaining 5% of UTIs result from hematogenous spread (1). These infections tend to occur in immunocompromised hosts and can be aggressive, causing severe pyelonephritis or renal abscess (5). The female urinary tract is prone to colonization with enteric bacteria, given the

close proximity of the urethra to the rectum, the moist mucosa surrounding the introitus, and the relatively short (3 to 4 cm) female urethra. The primary risk factors in young healthy women are recent sexual intercourse, use of a spermicide-containing contraceptive, and prior UTI (1,6,7).

The male genitourinary tract is less conducive to colonization and infection. The male urethra is longer, distant from the perineum, and surrounded by dry squamous epithelium (8). As most UTIs occur in older men, these infections are probably the result of incomplete bladder emptying or instrumentation of the genitourinary tract related to prostatic hypertrophy (4). Additional risk factors in healthy men include a lack of circumcision, anal intercourse, a sexual partner with the same uropathogen, and anatomic abnormalities, such as urethral strictures (4,8,9).

Asymptomatic bacteriuria (ASB) is simply the presence of bacteriuria in a patient without UTI symptoms. It is typically defined by a positive urine culture. ASB occurs in only 5% of healthy young women, but the incidence increases with age to as high as 40% in women older than 60 (3,10). Rates of ASB in elderly men are similar. ASB is more common in certain patient populations, such as patients with diabetes, spinal cord injury, indwelling catheters, and those undergoing hemodialysis (11). Although 30% of individuals with ASB develop symptomatic UTI within 1 year, clinical studies show little utility in making the diagnosis except in selected patient populations, most notably pregnant women (10–12).

The organisms responsible for UTIs are largely enteric bacteria. The most common uropathogens are enteric gram-negative bacilli of the class Enterobacteriaceae. *Escherichia coli* is responsible for 80% to 90% of UTIs in reproductive-aged females. *Staphylococcus saprophyticus* causes an additional 5% to 20% of UTIs in this group (10). Other causative organisms include *Proteus, Klebsiella, Citrobacter, Pseudomonas, Enterobacter, and Enterococci.* Institutionalized, catheterized, and immunosuppressed patients tend to develop UTIs caused by gram-positive cocci, Enterobacteriaceae species, and *Candida* (3).

The relative virulence of pathogens differs between complicated and uncomplicated UTIs. Bacterial virulence is crucial for overcoming defenses in the normal host (7). Uropathogenic bacteria are highly adapted to ascend, colonize, and proliferate in the normally sterile urinary tract. In contrast, virulence is less important in complicated UTIs, as host factors largely determine the risk of infection and clinical course (7). Organisms that rarely cause disease in healthy patients can cause significant morbidity in hosts with anatomic, metabolic, or immunologic abnormalities.

Recurrent UTI is defined as three or more episodes of UTI within 1 year. It occurs in 20% to 30% of women with acute cystitis, usually as the result of discrete uncomplicated infections (2). Recurrent infections in premenopausal women are generally not associated with underlying health problems or anatomic abnormalities. However, such patients should be identified for consideration of antibiotic prophylaxis (10). Postmenopausal women with recurrent UTI have higher postvoid residual volumes and reduced urinary flow when compared with age-matched controls (13). These patients may benefit from vaginal estrogen therapy (13). The most common cause of recurrent cystitis in men is chronic bacterial prostatitis.

CLINICAL PRESENTATION

Acute Cystitis

Symptoms of acute cystitis typically include dysuria, frequency, urgency, and suprapubic discomfort. However, patients may present solely with vague complaints, such as chills, malaise, and myalgias. Hematuria commonly occurs. Fever ($>38^{\circ}C$) and severe abdominal pain are rare and should prompt the emergency physician to consider upper tract disease or an alternative diagnosis.

Symptomatic Catheterized Patients

Urinary catheterization is responsible for most cases of nosocomial UTI. The incidence of infection for those with indwelling catheters is 5% per catheter-day (5). Such UTIs are, by definition, complicated,

with manifestations ranging from suprapubic pain, bladder spasms, and incontinence around the catheter to fulminant sepsis.

Acute Pyelonephritis

Acute pyelonephritis can present with variable severity, from a mild cystitis–like illness with flank pain to a more severe illness with fever, rigors, and vomiting. The absence of cystitis symptoms is common (10).

Sepsis

Sepsis in the setting of UTI is most likely to manifest in patients with indwelling catheters, immunosuppression, urinary obstruction, advanced age, or serious underlying medical problems. Elderly patients from extended care facilities are at greatest risk, where the rate of bacteremia from UTI approaches 60% (3). Such patients often present with nonspecific symptoms, including fever, confusion, dehydration, and generalized weakness (3).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute dysuria in emergency department (ED) patients includes primarily infectious and structural disorders. Infectious causes include urethritis, cystitis, pyelonephritis, vulvovaginitis, prostatitis, and epididymoorchitis. Structural causes of dysuria include local trauma, urethral strictures, urethral prolapse, prostatic hypertrophy, and genitourinary neoplasms. Other potential etiologies include vaginal atrophy secondary to hypoestrogenism, reactive arthritis (Reiter syndrome), vasculitis (Behçet syndrome), interstitial cystitis, and various psychogenic conditions.

The flank pain of pyelonephritis can occur with other disease processes. Patients with unilateral costovertebral angle tenderness may have a renal calculus, perinephric abscess, renal infarct, neoplasm, or traumatic injury. Flank pain may be a presenting symptom in vascular, neuromuscular, and pulmonary disease; potential etiologies include abdominal aortic aneurysm,

radiculopathy, muscular back pain, herpes zoster, lower lobe pneumonia, and pulmonary embolism.

ED EVALUATION

The emergency clinician should inquire about the presence and duration of urinary symptoms, such as dysuria, urgency, frequency, suprapubic pain, gross hematuria, foul-smelling urine, nocturia, poor urinary stream, and incontinence. Symptoms of upper tract disease should be sought, including high fever, vomiting, and flank or back pain. Physicians should ask whether the patient has external genital lesions, vaginal complaints, penile discharge, or testicular pain. A detailed sexual history including the possibility of pregnancy, nature of sexual practices, and method of birth control is also prudent. Finally, the patient's medical history should be explored to identify any criteria for complicated UTI (see Table 123.1).

Patient history can help the clinician differentiate between cystitis and urethritis. The urgency, frequency, and incontinence from bladder spasms, which often accompany the dysuria of acute cystitis, are uncommon in isolated urethritis. Urethritis generally presents with a more gradual onset in patients with concomitant vaginal or penile discharge.

The physical examination begins with an assessment of vital signs, general appearance, and hydration status. Examination of the genitourinary tract includes assessment for costovertebral angle tenderness, suprapubic mass or tenderness, and abnormalities of the external genitalia. A pelvic examination should be performed in women if the diagnosis is unclear or the symptoms suggest urethritis or vaginitis. A complete penile, testicular, and prostate examination is necessary in men to differentiate UTI from urethritis, epididymoorchitis, and prostatitis. Clinicians should exercise caution in the evaluation of pediatric (see Chapter 290) and geriatric patients, as they may lack localizing symptoms and signs.

A urine specimen should be collected by the method most appropriate for the patient's clinical status and capacity to cooperate with cleansing guidelines. For most alert, cooperative patients, a clean catch urinalysis can be utilized. The sample should be a

midstream specimen obtained after perineal or penile cleansing. In the presence of poor hygiene, morbid obesity, menstrual blood, copious vaginal discharge, or an anatomic abnormality, the preferred method for obtaining a urine specimen is an in-and-out urethral catheterization of the bladder. The main risk of catheterization is induction of UTI, but this occurs in less than 1% of healthy hosts (14). All specimens should be processed promptly after collection, as stagnation increases colony counts.

Urine dipstick testing relies on nitrite and leukocyte esterase testing to detect infection. The nitrite test depends on bacterial reduction of endogenous nitrates to nitrites and is more likely to be positive in the presence of gram-negative bacteria. The nitrite test may be falsely negative with low-count UTIs, urinary dilution, concurrent antimicrobial therapy, and infections caused by nonnitrate-reducing bacteria (1,15). Although the sensitivity of the nitrite test for culture-confirmed UTI ranges from 19% to 48%, the specificity is 92% to 100% (16). Therefore, a positive nitrite test strongly suggests infection, whereas a negative test does not exclude it. The leukocyte esterase test detects the presence of neutrophil granules and implies pyuria of greater than 8 to 10 white blood cells per high-power field. The sensitivity for the leukocyte esterase test ranges from 72% to 97%, whereas the specificity is 41% to 86% (16). False-positive leukocyte esterase results have been reported with contaminated urine samples or *Trichomonas* infection. Sterile pyuria is also possible, for example, in appendicitis. False-negative results can occur in urine containing glucose or ketones (16). The combination of negative nitrite and leukocyte esterase testing has a negative predictive value of 0.98 (17).

A normal dipstick analysis may obviate the need for urine microscopy. In 95% of cases, negative dipstick testing corresponds to a normal microscopic evaluation (18). As microscopy rarely changes therapy in this case, physicians must consider both the time delay and cost of the test. Full microscopic evaluation may be of assistance in cases where false-negative or false-positive results are expected.

The isolation and quantification of uropathogens in culture can be used to diagnose infection and guide clinical therapy. Traditionally, a

culture must exceed 10^5 colony-forming units (CFU) per mL of urine to confirm infection. However, clinical studies have found this threshold too stringent; 30% to 50% of patients with symptomatic UTI fail to grow 10^5 CFU/mL (15). Early infection, partially treated UTI, use of diuretics, recent voiding, or urinary obstruction may explain these low-count UTIs (15). In a clinical context suggestive of infection, bacterial growth exceeding 10^3 CFU/mL may be sufficient. Symptomatic catheterized patients with counts greater than 10^2 CFU/mL should also be considered infected. This reduced threshold for positive culture still allows clinicians to differentiate UTI from other causes of dysuria (10).

The vast majority of young, healthy women with UTI do not need urine cultures or antibiotic sensitivity testing. Cultures should be obtained in women with a complicated UTI, acute bacterial pyelonephritis, persistent fever of unknown origin, relapsing UTI, neutropenic fever, UTI in the setting of indwelling bladder catheterization or urethral stents, nosocomial urinary infections, or sepsis (19). Cultures may also prove useful in patients with a history that is strongly suggestive of UTI, but an inconclusive physical examination and urinalysis. Because UTIs in men are, by definition, complicated, more conservative evaluation with urine culture is warranted. Although culture results are not available to guide initial ED management, they can be of value to subsequent clinicians caring for the patient.

Additional laboratory studies should be tailored to the patient's history and clinical presentation. Individuals at risk for acute renal failure, such as patients with sepsis, urinary obstruction, or renal transplantation, should have the serum creatinine measured in the ED. If urogenital infection with *Chlamydia trachomatis* or *Neisseria gonorrhoeae* is suspected, cervical cultures, urethral swabs, or first-void urine testing should be performed. Pregnancy testing is indicated for all women capable of childbearing. Blood cultures should not be routinely performed in patients selected for outpatient treatment. Although blood cultures are positive in 18% to 29% of patients with pyelonephritis, the results rarely ($<2\%$) affect antimicrobial therapy, as the causative organism can be obtained

from urine culture (20). In adults, blood cultures may be useful when the diagnosis is unclear, a urine culture cannot be obtained, or bacteremic seeding of the kidneys is suspected.

Radiologic imaging is generally unnecessary in the ED evaluation of patients with UTI, as such studies rarely alter the therapeutic approach (4). Routine imaging of women with pyelonephritis is also not recommended, because the majority of these patients have normal anatomy. In contrast, radiologic imaging of young men with even a single urinary infection yields an anatomic abnormality in more than 30% of cases (4). Indications for emergent imaging are not clearly defined. Infected patients who are severely ill, have suspected obstructive urolithiasis or perinephric abscess, or fail to respond to antimicrobial therapy may require imaging with ultrasonography, computed tomography, or intravenous pyelography.

KEY TESTING

- Urinalysis and pregnancy testing
- Urine culture in patients with complicated UTI, pyelonephritis, or sepsis

ED MANAGEMENT

Acute Cystitis

Patients with uncomplicated acute cystitis can be treated as outpatients with oral antibiotics. As with all antimicrobial therapy, the choice of drug must be tailored to regional susceptibility patterns. Previous urine culture results, if available, maybe useful in agent selection. In vitro studies have found increasing resistance of common uropathogens to first-line agents (21,22). Despite this trend, trimethoprim–sulfamethoxazole (TMP–SMX) remains an excellent first-line agent in regions with a resistance rate less than 20% (3,22). Even patients with culture-proven resistance may achieve clinical cure because of the high urinary concentrations of this agent (1,3,6). Fluoroquinolones or nitrofurantoin remain viable alternatives. Three-day regimens offer comparable efficacy to longer courses (22).

However, if a patient is being treated with nitrofurantoin, a 7-day regimen tends to be more effective. (1,22). Single-dose therapy with fosfomycin tromethamine has been described, but cure rates are lower than with standard agents (23). Beta-lactam antibiotics cannot be recommended as first-line agents, given the high incidence of drug resistance (23). A urinary analgesic, such as phenazopyridine, may be given for symptomatic relief. See Table 123.2 for alternative antimicrobial regimens.

TABLE 123.2
Treatment Regimen for Urinary Tract Infections

Condition	Characteristic Pathogens	Recommended Treatment	Recommended Duration of Treatment
Acute uncomplicated cystitis	*Escherichia coli, S. saprophyticus, Proteus mirabilis, Klebsiella pneumoniae*	Trimethoprim/sulfamethoxazole (TMP–SMX) 160 mg/800 mg bid	3 d
		OR	
		Fluoroquinolones: ciprofloxacin 500 mg bid, ofloxacin 200 mg bid, levofloxacin 250 mg daily	3 d
		OR	
		Cefixime 500 mg daily	3 d
		OR	
		Nitrofurantoin (Macrobid) 100 mg bid	7 d
Recurrent cystitis	*E. coli, S. saprophyticus, P. mirabilis, K. pneumoniae*	Consider prophylaxis with: TMP–SMX 40/200 mg, nitrofurantoin 50 mg, norfloxacin 200 mg, cephalexin 250 mg, trimethoprim 100 mg daily	6 mos
		OR	
		Consider postcoital prophylaxis with TMP–SMX 40/200 mg	
Complicated urinary tract infection (outpatient therapy)	*E. coli, Proteus* species, *Klebsiella* species, *Pseudomonas* species, *Serratia* species, *Enterococci, Staphylococci*	Fluoroquinolones: ciprofloxacin 500 mg bid, ofloxacin 200 mg bid, levofloxacin 250 mg daily	7–10 d
Asymptomatic bacteriuria in pregnancy	*E. coli, S. saprophyticus, P. mirabilis, K. pneumoniae*	Nitrofurantoin (Macrobid) 100 mg bid	3 d
		OR	
		Cephalexin 250–500 mg qid	3 d
		OR	
		Fosfomycin 3 g sachet once	Single dose
Acute pyelonephritis, uncomplicated (outpatient treatment)	*E. coli, S. saprophyticus, P. mirabilis, K. pneumoniae*	Consider IV loading with:	10–14 d
		Gentamicin 3–5 mg/kg, or ceftriaxone 1 g, followed by:	
		Fluoroquinolones: ciprofloxacin 500 mg bid, ofloxacin 200 mg bid, Levofloxacin 250 mg daily	
		OR	
		TMP–SMX (160 mg/800 mg) bid	10–14 d
Acute pyelonephritis, severe (requiring hospitalization)	*E. coli, S. saprophyticus, P. mirabilis, K. pneumoniae*	Gentamicin 5 mg/kg IV daily	Daily until clinically improved, followed by 10–14 d of oral therapy above
		OR	
		Ceftriaxone 1 g IV daily	
		OR	
		Fluoroquinolones: ciprofloxacin 500 mg IV bid, ofloxacin 200–400 mg IV bid, levofloxacin 500 mg IV daily	
Complicated urinary tract infection or Urosepsis (severe illness requiring hospitalization)	*E. coli, Proteus* species, *Klebsiella* species, *Pseudomonas* species, *Serratia* species, *enterococci, staphylococci*	Gentamicin 5 mg/kg IV daily plus ampicillin 1 g IV q 6h	Daily until clinically improved, followed by 10–14 d of oral therapy above
		OR	
		Ceftriaxone 1 g IV daily	
		OR	
		Ticarcillin–clavulanate 3.2 g IV q8h	
		OR	
		Imipenem–cilastatin 250–500 mg IV q6–8h	
		OR	
		Fluoroquinolones: ciprofloxacin 500 mg IV bid, ofloxacin 200–400 mg IV bid, levofloxacin 500 mg IV daily	

Recurrent Urinary Tract Infection

Women with more than three UTIs within 1 year may benefit from prophylactic therapy. Postcoital antibiotic prophylaxis may benefit women whose recurrences are related to intercourse (2,3,21). Continuous daily antibiotic prophylaxis for 6 months with TMP–SMX, nitrofurantoin, norfloxacin, cephalexin, or trimethoprim has also been shown to decrease morbidity from recurrent UTIs (2,13,21). Potential side effects from these regimens include vaginal candidiasis and gastrointestinal symptoms. Unfortunately,

approximately 40% to 60% of these women can be expected to reestablish their pattern of frequent infections within 6 months of discontinuing antibiotics (3). Postmenopausal women with recurrent UTI may benefit from vaginal estrogen therapy, which can also ease the symptoms of atrophic vaginitis (13,24).

Much traditional teaching that emphasizes behavioral modification to reduce the risk of recurrent UTI has not been supported in studies. Specifically, the volume of fluid intake, timing of voiding relative to intercourse, and direction of wiping after voiding have no proven benefit (13). Clinical data on the consumption of cranberry products and lactobacillus probiotics are inconclusive or conflicting (13,25).

Men with recurrent cystitis have an increased incidence of chronic bacterial prostatitis (see Chapter 124). These patients will require a longer course of antibiotics and should receive follow-up with a urologist.

Pyelonephritis

The treatment for pyelonephritis is based on the nature and severity of symptoms. Patients who are febrile and vomiting should receive antipyretics, antiemetics, and intravenous fluids. Some authors advocate the use of single-dose parenteral therapy followed by oral therapy for 10 to 14 days (1,3,7). Acceptable parenteral agents include gentamicin and third-generation cephalosporins. Gentamicin offers the advantage of high urinary concentrations, efficacy against common uropathogens, and a low side effect profile with single-dose therapy (1). Nitrofurantoin is not a recommended agent for upper tract infections, as it may lack sufficient tissue penetration to eradicate disease in the kidney. Because up to 10% of patients develop worsening symptoms within 24 to 36 hours of ED discharge, early follow-up is recommended (1,3). Failure to improve within 48 to 72 hours often signals complicated infection and should prompt further evaluation.

Complicated Urinary Tract Infection

Because of the predisposing conditions in complicated infections, a longer course of therapy and closer follow-up are warranted to ensure a cure. Acceptable agents are listed in Table 123.2. Treatment should consist of a 7- to 10-day course of a fluoroquinolone or TMP–SMX (1,3,4,8). Nitrofurantoin should be avoided in men, given its inability to eradicate organisms in the prostate.

Urinary Tract Infection Complicating Pregnancy

Urinary infections in pregnant women warrant special attention as they require careful antibiotic selection and obstetric follow-up. Many antibiotics commonly used to treat UTIs are contraindicated in pregnancy, such as TMP–SMX and fluoroquinolones. Viable alternatives for treating the parturient include nitrofurantoin and cephalexin (3). A 7- to 10-day course of treatment is recommended for cystitis and a 14-day course for pyelonephritis (1,3). Consultation with the patient's obstetrician is necessary in cases of pyelonephritis.

Asymptomatic Bacteriuria

Treatment of ASB is not advocated except in selected patients at risk for complications (11). Pregnant women with ASB warrant a course of antimicrobial therapy. Although ASB occurs in only 4% to 7% of pregnant women, it is associated with serious maternal and fetal health threats. If untreated, 30% of such women will develop pyelonephritis, a condition associated with an increased risk of amnionitis, premature labor, low–birth-weight infants, and pregnancy-induced hypertension (1,12,22). Recommended ASB treatment regimens include 3 to 7 days of amoxicillin, an oral cephalosporin, or nitrofurantoin (see Table 123.2). Patients scheduled for invasive genitourinary procedures, not including routine catheter changes, should also receive a dose of antibiotics prior to the procedure to decrease the risk of bacteremia. According to Infectious Diseases Society of America (IDSA) Guidelines, there is no evidence to support ASB screening and treatment in patients with immunosuppression, organ transplantation, spinal cord injury, or indwelling catheters (11).

Sepsis

Septic patients require rapid identification and immediate resuscitative efforts. Airway assessment, supplemental oxygen, intravenous crystalloid, early antibiotics, and the judicious use of pressors are the main components of care. Although urine and blood cultures should ideally be obtained prior to antibiotic administration, the acquisition of samples for culture should not delay appropriate therapy. Examples of suitable antibiotics include a third-generation cephalosporin, imipenem–cilastatin, ticarcillin–clavulanate, or ampicillin in combination with an aminoglycoside (see Table 123.2).

CRITICAL INTERVENTIONS

- Identify complicated UTIs and select the antimicrobial agents and duration of therapy accordingly.
- Initiate early parenteral antimicrobial therapy in the patient with sepsis.

DISPOSITION

The involvement of consultants is unnecessary for most patients discharged from the ED with a diagnosis of UTI. Women with uncomplicated cystitis do not require follow-up unless symptoms persist or worsen. Cases of acute pyelonephritis may be referred to primary care physicians for subsequent management. Because of the high incidence of maternal and fetal complications, pyelonephritis in pregnancy has historically been treated as an inpatient (12). However, recent studies suggest that carefully selected women may be managed as outpatients with close obstetric follow-up (1,10,12). Men who develop cystitis prior to age 35 and men older than 50 with recurrent infections should be referred to an urologist (4). Finally, all patients with UTI in the setting of ureterolithiasis warrant urologic consultation in the ED.

Patients with UTI require admission if they have sepsis, severe pyelonephritis, or acute renal failure. Other candidates for admission are those with serious comorbidities, significant dehydration, intractable vomiting, severe pain, or failed outpatient management

(3). Older patients can exhibit striking mental status changes with UTI, and these individuals also require admission.

Common Pitfalls

- Failure to differentiate complicated from uncomplicated UTIs.
- Failure to consider UTI in pediatric or geriatric patients with nonspecific symptoms.
- Failure to perform a pelvic or genitourinary examination when indicated.
- Failure to collect an uncontaminated urine specimen or to recognize a contaminated one.
- Failure to consider local uropathogen susceptibilities in choosing antibiotics.
- Failure to ensure appropriate and timely follow-up.

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CHAPTER 124
Prostatitis

Herbert G. Bivins

Prostatitis is the term used to describe a variety of inflammatory conditions of the prostate. Prostatitis may occur at any age but usually occurs between the second and fifth decades of life (1). Prostatitis is the most common urologic diagnosis in men younger than 50 years of age and the third most common urologic disorder in men older than 50. It is estimated that the US National Ambulatory Survey that prostatitis accounts for approximately 1.5 million patient encounters annually (2,3). Despite being common, prostatitis is often difficult to diagnose, categorize, and treat.

Prostatitis is classified into four categories: I—Acute bacterial prostatitis; II—Chronic bacterial prostatitis; III—Chronic pelvic pain syndrome (CPPS), with or without inflammation. Category IV is termed asymptomatic inflammatory prostatitis and is a biopsy diagnosis, which will not be further discussed (4).

CLINICAL PRESENTATION

Acute bacterial prostatitis typically presents with fever, chills, malaise, and a tender prostate on examination. In addition, there may be pain in the perineum, rectum, testicles, or lower back. Systemic symptoms may be present and sometimes appear prior to the lower urinary tract symptoms of dysuria, frequency, and dribbling. There may be urinary retention secondary to bladder outlet obstruction from the inflamed, edematous prostate. Pain with ejaculation may occur as well as the finding of blood in the semen. Acute prostatitis generally occurs from migration of bacteria from

the urethra or bladder, through the prostatic ducts, and into the prostate. Acute prostatitis may also occur in patients with an indwelling Foley catheter, after instrumentation or catheterization of the urethra, or after prostatic biopsy (5). The typical presentation along with the clinical finding of an enlarged, tender prostate on physical examination is consistent with a diagnosis of acute bacterial prostatitis.

Chronic bacterial prostatitis is more common, and may present more subtly than acute prostatitis. Typically the patient is a middle-aged man with recurrent urinary tract infection. Patients may have perineal discomfort, frequency, urgency, or dysuria, or they may be asymptomatic. An incidental finding of bacteriuria, or pyuria, should alert the clinician to consider the diagnosis of chronic bacterial prostatitis. The prostate may be enlarged, tender, boggy, or normal. Chronic bacterial prostatitis may occur after an episode of acute prostatitis or without any recognized antecedent infection.

Chronic pelvic pain syndrome is more common than acute or chronic bacterial prostatitis, yet the etiology is unclear and may be multifactorial (6). Pain is the predominant presenting symptom and is usually located in the perineum, suprapubic area, penis, testicles, or lower back. Difficulty with urination (hesitancy, dribbling, frequency, and urgency) is also common (7). Symptoms may vary but need to be present for 3 months to be considered chronic.

DIFFERENTIAL DIAGNOSIS

On occasion, disorders of the lower back and abdomen may have presenting symptoms similar to those of prostatitis, but generally the differential diagnosis includes other disorders of the urinary tract and rectum (Table 124.1). Differentiating acute bacterial prostatitis from the chronic forms is not difficult. The history and physical examination usually confirm the diagnosis. Chronic forms of prostatitis may be difficult to differentiate. The gold standard for distinguishing among disorders of the urethra, bladder, and chronic prostatic syndromes has been the *Meares–Stamey four-glass test,* which is described later.

TABLE 124.1
Differential Diagnosis

Cystitis	Perineal abscess
Interstitial cystitis	Perirectal/perianal abscess
Urethritis	Proctitis
Epididymitis/orchitis	Pyelonephritis
Seminal vesiculitis	Urolithiasis
Benign prostatic hyperplasia	Vesicular calculi
Prostatic cancer	Sacroiliitis, discitis, osteomyelitis, piriformis muscle strain

ED EVALUATION

The diagnosis of acute bacterial prostatitis is usually obvious. Examination of the acutely inflamed prostate should be performed gently so as not to cause bacteremia. Massage of the prostate and catheterization of the urethra in acute bacterial prostatitis may cause bacteremia and should be avoided. Because urinalysis and urine culture are essential, it may be necessary to perform needle aspiration of the bladder if the patient is obstructed (2). Complete blood cell counts, electrolytes, and blood cultures are of little benefit unless the patient is toxic, immunocompromised, or other underlying medical conditions are present that require further laboratory analysis. Bacterial prostatitis occurs more often in patients with human immunodeficiency viral (HIV) infection. Signs and symptoms are the same but prostatic abscess formation is more common, and there may be unusual organisms such as *Haemophilus parainfluenzae* and *Cryptococcus neoformans* as the causative agents (8). The general incidence of prostatic abscess is low but should be considered if the prostate is fluctuant or cannot be examined because of severe pain, or if there is no response to therapy. The diagnosis may be confirmed by computerized axial tomography or transrectal ultrasonography (9,10). Other than to establish a diagnosis of prostatic abscess, there is little reason to image the prostate in the ED.

The diagnosis of chronic bacterial prostatitis should be considered in men with recurrent urinary tract infections, asymptomatic

bacteriuria, perineal discomfort, and other urinary tract symptoms. Traditionally the diagnosis was confirmed using the *Meares–Stamey four-glass urine test.* This test compares the first 10 mL of voided urine, a midstream urine sample, expressed prostatic secretions, and a postmassage urine specimen. The urine specimens are centrifuged and examined under high power for leukocytes, bacteria, fungal hyphae, red blood cells, and oval fat bodies. All four samples are sent for culture (11).

Distinguishing between the chronic forms of prostatitis is unnecessary in the ED. Not only is the four-glass urine test impractical in the ED, but a survey of urologists revealed that 34% of respondents never used the test and 47% rarely did, and treatment was not affected (12). There may be no difference of bacterial localization rates in prostatic specific specimens in men with CP/CPPS and controls (13). A two-sample urine test has been recommended as a simple replacement to the four-glass test (14). Midstream premassage urine and postmassage initial 10 mL urine samples are obtained. Microscopy and cultures categorize the majority of chronic prostatitis patients almost as accurately (91% sensitivity and specificity) as do prostatic secretions (eTable 124.1) (15).

eTABLE 124.1
Two-Glass Urine Test

	Premassage Urinalysis			*Postmassage Urinalysis*		
Category	WBC	Bacteria	Culture	WBC	Bacteria	Culture
I (acute)	++	+	+		Not indicated	
II (chronic)	+–	+–	+–	+	+	+
III A	–	–	–	+	–	–
III B	–	–	–	–	–	–

WBC, white blood cell.

KEY TESTING

- Urinalysis and culture. Further testing is unnecessary in most patients.

ED MANAGEMENT

Acute bacterial prostatitis can be a serious and potentially life-threatening disease. Treatment of the toxic patient requires parenteral antibiotics, adequate hydration, analgesics, and admission. Drug penetration of the normal prostate is complex and dependent on lipid solubility, degree of protein binding and ionization, size and shape of the molecule, and pH. With acute inflammation, there is an increase in prostatic permeability; therefore, acute bacterial prostatitis is generally responsive to a wide variety of antibiotic agents. A urine Gram stain may be helpful in guiding the initial therapy but the usual causes of infection are the Enterobacteriaceae gram-negative bacteria. *Escherichia coli* accounts for 65% to 85% of infections, and *Pseudomonas, Klebsiella, Proteus,* and *Serratia* sp account for 10% to 15%. *Enterococcus, Staphylococcus aureus,* and other gram-positive organisms may account for 5% to 10% of acute infections (16). There also have been recent reports of community-acquired methicillin-resistant *S. aureus* causing both acute prostatitis as well as prostatic abscess (17). In sexually active young men, *Neisseria gonorrhoeae* and *Chlamydia trachomatis* must be considered. *Mycoplasma* and *Ureaplasma* have also been implicated as causes of prostatitis (18).

The most commonly used oral antimicrobials for bacterial prostatitis have been trimethoprim-sulfamethoxazole (TMP–SMX) and the fluoroquinolones (16). Since there is increasing resistance to commonly employed antibiotics, it is essential to obtain a urine culture prior to empiric therapy (19). In many areas of the United States, the resistance of *E. coli* to TMP–SMX is greater than 25% (20). Fluoroquinolones have been shown to be superior to TMP–SMX, and levofloxacin once a day (500 mg) for 28 days is as effective as ciprofloxacin (500 mg) twice a day for 28 days (15). A total of 4 to 6 weeks of antibiotics may be required, owing to decreasing tissue penetration of the prostate as the inflammation resolves. Patients who cannot tolerate oral medications, appear toxic, are immunocompromised, have urinary retention, or for whom outpatient therapy has failed should be admitted and treated

with parenteral broad-spectrum antibiotics. A cephalosporin or aminoglycoside should be given along with a fluoroquinolone or ampicillin. For those patients who have failed outpatient quinolone therapy, imipenem, cefoxitin, or amoxicillin/clavulanic acid is effective (19). Outpatient therapy for acute bacterial prostatitis should include a fluoroquinolone or TMP–SMX (21) (Table 124.2). Although most patients respond to therapy, complications may include chronic bacterial prostatitis, epididymitis, bacteremia, prostatic abscess, and metastatic spread of the infection.

TABLE 124.2
Treatment Recommendations

NIH Consensus Category	Antibiotic/Dosage
Category I (Acute Prostatitis)	
Inpatient: Parenteral cephalosporin + quinolone or aminoglycoside + ampicillin Continue oral antibiotics based on culture results for 4 wks	Ceftriaxone 1–2 g IV qd, OR Cefoxamine 1–2 g IV q6h–q8h, OR Gentamicin or tobramycin 3–5 mg/kg/d + Levofloxacin 500 mg PO/IV qd, OR Ampicillin 1–2 g IV q6h
Outpatient: Oral quinolone or TMP-SMX for 4–6 wks	Levofloxacin 500 mg PO qd, OR Ciprofloxacin 500 mg PO bid, OR TMP–SMX 1 PO bid (160/800 mg bid)
Category II (Chronic Prostatitis)	
Oral fluoroquinolone or TMP–SMX (based on local resistance) for 4–12 wks	Levofloxacin 500 mg PO qd, OR Ciprofloxacin 500 mg PO bid, OR TMP–SMX 1 PO bid (160/800 mg bid)
Category III (Chronic Pelvic Pain Syndrome)	
Treat with analgesics, sitz baths Consider antibiotics as in category II in combination with α-blockers	(tamsulosin 0.4 mg PO daily)

Chronic bacterial prostatitis is usually caused by the same organisms. Treatment strategies for chronic bacterial prostatitis include both full-dose prolonged antibiotic therapy for 4 to 12

weeks, or daily suppressive therapy (3). The decision to place the patient on suppressive therapy is best left to the urologist or primary care physician.

Management of CPPS is often difficult for the physician and frustrating for the patient. Although this condition may be noninfectious, some clinicians will treat the inflammatory subtype with a trial of antibiotics for the possibility of infections caused by *Chlamydia, Mycoplasma,* or *Ureaplasma* (17). A study that compared tissue cultures from prostate biopsy of asymptomatic controls to patients with CPPS demonstrated no statistical difference (20). One Canadian multicenter, randomized, placebo-controlled study demonstrated no difference in symptom improvement after 6 weeks of levofloxacin, as compared to placebo (22). Recent studies suggest that treatment of CPPS with α-blockers, antibiotics, and anti-inflammatory medications may be beneficial (23,24). Symptomatic treatment with Sitz baths and nonsteroidal anti-inflammatory medications may also be helpful. Allopurinol, hormones, botulinum toxin, muscle relaxants, exercise, and a variety of nontraditional therapies have been recommended for CPPS, but there is insufficient evidence to justify their routine use in the ED (21).

CRITICAL INTERVENTIONS

- Initiate parenteral antibiotic therapy for toxic patients with acute bacterial prostatitis.
- Empiric treatment of acute bacterial prostatitis should cover infection with gram-negative rods.

DISPOSITION

Toxic patients with acute bacterial prostatitis should be admitted to the hospital for parenteral antibiotics. Because outpatient treatment of both acute and chronic bacterial prostatitis is prolonged and based on urinalysis, culture results, and, in many cases, biopsy, it is important to involve the patient's urologist or primary care physician in management and follow-up decisions. Patients with CPPS should be treated symptomatically and referred to a urologist.

If subspecialty referral is not easily obtainable, a trial of antibiotics, α-blockers, and anti-inflammatory medications for patients with newly diagnosed CPPS is reasonable (23,24).

Common Pitfalls

- Digital massage of the prostate and urethral catheterization should be avoided in acute bacterial prostatitis.
- Failure to place a suprapubic catheter in the setting of bladder outlet obstruction from an acutely inflamed prostate.
- Imaging of the prostate in the ED is unnecessary except when an abscess is suspected.

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CHAPTER 125

Fournier Gangrene

Gregory W. Hendey

Originally described in 1764 by Baurienne, perineal gangrene today bears the name of Jean-Alfred Fournier, a French dermatologist, who described a case in 1883 (1,2). Fournier gangrene is the most severe end of a spectrum of scrotal and perineal infections, ranging from cellulitis to abscesses to necrotizing gangrene. Primary abscesses of the scrotal skin may originate from infections of the hair follicles or sweat glands. These abscesses tend to be superficial and similar to those found elsewhere on the body. Deep scrotal and perineal infections usually arise, on the other hand, from infection of the urinary tract or scrotal skin or from perirectal disease. Urogenital sources include extravasation of infected urine caused by a urethral stricture or after urethral instrumentation. Superficial skin abscesses, if left untreated or inadequately treated, may spread along deep fascial planes. Anorectal sources tend to be deep-rooted abscesses that may have spread extensively by the time of diagnosis. Eventually, the tunica albuginea is penetrated, with spread to Buck fascia. Once Buck fascia is invaded, the next barrier is the Colles fascia. Infection may spread anteriorly along the Colles fascia to involve the scrotum.

Fournier gangrene is a type of necrotizing fasciitis characterized by the rapid spread of a severe subcutaneous infection, with massive scrotal and perineal induration and swelling, which progresses to scrotal wall necrosis within 24 hours if not recognized and treated. The morbidity and mortality of Fournier gangrene are high. Though early reports estimated the mortality to be as high as 80%, more recent reports are less than 40% (1,3). The usual age of affected

patients is 50 to 60 years, and diabetics and alcoholics are particularly at risk (1,4–7). The typical organisms include *Escherichia coli, Bacteroides fragilis, Clostridium* sp, and hemolytic streptococci, though community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) has been reported (4,8,9).

CLINICAL PRESENTATION

Deep scrotal abscesses and Fournier gangrene may present as generalized scrotal swelling. The onset may occur several days after instrumentation of a urethral stricture or in an inadequately treated diabetic with an initial superficial skin abscess. The patient may have a history of perirectal disease. Pain is usually intense, but initial physical examination of the affected area can be subtle. Eventually, fever and other constitutional symptoms emerge and may lead to hypotension and sepsis. Diabetic patients may present with ketoacidosis. The scrotum is usually edematous, indurated, erythematous, tense, and warm, with or without a localized area of fluctuance or necrosis.

DIFFERENTIAL DIAGNOSIS

Superficial scrotal skin abscesses seldom cause difficulty in diagnosis. A localized area of erythema with a smaller area of suppuration is found on examination. Most patients are afebrile and without constitutional symptoms. Superficial abscesses may be incised and drained under local anesthesia in the emergency department (ED).

Scrotal edema from congestive heart failure or lymphatic obstruction may appear similar to scrotal infection. Concomitant edema of the lower extremities, however, shifts the differential away from an infectious cause. Occasionally, edema of the scrotum occurs as a result of an allergic reaction, but the scrotum should not be tender to palpation, and the erythema and warmth are substantially less than those found in infectious causes. Cellulitis of the scrotum may present with significant edema, and the distinction from a deep abscess may be difficult. Severe cases of

epididymoorchitis may also present with scrotal induration that mimics a deep scrotal abscess or Fournier gangrene. Other skin conditions that may mimic Fournier gangrene include pyoderma gangrenosum and warfarin necrosis.

ED EVALUATION

Rapid diagnosis and treatment of bacteremia are the principles of the initial approach. When the diagnosis is clinically obvious, immediate treatment and consultation is warranted. In less apparent cases, bedside ultrasonography may be helpful in differentiating hernia, cellulitis, localized abscess, and gas collections in the scrotal wall to facilitate a more rapid diagnosis (10). Subcutaneous air may also be demonstrated on plain radiographs of the pelvis, on ultrasound, or on computed tomography (CT) scan, although this finding is not necessary to establish the diagnosis, which is largely clinical. If urethral obstruction is suspected as the inciting cause, a urethral catheter should be placed into the bladder. The rectum and perineum should be examined carefully for induration and fluctuance. Blood cultures and laboratory studies should be obtained in anticipation of surgery and postoperative critical care.

KEY TESTING

- CBC, electrolytes, lactate, blood cultures, type and screen
- Imaging as needed (plain films, ultrasound, CT scan) to make the diagnosis or define extent of disease

ED MANAGEMENT

Fournier gangrene requires aggressive medical resuscitation with intravenous (IV) fluids and broad-spectrum antibiotics, such as ampicillin/sulbactam (Unasyn) 3 g IV, ticarcillin/clavulanate (Timentin) 3.1 g IV, or piperacillin/tazobactam (Zosyn) 3.375 g IV, and Clindamycin 900 mg IV. Vancomycin 1 g IV should be added if MRSA is suspected.

These modalities should be instituted as soon as possible, while urologic consultation is obtained, and the operating room should be

alerted for emergency surgical debridement. Although aggressive resuscitation, supportive measures, and early antibiotics are important aspects of the initial emergency care for patients with Fournier gangrene, this is a surgical emergency, and the definitive care is operative. It is imperative to involve the surgeon early, without delaying for the results of laboratory or imaging studies. Surgical debridement tends to be extensive and often requires multiple procedures, including urinary and fecal diversions and skin grafting.

CRITICAL INTERVENTIONS

- Initiate fluid resuscitation and broad-spectrum antibiotic coverage as soon as the disease is recognized.
- Immediately consult a surgeon, as aggressive debridement is necessary in most cases. If appropriate care is unavailable, consider a rapid transfer to a facility with such services.

DISPOSITION

Surgical drainage with wide debridement and antibiotic therapy must be instituted rapidly because of the extremely aggressive nature of Fournier gangrene (7). Postoperative hyperbaric oxygen therapy has also been recommended and may promote wound healing (1,5,6,11).

All patients with scrotal cellulitis, deep abscess, or Fournier gangrene should be admitted to the hospital, and most will require surgery and critical care resources.

Patients should be transferred if surgical consultation or intensive care beds are not available.

Common Pitfalls

- Underestimating the severity of infection. With Fournier gangrene, a delay of several hours can make a significant difference in morbidity (1,4,7).
- Failure to rapidly institute fluid resuscitation, antibiotics, and surgical consultation.

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CHAPTER 126 Urolithiasis

Stephen R. Hayden and Michael P. Wilson

Calculous disease (from the Latin *calculo&hibar;sus* or “pebble”) of the urinary tract affects people of all ages (1). As many as 2 million outpatient visits per year may be related to urinary calculi, termed *urolithiasis* or more commonly “stones.” As many as 6% to 12% of adults may experience a symptomatic kidney stone during their lifetime (2). This incidence is variable according to the geographic location, climate, and season. The southeastern United States has been called the “stone belt,” because it is a geographic area with an unusually high incidence of urinary calculi, especially during the summer (3). The incidence of calculous disease in Caucasians is reported to be approximately twice that in African Americans and Asians. The male-to-female ratio is approximately 2:1. The disease is relatively uncommon in patients younger than 15 years, with the highest incidence during the third and fourth decades of life. There are four basic types of urinary calculi: calcium salts, struvite, uric acid, and cystine (3). The underlying pathophysiology of stone formation in the urinary tract is complex, likely involving supersaturation of the involved salt. Stones that contain calcium salts are by far the most common type of stone encountered (Table 126.1). Struvite (ammonium magnesium phosphate) is the second most common type and is associated with infection by urea-splitting organisms such as *Proteus, Klebsiella, Staphylococcus* sp, and *Providencia.* The third type of stone, from uric acid, is less common in its pure form, occurring with an estimated frequency of 10%. The fourth type of stone, from cystine, is rare, representing $<1\%$ of all stone disease. Patients who form cystine stones have the autosomal

recessive genetic disorder cystinuria. The natural history of urinary calculi varies according to the size of the stone (Table 126.2) (4). Most stones 5 mm or smaller will pass spontaneously, with higher rates of passage for calculi located in the midureter or more distally. Vesical calculi occur predominantly in males. Most bladder calculi present during adult life and are secondary to bladder outlet obstruction or foreign bodies in the bladder, such as an indwelling catheter. Calcium oxalate is the most common constituent of bladder calculi in the United States, although the incidence of struvite and hydroxyapatite calculi in the bladder is higher than in the kidneys.

TABLE 126.1
Distribution of Various Stone Types (by Predominant Compound)[a]

Stone Type	Percentage (%)
Calcium oxalate	72
Infection stones (struvite and carbonate apatite)	16
Uric acid	6
Cystine	1
Other	5

[a]Crystallographic analyses of 49,000 stones from Beck Analytical Services, Indianapolis, Indiana.

TABLE 126.2
Spontaneous Passage of Ureteral Stones by Size

Stone Size (mm)	Percentage Spontaneous Passage (%)
1	87
3	83
5	60
7	47
10	27

[a]Adapted from Coll DM, Varanelli MJ, Smith RC. Relationship of spontaneous passage of ureteral calculi to stone size and location as revealed by unenhanced CT. *AJR Am J Roentgenol*. 2002;178:101–103.

CLINICAL PRESENTATION

Patients with urinary calculi often present writhing in pain, unable to find a comfortable position. Although pain is the principal reason for an emergency department (ED) visit, hematuria and symptoms of urinary tract infection are common complaints. Many patients also have a history of previous stones. Calculous disease is rare in children and, when encountered, may indicate a genetic or metabolic disorder. Symptoms compatible with both a kidney stone and a urinary tract infection may suggest a true urologic emergency—an obstructing stone associated with infection. The pain of renal calculi is acute in onset because of rapid distention of the renal pelvis and upper ureter. It is visceral in nature, with waxing and waning of symptoms. Typically, the pain is localized to the flank, but may be referred to the ipsilateral testis or labia because of similar embryonic origin of these structures. As the stone moves down the ureter, the pain may move from the flank to the ipsilateral lower quadrant of the abdomen. As the stone nears the bladder, symptoms of frequency and urgency may occur. Nausea and vomiting are common, being most intense at the peak of the colic episode. The pain of renal colic, in which patients are unable to find a comfortable position, is in contrast to patients with peritonitis, who typically lie still because movement aggravates their pain. Tachycardia, tachypnea, and hypertension may be present because of sympathetic stimulation from the pain. A fever implies a concomitant urinary tract infection. Costovertebral angle tenderness is often present, and auscultation of the abdomen may reveal diminished bowel sounds because ileus commonly accompanies renal calculi. Typical symptoms of bladder, or *vesical calculi,* include pain on voiding and hematuria. The pain, which may be dull or sharp, is often severe, with exercise or sudden movement, at the end of micturition. Hematuria often occurs at the end of voiding. Interruption of the urinary stream from impaction of the stone at the bladder neck may occur. Frequency, urgency, and dysuria are present in up to 50% of patients. Urinary tract infection is common, especially if an indwelling catheter is present.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a patient with suspected urinary calculus is broad (Table 126.3). Urologic diseases that simulate urolithiasis may be divided according to anatomic site. Upper tract diseases include renal infarct and tumors. The upper ureter may be obstructed by blood clots or sloughed renal papillae; the latter are seen most commonly in patients with sickle cell disease, analgesic abuse, and diabetes mellitus. Ureteral obstruction may be secondary to prior urologic instrumentation, tuberculosis, ureteral strictures, surgery, intrinsic urothelial tumors, or extrinsic compression due to metastatic tumors or other masses. Important, nonurologic causes of flank pain include peritonitis, abdominal aortic aneurysm, appendicitis, diverticulitis, biliary colic, ovarian cyst, retroperitoneal lymphadenopathy from tumors (the most common of which is lymphoma), and retroperitoneal fibrosis. A Munchhausen-like syndrome featuring flank pain may be encountered in the ED. These patients are typically quite knowledgeable about urolithiasis. The hematuria often resolves when the urine is collected in the presence of a nurse or physician, and these patients typically require large doses of narcotics to alleviate pain. This group of patients poses a significant management problem for the physician, and the burden of proof is on the physician to rule out a true pathologic process.

TABLE 126.3
Diseases that Simulate Urolithiasis

Urologic Disease	Nonurologic Disease
Renal infarct	Appendicitis
Renal parenchymal tumors	Diverticulitis
Papillary necrosis	Biliary colic
Pyelonephritis	Intestinal obstruction
Hematoma	Abdominal aortic aneurysm
Ureteral stricture	Retroperitoneal adenopathy
Urinary retention	Tumor
	Ovarian cyst
	Endometriosis
	Musculoskeletal back pain

ED EVALUATION

It is important to be certain that an *obstructive* calculus does not coexist with urinary infection, because such patients are at significant risk for the development of urosepsis. The ED evaluation of patients with suspected renal stones should reflect these concerns. The most important initial laboratory test is the urinalysis. Most patients with urolithiasis have hematuria, but 10% to 15% do not. The degree of hematuria is not predictive of the severity of disease (5). A pH >7.5 in a fresh urine specimen suggests infection with urea-splitting organisms. Culture is helpful in such cases. Serum electrolyte levels are usually normal and it is not necessary to routinely test them. However, prolonged vomiting may lead to metabolic alkalosis. Serum creatinine levels are usually normal but can be elevated in cases of prolonged, high-grade obstruction. Hypercalcemia (calcium level >10.2 mg/dL) in a patient with nephrolithiasis may signal the presence of primary hyperparathyroidism. Leukocytosis is common because of demargination of white blood cells caused by the stress of renal colic and does not necessarily suggest infection. Radiologic studies are essential in establishing the diagnosis of urolithiasis. Approximately 90% of urinary calculi contain calcium, but many studies report that <50% are actually visualized on plain radiographs. An imaging study such as computed tomography (CT) scan is usually therefore necessary for the initial diagnosis of urolithiasis (6). The sensitivity and specificity of CT ranges from 96% to 100%, and the study is generally quite rapidly performed (7). CT demonstrates renal and ureteral calculi, including radiolucent calculi, and gives information regarding the presence or absence of hydronephrosis and the degree of obstruction (Fig. 126.1). Importantly, CT also provides important information about other retroperitoneal and intra-abdominal conditions in approximately 16% of cases (8). However, concern is growing about the cumulative radiation exposure of multiple CT scans, particularly in young people. In some cases, it is desirable to avoid both contrast and radiation (i.e., pregnancy). Ultrasound (US) is a viable alternative in this setting. US is approximately 16% sensitive for stones <7 mm, but perhaps as much as 75% sensitive

for stones ≤7 mm, and is highly sensitive for hydronephrosis (9). US may be most useful in patients with known calculous disease, as repeat CT scanning does not often change management in these patients (10).

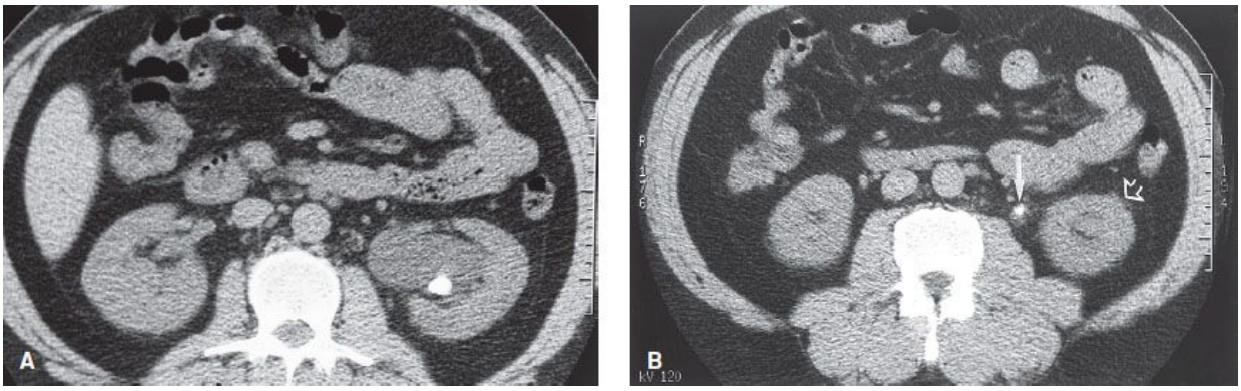


FIGURE 126.1 Noncontrast spiral computed tomography (CT). **A:** Large stone in the hydronephrotic left kidney. **B:** A 5-mm stone in the ureter, surrounded by soft tissue—the "soft-tissue rim" sign (*solid arrow*). Also note minimal left perinephric stranding near inferior pole of kidney (*open arrow*). (From West OC, Tamm EP, Kawashima A, et al. Nontraumatic emergencies. In: Harris JH Jr, ed. The Radiology of Emergency Medicine, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2000:622, with permission.)

KEY TESTING

- Urinalysis and pregnancy test
- CT scan or US as discussed above

ED MANAGEMENT

The management goals in the ED are to make the proper diagnosis and provide relief of the pain. Analgesia should be provided simultaneously with diagnostic testing. Morphine and hydromorphone are common parenteral narcotics used in treating colic, and large, repeated doses may be necessary to relieve the initial pain. Anticholinergic or spasmolytic medications commonly used in Europe have not been found to be uniformly useful in the United States. The pain of ureteral colic is mediated by

prostaglandins released by the ureter in response to dilation. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis and decrease glomerular filtration. Ketorolac (Toradol) is the only parenteral NSAID available in the United States, and it has been shown to be as effective as opioids in relieving the pain of ureteral obstruction (11). Ketorolac is considered by many as the agent of choice for initial management of renal colic. Maximal pain relief using ketorolac has been shown to occur approximately 45 to 60 minutes after a parenteral dose. It is reasonable to treat patients with severe pain with an opioid analgesic given simultaneously with an initial dose of an NSAID such as ketorolac or ibuprofen. NSAIDs should be used with caution in patients with a history of gastrointestinal bleeding, renal insufficiency, or cardiovascular disease. Acute decreases in renal blood flow (35%) were noted after acute infusion of ketorolac in a unilateral ureteral obstruction dog model (12). Acute, transient renal failure occurred in six patients with cardiovascular disease when given ketorolac (13). Nausea and vomiting are common with ureteral colic and can be exacerbated by opioids. In such patients, administration of an antiemetic agent is appropriate.

IV fluid therapy has not been shown to reduce pain or facilitate stone passage in acute urolithiasis and is not necessary unless the patient is volume depleted. Stone-dissolving agents play a limited role in acute treatment, and the main options are either conservative or surgical (14).

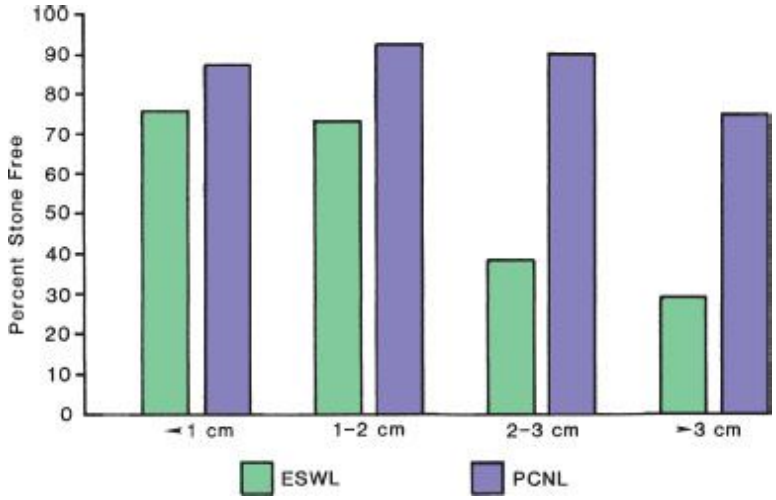
Recent evidence suggests that the selective α-blocker tamsulosin (Flomax), when added to standard pain control regimens, may increase the rate of successful stone passage within 1 month and reduce the time to successful stone passage by 2 to 6 days (15). The recommended dose of tamsulosin is 0.4 mg per os (PO) daily for 7 to 14 days or until stone passage occurs. Tamsulosin or other α-blockers are recommended over other types of medical expulsive therapy such as calcium channel blockers (16), but their efficacy remains disputed.

Infected stones can be associated with significant morbidity, especially in the setting of high-grade urinary obstruction (17). The common organisms in urine and blood cultures are *Escherichia coli,*

Proteus, and *Klebsiella* sp. Bacteremia is seen in 70%, and septic shock occurs in approximately 20%. Antimicrobial coverage, usually with fluoroquinolones, is directed at these organisms. Infection in the setting of high-grade obstructive uropathy requires emergent decompression. Given the risks of urosepsis, the American Urological Association further recommends that patients with urolithiasis and bacteriuria but without clinical signs of urinary tract infection should also be treated with appropriate antibiotics (16).

Urologic Interventions

The acute management of urinary tract stones is dependent on the presence of related complications, namely renal impairment or infection (acute obstruction alone is not a primary indication for intervention) (18). Emergency drainage can be achieved by placement of either a nephrostomy catheter or a retrograde stent. The choice between the two is often based on local experience and resources, but a nephrostomy may be preferable in the presence of significant sepsis and thick pus. Several technologic advancements have revolutionized the treatment of symptomatic urolithiasis in the past several decades (Table 126.4). The most important of these advancements has been the development of extracorporeal shock wave lithotripsy (ESWL). This technology has been proven effective in the management of 85% to 90% of cases that require intervention. Patients with large stones (i.e., >2 cm in diameter), cystine stones, and staghorn calculi are much less likely to become stone-free with ESWL monotherapy (eFig. 126.1). Ureteral calculi can also be managed effectively with ureteroscopy with or without stenting. This allows visualization of the entire ureter from the bladder to renal pelvis and removal of ureteral calculi under direct visualization. In general, upper ureteral calculi tend to be managed with ESWL or nephroscopy, whereas ureteroscopy is commonly used for distal ureteral stones (15,18). An important goal is to prevent further stone formation. Medical therapy based on stone analysis can dramatically reduce the incidence of recurrent stone formation (15). This evaluation may be initiated in the ED by checking serum electrolyte levels.



eFIGURE 126.1 Percentage of patients who are stone-free after extracorporeal shock wave lithotripsy (ESWL) and percutaneous nephrostolithotomy (PCNL), stratified by initial stone size. Most ureteral calculi are <2 cm in diameter.

TABLE 126.4
Current Options for Urolithiasis Management

1. Open surgery
2. Percutaneous nephrostolithotomy
3. Ureteroscopy
4. Extracorporeal shock wave lithotripsy
5. Observation

CRITICAL INTERVENTIONS

- Search for evidence of concomitant urine infection or bacteriuria.
- Provide adequate analgesia with a combination of opioids and NSAIDs.

DISPOSITION

Most patients with adequate control of symptoms and without signs of infection may be treated as outpatients with oral analgesics and antiemetics. Those with isolated pyuria, without other clinical signs of infection, may often be treated as outpatients. Pending the results of currently ongoing research, medical expulsive therapy with α-

blockers such as tamsulosin may be offered. Patients should be counseled on the side effects of medical expulsive therapy, including that this is an off-label use of these medications. They should be instructed to strain the urine and save any stones for analysis, and should be instructed to seek immediate medical for recurrent severe pain, persistent vomiting, or onset of fever. Outpatient urologic follow-up should be arranged within 2 weeks for all stones, and sooner for those with large stones.

The most common factor necessitating admission is severe, refractory pain. Persistent nausea and vomiting, obstruction with clinical signs of infection, renal stones >10 mm, and urinary extravasation on CT are other indications for admission (Table 126.5). Infection in the presence of high-grade obstruction from a stone is a urologic emergency that necessitates not only admission but also immediate urologic intervention. Drainage can be accomplished either by cystoscopy and passage of a ureteral catheter or by placement of a percutaneous nephrostomy tube. Antibiotics alone are not adequate therapy in these circumstances because the patient can otherwise experience continued bacteremic showering, progression to frank urosepsis, and rapid destruction of the involved kidney. Delay in drainage can lead to significant morbidity and death. Another factor influencing the disposition is the stone size. Calculi <5 mm usually pass spontaneously, whereas those >8 mm rarely do (14). Patients with high-grade obstruction are more likely to require intervention and admission. Patients with a solitary kidney or underlying intrinsic renal disease are more likely to experience a significant decrease in renal function with any degree of obstruction, so the threshold for admission of such patients is lower. Calculi that develop in patients with a renal transplant are usually managed in the inpatient setting to best preserve the graft.

TABLE 126.5

Indications for Admission
Obstruction with clinical signs of infection
Pain not controlled by oral analgesics
Persistent nausea and vomiting
Urinary extravasation
Hypercalcemic crisis
Relative Indications for Admission
High-grade obstruction
Solitary kidney
Intrinsic renal disease
Large obstructing stone
Long duration of symptoms
Inadequate social situation

Common Pitfalls

- The most common misdiagnosis in patients ultimately found to have abdominal aortic aneurysm is kidney stone. CT is helpful in making the correct diagnosis.
- Pain not responding to appropriate pain control measures is often associated with high-grade obstruction.
- Admission may be indicated for patients with systemic signs of urinary tract infection.
- Oral antibiotics are recommended for patients with bacteriuria, even in the absence of infection.

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CHAPTER 127

Urinary Incontinence and Retention

Stephen J. Wolf

Micturition is a process that relies on the nervous, musculoskeletal, and genitourinary systems. Disruption of any of these systems can potentially lead to urinary dysfunction, resulting in incontinence or retention. The key aspect for an emergency physician in treating patients with incontinence or retention is ruling out emergent causes or complications of the urinary dysfunction (e.g., spinal cord compression or acute postobstructive nephropathy). Often times in doing this, the emergency physician is able to identify key contributing pathology. Once emergent issues are ruled out, most patients can be referred for an outpatient workup of their urinary complaints.

The physiology of micturition involves both conscious (somatic) and unconscious (autonomic) regulation. A cholinergic parasympathetic sacral reflex arc is fundamental in this process and involves the bladder wall, the detrusor muscle, and the vesicular sphincter. At low bladder pressures and distention, parasympathetic tone is low, leading to high urethral sphincter tone and low detrusor activity via the pudendal nerve. β-Adrenergic sympathetic stimulation from levels T10 to T12 also contributes to detrusor and bladder relaxation, while α-adrenergic innervation of the vesicular sphincter results in its resting tone. All of these mechanisms work to promote urine storage and are, in part, modulated by pontine urinary centers.

When bladder distention increases and voiding is desired, micturition is achieved by increasing parasympathetic tone and decreasing sympathetic tone. This, combined with subcortical stimulation of the pontine urinary center and somatic stimulation of the bladder, results in bladder wall contraction and sphincter relaxation. Because sympathetic fibers utilize α- and β-adrenergic receptors and the parasympathetic fibers utilize cholinergic receptors, they are vulnerable to pharmacologic manipulation. Thus, physical or pharmacologic disruption of these systems can result in urinary dysfunction.

CLINICAL PRESENTATION

Urinary incontinence is the involuntary loss of urine, often associated with social embarrassment, isolation, depression, and hygienic complications (1). It can be attributed to a sudden increase in intra-abdominal pressure (stress incontinence), involuntary bladder contractions (urge incontinence), a mixture of the two (mixed incontinence), overflow in the setting of urinary retention (overflow incontinence), complete disruption of the continence apparatus (true incontinence), or nonpathologic causes (functional incontinence) (1–6).

Urinary retention is the inability to void voluntarily, resulting in bladder distention. With this distention, symptoms of prostatism often develop, including frequency, urgency, hesitancy, dribbling, decrease in voiding stream, and a sense of incomplete emptying (1). This can further progress to acute or chronic postobstructive nephropathy. These symptoms may be exacerbated with the application of suprapubic pressure (the *Credé maneuver*). In the past, this maneuver has been used to initiate voiding in patients with retention; however, it is not recommended because of high complication rates and poor efficacy (7,8).

Although urinary retention is often considered a disorder of elderly men with enlarged prostates, it can affect men and women of all ages and even is seen in children. Often the retention is insidious in its onset, resulting from chronic progressive obstructive

or neurosensory causes (e.g., diabetes); however, acute presentations do occur, especially in the setting of urologic infections, certain medications, or neurologic disease.

DIFFERENTIAL DIAGNOSIS

Urinary Incontinence

Stress urinary incontinence (SUI) results when a rapid rise in intra-abdominal pressure is transmitted to the bladder, thereby causing a leakage of urine (3,4). It may result from sneezing, coughing, laughing, exercise, and so forth. Normally, the vesiculourethral anatomy is such that this transmitted abdominal pressure causes a narrowing of the posterior ureterovesical angle, making leakage of urine more difficult. However, this is not the case if there is hypermobility of the urethra or laxity in the intrinsic urethral sphincter. Nearly 85% of SUI occurs in women who have given birth, which can cause laxity of the anterior vaginal wall and pelvic floor, resulting in urethral hypermobility (5,9). Other risk factors include obesity and previous urinary incontinence surgery. Deficiency of the intrinsic urethral sphincter may also result from mechanical issues (trauma, surgery, and chronic bladder overdistention) or neurophysiologic issues (estrogen deficiency, diabetes, corticosteroid therapy, and radiation therapy). Finally, although the majority of SUI occurs in women, transurethral resection of the prostate (TURP) is a particular risk factor in men, whereas structural abnormalities should be considered as a cause for SUI in children.

Urge incontinence occurs when there is uninhibited involuntary contraction of the detrusor muscle and bladder wall (*detrusor instability*) (4). This is often called a "spastic bladder" or an "overactive bladder." Detrusor instability is the most common cause of urinary incontinence among the elderly, with a prevalence of 40% to 70% (2). Urinary frequency and urgency are common symptoms. Up to 90% of these cases are considered to be idiopathic. The remaining 10% result from bladder wall irritation/inflammation, urethral syndrome, or neurologic causes

(10). Bladder wall irritation and inflammation are usually caused by urinary infections. Treatment often results in resolution of the urge incontinence. Cystitis may also be caused by calculi, radiation, medications (cyclophosphamide, bacille Calmette–Guérin vaccine), or carcinoma in situ. *Interstitial cystitis* is a unique idiopathic, noninfectious cause of urge incontinence, with inflammation of the muscular layers of the bladder wall. It usually affects women in their third decade of life and results in progressive vesicular fibrosis, eventually leading to decreased bladder compliance and capacity.

Urethral syndrome may also lead to urge incontinence. It most commonly affects women and is a syndrome that consists of urgency, frequency, and dysuria. It is often clinically misdiagnosed as infectious cystitis, but urine cultures are negative and the urinary sediment is noninflammatory, showing squamous epithelial cells.

Neurologic causes of urge incontinence include, but are not limited to, stroke, multiple sclerosis, hydrocephalus, and suprasacral spinal cord lesions (acute cord compression or cauda equina syndrome). In these instances, the normal physiologic relations between the sacral detrusor-sphincter reflex arc and the pontine urinary centers can be disturbed, resulting in detrusor hyperreflexia as opposed to instability.

The differentiation between stress and urge incontinence is not always straightforward, and the clinical pictures overlap, yielding a *mixed incontinence* diagnosis. Fifty percent to 60% of patients presenting for evaluation of SUI also have an urgency component (5).

Overflow incontinence is a form of incontinence that occurs in the setting of obstructive urinary retention. Obstruction can result in constant dribbling, frequency, and an urge incontinence pattern with detrusor instability.

True incontinence resulting from complete disruption of the continence apparatus or fistula formation, functionally produces a “drain-spout urethra.” This can be due to trauma, surgeries (TURP or previous urethral surgeries), vaginal or cesarean deliveries, malignant erosion or ischemic disease from operative, chemical, or

radiation factors. Congenital abnormalities are also a cause for true incontinence in children.

Finally, nonpathologic or *functional incontinence* should be considered in the differential diagnosis. Patients with functional incontinence have normal anatomy and function, but the incontinence is due to psychological factors or physical limitations in getting to the bathroom. Such constraints could include altered mental status, ethanol intoxication, isolated urinary tract infection, medication use, depression, excessive urine production, or restricted mobility. Other nonpathologic causes of incontinence include enuresis in the pediatric population and incontinence for other psychologic gains. The latter is associated with a sparing of nighttime incontinence while the patient sleeps.

Medications often contribute to urinary incontinence by causing detrusor instability, decreased sphincter tone, functional incontinence, or urinary retention resulting in overflow incontinence. Table 127.1 lists classes of medications that may contribute to urinary incontinence. A helpful mnemonic for transient causes of urinary incontinence is DIAPPERS (Table 127.2).

TABLE 127.1
Medications Associated with Voiding Dysfunction[a]

Drug Classes that can Contribute to Urinary Incontinence
Alcohol
Caffeine (11)
Diuretics
Sedative–hypnotics
Sympatholytics
Drug Classes that can Contribute to Urinary Retention[b,c]
α-Adrenergic agents
Antiarrhythmic
Anticholinergics
Antidepressants
Antihistamines
Antiparkinsonian agents
Antipsychotics
Antispasmodics
β-Adrenergic agents
Calcium channel blockers
Opioids

[a]Prescription and over-the-counter.
[b]Medications that alter sensorium and can also contribute to urinary incontinence.
[c]Medications that contribute to urinary retention and can also lead to overflow urinary incontinence.

TABLE 127.2
DIAPPERS Mnemonic for Causes of Transient Urinary Incontinence

*D*elirium/confusional state
*I*nfectious
*A*trophic urethritis/vaginitis
*P*harmacologic agents
*P*sychologic
*E*xcessive urine output
*R*estricted mobility
*S*tool impaction

Urinary Retention

Urinary retention is most often the result of obstruction; however, it can also result from neuropathologic disease, pharmacologic side

effects, or psychogenic causes (1). Special congenital considerations also arise when considering the etiology of urinary retention in the pediatric population (Table 127.3). Urinary retention needs to be delineated from anuria and oliguria, which is a lack or decrease of urine production from the kidneys and not an issue of voiding dysfunction.

TABLE 127.3
Obstructive Causes of Urinary Retention

Functional

- Benign prostate hypertrophy
- Bladder calculi
- Bladder neck stenosis
- Blood clot
- Cancer (e.g., prostate, bladder, urethral, cervical, and colon)
- Cystocele
- Iatrogenic (e.g., previous anti-incontinence procedures)
- Meatal stenosis
- Phimosis–paraphimosis
- Pregnant uterus
- Prolapsed uterus
- Rectocele
- Trauma
- Urethral obstruction (e.g., calculi, inflammation, trauma, and tumor)
- Urethral diverticulum
- Urethra stricture (male predominance)

Infections/Inflammatory

- Cystitis
- Genital herpes
- Periurethral abscesses
- Prostatitis
- Sexually transmitted diseases
- Tuberculosis
- Urethritis
- Vesicoureteral reflux (female predominance)

Additional Pediatric Causes

- Benign hyperplasia of the prostatic utricle
- Congenital obstructed duplications of the urinary system
- Constipation
- Cystic enlargement of the posterior urethra
- Foreign bodies
- Hydrocolpos (from an imperforated hymen)
- Urethral valves (posterior or anterior)
- Ureterocele
- Ureteropelvic junction narrowing
- Ureterovesical junction narrowing
- Vaginal atresia/vaginal stenosis

Obstructive urinary retention can be a result of multiple etiologies and occurs much more frequently in men (see Table 127.3). Benign prostatic hypertrophy is the most common etiology, usually occurring in the sixth decade of life. Prostate cancer is a less common cause of obstruction and is associated with a marked elevation of prostate-specific antigen level (1). Fibromuscular contracture of the bladder outlet can occur in the younger male. At the level of the bladder outflow tract, calculi, blood clots, tumor, or polyps can all cause obstruction. At the level of the urethra, obstruction can be secondary to inflammation or stricture. Inflammatory causes include urethritis, prostatitis, tuberculosis, echinococcosis, and herpes simplex. Strictures can result from gonococcal urethritis, trauma, surgery, or radiation but tend not to be caused by nongonococcal urethritis (1). A higher incidence of psychogenic urinary retention tends to be found in women.

Neuropathologic causes of urinary retention deserve special attention (Table 127.4). Neurologic lesions (e.g., trauma, mass lesions, and infections) at the level of the sacral nuclei can disrupt the spinal reflex arc, thereby causing a flaccid paralysis of the bladder and an inability to void. *Suprasacral lesions* of the spinal cord or central nervous system may initially result in spinal shock–type physiology with urinary retention, but usually progress to overflow and urge incontinence with detrusor hyperreflexia, owing to the lack of upper-motor neuron control. However, a complication of suprasacral injuries can be *detrusor-sphincter dyssynergy,* in which there is external sphincter spasm during bladder contraction, resulting in urinary retention.

TABLE 127.4
Neuropathologic Causes of Urinary Retention

Suprasacral Pathology Resulting in Detrusor-Sphincter Dyssynergy

- Encephalitis
- Hydrocephalus
- Meningitis
- Parkinson disease
- Shy–Drager syndrome (12)
- Spinal cord trauma
- Spinal cord tumors (benign, primary, malignant)
- Spinal/paraspinal infections (abscesses, osteomyelitis, discitis)
- Stroke
- Tabes dorsalis

Sacral Pathology Resulting in the Disruption of the Reflex Arc

- Inflammatory polyradiculopathy
- Sacral spinal/parasacral infections
- Sacral dysgenesis
- Sacral trauma

Supra Sacral or Sacral Pathology Resulting in an Impaired Spinal Reflex Arc

- Diabetes mellitus
- Landry–Guillain–Barré syndrome (13)
- Multiple sclerosis (14)
- Pernicious anemia
- Poliomyelitis
- Syringomyelia
- Transverse myelitis
- Isolated bladder atony and urinary retention

Finally, various medications, both prescription and over-the-counter, can precipitate urinary retention (see Table 127.1). Anticholinergic medications inhibit parasympathetic tone and promote urinary retention. Likewise, α- and β-adrenergic medications cause bladder wall relaxation and an increase in urethral sphincter resting tone. This risk is even greater in the setting of other risk factors, for example, a male patient with benign prostatic hypertrophy taking an over-the-counter cold medicine with diphenhydramine.

ED EVALUATION

Urinary Incontinence

The emergency department (ED) evaluation of urinary incontinence should be focused on identifying acute emergent or correctable causes. Most emergent causes are neurologic, resulting in detrusor hyperreflexia, whereas most correctable causes are infectious, overflow, or medication related. The evaluation should focus on a thorough history covering past medical, surgical, psychosocial, and medication histories. Any of these elements may yield clues to the etiology of incontinence. The physical examination should include a thorough neurologic examination, including mental status, gait, deep-tendon reflexes, saddle sensation of the perineum, rectal tone, and the bulbocavernosus reflex. An absent bulbocavernosus reflex in male patients is almost always associated with a neurologic lesion. In women, it can be absent up to 30% of the time (1).

SUI is often implied by the history and is accompanied by a normal physical examination. If needed, a provocation test for SUI can be performed by instilling 200 to 300 mL of sterile saline into the bladder after the measurement of a postvoid residual (PVR) (5). The patient can then be asked to sneeze, cough, or strain. Isolated leakage suggests SUI. Furthermore, if the *Marshall test,* digital urethral support during a provocation test, prevents the incontinence, the diagnosis is confirmed. Leakage with an inability to stop further urine flow during a provocation test suggests urge incontinence with detrusor instability. Urge incontinence may require investigation into associated signs and symptoms (e.g., back pain) for inflammatory etiologies and/or neurologic etiologies. Associated back pain or an abnormal neurologic examination warrants evaluation for overflow incontinence associated with an obstructive urinary retention.

Urinalysis and urine cultures should also be obtained. They may assist in the diagnosis of infection and noninfectious inflammatory causes.

Emergent urology consultation is not usually necessary, and extensive urologic evaluation is reserved for the outpatient setting. When acute neurologic causes of incontinence are suspected,

imaging studies, neurologic, or neurosurgical consultation should be obtained as needed.

Urinary Retention

Evaluation of acute or chronic urinary retention in the ED should be directed at identifying the cause, when possible, and evaluating for the sequela of renal parenchymal damage. Neurologic causes must be carefully excluded. Special attention should be paid to the review of the patient's medication history, the rectal examination, and a thorough neurologic examination. These can provide significant information as to the potential emergent etiologies of the urinary retention. It should be noted that a normal prostate on examination does not exclude prostatic cause from the differential diagnosis.

Two tests are particularly helpful. A PVR of more than 100 mL suggests retention. A bedside ultrasound can document bladder distention suggestive of outlet or urethral obstruction. This may be especially useful if symptoms persist in the setting of perceived adequate drainage.

Laboratory evaluation of patients found to have urinary retention should include a urinalysis with culture, blood urea nitrogen (BUN), and serum creatinine. The urinalysis can provide clues to infectious etiologies, calculi, or tumors, whereas the urine culture is necessary for detecting subclinical infections. Postobstructive nephropathy is often characterized by an elevated BUN/creatinine (Cr) ratio (i.e., >10). If new or previously undiagnosed renal insufficiency is present, a more complete workup with electrolytes and a renal ultrasound looking for hydronephrosis, hydroureter, or renal parenchymal damage is indicated.

KEY TESTING

Urinary Incontinence

- Blood Sugar, Urinalysis and culture
- Neurologic imaging (when indicated)

Urinary Retention

- Postvoid residual or postvoid volumetric bladder scan

- BUN and creatinine
- Urinalysis and culture
- Renal ultrasound (when indicated)
- Neurologic imaging (when indicated)

ED MANAGEMENT

Urinary Incontinence

Emergent neurologic causes should be addressed as dictated by the suspected etiology, such as ordering emergent magnetic resonance imaging (MRI) in cases of suspected spinal cord compression. Transient causes (see Table 127.2) should also be addressed (e.g., administering antibiotics for infectious cystitis or withholding offending medications when possible).

Further management of stress, urge, true, functional, and nonpathologic incontinence falls into the realm of outpatient urologic consultation. The management of SUI and true incontinence is often surgical, with repositioning of vesicourethral angle (e.g., bladder neck suspensions and pubovaginal slings). Alternatives for SUI include Kegel exercises, weight reduction, estrogen replacement, electrostimulation methods, and α-agonists (pseudoephedrine, phenylpropanolamine) for increasing bladder neck and urethral tone (2). Periurethral collagen injection therapy and urethral occlusion devices have also been used with moderate success for treating SUI (3). Anticholinergic medications (propantheline, hyoscyamine) increase the tolerable bladder volume and decrease involuntary bladder contractions (15). Tricyclic antidepressants (doxepin, imipramine) can also be used to increase bladder tone gives their central and peripheral anticholinergic effect. Oxybutynin and dicyclomine inhibit involuntary bladder contraction through anticholinergic effects and cause smooth muscle relaxation in the bladder wall. Tolterodine has similar effect as oxybutynin via antimuscarinic activity.

Urinary Retention

Initial management of urinary retention should focus on identifying serious neurologic causes and obtaining symptom relief through bladder decompression. Decompression can be accomplished with a well-lubricated 16 to 18Fr catheter and should be done in a timely manner. If this is unsuccessful, attempts can be made with a coudé catheter. Its angulated tip can facilitate catheter passage beyond the median lobe of the prostate. If a urethral catheter cannot be placed, temporary relief may be provided by placing a suprapubic catheter. This requires a palpable bladder and the absence of a history of prior suprapubic surgery. If there is doubt about bladder distention (as in the obese patient), ultrasound confirmation is advised. For percutaneous drainage techniques, a simple midline puncture is made one fingerbreadth above the symphysis pubis, with the trocar or needle directed slightly caudally and then advanced until urine is returned. The catheter or tubing is then advanced, the needle is withdrawn, and the drainage catheter is secured in position.

Traditionally, a single straight catheterization (in and out) of patients with urinary retention has not been recommended, as recurrence of symptoms is likely, and the risk of infection is high. More recently trials without catheter (TWOC) in men with prostatic hypertrophy using concomitant α-adrenergic blockade following initially catheter decompression have shown some success (48% to 62%), particularly in younger patients with low PVR volumes (10).

Bladder mucosal hemorrhage and postobstructive diuresis are two complications of bladder decompression, particularly in the patient with chronic urinary retention. Bladder mucosal hemorrhage is thought to be the result of sudden expansion of bladder wall veins after decompression (1). In the past, clamping of the catheter after a certain amount of drainage was recommended in an attempt to avoid this complication. However, it has been shown that the hydrostatic pressure in the bladder begins to fall immediately with catheter placement and falls markedly within the first 100 mL of urine drained. Therefore, clamping of the catheter does not affect the risk of mucosal hemorrhage and is not indicated (1,17).

Postobstructive diuresis may occur after the decompression of obstructive urinary retention at a rate up to or >1 L/hr. However, it

is believed that this diuresis is an appropriate correction of volume overload. Therefore, milliliter-for-milliliter replacement of this diuresed fluid is not indicated. What is indicated is replacement of the concomitant electrolyte loss that accompanies the diuresis. This can often be done through administering a maintenance rate of one-half isotonic saline during the diuresis (18).

CRITICAL INTERVENTIONS

- Exclude serious neurologic disease (e.g., spinal cord compression) as the cause of acute urinary dysfunction.
- Place a bladder catheter immediately to relieve the discomfort of bladder distention in patients with acute urinary retention.

DISPOSITION

Patients with an obstructive uropathy usually require continuous urinary drainage. The patient in otherwise good health with no ancillary requirements for hospital care may be discharged from the emergency department with Foley catheter drainage collected into a leg bag. Follow-up should be arranged prior to discharge, and there should be a thorough discussion with the patient about when to seek further medical attention. Urinary retention related to drugs or medication requires referral to the prescribing physician for recommended adjustment or substitution therapy.

Patients with an emergent neurologic cause of urinary incontinence or retention should be admitted or transferred if appropriate specialty consultation is not available.

Common Pitfalls

- Failure to diagnose a true neurologic emergency such as cord compression or cauda equina syndrome in the patient with urinary retention or incontinence.
- Failure to inquire about over-the-counter medication use.
- Overly aggressive attempts at catheter insertion, resulting in urethral injury.

- Failure to detect associated infection or postobstructive nephropathy in the elderly patient with urinary retention.
- Failure to consider multiple sclerosis and diabetes in a woman with urinary retention.

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CHAPTER 128 Genitourinary Stents and Catheters

Jonathan E. Davis

URETHRAL CATHETERS

The need to place urinary catheters is common in the emergency department (ED). The reasons for placement vary widely and include the relief of urinary retention, monitoring urinary output for resuscitation efforts, treatment of gross hematuria, and obtaining a urine specimen. Urethral catheter placement is usually a routine and uncomplicated procedure but can sometimes be challenging. As with any other procedure, there are accompanying risks and complications. Emergency physicians should be able to utilize different types of catheters, be able to overcome the common difficulties encountered placing them, and be aware of the acute and chronic complications of urinary catheters.

Urinary catheter placement in the male patient may be complicated by several factors related to the length and path of the urethra. Common pathologic conditions may also make urinary catheter placement difficult (eTable 128.1). Meatal stenosis, either from prior infections, congenital malformation, or previous trauma can be diagnosed when the meatus of the penis is fibrotic and nondistensible. A dilation procedure performed by a urologist may be necessary for catheter placement to be successful. Hypospadias is a congenital condition in which the true urethral lumen is on the ventral aspect of the penis, making catheterization difficult. In a patient with known hypospadias, the glans penis should be inspected to identify a true urethral meatus, as there is often a blind-ended

lumen on the glans penis. The conscious patient should be able to state which lumen is functional. Once the lumen is identified, catheterization may proceed in the standard fashion.

eTABLE 128.1
Approach to Difficulties in Male Catheterization

Condition	Issue	Workaround Strategy
Phimosis	Inability to identify the urethral meatus because of a tight phimotic opening	Dilate the phimotic opening sufficiently to identify the urethral meatus and blindly pass the catheter Dorsal slit of the foreskin to expose the glans and urethral meatus in extreme cases
Foreskin edema	Edema may obscure glans penis and urethral meatus	Attempt to identify cause of edema; exclude paraphimosis or foreign body strangulation Manually compress the swollen foreskin by hand or between opposing cold packs If unsuccessful, snugly wrap the distal penis in a compressive dressing for 10 min
Meatal stenosis	Urethral meatus may be either congenitally or secondarily narrowed by scarring	Trial of smaller caliber catheter If larger caliber catheter necessary, meatal dilation or meatotomy might be necessary under the direction of a urologist
Urethral stricture	May develop as a result of trauma, infection (especially STIs), lower urinary tract instrumentation, or long-term indwelling catheter drainage	Trial with coudé catheter However, manual force should not be used to negotiate or to dilate urethral strictures—may lead to false passages, bleeding, and increased scarring Consideration of urethral dilation using filiforms and followers under the direction of a urologist
External urethral sphincter spasm	Voluntary or involuntary contraction of the urogenital diaphragm (external sphincter), produces spurious urethral resistance with catheter passage of about 16 cm from the urethral meatus	Encourage patient to lay supine and take slow, deep breaths, consciously trying to relax the perineum and rectum Plantar flexion of the toes and ankles may also aid relaxation of the pelvic floor Gentle but steady pressure exerted on the syringe or the catheter along with steps above may aid passage External sphincter is composed of striated muscle that fatigues within a few minutes If continued resistance, assume an anatomic abnormality and consider RUG prior to further instrumentation
High bladder neck	Enlarged intravesical portion of the prostate with a secondary high-riding bladder neck Typically resistance after the catheter has been passed 16–20 cm into the urethra	Slow instillation or injection of 20–30 mL of sterile lubricating jelly If unsuccessful, consider trial with coudé catheter; may be enhanced by digital compression of the prostate by digital rectal examination
Pelvic trauma, straddle injury	Partial or complete urethral injury might occur Injudicious catheterization has the potential for conversion of a partial injury (may heal with little or no scarring) to a complete urethral injury (often requires surgical repair and usually results in some degree of postoperative morbidity) Blood at the urethral meatus; a "high-riding" or abnormal-feeling prostate on rectal examination; and penile, scrotal, or perineal ecchymoses might be evidence of potential urethral or bladder injury, but have poor sensitivity	Consider precatheterization RUG in suspect cases Maintain a low threshold for urologic consultation Suprapubic catheter placement may be necessary in certain cases

RUG, retrograde urethrogram; STIs, sexually transmitted infections.

The male urethra is divided into the anterior (penile, bulbous) and posterior (membranous, prostatic) portions (Fig. 128.1). The penile and bulbar urethras are the most common sites of urethral strictures. Strictures are usually noticed when the catheter cannot be advanced more than halfway into the bladder, and the procedure is often accompanied by significant discomfort. There should not be attempts to force the catheter through a stricture. This force may create false

passages in the urethra, which can lead to urethral diverticuli, incontinence, infection, and fistula formation. If this situation is encountered, further attempts to place the catheter should be discontinued until a urology consult is obtained. The stricture may require a dilatation procedure or urethroplasty.

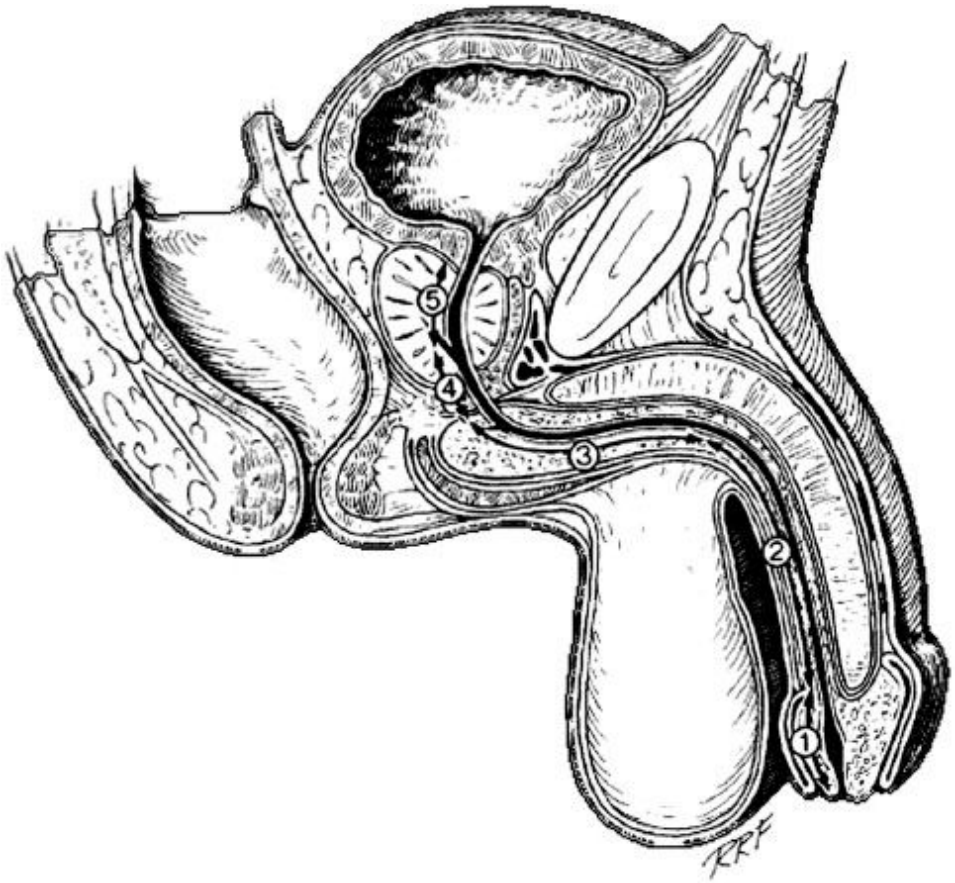

FIGURE 128.1 Anatomy of the male urethra. (1) Fossa navicularis, (2) pendulous urethra, (3) bulbous urethra, (4) membranous urethra, and (5) prostatic urethra. (From Jordan GH, Schellhammer PF. Urethral surgery and stricture disease. In: Droller M, ed. *Surgical Management of Urologic Disease.* St. Louis, MO: Mosby Year Book; 1992:394.)

The site for the most common problems for placement of male urinary catheters is the prostatic urethra, where the lobes of the prostate create a narrowed lumen. The incidence of benign prostatic hypertrophy (BPH) increases dramatically with advancing age, and

the vast majority of men older than 70 years have the anatomical changes, signs, and symptoms of BPH. There are a few basic techniques that can help in passing the tip of the catheter around an enlarged prostate. The use of a coudé catheter is often helpful. This catheter has a firm, upturned end which slips over the enlarged gland (1). Other techniques include placing a finger in the rectum and applying gentle pressure to the prostate as the catheter is passed, or injecting a water-soluble lubricant retrograde into the urethra to decrease friction. Patients who have undergone a radical or simple prostatectomy commonly have bladder neck contractures, and coudé catheters are similarly helpful in these patients. In instances when the ED placement of a catheter has been unsuccessful, urology consultation may be necessary.

Although the vast majority of difficult catheterizations occur in men, occasional difficulties arise in the catheterization of women. Women have short, straight urethras, which are easy to traverse with a standard urethral catheter. At times, however, identifying the urethral meatus can be problematic. Obese women may have redundant labial tissues, which can make visualization of the meatus difficult. Placing the patient in the frog-leg position, using adequate lighting, and having an assistant retract redundant tissue will often aid in the location of the urethral meatus and subsequent placement of the catheter.

Occasionally, prolapse of the pelvic organs (cystocele, enterocele, rectocele, or uterocele) can obscure the view of the female meatus. Simply applying gentle pressure to the offending organ should assist in bringing the meatus into view. Some women have a partially prolapsed urethra called a caruncle, which can distort the normal anatomy. A standard urethral catheter can usually be placed around the caruncle without difficulty.

Complications from the placement of urinary catheters occur uncommonly. If too much pressure is applied to a urethral catheter that is being impeded by a stricture or large prostate, a false passage can be created. This is a result of undermining the urethral mucosa; the consequences may include significant hematuria, stricture formation, and infection. In certain situations involving pelvic

trauma, urethral integrity should be assured via a retrograde urethrogram (RUG) prior to the placement of a urinary catheter (Fig. 128.2).

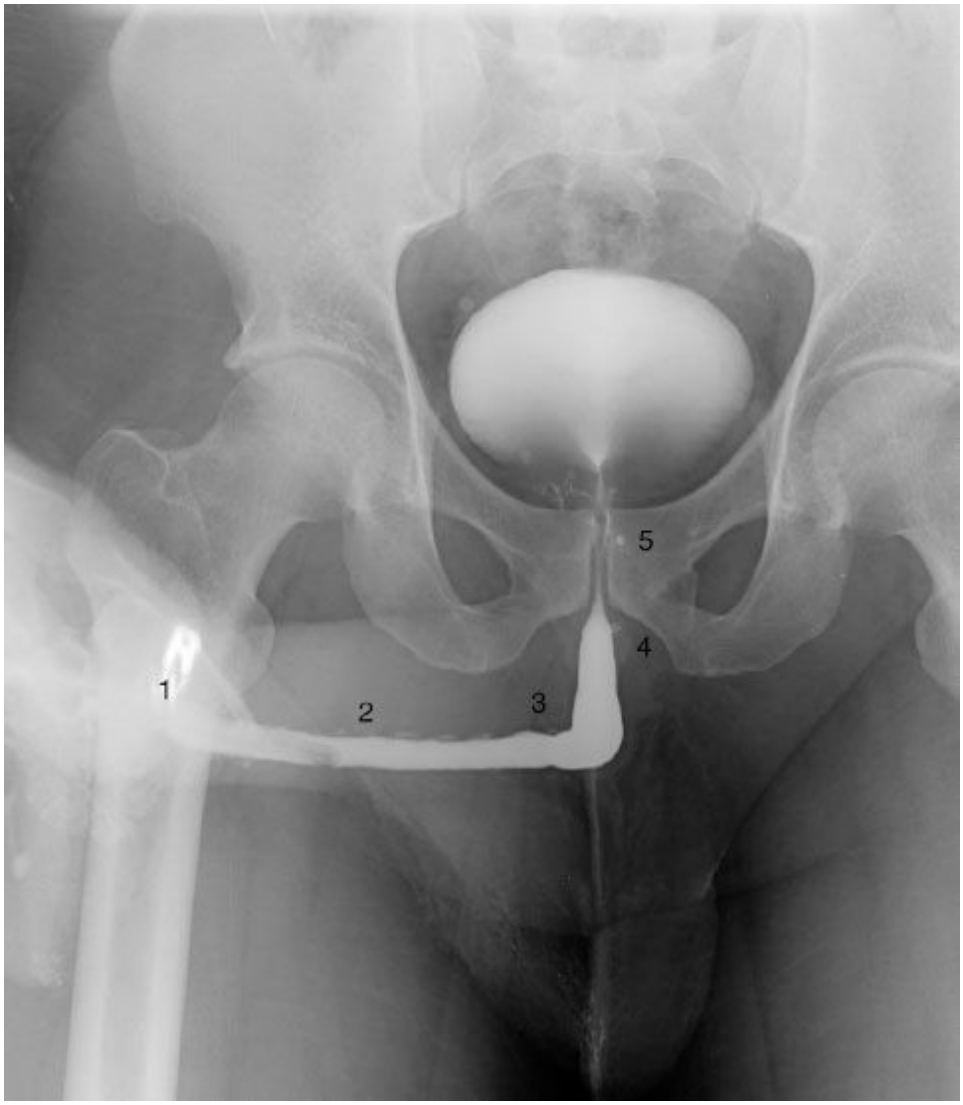

FIGURE 128.2 Anatomy of the male urethra, normal retrograde urethrogram. (1) Fossa navicularis, (2) pendulous urethra, (3) bulbous urethra, (4) membranous urethra, and (5) prosthatic urethra. (Courtesy of Michael Antonis, DO, RDMS.)

Occasionally a urethral catheter cannot be removed from a patient because the balloon will not deflate. The easiest maneuver is to cut the valve off the end of the catheter, which may facilitate removal. If this technique fails to relieve the obstruction, a guidewire can be

introduced into the balloon lumen of the catheter to attempt to relieve a balloon port obstruction preventing egress of balloon contents. If this method fails and the catheter needs to be removed emergently, a urologist may have to perform invasive maneuvers to better facilitate catheter removal.

A catheter may be forcibly pulled out of the bladder in patients with altered sensorium or other issues. Replacing the catheter is usually not difficult, but consideration should be given to any resulting injuries. Repeatedly pulling out a urinary catheter puts the patient at risk for developing incontinence secondary to external sphincter damage, and may also lead to hematuria with significant blood loss. If a urethral catheter that has been removed traumatically cannot be replaced easily, urology consultation should be obtained, and performance of a RUG should be considered.

Urinary tract infection is a complication of a long-term urethral catheter. The duration of catheterization is the most important risk factor for the development of catheter associated bacteriuria (2). The incidence of bacteriuria with indwelling catheterization is 3% to 8% per day. The rate might be considerably higher in hospitalized, elderly, debilitated, or postpartum patients. By 1 month, nearly all patients with an indwelling catheter will have bacteriuria. Urinary catheterization is the leading cause of nosocomial infection (2). Other less frequent complications of long-term indwelling urethral catheterization include bladder stones, recurring bladder spasm, periurethral abscesses, urethral stricture formation, bladder perforation (3), and urethral erosion (4).

When a catheterized patient presents with a urinary tract infection, the catheter should be changed. Patients with long-term need for catheterization should have them changed monthly. Antibiotic treatment is usually not indicated for asymptomatic patients, and may in fact select for antibacterial resistance. Many studies have documented the overuse of urethral catheters, and the best strategy for preventing catheter-related infections is the more judicious use (5).

Other problems from long-term indwelling catheters include local infections (epididymitis, balanitis, and prostatitis), erosive

hypospadias, and bladder stone formation (6). In general, urethral catheters are not the treatment of choice for debilitated or incontinent patients, and their indications should be carefully considered. Other options include intermittent catheterization, condom catheters, and suprapubic catheters.

THREE-WAY IRRIGATION CATHETERS

Placement of a three-way irrigation catheter may be required in ED patients complaining of gross hematuria and exhibiting symptoms of bladder obstruction. Gross hematuria is often complicated by obstruction secondary to the formation of blood clots. Significant bleeding should be treated aggressively with three-way catheter placement and bladder irrigation to maintain patency of the urethra and to accurately monitor the amount of bleeding. If gross hematuria persists or copious blood clots are encountered, continuous bladder irrigation can be therapeutic.

A three-way irrigating catheter is needed in patients who require continuous bladder irrigation. Three-way catheters have three ports, one providing standard access to urinary drainage, a second to instill irrigating solution, and a third to control the inflation of the balloon. Sterile saline or water may be infused passively through the irrigation port using a reservoir (Kelly) bag placed above the level of the bladder. There are several types of three-way catheters, ranging from a soft plastic coudé type to others with large holes at the distal end to facilitate the passage of large clots. When there is significant bleeding and clot formation, the three-way catheter with the largest tolerated diameter should be used.

SUPRAPUBIC CATHETERS

Suprapubic catheters are placed in patients for a variety of reasons revolving around a need for alternative bladder drainage. Suprapubic catheters that have been in place for longer than a month form a mature fistulous tract and therefore can be removed and changed without fear of losing tract patency. Changing the catheter over a guidewire facilitates this procedure. Before replacing a suprapubic

catheter, the bladder should be filled with saline or water to facilitate the correct placement of the new catheter into the bladder.

Suprapubic catheters may also become obstructed with mucous or debris. The catheter should be flushed to attempt to relieve the obstruction, which is similar to the procedure used with a standard urinary catheter. Suprapubic catheters should be replaced every 4 to 6 weeks or when they are suspected to be the nidus of an infection.

Occasionally there is a need to emergently place a suprapubic catheter in the setting of urinary retention when standard catheterization has failed, or in the setting of a traumatic urethral disruption. This should be performed by a consulting urologist when one is available, though the procedure is straightforward. Several techniques are described, the most common involving a percutaneous Seldinger technique, threading the catheter over a guidewire placed into the bladder via a suprapubic needle puncture. Patients who are significantly obese, have had prior abdominal or genitourinary surgery, or have had multiple prior suprapubic catheters are suboptimal candidates for percutaneous suprapubic tubes and usually require an open procedure in a more controlled operative setting to reduce the risk of complications.

URETERAL STENTS

The placement of ureteral stents is a common practice in urology to facilitate adequate urine flow through the ureter. The most common reason is for stone disease. A ureteral stent may be placed after a large kidney stone is treated. The most common stents are double-J stents that can be identified on plain films by the curls that are in both the bladder and the renal pelvis. Emergency physicians should be aware of their indications, complications, and side effects.

Stents are placed to allow the unimpeded passage of urine and to aid in the passage of stones into the bladder. Patients who have signs and symptoms of infected urine and also have signs of urinary obstruction (e.g., by stones or strictures) often have stents placed emergently to allow adequate drainage of urine and to prevent septic complications (see also nephrostomy tubes below).

Pain is the most common complication associated with urethral stents. The pain usually results from irritation of the mucosa of the renal pelvis or the bladder. Patients commonly complain of flank pain, dysuria, frequency, gross hematuria, and urgency. The symptoms usually abate in time but may require the use of narcotic pain medications. Symptoms may also be alleviated by oral anticholinergic agents, which may be started in consultation with a urologist. Other complications include infection, migration, obstruction, and encrustation. Bacterial colonization of ureteral stents is common. Patients with a urinary stent in place who exhibit signs or symptoms of urinary infection should be promptly treated with antibiotics, including adequate coverage for *Pseudomonas* species (7). Urology consultation is prudent in this situation.

Large obstructing ureteral calculi (e.g., greater than 10 mm in diameter) may impede the retrograde passage of a ureteral stent. Occasionally, a patient's anatomy does not allow perfect alignment of the ureteral stent in either the bladder or the renal pelvis, leading to stent migration. The stent can move proximally in the ureter or distally toward the bladder and often fails to function correctly. A one-view abdominal radiography (kidneys, ureters, and bladder [KUB]) is helpful in assessing stent location (Fig. 128.3).

FIGURE 128.3 A kidneys, ureter, and bladder view showing a stent in proper placement.

Stent encrustation (stone formation around a stent) and obstruction may occur when ureteral stents are not removed or changed for long periods of time. Patients can develop hydronephrosis or renal failure as a result. Urgent consultation for stent removal or replacement is often necessary.

NEPHROSTOMY TUBES

The primary urgent indication for percutaneous nephrostomy (PCN) catheter placement is to relieve an obstructed, infected renal collecting system (pyonephrosis). Pyonephrosis represents infection (pus) that is under pressure (obstructed collecting system). Pyonephrosis is associated with significant morbidity and mortality if not treated swiftly and aggressively. Relief of obstruction remains the cornerstone of treatment, with appropriate broad-spectrum intravenous antimicrobials playing an important adjunctive role.

Retrograde ureteral stents and PCN catheters have been demonstrated to be equally effective in relieving obstruction, with similar complication rates (8). The advantages of PCN catheters include: wide variety of available catheter sizes, ability to irrigate the catheter to avoid or alleviate clogging, direct measurement of urinary output from the affected kidney, and minimizing ureteral manipulation as to decrease the risk of precipitating sepsis or ureteral rupture. In addition, the procedure can typically be performed under local anesthesia with procedural sedation. Depending on institutional capabilities and local protocol, the procedure can be performed by an interventional radiologist. Advantages of cystoscopic ureteral stenting over PCN include decreased bleeding risk by avoiding puncture of the highly vascular renal capsule, lack of an external catheter exiting the flank, and often less postprocedural patient discomfort.

Emergent PCN is also utilized in the treatment of obstructive uropathy from a variety of causes associated with acute renal failure. Another general indication for PCN catheter placement is access to the renal collecting system for diagnostic or therapeutic procedures. PCN catheter placement may also be utilized as a secondary procedure if initial ureteral stent placement is unsuccessful, or fails to alleviate signs or symptoms of pyonephrosis. Major complications of PCN include sepsis, hemorrhage, vascular injury, bowl injury, or pleural complications. Complications occur in 2% to 6% of procedures, and have a higher frequency when PCN is performed after-hours likely owing to the overall higher risk profile of patients necessitating emergency intervention (Fig. 128.1) (9).

The decision regarding cystoscopy with ureteral stent versus PCN catheter placement for the treatment of pyonephrosis is multifactorial, and typically guided by a urologist in conjunction with an interventional radiologist if necessary. In general, however, emergent PCN catheter decompression is the treatment of choice in septic or otherwise unstable patients given anesthetic risks. In less extreme circumstances, a trial of cystoscopic ureteral stent placement is typically advocated as the first line in treatment.

URINARY CONDUITS

Bowel is sometimes used to serve as a surgically created conduit for urine; for example, this may be done after radical cystectomy for invasive bladder cancer. The most common form of urinary conduit is an ileal conduit formed by a small piece of ileum that has been removed and attached to the ureters. The distal end is then made into a stoma at the abdominal wall, and the urine is collected in an external urostomy bag. Other procedures include formation of a neobladder that is orthotopically placed, allowing the patient to void in the normal fashion. Another option is the formation of a stoma that may be catheterized through the umbilicus using a straight catheter.

As with any large abdominal and pelvic operation with bowel manipulation, patients may later develop a small bowel obstruction. Hernias can develop around the stoma (parastomal) or at the surgical site (incisional). Because the ureter is sutured to the bowel, a stricture can develop at the anastomosis, potentially causing hydronephrosis, insidious renal failure, pyelonephritis, or urosepsis. Because the ureteroileal anastomosis allows the free reflux of urine, pyelonephritis is common in these patients. Because conduits are chronically colonized with fecal flora, positive urine cultures should typically be treated only if the patient is symptomatic.

CRITICAL INTERVENTIONS

- Quickly place a urinary catheter to relieve acute urinary retention.
- Use a coudé-tip catheter for difficult placement of the catheter if the prostate or bladder neck is the area of obstruction.

- Place a three-way irrigating catheter for treatment of gross hematuria with clots.
- Urinary obstruction with associated infection (pyonephrosis) is an emergency, necessitating prompt decompression of the collecting system by cystoscopy with ureteral stent or by placement of a PCN tube.
- Perform a RUG prior to attempts at urinary catheterization if there is any question about urethral integrity.

Common Pitfalls

- Overzealous attempts by staff to place a urinary catheter leading to the formation of a false passage.
- Failure to consult urology after unsuccessful attempts at catheter placement.
- Overuse of antibiotics in the asymptomatic patient with a chronic, colonized catheter.
- Failure to treat pyonephrosis promptly by decompression of the urinary collecting system.

ACKNOWLEDGMENT

We wish to acknowledge the work of Dr. Paul E. Pamphrus on the previous edition of this chapter.

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SECTION XII
Gynecologic Emergencies

Section Editor: GREGORY W. HENDEY

CHAPTER 129 Pelvic Pain

Joseph C. Schmidt

CLINICAL PRESENTATION

Pelvic pain is a common emergency department (ED) presentation. It is often accompanied by various symptoms including fever, vomiting, dysuria, vaginal discharge, or bleeding. The practitioner must rapidly differentiate among etiologies that range from benign to life-threatening. This differentiation requires a complete but focused history and physical examination combined with a broad knowledge of potential disease processes to generate an appropriate differential diagnosis. This differential can then be tested by using appropriate diagnostic studies and generating an assessment and plan that will allow for the timely treatment and disposition of the patient.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of pelvic pain is broad and falls into two main categories. This discussion is focused on the presentation of acute pelvic pain, which by definition is pain of <6 months in duration. Chronic pelvic pain will be mentioned only in the context that a diligent evaluation of the patient with chronic pain must be accomplished to avoid missing a more worrisome complication or new diagnosis.

The differential diagnosis of acute pelvic pain encompasses multiple organ systems (Table 129.1). A useful organizational strategy is to divide the patients into functional categories according to reproductive status. This approach highlights the special

consideration of each group. Children and prepubertal adolescents have a number of unique issues (Table 129.2). Likewise, postmenopausal women are at risk for conditions that are uncommon in other age groups (Table 129.3). The remainder of the section highlights the most common and important etiologies in each category. It is important to remember that significant overlap between these categories does occur.

TABLE 129.1
Differential Diagnosis of Acute Pelvic Pain

Gynecologic/Obstetric

1. Pregnancy related
   a. Ectopic pregnancy
   b. Abortion, threatened or incomplete
   c. Septic abortion
2. Acute infections
   a. Endometritis
   b. Pelvic inflammatory disease
   c. Tubo-ovarian abscess
3. Adnexal disorders
   a. Hemorrhage/rupture of ovarian cyst
   b. Torsion of adnexa
   c. Twisted paraovarian cyst
4. Recurrent
   a. Mittelschmerz (midcycle pain)
   b. Primary/secondary dysmenorrhea
   c. Endometriosis

Gastrointestinal

1. Gastroenteritis
2. Appendicitis
3. Bowel obstruction
4. Perirectal abscess
5. Diverticulitis
6. Inflammatory bowel disease
7. Irritable bowel syndrome

Genitourinary

1. Cystitis
2. Pyelonephritis
3. Urolithiasis

Musculoskeletal

1. Abdominal wall hematoma
2. Psoas hematoma
3. Hernia

Vascular

1. Pelvic thrombophlebitis
2. Aneurysm
3. Ischemic bowel

Modified from Jolin JA, Rapkin A. Pelvic pain and dysmenorrhea. In: Berek JS, ed. *Novak's Gynecology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2002:421–452.

TABLE 129.2
Differential Diagnosis of Prepubertal Pelvic Pain

Reproductive

1. Trauma
   a. Laceration
   b. Hematoma
   c. Sexual abuse
2. Vaginal foreign body
3. Vaginal infection
4. Vulvar dermatitis
   a. Chemicals
   b. Poor hygiene
   c. Allergic dermatitis
   d. Parasitic infestation (pinworms)
5. Outflow tract obstruction
   a. Imperforate hymen
   b. Labial adhesions
   c. Congenital abnormalities
6. Dysmenorrhea

Gastrointestinal

1. Appendicitis
2. Gastroenteritis
3. Obstruction
4. Constipation
5. Volvulus

Musculoskeletal

1. Muscle tendon injury
2. Growth plate injury
3. Ligamentous injury
4. Avulsion fracture
5. Inguinal hernia
6. Intervertebral disc herniation

Urologic

1. Nephrolithiasis
2. Cystitis
3. Pyelonephritis
4. Urethritis

Other

1. Diabetic ketoacidosis
2. Sickle cell crisis
3. Neoplasms

Modified from Wheeler SJ, Sornsin SM. Pelvic pain in women. In: Schwartz GR, Cayten CG, Mangelsen MA, et al., eds. *Principles and Practice of Emergency Medicine*. Philadelphia, PA: Lea and Febiger; 1992:535–546 and Schroeder B, Sanfilippo JS. Pelvic pain in children and adolescents. In: Carpenter SEK, Rock JA, eds. *Pediatric and Adolescent Gynecology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2000:281–292.

TABLE 129.3
Differential Diagnosis of Postmenopausal Pelvic Pain

Gynecologic
1. Vaginitis
   a. Atrophic
   b. Infectious
   c. Allergic
2. Uterine prolapse
3. Cervical polyps
4. Uterine fibroids
5. Endometrial hyperplasia
6. Neoplasm
   a. Uterine
   b. Ovarian

Gastrointestinal
1. Rectocele
2. Diverticulitis
3. Neoplasm
4. Appendicitis
5. Ischemic bowel

Urologic
1. Infection
   a. Cystitis
   b. Urethritis
   c. Pyelonephritis
2. Cystourethrocele

Modified from Wheeler SJ, Somsin SM. Pelvic pain in women. In: Schwartz GR, Cayten CG, Mangelsen MA, et al., eds. *Principles and Practice of Emergency Medicine*. Philadelphia, PA: Lea and Febiger; 1992:535–546, with permission.

Prepubertal

The approach to pelvic pain in the prepubertal patient requires attention to a broad spectrum of organ systems, though gastrointestinal and urologic causes are the most common. Significant gynecologic pathology is uncommon. Pelvic pain related to accidental perineal trauma is not uncommon, but a high index of

suspicion should be maintained for possible sexual abuse. Any suspicion of abuse warrants a complete investigation. In the peripubertal age group, complications of sexual activity should be considered. In this age group, symptoms surrounding menarche are also common. In younger children, vulvovaginitis can arise from chemical irritation (i.e., bubble bath) or a vaginal foreign body.

Reproductive Age

Gynecologic and obstetric etiologies of pelvic pain increase in frequency as women enter reproductive age.

Ectopic pregnancy (EP) is more fully discussed in Chapter 137. The classic presentation of EP is catastrophic pain in association with missed menses and vaginal bleeding. Multiple variations of this presentation are common. Early stretch and growth of the ectopic gestation in the fallopian tube can result in mild pain caused by tubal distention and contraction. Intermittent leaking of blood, which often precedes rupture by several days, will cause mild, focal, and intermittent peritoneal irritation, which is often poorly characterized by the patient. Risk factors for EP included a history of infertility, use of an intrauterine device, prior tubal ligation, or other pelvic surgery (1). Because of the diversity of presentations, almost one-half of ectopic pregnancies are missed on initial physician contact (2).

Miscarriage in any of its forms can cause pelvic pain. Examination of the cervical os may differentiate a threatened abortion (closed os) from an inevitable or incomplete abortion. Septic abortion presents with a tender, boggy, palpable uterus and fever. Traction on the round ligament and other pelvic structures as the uterus grows during pregnancy can cause significant but transient pain.

Torsion of the ovary or other adnexal structures is a gynecologic emergency. The pain associated with torsion is generally intense, severe, and unilateral, with frequent radiation to the back or thigh. The pain may be intermittent and associated with nausea and vomiting. An adnexal mass may be palpable. Common predisposing factors include pregnancy, ovarian hyperstimulation syndrome, and

ovarian or paraovarian cyst disease. Because the ovary and the kidney have the same innervation (T10 to T11), the clinical picture may mimic renal colic.

Pelvic inflammatory disease (PID) is discussed more fully in Chapter 130. A dull lower abdominal pain, most often bilateral, characterizes uncomplicated PID. Onset is more frequent within 1 week of menses, but the pain may be subacute and develop over several days. If infection extends beyond the endometrium and tubes, pain can become more severe and peritoneal irritation is seen. Clinical signs and laboratory parameters tend to be nonspecific and can include fever, vaginal discharge, cervical motion tenderness (CMT), uterine or adnexal tenderness, and, rarely, a mass. Risk factors include multiple sex partners, prior PID, young age, and either no contraception or the use of an intrauterine device (3,4).

Tubo-ovarian abscess (TOA) may occur with severe PID, particularly when caused by or associated with anaerobic organisms. TOA is the most common intra-abdominal abscess in premenopausal women. The mortality of PID has been reported to be as high as 8.6% when associated with rupture (5). Some TOAs are detected when PID fails to resolve with appropriate antibiotic treatment. In other cases, sterile hydrocele or pyosalpinx results from a remote acute infection. The most common signs and symptoms include abdominal pain, fever, and a palpable pelvic mass (6). Rupture of an abscess causes sudden, frank pain resulting from peritoneal contamination, and it is a gynecologic emergency.

Primary dysmenorrhea often occurs in adolescents, usually within 1 to 2 years of menarche. This diagnosis is very common, with 60% of menstruating women reportedly suffering some level of symptoms (7). Pain caused by myometrial contractions occurs just before or coincident with menstruation, and it is described as severe, crampy, and suprapubic. Pain tends to occur with every menstrual period and may be incapacitating, particularly for the first 1 to 2 days of menses. Secondary dysmenorrhea can occur at any age in a menstruating woman and is most often associated with endometriosis. The rate of dysmenorrhea decreases with increasing age. In a study of 165 university students aged 17 to 19 years,

dysmenorrhea caused absenteeism or loss of activity at least once for 42% of the women studied. The most significant associated risk factors were early age at menarche, long menstrual periods, smoking, alcohol intake, and obesity (greater than the 90th percentile) (8).

Sexual abuse has also been strongly associated with dysmenorrhea and chronic pelvic pain. In a study of 581 nonpregnant women aged 18 to 45 years with complaints of dysmenorrhea and chronic pelvic pain, there was a childhood incidence of sexual abuse of 26% and an adult incidence of 28% (9). Other studies also support a significant association between a history of sexual abuse and chronic pelvic pain (10).

Uterine myomata, or fibroid tumors, of the uterus are common, particularly during later reproductive years. Myomata often cause heavy, irregular, and crampy menses. These tumors may undergo ischemia, necrosis, hemorrhage, or torsion. Torsion of the fibroid causes a sharp increase in severity of pain. Physical examination in a patient with fibroids reveals a tender, enlarged, and often irregular uterus. Myomata may also interfere with fertility, increasing the risk of spontaneous abortions (11).

Mittelschmerz is unilateral adnexal pain at the time of ovulation, resulting from leakage of blood or fluid from the Graafian follicle. Sudden, sharp, well-localized peritoneal irritation is usually found without fever, hypotension, or signs of inflammation or infection. An adnexal mass is infrequent. Occasionally, symptoms can be severe and generalized, but they classically decrescendo and resolve within 24 to 48 hours. In some patients, midcycle pain is recurrent and predictable.

Ovarian cyst disease may occur at any age. Simple functional cysts may contain follicular fluid or blood. Corpus luteum cysts are extremely vascular; ruptured corpus luteum cysts are common in pregnancy, presenting with sudden unilateral pain that is usually mild and localized. Less common are dermoid cysts, endometriomas, and serous and mucinous cysts. With cyst rupture, rapid onset of pain is characteristic, and local peritoneal irritation is common, but fever and systemic signs are rare. Pain may be diffuse if cyst fluid or

blood contaminates the entire abdominal cavity. Rarely rupture with significant hemorrhage that may lead to hypovolemia and hemodynamic instability (12). Unruptured ovarian cysts may also cause pain if the cyst distends rapidly or if torsion occurs.

Appendicitis is the most common nonobstetric surgical emergency in pregnancy. It is particularly difficult to diagnose in women, reflected by the 25% to 50% negative laparotomy rate for women in reproductive years (13). Diagnosing appendicitis becomes more difficult as pregnancy progresses because the uterus obscures the examination and distorts the location. Delays in surgical management in pregnancy result in increased morbidity for both the mother and the fetus (2,13). CMT may occur in either PID or appendicitis, and pyuria occurs in 10% to 20% because of the proximity of the ureters to the adnexa and appendix. The presence of significant bilateral adnexal tenderness and longer symptom duration (>3 days) may suggest PID, but imaging or laparoscopy may be required to differentiate the two.

Urologic causes of pelvic pain include cystitis, pyelonephritis, and renal calculi. Pyelonephritis usually presents with suprapubic tenderness and costovertebral angle tenderness. Renal calculi typically cause severe unilateral, colicky pain. The patient may have a history of renal calculi, and hematuria is frequently present. A Bartholin gland cyst or abscess can cause incapacitating pelvic pain. The glands are located in the labia minora at approximately the 4 and 8 o'clock positions. Two potential ED treatment strategies are placement of a Word catheter or marsupialization of the cyst (14).

Postmenopausal

Pelvic pain in the postmenopausal patient adds a unique set of concerns to those already mentioned. In this age group, atrophic vaginitis is a common problem but should be a diagnosis of exclusion. Malignancies of both the reproductive and gastrointestinal systems increase with age. Urinary tract infections also increase in frequency; however, caution must be used in attributing symptoms to a questionable urinalysis. Diverticulitis can

occur in younger women but is more common in this age group. Finally, ischemic bowel must be considered, especially when pain is out of proportion to the physical examination findings.

ED EVALUATION

An appropriate history includes a description of the pain—onset, progression, quality, character, intensity, and radiation—as well as the reason for the ED presentation. The menstrual history includes gravidity, parity, date, and duration of the last two menstrual periods; regularity; any recent menstrual abnormalities; as well as time of menarche and menopause, when applicable. A history of sexually transmitted diseases (STDs), use and type of contraceptives, recent vaginal discharge, breast symptoms, dyspareunia, and urinary complaints should be obtained. Gastrointestinal complaints must also be evaluated, including nausea, vomiting, diarrhea, or constipation. A history of fever and chills should be noted.

The physical examination should be direct but complete. General appearance may be helpful, although individual pain thresholds vary greatly. The patient who avoids movement may have peritoneal irritation, whereas the patient rocking in distress suggests a viscus under pressure. Alterations in vital signs may help identify systemic infection, sepsis, or significant hypovolemia. Abdominal, pelvic, and rectal examinations are mandatory in all women with pelvic pain.

The abdominal examination should focus on a search for masses or palpable organs, localizing areas of tenderness, and demonstrating peritonitis. Peritonitis is detected by performing maneuvers that move the peritoneum but do not put pressure on visceral organs (heel tap, cough, light percussion, pelvic jarring, and general patient movement). “Rebound” tenderness has been the classic procedure for demonstrating peritoneal irritation, yet it may be the least accurate for diagnosing peritonitis. Interobserver variability is substantial, and the test causes unnecessary pain in patients with potentially surgical disease (15).

The pelvic examination should include inspection of the external genitalia as well as the introitus and cervix. The bimanual examination assesses uterine size, palpable masses, and CMT. CMT is often considered pathognomonic of PID, but other diseases such as appendicitis, cyst rupture, and EP also produce pelvic–peritoneal irritation and CMT. A uterus that is fixed and poorly mobile often indicates adhesions secondary to endometriosis, tumor, or prior infection. Rectal examination involves palpation for focal pain, masses, induration, nodularity, or blood.

A sensitive qualitative pregnancy test (urine or serum) for the β-subunit of human chorionic gonadotropin (β-HCG) is essential for evaluation in all women of childbearing age. With a low threshold (<50 mIU/mL International Reference Preparation), false-negative pregnancy tests occur in <1% of patients, even with an abnormal pregnancy (ectopic or miscarriage). A quantitative serum β-HCG may also assist in the interpretation of ultrasound results in first-trimester pregnancies and allow tracking of pregnancy progression at follow-up. Significant pelvic pathology may exist despite a normal complete blood count. However, an increased white blood cell count may reflect systemic infection, and chronic blood loss may be suspected if a low hematocrit is obtained.

An uncontaminated urinalysis is needed to diagnose a urinary tract infection and may assist in differentiating renal colic from ovarian torsion. Vaginal wet mount can indicate various causes of vaginitis (rarely a cause of pelvic pain, but possibly a marker for STD exposure). Cervical cultures or tests to detect *Neisseria gonorrhoeae* and *Chlamydia trachomatis* may assist in the diagnosis of PID.

Pelvic ultrasound is the primary imaging modality if the suspected etiology involves the reproductive tract. Emergency physicians increasingly perform these tests, and several studies have suggested that this practice is safe, accurate, and efficient (16–18). Transvaginal ultrasound can reliably identify intrauterine pregnancy in the first trimester. A gestational sac and fetal pole should be seen by 5 weeks, and fetal heartbeat should be seen by approximately 8 weeks. Pelvic ultrasound is also adept at identifying adnexal masses

and, with the use of Doppler flow technology, can confirm perfusion of the ovaries.

CT may be useful in the diagnosis of pelvic pain of otherwise unclear etiology. CT has become the primary imaging modality for renal colic, and it is an appropriate study when appendicitis or other bowel pathology leads the differential diagnosis.

Laparoscopy is the gold standard study in the diagnosis of pelvic pain. Laparoscopy remains the procedure of choice to confirm the diagnosis for the patient who is acutely ill or for whom surgical disease (e.g., appendicitis) cannot be excluded. In a study of laparoscopic examination of 316 women with acute pelvic pain, >76% had an abnormal laparoscopic examination, and 45% of those with abnormal laparoscopic examinations had EP (19).

KEY TESTING

- Urinalysis and pregnancy testing
- Pelvic ultrasound, CT scan, or laparoscopy in selected cases

ED MANAGEMENT

The ED treatment of the patient with pelvic pain can be broken down into several critical questions.

Is the Patient Hemodynamically Stable?

Large-bore intravenous access, monitoring, and crystalloid fluid resuscitation are the first steps in managing the unstable pelvic pain patient. Early operative intervention is indicated when patients are persistently unstable. When multiple etiologies are being considered, it is reasonable to simultaneously consult the appropriate services.

Is the Patient Pregnant?

Early establishment of pregnancy status is critical. It should occur as early as possible and occur concurrent with resuscitation when

necessary. A positive pregnancy test requires effort to be focused first on confirming or excluding EP.

Does the Patient Have Severe Pain or Peritoneal Signs?

The presence of peritonitis requires a diligent search for surgically correctable etiologies. Early consultation for consideration of direct operative evaluation is prudent. Atypical presentations or severe pain without evidence of peritoneal irritation may require appropriate imaging studies to further focus the differential diagnosis. Pain control should be a primary goal, and evidence suggests analgesia may improve diagnostic accuracy (20).

Does the Pelvic Examination Reveal Evidence of Infection?

Pelvic examination findings suggestive of PID in the absence of severe pain or peritonitis can be treated by a number of approved regimens (see Chapter 130). Imaging in PID is limited to the evaluation of possible complications such as TOA.

Does the Patient Have an Alternative Diagnosis?

An alternative diagnosis should be considered in the stable, nonpregnant patient with mild-to-moderate symptoms and no evidence of PID. Urologic and gastrointestinal etiologies are most common. If other diagnoses are reasonably excluded, symptom control and outpatient referral are indicated.

CRITICAL INTERVENTIONS

- Provide aggressive resuscitation and monitoring of unstable pelvic-pain patients

DISPOSITION

Admission is necessary for potential surgical disease, including appendicitis, selected cases of PID, and EP associated with significant symptoms.

Observation may be necessary if a surgical etiology is possible, pain remains severe, or vomiting and other signs of systemic toxicity are worrisome to the clinician. Observation is appropriate for patients with focal peritonitis secondary to presumed cystic rupture or for suspected early appendicitis. Patients observed in the ED should have serial examinations and clear criteria for admission.

If a patient is discharged from the ED with pelvic pain in which the etiology is uncertain but the patient is stable, instructions for appropriate and early follow-up are imperative. Any woman with abdominal pain who is discharged from the ED must be instructed to obtain a repeat evaluation if her pain continues or worsens. Because many causes of pelvic pain, particularly when the pain is chronic, are not amenable to ED diagnosis, there will exist a population of patients for whom exclusion of surgical disease, short-term pain relief, and referral for definitive diagnosis are the appropriate actions in the ED.

Common Pitfalls

- Failing to recognize the severity of illness by relying inappropriately on vital signs.
- Failing to obtain pregnancy testing particularly around the time of menarche and menopause or in those who report birth control use or history of sterilization procedures.
- Attributing pelvic pain to urinary tract infection when the urinalysis is questionable and other causes have not been ruled out.
- Failing to recognize that CMT is neither specific nor sensitive for PID.

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CHAPTER 130

Pelvic Inflammatory Disease

Alfred Sacchetti

Pelvic inflammatory disease (PID) is a generic term that describes infection-related inflammatory changes of the upper genital tract in women. PID may include any combination of endometritis, salpingitis, tubo-ovarian abscess, or pelvic peritonitis. In the majority of cases *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are implicated; however, PID may also be caused by other organisms, including anaerobic bacteria, *Gardnerella vaginalis, Haemophilus influenzae,* enteric gram-negative rods, *Streptococcus agalactiae, Mycoplasma hominis, Mycoplasma genitalium,* and *Ureaplasma urealyticum* (1). More than 100 aerobic and anaerobic bacterial strains have been recovered from the pouch of Douglas or high cervical cultures in patients with PID (2). Sexually transmitted infections (STIs), including PID are most common in the second and third decades of life, with most cases in women under 25 years of age. In 2011 the prevalence of chlamydial infections was 648.9 per 100,000 women and gonorrhea was 104.2 per 10,000 for both sexes (3–5). Child abuse must be suspected in any prepubertal female with the diagnosis of salpingitis.

Most pelvic infections originate from colonization of the vagina or cervix. From this site, the pathogens ascend through the cervical os into the lower uterine segment and uterine cavity. Normal cervical mucus presents a natural barrier to vaginal organisms; however, both *N. gonorrhoeae* and *C. trachomatis* appear able to produce uterine infections despite this protection. Certain cervical

conditions, including recent menses, surgical cervical procedures, foreign bodies (intrauterine devices [IUDs]), and various hormonal changes during a menstrual cycle, decrease the defensive ability of the cervix. The hormonal changes induced by oral contraceptive agents enhance rather than reduce the bacteriostatic properties of the cervix if administered prior to colonization. There is evidence that oral contraceptives may mask the symptoms of chlamydial infection once it does become established.

Once entry into the uterus has been gained, the uterine lining becomes inflamed. In postpartum patients, the myometrium becomes infected, but in other patients, this inflammation is seldom invasive and is limited to the endometrium. The inflammation may produce uterine bleeding, but in the nongravid uterus, this is seldom clinically significant. The pathogens then continue their migration through the fallopian tubes. In the case of mycoplasmal infection, ascension may occur by way of parametrial structures rather than through the uterine cavity.

Initially, tubal infection is limited to the mucosa of the lumen, but the inflammation rapidly extends through the full thickness of the tubes. This transmural reaction of the fallopian tubes often causes the early pain of pelvic infection. The inflammation initiated by *N. gonorrhoeae* or *C. trachomatis* frequently overwhelms the normal uterine defense mechanisms and results in infections from opportunistic pathogens, particularly *Bacteroides* sp (6).

In severe cases of salpingitis, the purulent material from the fallopian lumens exudes through the open fimbriae into the abdominal cavity, producing peritonitis. The infection of the endometrium and fallopian tubes results in an inflammation of the surrounding parametrial structures. Although these structures may not undergo actual infection by the invading pathogens, their proximity to the true infection produces a severe parametritis in many patients. Escape through the end of the right fallopian tube and ascension to the right colic gutter may result in inflammation around the liver. *Fitz-Hugh–Curtis syndrome* (perihepatitis) is usually associated with *C. trachomatis* but may occur in 8% to 10% of all cases of salpingitis. Although typically associated with STIs, this

syndrome may result from any intra-abdominal inflammatory process (7).

Inflammation and stagnation of host defenses, particularly in the fallopian tubes, allow for the possibility of unchecked bacterial growth. A tubo-ovarian abscess may develop; originating in the fallopian tube, the abscess may extend to involve the fimbriae and ovary as well. The bacterial content of a tubo-ovarian abscess is mixed, with a preponderance of anaerobes (4).

CLINICAL PRESENTATION

A clinical diagnosis of PID may be difficult because of the wide variation in signs and symptoms. No single historical, physical, or laboratory finding is both sensitive and specific for the diagnosis of acute PID. The Centers for Disease Control and Prevention (CDC) estimate that a clinical diagnosis of PID has a positive predictive rate of 65% to 90% for salpingitis when compared to laparoscopy (1). In a separate study, clinicians failed to recognize *N. gonorrhoeae* or *C. trachomatis* in 38% of infected women and overtreated 88% of women with no infection from these pathogens (8). Similarly in a review of only emergency department encounters, laboratory specimens confirmed infections for gonorrhea in 4.4%, for chlamydia in 10%, and for both in 2.6% of patients with a diagnosis of PID (9). Mild or nonspecific complaints may go unrecognized by the clinician (e.g., abnormal bleeding, dyspareunia, or vaginal discharge). Most authorities recommend a low threshold for diagnosis of PID because of the long-term effects and potential damage to the reproductive system of women. The CDC now recommends empiric treatment for PID if no other explanation can be found for lower abdominal pain in sexually active females with cervical motion tenderness, uterine tenderness, or adnexal tenderness. Table 130.1 summarizes findings consistent with PID.

TABLE 130.1
Diagnostic Findings in Pelvic Inflammatory Disease (PID)

Minimal Criteria for the Clinical Diagnosis of PID

Empiric treatment of PID should be instituted in sexually active females considered at risk for an STI who have lower abdominal or pelvic pain and one or more of the following findings.

Cervical motion tenderness

Uterine tenderness

Adnexal tenderness

Additional Criteria

The presence of more severe clinical signs warrant more elaborate diagnostic evaluations and more aggressive treatment to assure the correct diagnosis and prevent possible morbidities.

Oral temperature >38.3°C (101°F)

Abnormal cervical or vaginal mucopurulent discharge

Presence of white blood cells on saline microscopy of vaginal secretions

Elevated erythrocyte sedimentation rate

Elevated C-reactive protein

Laboratory documentation of cervical infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*

PID-Specific Criteria

Histopathologic evidence of endometritis on endometrial biopsy

Tubo-ovarian abscess, thickened or fluid-filled tubes on transvaginal sonography, magnetic resonance imaging (MRI), or other radiologic tests

Laparoscopic abnormalities consistent with PID

Adapted from Centers for Disease Control and Prevention. Sexually Transmitted Disease Guidelines 2010. Available online at http://www.cdc.gov/std/treatment/2010/pid.htm.

Although attempts have been made to distinguish between features of infection caused by *N. gonorrhoeae* and *C. trachomatis,* they have not been consistent or reliable. *N. gonorrhoeae* salpingitis develops in the first few days after menses, producing a purulent vaginal discharge and severe pelvic pain. *C. trachomatis* infection may occur at any point in the menstrual cycle and results in less cervical discharge and milder symptoms. More important, however, is that both of these infections frequently coexist in 35% to 42% of patients (10).

The patient with a pelvic infection almost invariably presents to the ED with a complaint of lower abdominal pain. Inflammation of the endometrium, fallopian tubes, and parametrial structures usually produces diffuse bilateral pelvic pain. When questioned,

most women describe a dull, constant, poorly localized pain, although almost any characterization of the pain has been reported. Because of the sensitive nature and social stigma of STIs, physicians should be empathetic and tactful in eliciting the patient's history. Pelvic pain is seldom the only presenting complaint. *N. gonorrhoeae* or *C. trachomatis* cervicitis results in a vaginal discharge in over 50% of patients, whereas abnormal vaginal bleeding is seen in 30%. Gastrointestinal complaints, including nausea and vomiting, are less common but may be present. Urinary tract symptoms are common, with 20% of laparoscopically proven pelvic infections associated with irritative voiding symptoms (10). Pelvic infection should be suspected in patients who complain of dysuria or suprapubic pain that occurs only during micturition. Classic urinary tract presentations including urgency, frequency, and dysuria have been reported in 33% to 53% of women found to have STI.

A temperature greater than 38°C (100.4°F) is found in only 33% of patients. Fever supports the diagnosis but does not confirm it, nor does its absence preclude the diagnosis of PID. The abdominal examination commonly reveals tenderness in both lower quadrants, although one side may be more tender. Peritoneal signs indicate a more severe infection, with free exudate in the pelvis or abdomen, and intraperitoneal extension should be considered. If perihepatitis is also present, there may be tenderness in the right upper quadrant.

Pelvic examination must be approached carefully if meaningful information is to be gained. Because of pain or previous experience, this examination may be very difficult for many patients. Speculum examination may reveal a vaginal discharge. A markedly inflamed purulent cervix is indicative of an acute cervicitis and is supportive of some degree of pelvic infection. Normal appearing cervical discharge, and the absence of white blood cells on either Gram stain or a saline preparation of vaginal fluids, makes the diagnosis of PID very unlikely (1).

Bimanual examination begins with careful testing for cervical motion tenderness. Gentle motion of the cervix should be attempted initially, as an overly aggressive examination may produce reflexive guarding by the patient and severely limit the remainder of the

evaluation. Elicitation of pain with either lateral or anteroposterior motion of the cervix is sensitive but not specific for pelvic infection. The emergency physician must remember that other causes of pelvic irritation: fluid from ruptured cysts, appendicitis, and blood from ectopic pregnancies can also produce this sign. The uterus is frequently firm but tender. Bilateral adnexal tenderness is one of the most consistent physical findings in studies evaluating diagnostic criteria for salpingitis. An adnexal mass may be appreciated but is not a consistent finding. Findings on pelvic examination may be atypical in patients who have had multiple prior infections or tubal ligation. Obstruction of the fallopian tube may prevent extension of the infection beyond the proximal tube, limiting the degree of adnexal tenderness.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of lower abdominal pain in women should include at least three possibilities: (a) ectopic pregnancy, (b) PID, and (c) appendicitis. Ovarian cyst, urinary tract infection, gastrointestinal hernia, and ovarian torsion should also be considered. Ectopic pregnancy is addressed in Chapter 137, and the approach to pelvic pain is described in Chapter 129. All women with pelvic pain, regardless of their menstrual history, should have a pregnancy test; the only exception is the woman who has had a hysterectomy (1). Salpingitis is the most common incorrect diagnosis in missed ectopic pregnancy and should be considered only after ectopic pregnancy has been excluded (1). The coexistence of infection and pregnancy is possible but unusual, because a mucous plug forms after implantation, preventing the spread of lower genital infections into the upper genital system. However, there is a brief window between insemination and mucous plug formation during which infection may occur. Appendicitis may be differentiated from PID by its unilateral nature, but this is by no means diagnostic.

ED EVALUATION

When PID is suspected, additional support for the diagnosis may be obtained through laboratory analysis. Because of the time interval between the collection of specimens and the return of results, a system should be in place for follow-up of patients undergoing any STI-related testing.

Gonorrhea cultures are obtained by placement of a sterile swab 1 to 2 cm into the endocervical canal, with rotation of the swab for 10 to 30 seconds. Following collection, the swab should be immediately plated on either chocolate agar or Thayer–Martin agar.

Chlamydia detection techniques include culture, antibody detection (enzyme-linked immunosorbent assay [ELISA] and fluorescent), and nucleic acid probes. In contrast to gonorrhea testing, nonculture techniques are the preferred detection procedures for the diagnosis of *C. trachomatis.*

Nucleic acid probe tests have been developed for both of these organisms. These tests are very sensitive and specific and may be applied not only to cervical specimens but also to urine and vaginal swabs. The additional advantage of this testing technique is that it permits home screening of patients for STIs (11–13).

Additional laboratory studies should include urinalysis to rule out urinary tract infection and a urine or serum pregnancy test. A complete blood count may be obtained for use in some disposition decisions, but the clinician should recognize that the test has limited usefulness. Serology for syphilis and human immunodeficiency virus (HIV) testing should be considered in patients with clinical PID or arranged at follow-up for those with laboratory-proven infections.

Imaging studies are helpful in patients with severe symptoms and those in whom the diagnosis is in question. Ultrasonographic findings indicative of PID include thickened fluid-filled fallopian tubes, free pelvic fluid, and tubal hyperemia. Cases progressing to tubo-ovarian abscesses may also demonstrate a complex adnexal mass, echogenic cul-de-sac fluid, and pyosalpinx (1,14). Computerized tomography may be needed in some patients in whom PID cannot be distinguished from appendicitis or other gastrointestinal pathology.

KEY TESTING

- Urine or serum pregnancy testing
- Gonorrhea and chlamydia testing
- Ultrasound or CT as needed to exclude tubo-ovarian abscess or appendicitis

ED MANAGEMENT

Treatment regimens for PID change periodically and it is advisable to monitor the recommendations of the CDC as well as local health agencies regarding treatment of STIs. *N. gonorrhoeae* has continued to demonstrate increasing resistance to all classes of antibiotics including quinolones and cephalosporins (15). Table 130.2 contains the 2010 treatment guidelines for PID. The management of acute pelvic infection centers on prompt antibiotic therapy directed against both *N. gonorrhoeae* and *C. trachomatis*. The goal of treatment is to prevent continued or worsened infection and limit the complications of PID, including chronic pain, ectopic pregnancy, infertility, and chronic infection.

TABLE 130.2
Antibiotic Therapy of Pelvic Inflammatory Disease

Parenteral Treatment
Regimen A
Cefotetan 2 g IV every 12 hrs
OR
Cefoxitin 2 g IV every 6 hrs
PLUS
Doxycycline 100 mg PO or IV every 12 hrs
Regimen B
Clindamycin 900 mg IV every 8 hrs
PLUS
Gentamicin IV/IM 2 mg/kg load followed by 1.5 mg/kg q8h. Single daily dosing (3–5 mg/kg) may be substituted
Alternative Regimen
Ampicillin/sulbactam 3 g IV every 6 hrs
PLUS
Doxycycline 100 mg PO or IV every 12 hrs
Oral Treatment
Regimen A
Ceftriaxone 250 mg IM
PLUS
Doxycycline 100 mg PO twice daily for 14 d
WITH or WITHOUT
Metronidazole 500 mg PO twice daily for 14 d
Regimen B
Cefoxitin 2 g IM along with probenecid 1 g PO
PLUS
Doxycycline 100 mg PO twice daily for 14 d
WITH or WITHOUT
Metronidazole 500 mg PO twice daily for 14 d
Regimen C
Alternate third-generation cephalosporin such as ceftizoxime or cefotaxime may be substituted depending on hospital formulary
PLUS
Doxycycline 100 mg PO twice daily for 14 d
WITH or WITHOUT
Metronidazole 500 mg PO twice daily for 14 d
Patients with severe allergic reactions to cephalosporins are rare and occur in <5% to 10% of patients with historical penicillin allergies. Patients who do not tolerate cephalosporins may be treated with spectinomycin 2 g IM. If spectinomycin is not available, then azithromycin 2 g orally may be effective. Use of azithromycin should be extremely limited to prevent emergence of resistance to this organism. Again these patients need to be followed carefully.[a]

[a]Recommendations for cephalosporin allergic patients adapted from Centers for Disease Control. Updated recommended treatment regimens for gonococcal infections and associated conditions: United States, April 2007. Available online at http://www.cdc.gov/std/treatment.

Adapted from Centers for Disease Control and Prevention. Sexually Transmitted Disease

Treatment of uncomplicated cervicitis or urethritis with single-dose antibiotic regimens has been described. Options reported include oral azithromycin (1 g), plus cefpodoxime (400 mg) or cefuroxime axetil (1 g). In penicillin-allergic patients, the use of a single 2-g dose of azithromycin has also been described, although there are fears that this may only precipitate resistance (16). The clinician may consider such therapies more convenient; however, none of these have been formally endorsed by the CDC for upper tract or established pelvic infections (1).

Patients coinfected with HIV do not require any significant modifications in their treatment regimens for PID. These patients are more likely to have infections with *M. hominis, Candida* and *Streptococcal* sp, and human papillomavirus (HPV). However, disposition and determination of the need for hospitalization should be based on the patient's overall clinical condition and not the presence of both PID and HIV.

The presence of an IUD has been reported to increase the incidence of pelvic infections, although this effect appears to be limited to the first 3 weeks after insertion of the device. There is no evidence that an IUD needs to be removed in a patient diagnosed with an acute upper genital tract infection. However, close follow-up with gynecologic consultation appears prudent in these patients (17).

Because infected males may be asymptomatic or deny symptoms, women with pelvic infections are at risk for reinfection if they continue relations with an infected male. Empiric treatment is recommended for any male who has had sexual contact with a woman diagnosed with a pelvic infection in the 60 days prior to her manifestation of symptoms (1).

CRITICAL INTERVENTIONS

- Rule out tubo-ovarian abscess in patients with PID and severe unilateral pelvic tenderness.

- Initiate parenteral antibiotics for toxic patients with PID and for those with tubo-ovarian abscess.
- Initiate empiric antibiotic treatment for patients suspected of having PID, pending return of confirmatory test results and having early follow-up arranged.

DISPOSITION

Suggested criteria for admission are listed in Table 130.3. Hospitalization is frequently indicated for pregnant patients. There are no data to recommend inpatient management over outpatient therapy for adolescent patients.

TABLE 130.3
Admission Criteria for Patients with PID

1. Surgical emergencies (e.g., appendicitis) cannot be excluded.
2. Pregnancy.
3. Patient does not respond clinically to oral antimicrobial therapy.
4. Patient unable to follow or tolerate an outpatient oral regimen.
5. Patient has severe illness, nausea and vomiting, or high fever.
6. Patient has tubo-ovarian abscess.

Note: None of these criteria is absolute; all should be applied on an individual basis.
Clinical criteria for improvement within 72 hours consist of defervescence, reduction in direct or rebound abdominal tenderness, and reduction in uterine, adnexal, and cervical motion tenderness within 3 days of initiation of therapy.
Adapted from Centers for Disease Control and Prevention. Sexually Transmitted Disease Guidelines 2010. Available online at http://www.cdc.gov/std/treatment/2010/pid.htm.

Outpatient management is appropriate for those patients not meeting criteria for admission shown in Table 130.3. All discharged patients should receive follow-up care to ensure response to treatment. If cultures are obtained, a mechanism should be in place to ensure that patients and their physicians or the public health department are notified of positive results.

Common Pitfalls

- The differential diagnosis of women thought to have PID must include ectopic pregnancy and appendicitis.

- The clinician should question the diagnosis of PID in any patient with unilateral pelvic pain.
- Pregnancy must be ruled out.
- Serologic testing for syphilis and HIV testing counseling are indicated for most women with a documented sexually transmitted disease.

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CHAPTER 131

Vaginal Bleeding in the Nonpregnant Patient

Eric Anderson and Margaret McKenzie

Vaginal bleeding from multiple causes is a common problem encountered in emergency medicine (1). Abnormal uterine bleeding affects 20% to 30% of women at some time during their reproductive years (2). It is incumbent upon the emergency physician to rapidly distinguish between life-threatening bleeding and bleeding that can be evaluated in the emergency department (ED) and referred for further evaluation by a gynecologist. Complications of symptomatic vaginal bleeding include iron-deficiency anemia, fatigue, depression, and disturbance in sexual function, as well as disturbances of social and occupational activities (3).

CLINICAL PRESENTATION

Important considerations when evaluating vaginal bleeding in the emergency setting include understanding the various etiologies of such bleeding presentations. Pregnancy must be ruled out in all women of childbearing age. Abnormal vaginal bleeding may or may not be associated with the menstrual cycle. Bleeding that occurs at the usual time of menses but is more copious or longer than usual is termed *menorrhagia.* Bleeding that occurs at irregular intervals or between normal menses is termed *metrorrhagia,* while irregular and excessive bleeding (>80 mL of blood per cycle) is termed *menometrorrhagia. Oligomenorrhea* is decreased menstrual frequency,

while *polymenorrhea* is increased menstrual frequency. Menstrual blood loss of less than 5 mL per cycle in termed *hypomenorrhea.* Normal cycle values are illustrated in Table 131.1. Variation in the use and definitions of these terms has prompted the development of a new classification system, PALM COEIN, to describe abnormal uterine bleeding based on the etiology. This acronym signifies Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory disorder, Endometrial, Iatrogenic and Not yet classified as potential causes for the abnormal vaginal bleeding (4). This classification is based on anatomic (PALM) and physiologic (COEIN) findings which may not be known at the time of ED evaluation.

TABLE 131.1
Normal Menstrual Cycle Values

	Normal (5th to 95th Percentile)	Abnormal
Frequency of menses (d)	24–38	<24 or >38
Duration of flow (d)	4.5–8	<4.5 or >8
Blood loss (mL)	5–80	<5 or >80
Menarche onset age (yr)	9–14 (mean 12.9)	<8, >14

Frequency, duration, and blood loss: Adapted from Munro M. Classification of menstrual bleeding disorders. *Rev Endocr Metab Disord*. 2012;13:225–234.

Abnormal bleeding due to anovulation is more typically variable and the amount and timing of the bleeding is less predictable and is a common cause for the vaginal bleeding that presents to the Emergency room (3). Anovulatory cycles occur more commonly in perimenarchal and perimenopausal patients as well as patients with metabolic abnormalities like the classic polycystic ovarian syndrome. In perimenarchal girls anovulatory bleeding occurs as a result of immaturity of the hypothalamic–pituitary–ovarian axis.

DIFFERENTIAL DIAGNOSIS

It is imperative that the emergency physician determine whether the presenting vaginal bleeding is a complication of pregnancy. A

pregnancy test should be performed on all reproductive age patients regardless of the stated history of sexual activity. It is best to interview adolescent patients about sexual activity, alcohol and illicit drug use without parents present. It may be appropriate to ask parents if they suspect sexual activity alcohol or illicit drug use separate from the patient as well.

Sexually transmitted infections (STIs) are usually included in the differential diagnosis of vaginal bleeding. However, a recent article calls that dogma into question. Bernwald et al. studied *Chlamydia trachomatis* and *Neisseria gonorrhea* rates in ED patients. The patients with and without vaginal bleeding had comparable rates of STI (6).

The normal menstrual cycle is characterized by growth of the endometrium under the influence of estrogen. After ovulation progesterone increases and the endometrium matures. At the end of the cycle, estrogen and progesterone levels decrease and the endometrial surface sloughs resulting in menstruation. The transition to menopause is marked by unopposed estrogen stimulation of the endometrium which results in sporadic anovulatory cycles. In the absence of progesterone this results in unpredictable endometrial sloughing and vaginal bleeding (7).

Approximately 10% of bleeding in postmenopausal patients will be found to be related to a gynecologic or metastatic malignancy. Eighty to ninety percent of patients diagnosed with endometrial cancer present with vaginal bleeding (8–10). Endometrial cancer is the most common gynecologic malignancy with a lifetime incidence of 2.6% in women of the United States (7). It is followed by cancer of the ovary, cervix, and vagina in descending order (7). Ovarian cancer is the leading cause of gynecologic deaths. Vaginal cancer is usually metastatic from another primary source (7).

Women with various bleeding disorders often present to the ED with menorrhagia. Von Willebrand disease (VWD), a platelet adhesion disorder, occurs in 13% of women with chronic menorrhagia (11,12). Conversely 74% to 92% of women with VWD experience menorrhagia. VWD is the most common inherited bleeding disorder worldwide. It has been estimated that approximately half of patients presenting with unexplained

menorrhagia had a defect in platelet aggregation and/or release (12).

Systemic illnesses that can manifest as vaginal bleeding include marked obesity, hypothyroidism, hyperthyroidism, and liver cirrhosis with resulting coagulopathy.

Iatrogenic causes of uterine bleeding include oral, subdermal, or injectable sex steroids used for contraception hormone replacement therapy, treatment of hirsutism, dysmenorrhea, premenstrual syndrome, acne, or endometriosis (1). There may be transient abnormal bleeding for 1 to 2 cycles after emergency contraception use of levonorgestrel oral or intrauterine (13,14).

Bleeding from cervical polyps can occur as a result of coitus and may be minor or copious, while endometrial polyps present with intermenstrual bleeding. The presence of benign uterine lesions including polyps and fibroids peaks between 40 and 50 years of age even though they can occur at any age (15).

ED EVALUATION

Pregnancy status should be assessed in all reproductive age women presenting to the ED with a complaint of vaginal bleeding. Important historical elements include date of last **normal** menstrual period, sexual activity, prior pregnancies, and STIs. Details of the presenting bleeding history should include questions that might suggest orthostatic symptoms, when bleeding started, if bleeding is constant or intermittent, presence and description of abdominal pain, presence of foul vaginal discharge, and use of sex steroids or recent discontinuation of sex steroids or other inciting factors. Questions about the amount of bleeding, beyond spotting versus frank bleeding, are of limited value and often inaccurate (16). History should be taken without family and friends in the room as the patient may want to keep private certain elements of her sexual and reproductive history. Adolescents should be questioned in private for the same reasons. History of physical assault, sexual abuse, and genitourinary trauma should be obtained (Table 131.2).

TABLE 131.2
Causes of Nonpregnancy-Related Vaginal Bleeding

Anatomic	Congenital anomalies, polyps (uterine, cervical, urethral prolapse, uterine fibroids)
Coagulopathy	DIC, leukemia, thrombocytopenia, von Willebrand disease, thrombotic thrombocytopenic purpura, and immune thrombocytopenic purpura, prothrombin deficiency
Endocrine	Addison disease, congenital adrenal hyperplasia, Cushing syndrome, diabetes (poorly controlled), hyperprolactinemia, hyperthyroidism, hypothyroidism, polycystic ovary disease, primary ovarian dysfunction, postnatal withdrawal of maternal hormones
Foreign bodies	Condoms, cotton balls, IUD, sexual device, tampon, tissue paper, toy
Hormonal	Administration of exogenous sex steroids, anovulatory cycle
Infections	Cervicitis, chlamydia, condyloma acuminatum, gonorrhea, trichomonas, tuberculosis, UTI, vaginitis
Medications	Birth control pills, coumadin, heparin, phenobarbital, phenytoin
Neoplasm	Cervix, uterine, vagina, metastatic or erosive from elsewhere
Trauma	Blunt, sharp, sexual trauma
Other	Crohn disease of vulva, emotional stress, excessive dieting, excessive exercise, premature menarche (children)

DIC, disseminated intravascular coagulation; IUD, intrauterine device; UTI, urinary tract infection.

Upon physical examination those who appear pale, weak, tachycardic, or hypotensive should be assumed to have experienced a significant blood loss and attended to in a timely fashion. Pale conjunctivae, pale skin, and diaphoresis all imply a significant blood loss. Examination of the abdomen, perineum, and pelvis may reveal the cause of the bleeding or guide further testing. A rectal examination may be needed if there is no sign of blood on the pelvic examination. It may be necessary to obtain a catheterized urine specimen in patients who insist on vaginal bleeding but have no evidence of blood on pelvic or rectal examination. Skin should be examined for bruises that may indicate a coagulopathy or physical abuse.

Laboratory assessment in the uncomplicated patient should include a urine pregnancy test and possibly a urinalysis. Unstable

patients require a workup to assess the amount of bleeding and preliminary evaluation of the cause of the bleeding. Complete blood count (CBC), clotting studies, electrolytes, pregnancy test, and type and screen should be performed in unstable patients. Liver and thyroid function studies are useful in the minority of patients where these etiologies of the bleeding are a possibility.

Imaging with ultrasound may be useful in the patient with suspected uterine fibroids, polyps, mass or cervical or vaginal masses, or vascular malformations. Imaging with CT or MRI is useful in further delineating the etiology and extent of a mass or vascular malformation that may contribute to the bleeding.

KEY TESTING

- Urinalysis and pregnancy testing
- CBC, coagulation studies, and type and screen in those with significant blood loss

ED MANAGEMENT

The vast majority of patients will not present with life threatening bleeding and so will be evaluated and discharged home for outpatient follow up. A through history, physical examination, and pregnancy testing.

Treatment for patients in hemorrhagic shock should be initiated with two large bore IVs and fluid resuscitation and blood and blood products as needed. Early gynecologic consultation should be made as there are several treatment options in these patients.

Once resuscitation has begun, priority is to prevent and decrease further blood loss. Immediate interventions include examination under anesthesia to properly locate the source of the bleeding in cases of excessively heavy bleeding. Intrauterine Foley balloon placement is effective at significantly decreasing acute blood loss (17). IV administration of high-dose conjugated estrogen stopped abnormal uterine bleeding in 71% of women compared to 38% in placebo group (18,19). Dosage is 25 mg IV every 6 hours for 24 hours followed by oral combined estrogen/progestin therapy. Side

effects include nausea and vomiting which can be treated with antiemetics.

In cases where patients are poor surgical candidates, but are stable enough, uterine artery embolization offers a solution to control acute heavy bleeding until medical therapy can be effective (20). Hysterectomy is a last ditch alternative when therapy for acute heavy bleeding fails and fertility is no longer desired.

Since 40% to 80% of women treated for heavy menstrual bleeding have no anatomic pathology, pharmacologic therapy represents a great treatment alternative in the emergency setting (21). Nonsteroidal anti-inflammatory drugs (NSAIDs) work by decreasing prostaglandin levels in the endometrium and have been shown to decrease menstrual blood loss by at least 30% when compared to placebo (18,21). Doses include naproxen 250 to 275 mg or ibuprofen 200 to 400 mg or mefenamic acid 500 mg three times daily starting 24 to 48 hours prior to the onset of menstrual blood flow.

Tranexamic acid, an antifibrinolytic agent, inhibits endometrial plasminogen activator, thus stabilizing clots and represents an attractive option in the emergency setting. Oral forms are now approved for use in the United States and are advantageous because of the oral dosing and fast onset of action, with relatively few side effects. Its use is contraindicated in patients with active thromboembolic disease. Current dosing regimens for tranexamic acid are two 650 mg tablets orally for three times daily for a maximum of 5 days per cycle. Studies show a 40% reduction in menstrual blood loss compared to placebo (18,22).

Desmopressin is a synthetic analog of vasopressin and can be used to manage severe acute heavy vaginal bleeding and menorrhagia in patients with hemophilia A and VWD. Current doses of 4 μg/mL injection or IV have been approved for use in these patient groups (18).

Hormonal options for the management of vaginal bleeding in the nonpregnant patient include combination estrogen–progestin contraceptives (oral, transdermal, or vaginal ring), continuous oral intrauterine or injectable progestins, cyclic progestins or danazol

(oral or vaginal). Selection depends on the need for contraception, coexisting or risk factors for some diseases, and desire for fertility.

Low-dose combined oral contraceptive options are effective for decreasing blood loss by 40% to 50% in some studies. In the emergency setting, combination oral contraciptive pills may be offered in a high-dose fashion when not contraindicated, starting with four pills daily in divided doses for 48 hours then decreasing to three pills daily for 48 hours then two pills daily and then to one pill daily until the pack is complete. This regimen has been shown to be effective in the emergency setting until the patient can follow up as an outpatient.

Progestins work by limiting endometrial growth, inhibiting the synthesis of estrogen receptors, and inhibiting luteinizing hormone. In the emergency setting, megestrol acetate in doses of 40 to 80 mg twice daily has been shown to decrease acute heavy bleeding allowing time for patient to undergo proper evaluation by decreasing blood loss (18). Other regimens include norethindrone 5 mg up to three times daily or medroxyprogesterone acetate 2.5 to 10 mg twice daily to control heavy bleeding. Long-acting progestin only injections have no role in the emergency setting.

Intrauterine progestin-releasing systems are effective in reducing bleeding by 86% in 3 months and 97% at 6 months. These intrauterine systems work by causing the endometrium to become insensitive to ovarian estradiol leading to atrophy of the endometrial glands and suppression of endometrial growth and activity. The effects are reversed by removal of the device. Side effects of intrauterine progestin-containing systems include spotting at irregular intervals, headache, acne, vaginitis, pelvic pain, breast tenderness, and rarely breast tenderness (18).

Danazol is a synthetic steroid with weak androgenic properties. Danazol induces endometrial atrophy relatively quickly by inhibiting estrogen and progesterone receptors (18,23). Minimal, randomized control trial data is available for the use of this agent in the acute setting. Doses of 100 to 200 mg/d have been found to be more effective than other progestins for the control of heavy menstrual bleeding (18,23). Side effects include weight gain,

hirsutism, and acne and counseling patients on expectations is essential for compliance.

CRITICAL INTERVENTIONS

- Resuscitate patients with signs and symptoms of significant blood loss
- Assess pregnancy status as a critical intervention

DISPOSITION

Patients with severe symptoms due to excessive bleeding should be admitted. However, the vast majority of patients are not acutely ill and can be safely discharged home to follow up with a gynecologist or their primary care physician, with or without hormonal therapy. These patients should be evaluated for pregnancy and treatable infections while in the ED.

Patients should be informed of the preliminary nature of the findings and disposition and the need to follow up for further evaluation and care of their symptoms.

Common Pitfalls

- Failure to obtain sexual history from patients in private.
- Failure to refer for further evaluation after the ED evaluation since the exact cause of the bleeding is often not established in the ED.
- Failure to consider medications as possible etiology or contributing cause of the bleeding.

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CHAPTER 132 Vaginitis

Ericka L. Powell

Vaginal discharge and discomfort is the most frequent gynecologic complaint of women during their reproductive years. Vaginitis is the inflammation of the vaginal mucosa and vulva that often causes vaginal discharge, irritation, itching, and odor. Vaginal infection may also cause dyspareunia and dysuria. Vaginitis in women aged 14 to 49 is typically due to *Candida, Trichomonas,* and *Gardnerella* species (1). Noninfectious causes include allergies, immune dysfunction, and chemical irritation. Vaginitis after menopause is typically related to atrophy of the vaginal mucosa from decreased estrogen levels.

Evaluation in the emergency department (ED) includes the three "Ps"—pelvic examination, partners (sexual history), and pH combined with microscopic evaluation of the vaginal discharge on wet mount. This approach will yield a diagnosis in the majority of cases. Vaginal cultures have remained the gold standard for diagnosing the cause of vaginitis, although recent developments in point-of-care testing and polymerase chain reaction (PCR) tests may be more sensitive (2,3).

CLINICAL PRESENTATION

The etiology of vaginitis determines the patients' predominant symptoms and clinical presentation. When taking the history, it is important to distinguish changes in the patient's normal physiologic vaginal discharge, which vary with age, pregnancy, use of exogenous hormones, and menstrual cycle.

Candida vulvovaginitis, commonly called a yeast infection, is caused by the fungus *Candida albicans.* These filamentous organisms

penetrate the mucosal surface, causing local tissue lysis and hyperemia. Fungi can be cultured from the vagina in up to 20% of asymptomatic women; they are commensals in the vaginal ecosystem until it is disturbed. Diabetes, immunosuppression (e.g., AIDS or chronic steroid use), and hormonal shifts as occur in pregnancy increase the likelihood of a yeast infection; low-dose oral contraceptives do not (4). *Candida* is typically not associated with other causes of vaginitis: *Trichomoniasis* or *Gardnerella.*

The hallmark complaint of patients with candida vulvovaginitis is vulvar itching and burning associated with dysuria and dyspareunia. Patients complain of a thick white "cottage cheese" discharge that is odorless. The quantity of discharge may vary.

Trichomoniasis is the most common nonviral mediated sexually transmitted disease (STD) in the United States. Non-Hispanic black women are ten times more likely to have this infection. Other risk factors include poverty, lower educational level, and greater number of sexual partners (5,6). *Trichomonas vaginalis,* a unicellular flagellated protozoan, is sexually transmitted and has been isolated in virtually all genitourinary structures of men and women. These protozoa cause urethritis and cervicitis. Trichomoniasis often presents concurrently with bacterial vaginosis (BV), gonorrhea, and other STDs. This infection has also been associated with preterm labor (5).

Patients with trichomonas vaginitis often complain of a thin, copious, malodorous discharge.

BV is the most common cause of vaginal discharge. This infection is diagnosed in 25% of pregnant women and up to 18% women deny recent sexual activity (1). The normal vaginal environment is a dynamic balance of endogenous bacterial flora, including *Lactobacillus,* which helps to maintain a relatively acidic pH of 3.8 to 4.2. Various events may cause the *lactobacilli* to be replaced by high concentrations of anaerobes, particularly *Gardnerella* species, a gram-negative rod. BV is a synergistic polymicrobic infection in which the vaginal flora become primarily anaerobic. This does not produce inflammatory changes; hence the term *bacterial vaginosis* rather than vaginitis.

Women with BV complain of “fishy” vaginal odor and discharge. This odor tends to increase after sexual intercourse when alkaline sperm trigger the release of aromatic amines.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for patients presenting with symptoms of vaginal discharge, itching, or pain includes vaginitis and other infections such as gonorrhea, chlamydia, and herpes. A Bartholin cyst or abscess may present with vaginal pain or itching, and a retained foreign body may present with a malodorous discharge. Less commonly, a rectovaginal fistula or a cervical or uterine neoplasm may present with a chief complaint of vaginal discharge. Various forms of dermatitis may have similar presenting complaints.

ED EVALUATION

Patients with vaginitis can generally be diagnosed and treated based on the ED history, physical examination, wet mount findings, and pH testing. Occasionally, the diagnosis is revealed later on culture results or urinalysis.

In patients with candidiasis, the vulva may appear erythematous, excoriated, and edematous. There may be satellite pustules at the margins of the infection. The vagina may be sore on speculum examination, and a thick white “cottage cheese” discharge may be adherent to the walls of the vagina. The vaginal pH is typically <4.5. This diagnosis is often based on clinical criteria. Diagnostic testing typically requires examining vaginal discharge under a microscope. A small sample of vaginal discharge is placed on a slide with two drops of normal saline and one to two drops of 10% to 20% solution of KOH. This preparation must be scrutinized at multiple power fields to identify the mycelia or pseudohyphae of *Candida,* which have the appearance of tangled branching chains or oval spores (Fig 132.1). The sensitivity of this method varies based on experience, clinical setting, and training when compared to the gold standard yeast culture (3). Although rapid laboratory tests for yeast have been reported to be more sensitive, specific, and cost-effective, these studies are not widely used in the ED (7,8).

Trichomoniasis is characterized by a profuse malodorous “frothy” discharge on physical examination. The discharge is thin and copious and may be grey-yellow or green. Unlike candidiasis, speculum examination reveals inflammation limited to the vaginal walls and the labia minora. Colpitis macularis, “strawberry” cervix, occurs in a small percentage of women, and up to 50% of patients are asymptomatic (9).

Wet mount preparation should be done as soon as possible after collecting a specimen. Trichomonads can be easily distinguished from white blood cells (WBCs) on low-power microscopy (see Fig. 132.1). They are slightly larger than a WBC and show a “corkscrew” motility. It may be difficult to visualize the entire organism if the vaginal smear specimen is cold or undiluted or if the organism is covered by WBCs. In this situation, only the beating flagella are visualized among the WBCs. WBCs on wet mount are a common finding in *Trichomonas* infection, other STDs, and atrophic vaginitis but are not typical of candidiasis or BV. Wet mount examination has a specificity of up to 70% but a relatively low sensitivity. The pH of the discharge is typically elevated, between 5 and 7. *Trichomonas* infection is frequently diagnosed on Pap smear and can also be found on urine samples. PCR testing is not routinely done, and the reported sensitivity and specificity are variable (10,11).

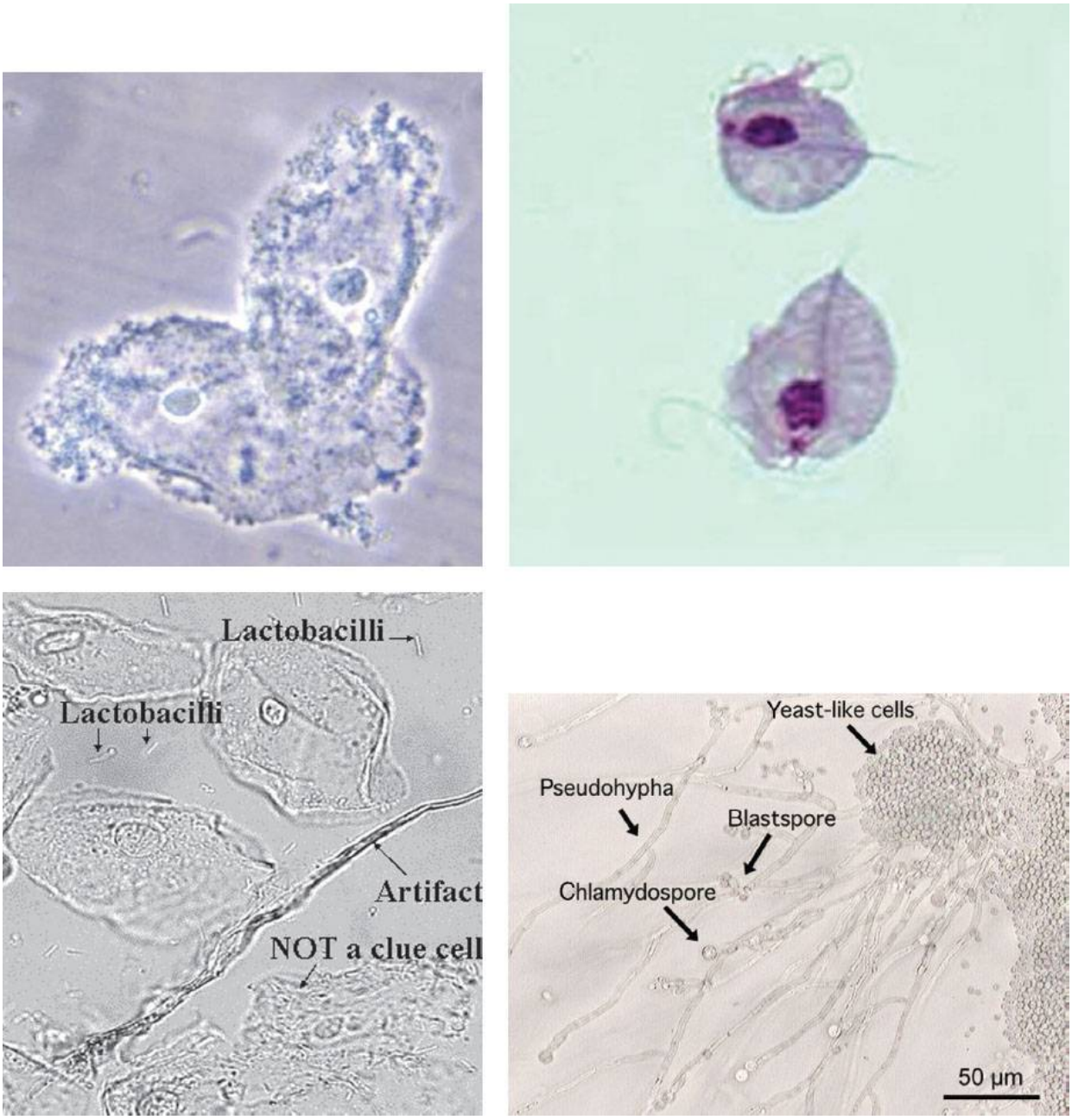

FIGURE 132.1 Wet mount findings in bacterial vaginosis, trichomonas vaginitis, and candida vaginitis.

Patients with BV often have a thin white or grey discharge that is noted on speculum examination to adhere to the vaginal walls. The examiner may notice bubbles in the vaginal discharge. If the cervix is friable or erythematous, the patient should be evaluated for concomitant infections with other STDs. The wet mount microscopic

findings associated with BV have been historically based on Amsel criteria, which include the following:

1. Thin homogenous grey or white discharge
2. Clue cells on microscopy (see Fig. 132.1, bacterial studded vaginal epithelial cells)
3. vaginal fluid pH >4.5
4. positive whiff test (release of fishy amine odor with 10% KOH)

To make the diagnosis of BV, three of the four criteria must be present (12).

An alternative method of diagnosis is Gram stain of a vaginal smear to identify and quantify colonies of anaerobes. The accuracy of diagnosis increases when both tests are used in combination (13). A more rapid BV test with improved sensitivity (BVBlue, Gryphus Diagnostics, LLC, Birmingham, AL) is now available but rarely used. This is a point-of-care chromogenic diagnostic test based on the presence of elevated sialidase enzyme in vaginal fluid samples (14).

KEY TESTING

- Wet mount and pregnancy test
- Vaginal cultures in selected patients

ED MANAGEMENT

Treatment regimens for vaginitis have remained relatively the same over many years. Table 132.1 summarizes the treatment of vaginitis of various etiologies. Recurrence rates for vaginitis are particularly high for *Candida* but also relatively common with *Trichomomas.* Women with resistant infections may need to be referred for additional testing and evaluation for an underlying immunocompromised state. Vaginal culture should be done on all individuals with recurrent vaginitis. Resistant strains of *T. vaginalis* have been reported (15).

TABLE 132.1
Differential Diagnosis and Treatment of Vaginitis

	Candida	Trichomonas	Bacterial Vaginosis
Discharge features	Thick, clumpy white; amount varies	Copious malodorous frothy, homogenous grayish yellow or green	Thin malodorous homogeneous grey or white; moderate amount
pH	<4.5	Between 5 and 7	>4.5
Wet mount	Mycelia, spores/pseudohyphae, WBCs, and epithelial cells[a]	Many WBCs, motile corkscrew trichomonads	Scant WBCs with many clue cells
Whiff test	Negative	Usually positive	Positive
Standard therapy	"Azole" intravaginal cream[b]	Metronidazole 2 g PO single dose or tinidazole 2 g PO single dose	Metronidazole 500 mg PO BID for 7 d or metronidazole gel 0.75%, (5 g) intravaginally for 5 d or clindamycin cream 2%, (5 g) intravaginally at bedtime for 7 d
Alternative therapy	Fluconazole 150 mg PO single dose	Metronidazole 500 mg PO twice daily for 7 d	Metronidazole 2 g PO single dose or clindamycin 300 mg PO twice daily for 7 d
Pregnancy treatment	Clotrimazole 1% 5 g at bedtime intravaginally for 7 d	Clotrimazole 100 mg qhs for 7 d 1st trimester only Metronidazole 2 g oral single dose	Metronidazole 500 mg PO twice daily or 250 mg tid for 7 d or clindamycin 300 mg PO twice daily for 7 d
Partner therapy	None indicated	Metronidazole 2 g oral single dose	None indicated

[a]KOH prep must be used to see fungal elements.
[b]Clotrimazole 1% OTC for 7–14 d, ketoconazole, butoconazole 2% for 3 d.

Candida albicans is typically treated with fungicidal imidazole derivatives. These inexpensive intravaginal preparations are available over the counter and are tolerated by most women. A single oral dose of fluconazole (150 mg) has cure rates similar to those of topical therapies (16). Candidiasis is not sexually transmitted, and partner treatment is not recommended unless males have signs and symptoms of balanitis. Pregnant women should not receive oral fluconazole (5).

T. vaginalis can be cured with single-dose metronidazole (2 g). An alternative treatment regimen consists of metronidazole 500 mg twice daily for 7 days, but compliance is lower. Metronidazole gel is less effective against *T. vaginalis* (<50%) and is not recommended. Tinidazole has been approved by the Food and Drug Administration as an alternative treatment that is very useful for *T. vaginalis* resistant to metronidazole (17). Multiple studies have failed to show teratogenic effects of metronidazole, and symptomatic pregnant patients can be treated with a single oral 2-g dose (10). Patients taking metronidazole should avoid alcohol during treatment and for 24 hours after the last dose to avoid a "disulfiram-like" reaction (18). Patients with an allergy to metronidazole should be referred for desensitization. Other medications such as clotrimazole have higher treatment failure rates. It is imperative to recommend treatment to

all sexual partners of women with diagnosed *Trichomonas*. Reinfection is twice as likely if all partners are not treated. Asymptomatic patients who have positive urine cultures or pap tests should also be treated, as a third of these women can be expected to become symptomatic within 3 months.

Symptomatic patients with BV can be treated with oral and vaginal preparations of metronidazole or clindamycin. All symptomatic pregnant patients should be treated with oral therapy. Intravaginal clindamycin cream has been reported to have adverse effects in pregnancy, including preterm delivery (18). An obstetrician should be consulted on asymptomatic pregnant patients who have diagnosed with BV.

CRITICAL INTERVENTIONS

- Treat infectious causes of vaginitis

DISPOSITION

Patients with simple vaginitis can be treated as outpatients, with follow up by their primary care physician or gynecologist. Those with trichomoniasis should undergo screening for other STDs, along with referral to community resources for counseling regarding safe sex practices and human immunodeficiency virus.

Common Pitfalls

- Failure to perform a thorough history and speculum examination.
- Failure to evaluate for *Candida* and *Trichomonas* in patients complaining of dysuria.
- Neglecting to refer patients for counseling regarding high-risk sexual behaviors and testing for HIV and other STDs.
- Failure to instruct patients to avoid alcohol during a course of metronidazole.
- Failure to recommend treatment for partners of patients with trichomoniasis.

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CHAPTER 133 Bartholin Gland Cyst's and Abscess

Flavia Nobay and Ryan P. Bodkin

BARTHOLIN CYST

The Bartholin glands (vestibular glands) sit at the 4 and 8 o'clock positions deep to the labia minora. Their function is to produce moisture for the posterior vestibule of the vagina (1,2). The Bartholin duct is a 2.5-cm structure that connects the glands to the vaginal orifice and is the conduit for these secretions, exiting onto the vestibule at either side of the vaginal orifice inferior to the hymen. The gland begins producing mucus at puberty and starts involution by 30 years of age, therefore cysts and abscesses of this region typically occur in women of childbearing years, most commonly between 20 and 29 years of age. Mucus retention, trauma, infection, inflammation, or physical blockages of the Bartholin ducts are etiologies for cyst and abscess formation and account for 2% of all gynecologic visits per year (1–3).

CLINICAL PRESENTATION

Most Bartholin cysts are asymptomatic and incidentally noted. Patients who present with a Bartholin cyst will complain of unilateral swelling, pressure and discomfort with walking, intercourse, or exercise over the course of days. Typically, a Bartholin cyst or abscess will be seen or felt unilaterally at the posterior vaginal introitus pointing medially (eFig. 133.1). Bartholin cysts are described as feeling soft or fluctuant and are usually well contained. Symptoms are based on the cyst's size with smaller ones being

asymptomatic (1 to 3 cm) and larger ones causing discomfort (4 to 8 cm) (4). A cyst does not need to pre-exist for an abscess to occur. Patient with severe pain or a rapidly expanding mass with intense pressure should raise concern for a Bartholin abscess (5,6). An abscess will have varying degrees of warmth, surrounding edema, and erythema extending into the superior portions of the labia. In some cases, cellulitis extends from the abscess causing more diffuse pelvic pain and low-grade fevers. Systemic illness is infrequently seen unless significant underlying medical illnesses coexist (6).

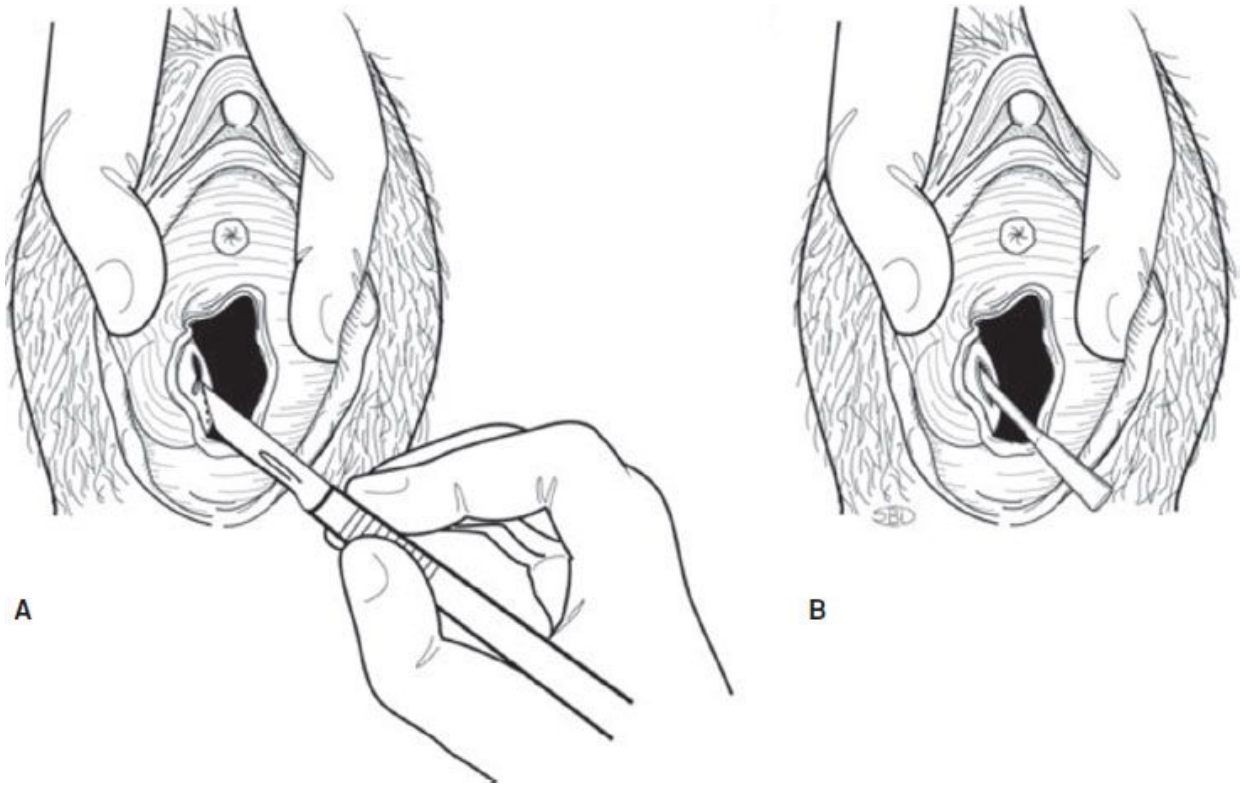


FIGURE 133.1 Treatment options of a Bartholin gland abscess. **A:** Incision and drainage: Make a 0.5 cm vertical incision over the vaginal mucosal side of the labia minora. **B:** Word catheter insertion: Insert the Word catheter as shown, inflate the balloon with approximately 3 mL saline. (From Simon RR, Ross C, Bowman SH, et al. *Cook County Manual of Emergency Procedures*. Philadelphia, PA: Lippincott Williams & Wilkins, 2011.)

eFIGURE 133.1 Abscess of Bartholin gland. © 1992, National Medical Slide Bureau, CMSP.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a tender mass in the vaginal introitus is extensive (Table 133.1). Along with Bartholin cyst/abscess, providers must consider genital warts, herpes, syphilis, hematoma, hidradenoma, lipoma, as well as other varying anatomical cysts (5,6). Women over 40 years old have additional concerns for gynecologic malignancy. Although these diagnoses are rare (incidence of 4% of all gynecologic malignancies), a unilateral vulvar mass is a common clinical presentation for women with vulvar and Bartholin malignancy (7,8). Evidence such as age, time of onset, and systemic symptoms may help differentiate Bartholin and vulvar tumors from nonmalignant masses. Malignancies are described as irregular shaped, firm, fixed, and persistently indurated. Outpatient biopsy of the mass should be considered for any patient over the age of 40 presenting with a first time Bartholin or vulvar mass (8,9).

TABLE 133.1
Differential of Bartholin Cysts or Abscesses

Bartholin gland tumors	Squamous cell carcinoma, adenocarcinoma, adenoid cystic carcinoma, and transitional cell carcinoma
Vulvar masses	Hematoma, fibroma, lipoma
Cysts	Vestibular mucous cysts, inclusion cysts, Gartner duct cysts, Skene duct cysts, canal of Nuck cysts, sebaceous cysts
Sexually transmitted infections	Human papillomavirus, herpes simplex virus
Nonmalignant masses	Leiomyomas, fibromas
Inflammation	Hidradenitis suppurativa
Anatomical abnormalities	Hernias, urethral diverticula

From Boardman LA, Kennedy CM. Benign vulvovaginal disorders. In: Gibbs RS, Karlan BY, Haney AF, et al., eds. *Danforth's Obstetrics and Gynecology*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:625–647 and Stillman FH, Muto MG. The vulva. In: Ryan KJ, Berkowitz RS, Barbieri RL, eds. *Kistner's Gynecology: Principles and Practice*. 6th ed. St. Louis, MO: Mosby; 1995:66–68.

ED EVALUATION

Patients with Bartholin duct cysts and abscesses require a careful history and physical examination. A complete history will include time of onset and duration of illness, systemic symptoms, a sexual history, and a gynecologic history including documentation of previous vulvar abnormalities. The physical examination should include visual and digital inspections of the external genitalia. If a vaginal discharge is present, a pelvic examination with appropriate cultures for sexually transmitted infections should be obtained.

Routine imaging and blood tests are not required for a Bartholin cyst. Cultures are helpful in understanding the changing microbiologic landscape of Bartholin abscesses. Bartholin cysts are generally considered sterile and abscesses are considered to be polymicrobial (10,11). The previous association of Bartholin abscesses with sexually transmitted infections has decreased from approximately one-third of isolates to less than a fifth of isolates (8% to 16%) with *Neisseria gonorrhoeae* and *Chlamydia trachomatis* as the primary causative agents (12). Escherichia coli, *Bacteroides fragilis* and Methicillin-resistant *Staphylococcus aureus* (MRSA) are increasingly isolated from Bartholin abscesses (13–15). Pregnancy testing should be obtained on all patients of childbearing age.

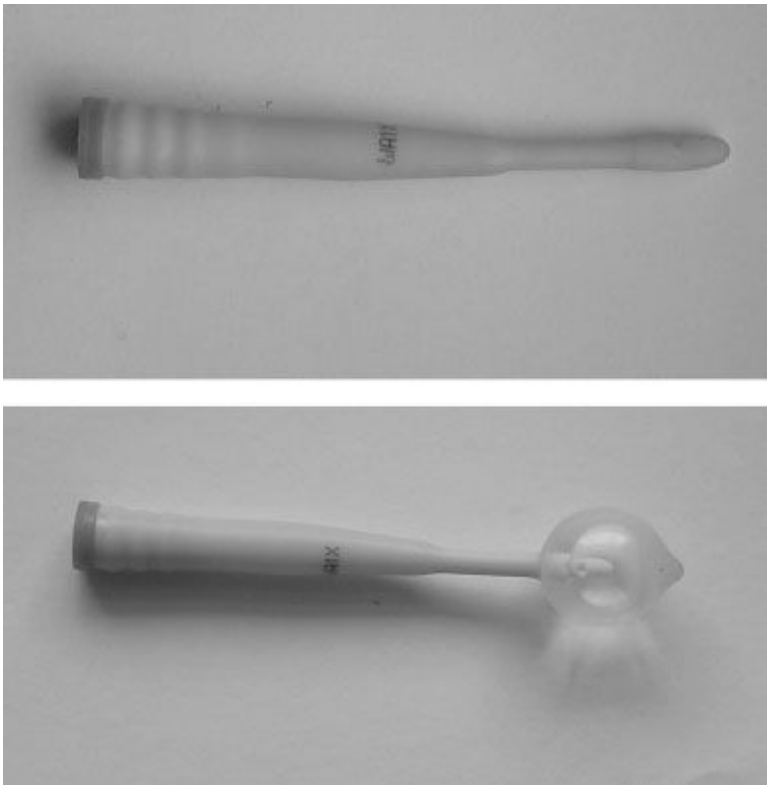
KEY TESTING

- Routine testing and imaging are not helpful in most cases

ED MANAGEMENT

An asymptomatic, small Bartholin cyst should be conservatively managed without antibiotics. Similarly, small cysts that are minimally uncomfortable may be referred to an outpatient gynecologist for treatment. Abscesses that have already ruptured require only analgesia and local care with Sitz baths and warm compresses (4).

Cysts that are large enough to cause significant discomfort and Bartholin abscesses should be incised and drained in the ED. Most incision and drainage (I + D) procedures can be performed under local anesthesia with the aid of oral or intravenous pain medications. If a fistula tract is created, this procedure can lower the currently cited rate of recurrence of a Bartholin cyst or abscess of up to 17% (16). Inserting a Word catheter or Vaseline gauze for 4 to 6 weeks at the time of I + D allows for epithelization of the cyst or abscess cavity creating the desired tract. The Word catheter is a latex catheter with a balloon tip, which is filled with 3 mL of saline after insertion (eFig. 133.2).



eFIGURE 133.2 Word catheter before and after instillation of 3 cc sterile water. (From Fleisher GR, Ludwig S, Henretig FM, et al. Textbook of Pediatric Emergency Medicine. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.)

Local anesthesia, and incision of the abscess or cyst should be on the mucosal surface of the labia minora (eFig. 133.3). The small vertical incision/puncture made with a no.11 scalpel blade should lie parallel but external to the hymenal ring at the 5 or 7 o'clock position. Incisions of the skin surface of the labia minora can result in increased complications. The incision (0.5 to 1 cm) should be large enough to allow for pus to be expelled and the Word catheter or gauze to be inserted but not fall out (Fig. 133.1). Tucking the catheter into the vagina after insertion increases patient comfort (17). In an effort to decrease recurrence rates and comfort for the patient, new therapies have been suggested for treatment in the ED, however no large studies have been performed to validate efficacy (18).

eFIGURE 133.3 The Bartholin gland abscess should be approached from the mucosal surface for local anesthesia, aspiration, or incision and drainage. (From Kovac SR. Advances in Reconstructive Vaginal Surgery. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.)

Bartholin cysts or localized abscesses that are properly drained do not require antibiotics. If a patient is at high risk for a sexually transmitted infection, CDC guidelines for antibiotics treatment should be started after culture of the abscess (http://www.cdc.gov/sTD/treatment/2010) (19). Women who are at risk of complicated infections (immunocompromised, presence of cellulitis, or systemic signs of infection) should be treated with broad-spectrum antibiotic that includes MRSA coverage for 1 week (2,20).

DISPOSITION

All patient should be referred to a gynecologist for close follow up. Patients with recurrent abscesses, cysts, age greater than 40, or patients with concerning signs of symptoms for malignancy will need more urgent referral to an outpatient gynecologist. Sitz baths, pelvic care, warm compresses, and oral pain medication can increase patient comfort. Outpatient antibiotics are dependent on the clinical scenario. Patients should refrain from vigorous exercise or vaginal

intercourse while the catheter is in place to prevent expulsion. If the Word catheter or packing falls out prematurely, it can be reinserted in the ED or referred to the gynecologist.

Common Pitfalls

- Moderate sized Bartholin cysts only require I + D if symptomatic, Bartholin abscesses should be drained regardless of size.
- Bartholin cysts do not require antibiotics, only selected populations with Bartholin abscesses require antibiotics.
- The incision for the I + D should be made on the mucosal surface as opposed to the skin side of the vaginal introitus.
- Confirm the patient's allergies before placing the latex-based Word catheter.

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CHAPTER 134

Breast Masses and Infections

Minal Amin and John M. Howell

Effective ED evaluation of a breast mass depends on recognition of two major processes: Cancer and infection. Mastitis and breast abscesses usually occur in lactating women, but may also represent inflammatory carcinoma in the elderly (3,6,9). Cancer, on the other hand, may present in a manner similar to that of fulminant mastitis (6,9). Mastalgia, a palpable breast mass, and nipple discharge represent common complaints in patients seeking medical attention (6). Hence, initial evaluation of a breast mass may be difficult, challenging, and highly relevant to ultimate patient outcome.

CLINICAL PRESENTATION

Approximately 80% of breast lesions are benign and present as smooth, movable, and discrete masses with regular margins (Table 134.1). Fibrocystic changes (FCCs) and fibroadenomas (FAs) are the most common and second most common benign breast disorders in women (2,4).

TABLE 134.1
Physical Findings Suggestive of Benign and Malignant Breast Masses

Benign	Malignant
Soft or firm on palpation	Firm or hard on palpation
Discrete, regular margins	Indistinct margins
No attachments, mobile	Attached to skin or deep fascia, fixed
More likely to be tender	Less likely to be tender
No discharge	Bloody discharge
No skin changes	Dimpling of skin, nipple retraction

Cancerous lesions are hard with distinct edges that are serrated and irregular. Skin changes range from none to local edema or frank ulceration (3,5,7). Fibrosis may shorten the Cooper ligament and cause skin dimpling, a process also seen in fat necrosis (5,7). Bloody nipple discharge suggests ductal carcinoma (8). More commonly, it may reflect the presence of a solitary benign intraductal papilloma (7). Lymph nodes involved in the spread of breast cancer are initially rubbery and shotty. Ultimately, they harden with progressive infiltration. The axillary ipsilateral node glands are most commonly involved followed by the internal mammary and supraclavicular sites (5,7).

Erythema, edema, tenderness, and induration are late skin changes in the setting of breast cancer, but they are commonly seen in lactation mastitis typically 1 to 3 months postpartum (4,6,7). Chronic, relapsing nonpuerperal infection can develop in the subareolar ducts. This is known as periductal mastitis or duct ectasia and has been linked to diabetes and smoking (5). Fluctuance is the hallmark of a superficial abscess. Fluctuance may not be apparent if deep intramammary and retromammary loculations are present in the breast musculature (Fig. 134.1) (10). A “peau d’orange” appearance characterized by diffuse erythema and edema, mastitis, or abscess in a nonlactating woman should serve as a warning sign of inflammatory cancer (3,6,7,9).

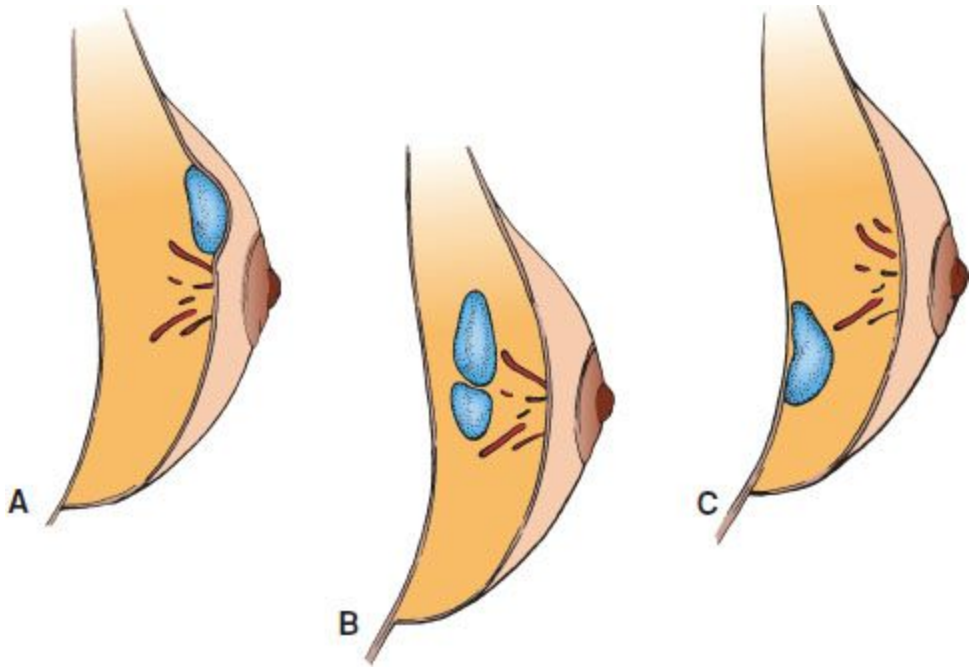

FIGURE 134.1 Breast abscesses. **A:** Superficial abscess. **B:** Intramammary abscess. **C:** Retromammary abscess.

Postmenopausal breast abscesses are commonly subareolar, often presenting with pain and erythema. They are occasionally associated with chronic fistulas from the subareolar ducts to the periarolar skin (5). Expressing pus from the nipple or areola can identify a mammillary fistula. Nipple retraction and inversion are also seen (5). Although rare, recurring subareolar abscess (Zuska disease) is a bacterial infection of the breast that is characterized by a triad of draining cutaneous fistula from the subareolar tissue; a chronic thick, pasty discharge from the nipple; and a history of multiple, recurrent mammary abscesses (4).

Breast bud enlargement occurs in the first 1 to 2 weeks of life in 60% of neonates. These enlarged breast buds may become infected, usually with either *Staphylococcus aureus* or *Escherichia coli.* The clinical presentation is either simple cellulitis or abscess (8).

Paget disease of the nipple reflects carcinoma of the mammary ducts underlying the nipple areola complex. It represents 2% to 4% of breast malignancies. Initially, it appears as an eczematoid rash

and then progresses to chronic skin inflammation with a surface crust. It can be confused with benign breast disease (5,11).

DIFFERENTIAL DIAGNOSIS

Cancer

One in eight women in the United States develops breast cancer. An estimated 234,580 new cases of breast cancer in women and 2,240 in men will be diagnosed in 2013 (1). It is the leading cause of death in women between the ages of 44 to 50. Yearly, approximately 40,000 women die of breast cancer (1,2). Seventy percent to 80% of women diagnosed with breast cancer will have no family history. Primary risk factors for breast cancer are age greater than 50 and being female (1,2). Risk factors for breast cancer are listed in Table 134.2. Absolute risk is listed in Table 134.3. In women who are younger than 25 years of age, fewer than 5% of breast masses are malignant. The incidence of breast cancer rises significantly during childbearing years. By the age of 70, more than 75% of breast masses are malignant (12). Discussions of breast cancer histopathology and staging are beyond the scope of this chapter and are contained elsewhere (2,7).

TABLE 134.2
Risk Factors and Relative Risk of Breast Cancer

Risk Factors	Estimated Relative Risk
Advanced age >60	>4
Family history	
• Ovarian cancer in women <50 yrs	>5
• One first-degree relative	>2
• Two or more first-degree relatives	>2
Personal history	
• Personal history	3–4
• + BRCA1/BRCA2 mutation	>4
• Breast biopsy with atypical hyperplasia	4–5
• Breast biopsy with LCIS or DCIS	8–10
Reproductive history	
• Early age at menarche <12 yrs	2
• Late age of menopause	1.5–2
• Late age of first-term pregnancy (>30 yrs)/ nulliparity	2
Use of combined estrogen/progesterone HRT	1.5–2
Current or recent use of oral contraceptives	1.25
Lifestyle factors	
• Adult weight gain	1.5–2
• Sedentary lifestyle	1.3–1.5
• Alcohol consumption	1.5

LCIS, lobular carcinoma in situ; DCIS, ductal carcinoma in situ; HRT, hormone replacement therapy.

TABLE 134.3
Absolute Risk of Breast Cancer in American Women by Age

Current Age	Absolute Risk of Developing Breast Cancer in Next 10 yrs (%)
20	1 in 1,681 (0.06)
30	1 in 232 (0.4)
40	1 in 69 (1.4)
50	1 in 42 (2.4)
60	1 in 29 (3.4)
70	1 in 27 (3.7)
Lifetime risk	1 in 8 (12.4)

From American Cancer Society, Breast Cancer Facts & Figures 2011–2012 and Cancer Facts & Figures 2013.

Benign Neoplasms

FCCs, formerly called fibrocystic disease, comprise the most frequent benign disorder of the breast (4). They are noncancerous changes in breast tissue. They cause mastalgia, tenderness, and nodules to arise in one or both breasts prior to menses in women between 20 and 50 years of age (4). Fibrocystic breast changes are classified proliferative or nonproliferative (up to 70% of biopsies) (4). Proliferative changes are associated with ductal hyperplasia and must be followed longitudinally as there is a four- to fivefold increase in breast cancer in these women (2).

FAs are the second most common benign neoplasms of the breast (2,4). They occur most commonly in younger women between the ages of 15 and 35 and are considered a disease of early reproductive life. They are nontender, well defined, spherical, firm, and highly mobile. In most cases, FAs are managed conservatively as they do not increase the risk of breast cancer. Women who are older have complex FAsor a family history of breast cancer have a higher incidence of cancer (4).

Lipomas are superficial and occur in any quadrant of the breast. They are benign tumors composed of mature fat cells and are well defined, smooth, lobulated, and nontender. It may be clinically difficult to distinguish lipomas from other conditions, thus causing diagnostic and therapeutic challenges (4).

Mondor Disease

Mondor disease is thrombosis of the superior epigastric, thoracoepigastric, or lateral thoracic veins as they traverse the breast. It is characterized by the sudden appearance of a red tender and palpable cord. The cord subsequently becomes a fibrous band associated with tension and skin retraction. Although Mondor disease is self-limited and usually diagnosed with ease (13,14), emergency physicians must be aware of its existence to properly diagnose it and to rule out the presence of systemic disorders, especially breast cancer (13,14).

Idiopathic Granulomatous Mastitis

Idiopathic granulomatous mastitis (IGM) is a rare inflammatory breast disease of unknown etiology. The clinical presentation can mimic an abscess, infectious mastitis, or mammary carcinoma and can be misdiagnosed as cancer. IGM is associated with women who are parous and have a history of oral contraceptive use. Glucocorticoid therapy, resection, and methotrexate are treatment options (15,16). The recurrence rate has been reported as 5% to 50% in the literature (17).

Mastitis and Abscess

Infectious complications may be seen in up to 10% of lactating women (18). Lactation mastitis occurs in 2% to 3% of women and breast abscess between 5% to 11% of women with mastitis (19). A postpartum breast abscess is caused by normal skin pathogens that invade through cracks in the nipple (2,4,10). Staphylococci are the most common causative agents (2,4). Streptococci are cultured less often (8). Preventive measures include nipple hygiene (cleaning), hand washing, cleansing of the infant's skin, and early recognition (8).

Postmenopausal breast abscesses are distinct from puerperal forms in cause and presentation. Approximately 90% are subareolar. They often arise from mixed infections that include aerobic and anaerobic flora (5). They are associated with ductal ectasia, a chronic inflammation of major ducts below the nipple and areola. Recurrence rates after simple incision and drainage exceed 39% (3). Mammillary fistulas occasionally form between the areola and infected lactating glands (8,9).

Fat necrosis may present as a tender lump in the breast, typically as a result of trauma in 50% of cases (2,3,4). It is a benign, nonsupportive inflammatory process of the adipose tissue. The mass usually does not enlarge but may be ill-defined, spiculated, and associated with skin retraction. It is a mimic of breast cancer (2,3,4).

ED EVALUATION

Evaluation in the emergency department (ED) hinges upon the information gathered during the history and physical examination. As noted previously, many features including the size, location, tenderness, skin changes, and rapidity of onset help in narrowing the differential. The important distinction is cancer versus infection. Patients with a mass suspicious for cancer usually require no further ED evaluation but need expeditious outpatient referral. Patients with signs or symptoms of metastatic cancer should have further ED evaluation including laboratory and imaging studies to search for complications and the extent of spread. Ultrasound may be helpful in diagnosing a breast abscess if the clinician is uncertain. Sonographic evidence suggestive of a breast abscess includes a hypoechoic rim and adjacent interstitial fluid (20,22).

KEY TESTING

- Consider ultrasound if abscess is suspected

ED MANAGEMENT

Simple mastitis in the lactating woman, without abscess formation, is treated with antimicrobials that are effective against staphylococci and streptococci (2,5). Cephalexin (250 to 500 mg four times a day), dicloxacillin (250 to 500 mg four times a day), or erythromycin (250 to 500 mg four times a day) in penicillin-allergic patients is appropriate. Breastfeeding should be encouraged with manual pumping, if needed, along with local heat and empiric antibiotic therapy (2,4,5). Simple nonlactating breast infections should be treated with amoxicillin–clavulanic acid at 875 mg twice a day (3,5).

Superficial abscesses can be treated in the ED. Ultrasound-guided needle aspiration is emerging as a treatment of choice for most breast abscesses. It causes less scarring and does not require general anesthesia. Repeated aspiration and oral antibiotics may be necessary (8,10).

Neonatal breast bud infections should be treated with parenteral antibiotics (e.g., ampicillin 50 mg/kg and cefotaxime 50 mg/kg) after cultures of the blood and urine. Incision and drainage may be necessary and should be performed peripherally to avoid cosmetic complications (21).

CRITICAL INTERVENTIONS

- Refer all patients with a suspicious breast mass for expeditious outpatient evaluation.
- Drain superficial breast abscesses, with ultrasound guidance as needed.

DISPOSITION

Women suspected of having breast cancer should be referred immediately to a consultant who is experienced in the diagnosis and management of breast disorders. Outpatient arrangements for mammography with subspecialist referral should be made for all patients who are not pregnant and at least 20 years old. As there is an appreciable rate of false-negative mammography (3,19), patients should be counseled that a negative study does not invariably mean absence of disease.

Mastitis may be difficult to distinguish clinically from cellulitis, abscesses, or inflammatory cancer. Patients should be closely followed within 24 hours. Mammillary fistulas should be referred to a surgeon for excision and definitive closure (8–11). Postmenopausal abscesses also necessitate surgical consultation due to high recurrence rates after drainage (3,8–10,22).

Patients with suspicious breast masses need not be admitted unless they have advanced disease or complications on presentation, intractable pain, or important psychosocial issues necessitating admission. In general, the initial evaluation of suspicious breast masses is done on an outpatient basis.

Women with mastitis who are toxic-appearing should be admitted and placed on intravenous antibiotics. Women with simple

infections that do not improve or that worsen after 24 hours should also be admitted.

Consider transfer or referral when no physician experienced in the management of breast disorders is available. Patients must be stable and have no evidence of septic shock. Antibiotics and pain control should be initiated prior to transfer.

Common Pitfalls

- Inflammatory cancer may present with erythema, edema, and tenderness. Infection in a nonlactating breast and failure of postpartum mastitis to resolve in a timely manner should suggest the possibility of cancer.
- Inadequate drainage of a breast abscess may lead to chronic infection with substantial morbidity and cosmetic deformity.
- Misdiagnosis of a deep breast abscess as mastitis.

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CHAPTER 135

Sexual Assault

Carolyn Sachs

Emergency physicians, more than any other medical professionals, provide care for violently injured and abused patients. With victims of sexual assault in particular, emergency physicians must be attentive to the physical, emotional, and judicial needs of the patient. The legal definition of *sexual assault* varies by state and country. In general, sexual assault denotes any physical act of sexual contact without legal consent (1). Perpetrators of sexual assault may use physical force to overcome the victim's lack of consent, but this is not required. Lack of voluntary consent for sexual contact because of intimidation, threats, or incapacitation equally fulfills the definition of sexual assault (2). Rape is a subset of sexual assault, which involves nonconsensual genital, anal, or oral penetration (3).

The National Crime Victimization Survey, a random-digit dial telephone survey collects data yearly on nonfatal violent crimes against males and females 12 years of age and older, reported a steady decrease in the number of sexual assaults estimated yearly over the last 20 years. The most recent data available (2011) from this survey show an incidence of 243,805 sexual assaults per year, down from 898,239 in 1993. However, even survey methodology undercounts assault as it does not sample those populations without a home telephone who are more likely to be victimized and still suffer from low disclosure rates due to shame and fear (4).

This chapter provides information for the emergency practitioner needing to treat and examine the sexually assaulted patient in the absence of immediate access to a specialized sexual assault provider program.

Male victims of sexual assault also require appropriate care and treatments. Although this chapter does not provide a separate discussion pertaining to the male victim, much of what is discussed has applicability to both male and female victims. For a discussion of pediatric sexual abuse, see Chapter 292.

CLINICAL PRESENTATION

Sexually assaulted patients may present immediately to the emergency department (ED) or be brought to the ED by law enforcement personnel. In either case, the ED staff should be aware of the guiding principle of providing compassionate and confidential treatment in a timely fashion. A victim may be accompanied by friends or family, who should be allowed to stay with the victim in accordance with her wishes. If the victim presents alone, staff should offer her the chance to call a companion or a rape crisis advocate to remain with her during the ED stay.

ED EVALUATION

Physicians must first treat any life- or limb-threatening physical injury. A minority of sexually assaulted patients will require such immediate intervention, but in the rare case of coexistent severe trauma, care should be taken not to destroy or alter evidence on the patient's body if possible. Some states mandate physicians to notify law enforcement when treating a sexually assaulted patient. Emergency physicians must be familiar with their own state laws regarding reporting. Even when reporting is mandatory, patients may elect not to talk with police (5).

In the ED, the patient should be placed into a private room. Physicians should use a compassionate tone to explain the procedure of the examination and forensic evaluation and to obtain written informed consent for these. Obtaining this consent carries important psychological implications after a sexual assault in which a victim was denied this right. If the hospital has an arrangement with a special sexual assault team, that team should become involved as early as possible. An increasing number of institutions

have sexual assault nurse examiner (SANE) programs, which provide highly specialized treatment for sexual assault victims (6).

The ED evaluation begins with an appropriately tailored history rather than an exhaustive account of the details of the encounter. Recounting sexual violence can be very traumatic. The history should include information necessary for medical treatment, to complete any standardized state forms, and for the collection of evidence. This information may be important when trying to correlate physical findings or corroborating evidence. eTable 135.1 lists the many elements of the history that law enforcement personnel may request for historical forensic documentation.

TABLE 135.1
Single-Dose Therapy for Preventing Sexually Transmitted Disease after Sexual Assault

Medication	Dose
Prevention of Gonorrhea (GC)	
Ceftriaxone	250 mg IM (recommended by CDC)
or	
Cefixime	400 mg PO (second line if ceftriaxone not available)
or	
Azithromyacin	2,000 mg PO (also active against chlamyida)
Prevention of Chlamydia	
Azithromyacin	1,000 mg
Prevention of Trichomonas and Bacterial Vaginosis	
Metronidazole	2,000 mg (optional)

eTABLE 135.1
Important Elements in the Sexual Assault History

- Time, date, and place of assault if known
- Type of force or coercion if used (e.g., weapons, held down, restraints)
- Threats (e.g., "threatened to hurt my parents if I resisted")
- Number and description of assailants
- Use of alcohol or drugs by patient (voluntary or forced)
- Lapses in consciousness (due to trauma or toxins including "date rape" drugs)
- Type of assaultive contact (kissing, licking, fondling, or penetration of mouth, breasts, body, genitals, and/or anus)
- Condom use
- Perpetrator ejaculation and location (to guide specimen collection)
- Postassault activities such as bathing, urinating, defecating, gargling, eating, brushing teeth, genital wiping or washing, douching
- Pre-existing injuries, genital infections, or abnormalities that may alter the expected appearance
- Recent voluntary intercourse (within 5–7 d of assault)
- Pertinent past medical history (medications, medication allergies, tetanus and hepatitis B immunization status, HIV status if known, current method of birth control, last menses)

A pertinent gynecologic history should include gravity, parity, last menstrual period, contraceptive history, recent intercourse besides the current assault, history of recent sexually transmitted disease (STD), and any gynecologic surgery. If the victim is on an oral contraceptive, she should be asked if she has missed taking any pills. All of this information will assist in deciding what type of medical treatment is necessary.

Before beginning the physical examination, the physician should be sure the patient understands that she is in control of every element of the examination and may refuse at any point. The objectives of the physical examination are to determine the need for medical treatment, to gather specimens for analysis, and to document observations that may be used to corroborate the victim's account. Law enforcement may want to take photographs before she undresses. Gloved hands must be used to collect clothing after the victim disrobes while standing on a clean sheet. Clothes must be placed into paper rather than plastic bags, as plastic restricts air circulation and may lead to fungal or bacterial growth that can degrade biological evidence.

Examiners should inspect skin for scratches, lacerations, abrasions, contusions, or bite marks. The mouth should be examined for injury, with special attention to the inner lip and palate, where

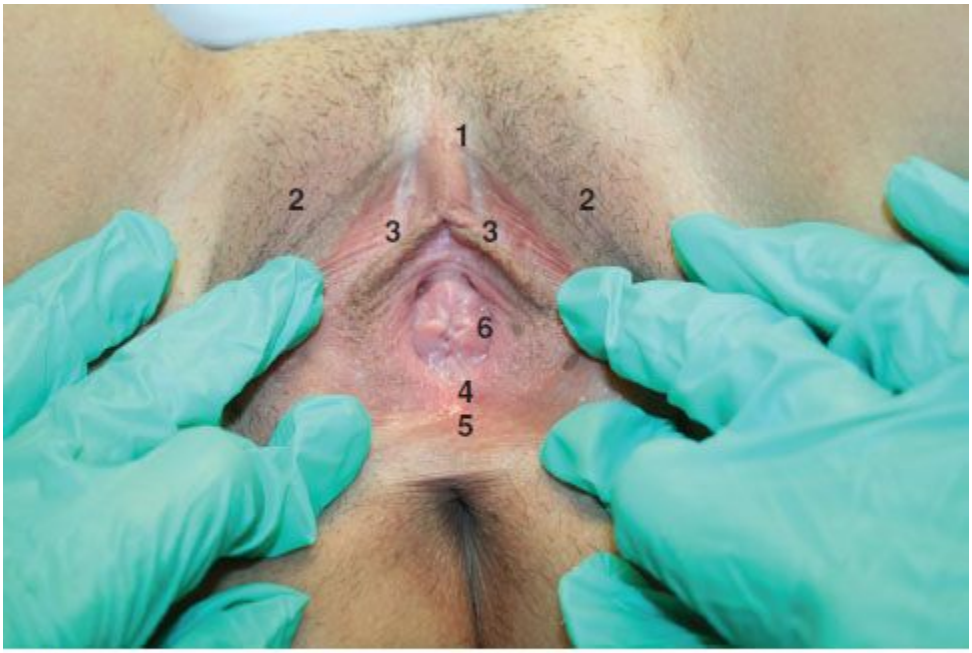
direct trauma often leaves abrasions and contusions. If the patient reports oral sexual contact within the previous 12 hours, buccal swabs should be collected for potential evidence by running them between the buccal mucosa and teeth. The local crime laboratory may also request a buccal swab to be used as a reference sample of the victim's DNA. In addition to documentation of body trauma, any foreign material, such as hair, blood, or semen, should be noted and collected.

If relevant, examiners may collect foreign material from under the fingernails, or alternatively trim the nails over a clean piece of paper. Any material obtained should be bundled with the paper and placed in an appropriate envelope. Examination of the skin may reveal lightly crusted areas that are suspicious for semen. These should be collected with a swab moistened with saline or water. A Woods lamp may help to identify these areas because semen fluoresces under ultraviolet light; however, other substances also fluoresce, so this test is nonspecific (7).

The external genitalia should be checked for trauma and evidence of semen, which should be swabbed as previously described. If it is present on pubic hair, the matted hairs should be trimmed and collected. In patients with pubic hair, this hair may be combed to find strands of the assailant's hair. Examiners should place a clean piece of paper below the patient's buttocks and comb through the hair onto the paper. Hairs, comb, and paper are then folded up and placed in evidence collection bags. Some crime laboratories request plucked pubic hairs for victim reference. However, these hairs are rarely needed because DNA from the victim is obtained from blood or buccal cells, and hair can be provided later (8).

The physician should describe the location, shape, and color of any genital injury using proper anatomic terms. Figure 135.1 shows the female genital areas most likely to display injury after rape (posterior forchette, hymen, labia minora). If photographs are taken, it is often helpful to highlight injury with the use of toluidine blue dye, although this may be considered an advanced technique and not readily available in most EDs. A small amount of the blue dye can be applied to the perineum at the area of suspected injury and

the excess wiped off with a lubricant-moistened cotton ball or gauze. Injured areas often display linear blue stain, because the dye is taken up by the nuclei of exposed submucosal cells. Labial separation and traction can assist examiners in viewing the perineum and hymen. Examiners should attempt to inspect the entire perimeter of the hymen using a swab or a Foley catheter inserted through the hymenal orifice and inflated (9). Examiners may use magnification to enhance identification of injury.



1. Clitoris
2. Labia majora
3. Labia minora
4. Fossa navicularis
5. Posterior fourchette
6. Hymen

FIGURE 135.1 Female genital anatomy. (Used with permission and state no reproduction or use without the explicit written consent of Malinda Wheeler, RN, FNP, SANE-A, SANE-P, Founder and Director of Forensic Nurse Specialists.)

The vaginal wall should be inspected for injury after gentle insertion of a speculum lubricated only with warm water. Pooled secretions in the posterior fornix should be aspirated and placed in a sterile receptacle or collected with sterile swabs. Some areas request vaginal washings, obtained by instillation and aspiration of 5 to 10 mL of nonbacteriostatic sterile saline solution. Although the Centers

for Disease Control (CDC) recommend culturing for gonorrhea and chlamydia during the speculum examination, this step may be omitted in patients who have received appropriate prophylactic antibiotics (10).

A bimanual examination is not a routine part of the sexual assault examination. The anal area should be examined for injury in all victims. If the patient has anal pain, reports anal penetration, or has experienced a lapse in consciousness, anoscopy should be performed to look for internal anal and rectal injury. Anal and/or rectal swabs should be obtained. Anoscopically visible injury may be found even when the external anal examination is normal; this may be especially important in male victims (11).

All swabs need to be thoroughly air dried, packaged, and labeled with the patient's information, the name of the examiner, the date, and site. Examiners may choose to prepare a wet mount of the vaginal or rectal swabs to detect motile and nonmotile sperm. Motile sperm are not usually found after 12 hours. Most ED sexual assault examiners omit this step because of lack of formal training. Criminal laboratories may identify nonmotile sperm in vaginal secretions 72 hours or longer after intercourse and in a cervical sample up to 3 weeks after intercourse (12).

Law enforcement personnel may request samples of the victim's blood for DNA reference and for drug and alcohol testing. Testing may also be indicated for hepatitis B, hepatitis C, human immunodeficiency virus (HIV), and syphilis serologies. Urine pregnancy testing should be performed because this may affect the choice of pharmacologic treatment.

The findings on the history and physical examination and complete information concerning collected specimens should be documented thoroughly at the time of the examination.

KEY TESTING

- Detailed, standardized forensic examination when indicated

ED MANAGEMENT

The ED treatment of the sexually assaulted patient includes psychosocial support, treatment of physical injuries, pregnancy prevention, and prevention of STDs.

Psychosocial support begins with the first individual responsible for patient contact. All staff must be sensitive and maintain strict patient confidentiality, and prior arrangements should be made with social work or a rape crisis volunteer to provide immediate support and assistance with the evaluation procedure.

Medical treatment of traumatic injuries suffered during the assault does not differ from routine treatment, but it should be performed in a way that does not compromise potential evidence, if possible. For example, if the patient requires urinary catheterization, external genital swabs should be collected prior to the preparatory precatheter cleansing, and bite wounds should be swabbed for evidence prior to irrigation.

Pregnancy prevention, or "emergency contraception," should be offered to all patients of childbearing age. Levonorgestrel (1.5 mg), known commercially as "Plan B One-Step," has proven exceedingly safe and is currently available in the United States without a prescription. It is effective for up to 5 days after intercourse and has not been associated with teratogenicity if the patient becomes pregnant from the rape or other intercourse in the preceding 7 days (13).

The risk of contracting an STD as the result of sexual assault has been estimated to be 5% to 10%, and varies according to geographic area and assault characteristics. Thus, prophylaxis should be offered to all victims. The most frequently diagnosed infections among women who have been sexually assaulted are gonorrhea, chlamydia, trichomoniasis, and bacterial vaginosis (14).

Current treatment recommendations (Table 135.1) include ceftriaxone 250 mg IM for the prevention of gonorrhea, and single-dose azithromycin (1 g) to prevent chlamydial infection (10). The need to prevent trichomoniasis and bacterial vaginosis is less urgent, and the treatment (metronidazole) may cause abdominal pain and vomiting in some individuals.

Hepatitis B virus vaccine should be given to unimmunized or inadequately immunized patients (10). Hepatitis B immune globulin should be reserved for high-risk exposures involving a known hepatitis B–positive assailant.

Victims may be particularly concerned about the transmission of HIV. The risk of transmission of HIV from one episode of unprotected receptive vaginal intercourse with an infected individual is approximately 1 in 1,000. The estimated risk with unprotected receptive anal intercourse is between 8 and 32 in 1,000 (15). However, the risk may be higher in sexual assault victims as a result of tissue injury. Unfortunately, there is no evidence that postexposure prophylaxis (PEP) after sexual exposure prevents infection (16). If considered, PEP should be given as soon as possible and is not indicated more than 72 hours after exposure (Table 135.2). The CDC recommends PEP only for HIV-negative victims with vaginal, anal, or oral penetration by a perpetrator *known to be HIV-positive,* and they make no recommendation in other sexual assault scenarios (14). The risks and side effects of antiretroviral therapy must be discussed with the patient. Repeat HIV-antibody testing is recommended approximately 2 to 3 months after the assault.

TABLE 135.2
Postexposure Prophylaxis of HIV for Adults Including Lactating Women and Adolescents >40 kg

Drug	Strength/ Form	Dose	Duration
Zidovudine (AZT) and	300 mg tablet	1 tablet every 12 hrs	28 d
Lamivudine (3TC)	150 mg tablet	1 tablet every 12 hrs	28 d

CRITICAL INTERVENTIONS

- Provide immediate psychosocial support during the ED evaluation.

- Assess and treat for serious physical injuries.
- Offer prophylaxis for pregnancy and sexually transmitted diseases.

DISPOSITION

Admission to the hospital may be required in the case of significant physical trauma. in addition, ED practitioners may need to consult with a surgical specialist (gynecologist, urologist, or general surgeon) for significant vaginal, penile, or anal trauma that requires surgical care.

Sexual assault may trigger severe depression and even suicidality. Emergency physicians should assess each patient for suicidality and take appropriate steps to assure timely intervention with a mental health professional, if necessary. In most areas in the United States, rape crisis advocates can provide timely support to victims during the examination and in follow-up. The importance of planned psychological follow-up from the ED cannot be overemphasized. Survivors may suffer from rape trauma syndrome (RTS), a pattern of symptoms similar to posttraumatic stress disorder (PTSD) (17). The patient should be reevaluated approximately 1 to 2 weeks after the initial medical evaluation to determine the need for further counseling. It is advisable for a member of the medical team (e.g., a social worker) to contact the victim after discharge to address any concerns and to encourage appropriate follow-up care.

The sexual assault victim may be discharged from the ED in the company of relatives or friends. Follow-up care must be arranged before discharge. This should include medical follow-up with a primary care physician or gynecologist at 2 weeks and 6 weeks after the assault to reevaluate for pregnancy and STDs.

Common Pitfalls

- Failure to appropriately collect, transfer, and document specimens, with an appropriate chain of evidence.
- Failure to be familiar with requirements and protocols that may vary with the institution and state.

• Failure to offer prophylactic therapy for pregnancy and STDs.

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SECTION XIII
Obstetric Emergencies

Section Editor: GREGORY W. HENDEY

CHAPTER 136

First-Trimester Vaginal Bleeding

Pamela L. Dyne

Vaginal bleeding (VB) in early pregnancy is a very common emergency department (ED) complaint. The differential diagnosis is relatively short, with ectopic pregnancy being the most serious, and threatened miscarriage being the most common. An understanding of the definitions, classifications, and management options is important for efficient management in the ED and effective communication with consultants. Septic spontaneous miscarriage and gestational trophoblastic disease (GTD) (molar pregnancy) are also discussed in this chapter.

CLINICAL PRESENTATION

The patient's clinical history can be instrumental in making diagnoses in most disease processes, and early pregnancy bleeding is no different. Although many patients presenting to the ED with VB know if they are pregnant, many do not. In one multicenter study involving several different types of EDs, 63% of women who thought they were pregnant were correct. However, 7% who said there was no chance they could be pregnant and 10% of those reporting a normal last menstrual period (LMP), were in fact pregnant (1). Another more recent study in a suburban University hospital suggests 100% negative predictive value of a woman stating that pregnancy was impossible (2). Therefore, a negative history for pregnancy may or may not be completely reliable,

depending on the patient population. Approximately 20% of all pregnancies are complicated by first-trimester VB, and about 50% of them will end in spontaneous abortion (3).

DIFFERENTIAL DIAGNOSIS

Table 136.1 defines the spectrum of spontaneous miscarriages, with their clinical, laboratory, and ultrasound findings. In virtually all cases of bleeding in the first 20 weeks of pregnancy, a careful investigation utilizing history and physical examination, β human chorionic gonadotropin (β-hCG) levels, and transvaginal ultrasound can establish either the correct diagnosis or a logical management plan that will safely lead to a correct diagnosis. If the bleeding is experienced around the time of or just after the expected normal menses, *implantation bleeding* should be considered. This is a fairly common occurrence with a benign physiologic cause. As the embryo burrows into the highly vascular decidual tissue, blood escapes into the uterine cavity and out through the cervix. It ranges from a pinkish discoloration of the vaginal discharge to bleeding equivalent to that of a menstrual period. It can last 1 or 2 days but usually not longer. Most commonly, it occurs in the fifth or sixth week after the LMP and women may mistake this bleeding for a normal menses, making it a common cause of inaccurate dating of gestational age.

TABLE 136.1
Spontaneous Abortions

Term	Clinical	US Findings
Threatened abortion	Vaginal bleeding (VB) or abdominal pain, os closed	Embryo with cardiac activity, or empty gestational sac (5–6.5 wks), empty uterus (3–5 wks), or subchorionic hemorrhage with any of the above
Complete abortion	VB, benign examination, os closed, falling β-hCG	Empty uterus
Incomplete abortion	VB, benign or tender examination, os open or closed, slowly falling or plateau β-hCG	Thickened, irregular endometrium (>5 mm double stripe)
Abortion in progress/ inevitable abortion	VB, os open	Gestational sac in process of expulsion
Embryonic demise (missed abortion)	Varied, os closed	Embryo lacking cardiac activity with CRL >5 mm
Blighted ovum (anembryonic gestation, embryonic failure)	Varied, os open or closed	Gestational sac too big to not have embryo (>20 mm)
Septic abortion	Varied, os open or closed, abdominal tenderness, peritoneal signs, CMT, foul cervical discharge	Thickened, irregular endometrium (>5 mm double stripe)

β-hCG, beta human chorionic gonadotrophin; CRL, crown-rump length; CMT, cervical motion tenderness.

Septic spontaneous miscarriage is another clinically important cause of VB. Fortunately, the estimated fatality rate from septic spontaneous miscarriage is very low, ranging from 0.4 to 0.6 per 100,000 spontaneous miscarriages. Patients may also present with complications of induced abortion, and this is discussed in detail in Chapter 139.

GTD, also known as *molar pregnancy,* is an abnormal proliferation of the trophoblastic cells. Frequently, GTD presents with abnormal bleeding mimicking an incomplete or threatened miscarriage. Other signs are passage of hydropic villi (that tend to have a grapelike

appearance) through the vagina. Uterine size may be larger (50%) or smaller (25%) than the estimated gestational age, and there may be enlarged cystic ovaries resulting from theca-lutein cysts. The β-hCG level is usually higher than expected for gestational age (generally greater than 100,000 mIU/mL). Common patient complaints include severe nausea or vomiting, and less commonly, there may be signs of preeclampsia or hyperthyroidism. The definitive diagnosis is made by histologic evaluation of the tissue, which is frequently not done until after surgical evacuation. GTD is more commonly seen in those of Asian descent, those who had a prior molar pregnancy, and first pregnancies in the early or late years of childbearing (<15 or >35 years old). In the general population, the incidence is 1 in 1,000, although it may be as high as 1% in the Asian population. The condition is usually benign; however, at the more serious end of the spectrum of GTD is choriocarcinoma, a frankly malignant lesion that is usually responsive to chemotherapy. If GTD is suspected, the uterus should be evacuated as soon as possible, although this is not an emergency unless signs of preeclampsia or hemodynamic instability are present. Nevertheless, the patient should be seen by an obstetrician-gynecologist within the next 24 hours so that definitive therapy can be arranged. Prior to discharge from the ED, the thyroid status should be evaluated so that therapy for secondary hyperthyroidism can be initiated prior to any operative intervention.

In addition to the pregnancy-related etiologies discussed previously, bleeding may be caused by lesions entirely unrelated to the pregnancy, such as structural or infectious lesions on the cervix or vagina, or from the urinary or gastrointestinal (GI) tract. Table 136.2 summarizes these nonpregnancy-related causes of VB that may occur in pregnancy.

TABLE 136.2
Nonpregnancy-Related Causes of Vaginal Bleeding

Diagnosis	History and Physical Findings	Diagnostic/ Confirmatory Tests
Nephrolithiasis	Varied, abdominal pain, hematuria	Renal ultrasound, cath UA
Cystitis	Varied, abdominal pain, hematuria	Cath UA
Lower GI tract bleeding	Varied, BRBPR, hemorrhoids	Hemoccult testing, physical examination
Cervical cancer	Vaginal discharge, cervical lesion	Cervical biopsy (not recommended for in ED or during pregnancy)
Cervicitis or bacterial vaginosis	Varied, abnormal discharge, pain, spotting	Wet prep, cervical cultures
Cervical ectropion	Postcoital bleeding, friable columnar epithelium seen on endocervical canal	Physical examination
Cervical polyps	Pinkish buds protruding from cervical os	Physical examination
Vaginal wall trauma, foreign body, or neoplasm	Varied	Physical examination

UA, urinalysis; BRBPR, bright red blood per rectum.

ED EVALUATION

The initial focus of the ED evaluation of a woman with first-trimester VB is on ruling out ectopic pregnancy (see Chapter 137). Once ectopic pregnancy has been excluded, the task is to further classify the type of bleeding. This is done through a synthesis of the history and physical examination, laboratory and ultrasound information, and serial assessments.

The history obtained in the ED should include the quantity of VB, passage of clots or tissue, and evolution of symptoms. The amount and character of the bleeding has been shown to help differentiate between threatened abortion and miscarriage (4). Symptoms consistent with urinary tract infection (UTI) or uterine infection should be elicited. The physical examination begins with assessment of the vital signs with prompt intervention if they are suggestive of hemodynamic compromise. Evaluation for tenderness at the costovertebral angles, abdomen, and suprapubic area should be

performed. Traditionally the physical examination should include a speculum and bimanual pelvic examination, with specific attention paid to the evaluation of the status of the internal cervical os and assessment of the degree of uterine and adnexal tenderness. Multiparous patients will often have a soft and slightly dilated external os, but it is the internal os that must dilate in order for passage of products of conception (POC) to occur. Often the cervix has a conical shape, with the internal os as the point of the cone. If the examining finger is able to *gently* pass through the end-point of the cone, the internal os is open. If the examining finger is not able to *gently* penetrate the point of the cone, the internal os is closed. One should not aggressively force a finger or any instrument through the internal os to determine its integrity. To do so can cause injury to the cervix, and theoretically cause a miscarriage. The uterus should not be tender unless POC are retained or are passing through the cervix at that time.

In a 2009 review, Isoardi took the position that routine pelvic examination is not supported by the literature. She concluded that the pelvic examination does not provide additional diagnostic information over transvaginal ultrasonography used in conjunction with quantitative β-hCG. However, she noted that a pelvic examination should be performed when ultrasonography and quantitative β-hCG testing are unavailable or the results inconclusive, and in those presenting with severe bleeding, since the removal of endocervical products can be an important resuscitative measure (5). The argument in favor of routine pelvic examination is to detect an open os or POC, or to find other causes of bleeding such as cervical polyps or lesions.

There are several laboratory tests that are helpful in the evaluation and management of ED patients with VB in early pregnancy. They include a urine pregnancy test, a urinalysis, blood type and Rh, complete blood count (CBC), and serum quantitative β-hCG. A thorough understanding of the indications and utility of these tests is important for proper interpretation of their results.

The urine pregnancy test is 99.4% sensitive for diagnosing pregnancy at approximately the same time as the woman misses her

period, or when the serum β-hCG level is greater than 25 mIU/mL. False negatives occur when the serum β-hCG is between 10 and 50 mIU/mL, and when the urine is dilute (<1.015 specific gravity). The urine pregnancy test quickly establishes the pregnancy status and should be a routine order for patients with VB, regardless of the menstrual history (6).

A urinalysis should be ordered in all pregnant VB patients to diagnose UTI, regardless of symptoms. UTI is a risk factor for miscarriage. Asymptomatic bacteriuria and pyuria are relatively common in pregnancy, occurring in 2% to 11% of pregnant women. Up to one-fourth of these asymptomatic women go on to develop upper tract infections (7). Thus it is important to screen for and treat UTI in pregnant patients to potentially prevent miscarriage.

Routine screening for Rh status in the pregnant patient with VB has been controversial. The American College of Emergency Physicians Clinical Policy subcommittee recently reviewed this topic and concluded that while there is sufficient high-quality literature to support the administration of 50 μg of Rh(D) immune globulin to Rh-negative women who have documented first-trimester loss of an established pregnancy to prevent Rh alloimmunization, there is insufficient evidence either for or against its use in threatened miscarriage or ectopic pregnancy (8). However, it has become a common practice to give Rh immune prophylaxis to Rh-negative pregnant women with VB.

A CBC may be helpful in estimating the amount of blood loss, or to serve as a baseline for subsequent visits. The *quantitative* β *human chorionic gonadotropin,* or β-hCG, is a measure of trophoblastic tissue activity, which is a marker for the volume of living trophoblastic tissue and a function of renal clearance. Both ectopic and intrauterine pregnancies (IUPs) produce β-hCG, although they usually differ in the rate at which the quantitative β-hCG level increases. Patients with ectopic pregnancy or an abnormal IUP both tend to have a lower quantitative β-hCG level than those with viable IUPs at a given gestational age (6,9). Because of the large range of β-hCG for each stage of embryonic development, a single value of β-hCG is not useful for differentiating among normal IUP, abnormal

IUP, and ectopic pregnancy. However, the rate of rise in the β-hCG level can be quite helpful. Initial work by Kadar et al. on subjects with symptomatic first-trimester pregnancies resulted in the often-quoted "β-hCG doubling time" of early gestations, namely a 66% rise in 2 days. For normal gestations, the β-hCG peaks at about 100,000 at about 10 weeks EGA, and then falls to a steady state of about 20,000 to 50,000 for the duration of pregnancy (10). More recently Barnhart et al. studied 287 symptomatic first-trimester pregnancy patients over 5 days from presentation of their symptoms, and found that the median rise of β-hCG was 1.5 times after 1 day (50% increase), and 2.24 after 2 days (124% rise). The smallest increase for a normal viable IUP was 24% at 1 day and 53% at 2 days (11). Given this variability, it is important to interpret serial hCG data carefully. Furthermore, a "normal" rise in β-hCG does not eliminate the possibility of miscarriage or ectopic pregnancy, and such diagnoses should be established definitively using methods such as ultrasonography (12).

The primary value of *pelvic ultrasonography* in the evaluation of a pregnant VB patient is to confirm the presence of an IUP, which ostensibly rules out ectopic pregnancy. Ultrasound is also useful in evaluating the prognosis for a threatened gestation because there are sonographic findings consistent with normal gestational development at various levels of β-hCG. The hormones of pregnancy cause an early uterine decidual reaction that may be seen on ultrasound soon after a missed menses, but this is nonspecific and occurs with both IUP and ectopic pregnancy. The earliest sonographic landmark of an IUP is the gestational sac. With endovaginal ultrasound, this can be visualized at between 30 and 33 days gestational age.(13). The gestational sac typically lies eccentrically within the decidua of the endometrium, and may be seen to have two sonographically distinct layers which are referred to as the double sac sign (DSS) (Fig. 136.1) or an intradesidual sign (IDS), and is what radiologists have historically used to define findings consistent with an IUP. Recent literature has shown that there is poor interexaminer agreement regarding the presence of these signs. Therefore a round or oval intrauterine fluid collection in

a woman with positive β-hCG should be considered to be an IUP, regardless of the presence or absence of a DSS or IDS (14). The yolk sac seen within the gestational sac is the next sonographic landmark of the developing pregnancy and is seen between 34 and 38 days after the LMP. The embryo and cardiac activity are seen concurrently and reliably adjacent to the yolk sac between 39 and 43 days gestation by endovaginal ultrasound (13). Table 136.3 lists the sonographic findings of early pregnancy development with their corresponding discriminatory levels of β-hCG and gestational ages.

TABLE 136.3
Sonoembryology of Early Pregnancy

Sonographic Landmarks of Early Pregnancy	EGA (wks)	Serum Quantitative β-hCG (mIU/mL)
Gestational sac	4.5	500–1,000
Yolk sac	5.5	1,000–7,500
Embryo with cardiac activity	6.5	5,000–23,000

EGA, estimated gestational age; β-hCG, β human chorionic gonadotropin.

FIGURE 136.1 Transvaginal ultrasound of a gestational sac, showing the "double ring."

The sonographic finding that is most reassuring for a favorable prognosis is the presence of normal fetal heart rate (FHR). Dede et al. found that for patients with first-trimester VB who had slow FHR detected by pelvic ultrasound (<130) had a predictive value of 92.6% for spontaneous fetal loss before 20 weeks gestation. Another sonographic finding that correlates with a poor outcome is a shorter than normal cervical length (<40 mm), which was found to be 80.8% sensitive and 54.7% specific for fetal loss before 20 weeks gestation (15). The effects of a subchorionic hematoma, gestational age, and maternal age together on gestational prognosis have been investigated. A subchorionic hematoma greater than two-thirds the circumference of the chorion had a twofold increase in the rate of spontaneous abortion (19%) compared to those with a smaller hematoma (9%). In addition, the spontaneous abortion rate for women over age 35 was twice that for younger women, 14% versus 7%, respectively (16).

Molar pregnancy has a characteristic but unusual pattern on ultrasound that is referred to as a *snowstorm pattern* (Fig. 136.2).

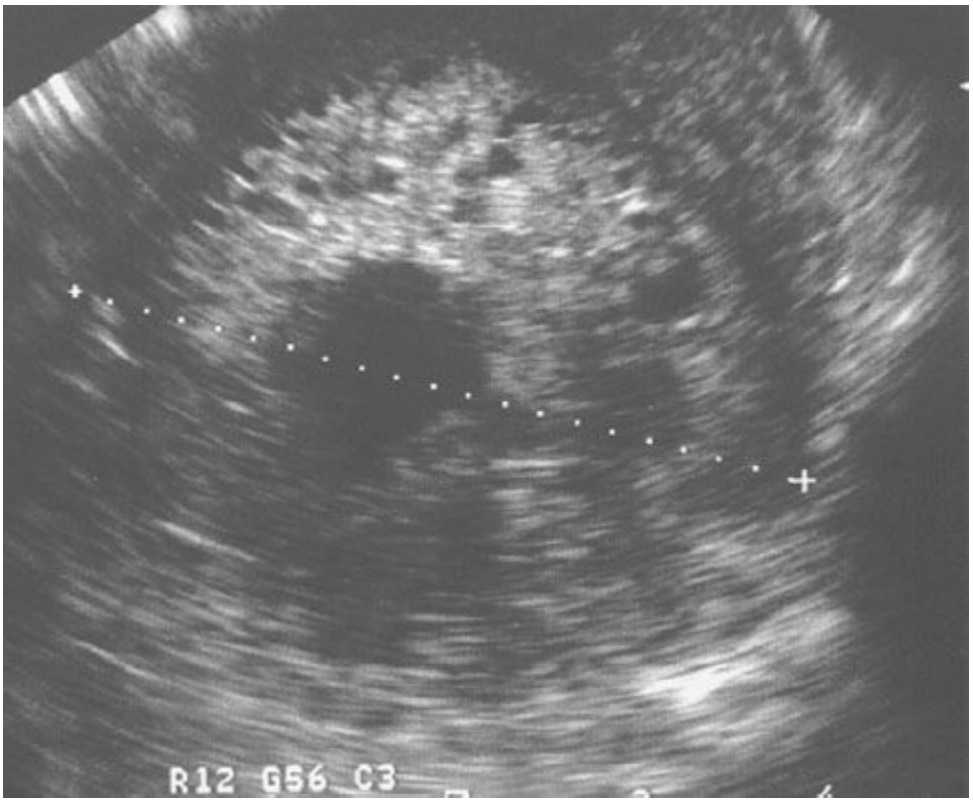

FIGURE 136.2 Transvaginal ultrasound of a molar pregnancy, with typical "snowstorm" appearance.

KEY TESTING

- Serum quantitative β-hCG, urinalysis, type and Rh
- Pelvic ultrasound

ED MANAGEMENT

The first consideration in management of a first-trimester patient who has VB is hemodynamic status. A patient who is bleeding heavily and hemodynamically compromised should be resuscitated with intravenous fluids. Obtain type-specific blood for transfusion if the patient's hemodynamic status does not respond to 2 L of crystalloid. Gynecology should be consulted immediately as the hemodyamically compromised patient will most likely need either an emergency dilation and curettage (D&C) if there is evidence of intrauterine POC, or emergency laparoscopic surgery for presumptively ruptured ectopic pregnancy. Early bedside ultrasound

is critical in the unstable patient to determine whether there is an IUP or free fluid. Bedside sonography by emergency physicians is highly accurate in the determination of IUP compared to that performed by radiology (17).

It may also be necessary to remove POC in the open cervical os by *gentle* traction with a ring forceps, thereby completing a spontaneous miscarriage. If more than gentle traction is required, there may be incomplete separation of tissue from the endometrium. In that case, it is advised to not simply pull harder, as mechanical separation can result in severe hemorrhage; rather, obtain gynecologic consultation for assistance. When this tissue is completely removed, a rapid decrease in bleeding and pain should follow. If ultrasound does not suggest further retained POC, the patient should be observed for a few hours to ensure continued clinical resolution of bleeding and cramping, as well as the internal cervical os at least beginning to close. Such patients usually can be discharged with gynecologic follow-up. Patients who continue to have heavy bleeding, pain, tenderness, or a persistently open internal cervical os are presumed to have retained POC and should receive gynecologic consultation for possible D&C.

For patients diagnosed in the ED with a nonviable gestation, be it an embryonic demise (aka blighted ovum), an incomplete miscarriage (aka retained POC), or early fetal demise (aka missed miscarriage), there are three different possible management strategies: expectant, surgical, and medical. Expectant management allows time for the spontaneous passage of the POC. Surgical management is usually by D&C. Medical management uses an antiprogesterone medication, usually misoprostol, to aid in the expulsion of POC. A 600- or 800-μg tablet-form dose of misoprostol may be administered orally or intravaginally on day 1, and a second dosage may be self-administered by the patient on day 3, if clinically indicated. Studies suggest that both dosages and routes of administration have equal efficacy, with an overall success rate of 71% to 92%. The addition of pretreatment with oral mifepristone does not improve on the success rate of misoprostol alone (18). Patients with incomplete miscarriage who have had bleeding within

the previous 24 hours have the best success rate (87% to 92% successful), and those with embryonic failure or fetal demise who have not had recent bleeding tend to have less success with medical management (71% to 77% successful) (19).

Trinder et al. studied 1,200 women in a randomized controlled trial of the three management strategies of miscarriage. All three strategies had a low incidence of uterine infection (2% to 3%). Upon follow-up at 10 to 14 days, ultrasound evidence of retained POC was present in 10%, 36%, and 20% of the surgical curettage, expectant, and medical management groups, respectively, and the mean duration of bleeding was 8, 12, and 11 days, respectively. All groups returned to daily activity in about 2 days (20). Other smaller studies have also shown better success rates for medical management over expectant management, with the most significant difference in those with early fetal demise (9). Therefore, it seems reasonable to offer all three management strategies to women, and allow participation in the decision (21,22). Patient satisfaction varies greatly across management strategies (23).

Septic spontaneous miscarriage is a polymicrobial infection and should be treated immediately with broad-spectrum intravenous antibiotics, evacuation of the uterus and admission. In addition, blood and cervical discharge should be obtained for culture. Disseminated intravascular coagulation is sometimes seen in this setting, either as a result of prolonged retention of fetal tissue caused by release of necrotic tissue into the bloodstream or in women who have developed frank septic shock.

It is a common practice to give Rh immune prophylaxis to Rh-negative pregnant women with VB as described above (8). If the gestation is less than 12 weeks, a dose of 50 μg is sufficient. However, as pregnancy dating is difficult and inaccurate, some recommend that all unsensitized Rh-negative women with VB receive 300 μg of Rh immune globulin in the first or second trimester. This should be given before the patient leaves the ED, but protection occurs if it is administered within 72 hours of bleeding. It is not necessary to repeat the dosage at subsequent visits for subsequent bleeding before 20 weeks of gestation. Another 300-μg

dose should be administered in the third trimester or prior to delivery.

CRITICAL INTERVENTIONS

- Aggressively resuscitate unstable patients with suspected ectopic pregnancy and obtain early gynecologic consultation.
- Administer broad-spectrum antibiotics to patients with suspected septic spontaneous miscarriage or infected retained POC.
- Obtain gynecologic consultation for women diagnosed with miscarriage in the ED to decide on a management strategy, be it D&C, expectant, or medical management with misoprostol.

DISPOSITION

Patients who are hemodynamically stable, appear nontoxic, are not in pain or bleeding heavily, and have reliable access to gynecology follow-up may be sent home. If a patient is known to not have an ectopic pregnancy, then once the result of the urinalysis and Rh screen have been interpreted and the patient treated accordingly, the patient with either threatened or completed spontaneous miscarriage may have routine (1 to 2 week) gynecologic follow-up. These patients often need serial β-hCG measurements, and it should be determined prior to discharge where this should occur. There is no evidence that reduction in activity or medical therapy will affect the outcome of the threatened miscarriage. Despite this, rest is often prescribed for social and psychological reasons. It is important to emphasize to a patient and her partner that normal pregnancies tolerate normal physical activity. Patients with miscarriage will be dispositioned per the recommendations of the consulting gynecologist, as discussed above.

All patients who are discharged from the ED should be encouraged to return immediately if they develop worrisome symptoms such as fever, intolerable pain, or symptoms consistent with severe anemia. Most importantly, all patients with VB should be reassured that the cause of their bleeding and/or miscarriage is not their fault and that there is nothing they can do to prevent

miscarrying an abnormal pregnancy. Patients and family members may have many misconceptions about this, and correct information can be very important to the psychological well-being of these patients. The emotional response to a spontaneous miscarriage is variable, from relief to overwhelming grief. A sensitive approach to these families is a critical part of treatment and is often the most significant effect a clinician can have. Offering referral to professional counseling or support groups should be a routine part of managing these women, and preprinted discharge instructions with appropriate referral phone numbers may be very useful.

Common Pitfalls

- Failure to consider ectopic pregnancy in the first trimester of pregnancy.
- Underestimating the amount of blood loss. Because these patients tend to be healthy young women, they can maintain nearly normal vital signs despite large volume losses, until abrupt decompensation occurs.
- Failure to give antibiotics early in the course of a suspected septic spontaneous miscarriage.

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CHAPTER 137
Ectopic Pregnancy

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A leading cause of maternal morbidity and mortality in the United States is ectopic pregnancy. It is also a major factor in decreasing the future fertility of the affected woman. Unfortunately, the frequency of ectopic pregnancies in the United States has increased by fivefold since 1970 (1). Pooled data indicate that the current incidence of ectopic pregnancy is about 19 per 1,000 pregnancies (2% of all pregnancies in women in the United States will be ectopic) (2). Furthermore, it is estimated that of 100 women with a history of ectopic pregnancy, approximately 50% will be infertile, 35% to 40% will subsequently have a successful pregnancy, and 10% to 15% will experience a second ectopic pregnancy (3).

Ectopic pregnancy is the result of implantation of a fertilized ovum at a site other than the endometrium of the uterine cavity (4). The most frequent site of implantation is the lateral two-third of the fallopian tube (80%) (Fig. 137.1). About 15% implant is in the medial one-third. Interstitial or cornual implantation occurs in approximately 3% of ectopic gestations. Interstitial and abdominal implantations carry the greatest risk of mortality because of their hemorrhagic tendencies (5). Extratubal ectopic gestations occur in about 5% of cases: in the ovary (3%), within the abdominal cavity (2%), or in the cervix (rare). Interstitial pregnancies (where the fertilized egg implants in the intrauterine portion of the fallopian tube) occur in $<3\%$ of tubal pregnancies (6). Combined intrauterine and extrauterine gestations (*heterotopic pregnancy*) were formerly very rare, with an estimated incidence of 1 in 30,000 pregnancies (7). Combined pregnancies are now estimated to occur in up to 1 in

3,000 normal patients and 1 in 100 patients being treated with assisted reproductive technologies (8), particularly if the woman had previously received clomiphene citrate (9).

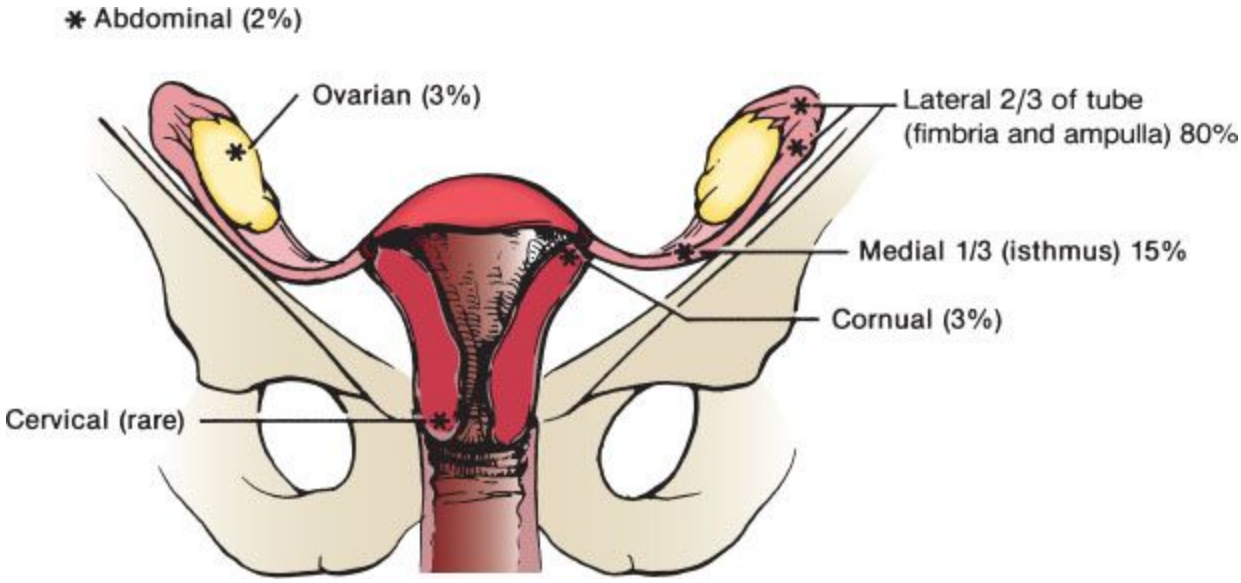

FIGURE 137.1 Sites of implantation in ectopic pregnancy.

The most common predisposing factors include intrinsic or extrinsic abnormalities of the fallopian tube and abnormal development of the embryo itself. Abnormalities of the fallopian tube are the most important cause of ectopic pregnancy. The most common source of tubal pathology is pelvic inflammatory disease (PID). The risk of ectopic pregnancy is known to be several times more likely among women with a history of salpingitis (7). All pathogens, including *Chlamydia* and *Neisseria gonorrhoeae,* are believed to cause tubal distortion and scarring, which adversely affect tubal patency and motility. Subacute infection with less virulent organisms may actually increase the amount of residual tubal pathology because diagnosis and treatment may be delayed.

There are multiple risk factors for developing an ectopic pregnancy. However, up to 42% of women with ectopic pregnancy have no risk factors (10). Table 137.1 lists several important population characteristics. Increasing age at the time of conception is a risk factor for developing an ectopic pregnancy. The risk of

ectopic pregnancy is threefold greater in older patients than in younger (11).

TABLE 137.1
Rates of Ectopic Pregnancy for Various Population Subgroups

Population Characteristic	Ectopic Pregnancies as a Percentage of Total Pregnancies in Each Population Group (%)
Overall	0.94
Age (yrs)	
15–19	0.45
20–29	0.82
30–39	1.42
Contraception	
Oral contraceptives	0
Barrier	0.002
Intrauterine device	14
One or more episodes of salpingitis	6.9
Prior tubal sterilization	16
Prior ectopic pregnancy	11.2

Adapted from Weström L, Bengtsson LP, Mårdh PA. Incidence, trends, and risks of ectopic pregnancy in a population of women. *Br Med J (Clin Res Ed)*. 1981;282:15–18.

Fourteen percent of all pregnancies in women with an intrauterine device (IUD) are ectopic. The IUD does not prevent ovulation, as does the oral contraceptive, but interferes with intrauterine implantation of the ovum. Therefore, a woman wearing an IUD is potentially at risk for tubal implantation if her ovum becomes fertilized. Additionally, IUD wearers are frequently subjected to delayed diagnosis of ectopic pregnancy. Health care providers may confuse the symptoms caused by an ectopic pregnancy with those related to the mechanical or inflammatory response to an IUD and fail to consider the possibility of an ectopic gestation.

Ectopic pregnancy must be considered after tubal sterilization procedures. Sixteen percent of women who become pregnant after tubal sterilization have an ectopic gestation. This probably

represents partial recanalization, allowing access of the sperm to the ovum, but impaired passage of the fertilized ovum to the uterine cavity. Like IUD wearers, patients who have had prior tubal sterilization are frequently subjected to a delay in diagnosis.

Women who have had an elective abortion within the preceding 2 weeks and who present with symptoms referable to the genital tract are at risk of having an undiagnosed ectopic pregnancy. Confirmation of products of conception in the pathology specimen is necessary to exclude the diagnosis of ectopic pregnancy. This is a frequent problem in large urban clinics with a high incidence of therapeutic abortions performed with unreliable follow-up (12). Although many of the features discussed increase the risk of ectopic pregnancy, no combination of risk factors confirm or exclude the diagnosis with a high degree of certainty (13).

The major life-threatening condition associated with an ectopic pregnancy is intra-abdominal hemorrhage with shock, causing approximately 85% of fatalities from ectopic pregnancy. Misdiagnosis contributes to half of the fatalities (5).

CLINICAL PRESENTATION

Any female with lower abdominal pain or vaginal bleeding with a positive pregnancy test should be suspected of having an ectopic pregnancy. The “classic” triad of amenorrhea, vaginal bleeding, and abdominal pain is neither sensitive nor specific for ectopic pregnancy. Of patients with ectopic pregnancies, approximately 15% present with this classic picture, and of patients with the classic constellation of signs and symptoms, only 14% actually have an ectopic gestation (14).

Abdominal pain is the most common symptom and is reported in more than 97% of patients. Abnormal vaginal bleeding is present in 55% to 86% of cases (12,15). A “normal” menstrual history is obtained in 15% to 30% of patients, and abdominal pain occurs *without* bleeding in up to one-third of patients. It should be emphasized that consideration of an ectopic pregnancy is based on a history of abdominal pain and a positive pregnancy test in the first

trimester. The quality, character, and location of the pain are highly variable. It may be cramping, colicky, steady, or dull. Flank or lower back pain may be noted, or tenesmus may occur from rectal irritation caused by blood in the cul-de-sac. The pain may be localized to either lower quadrant or may be generalized, suggesting hemoperitoneum. Profuse vaginal hemorrhage occurs in the minority of cases and suggests rupture of a cornual implantation. Between 6% and 16% of patients who present to an ED with first trimester bleeding will ultimately be found to have an ectopic pregnancy.

Vital signs are typically normal, except in those patients with significant blood loss. This will be manifested by orthostatic hypotension, tachycardia, or shock. Paradoxical bradycardia may be seen. Any woman of childbearing age who presents with signs of hemorrhagic shock without historical or physical evidence of trauma has a ruptured ectopic pregnancy until proven otherwise.

Tenderness on pelvic examination is the most common sign and is present in 83% to 97% of cases (12,15). The physical findings depend on whether intraperitoneal irritation has occurred from leakage or rupture of the ectopic gestation. A palpable mass may represent the ectopic gestation or may be felt on the side opposite the ectopic gestation, possibly representing a corpus luteum cyst rather than the ectopic pregnancy itself.

Patients with ectopic pregnancy are more likely to have moderate-to-severe sharp abdominal pain with abdominal or pelvic tenderness and a small uterus on physical examination. Peritoneal signs are uncommon but highly predictive of ectopic pregnancy. However, no constellation of findings (by either history or physical examination) can confirm or exclude the diagnosis of ectopic pregnancy with a high degree of reliability (13).

DIFFERENTIAL DIAGNOSIS

Given the broad spectrum of patient complaints and physical findings, the differential diagnosis of ectopic pregnancy is proportionally broad. The most common pelvic conditions that

share clinical aspects of ectopic pregnancy include PID, threatened or incomplete abortion, corpus luteum or follicular cyst, ovarian torsion, endometriosis, gastrointestinal disorders, dysfunctional uterine bleeding, mittelschmerz, and intrauterine pregnancy.

PID is commonly confused with ectopic pregnancy. The signs and symptoms may be identical, and the same population is at risk. A significant percentage of normal intrauterine pregnancies are associated with pelvic pain and vaginal bleeding in the first trimester, as are almost all cases of nonviable intrauterine pregnancies. Rupture of a corpus luteum cyst of pregnancy is associated with a positive pregnancy test, pain, and a tender pelvic mass—identical to signs and symptoms of ectopic pregnancy.

Gastrointestinal disorders to be differentiated include appendicitis, diverticulitis, irritable bowel syndrome, and gastroenteritis. Nephrolithiasis should also be considered.

Patients who merit special attention are those with a history of PID, tubal ligation, an IUD, or a recent abortion. An especially high-risk group includes those undergoing infertility treatment with embryo transfer procedures or ovulation-inducing agents.

ED EVALUATION

The evaluation of suspected ectopic pregnancy may be organized into three general categories based on hemodynamic stability (Table 137.2).

TABLE 137.2
Categories for Evaluating Suspected Ectopic Pregnancy Based on Hemodynamic Stability

CATEGORY A

Patients presenting in hypovolemic shock

CATEGORY B

Patients of reproductive age presenting with complaints and physical findings indicative of an acute abdomen but who are hemodynamically stable

CATEGORY C

Patients presenting with abdominopelvic complaints suggestive of an ectopic pregnancy but who are clinically judged to be at low risk of immediate deterioration

The history should emphasize the patient's reproductive past, menstrual history, and risk factors and a chronologic review of the nature and intensity of the symptoms.

The physical examination should focus on changes associated with normal pregnancy and signs of peritoneal inflammation or significant blood loss. Uterine size, adnexal masses, appearance of cervix and os, and rectal examination should be noted. Serial abdominal examinations may aid in the assessment. A pelvic examination should be repeated only as necessary because of the concern that overly aggressive palpation may precipitate rupture.

Laboratory studies should include a urinalysis and a pregnancy test. For patients in categories A and B (Table 137.2), a hematocrit and a blood bank specimen are necessary.

Sensitive qualitative urine pregnancy tests with a human chorionic gonadotropin (β-hCG) threshold of 20 mIU/mL should be used as a screening test for possible ectopic gestation. Modern assays using monoclonally derived, enzyme-tagged antibodies meet this sensitivity requirement, enabling detection of pregnancy 1 week after conception (3 weeks gestational age). Nearly all patients with an ectopic pregnancy will have a positive pregnancy test (16). The chance for a false-negative result exists when the serum β-hCG level is low and the urine is dilute (specific gravity <1.010). Thus, a patient highly suspected of harboring an ectopic gestation who has a dilute urine and a negative urine pregnancy test should have a quantitative serum β-hCG radioimmunoassay.

Patients in category C (Table 137.2) may benefit from serial quantitative serum β-hCG level determinations (17). Serum β-hCG levels rise exponentially during the first 6 weeks of gestation and peak at approximately 100,000 mIU/mL. A single quantitative serum β-hCG value serves to confirm pregnancy, aids in "dating" the pregnancy, and may help in the interpretation of ultrasound results (as described later). Serial quantitative serum β-hCG levels normally double every 2 days in early normal *intrauterine* pregnancies. Abnormal gestations, both intrauterine and extrauterine, have prolonged doubling times (18). Patients in whom serum β-hCG levels do not increase by more than 66% (1.66-fold increase) in 48 hours are likely to have an abnormal pregnancy and should have further evaluation. Serial serum quantitative β-hCG determinations can be used in stable patients to more accurately detect a nonviable intrauterine or ectopic gestation.

The gestational sac of a normal intrauterine pregnancy becomes visible with transabdominal ultrasonography at 5 to 6 weeks of gestation, corresponding to a quantitative β-hCG of 6,000 to 6,500 mIU/mL (8). With transvaginal sonography, a gestational sac is commonly visualized when the β-hCG level exceeds 1,000 to 2,000 mIU/mL (2). The level of β-hCG at which sonographic findings of an intrauterine pregnancy should be visible is often referred to as the *discriminatory zone* (19). Intrauterine pregnancy or findings suggestive of an ectopic gestation may be seen with very low β-hCG levels. Low β-hCG levels should, therefore, not be used as a basis for delaying ultrasonography when ectopic pregnancy is suspected. Ultrasonography results are operator-dependent, and the technique has a high incidence of nonspecific findings with gestational ages earlier than 5 to 6 weeks. With transvaginal ultrasonography, a gestational sac is identified and localized outside the uterus in about 62% of ectopic pregnancies (7). False-negative and false-positive results occur in up to 25% of patients (20). Although a positive diagnosis of ectopic pregnancy can be made by identifying an extrauterine gestation, in practice ultrasonography is more helpful in excluding the diagnosis when it demonstrates an intrauterine

pregnancy, because simultaneous intrauterine and ectopic gestation is uncommon.

The correlation of ultrasonographic findings with quantitative serum β-hCG levels is essential to the efficient diagnosis of ectopic pregnancy. This is especially true when the quantitative β-hCG level is above the discriminatory zone (18). The absence of an intrauterine gestational sac with a serum β-hCG titer above the discriminatory zone suggests ectopic pregnancy with a positive predictive value reported as high as 86% (21). However, β-hCG values as high as 6,567 mIU/mL with no intrauterine pregnancy seen on transvaginal ultrasonography (empty uterus) and eventual diagnosis of intrauterine pregnancy have been documented (22). The ultrasonographic absence of an intrauterine sac, with β-hCG levels below the discriminatory zone, does not allow the definitive diagnosis of an ectopic pregnancy but mandates close follow-up and serial testing.

Serum progesterone levels are sometimes used to screen for ectopic pregnancies. Only 1% to 2% of cases of ectopic pregnancy will be associated with a progesterone level of >5 ng/mL, and only 0.16% of viable pregnancies will be associated with levels <5 ng/mL. Thus, if the progesterone level is abnormally low and the hCG levels are abnormally or erratically rising, a nonviable pregnancy (possibly ectopic) should be suspected. In the ED, progesterone levels are generally not available, but some patients may have had levels determined in an outpatient setting, which may be useful.

Because pregnancy can be detected by laboratory testing at approximately 3 weeks of gestation and by ultrasonography at 5 to 6 weeks, there is a 2 to 3 week period during which a pregnancy can be detected but not located by ultrasound. Routine laparoscopy in this setting would result in a high incidence of unnecessary diagnostic laparoscopies for normal, early intrauterine pregnancies (11). Therefore, patients in category C (Table 137.2) who are stable, reliable, and present during the period of uncertainty are best evaluated by serial serum quantitative β-hCG levels when the initial

sonogram is nondiagnostic. Failure of β-hCG levels to increase normally suggests an ectopic or other abnormal pregnancy.

Culdocentesis is a simple, rapid, and accurate method of detecting intraperitoneal blood. It has been largely replaced by ultrasound in the ED evaluation for ectopic pregnancy (23).

KEY TESTING

- Quantitative serum β-hCG
- Complete blood count
- Type and screen
- Pelvic ultrasound (transvaginal, if available)

ED MANAGEMENT

Management is guided by the patient's hemodynamic status, reliability for follow-up, and the availability of ultrasonography (Fig. 137.2) (7).

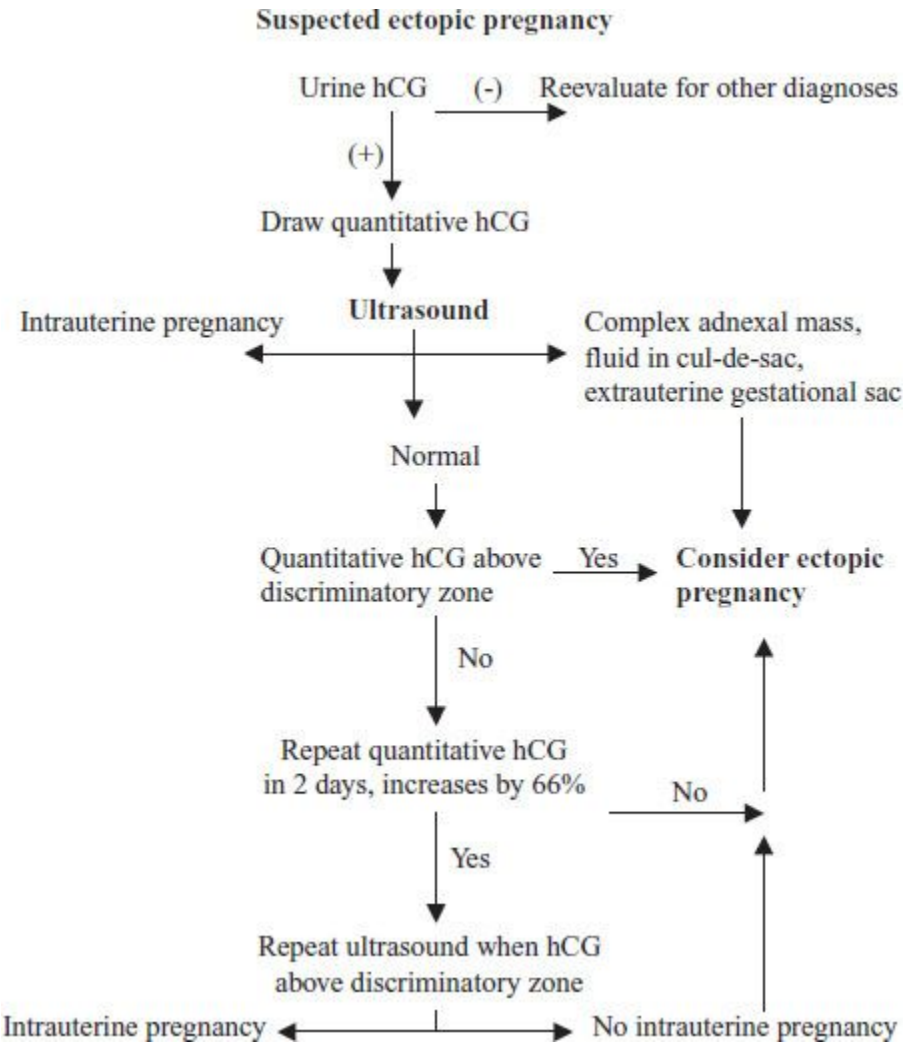

FIGURE 137.2 Algorithm for evaluation and management of suspected ectopic pregnancy.

Patients in category A should be treated for hemorrhagic shock.

- Place the patient in Trendelenburg position
- Administer high-flow oxygen
- Establish large-bore peripheral venous access
- Begin crystalloid infusion
- Obtain baseline blood samples including blood bank
- Transfuse O-negative, type-specific, or cross-matched blood, depending on the response to initial therapy
- Immediate gynecologic consultation

Patients in category B are hemodynamically stable but have potential for rapid progression to category A. Anticipation of fluid

resuscitation and rapid confirmation of the diagnosis dictate the course of evaluation and management. Large-bore venous access should be established. Baseline blood studies include complete blood cell count, Rh typing, and type and screen for potential transfusion. A urine pregnancy test and quantitative β-hCG should be rapidly performed and, if positive, followed by ultrasonography. Patients in category B, by definition, have an acute abdomen and therefore warrant urgent consultation.

Patients in category C, who are stable and ambulatory, are the most common, and pose the greatest diagnostic and management challenges. Figure 137.2 provides a useful algorithm. The evaluation of a possible ectopic pregnancy starts with a urine pregnancy test for *all* women of childbearing age who present with abdominopelvic pain. The only exception is the woman who has had a hysterectomy. The presence of an IUD, tubal ligation, a partner with a vasectomy, or incidental trauma should not deter consideration of an ectopic pregnancy. The diagnosis should be pursued until reasonably eliminated.

Medical Therapy for Unruptured Ectopic Pregnancy

Carefully selected patients with an unruptured ectopic pregnancy may be treated nonsurgically by a gynecologist. Methotrexate may be used for these cases when given orally, intramuscularly, or intravenously, along with leucovorin rescue to prevent toxicity to bone marrow. Recommended regimens include single-dose methotrexate/leucovorin or multi-dose methotrexate/leucovorin. The multi-dose regimen is more effective, but the single-dose regimen is more widely used. Regardless of the regimen that is chosen, more side effects are associated with a higher likelihood of successful treatment. The reported overall success rate for methotrexate (both single and multi-dose therapy) is 89% (24). Methotrexate as a single intramuscular injection can be given to women who are (a) hemodynamically stable (including the absence of a hemoperitoneum), (b) highly compliant, (c) have an initial β-

hCG level <5,000 IU/L, and (d) have no evidence of fetal cardiac activity (6).

Patients treated medically for ectopic pregnancy may experience abdominal pain 3 to 7 days after treatment. This is thought to be secondary to methotrexate-induced tubal abortion. It may be difficult to differentiate expected pain from pain owing to rupture of a persistent ectopic pregnancy. Patients presenting with abdominal pain in this timeframe after methotrexate administration should have a complete blood count and ultrasound to rule out significant free fluid in the cul-de-sac and should be evaluated for other causes of abdominal pain. The patient may need consultation and/or admission to the hospital for observation. Hemodynamic instability or a falling hematocrit mandates surgical intervention.

Stable patients with an ectopic pregnancy and no cardiac activity on ultrasound may be followed up with serial examinations and repeat quantitative β-hCG levels. If the levels continue to fall, no invasive interventions may be necessary. In addition to the repeat β-hCG levels, repeat transvaginal ultrasonic scanning should be considered to ensure reabsorption of the embryo (15).

CRITICAL INTERVENTIONS

- Obtain immediate gynecologic or surgical consultation in patients who are in shock and who have a positive pregnancy test
- Initiate resuscitation with fluids and/or blood as appropriate

DISPOSITION

Given the broad spectrum of presentations and the lack of pathognomonic findings in suspected ectopic pregnancy, there should be a low threshold for requesting consultation from the gynecology, radiology, and surgery services. Early notification of consulting services for patients in categories A and B may allow early mobilization of operating room personnel. The timing for consultation for patients in category C is more flexible and dependent on results of ED testing, local resources, consultant

availability, and whether the patient has a previously established relationship with a gynecologist.

All patients in categories A and B require admission. Category C patients may be discharged with follow-up in 48 hours, except in the following instances:

- No intrauterine pregnancy can be visualized on ultrasonography *in a symptomatic patient* with a quantitative serum β-hCG level above the discriminatory zone.
- There are progressive symptoms or physical findings.
- The patient is unreliable for follow-up.
- There is free fluid on ultrasound.

The usual timing of follow-up is 48 hours, the standard sampling interval for quantitative serum β-hCG levels. Most outpatients will be evaluated by this method. A system should be in place to follow up on serial hCG levels or pathology results in women who have passed tissue or undergone uterine evacuation procedures in the ED for suspected incomplete abortion. If the pathology report shows "no chorionic villi," ectopic pregnancy is the likely diagnosis, and the patient should be urgently referred to an obstetrician/gynecologist or the ED for further evaluation.

In general, patients should be transferred only if the hospital lacks the diagnostic, surgical, or gynecologic resources required to manage the patient.

Common Pitfalls

- Failure to consider the diagnosis of ectopic pregnancy, especially in women with few signs or symptoms.
- Clinical findings consistent with ectopic pregnancy should outweigh any single negative test result.
- Delays have been documented in cases that involve women who have undergone tubal sterilization, women with an IUD in place or recently removed, and women who have undergone a recent spontaneous or therapeutic abortion. Ectopic pregnancy does occur in these groups and must be ruled out.

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CHAPTER 138

Hyperemesis Gravidarum

Lori Weichenthal

Although nausea and vomiting are quite common in pregnancy, affecting 70% to 85% of all pregnant women, hyperemesis gravidarum, the most severe manifestation of this disorder, is far rarer, with an incidence rate of only 0.3% to 2% (1,2). Defined as persistent vomiting accompanied by weight loss exceeding 5% of prepregnancy weight that is often associated with ketonuria, severe dehydration, and electrolyte imbalance, hyperemesis can cause significant maternal morbidity if not treated early and aggressively (3). Although the pathogenesis of hyperemesis remains unknown, many theories relate it to hormonal, neurologic, metabolic, toxic, and psychogenic factors. It is agreed that human chorionic gonadotropin (hCG) serum levels are a likely causative factor, given that they peak in the first trimester when severe nausea and vomiting are typically seen and that hyperemesis is more common in women with multiple fetuses and gestational trophoblastic disease, both of which are characterized by higher serum hCG levels (4,5).

CLINICAL PRESENTATION

Hyperemesis gravidarum is a clinical diagnosis, suggested by the findings of intractable vomiting, weight loss, and ketouria beginning in the first trimester of pregnancy. Abdominal pain and fever are uncommon in hyperemesis and should suggest an alternative diagnosis. The onset of symptoms is typically between 4 and 10 weeks of gestation, and hospitalization rates peak at 9 to 10 weeks

(6). Nausea and vomiting that develop beyond 10 weeks of gestation are generally thought to be due to another cause.

Patients with hyperemesis have few distinct physical findings besides those associated with dehydration, such as vital sign abnormalities (tachycardia with or without hypotension), dry oral mucosa, and poor skin turgor. Laboratory abnormalities may or may not be present but can include electrolyte abnormalities such as hypokalemia, metabolic alkalosis, increased blood urea nitrogen; elevated urine-specific gravity and ketonuria; increased hematocrit due to hemoconcentration; mild abnormalities in liver enzyme values; and mild hyperthyroidism.

DIFFERENTIAL DIAGNOSIS

Hyperemesis is generally a diagnosis of exclusion, based on its development in early pregnancy and gradual resolution over time. The differential diagnosis of nausea and vomiting in the pregnant women is extensive and includes disorders related and unrelated to pregnancy (Table 138.1). Some common disorders for the emergency physician to consider include pyelonephritis, appendicitis, cholelithiasis, pancreatitis, gastritis, central nervous system disorders, and toxic and metabolic disturbances. As mentioned, development of nausea and vomiting after 10 weeks gestation should suggest another diagnosis. Other symptoms that should make the EP consider an alternative diagnosis include abdominal pain, fever, headache, diarrhea and/or constipation, abnormal neurologic findings, or hypertension.

TABLE 138.1
Differential Diagnosis of Nausea and Vomiting in Pregnancy

Toxic/Endocrine	Infectious	CNS	Disorders of the Gut
Chemotherapeutics	Gastroenteritis	Migraine	Obstruction
Aspirin	Otitis media	Malignancy	Gastroparesis
NSAIDs	Pyelonephritis	Hemorrhage	GERD
Narcotics		Infarction	Irritable bowel
β-Blockers		Hydrocephalus	Peptic ulcer
Calcium channel blockers		Emotional responses	Cholecystitis
Erythromycin		Psychogenic	Pancreatitis
Sulfonamides		Eating disorders	Hepatitis
Sulfasalazine		Labyrinthitis	Crohn's
Azathioprine			Appendicitis
Anticonvulsants			
Theophyline			
ETOH			
DKA			
Hyper/hypopara-thyroidism			
Adrenal insufficiency			

NSAID, nonsteroidal anti-inflammatory drug; ETOH, ethanol; DKA, diabetic ketoacidosis.

ED EVALUATION

When a pregnant woman presents to the emergency department (ED) with nausea and vomiting, a careful history and physical examination should be obtained to assess the severity of symptoms and physical findings, to determine the need for aggressive resuscitation, and to help exclude alternative causes. Important historical considerations include the time of onset of nausea and vomiting during pregnancy and other related symptoms. It is also important to note any medications or herbal preparations that the patient is using. On physical examination, it is important to assess for signs of dehydration, including vital sign abnormalities, dry oral mucosa, and poor skin turgor. The physician should look for physical examination findings such as fever, abdominal tenderness, costovertebral tenderness, jaundice, goiter, or neurologic deficits that might suggest another diagnosis. A pelvic examination is necessary if the patient has abdominal or pelvic pain, vaginal

discharge, or bleeding. A measurement of weight should also be obtained.

Diagnostic tests to consider include serum electrolytes, a urinalysis, a complete blood count, liver function tests, and serum-free T4 concentrations. An elevated hematocrit and blood urea nitrogen may be present owing to hemoconcentration. Hyper- or hyponatremia and hypokalemia may be present when vomiting has been profuse or persistent. Urinalysis is helpful in gauging the degree of dehydration and ketonuria and for looking for signs of urinary tract infection. Pelvic ultrasound examination might be helpful to exclude gestational trophoblastic disease or multiple gestations. Other imaging studies should be ordered as clinically indicated or as directed by laboratory findings.

KEY TESTING

- Urinalysis and serum electrolytes

ED MANAGEMENT

For patients who appear clinically dehydrated or who have ketonuria, intravenous rehydration should be initiated with D5 lactated Ringer's or D5 normal saline solutions. Typically, an initial bolus of 1 to 2 L is given, and further hydration is determined by the patient's response. Vital signs, symptoms, and urine output should be monitored. Antiemetics are frequently required and should be administered intravenously. Ondansetron has become the most common antiemetic used for the treatment of hyperemesis in the ED, owing to its efficacy and safety profile in pregnancy (class B) (7). Metoclopramide, which is also considered safe in pregnancy, is also frequently used, as are promethazine and prochlorperazine, whose safety in pregnancy have not been well established (Table 138.2). Many recommend giving thiamine, 100 mg IV, to women who have experienced significant nausea and vomiting, as Wernicke encephalopathy is a rare but serious complication of hyperemesis (8).

TABLE 138.2
Antiemetics Used to Treat Hyperemesis

Drug	PO Dose (mg)	PR Dose	IV Dose (mg)	Pregnancy Class
Metoclopramide	10–30	N/A	10	B
Ondansetron	4–8	N/A	4–8	B
Dolasetron	100	N/A	12.5	B
Prochlorperazine	5–10	25 mg	10	C
Promethazine	12.5–25	12.5–25 mg	12.5–25	C

It has recently been suggested that corticosteroids are of potential benefit in the treatment of hyperemesis gravidarum, but they may be associated with an increased risk of oral clefts if used in the first trimester (9). Thus, corticosteroids should be used only as a last resort and in consultation with an obstetrician (1).

CRITICAL INTERVENTIONS

- IV fluid resuscitation as needed
- Antiemetics

DISPOSITION

Women who have intractable vomiting despite aggressive therapy, have persistent electrolyte abnormalities or ketosis, and who have lost more than 10% of their prepregnancy weight generally require admission for further therapy and observation. Approximately 5% of patients with hyperemesis require hospitalization (10)

In patients without laboratory abnormalities, the goal is to correct the dehydration and to ensure that the patient can tolerate oral intake prior to discharge from the ED. Some patients may require an orally or rectally administered antiemetic for use as an outpatient to control their symptoms, though many women can manage their symptoms through behavioral modifications and dietary changes. Women should be counseled to avoid environmental triggers and to eat small, frequent high-carbohydrate, low-fat meals (11). One randomized controlled study found that ginger extract, 1 g daily,

reduced the nausea and vomiting associated with early pregnancy (12). Other adjunctive treatments, including hypnosis, psychotherapy, vitamin B_6 (pyridoxine), and acupressure have also shown promise.

Women who are discharged home should be educated on the expected course of their symptoms, should have close follow-up arranged with their healthcare provider, and should be advised to seek medical help sooner if symptoms change or become more severe or if they develop dizziness or inability to take anything by mouth.

Common Pitfalls

- Failure to aggressively rehydrate women with significant dehydration.
- Failure to consider alternative diagnoses in pregnant women with nausea and vomiting.

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CHAPTER 139

Postabortion Complications

Lynne McCullough

Since *Roe v. Wade* in 1973, legalized abortions have become one of the most frequently performed surgical procedures in the United States and one of the most prevalent means of fertility control worldwide (12). The number of abortions performed in the United States had declined each year from 1990 to 2005, followed by a plateau from 2005 to 2008. In 2009, CDC surveillance data reported 784,000 abortions to the Centers for Disease Control, representing the single largest decrease in the last decade (20). Since the US FDA approved mifepristone use for medical abortion in 2000, medical abortions have been growing in popularity as a nonsurgical alternative for termination of pregnancy, with their percentage increasing from 1% in 2000 to 13% of all abortions in 2005 (20).).

In the 3 years following *Roe v. Wade,* the mortality rate associated with surgical abortion decreased from 4.1 to 1.1 per 100,000, and from 1988 to 1997, mortality declined further to 0.7 per 100,000 (2). Although the rate of complications increases with advanced gestational age, serious complications of elective abortion are rare at any age. The overall complication rate is less than 1% (6), and the proportion of women with a reportable complication of medical abortion using mifepristone has been reported to be 2.2 per 1,000 (15,21).

CLINICAL PRESENTATION

Complications after an induced abortion may be divided into (a) early (immediate, or within 3 hours of the procedure), (b) delayed (after 3 hours to 28 days), and (c) late (more than 28 days after the procedure). After elective termination of pregnancy, patients may present to the emergency department (ED) complaining of pain, bleeding, or fever. The degree of discomfort, height of the fever, amount and quality of the bleeding, as well as the patient's past medical history are all relevant pieces of information.

The most commonly encountered complications of induced abortion are delayed, presenting within the first few days after the procedure. Pelvic infections are the most common complication of surgical abortion procedures, occurring in 0.1% to 12% of all patients undergoing elective pregnancy termination (20,23). If symptoms occur within 2 to 3 days of the procedure, approximately 70% have retained products of conception (POC) and secondary infection (6). As infection is common, it is prudent to maintain a high index of suspicion and expedite the administration of antibiotics to minimize complications such as sepsis, chronic pelvic pain, dyspareunia, and infertility. Risk factors for infection include age younger than 20, previous pelvic inflammatory disease, presence of a pathogen in the cervix at the time of the surgical abortion and nulliparous status (22). However, it is important to note that most infections occur in women with no risk factors for disease (20).

Mild bleeding is to be expected after an induced surgical or medical abortion, but persistent or heavy bleeding is unusual and most commonly a result of retained POC (6). After medical termination, patients are generally instructed to seek medical attention if they saturate two full-thickness sanitary pads per hour for 2 consecutive hours (19).

Less commonly, patients present immediately after an abortion procedure with a complication such as uterine perforation, hemorrhage secondary to uterine atony (more common in multiparous patients), retained POC, previously undiagnosed coagulopathy, cervical lacerations, anesthesia complications,

amniotic fluid or pulmonary embolism, or disseminated intravascular coagulopathy (DIC) (5).

Late complications such as cervical stenosis and "*Asherman syndrome,*" the development of intrauterine adhesions, may present to the ED with amenorrhea associated with increasing abdominal distention and cyclical pelvic pain (20). These late complications are relatively uncommon and do not represent true emergencies to be managed in the ED.

DIFFERENTIAL DIAGNOSIS

As the most common chief complaints include abdominal pain, pelvic pain, vaginal bleeding, and fever, the differential is broad. Symptoms may be either a direct result of, or completely unrelated to, the recent pregnancy termination. Postprocedural complications of surgical termination include disorders such as uterine perforation, uterine atony, retained POC, trauma, undiagnosed ectopic pregnancy, endometritis, peritonitis, delayed hemorrhage, and cervical stenosis. The complications seen after medical abortion also include infection and hemorrhage, although uterine bleeding and painful uterine contractions are anticipated consequences (24). Surgical and medical abortion have similar overall efficacy, and failed termination can occur with both approaches (16).

Uterine perforation occurs in 0.01% to 0.1% of first-trimester procedures, and in 3% to 8% of those performed in the second trimester. It is probably underdiagnosed until the time of the surgical procedure and is a rare cause of serious sequelae (13,14,18). Patients may present with complaints of abdominal pain, referred scapular pain, symptoms consistent with bowel obstruction secondary to entrapped mesentery in the perforation, low-grade temperature, rectal pressure, and excessive or persistent vaginal bleeding.

Cervical laceration is a relatively common complication (1%) that is rarely serious (15).

DIC is the most likely form of coagulopathy in the previously healthy patient in the postabortion setting. DIC is more common in

second-trimester terminations, cases of prolonged intrauterine demise, and in cases of massive blood loss (6,20).

Incomplete abortion with retained POC is a relatively common complication of suction evacuation (0.03% to 0.5% of first-trimester abortions) that is characterized by a slightly tender or enlarged uterus in the setting of excessive bleeding (14). This condition should also be considered when heavy bleeding is unresponsive to uterotonic agents.

Acute hematometra, or "postabortal syndrome," a collection of retained blood in the uterine cavity, occurs most commonly in late first-trimester or early second-trimester abortions. The overall incidence is fewer than 5 in 1,000 cases (6,14). Patients typically complain of rapid onset of lower pelvic pain not associated with increased bleeding or unstable vital signs. They may complain of intermittent expulsion of maroon clots with pelvic pressure and low-grade temperature.

Endometritis had a reported incidence of 0.46%, with sepsis in 0.028% in one study from 1990 (14). Infections are typically polymicrobial, including gram-positive and gram-negative anaerobes, facultative or obligate anaerobes, *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (25). *Endomyoparametritis* defines spread of the intrauterine infection to the myometrium and or parametrial structures (i.e., the fallopian tubes; the round, uterosacral, and broad ligaments; and the peritoneum covering those structures). Patients will complain of the postabortal triad of symptoms (pain, bleeding, and fever); foul-smelling discharge may be identified, and leukocytosis is common.

Septic pelvic thrombophlebitis "*right ovarian vein syndrome*" occurs in approximately 1 in 10,000 pregnancies, typically from the late first trimester onward and is the result of progression of endomyoparametritis (8). It can also be secondary to damage to the pelvic venous system during surgical abortion, leading to the development of a thrombus that becomes secondarily infected.

Sepsis and toxic shock syndrome (TSS) associated with Clostridium sordellii following medical abortion has resulted in 6 reported deaths from 560,000 early medical terminations since 2000 (7). In these

cases, the patients presented with minimal signs and symptoms until the infection was fulminant and shock became evident (3). Complicating matters, the side effects of misoprostol (e.g., abdominal discomfort, vomiting, and diarrhea) can be similar to the initial symptoms of patients who ultimately developed toxic shock (11).

Similar symptoms of pain, bleeding, and fever may be produced by disorders unrelated to the procedure, such as appendicitis, pyelonephritis, kidney stone, diverticulitis, pelvic inflammatory disease, endometriosis, menses, and ovarian cyst rupture.

ED EVALUATION

A focused medical history should be taken to include the number of prior pregnancies; the estimated gestational age of the fetus at the time of termination; the date, time, and method of the abortion; any prior history of pelvic infection or known coagulopathy; the patient's Rh status; the results of any preprocedure evaluation, as well as any known complications that may have occurred during or immediately after the procedure.

Patients with significant bleeding or signs of shock require more laboratory testing, including a complete blood count (CBC), type and screen or cross, along with coagulation studies. The evaluation of suspected DIC includes checking platelet and fibrinogen levels, coagulation studies, and fibrin degradation products. Febrile patients should have blood cultures obtained as well. An Rh type should be considered if the patient's type is unknown so that the need for RhoGAM can be identified. A quantitative β-hCG level may be helpful in the event that a missed ectopic or failed abortion is in the differential, and the level may be compared to a prior one, if it is available.

The physical examination should include a complete pelvic evaluation, including direct visualization with a vaginal speculum and bimanual palpation. Pelvic examination may reveal the source of mechanically induced bleeding, as from a cervical laceration or retained POC in the cervical os. It also may reveal the source of pain

and fever. The presence of a nonfirm, boggy uterus suggests uterine atony. A tender uterus may be consistent with either retained POC, continued bleeding into the uterus, or the development of endometritis.

Pelvic ultrasound is a very useful adjunct in the evaluation of postabortive patients in the ED and can demonstrate retained POC, uterine abnormalities that may have led to an incomplete evacuation of the uterus (i.e., an accessory uterine horn or septum), hemoperitoneum, or an unexpected ectopic gestation. A quantitative β-hCG level may also be helpful in diagnosing ectopic pregnancy by demonstrating a persistent level despite anticipated termination of the pregnancy. The β-hCG levels should fall 66% within 48 hours of the abortion procedure but may decline much more slowly over the next several weeks (20).

Clinicians should maintain a high index of suspicion for TSS associated with *C. sordellii* in patients who present with mild flu-like illness after medical abortion. Strong consideration should be given to sending a CBC in these patients, as the index cases have consistently manifested marked leukocytosis and hemoconcentration (owing to third spacing) out of proportion to their mild clinical presentation. In clear cases of TSS, antibiotics such as clindamycin and imipenem–cilastatin should be initiated, in addition to airway and cardiovascular support as needed. Steroid administration and dilation and curettage should be considered in consultation with gynecology; hysterectomy is sometimes necessary (7).

KEY TESTING

- Postabortion bleeding: CBC, type and screen, coagulation studies, quantitative β-hCG, ultrasound
- Fever: Consider blood cultures, lactate, DIC panel, depending on the severity of illness

ED MANAGEMENT

For patients with significant bleeding or signs of shock, two IV lines should be established with normal saline boluses initiated while the

evaluation is taking place. The cause of excessive bleeding can usually be identified by visualization of the cervix on vaginal speculum examination or with bimanual palpation. While evaluating a patient for the potential cause of excessive bleeding, consider uterine tamponade with a Foley catheter balloon, the use of uterotonic agents, and the possibility of pelvic vessel embolization for persistent excessive bleeding (4).

Uterine atony, characterized by a soft, nontender uterus and a steady trickle of blood from the cervix, should be treated with manual uterine massage, intramuscular, intravenous, or intracervical uterotonic agents (Table 139.1) (6,20,25).

TABLE 139.1
Uterotonic Agents (to be Used Sequentially)

Methylergonovine maleate (Methergine)	0.2 mg IM, may repeat and continue oral treatment with 0.2 mg TID for 3 d
Oxytocin[a]	10 U IV bolus or 10 U IM, consider 40 U in 1,000 mL normal saline to infuse at a rate necessary to control bleeding for persistent and severe hemorrhage[b]
Vasopressin	2.5–4.0 units injected directly into the cervix
Misoprostol	400 µg orally
Carboprost tromethamine 15(S)-methyl PGF2α	200 µg/10 mL saline in a transvaginal intrauterine injection or 250 µg IM

[a]Can be given IM or IV. The number of oxytocin receptors in the uterus rises throughout pregnancy; therefore, a diminished response may be seen in first trimester of pregnancy.
[b]Water intoxication can be seen secondary to the mild antidiuretic properties of oxytocin.
Adapted from Stubblefield P, Borgatta L. Complications of induced abortion. In: Pearlman M, Tintinalli J, Dyne P, eds. *Obstetric & Gynecologic Emergencies*. New York, NY: McGraw-Hill; 2003:65–86.

Uterine perforation should be treated empirically with antibiotics when this diagnosis is being considered (Table 139.2), and prompt gynecologic consultation should be obtained. Diagnosis and definitive management are accomplished with explorative laparoscopy or laparotomy when indicated.

TABLE 139.2
Antibiotic Regimens for Postabortal Infectious Complications

Uterine perforation (suspected or proven)	Doxycycline 100 mg PO (if nonsurgical management) and cefoxitin 1 g IV before laparotomy[a]
Endometrial infection, mild, oral regimen	Doxycycline 100 mg BID for 10 d with metronidazole 500 mg TID for 7 d; amoxicillin and clavulanic acid 500 mg TID for 7 d[b]
Ascending infection, abscess or sepsis, IV regimen indicated	Cefoxitin 2 g QID or cefotetan 2–3 g with doxycycline 100 mg BID or clindamycin 600 mg QID[c] or clindamycin 600 mg/gentamicin 3–5 mg/kg/d[d]
Suspected *C. sordellii* infection	Clindamycin and imipenem–cilastatin, consider steroids[e]

[a–c]Darney PD, Horbach NS, Korn AP. First-trimester abortion. In: *Protocols for Office Gynecologic Surgery*. Boston, MA: Blackwell Science; 1996:158–193.
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[e]Department of Health and Human Services. *Emerging Clostridial Disease Workshop: Summary of Proceedings*. Atlanta, GA, May 11, 2006. Rockville, MD: Author, 2006.

Cervical lacerations are usually minor injuries, with bleeding that can be controlled by the topical application of silver nitrate. If more significant lacerations are identified, they can be repaired in the ED with 0-chromic catgut on a CT-1 needle in most cases (6).

The treatment of DIC includes fluid volume and clotting factor replacement with fresh-frozen plasma (FFP), cryoprecipitate, and in severe cases, packed red blood cells. Most important is the attempt to identify and treat any stimulus of DIC, such as retained POCs or infection. Frequent monitoring of coagulation parameters is also indicated. Each unit of FFP (200 to 250 mL) raises fibrinogen levels 25 mg/dL. In early DIC, 4 to 8 units of FFP is usually adequate to restore clotting function (20).

Incomplete abortion with retained POC is usually treated with dilation and curettage. However, if POC are identified in the cervical os on speculum examination, they should be removed immediately to reduce the incidence of continued bleeding.

Acute hematometra, or "*postabortal syndrome,*" should be treated with prompt suction and evacuation of the uterus, which leads to

symptom resolution. A low-grade temperature does not typically indicate infection, and it resolves after evacuation (20).

Endometritis should be treated with uterine evacuation if retained POC are suspected, and outpatient antibiotic regimens for pelvic inflammatory disease are appropriate for mild-to-moderate postabortal endometritis (9). If the patient is toxic or fails outpatient therapy, she should be admitted for parenteral treatment (20). *Endomyoparametritis* requires parenteral antibiotics, as serious complications such as bacteremia may occur in 5% to 10% of these infections, abscesses may form, and the patient may develop a sepsis syndrome. In patients presenting with high fever, tachycardia, marked tenderness to palpation, and leukocytosis, a pelvic ultrasound or a CT of the abdomen and pelvis should be performed to evaluate for an abscess (9).

Septic pelvic thrombophlebitis, or "*right ovarian vein syndrome,*" may be diagnosed by computed tomography or magnetic resonance imaging as well as by prompt clinical improvement after empiric heparin for patients with septic abortion who are unresponsive to parenteral antibiotic therapy (8).

CRITICAL INTERVENTIONS

- Stop any sources of continued bleeding that are accessible to direct pressure or tamponade.
- For hypovolemic or septic patients, initiate supportive care with IV fluids, blood, and antibiotics, as needed.
- Obtain immediate gynecologic or surgical consultation for patients with persistent bleeding or suspected uterine perforation.

DISPOSITION

Patients who present with postabortal bleeding can be safely discharged home following an evaluation that has ruled out ectopic pregnancy, retained POC, and demonstrates that the patient is hemodynamically stable. For patients who require uterotonic agents to assist a poorly responsive uterus, cervical repair of a laceration,

or in whom a uterine perforation is suspected, gynecologic consultation should be obtained and close follow-up arranged if the patient is stabilized for disposition to home.

In cases of mild endometritis, the patient may be discharged on oral antibiotics as listed in Table 139.2. Close follow-up should be arranged, and precautions should be provided to return to the ED or her doctor should include nonresolution of symptoms in 48 to 72 hours or worsening pain, increased fever, or other systemic signs of illness.

Gynecologic consultation and hospitalization are indicated for toxic-appearing or septic patients, those with infection that has spread beyond the endometrium, ongoing hemorrhage, or DIC. Gynecologic consultation should also be obtained when POC are identified, when vaginal bleeding is unresponsive to uterotonic agents, when uterine perforation is suspected, or when an ectopic pregnancy is identified.

Common Pitfalls

- Failure to identify retained POC in the postabortal patient.
- Failure to identify a failed abortion (i.e., an intact gestation).
- Failure to identify ectopic pregnancy in patients who have undergone dilation and curettage but in whom POC were not demonstrated on pathologic examination.
- Inadequate examination of the intravaginal structures to rule out cervical laceration as the source of bleeding.

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CHAPTER 140

Hypertensive Disorders of Pregnancy

Jan Marie Shoenberger

During the past 20 years, the incidence of hypertensive disorders during pregnancy has increased. The current leading cause of maternal mortality in the United States is disease of the heart and blood vessels, which includes hypertensive disorders during pregnancy (1,2). It is important to differentiate hypertensive disorders that antedate pregnancy (i.e., chronic hypertension) from a potentially more ominous disease specific to pregnancy—preeclampsia. Preeclampsia is a pregnancy-specific disorder that is defined as an elevation of the blood pressure with new onset proteinuria.

The causes of hypertension in pregnancy are multiple. The Working Group on Research on Hypertension during Pregnancy (3) has categorized hypertension during pregnancy into four categories (Table 140.1).

TABLE 140.1
Classification of Hypertensive Disorders in Pregnancy

Category	Definition
Chronic hypertension	HTN (BP ≥140/90) present before pregnancy or diagnosed before 20 wks gestation
	HTN that is diagnosed during the pregnancy and fails to resolve by 12 wks postpartum
Gestational hypertension	HTN that develops during the pregnancy
	No proteinuria
	If the HTN resolves by 12 wks postpartum, the diagnosis is changed to transient HTN
Preeclampsia/ Eclampsia	HTN presenting after 20 wks gestation with proteinuria (>300 mg in a 24-h collection or ≥1+ on urine dip)
	In the absence of proteinuria, the disease should be highly suspected when HTN appears accompanied by the following symptoms: headache, blurred vision, abdominal pain, low platelets, elevated liver enzymes
Preeclampsia superimposed on chronic hypertension	Underlying diagnosis of HTN with development of new-onset proteinuria (as defined above)
	In women with HTN and proteinuria before 20 wks gestation who have any of the following: sudden increase in proteinuria, sudden increase in blood pressure, thrombocytopenia, increased liver enzymes

Data from Report of the National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy. *Am J Obstet Gynecol.* 2000;183:S1–S22.
HTN, hypertension; BP, blood pressure.

1. Chronic hypertension
2. Gestational or transient hypertension
3. Preeclampsia/eclampsia
4. Preeclampsia superimposed on chronic hypertension

Recognizing and treating elevated blood pressure during pregnancy is important for maternal and neonatal health. Recent evidence shows that elevated blood pressure during pregnancy is a marker of high risk for the development of cardiovascular disease, chronic kidney disease, and diabetes mellitus later in life (4).

CLINICAL PRESENTATION

Chronic Hypertension

In pregnant women, chronic hypertension is defined as elevated blood pressure (BP) that is present and documented before pregnancy. In women whose prepregnancy BP is unknown, the

diagnosis is based on the presence of elevated BP measured on two or more occasions before 20 weeks of gestation. It can also be diagnosed when hypertension is diagnosed for the first time during pregnancy and does not resolve postpartum. Differentiation of chronic hypertension from preeclampsia is important, as the latter may necessitate inpatient management, whereas the former may be treated on an outpatient basis, if mild. The presence of chronic hypertension increases the risk of developing superimposed preeclampsia (the most frequent complication associated with hypertension during pregnancy), abruptio placenta, and preterm delivery. Because it is difficult to determine which pregnant women with chronic hypertension will become complicated, all patients with this diagnosis should be considered high risk and followed closely (5).

Gestational or Transient Hypertension

Gestational or transient hypertension is defined as the development of first-time hypertension after 20 weeks gestation without proteinuria. This diagnosis covers patients with the preeclampsia syndrome who have not yet manifested proteinuria as well as women who do not have preeclampsia. The final determination that the patient does not have preeclampsia can be made only postpartum. If preeclampsia has not developed and the BP has returned to normal by 12 weeks postpartum, the diagnosis of transient hypertension can be confirmed. If the BP elevation persists, the patient now has chronic hypertension.

Preeclampsia and Eclampsia

Preeclampsia is a condition of pregnancy that occurs most often after the 20th week of gestation. By definition, it is characterized by new-onset hypertension (systolic BP of $\leq$140 mm Hg or diastolic BP of $\leq$90 mm Hg) combined with proteinuria, defined as more than 300 mg in 24 hours. In the emergency department (ED), 24-hour urine collection data are typically not available. A rough estimate of the required amount of proteinuria is a reading on a urine dipstick of at

least 1+ protein in a urine specimen with no evidence of urinary infection. Because proteinuria may be a delayed manifestation of preeclampsia, clinicians are advised to be suspicious when new-onset elevated BP is accompanied by any of the following: headache or blurry vision, epigastric or right upper quadrant pain or abnormal laboratory tests, specifically thrombocytopenia and abnormal liver enzymes. These latter elements are the hallmarks of the *HELLP syndrome,* a variant of preeclampsia, which is characterized by hemolytic anemia (*H*), elevated liver enzymes (*EL*), and low platelets/thrombocytopenia (*LP*), as well as by the classic hypertension and proteinuria. The clinical presentation of HELLP syndrome is variable; 12% to 18% of affected women are normotensive and 13% do not have proteinuria (6).

Preeclampsia can be classified into mild and severe disease based on the degree of BP elevation and the presence of the signs and symptoms of HELLP syndrome. In either case, obstetric consultation is advised. Eclampsia is defined as the occurrence of seizures in a woman with preeclampsia. The seizures should not be attributable to other causes.

Preeclampsia Superimposed on Chronic Hypertension

Any existing hypertensive disease predisposes the gravid woman to the development of preeclampsia/eclampsia. The outcome for mother and child with preeclampsia superimposed on existing hypertension is worse than with de novo preeclampsia. Differentiating superimposed preeclampsia from worsening chronic hypertension can be challenging. The diagnosis of superimposed preeclampsia is highly likely if the patient has new-onset or worsening proteinuria, a sudden increase in previously well-controlled BP, thrombocytopenia, or elevated liver enzyme tests.

DIFFERENTIAL DIAGNOSIS

The diagnostic challenge in a gravid patient with hypertension revolves primarily around distinguishing between chronic

hypertension, gestational/transient hypertension, and preeclampsia/eclampsia (see Table 140.1).

Seizures in a woman after 20 weeks of gestation without a previous diagnosis of preeclampsia must be accompanied by two of the following within 24 hours of presentation to be considered eclamptic: hypertension, proteinuria, thrombocytopenia, or increased liver enzyme levels. Eclampsia can also occur in the postpartum period and cases of seizure activity occurring as late as 23 days postpartum have been attributed to eclampsia (7).

ED EVALUATION

When considering diagnoses related to hypertension in pregnancy, it must be ensured that the BP is being measured correctly, with an appropriate sized cuff and with the patient in a seated position. If the BP is found to be elevated, determine which of the four categories of pregnancy-related hypertension is most likely. Assessment of the fetus by ultrasound and fetal heart monitoring is also indicated. Aspects of the history that may be important in determining whether or not the patient has preeclampsia include complaints of headache, visual or neurologic disturbances, and persistent epigastric or right upper quadrant pain. Although some patients develop peripheral edema, this is not a diagnostic criterion for preeclampsia (8).

Any pregnant woman found to have an elevated BP should have a urine dip performed. If protein is detected, preeclampsia should be considered to be the diagnosis until proven otherwise. Other tests that should be ordered include a formal urinalysis, a comprehensive metabolic panel to check renal function, a complete blood count (CBC) to check for thrombocytopenia, serum transaminase levels, and serum uric acid (increased levels suggest the diagnosis of preeclampsia). Women with severe preeclampsia should also have the following tests ordered: serum albumin (indicating the extent of endothelial leakage), lactic acid dehydrogenase (indicating the presence of hemolysis), a coagulation profile, and a blood smear if HELLP syndrome is suspected (3). Evaluation of the fetus by ultrasound and fetal heart monitoring is indicated when there is moderate-to-severe hypertension.

KEY TESTING

- Urine dip for protein
- CBC, metabolic panel, LFTs
- Ultrasound, fetal monitoring

ED MANAGEMENT

Mild-to-moderate chronic or gestational hypertension is less likely to produce end-organ damage, and treatment has been shown to neither improve neonatal outcomes nor prevent superimposed preeclampsia. A recent Cochrane review on this topic concluded that there is insufficient evidence to guide how tightly hypertension should be controlled to improve maternal and neonatal outcomes for pregnant women with nonsevere pre-existing or nonproteinuric gestational hypertension (9). However, there is general agreement that BP in the range of 150 to 160 mm Hg systolic and/or 100 to 110 mm Hg diastolic and greater should be treated.

Methyldopa, labetalol, and nifedipine are oral agents commonly used to treat chronic hypertension in pregnancy. Table 140.2 outlines these medications. Oral hypertensive agents to avoid during pregnancy include the ACE inhibitors and angiotensin receptor blockers (ARBs). Treating women at high risk for the disease in early pregnancy with low-dose aspirin (75 mg/d) has been shown to be effective in reducing the incidence of preeclampsia (10).

TABLE 140.2
Oral Medications Used to Treat Mild–Moderate HTN in Pregnancy

Generic Name	Starting Dose	Maximum Dose (24 hrs)	Mechanism of Action	Side Effects
Methyldopa	250 mg bid	4 g	Central acting α-2 adrenergic agonist	Sedation and fatigue, hemolytic anemia, depression
Labetalol	100 mg bid	2,400 mg	α- and β-blockers	Avoid in asthma and CHF
Nifedipine/NifedipineXL (long acting)	10 mg bid/30 mg qd	120 mg	Calcium channel blocker	
Hydralazine	50–300 mg in 2–4 divided doses	300 mg	Direct vasodilator	Headache, nausea, drug-induced lupus (seen with long-term use)

Therapy for preeclampsia and eclampsia is based on basic principles that come from our limited understanding of the disease.

First, delivery of the fetus is the ultimate and ideal treatment for the mother, but the risks to the fetus at the time of diagnosis must be considered. Second, poor perfusion appears to be a hallmark of the disease; thus, measures to improve and maintain organ perfusion (i.e., oxygen, careful BP control) will benefit the patient.

When the diagnosis of preeclampsia/eclampsia is made in the ED, the obstetrician should immediately be consulted. The following actions should be taken:

- Maintain oxygen delivery to both mother and fetus.
- Maintain continuous fetal monitoring.
- Minimize the aspiration risk by placing the mother in the left lateral decubitus position if seizure activity is present.
- In most cases, volume replacement therapy is not indicated except as needed to maintain a urine output of 1 to 2 mL/kg/hr. Overly aggressive fluid therapy may actually precipitate pulmonary edema (11).
- Monitor urine output using a Foley catheter.
- Treat BP (**Tables 140.2** and **140.3**).
- Treat seizures with magnesium sulfate (see below).

As previously noted, the final step in the treatment of preeclampsia/eclampsia involves delivery or termination of the pregnancy with the least harm to the infant and mother. Timing of delivery is determined by the mother's clinical condition and by gestational age, evidence of fetal lung maturity, and fetal compromise (12).

Table 140.3 outlines the most commonly used medications that are used to control BP in preeclampsia/eclampsia as well as severe hypertension without proteinuria.

TABLE 140.3
Medications Used to Treat Moderate–Severe HTN in Pregnancy

Generic Name	Dose	Infusion	Comments
Labetalol	10–20 mg IV then 20–80 mg IV every 20–30 min, maximum of 300 mg	1–2 mg/min	Risk of neonatal hypoglycemia at high doses
Hydralazine	5 mg IV then 5–10 mg every 20–40 min	0.5–10 mg/hr	
Nifedipine	10 mg orally up to 5 doses	N/A	
Sodium nitroprusside	N/A	0.25–10 µg/kg/min	Should only be used in cases refractory to other therapy

Magnesium sulfate is the drug of choice for seizure control in eclampsia, and has been shown to be superior to both diazepam and phenytoin (13). Magnesium therapy should also be employed in severe preeclampsia for seizure prophylaxis. The goal of therapy is to raise the maternal magnesium plasma level to a range of >4 mEq/mL. The most commonly employed protocol in the United States recommends a 6-g IV loading dose over 20 minutes, followed by an infusion at 2 g IV per hour (14). A commonly used loading dose of 4 g will achieve a therapeutic maternal plasma level; the effect, however, is transient, and the level will fall within 60 minutes. The side effects of magnesium sulfate range from mild effects such as flushing, loss of deep tendon reflexes, and double vision, to life-threatening consequences such as excessive bleeding, respiratory depression, muscle paralysis, and cardiac arrest. When magnesium toxicity is suspected (Table 140.4), calcium gluconate 1 g may be administered to antagonize the effects. The antagonism is transient, however, and continuous monitoring is warranted.

TABLE 140.4
Effects of Magnesium Sulfate on the Mother

Serum Level (mg/dL)	Clinical Effects
1.5–2.5	Normal
4–8	Therapeutic for seizure prophylaxis
8–12	Loss of patellar reflexes, double vision, flushing, somnolence, slurred speech
15–17	Muscle paralysis
30–35	Cardiac arrest

Magnesium sulfate administration should continue until 24 hours after delivery. Signs of improvement include a decrease in BP, improvement in sensorium, and an increase in urine output. Magnesium is excreted by the kidney, so in those cases in which urinary output is decreased or in the presence of renal failure, magnesium doses should be adjusted to avoid toxicity. Although there may be an initial decrease in BP for the first 30 to 45 minutes after the initiation of magnesium treatment, the drug itself is not an antihypertensive agent. As such, another drug should be added to the treatment regimen to control BP and minimize further end-organ damage.

Fetal magnesium may have equilibrated with the mother's, causing hypotonia, respiratory depression, or hypotension in the neonate after delivery. Calcium gluconate may be administered to the infant in those cases.

In cases in which eclampsia is complicated by status epilepticus, intubation and muscular paralysis are indicated.

CRITICAL INTERVENTIONS

- Treat the seizures of eclampsia with magnesium sulfate
- Aggressively treat the hypertension of severe preeclampsia
- Emergently consult an obstetrician for patients with suspected preeclampsia or eclampsia, as delivery is ultimately indicated.

DISPOSITION

For patients with chronic or gestational hypertension without proteinuria, outpatient medical management can be considered for individuals with mild–moderate elevations in BP. In cases of

moderate-to-severe hypertension or proteinuria, obstetric consultation should be obtained in the ED. The need for admission of patients with preeclampsia should be determined after discussion with the obstetrician, and discharge should occur only if close follow-up is feasible.

Except in those cases in which a higher level of care is needed, patients experiencing symptomatic preeclampsia or those with eclamptic seizures are not candidates for transfer. The dynamic nature of the disease, the need for continuous monitoring during therapy, and the high fetal and maternal mortality make this disease inappropriate for interfacility transfer.

Common Pitfalls

- The diagnostic elements of preeclampsia—hypertension and proteinuria—may not occur simultaneously, may be present as part of another disease process, or may be present as part of a normal pregnancy.
- During treatment for eclampsia, the serum magnesium level and the patient's clinical condition must be monitored closely to avoid over- or undertreatment.
- Seizure activity in the third trimester of pregnancy or immediately after delivery may be due to eclampsia and requires high-dose magnesium therapy (6-g loading dose). If the patient is not responsive to magnesium sulfate, other etiologies of seizures should be sought.

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CHAPTER 141

Third-Trimester Vaginal Bleeding

Moss H. Mendelson

Vaginal bleeding after 20 weeks' gestation is not uncommon and can be frightening to the patient as well as to the physician. Definitive treatment, if required, should be performed by an obstetrician. The emergency physician must stabilize the patient hemodynamically and should be aware of the differential diagnosis, the studies necessary to define the problem, as well as the indications for transfer if limited facilities exist for management of the mother or the premature or distressed newborn.

Placental abruption (abruptio placentae), premature separation of part of the placenta from the uterine wall, complicates 1% to 2% of all pregnancies. Risk factors include hypertension and maternal tobacco and cocaine use. In addition, abdominal trauma with transmission of forces to the uterus can cause shearing of the placenta from its attachments (1).

Placenta previa, which accounts for about 20% of third-trimester bleeding, is a placenta that overlaps the cervix to varying degrees. Placenta previa is more common with a uterus scarred from previous cesarean section and with advanced maternal age. Of placentas that overlie the cervix before 20 weeks' gestation (approximately 5% of pregnancies), <10% remain so at delivery (2). The other 50% of patients who experience late bleeding often have no definite cause identified. It is believed that most episodes of bleeding represent small marginal separations of the placenta, but this cannot usually be proven. Other causes of bleeding in later

pregnancy include vaginal or cervical trauma, lower genital tract infections, polyps, or hemorrhoids.

The alterations in maternal cardiovascular physiology that occur during pregnancy affect evaluation and management, as well as the clinical course of disease. Maternal blood volume expands by about 1.5 L during a normal pregnancy, resulting in a dilutional anemia that is physiologic (hematocrit 32% to 34%). Pregnant patients also manifest a baseline increase in heart rate (90 to 100 beats/min) and stroke volume, resulting in a cardiac output 30% to 40% higher at term than seen in the nonpregnant state. Systematic vascular resistance is decreased, however, and the net hemodynamic result of these changes is a blood pressure lower than that in the nonpregnant state. Finally, the uteroplacental bed does not have any autoregulatory function; placental blood flow is determined strictly by maternal blood pressure and cardiac output. Because of expanded maternal intravascular volume, signs of extensive blood loss can occur late, and significant fetal hypoperfusion can develop before maternal signs of shock are apparent. Pregnancy is also associated with a rise in concentration of many clotting factors (especially fibrinogen), resulting in a hypercoagulable state.

CLINICAL PRESENTATION

The patient with bleeding after 20 weeks' gestation may present with a spectrum of signs and symptoms ranging from painless spotting or bloody mucoid discharge to dark or exsanguinating bleeding and severe uterine pain. Placenta previa most often presents as bright red, painless vaginal spotting. The bleeding is rarely severe (except during labor or after pelvic examination with probing of the cervical os). The patient may already be aware of an abnormal placental location. The patient with placental abruption more often has dark, variable bleeding accompanied by uterine tenderness and irritability, manifested by intermittent or steady cramping. Bleeding between the placenta and uterine wall may result in significant occult blood loss, with maternal and fetal compromise, but without evidence of significant external bleeding.

Fetal distress (heart rate out of the normal range of 120 to 160 beats/min) can occur if a significant degree of separation has occurred. Abruption may also trigger maternal coagulation, thereby resulting in evidence of consumptive coagulopathy, with bleeding from needlesticks, urine, and other sites.

DIFFERENTIAL DIAGNOSIS

The main disorders that must be considered in the pregnant patient with vaginal bleeding are placental abruption and placenta previa. Other possibilities include bleeding from a cervical or vaginal lesion or from a nonvaginal source such as genitourinary (cystitis, urethritis, and nephrolithiasis) or gastrointestinal (hemorrhoids, polyp, and ulcer).

ED EVALUATION

The patient with vaginal bleeding should first be assessed hemodynamically. With significant maternal blood loss, fluid resuscitation should be initiated during the initial evaluation. Blood should be sent for complete blood cell count, prothrombin time, partial thromboplastin time, and fibrinogen levels. The patient's blood should be typed and crossmatched, as blood transfusion may be necessary. The mother's Rh type should be determined and a Kleihauer–Betke test sent to determine whether significant fetomaternal transfusion has occurred (3). Continuous fetal monitoring should be established as quickly as possible in these high-risk patients, so as to identify signs of fetal distress. Bradycardia <120 beats/min, tachycardia >160 beats/min, decelerations, and loss of beat-to-beat variability all can indicate fetal hypoxemia and acidosis, with an increased risk of fetal demise.

History should include known obstetric problems and ultrasonographic diagnoses. Other historical information includes amount of bleeding, passage of clots, character of blood (bright red or dark, older blood), presence of uterine cramping or pain, prior cervical or vaginal lesions or infection, drug use, and history or evidence of abdominal trauma (including domestic violence).

The initial focus of the physical examination should be to determine whether the patient is severely hypovolemic, whether the bleeding is in fact vaginal (as opposed to urinary or rectal), and whether delivery is in progress. Abdominal examination should confirm uterine size as well as the presence of contractions or tenderness to palpation. Though an external inspection is appropriate, *vaginal examination should not be performed in the ED* because it may precipitate severe hemorrhage and fetal compromise.

Ultrasonography is the diagnostic modality of choice for late pregnancy bleeding. The major purpose of ultrasonography is to locate the placenta and define its relationship to the cervix. In addition, information regarding gestational age and general fetal well-being may be obtained. Transabdominal ultrasound (TAS) is usually performed first but is noted to have a false-positive rate of 2% to 6% for placenta previa. False-positives can be caused by obesity, a posterior placenta, a full bladder, or a focal myometrial contraction. Endovaginal sonography (EVS) eliminates many of these false-positives and has been proven safe in many studies. Although TAS is easily performed in the ED and may yield helpful information, EVS should not be done in the ED in patients with third-trimester vaginal bleeding (1,4).

On the other hand, ultrasonography is insensitive for abruption. Findings in abruption are variable and are affected by the type of abruption (retroplacental or subchorionic) and the timing of the study in relationship to the onset of bleeding. Retroplacental bleeding may have a sonographic appearance very similar to that of a normal placenta, creating an area of thickened placenta or an area mistaken for a fibroid or contraction. Marginal bleeding may be recognized sonographically as a hematoma, although the amount of blood identified on ultrasound may significantly underestimate true losses. Evidence of abruption by ultrasound is helpful to the obstetrician in developing a care plan for the patient and can be followed up with serial examinations. A negative study does not eliminate abruption from the differential and, in fact, a patient with late pregnancy bleeding and an ultrasound negative for placenta previa is often assumed to have abruption. With abruption, fetal

monitoring becomes the primary tool for management decisions (1,5).

A vaginal examination is ideally performed after ultrasonography, by the obstetrician, in an operating suite capable of rapid surgical delivery with fetal resuscitation, in the event that severe bleeding is triggered. If immediate obstetric consultation is not available, patients with significant bleeding should be prepared for transport to a facility that is able to provide appropriate obstetric and neonatal services. In this situation, if the bleeding is not severe, a cautious vaginal examination in the ED is reasonable, after placenta previa has been excluded with transabdominal ultrasonography. The purpose of the examination is to exclude vaginal or cervical lesions that cause bleeding. Neither fingers nor instruments should be placed in the cervical os, because uncontrolled bleeding from a placenta previa can be triggered by such manipulation.

KEY TESTING

- Transabdominal ultrasonography to locate the placenta and obtain an overview of fetal age and status
- Fetal Monitoring should be initiated early
- Type and screen, CBC, PT, PTT, and fibrinogen level

ED MANAGEMENT

Prehospital triage of the woman with bleeding after 24 weeks of gestation (as estimated by the uterus being palpable above the umbilicus) should be to a facility that can manage a potentially high risk or premature delivery. The prehospital management should consist of assessment of the amount of bleeding from evidence at the scene and the degree of current perineal bleeding, administration of maternal supplemental oxygen, positioning of the patient on her left side, and intravenous administration of fluids en route.

For patients with late pregnancy vaginal bleeding, the ED should ideally be a place of cardiovascular stabilization and triage only; there is a paucity of evidence in this area, and case-by-case decision making by the obstetrics team is mandatory. If there is

hemodynamic compromise secondary to hemorrhage, fluid resuscitation should be initiated rapidly with crystalloid. In the mother with rapid exsanguination, O-negative blood and the use of massive transfusion protocols may be required. In cases of severe bleeding, especially with abruption, disseminated intravascular coagulation (DIC) should be anticipated. The blood bank should be notified of the potential need for fresh frozen plasma and platelets. Fetal heart rate should be quickly measured, with initiation of continuous monitoring if possible. Rapid transport to the obstetric suite is the goal (1,2,5).

In the patient with less emergent bleeding, referral to the obstetric unit is preferred for definitive diagnosis. The standard method of evaluation is ultrasonography followed by vaginal examination in a delivery suite, where the discovery of a fetus-threatening placenta previa can be treated with rapid delivery. In the patient with presumed or visible abruption, admission to a high-risk prepartum unit for continuous monitoring is appropriate. Continued fetal well-being should always be documented if the patient spends any significant time in the ED, because hypovolemia is frequently detected by signs of fetal distress before there are changes in the mother's vital signs. If the mother is Rh-negative (with an unknown or Rh-positive father) or if a Kleihauer–Betke test is positive for fetomaternal hemorrhage, RhoGAM should be administered. If fetomaternal hemorrhage in excess of 15 mL of fetal RBCs has occurred, additional RhoGAM may be necessary (consider 10 μg for every additional 0.5 mL fetal RBCs) (3).

CRITICAL INTERVENTIONS

- Do not perform an internal vaginal examination in the ED for third-trimester pregnant patients with vaginal bleeding.
- Provide aggressive volume resuscitation as appropriate. Anticipate the need for massive transfusion and DIC in patients with severe bleeding.
- Immediately consult an obstetrician or arrange transfer to a suitable facility if necessary.

DISPOSITION

All patients with late pregnancy vaginal bleeding require obstetric consultation. The only exception is the patient who is discovered to have bleeding from a nonvaginal source, such as an external hemorrhoid. If necessary, interfacility transfer to a high-risk unit should be accomplished after initial diagnosis or assessment by an obstetrician and is usually performed by specialized obstetric or high-risk neonatal transport units. In general, predelivery transport is safest and is associated with the best outcome, but it must be accomplished in a controlled fashion, with personnel capable of supporting the mother and managing fetal distress or a premature delivery en route.

Common Pitfalls

- Vaginal examinations should be limited to visual inspection of the perineum to look for obvious nonuterine bleeding sources. Fingers or instruments should *never* be placed in or near the cervix, as uncontrolled bleeding from a placenta previa can result.
- Coagulopathy should be considered in patients with severe hemorrhage, as clotting factors are consumed when significant bleeding occurs with abruption, and coagulopathy can seriously compromise the mother's ability to limit uterine bleeding.

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CHAPTER 142

Emergency Delivery

Michael D. Burg

Although the ED and the prehospital environment are suboptimal locations for deliveries, they can and do occur there. Exact incidence data for these deliveries are not available, but studies suggest that prehospital or ED deliveries are uncommon but not rare (1–5). These deliveries are associated with increased rates of maternal and neonatal complications (1,3).

The ED usually lacks sophisticated fetal monitoring devices, practiced obstetrical personnel, and advanced delivery technologies to optimize outcomes for mothers and babies. In addition, pregnant women who receive little or no prenatal care, abuse drugs or alcohol, and have limited access to healthcare are overly represented in the ED patient population (1,6).

CLINICAL PRESENTATION

Pregnant patients present to the ED with various delivery- and pregnancy-related conditions, including: premature rupture of the membranes (PROM), preterm labor, shoulder dystocia, preeclampsia and eclampsia, fetal distress, nuchal umbilical cord, breech presentations, postpartum hemorrhage, prolapsed umbilical cord, and meconium staining. Depending on practice setting and obstetric consultant availability, emergency physicians may be required to manage these patients. A basic understanding of these conditions and an organized approach to their management is essential for treatment of these stress-provoking, challenging patients. Patients in

the third trimester of pregnancy may also present with labor symptoms, such as pelvic cramping and low-back pain.

DIFFERENTIAL DIAGNOSIS

All near-term pregnant women presenting to the ED with abdominal pain should be considered to be in labor until proven otherwise. The challenge lies in differentiating true labor, false labor, and other disorders mimicking labor.

Consider preterm labor whenever a woman in the second half of pregnancy experiences recurrent abdominal or pelvic symptoms lasting more than 1 hour (7). Worldwide, about 10% of infants are born preterm and preterm births result in increased morbidity and mortality (8).

True labor is defined by regular, rhythmic, progressive uterine contractions producing effacement and dilation of the cervix (9). *False labor* (Braxton Hicks contractions) consists of short irregular uterine contractions without cervical effacement or dilation. Braxton Hicks contractions do not intensify in strength or frequency and tend to resolve with mild sedation and analgesia (9). False labor can stop spontaneously or progress to true labor. Alternatively, musculoskeletal low-back pain and many abdominal conditions, such as appendicitis, may be confused with labor pains.

ED EVALUATION

Assessment of a pregnant patient at >20 weeks gestational age with any complaint possibly referable to the pregnancy must include an evaluation for pregnancy-related problems. Fetal distress, preterm labor, imminent delivery, hemorrhage, severe preeclampsia, eclampsia, prolapsed umbilical cord, among other conditions may necessitate immediate ED management or transfer to L & D.

Perform a focused history and physical examination. Specific relevant history includes the presence and character of uterine contractions, vaginal fluid leakage, vaginal blood loss, and past medical and surgical history with an emphasis on obstetric and gynecologic history.

Scant dark vaginal blood loss generally signals “bloody show” or passage of the cervical mucous plug. Active or large-volume vaginal bleeding may indicate placenta previa (generally painless) or placental abruption (most often painful) (10).

Patients in active labor generally present with abdominal or back pain or cramps although some experience symptoms such as nausea, vomiting, urinary urgency, incontinence, and anxiety. Some – notably teenagers – may deny any possibility of pregnancy or missed menses.

Review the patient’s prenatal care record noting any complications associated with the present pregnancy. Detail the history of present illness. Fever, chills, headache, visual disturbances, seizures, excessive weight gain, fluid retention, and epigastric or right upper quadrant abdominal pain are important review of systems findings.

Maternal vital signs should be within the normal range for the stage of pregnancy and appropriate to the clinical setting. If fever, hypertension, hypotension, tachypnea, or tachycardia occur, they must be investigated.

Assess the fetal heart rate (normal third trimester range, 120 to 160 beats/min) with either hand-held Doppler or transabdominal ultrasound. Ultrasound allows a more complete pregnancy evaluation and reveals fetal presentation and gestational age, fetal cardiac activity and breathing, amniotic fluid volume, placenta previa, or placental abruption among other conditions.

Perform a general physical examination focusing first on the airway and cardiopulmonary system, neurologic function, and the gravid abdomen. Note any edema, particularly of the face and hands. Fluid retention often accompanies normal pregnancy; however, edema or proteinuria with hypertension, headache, or visual changes and right upper quadrant or epigastric discomfort suggests preeclampsia (7).

Abdominal examination, augmented by transabdominal ultrasound, concentrates on approximating the fetal age. In the hypotensive, tachycardic, or febrile gravida, important etiologic clues may be found during the abdominal examination. Place the

hypotensive gravida in left lateral decubitus position to reverse hypotension caused by the gravid uterus compressing the inferior vena cava and compromising cardiac filling. However in appropriate circumstances consider other causes of hypotension including blood loss, sepsis, and dehydration.

By 20 weeks of gestation, the uterine fundus is generally level with the umbilicus. From 20 to 34 weeks, the distance from the pubic symphysis to the fundus in centimeters approximates the gestational age in weeks (7).

Time permitting (and/or ultrasound unavailable) use Leopold Maneuvers to evaluate fetal position (Fig. 142.1). First palpate the uterine fundus to locate the head, or the buttocks and legs. Next, palpate the uterine sides to identify the fetal back. Finally, palpate just above the pubic symphysis to feel which fetal part is low in the pelvis. In most cases the round hard fetal head will be palpable in the lower pelvis. Ultrasound is far more reliable than these maneuvers to determine fetal lie (7).

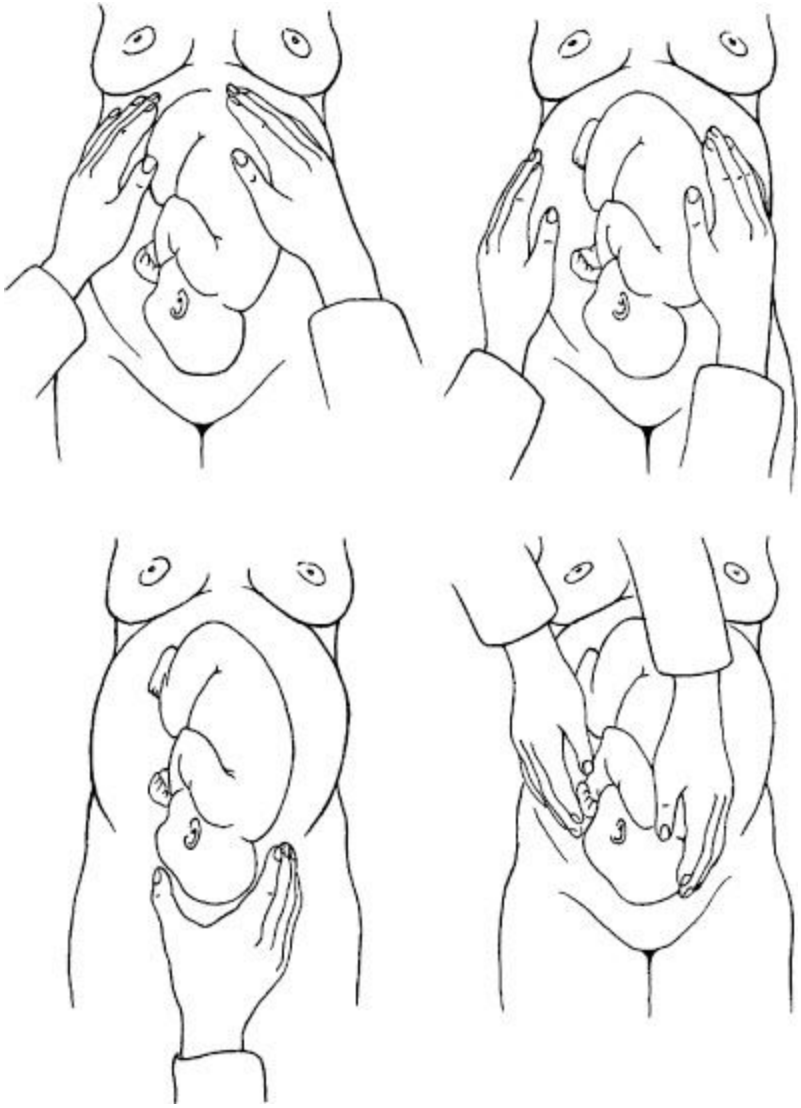

FIGURE 142.1 Leopold maneuvers to evaluate fetal position. (From Beckmann CRB, Ling FW, Laube DW, et al. *Obstetrics and Gynecology*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2002.)

After the abdominal examination, perform a sterile digital vaginal examination. Vaginal bleeding, which should trigger a concern for placenta previa or placental abruption, is a contraindication to digital vaginal examination. If either of these two entities is suspected, transfer the patient expeditiously to L & D for further evaluation and do not perform a vaginal examination in the ED (see Chapter 141).

Another contraindication to ED digital vaginal examination is suspected rupture of the membranes. Spontaneous rupture of the membranes (SROM), manifested by vaginal leakage of clear or faintly cloudy fluid, is defined as rupture of the chorionic and amniotic membranes and is confirmed by a nitrazine-paper test of pooled vaginal fluid or by microscope slide “ferning” (11,12). SROM may occur before or during active labor and should be strongly suspected on the basis of patient history or when fluid is observed flowing from the cervical os or is seen pooling in the vagina. The nitrazine paper test relies on the fact that amniotic fluid pH approximates that of serum and will turn the normal yellow nitrazine-impregnated paper blue. Vaginal fluid has a more acidic pH. Amniotic fluid forms a characteristic fernlike appearance (ferning) when it is allowed to air-dry on a glass microscope slide (12).

Diagnosing SROM is an important decision branch point for three reasons. First, SROM may signal the onset of active labor (11). Second, umbilical cord prolapse through the cervical os may occur as intrauterine fluid volume suddenly decreases. Third, the risk of intrauterine infection rises with increasing time after SROM (12). To minimize the risk of intrauterine infection (chorioamnionitis or endometritis), a sterile speculum examination should be performed if membrane rupture is suspected and the number of such examinations should be minimized. During the sterile speculum examination, the cervical length, dilation, and consistency are evaluated visually, *not* manually (12).

The primary purpose of the vaginal examination is to evaluate labor progression by assessing cervical effacement (thinning), cervical dilation, and fetal station. Cervical effacement is expressed as a percentage from 0 to 100, with 0% representing a completely uneffaced cervix (about 2 cm in length) and 100% representing a maximally thinned cervix. Cervical dilation refers to the os’s diameter. A 10-cm cervical os is completely dilated. Fetal station is determined by comparing the level of the presenting fetal part to the maternal ischial spines, which represent zero station. Negative station indicates that the presenting fetal part is above the level of

the spines, and positive station indicates that the presenting part is below the level of the spines (7).

PROM refers to membrane rupture before labor onset and occurs in up to 8% of pregnancies. PROM prior to 37 weeks gestational age is preterm PROM (7).

Preterm labor diagnosis is sometimes difficult because of nonspecific symptoms at presentation. Generally, a gravida at <37 weeks gestational age, with regular contractions, cervical dilation of 3 cm or more, and effacement of 80%, is considered to be in preterm labor. Serial examinations are indicated in patients with contractions and only minimal cervical dilation. Ultrasound-aided assessment of fetal breathing may help discriminate between the true and the false labor, as the fetus usually stops breathing in true labor. A high correlation between preterm PROM and preterm labor has been observed. Intrauterine death, nonviability of the fetus, and pregnancy-related maternal medical problems that require early delivery (e.g., severe preeclampsia) are contraindications preterm labor treatment (7).

Laboratory tests, if not already documented, include complete blood cell count, blood type and Rh status, antibody screen, rubella titer, and tests for syphilis, hepatitis and HIV, among others, depending on clinical considerations.

KEY TESTING

- Ultrasound, fetal monitoring
- Ferning and nitrazine

ED MANAGEMENT

Preterm Labor

The preterm labor treatment goal is to prevent or postpone delivery between 22 and 34 weeks gestational age. Unless contraindications exist, begin medical management with admission for lateral decubitus bed rest and maternal hydration. Use tocolytics—uterine contraction suppression agents—to prevent or delay preterm delivery. During the time gained by tocolysis, medications to

stimulate fetal lung maturation are given, and transfer to a facility with specialized neonatal care is arranged (7).

Management controversies exist, but prostaglandin inhibitors (i.e., indomethacin) are reasonable first-line tocolytics. Nifedipine can be used as well. Give 10 mg orally with repeated doses every 15 minutes to a total of 40 mg within the first hour if initial doses are ineffective. Hold for hypotension. If possible, consult an obstetrician before using magnesium sulfate since it may be ineffective and possibly associated with increased infant mortality (13,14).

Tocolysis fails in many patients but treatment may provide time for transfer and the start of fetal lung maturation therapy.

Normal Delivery

Normal delivery involves uterine expulsion of the products of conception—fetus, placenta, and membranes—by the combination of involuntary uterine contractions and voluntary muscular efforts. It is a physiologic—not a pathologic—process; therefore physician involvement in a normal delivery often consists of facilitation and support (5).

Labor is divided into three stages, with phases within to follow its progression and to help identify problems requiring physician intervention (5).

The first stage (cervical stage) begins when contractions become regular and progressively stronger, longer, more frequent, and coordinated (latent phase). Its duration is variable—a few hours to several days—depending on maternal factors. Cervical effacement with minimal dilation generally occurs. With care not to rupture membranes prematurely, identify presenting parts and determine fetal station. Frequent vaginal examinations are unnecessary and increase infection risk (9). The active phase of cervical dilation follows, and is usually shorter, averaging 5 hours in nulliparas and 2 hours in multiparas. The deceleration phase, marked by slowing cervical dilation signals the end of the first stage. Depending on local resources and transfer time, patients in the first stage may be considered for transfer to an obstetrician.

The second stage of labor commences with full cervical dilation and the woman experiencing an urge to push. It culminates with newborn delivery. To facilitate assessment and intervention, position the parturient in either the dorsal lithotomy or left lateral decubitus position. Cleanse and sterilely drape the perineum. Don universal precautions.

During labor's second stage, strong regular 1- to 2-minute uterine contractions occur in 3- to 5-minute cycles. During contractions, encourage efforts to bear down; between contractions, encourage rest. Assess fetal heart rate after each contraction. Between contractions, periodically perform sterile digital vaginal examinations to evaluate labor's progression. Coach the parturient during contractions and communicate calmly between contractions to facilitate a coordinated controlled delivery. Delivery is eminent when the presenting part begins to distend the perineum. During this critical interval, instruct the parturient to pant, not push, allowing slow crowning and controlled delivery of the head.

Episiotomy use in normal delivery has diminished but indications include malpresentations, shoulder dystocia, and eminent perineal tear. A description of this procedure can be found in standard obstetrics texts (7,9).

Use the modified Ritgen maneuver to promote delivery while minimizing maternal perineal injury. Apply direct pressure to the perineum with a draped hand (indirectly putting pressure on the fetal chin), to effect slight fetal head extension. Simultaneously, place your other hand gently on the fetal head, positioning it with its smallest diameter as the presenting part and preventing uncontrolled fetal head movement as it clears the perineum (5,9).

As the head delivers, it will rotate transversely. If a nuchal cord is seen, slip it gently over the fetal head. Doubly clamp and cut an irreducible nuchal cord and perform a rapid delivery. In conjunction with controlled minimal maternal efforts, apply gentle bimanual traction on the fetal head, downward initially then upward, to deliver the anterior and posterior shoulders, respectively. After the shoulders deliver, the body will follow easily. Position the newborn slightly lower than or even with the perineum until the umbilical

cord is clamped and cut. Cut the cord between clamps 4 to 5 cm apart with the proximal clamp applied 5 to 10 cm from the newborn's abdomen (7,9). Dry, bundle, and present the newborn to the mother.

The second stage of labor averages 50 to 60 minutes in nulliparas and 15 to 20 minutes in multiparas (7).

Labor's third stage begins after newborn delivery and ends with placental delivery, usually within 30 minutes. Signs of eminent placental delivery include umbilical cord lengthening, a gush of uterine blood, and the uterus becoming more globular and rising in the abdomen. Maternal efforts are usually sufficient to deliver the placenta but can be aided by *gentle* umbilical cord traction. Keep in mind that uterine inversion is a potentially disastrous complication of pulling on the cord (7). Apply manual pressure just superior to the pubic symphysis to help prevent uterine inversion (5,7). Inspect the placenta and membranes for completeness. Consider manual removal if the placenta is incompletely delivered at 30 minutes (7).

After delivery assess the uterus frequently for an appropriately contracted postdelivery state. Massage the uterus to maintain uterine tone. In addition, titrate oxytocin to decrease the risk of postpartum hemorrhage due to uterine atony.

Perform an initial newborn assessment. Examine the mother for birth canal and perineal tears—which can cause significant blood loss—and repair these promptly (5).

SHOULDER DYSTOCIA

Failure of delivery of the shoulders after delivery of the head (usually due to impaction of a fetal shoulder against the pubic symphysis) is termed shoulder dystocia and complicates up to 2% of vaginal deliveries (12,15,16). The risk of shoulder dystocia rises with fetal weight. Suspect this complication when the anterior shoulder fails to deliver or when the fetal head appears and then retracts into the introitus ("turtle" sign) (12).

Shoulder dystocia contributes to neonatal morbidity and mortality and is associated with aspiration, asphyxia, brachial plexopathies,

and humeral and clavicle fractures (5,15). Maternal postpartum hemorrhage risk is increased as well (15).

Manage this complication by reducing time between delivery of the fetal head and body and minimizing traction on the fetal head and neck, which can worsen the shoulder impaction and/or cause fetal injury (5). A variety of maneuvers to accomplish these goals have been described and it is unclear about which of them—alone or in combination—is best (15–17). While calling for obstetrical back-up consider the following:

- Bladder drainage—creates anterior space.
- Episiotomy—may allow posterior shoulder delivery.
- Hyperflex the maternal thighs onto the abdomen (McRoberts maneuver) (Fig. 142.2)—moves the pubic symphysis anteriorly and cephalad, may allow delivery of the impacted shoulder.

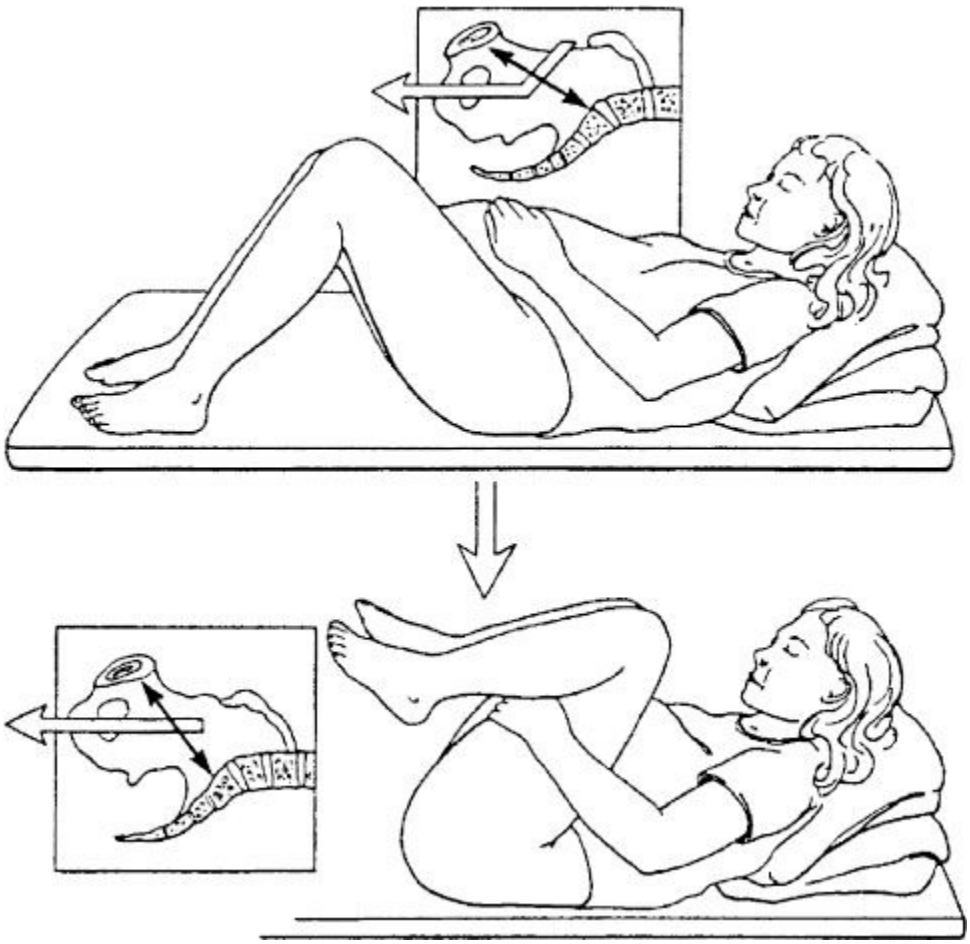

FIGURE 142.2 Hyperflexion of the hips improves pelvic alignment in the management of shoulder dystocia. (From Beckmann CRB, Ling FW, Laube DW, et al. *Obstetrics and Gynecology*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2002.)

- Having an assistant apply maternal suprapubic pressure while you apply gentle downward traction on the fetal head.

The combination of McRoberts maneuver and suprapubic pressure resolves a substantial number of shoulder dystocias and is safe, quick, simple, and noninvasive. In addition, the "all-fours" maneuver alone (placing the parturient on her hands and knees) resulted in an 83% success rate in one 1998 study (15). More recently, axillary traction has been proposed as a simple effective way to resolve shoulder dystocia after McRoberts maneuver and suprapubic pressure have failed. In this technique, the operator slides his index digit into the posterior axilla, and—with his thumb over the clavicle and his long digit over the proximal humerus—applies axillary traction following the maternal sacral curve, delivering the posterior shoulder first while the anterior shoulder pivots around the pubic symphysis (17). This technique has not been well studied.

Fetal Distress

Measure the fetal heart rate every 15 minutes during labor stage 1 and every 5 minutes during labor stage 2 using Doppler or ultrasound. Begin your assessment at the end of a contraction and continue for a minute. During the third trimester, normal fetal heart rates range from 120 to 160 beats/min (18).

A sustained fetal heart rate >160 beats/min is fetal tachycardia, possibly a manifestation of maternal temperature elevation, medications, fetal distress, and others. Brief (<20 seconds) fetal heart rate accelerations occur often during labor and are normal (9).

Fetal bradycardia is a heart rate <120 beats/min. Brief bradycardic spells—during contractions and ending shortly thereafter—are normal (early decelerations) and likely due to

pressure on the fetal head. Fetal heart rate slowing which lasts long after contractions may signal uteroplacental insufficiency (late decelerations). Decelerations unrelated to uterine contractions may indicate umbilical cord compression (9).

Nuchal Umbilical Cord

After fetal head delivery, check for a nuchal cord visually and manually with a finger sweep of the neck. This occurs commonly, although some reduce spontaneously. Occasionally, two or more nuchal cord loops are found. If possible, simply lift the cord loops up and over the fetal head. If the cord loops will not reduce easily, doubly clamp and cut the cord and rapidly complete the delivery (9).

Breech Presentation

This occurs when the fetal buttocks or legs are closest to the cervix (and consequently deliver first) and complicates a small percentage of deliveries. Breech presentations are closely associated with prematurity and birth weight. Predisposing factors include congenital and uterine abnormalities. Breech presentations heighten perinatal morbidity and mortality risk (7).

Suspect breech presentations during Leopold maneuvers (Fig. 142.1) or during examination of the dilated cervix. Confirm with ultrasound.

Breech delivery is difficult because the presenting parts insufficiently dilate the cervix while successively larger and less compressible parts (especially the fetal head) attempt to pass. Fetal head entrapment and umbilical cord prolapse can occur (5,7).

Breech presentation delivery methods and cesarean section indications can be found in obstetrics texts (7). Immediately consult an obstetrician if a breech presentation is confirmed or suspected.

Prolapsed Umbilical Cord

Umbilical cord passage through the cervix before the presenting fetal part is termed umbilical cord prolapse. It is uncommon but potentially lethal and must be recognized and managed expeditiously (7,19).

Amniotic membrane rupture with a sudden decrease in intrauterine fluid volume is a risk factor for cord prolapse. Suspect cord prolapse and compression if fetal bradycardia occurs (19).

If fetal distress/bradycardia occurs, immediately perform a vaginal examination to check for cord prolapse. Treat by elevating the presenting part off the umbilical cord to restore fetal blood flow (19). Maintain this elevation until delivery occurs (usually by cesarean section) and avoid umbilical cord manipulation (7,19).

Meconium Staining of Amniotic Fluid

Meconium is fetal fecal material and contaminates amniotic fluid in a substantial number of deliveries. Meconium aspiration can cause lung disease and death.

Routine intrapartum suctioning of infants exposed to meconium is no longer recommended. However, endotracheal intubation and tracheal suctioning are indicated for those with respiratory depression (20).

Perimortem Cesarean Section

For pregnant cardiac arrest patients $\leq$24 weeks gestational age consider perimortem cesarean section as a potential lifesaving intervention for the mother and fetus (12,18). Continue resuscitation during and after the procedure because maternal survival after perimortem cesarean section has been reported. Perform the procedure within 5 minutes of maternal arrest to optimize the outcome (18). Obtain immediate obstetric, surgery, and neonatal consultations.

To perform the procedure, create a vertical midline incision into the peritoneal cavity from the maternal epigastrium to the public symphysis. Avoiding bowel and bladder and the underlying fetus, incise the uterus from the fundus to the bladder reflection. Remove

the fetus and doubly clamp and cut the umbilical cord. Consider removing the placenta as well. Within reason, employ sterile/clean surgical technique throughout, provide hemostasis and minimize damage to adjacent maternal organs (10).

CRITICAL INTERVENTIONS

- Attempt to resolve shoulder dystocia with appropriate maneuvers
- Reduce a nuchal umbilical cord
- Elevate the presenting part off of a prolapsed cord
- Obtain early, emergent obstetrics consultation

DISPOSITION

Unless delivery is eminent, transfer preterm labor patients to an obstetric unit capable of providing the required care. If transfer of preterm labor patients is not possible, initiate emergent care as necessary and obtain immediate obstetrical consultation and involvement. Move patients who deliver in the ED to L & D for postdelivery obstetrical care. Patients with delivery complications or episiotomies require postdelivery evaluation and treatment by an obstetrician. Well-appearing term newborns should be transferred to the nursery. Preterm newborns and those in distress require ED resuscitation and transfer to a neonatal intensive care unit.

Common Pitfalls

- Failure to diagnose preterm labor.
- Failure to diagnose and prepare for eminent delivery.
- Failure to obtain early obstetrical consultation.
- Failure to recognize nonspecific signs and symptoms (i.e., low-back pain, abdominal pain) as labor.
- Lack of equipment and expertise for critical neonatal and maternal care.

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CHAPTER 143

Postpartum Emergencies

Moss H. Mendelson and Joseph P. Lang

Patients present to the emergency department (ED) with a variety of diseases in the postpartum period. Anatomic and physiologic changes before, during, and after delivery predispose to many of them, and some are life-threatening.

In the third trimester, maternal blood volume is 35% to 50% higher than normal, the plasma volume is increased by 1,200 mL, and the red blood cell volume is increased by 250 mL. Cardiac output is increased by about 1.5 L/min; 600 mL/min of blood flows through the placental site at term. Consequently, uterine and ovarian veins handle a 60-fold increase in volume during pregnancy. In addition, the hypercoagulable state of pregnancy and the trauma from delivery predispose to disseminated thrombosis in the puerperium, experienced as deep venous thrombosis (DVT) or cerebrovascular accident.

The postpartum uterus returns to its nonpregnant anatomic shape and position by loss of cellular fluid and protein and consequent reduction in cell size. Most involution occurs in the first week postpartum. The uterus resumes its intrapelvic position by 2 weeks and normal size by palpation at 6 weeks postpartum. The mean time to ovulation is 70 to 75 days in nonlactating mothers and 190 days in those who lactate. Vaginal bleeding generally diminishes several hours after delivery to a red-brown discharge, which may last through day 3 or 4 postpartum. A mucopurulent discharge may wax and wane over 4 to 6 weeks. Menstruation resumes by about 12 weeks in most nonlactating women (mean, 7 to 9 weeks) but may be delayed in breastfeeding mothers up to 36 months.

POSTPARTUM HEMORRHAGE

Clinical Presentation

Postpartum hemorrhage may be divided into early (<24 hours) and late (between 24 hours and 6 weeks) presentations (Table 143.1). Early postpartum hemorrhage is most often due to uterine atony. Bleeding can be brisk, and shock can develop rapidly. Maternal vital signs are often falsely reassuring, and blood loss can be hidden within the uterus and/or pelvis, making recognition of significant bleeding difficult in some cases. Late causes of hemorrhage include infection, delay in placental site involution, and retained placental parts. There may also be a normal, transient increase in bleeding in the second postpartum week owing to sloughing of the eschar that covers the placental attachment site (1).

TABLE 143.1
Causes of Postpartum Hemorrhage

Early Hemorrhage (<24 hrs)
Uterine atony
Genital tract laceration
Retained placental parts
Placenta accreta
Hematoma
Uterine inversion
Uterine rupture
Coagulopathy
Late Hemorrhage (up to 6 wks)
Infection (endometritis)
Retained placental parts
Delayed placental site involution
Sloughing of placental site eschar

Differential Diagnosis

Uterine atony is responsible for most cases of early postpartum hemorrhage. Failure of the uterus to contract properly allows continued blood loss from the placental site. Myometrial

dysfunction occurs more frequently if the uterus has been overdistended (multiple gestations, hydramnios, multiparity, and macrosomia); if there has been precipitous or prolonged labor, general anesthesia, or previous postpartum hemorrhage; if leiomyomas or amnionitis is present; or if fetal demise or amniotic fluid embolus occurs. Adherent fragments of placenta can also interfere with myometrial contractile function.

Minor *pelvic trauma* occurs in almost all deliveries. However, some vaginal and cervical lacerations may lead to severe hemorrhage. Pelvic vessels can be injured in the process of delivery, causing a pelvic hematoma. Vulvar hematomas are the most common; because the bleeding is bounded by superficial fascial planes, the hematoma usually dissects to the skin and is visible. Deeper vaginal hematomas can be occult and accumulate a significant amount of blood, extending into the pelvic space under the peritoneum. Patients may present with complaints of rectal pressure. Retroperitoneal hematomas are the least common but most dangerous type of hemorrhage. They are associated with significant blood loss, usually the result of trauma to a branch of the hypogastric artery, and can present with shock.

Retained placenta is a common cause of both immediate and late postpartum hemorrhage. Premature, assisted delivery of the placenta increases the risk for retained fragments, which can result in impairment of full uterine contraction and failure to develop hemostasis. *Placenta accreta,* an abnormally deep attachment of the placenta to the myometrium, is suspected if placental delivery is difficult and no cleavage plane between placenta and uterus is found at manual exploration (2,3).

Uterine inversion is uncommon and is more likely if traction is exerted on the umbilical cord. Inversion is usually recognized soon after delivery of the placenta. If the uterine corpus passes through the cervix, the inversion is complete; if not, it is incomplete and may be occult. The patient presents with acute onset of abdominal pain, hemorrhage, and shock. Often, hypotension occurs before significant visible blood loss (4).

Uterine rupture can be catastrophic and often results in fetal and even maternal demise, although the clinical spectrum of morbidity is broad. Factors associated with a rupture include previous curettage, cesarean section (especially with a high uterine incision) or rupture, hydramnios, multiple fetuses, and placenta accreta. Although more common in a previously scarred uterus, rupture of the nonscarred uterus does occur.

Coagulopathy can complicate postpartum hemorrhage of any etiology. In addition, abruption, amniotic fluid embolus, and pregnancy-induced hypertensive disease can cause consumptive coagulopathy, thereby leading to postpartum hemorrhage.

The differential diagnosis of late postpartum hemorrhage includes endometritis, retained placental parts, placental site subinvolution or eschar sloughing, and resumption of menses (1).

ED Evaluation

The care of the patient with postpartum bleeding should begin with an assessment of the extent of blood loss along with concomitant resuscitation if hypovolemia and/or shock are present. In all cases of significant immediate postpartum bleeding, laboratory studies should include a complete blood count (CBC) and coagulation studies. Early establishment of vascular access is critical. A sample should be sent to the blood bank in case transfusion is necessary.

Abdominal and bimanual examinations are necessary to identify the size, position, shape, and tone of the uterus, and the placenta (if available) should be inspected for completeness.

Ultrasonography may aid in narrowing the differential in stable patients with both early and late postpartum hemorrhage. Ultrasound of the uterine cavity can be used to help rule out retained placental tissue by demonstrating a normal uterine stripe. Ultrasound may also be able to distinguish between retained tissue (echogenic mass) and a large intrauterine clot (sonolucent). Occult hematomas can be identified and those patients rapidly triaged to angiography and subsequent embolization. Computed tomography (CT) scanning, although more time-consuming, may also show

hematomas that would be amenable to percutaneous drainage (5). However, the exact role of CT in the patient with postpartum hemorrhage remains unclear.

KEY TESTING

- CBC, coagulation studies, type, and screen
- Ultrasound

ED Management

Patients with significant blood loss require aggressive resuscitation with IV fluids and blood transfusion as needed. If the uterus feels boggy and *uterine atony* is suspected, manual massage should be performed as follows: One hand massages in a circular fashion on the abdomen, with intravaginal fingers massaging the uterus upward. Massage may cause temporary uterine contraction, with recurrent bleeding after relaxation. Pharmacologic treatment (Table 143.2), started concomitantly, includes drugs that increase uterine muscular tone (oxytocin, prostaglandins, and ergot alkaloids). Intravenous infusion of oxytocin is the first-line treatment.

TABLE 143.2
Medical Management of Uterine Atony

Drug	IM Dose	IV Administration	Side effects
Oxytocin	10 U	20–30 U in 1 L normal saline at 200 mL/hr	Hypotension if given as bolus; cramping
Ergonovine maleate	0.2 mg		Cramping
Methylergonovine	0.2 mg		Cramping
15-Methyl-prosta-glandin	0.25 mg		Nausea and vomiting

IM, intramuscular; IV, intravenous.

If bleeding continues, the birth canal should be inspected for trauma. Vaginal or cervical lacerations longer than 2 cm or those that are bleeding should be repaired. Adequate exposure is needed,

which may require general anesthesia and an OR suite. With persistent bleeding or a placenta that appears incomplete, digital exploration of the uterine cavity may be indicated to look for retained placental fragments or uterine rupture. If placental elements remain, an obstetrician should be consulted for further management (2).

Management of *uterine inversion* includes manual restoration of uterine anatomy, followed by removal of the placenta if it remains attached. Manual replacement through the vagina is usually successful. The uterus is compressed between both hands intravaginally and gradually replaced. General anesthesia or tocolytics may be required to allow adequate uterine relaxation. Only after replacement of the uterus oxytocin is started (3).

Refractory bleeding from any source may require emergent surgical intervention or arterial embolization by an interventional radiologist. Uterine rupture, once diagnosed, almost always requires surgery. Retroperitoneal hematomas frequently require invasive intervention. Increasingly, angiographic embolization is being utilized in refractory cases of bleeding. Very high success rates for embolization have been cited, even in cases that have failed traditional surgical intervention. Its use depends upon local resources, availability, and skill levels of the personnel involved (6). Intrauterine tamponade with packing or a balloon device is a temporizing measure that should be considered as surgical or embolization intervention being mobilized. Balloon devices specifically designed for uterine tamponade are simple to use and are gaining acceptance over more traditional methods such as gauze packing (2,7).

Traditional therapy of late postpartum hemorrhage has been curettage. However, placental tissue is often not retrieved, and bleeding may worsen after the procedure. With the ability of uterine ultrasound to rule out retained placental parts, the initial therapy now focuses upon pharmacologic management (Table 143.2). If bleeding stops, the patient should be observed, but curettage may be indicated if bleeding persists or if retained placenta is seen by ultrasound (1).

CRITICAL INTERVENTIONS

- Initiate uterine massage and oxytocin therapy for suspected uterine atony.
- Resuscitate hypovolemic patients with IV fluids and blood products as needed.

Disposition

Many causes of early postpartum hemorrhage are best treated in the labor and delivery suite, where obstetric surgical facilities, including general anesthesia and skilled personnel, are available. The disposition of a patient with late postpartum hemorrhage depends on the amount of bleeding, the response to initial therapy, and the probable cause of the bleeding. Decisions are best made in consultation with the patient's obstetrician.

Common Pitfalls

- Underestimation of blood loss in postpartum hemorrhage. Visual estimations are notoriously inaccurate, and young women may have significant blood loss without developing typical signs of hypovolemia.
- Failure to administer oxytocin, even if uterine atony responds rapidly to manual massage. Oxytocin should be given as well to prevent subsequent uterine relaxation.
- Failure to detect a significant vaginal laceration, the second most common cause of postpartum hemorrhage

PUERPERAL FEVER

Clinical Presentation

Fever in the postpartum period may be classified as early (<48 hours) or late (>48 hours, <6 weeks). Patients may present with symptoms and signs that make the diagnosis obvious, such as findings associated with respiratory or urinary tract infection (UTI). Many causes of puerperal fever, however, have nonspecific

presentations. Lower abdominal pain may be due to persistent contractions or inflammation. Vaginal discharge can be scant or profuse in the face of endometritis or normal involution. Abdominal tenderness and foul-smelling lochia are nonspecific signs, as the tachycardia and decreased bowel sounds. Wound sites should always be examined for tenderness, dehiscence, induration, edema, erythema, and discoloration. Mastitis presents initially with fever, flu-like symptoms, and usually a localized, painful site in the affected breast, with erythema and induration. Septic thrombophlebitis may present with refractory fever or symptoms of pulmonary embolism (PE).

Differential Diagnosis

Early infections most often occur in the uterus and peritoneum after cesarean section or are related to the urinary or respiratory tracts. Late infections include uterine infection after vaginal delivery (usually the result of ascending endogenous organisms), abdominal and episiotomy wound infections, breast infections, or other complications such as abscess or thrombophlebitis. Table 143.3 outlines common causes of puerperal fever.

TABLE 143.3
Causes of Puerperal Fever

Site	Examples	Comment
Pelvic	Endometritis	Single most common cause of puerperal fever; suspect especially after cesarean section
	Wound infection	Requires local exploration, opening, and debridement
	Necrotizing fasciitis	Surgical emergency
	Pelvic abscess	Diagnosed by ultrasound
	Septic thrombophlebitis	Suspect with failure to respond to antibiotics for endometritis
Urinary	Pyelonephritis	Catheterized UA for diagnosis
Pulmonary	Atelectasis	
	Pneumonia	
Breast	Engorgement	Within 24–28 hrs; diffuse, bilateral erythema and distention
	Milk stasis	
	Mastitis	Fever, flu-like symptoms; focal erythema and tenderness
	Breast abscess	
Other	Bacteremia	
	Sepsis	
	Endocarditis	
	IV site	
	Viral syndrome	

UA, urinalysis; IV, intravenous.

Endometritis is infection of the endometrium (the decidua and adjacent myometrium), but often the process extends beyond the uterus into the parametrial tissue, causing a diffuse pelvic cellulitis. The incidence of postpartum uterine infection is 1% to 6% in vaginally delivered women (8). Cesarean section increases both the frequency and the severity of infection: Endometritis occurs in up to 10% to 20% of patients undergoing cesarean section, despite prophylactic antibiotics (9). Other risk factors include premature rupture of membranes, prolonged time from rupture of membranes to delivery, the number of cervical examinations performed, intrauterine manipulation, preterm labor, and low socioeconomic status. Endometritis can lead to sepsis, peritonitis, adnexal infections, pelvic abscess, septic pelvic thrombophlebitis, parametrial phlegmon, and toxic shock syndrome.

Most endometritis is the result of ascending, polymicrobial infection of normal cervicovaginal flora or pre-existing genital tract infection. The placental attachment site and the tissue trauma associated with delivery provide good growth media for bacteria.

Wound infections complicate about 3% of deliveries. Most infections are caused by skin or genital tract flora. Common pathogens include *Staphylococcus aureus,* groups A and B streptococci, *Escherichia coli, Proteus* species, and anaerobes (especially *Clostridium* and *Bacteroides*). If cesarean section is performed emergently or amnionitis is present, a higher rate of wound infection is noted. Many patients initially are given a diagnosis of endometritis but, despite antibiotic therapy, continue to spike temperatures because they require debridement and drainage (9). Complications of wound infection include wound dehiscence, gangrene (especially *Clostridium* species), necrotizing fasciitis (most commonly group A β-hemolytic streptococcal infection), and toxic shock syndrome.

Episiotomy and pelvic floor infections are an uncommon complication of deliveries. The fascial anatomy dictates the depth and spread of the infection and may obscure the findings. Causative bacteria include streptococci and staphylococci, gram-negative enterics, and *Bacteroides* species. Most infections are superficial and mild, limited to the skin and superficial fascia in the area adjacent to the episiotomy. More extensive disease can involve Scarpa fascia, causing a potentially life-threatening necrotizing fasciitis (8).

Septic pelvic thrombophlebitis develops from an infection of the placental site and associated thrombosed myometrial veins. Once established, the process can proceed beyond the local venous system to include the vena cava. Most often the process is unilateral and right-sided. Septic pelvic thrombophlebitis is most common after cesarean section.

Normal breast engorgement consists of distended, firm, nodular breasts in the first 24 to 48 hours postpartum, while lacteal secretion is developing. The condition is painful and often associated with mild transient fever. Milk stasis is the result of incomplete emptying of the milk glands. In 1% to 2% of postpartum

women mastitis develops, which is usually seen 2 to 6 weeks after delivery. *S. aureus* is the most common causative agent.

ED Evaluation

After a detailed obstetric history is taken, the examination should focus on the genital tract, wounds, the breasts, and the urinary and respiratory systems. Examination may reveal tenderness of the lower abdomen and a purulent or foul-smelling lochia. The uterus may be tender and boggy, with parametrial thickening. If an adnexal mass is palpable, it might represent an abscess or an infected hematoma. The entire perineum and genital tract should be inspected for signs of infection from a laceration or episiotomy. A rectovaginal examination should help identify parametritis or other abscesses or hematomas.

Laboratory evaluation should include blood cultures, a CBC, and a urinalysis. Endometrial culture should be considered but may be difficult to interpret because of cervical contamination. Chest x-ray may be indicated if pulmonary symptoms are present, and plain films of the pelvis may reveal soft-tissue gas if necrotizing fasciitis is present.

Further imaging studies may be helpful in puerperal fever when the source is unclear or there is no clinical response to initial antibiotic therapy. CT scanning in endometritis shows intrauterine debris, fluid, and gas in some patients. Ultrasound may reveal endometrial gas, which is sometimes associated with infection but is also seen in clinically well women. Ultrasound, CT scanning, and magnetic resonance imaging can be helpful in the diagnosis of several occult, intrapelvic, infectious sources, such as abscess, infected hematoma, and septic thrombophlebitis. Generally, ultrasound is the initial imaging study, with CT reserved for those with a negative or equivocal ultrasound. Pelvic venography may be required to diagnose septic thrombophlebitis (10).

KEY TESTING

- Ultrasound or CT scan for suspected pelvic abscess

ED Management

Endometritis is treated empirically. If the patient is toxic or has underlying medical problems (e.g., diabetes), or the clinician suspects anaerobic infection, clindamycin and gentamicin or clindamycin and a third-generation cephalosporin should be given. Ampicillin–sulbactam (Unasyn), ticarcillin–clavulanate (Timentin), piperacillin-tazobactam (Zosyn), and imipenem–cilastatin (Primaxin) are all effective single, broad-spectrum antibiotics (11). Data on the outpatient treatment of endometritis are limited. Most patients will require admission, although in some with mild late disease, oral agents can be appropriate. Consultation with an obstetrician is prudent prior to discharge.

Treatment of a wound infection may include opening and debriding the area under adequate anesthesia. If more than local cellulitis is suspected, exploration under general anesthesia should be considered. Necrotizing fasciitis is a surgical emergency requiring immediate consultation. Mortality approaches 100% in patients treated with antibiotics alone and drops to 50% with combined surgical and pharmacologic treatment. Abscesses and some superficial hematomas can be incised and drained (8).

If *septic thrombophlebitis* is suspected, anticoagulation and antibiotics for 7 to 10 days are usually necessary. The incidence of heparin-related bleeding in the postpartum state is low (1% to 2%). Low–molecular-weight heparins (such as enoxaparin) may be used in place of the more traditional use of heparin. Although it is widely prescribed, the utility of anticoagulation has been questioned in several small studies that found no benefit compared to the use of antibiotics alone (10).

Mastitis is usually treated with dicloxacillin or clindamycin orally, along with continued emptying of the breast. With prompt treatment, mastitis usually resolves within 48 hours. Breastfeeding can continue unless an abscess has formed. If an abscess has occurred, drainage is necessary, and breastfeeding should stop. If milk stasis develops without infection, more efficient emptying of the breast is needed. Nursing should continue, and treatment

includes breast support, ice, and analgesia. If the patient is not breastfeeding and conservative methods are not sufficient for relief of pain, suppression of lactation may be helpful. Bromocriptine has been withdrawn for lactation suppression, but other agents are available. Consultation with the obstetrician is indicated.

CRITICAL INTERVENTIONS

- Initiate parenteral broad-spectrum antibiotic therapy for febrile postpartum patients with endometritis.

Disposition

The disposition varies with the type and severity of illness. Patients with mastitis and minor wound infections may be treated as outpatients. Those with more severe infections, including necrotizing fasciitis, septic thrombophlebitis, deep abscesses, and most cases of endometritis, require inpatient parenteral antibiotic therapy.

Common Pitfalls

- Failure to aggressively resuscitate the patient with necrotizing fasciitis, which requires emergent surgical consultation, aggressive debridement, and antibiotic therapy.
- Failure to consider nongynecologic sources of postpartum fever, such as UTI or pneumonia.
- Assuming that breast pain and fever in the first 2 to 4 days postpartum are caused by mastitis. Engorgement often causes these symptoms and does not require antibiotics.

OTHER POSTPARTUM EMERGENCIES

Hypertensive Disease

Pregnancy-related hypertension is classified as *preeclampsia* and *eclampsia,* chronic hypertension, preeclampsia superimposed on chronic hypertension, and transient hypertension. These disorders occur most commonly in the antepartum setting and are discussed

in detail in Chapter 140. However, it should be noted that preeclampsia and eclampsia can both occur postpartum. Treatment is the same as for antepartum patients. New-onset preeclampsia or eclampsia requires admission to the hospital, often in the ICU, and should be managed by an obstetrician.

Neurologic and Endocrine Disease

The onset of some neurologic and endocrine disorders may occur during the weeks after delivery. Postpartum ischemic necrosis of the anterior pituitary (*Sheehan syndrome*) is a complication that may develop if severe postpartum hemorrhage with shock has occurred.

Postpartum *thyroiditis* can develop up to a year after delivery. It is three times more prevalent in type I diabetics. Symptoms of hyperthyroidism generally include fatigue and palpitations, and most commonly occur within 1 to 6 months after delivery. Antithyroid medication is not needed in most cases, as spontaneous resolution occurs in two-thirds. A small number of patients develop persistent hypothyroidism and require thyroid hormone replacement. Hypothyroidism should be considered in the differential of patients with postpartum depression (12).

In postpartum patients with headache, the differential is generally the same as in any other patient, but a few additional causes should be kept in mind. Headache may herald the onset of postpartum preeclampsia. Patients who have had spinal anesthesia during labor can have a “post lumbar puncture headache” that may require a blood patch. Patients with pre-existing migraine headaches often note improvement during pregnancy, possibly due to increased estrogen levels, but the headaches may return during the postpartum period. Treatment is similar to other migraine patients, though ergot alkaloids are contraindicated in the nursing mother (13).

The risk of both hemorrhagic and ischemic stroke peaks in the 6 weeks postpartum, and stroke remains responsible for a significant number of maternal deaths. Predisposing factors such as preeclampsia, chronic hypertension, diabetes, and hypotensive

episodes are noted in about one-third of patients. Although most events are thought to be thrombotic and due to hypercoagulability, embolic sources should also be considered (13). *Cortical venous thrombosis* has also been reported, particularly 1 to 4 weeks postpartum. Initial symptoms are variable and may include headache, lethargy, and vomiting. Seizures are common (up to 30%), and hemiplegia may occur (gradual onset). Care is supportive, although prophylactic anticonvulsant therapy is usually given. Most authors do not recommend anticoagulation, as bleeding frequently follows clot resolution. Mortality may be as high as 20%, despite aggressive supportive treatment (14).

Patients can present with intermittent symptoms due to reversible cerebral vasoconstriction (*postpartum cerebral angiopathy*); the patient presents with headache, vomiting, seizures, and focal neurologic signs. Angiography has shown multiple areas of segmental narrowing in the cerebral arteries, which tend to resolve spontaneously. Finally, postpartum women also have an increased incidence of idiopathic *Bell palsy,* which behaves as in other patients.

Thromboembolic Disease

The risk of thromboembolic disease in pregnancy is roughly five times higher than in the nonpregnant population. Although most thromboses develop in the antepartum period, recent data indicate that two-thirds of PE occur in the postpartum period. PE remains a significant cause of maternal death. Diagnosing DVT and PE can be difficult in the puerperium. Leg edema and calf soreness are common during the postpartum period, and pelvic thrombosis is often clinically silent until PE occurs (15). Treatment of thromboembolic disease in the postpartum generally parallels that of non-pregnant patients.

Cardiomyopathy

Peripartum cardiomyopathy is the development of cardiac failure in the last month of pregnancy or in the first 5 postpartum months, in

the absence of an identifiable cause or prior heart disease. The vast majority of these patients present in the first two postpartum months. In the US, the incidence probably ranges between 1 in 2,500 and 1 in 4,000. Patients often have superimposed preeclampsia, obesity, or coexisting obstetric infection or anemia. Clinically, patients present with signs and symptoms of left heart failure, including dyspnea, orthopnea, and rales. Most patients have nonspecific but abnormal electrocardiograms, often demonstrating ST-T wave changes or left ventricular hypertrophy. Chest radiography reveals cardiomegaly and pulmonary edema. An echocardiogram shows four-chamber enlargement and abnormalities of left ventricular contractility. The workup is directed at excluding other causes of heart failure. The emergency care is the same as other patients with congestive heart failure. Patients can become refractory to medical management, and long-term mortality ranges from 25% to 50%. Ten percent to 20% of patients die during their initial hospitalization. If the heart size returns to normal, the prognosis is good, but cardiomyopathy that persists after 6 months is a poor prognostic sign. PE is a common complication (16).

Psychiatric Disease

A woman's risk of psychiatric disease peaks in the first postpartum year. Fifty percent to 70% of postpartum patients experience "maternity blues." Typically starting on postpartum day 3 or 4, this is a mild depression, most prevalent in the first 2 weeks. It is probably a normal reaction to the stresses of childbirth. Common symptoms include tearfulness, irritability, and emotional lability.

Clinical depression occurs in about 7% to 10% of women, half of whom had no symptoms during or before the pregnancy. Risk factors include personality traits such as anxiety, neuroticism, cognitive style; poor marital adjustment; poor social support systems; and an excess of stressful life events. Stresses during the pregnancy and labor may also contribute (17).

Postpartum psychosis is rare. Usually, the disease has a rapid onset in the first few days postpartum, and mania is a common

feature. The duration of illness is usually 2 to 3 months.

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CHAPTER 144

Medical Treatment During Pregnancy

Ryan P. Bodkin and Nicole M. Acquisto

Treating the pregnant patient adds an additional level of complexity to the management of medical emergencies. Pregnant women are often excluded from clinical trials evaluating efficacy and safety and therefore much of the literature regarding medications during pregnancy derives from animal models. Providers must weigh the risks and potential adverse effects of medications on the developing fetus when managing emergent medical conditions. No medication should be prescribed without a clear indication, and medication exposure should be minimized by using the smallest effective dose for the shortest duration possible. This chapter addresses the relative safety of pharmacologic therapy that the emergency provider is likely to consider using in the pregnant patient and the management of common medical problems during pregnancy.

TERATOLOGY

Teratogenesis is the abnormal development of fetal organs. Major malformations occur in 2% to 4% of all newborns, 1% of which may be attributed to the adverse effects of medications (1). The period from 4 to 12 weeks after the first day of the last menstrual period is the time of greatest susceptibility of the embryo to organ malformation (1). During the later stages of pregnancy, drugs may still adversely affect the fetus and newborn, causing complications during delivery or in the postnatal period.

FDA PREGNANCY CATEGORY

In 1979, the United States Food and Drug Administration developed a five-category classification system to guide providers in the interpretation of the teratogenic risk associated with prescription and over-the-counter medications.

- Category A. Adequate, well-controlled human studies have not shown increased risk to the fetus.
- Category B. Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
- Category C. Animal reproduction studies have shown an adverse effect on the fetus; there are no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
- Category D. Well-controlled human studies have demonstrated fetal risk, but the benefit of use may be acceptable despite its potential risks.
- Category X. Studies have demonstrated animal or human fetal abnormalities and the risk of the drug clearly outweighs the potential benefits.

Practically speaking, category B classification reflects the safest medications in clinical practice. A select list of medications that are discussed in this chapter appears in Table 144.1. A category A classification is rare, as studies on drug safety are generally not performed in pregnant patients. Most often, category D and X medications are contraindicated.

TABLE 144.1
Common Medications Considered Relatively Safe During Pregnancy

Condition	Drug	Condition	Drug
Analgesia	Acetaminophen	Ear, nose, and throat	Diphenhydramine
	Morphine[a]		Chlorpheniramine
	Codeine[a]		Second-generation antihistamines (loratadine, cetirizine)
	Hydrocodone[a]		Dextromethorphan
	Oxycodone[a]		Codeine[a]
	Methadone[a]	Asthma	β-Agonists (albuterol, levalbuterol, terbutaline)
Cardiac	Methyldopa		Ipratroprium bromide
	Clonidine		Corticosteroids (inhaled)
	Hydralazine		Corticosteroids (systemic)[c]
	Labetalol		Epineprhine[c]
	Verapamil		Magnesium sulfate
	Nifedipine extended release	Gastrointestinal	Antacids (aluminum, magnesium, calcium containing)
	Amlodipine		Sucralfate
	Hydrochlorothiazide		H_2-receptor blockers (cimetidine, famotidine, ranitidine)
	Furosemide		Proton pump inhibitors (omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole)
	Adenosine		Ondansetron
	Lidocaine		Prochlorperazine
	Digoxin		Promethazine
Infectious	β-Lactams (penicillin, ampicillin, amoxicillin)		Pyridoxine
	Cephalosporins (ceftriaxone, cefixime)		Metoclopramide
	Nitrofurantoin[b]		Senna
	Aminoglycosides (gentamicin, tobramycin, amikacin)		Docusate
	Macrolides (azithromycin, clarithromycin, erythromycin base, erythromycin ethylsuccinate)	Anticoagulation	Heparin
	Metronidazole (oral)		Low–molecular-weight heparin (enoxaparin, dalteparin)
	Clindamycin (oral)		Fondaparinux
	Azole antifungals (vaginal)		Thrombolytics (alteplase, tenecteplase)[c]
	Acyclovir	Seizure	Carbamazepine
	Valacyclovir		Oxcarbamazepine
	Zidovudine		Benzodiazepines
	Permethrin	Psychiatric	TCAs (amitriptyline, doxepin, imipramine, nortriptyline)
Endocrine	Insulins		SSRIs (fluoxetine, citalopram, paroxetine, sertraline)
			Haloperidol
			Atypical antipsychotics (aripriprazole, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, clozapine)

[a]Except in long-term use or high doses.
[b]Do not use in the third trimester.
[c]Can use in severe disease.

A select list of medications that are discussed in this chapter appears in Table 144.2. Drugs may have dual classification that reflects safe use during one trimester of pregnancy and unsafe use in another. Information services are available to providers to assist in determining the safety of drugs during pregnancy:

TABLE 144.2
Common Medications that are Contraindicated in Pregnancy

Condition	Drug
Analgesia	Salicylates
	NSAIDs (ibuprofen, naproxen, ketorolac)
	Meperidine
Cardiac	ACE Inhibitors
	Angiotensin-receptor blockers
	Atenolol
	Diltiazem
	Amiodarone
	Ibutalide
Infectious	Nitrofurantoin[a]
	Sulfamethoxazole/trimethoprim[a]
	Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin)
	Erythromycin estolate
	Tetracyclines
	Doxycycline
	Metronidazole (vaginal)
	Clindamycin (vaginal)
	Azole antifungals (oral; fluconazole, ketoconazole, itraconazole)
	Lindane
Endocrine	Oral hypoglycemic agents
Ear, nose, and throat	Brompheniramine
	Decongestants (phenylephrine, pseudoephedrine, phenylpropanolamine)
Gastrointestinal	Antacids (sodium-bicarbonate containing)
	Nizatidine (high dose)
Anticoagulation	Warfarin
	Dabigatran
	Oral factor Xa inhibitors (rivaroxiban, apixaban)
Seizure	Phenytoin
	Phenobarbital
	Primidone
	Valpropic acid
	Valproate sodium
Psychiatric	Lithium

[a]Do not use in third trimester.

- MotherToBaby, a service of the Organization of Teratology Information Specialists (OTIS): (866) 626–6847;

http://www.mothertobaby.org
- Motherisk program: (416) 813–6780; http://www.motherisk.org

PAIN

Acetaminophen (category B) is the analgesic and antipyretic of choice throughout pregnancy. Large population-based studies have demonstrated no increase in congenital malformations with its use (2).

Aspirin (category D) is the most studied analgesic medication in pregnant women. Two large US studies have failed to demonstrate significant fetal risk from aspirin although it readily crosses the placenta. The Collaborative Perinatal Project studied more than 50,000 pregnancies and found no increase in stillbirth, reduced birth weight, teratology, or perinatal death among pregnant women exposed to low-dose aspirin (3). Additionally, the Michigan Medicaid Surveillance Study investigated 1,709 pregnancies with first-trimester exposure to aspirin and found no increase in congenital malformations (4). However, high-dose aspirin in third-trimester pregnancy may be harmful. Near the time of delivery, high-dose aspirin has been shown to increase the risk of infant bleeding, in particular central nervous system (CNS) hemorrhage (4). The use of aspirin near term may also cause premature closure of the fetal ductus arteriosus caused by prostaglandin inhibition (5).

Nonsteroidal anti-inflammatory drugs (NSAIDs) (category C/D), such as ibuprofen, naproxen, and ketorolac, are prostaglandin inhibitors and have been associated with premature closure of the ductus, causing infantile pulmonary hypertension (5). Although the Michigan Medicaid Surveillance Study found no teratogenicity among more than 3,000 first-trimester exposures to ibuprofen, oligohydramnios has been associated with NSAID use (4). It does appear that the adverse effects of NSAIDs on the ductus and amniotic fluid volume are reversible with discontinuation of the drug when used as a tocolytic (4). NSAIDs should be used with caution during pregnancy and they should not be used during the third trimester.

Most opioids are considered safe for use during pregnancy (category B/C). The Collaborative Perinatal Project monitored over

50,000 mother–child pairs. Of these, 563 had first-trimester exposure to codeine and 686 had first-trimester exposure to propoxyphene (3). There was no evidence of a causative relationship to major or minor fetal malformations. The same results were observed in those with exposures to morphine, hydrocodone, oxycodone, methadone, and meperidine. However, since meperidine is extensively metabolized to normeperidine, there is a risk of accumulation. This can cause excitation of the CNS and subsequent seizures and do not make this agent a good choice for pain control in the emergency department (ED) for the pregnant patient.

All of the opioid analgesics are considered category B or C when used in intermittent doses, but all are considered category D if used for prolonged periods or at high doses near term. Chronic opioids can cause respiratory and CNS depression in both mother and newborn. Additional, symptomatic withdrawal in infants can begin 48 hours up to 14 days postpartum. Slow opioid weaning, described as a 10% reduction every 3 days, may be utilized to prevent withdrawal symptoms (5).

ASTHMA

Asthma is a common medication condition to complicate pregnancy. It is estimated that 3.7% to 8.4% of pregnant women in the United States are affected (6). Pregnancy itself has a variable impact on chronic asthma. In patients with chronic severe asthma, pregnancy may cause worsening of the disease due to physiologic changes resulting in a reduction in total lung capacity and functional residual capacity. Poorly controlled asthma is associated with increased fetal mortality and recent guidelines have concluded that it is safer for pregnant women with asthma to be treated with pharmacologic agents than for them to continue with asthma-related symptoms (6).
β-Adrenergic agonists (category C) including albuterol, levalbuterol, and terbutaline have been used safely in pregnancy and do not increase the risk of congenital malformation (1,7). Adverse effects from these medications may cause fetal tachycardia and transient fetal hyperglycemia. The combination of a β-agonist and ipratropium bromide (category B), an anticholinergic agent, is often used during

asthma exacerbations. This combination is safe to use during pregnancy.

Corticosteroids (category B/C) readily cross the placenta where they are rapidly converted to less active forms. Inhaled corticosteroids are the preferred route of administration and considered safe for chronic asthma control (1,7). There is a potential for some systemic absorption and adverse effects from inhaled corticosteroids; however, their use can decrease the need for systemic administration. Systemic corticosteroid administration has been associated with a small fetal risk when used in the first trimester (6). Complications may include preeclampsia, preterm delivery, and low birth weight. In the ED the need for systemic corticosteroids in the pregnant patient may be necessary for acute asthma exacerbation treatment. The use of systemic corticosteroids has been shown to increase the risk of fetal malformations in animal models, but has been used extensively in humans during pregnancy and is not considered teratogenic (6).

Epinephrine (category C) has been shown to reduce uterine blood flow in animal studies and is therefore a concern in humans (5). Epinephrine has also been associated with an increase in fetal malformation. Although selective β_2 agonists are the preferred bronchodilators during pregnancy, epinephrine should be reserved for times when other agents fail to control severe symptoms.

Parenteral magnesium sulfate (category D) has been considered adjunct therapy for severe asthma exacerbations in the ED. It is thought to induce bronchial smooth muscle relaxation and increase bronchodilatory effects of β-agonists. It is likely that a single dose of magnesium is not harmful to the fetus although continuous infusions beyond 5 days for the treatment of preterm labor have been associated with low calcium levels and bone changes in the baby.

DIABETES

Despite advances in the screening and management of diabetes, perinatal mortality among infants of diabetic mothers remains 15% to 25% more than that seen in the general population (8). Pregnancies among diabetic women are more likely to be

complicated by preeclampsia, and the incidence of major malformations is three to four times higher, possibly caused by hyperglycemia during embryogenesis (9). Therefore, maintaining euglycemia during pregnancy is important. Maternal glucose readily crosses into fetal circulation where it can result in fetal hyperinsulinemia. Insulin acts as a potent fetal-growth stimulus, and excessive fetal growth (macrosomia) may result in injury to the fetus or mother during delivery.

During pregnancy, diabetic ketoacidosis (DKA) can develop rapidly and can occur with relatively low serum-glucose levels of 200 to 300 mg/dL. DKA during pregnancy is associated with a high rate of fetal loss and should be treated aggressively with crystalloid fluids and insulin. Insulin (category B/C) is safe in pregnancy. Traditional insulin preparations (insulin aspart, insulin lispro, regular insulin, and insulin NPH) are category B agents and most often used for diabetes control during pregnancy. There is less experience with newer agents (insulin glulisine, insulin determir, and insulin glargine) although most healthcare providers consider these safe to use in pregnancy. More importantly, perinatal morbidity and mortality are related to the degree of glycemic control which may be managed with a combination of insulin products (8).

Gestational diabetes affects approximately 3% of pregnant women. Most patients with gestational diabetes do well with diet modifications, and only 15% will require insulin therapy (8). In this pregnancy-related medical condition, patients cannot increase their insulin secretion to meet the higher demand. There is a low risk of fetal malformations because most of these women are euglycemic during early pregnancy, although fetal macrosomia is still a concern. Oral hypoglycemic agents are contraindicated in pregnancy because they cross the placenta and may cause fetal hypoglycemia as well as excessive fetal insulin secretion (10). Fetal hyperinsulinemia is associated with macrosomia, myocardial hyperplasia, stillbirth, and delayed lung maturation.

HYPERTENSION

Hypertension complicates 5% to 10% of pregnancies, and hypertensive disorders of pregnancy are a leading cause of maternal and perinatal morbidity (11,12). Untreated hypertension increases the risk of fetal death. Care must be taken not to overtreat the condition and cause maternal hypotension with placental hypoperfusion (7).

Centrally acting α-2 adrenergic agonists, such as methyldopa (category B) and clonidine (category C), are commonly used antihypertensive medications during pregnancy and have not been shown to have any adverse fetal or neonatal effects. Methyldopa is the oral medication of choice for the management of chronic hypertension in pregnant women. Hydralazine (category C) is a direct vasodilator and the parenteral medication of choice for the management of severe hypertension in pregnant women. Data are available that demonstrate more frequent, significant hypotension when compared to labetalol or short-acting nifedipine and therefore caution should be taken with its use (11). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (category C, first trimester; category D, second and third trimesters) should be avoided in pregnancy because of the risk of fetal renal toxicity and cranial structural defects.

Labetalol (category C) is a commonly used parenteral and oral β-blocker for the management of hypertension. It is not known to be teratogenic and has been shown to increase fetal pulmonary surfactant, which may be advantageous among premature infants. Newborns of mothers taking β-blockers should be monitored closely for neonatal bradycardia, respiratory depression, and hypoglycemia (13). Atenolol (category D) may increase the risk of intrauterine growth retardation (IUGR) when started in the first trimester and should be avoided.

Calcium channel blockers (category C) should be used only as a last resort during pregnancy. Available information mostly addresses the nondihydropyrodines (verapamil and diltiazem). Verapamil can theoretically cause fetal bradycardia, heart block, and hypotension, although clinical experience in pregnant women has not been associated with maternal or fetal adverse effects (13). Nifedipine has

been used more often in pregnancy, but in animal models, the immediate release formulation has been associated with intrauterine growth restriction and fetal death (5). Longer acting formulations such as extended release nifedipine or amlodipine are preferred. Thiazide diuretics such as hydrochlorothiazide (category B) and loop diuretics such as furosemide (category C) are not teratogenic but should be used with caution during pregnancy. An increased risk of perinatal mortality and congenital defects has been associated with these drugs, most likely a result of decreased maternal plasma volume and placental hypoperfusion (7,11,12).

DYSRHYTHMIAS

Sustained arrhythmias may occur more frequently in pregnancy due to hemodynamic, hormonal, and autonomic changes. In unstable, pregnant patients, cardioversion is still recommended (13). All antidysrhythmics cross the placenta (13). Still, several of these agents have long histories of safe use during pregnancy.

Adenosine (category C) is not associated with adverse fetal effects, likely due to its short half-life, and is effective in terminating atrioventricular node–dependent tachydysrhythmias during pregnancy.

Amiodarone (category D) is a class III antiarrhythmic agent that only crosses the placenta to a limited extent. However, it should only be used during pregnancy when absolutely necessary, because of several associated risks (13). The high-iodine content of amiodarone is thought to be responsible for an association with neonatal goiter, hypothyroidism, and IUGR. Ibutilide (category C), a class III antiarrhythmic agent, has been demonstrated to be teratogenic in animal studies and is not recommended during pregnancy (13).

The class IA antiarrhythmic agents, quinidine and procainamide (category C), are considered safe in pregnancy (13). Lidocaine (category C) is a class IB antiarrthythmic agent and is thought to be safe during pregnancy at appropriate doses. Large doses have been associated with low Apgar scores and neonatal lidocaine toxicity. Little information is available regarding the effects of mexiletine,

flecainide, propafenone, and sotalol during pregnancy, although none are known to be teratogenic (13).

Digoxin (category C) is considered safe during pregnancy when given in appropriate doses, although digoxin toxicity has been associated with fetal death and miscarriage (13). It is important to note that serum digoxin levels may decrease by 50% during pregnancy due to increased renal excretion (13). Serum levels must be closely monitored during pregnancy and postpartum digoxin requirements will likely decrease.

THROMBOEMBOLIC DISEASE

Pregnant women are at increased risk of deep venous thrombosis and pulmonary embolism. The incidence of venous thromboembolism is estimated at 0.76 to 1.72 per 1,000 pregnancies (5). This is fourfold greater than the occurrence in the nonpregnant population.

Unfractionated heparin (category C) and low–molecular-weight heparin (LMWH, category B) do not cross the placenta and are the anticoagulants of choice in pregnant patients (10). Due to increased renal excretion and therefore decreased half-life of the medication during pregnancy, twice daily administration is recommended (5). Furthermore, due to the weight-based dose strategy, frequent dose adjustments may be needed throughout the pregnancy. Fondaparinux (category B) is a direct factor Xa inhibitor and may be used as an alternative to heparin products during pregnancy (5). Warfarin (category X) is contraindicated in pregnancy because of its significant association (30%) with congenital malformations (10). The newer oral anticoagulant agents such as dabigatran (direct thrombin inhibitor), rivaroxaban (factor Xa inhibitor), and apixaban (factor Xa inhibitor) are not recommended for use in pregnancy (category C). Adverse effects associated with both dabigatran and rivaroxaban have been observed in animal studies (5).

Thrombolytics (category C) are relatively contraindicated in pregnancy. The theoretical risk of placental abruption and antipartum bleeding should be weighed against the potential benefits of thrombolytic treatment. There are several successful case reports with the use of thrombolytic agents during pregnancy with the

reported maternal bleeding rate of 1% to 6% (5). This is no different from the rate seen in the nonpregnant population.

SEIZURE DISORDERS

The treatment of seizure disorders during pregnancy requires a careful risk–benefit analysis. Although seizures increase the risk of miscarriage and hypoxic injury to the fetus, the risk of birth defects in women taking a single antiepileptic medication is doubled (14). This teratogenic risk is increased with the use of multiple antiepileptic medications (14). The best approach is to use a single agent at the lowest effective dose.

Phenytoin (category D) is a known human teratogen. Fetal exposure to phenytoin is associated with a 7% to 10% risk of IUGR, motor and developmental delays, facial dysmorphia, and limb abnormalities (7). Pregnant women who require treatment with phenytoin are generally also treated with vitamin K and folic acid to decrease the risk of neonatal coagulopathy and neural cord defects, respectively (7,14).

Phenobarbital and primidone (category D) may also contribute to folic acid deficiency and neonatal coagulopathy, though no conclusive evidence of teratogenicity has been demonstrated (7). Respiratory depression and barbiturate withdrawal symptoms may be seen in the neonate exposed to phenobarbital during late gestation.

Carbamazepine and oxcarbapazepine (category C) have been associated with craniofacial defects and developmental delays in infants exposed during gestation (7,14). As with phenytoin and phenobarbital, folic acid deficiency may develop and lead to neural tube defects. If these agents are used, fetal echocardiogram is recommended at 20 to 22 weeks gestation (5).

Valproic acid and valproate sodium (category X) are teratogenic in humans and should be avoided (7,10,14). Neural tube defects occur in approximately 2.5% of infants exposed to valproate in utero, which is up to 10 times that of the general population (7).

Benzodiazepines (category D) easily cross the placenta and concentrate in fetal tissues. A review of the literature found no

increase in the prevalence of congenital malformations in infants exposed to benzodiazepines (5). Nonetheless, with large perinatal doses, newborn apnea, hypotonia, hypothermia, and withdrawal symptoms may be seen.

Little information is available regarding the safety of the newer agents, felbamate, gabapentin, lamotrigine, levetiracetam, and topiramate, during pregnancy. These are all categorized as pregnancy category C agents (5).

PSYCHIATRIC DISORDERS

Tricyclic antidepressants (category C/D) such as amitriptyline, doxepin, imipramine, and nortriptyline and selective serotonin-reuptake inhibitors such as fluoxetine, citalopram, paroxetine, and sertraline have been evaluated in a meta-analysis to determine adverse effects on infant outcomes while administered during pregnancy. Neither of these classes of medications appear to cause major congenital anomalies, but both may be associated with a small increased risk of minor anomalies, prematurity, and neonatal complications (15).

Lithium (category D) is associated with the “floppy-baby” syndrome, characterized by neonatal hypotonia, cyanosis, and poor sucking. Lithium also increases the risk of cardiovascular abnormalities and may affect neonatal thyroid function (15).

Several large prospective trials have failed to demonstrate any teratogenic effects from phenothiazines and haloperidol (category C) (10). It has been recommended that these antipsychotic agents be discontinued 5 to 10 days prior to delivery to decrease the risk of neonatal extrapyramidal symptoms (10). The newer antipsychotic agents, aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone (category C) and clozapine (category B) have not been associated with teratogenic effects and there is an ongoing Atypical Antipsychotic Pregnancy Registry that is actively collecting information regarding the use of these agents during pregnancy.

GASTROINTESTINAL DISORDERS

During pregnancy, the lower esophageal sphincter is relatively relaxed and pressure on the abdominal contents from the uterus increases the frequency of heartburn symptoms. Similarly, nausea and vomiting are well-known features of early pregnancy and often require treatment.

Antacids containing aluminum, magnesium, and calcium are considered safe during pregnancy and no teratogenicity has been reported from animal studies (16). Sucralfate (category B) is not systemically absorbed and is safe during pregnancy. Sodium bicarbonate–containing antacids should be avoided due to the potential for maternal or fetal metabolic acidosis and fluid volume derangements (5).

H_2-receptor antagonists appear to be well tolerated during pregnancy. Cimetidine, famotidine, ranitidine, and nizatidine are all considered category B agents. Among 460 newborns in the Michigan Medicaid Surveillance Study, cimetidine use was not associated with an increased number of congenital defects (16).

Proton pump inhibitors do cross the placenta. Omeprazole is a category C agent, while others such as lansoprazole, esomeprazole, pantoprazole, and rabeprazole are category B agents. The Swedish Medical Birth Registry evaluated a cohort of 955 infants of mothers exposed to omeprazole, with no difference in birth weight, congenital malformation, or Apgar scores compared to the general population (17). Similarly, a recent cohort study of first-trimester exposure to any proton-pump inhibitor in 840,968 live births found no statistical differences in birth defects (18).

Ondansetron (category B) is considered the first-line treatment of hyperemesis and early pregnancy–induced nausea. Phenothiazine agents such as prochlorperazine and promethazine (category C) are commonly used antiemetics that cross the placenta, but have not been shown to be teratogenic (7,10). The Collaborative Perinatal Project monitored 50,282 mother–child pairs and found no evidence of an increased risk of malformation associated with prochlorperazine or promethazine (19). Metoclopramide (category B) was evaluated in the Michigan Medicaid Surveillance Study, with no significant increase in malformations beyond that expected in the

general population (16). Pyridoxine (vitamin B6) is considered safe to use in pregnancy and a 3- to 5-day course is commonly recommended to decrease vomiting episodes and nausea scores in pregnant women (5).

Laxatives which act locally in the gastrointestinal tract, such as castor oil, senna, milk of magnesia, and docusate, are safe for use in pregnancy.

URINARY TRACT INFECTION

Urinary tract infections (UTIs) are the most common infectious complication during pregnancy. Asymptomatic bacteriuria is present in 1.9% to 9.5% of pregnant women and there is a 20- to 30-fold increased risk of developing pyelonephritis if untreated compared to pregnant women without bacteriuria (20). Bacterial pathogens responsible for UTI in pregnant patients are similar to those in the general population with *Escherichia coli* accounting for more than 75% of cases. Cystitis and asymptomatic bacteriuria should both be treated in the pregnant patient for 3 to 7 days (20).

Pyelonephritis is a serious condition in the pregnant patient. Preterm labor and premature delivery have been associated with pyelonephritis, although the physiologic mechanism for this phenomenon is not clear. Approximately 15% of pregnant women with pyelonephritis become bacteremic. Initial parenteral treatment in the inpatient setting should be considered. Pyelonephritis and other complicated UTIs (e.g., in a diabetic patient) should be treated for 10 to 14 days (20). All antibiotics cross the placenta, but many have been used for a number of years without reports of adverse fetal effects.

Cephalosporins (category B) are the most commonly prescribed antibiotic in this population and are considered safe during pregnancy (10,21).

β-Lactam antibiotics such as ampicillin and amoxicillin (category B) are considered safe in pregnancy (20), although these agents are not often considered first-line therapy for UTI in pregnant patient due to a high percentage of *E. coli* resistance (30% to 50%).

Nitrofurantoin (category B) is commonly used during pregnancy but may cause neonatal hyperbilirubinemia when used in the third trimester and should be avoided during this time.

Sulfonamides are considered safe during early pregnancy. However, during the third trimester, their use is contraindicated because they compete with bilirubin for albumin-binding sites and may cause kernicterus (10,21). Trimethoprim is a folate antagonist and is not recommended during pregnancy, so combination agents such as trimethoprim/sulfamethoxazole (category C) should be avoided (21).

Aminoglycosides (category C) such as gentamicin, tobramycin, and amikacin may be used to treat resistant gram-negative infections in pregnant women (21). Aminoglycosides have been associated with a high prevalence of transient renal dysfunction in the pregnant patient. Fluoroquinolones (category C) such as ciprofloxacin and levofloxacin are contraindicated during pregnancy because of reports of irreversible arthropathy in immature animals.

RESPIRATORY TRACT INFECTIONS

Macrolides such as azithromycin and erythromycin (category B) are commonly used to treat pneumonia in pregnancy (10,21). Clarithromycin is used less often since it is a category C agent. Cephalosporins are category B and safe to use during pregnancy. Respiratory fluoroquinolones (category C) such as levofloxacin and moxifloxacin are contraindicated.

Tetracyclines and doxycycline (category D) should be avoided during pregnancy because of the risk of genitourinary and limb malformations (10,21). Tetracyclines also chelate calcium and may stain teeth and bones if given after 5 months of gestation (10,21).

Streptococcal pharyngitis is not treated differently during pregnancy. Penicillin (category B) and its derivatives are considered safe. In the penicillin-allergic patient, azithromycin, erythromycin, or clindamycin (category B) can be considered.

Antihistamines and decongestants are commonly used for symptomatic relief in patients with upper respiratory infections. However, many over-the-counter medications are not recommended

for use during pregnancy. Diphenhydramine and chlorpheniramine are category B agents and can be used during pregnancy. Brompheniramine (category C) is a well-known teratogen and is contraindicated in the pregnant patient. Second-generation antihistamines such as loratadine and cetirizine are category B agents and considered safe during pregnancy. Decongestant medications such as phenylephrine, pseudoephedrine, and phenylpropanolamine have been associated with teratogenicity in animals and minor fetal malformations in humans and are category C agents. These should be used with caution during pregnancy. Dextromethorphan and codeine (category C) are considered safe for use as antitussive agents during pregnancy.

GENITAL TRACT AND SEXUALLY TRANSMITTED INFECTIONS

Neisseria gonorrhoeae and *Chlamydia trachomatis* cervicitis may cause significant maternal and fetal adverse effects when left untreated (5). Infection with *N. gonorrhoeae* may lead to premature rupture of membranes, preterm labor, and chorioamnionitis (5). In addition, there is concern with neonatal transmission during birth. Cephalosporins (category B) such as ceftriaxone or cefixime are safe for the treatment of *N. gonorrhoeae.* Azithromycin (category B) 2 g administered orally as a single dose may be used for patients who are allergic to cephalosporins (22). To treat *C. trachomatis,* azithromycin 1 gm orally as a single dose can be safely used. Fluoroquinolones and doxycycline are contraindicated during pregnancy (22).

Syphilis can cross the placenta at any stage of pregnancy, with potentially devastating fetal effects. Treatment with parenteral agents such as penicillin G benzathine (category B) is preferred to oral therapy (22). Those with a penicillin allergy should undergo skin desensitization.

Vaginitis caused by *Trichomonas vaginalis* and bacterial vaginosis (BV) may increase the risk of premature rupture of membranes and preterm labor. Oral metronidazole (category B) is the recommended treatment. Multiple studies have failed to show an association between metronidazole during pregnancy and fetal teratogenic or

mutagenic effects (22). Oral clindamycin may also be used, but intravaginal clindamycin cream administered at 16 to 32 weeks gestation is associated with an increase in low birth weight and neonatal malformations (22).

Topical antifungal vaginal creams (including clotrimazole, miconazole, and nystatin) for Candida vaginitis are considered safe during pregnancy (22). However, oral fluconazole, ketoconazole, and itraconazole (category C/D) are associated with fetal malformations and should be avoided during pregnancy.

Human papillomavirus infections during pregnancy may obstruct the vaginal canal and increase the risk of hemorrhage during delivery. Topical pharmaceutical agents such as podophyllin, podofilox, imiquimod, or sinecatechin are not recommended in pregnancy (5). Current treatment recommendations during pregnancy are carbon dioxide ablation, liquid nitrogen cryotherapy, or surgical excitation (5). Herpes virus infection during pregnancy raises concern for perinatal transmission. The neonatal infection rate is nearly 50% with vaginal delivery during a primary maternal outbreak. Acyclovir intravenous and oral as well as valacyclovir (category B) have not been associated with an increase in birth defects compared to the general population in a voluntary data registry of 1,129 pregnant patients (22,23).

In pregnant women with human immunodeficiency virus (HIV) there is a concern for fetal transmission. There are reports of safety and a reduction in perinatal transmission among HIV-positive pregnant women who are treated with zidovudine (24). Pregnant patients with HIV infection can be treated with certain multidrug antiretroviral regimens and this should be coordinated with an infectious diseases provider.

OTHER SELECTED INFECTIONS

Scabies during pregnancy can be treated with pyrethroids. Lindane is potentially neurotoxic and was found to be possibly associated with hypospadias in the Michigan Medicaid Surveillance Study (10).

Varicella has a potentially devastating course in pregnancy. Fetuses exposed to varicella in the first trimester are prone to limb

and digit abnormalities, microphthalmos, and microcephaly. Infection in the last two trimesters is less threatening. Peripartum varicella infection (from 5 days before delivery to 2 days after delivery) places the fetus at high risk for morbidity and mortality. Varicella-immune globulin should be given within 96 hours to an exposed pregnant patient with no history of chicken pox and a negative antibody titer.

IMMUNIZATIONS DURING PREGNANCY

Benefits of vaccinating pregnant women usually outweigh the risks when possible exposure is likely. There is no evidence of increased fetal harm when inactivated viral or bacterial vaccines are given to pregnant women. Live vaccines should be avoided during pregnancy because of the theoretical risk of infection and transmission to the fetus (25). Avoidance of administration during the first trimester is preferred since the vaccination itself may cause high fevers, which have been associated with neural tube defects (25). Commonly immunizations that are safe during pregnancy include hepatitis A, hepatitis B, inactivated influenza, pneumococcal, human diploid cell rabies, tetanus and diphtheria toxoid (Td), and tetanus, diphtheria, and acellular pertussis (TdaP) vaccines. Passive immunization of pregnant women with immune globulin preparations has not been associated with risk to the fetus (25). These immune globulin preparations include tetanus, rabies, hepatitis B, and varicella zoster.

Common Pitfalls

- Given the importance of minimizing risk to the fetus, no medication should be prescribed unless it is clearly indicated.
- Medication exposure should be minimized by using the smallest effective dose for the shortest treatment time.
- Medications that have had extensive use and well-understood safety profiles are preferable to newer medications.
- Some medications may be safe to use in certain trimesters of pregnancy and not others.

ACKNOWLEDGMENTS

We thank Flavia Nobay and Daniel Hays for their contributions to previous editions of this chapter.

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SECTION XIV
Musculoskeletal Emergencies

Section Editor: GREGORY W. HENDEY

CHAPTER 145 Hand and Wrist Pain

Gary M. Vilke

Injuries of the hand and wrist caused by repetitive motions are most commonly associated with occupational activities. They are occurring with increasing frequency and have a tremendous economic impact on the workforce. This chapter discusses the most common of these entities.

KEY TESTING

- These conditions are diagnosed by history and exam. Laboratory and imaging are not necessary in most cases.

CLINICAL PRESENTATION

Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) involves the median nerve at the wrist and is the most commonly encountered compressive peripheral neuropathy. At the wrist, the median nerve along with the flexor tendons and their sheaths pass through an anatomic tunnel that is formed dorsally by the carpal bones and volarly by the fibrous, but rigid, transverse carpal ligament. Any condition that decreases the internal diameter of the canal or increases the volume of the contents within the canal can potentially reduce capillary blood flow rates below the level which is essential for the maintenance of flow to median nerve and induce CTS. Numerous clinical conditions have been noted to cause CTS, but the disorder is most commonly idiopathic. Occupational causes include typing and

key entry jobs, repetitive use of tools, and repetitive grasping motions (1).

Females account for more than 78% of all cases of CTS, with the typical age range at diagnosis being between 40 and 60 years. The clinical presentation is often bilateral, with the patient classically complaining of numbness, tingling, burning, or paresthesias in the hand along the thumb, index, middle, and radial aspect of the ring fingers. These symptoms characteristically awaken the patient from sleep and may be relieved by shaking the hand and wrist. A nocturnal pain pattern is considered the hallmark of CTS and symptoms generally increase in frequency and intensity as the syndrome progresses. The symptoms are often exacerbated by wrist flexion, and patients may also complain of weakness or clumsiness in the hand manifested by difficulty with fine-motor functions such as picking up objects, holding items, and fastening buttons.

Guyon Canal Syndrome

Guyon canal (ulnar tunnel) syndrome involves the ulnar nerve at the level of the wrist. The ulnar nerve provides the primary motor innervation to the intrinsic muscles of the hand as well as supplying sensation for a significant portion of the hand, including the skin over the hypothenar eminence, the little finger, and the ulnar side of the ring finger. The ulnar nerve and artery pass together into the wrist on the radial side of the pisiform bone via an anatomic space called the canal of Guyon, a 4-cm-long channel located between the pisiform bone and the hook of the hamate (2).

Patients with ulnar nerve compression at the wrist typically present with wrist pain that radiates into the ulnar two digits. Fractures of the hook of the hamate have been reported to account for 14% of all cases of ulnar nerve compression in the wrist (3). As repeated blows to the ulnar side of the hand have been implicated as a cause of ulnar neuropathy at the wrist, patients should also be asked about repetitive trauma. In recent years this disorder has been reported more frequently in cyclists (4,5).

Hypothenar Hammer Syndrome

Hypothenar hammer syndrome (HHS) involves trauma to the distal ulnar artery at the base of the hypothenar eminence, just distal to the volar carpal ligament, where it is no longer protected within Guyon canal and is covered only by skin, subcutaneous fat, and, in 85% of the population, the palmaris brevis muscle (6). Given its susceptible position, the ulnar artery is easily compressed between hard objects and the hook of the hamate. Repetitive ulnar artery injury can result in traumatic vasospasm, thrombosis, or aneurysm formation (7). These can occur any time the hypothenar aspect of the base of the palm is subjected to trauma, and thus HHS is most commonly seen in those individuals who use the palms of their hands to push, pound, or hammer as part of their regular activities (7). Some examples include carpentry, baseball, Frisbee, hockey, martial arts, mountain biking, and weightlifting.

HHS is a treatable syndrome that should be considered in patients presenting with complaints of symptomatic digital ischemia. Clinical findings in HHS include a male predominance, unilateral hand involvement, and the acute onset of pain followed by a more gradual development of Raynaud phenomenon, including increased sensitivity of the digits with exposure to cold and a lack of thumb involvement (6,8). At presentation, a patient may complain of one or more episodes of acute, lancinating pain over the hypothenar eminence that occurs after striking a blow with the palm of the hand. This pain typically radiates into the fourth and fifth fingers, and a dull, aching hypothenar pain may then ensue. Other patients describe an immediate pain episode that resolves completely over time. Then, days to weeks or months later, ischemic finger symptoms develop as a consequence of a slowly progressing thrombosis of the ulnar artery (9). More severe trauma to the ulnar artery can damage the internal elastic lamella, leading to formation of intra-arterial thrombi (6). Embolization of traumatized intima and thrombus cause digital ischemia by occluding the end arterial supply to the fingers. Thrombosis involving the adventitia may

affect periarterial sympathetic fibers, resulting in vasospasm that limits surrounding collateral circulation (9).

De Quervain Tenosynovitis

De Quervain tenosynovitis (DQT) is the most common tendonitis of the extensor tendons of the hand and wrist. It is a nonsuppurative tenosynovitis of the first dorsal compartment, or "tunnel" of the wrist through which the tendons of the hand's extrinsic extensor muscles pass (10,11). This compartment overlies the styloid process of the radius and contains the tendons of the abductor pollicis longus (APL) and the extensor pollicis brevis (EPB) (10). The APL tendon inserts at the base of the dorsum of the thumb's metacarpal, and the EPB tendon inserts at the base of the thumb's proximal phalanx. At the wrist, these tendons and their synovial sheaths lie between the carpal bones and a fibrous band called the *dorsal retinaculum*. Tasks involving repeated pronation and supination of the forearm combined with forceful exertion of the thumb beyond the point of fatigue are commonly implicated in DQT, which represents a derangement in the normal gliding of the APL and/or the EPB tendons (10). Activities reportedly causing DPT include excessive writing or keyboard use, washing clothes, chopping wood, sewing, and playing the piano. Often, symptoms begin within days of starting a new job or resuming an old one after a holiday (12).

Pain at the radial styloid is a classic and defining symptom of DQT, with a history of gradual onset of pain and the absence of fracture or acute trauma (13). It typically affects women more than men (approximately 5:1 to 10:1) and presents between the ages of 35 and 55 years (12). The pain is usually severe and constant and is exacerbated by thumb abduction, ulnar deviation of the wrist, and simple grasping. Patients with advanced cases may develop swelling and crepitus. The pain may radiate proximally into the forearm or distally to the thumb and may disturb sleep. Some patients may complain of weakness or an inability to use the affected hand secondary to the pain.

DIFFERENTIAL DIAGNOSIS

Cervical nerve root irritation or compression, especially at the C6 and C7 levels, may produce numbness in the median-innervated fingers, with pain radiating to the shoulder. However, cervical root radicular pain seldom bilateral or worse at night. Pronator syndrome, which is compression of the median nerve in the proximal forearm, can present similar to CTS; however, both Phalen test and Tinel sign should be negative.

Lesions at any location along the length of the ulnar nerve or the nerve roots from which it arises can cause symptoms of wrist or hand pain. Brachial plexus pathology may also be responsible for symptoms in the distribution of the ulnar nerve. Pancoast tumor, an apical tumor of the lung, can exert pressure on or grow into the brachial plexus, resulting in symptoms distant from the primary site (14). Thoracic outlet syndrome can also result in a brachial plexopathy.

The most common location of ulnar nerve compression is in the cubital tunnel of the elbow. Most patients presenting with a combined ulnar motor and sensory finding have compression from a ganglion. Anomalous muscle bellies, lipomas, giant-cell tumors, schwannomas, thickened ligaments, bipartite hamuli, and pisiform–hamate coalitions are also responsible for ulnar nerve compression at the wrist (3,15).

Collagen vascular diseases and various vasculitides and coagulopathies may all cause poor perfusion of the hands and fingers and could be mistaken for HHS. These disorders, however, tend to be systemic and have generalized findings. Buerger disease, also known as thromboangiitis obliterans, affects primarily young males and presents with Raynaud phenomenon. However, it is found almost exclusively in cigarette smokers and often involves both upper and lower extremities, whereas HHS is usually confined to a single hand.

Radial nerve entrapment can present similarly to DQT. Recently, individuals using cell phones or other handheld communication and gaming devices are developing a painful tendonitis from overuse of

the thumbs. Some have termed this as “texting thumb,” “Game-boy thumb,” or “Blackberry thumb” (16). Intersection syndrome, another tenosynovitis of the radial extensor tendons, may be confused with DQT. Patients with this disorder typically have pain, swelling, and crepitus in a more proximal, ulnar distribution in the region where the radial wrist extensors of the second dorsal compartment and the tendons of the first dorsal compartment intersect, rather that at the radial styloid as seen in DQT (17).

ED EVALUATION

Carpal Tunnel Syndrome

Physical examination may reveal decreased sensation to light touch or decreased two-point discrimination in the median nerve distribution. Phalen wrist-flexion test and Tinel sign are frequently found to be positive in CTS but are neither sensitive nor specific (1,18,19). The *Phalen test* is considered to be positive if holding the wrist in complete, but unforced, flexion for 30 to 60 seconds reproduces or exaggerates the numbness and paresthesias in the median nerve distribution. The *Tinel sign* is positive if light tapping over the median nerve at the wrist causes a tingling sensation distally along the median nerve. In more advanced cases, there may be weakness of the median-innervated thenar muscles, the abductor pollicis brevis, and the opponens. Thenar atrophy can develop and is best seen as a guttered appearance along the radial aspect of the thenar eminence that exposes the first metacarpal.

Guyon Canal Syndrome

Physical examination of a patient complaining of a painful wrist and hand with ulnar nerve complaints must include the neck. Painful or limited range of motion may suggest the presence of cervical disc disease. This should be followed by axial compression of the cervical spine, which may elicit radicular pain from a compressed nerve root. The elbow should be examined for evidence of swelling, deformity, inflammation, or masses. The ulnar nerve should be carefully palpated and percussed to assess for increased irritability.

Careful palpation over the hook of the hamate may reveal tenderness associated with an occult new fracture or a poorly healed old fracture.

The *Allen test* performed on both hands will help the clinician to ascertain the ulnar artery's contribution to hand perfusion. The modified Allen test is performed with the patient seated with the palms facing up, resting on the knees. The clinician compresses the radial artery with one thumb and the ulnar artery with the other thumb, thereby occluding the arterial supply to the hand. The patient rapidly clenches and opens the hand several times to exsanguinate the blood from the palm. If there is pathology in the ulnar artery, the palm will remain pale after the pressure over that vessel is released. In this case, blood supply returns to the palm only after the pressure over the radial artery is removed.

In patients with Guyon canal syndrome, the examiner should be able to elicit paresthesias of the ulnar fourth and fifth digits by putting the wrists into complete volar flexion or by percussing over the ulnar nerve at the level of Guyon canal. Impaired sensation of the ulnar dorsum of the hand to both light touch and two-point discrimination with weakness of the flexor digitorum profundus (FDP) muscles of the fourth and fifth digits is suggestive of an ulnar nerve lesion proximal to its bifurcation into motor and sensory branches at the wrist.

Interosseous muscle function can be evaluated by asking the patient to cross the index and middle fingers. *Froment sign* occurs when the adductor pollicis muscle, innervated by the ulnar nerve, is weak. This sign is elicited by having the patient tightly hold a piece of paper between the thumb and the radial side of the index finger while the examiner attempts to pull the paper from the patient (Fig. 145.1). Flexion at the interphalangeal joint of the thumb, indicating weakness of the adductor pollicis muscle, is confirmatory of a positive Froment sign. Comparison should be made with the patient's other hand.

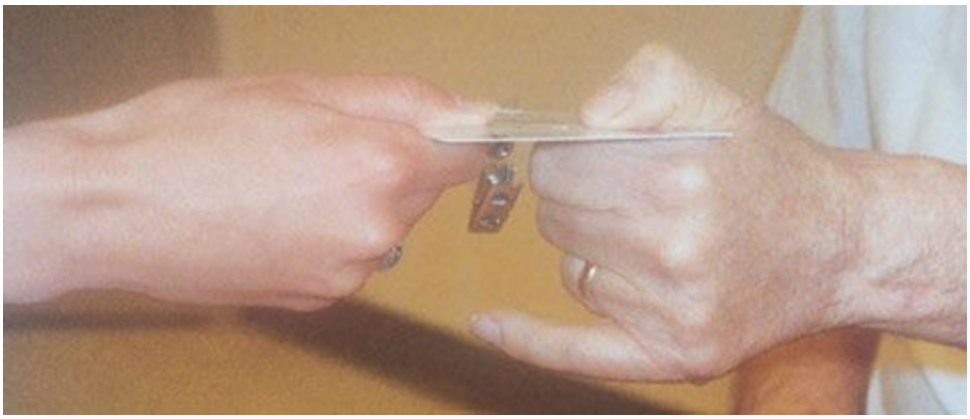

FIGURE 145.1 Froment sign. (From Berg D, Worzala K. *Atlas of Adult Physical Diagnosis*. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)

Hypothenar Hammer Syndrome

Physical findings in HHS are largely localized to the hypothenar eminence and the digits of the affected hand. Prominent calluses over the hypothenar eminence provide a clue about recurrent trauma to this area. Tenderness to palpation over the hypothenar area may indicate the presence of an ulnar artery aneurysm. Further examination may reveal the fingers or fingertips to be cold, pale, mottled, atrophic, or ulcerated (20). The Allen test should be performed, with a positive test suggesting ulnar artery pathology.

De Quervain Tenosynovitis

Examination of the wrist in mild cases may exhibit only subtle, localized swelling at the radial styloid (10,16). Swelling and erythema may be present in more severe cases. Tenderness or crepitus at the radial styloid is highly suggestive of DQT, with a positive Finkelstein test being diagnostic of this condition (11). The Finkelstein test requires that the patient flexes the thumb into the palm and then grasps it with the other fingers of the hand. The patient then actively ulnarly deviates the wrist (Fig. 145.2). Severe, sharp pain with this maneuver constitutes a positive test and is pathognomonic of DQT.

FIGURE 145.2 Finkelstein test.

Imaging and laboratory testing, such as radiographs, are typically not required in clinically straightforward cases of all the foregoing entities unless fracture is suspected, but cervical spine imaging may be useful if clinical symptoms suggest a cervical radiculopathy. Similarly, chest radiographs should be obtained if there is concern for an intrathoracic mass lesion causing a brachial plexopathy. Laboratory studies, in the absence of systemic clinical signs or symptoms, are unlikely to provide any useful information.

ED MANAGEMENT

Carpal Tunnel Syndrome

Wrist splints in neutral or slight extension should be utilized, particularly at night. The patient should avoid activities that aggravate symptoms, and nonsteroidal anti-inflammatory (NSAID) medications should be prescribed.

Guyon Canal Syndrome

The application of a wrist splint, avoidance of activities that aggravate symptoms, and use of NSAIDs should be initiated. Some

have studied using gloves to protect the ulnar nerve from compression during activities (4). A trial period of 1 to 3 months of nonoperative intervention is recommended; however, depending on the etiology, symptoms may or may not resolve during this time (3). The most radical treatment option is surgery to relieve tension over the volar carpal ligament to reduce nerve compression (5).

Hypothenar Hammer Syndrome

Most patients with HHS respond to proper therapy when promptly initiated (21). Local wound care of necrotic or ulcerated digits can be initiated in the emergency department (ED). The patient should be counseled to avoid cold environments and stop smoking, if applicable, and patients should wear mittens or gloves to help keep their hands and fingers warm and protected. Aspirin and low-dose calcium-channel blockers, such as diltiazem 30 mg PO qid or nifedipine 10 mg PO tid, may be prescribed as initial therapeutic agents (21). The prognosis for appropriately treated HHS is generally good, and surgery typically is not necessary. Patients must understand that response to therapy is predicated on discontinuing the repetitive trauma that is the cause.

De Quervain Tenosynovitis

Conservative treatment utilizing rest, application of heat, NSAIDs, and immobilization with a thumb spica splint is often inadequate (10,22). These modalities should be used in addition to the mainstay of treatment, which is steroid injection, a procedure that is up to 83% effective and may be performed by the ED physician (11,22).

Approximately 2 mL of a steroid preparation (Table 145.1) should be drawn up and mixed in a syringe with 0.5 mL of lidocaine. Pass a 25- or 27-gauge needle through the skin at the distal end of the first dorsal compartment. As the needle is slowly withdrawn, the steroid–lidocaine mixture should be easily injected into the tendon sheath (Fig. 145.3). Forced injection of steroids into a tendon is not desirable. A successful injection of the steroid–lidocaine mixture is indicated by the clinician's feeling the medication track distally

along the tendon sheath. Immediate relief of pain from the use of lidocaine is a good marker for appropriate placement (11). Patients should be advised that it may take several days for the steroid to begin relieving their pain and that, in the meantime, there is a possibility of a postinjection flare reaction. This painful phenomenon, sometimes seen after injection of steroids, usually resolves after a couple of days. A short course of opioid pain medications may also be necessary. Ultrasound has been used to facilitate the steroid injections with improved success rates (23).

TABLE 145.1
Corticosteroid Doses for Injection in De Quervain Tenosynovitis

Hydrocortisone 25–100 mg
Methylprednisolone 40 mg
Prednisolone suspension 20–40 mg
Triamcinolone 20 mg

FIGURE 145.3 Corticosteroid injection into the tendon sheath.

CRITICAL INTERVENTIONS

- Identify and instruct patients to stop or modify activities leading to a repetitive-use syndrome.

- Initial conservative therapy should include a period of immobilization, as well as treatment with an NSAID.

DISPOSITION

All patients with diagnosed repetitive injury disorder may be discharged with appropriate precautions and hand specialist referral. Patients with CTS may be referred back to a primary care physician for continued care and future referral to a hand surgeon if necessary. Patients with Guyon canal syndrome and mild HHS should see a hand specialist for followup for additional outpatient evaluation and treatment. In the absence of clarifying historic or physical features for HHS, referral for arteriography or arterial biopsy may be required to confirm or rule out the diagnosis of Buerger disease, which can be managed by the hand surgeon. If the patient with HHS has significant ischemic findings, consultation in the ED by the hand surgeon may be appropriate.

Patients treated with steroid injection for DQT should be advised to seek appropriate followup care with a hand surgeon for either repeat injection or consideration of surgical release if adequate relief is not achieved after the initial steroid injection.

Common Pitfalls

- Failure to perform a thorough physical examination of both upper extremities, as some abnormal findings may be physiologic and not pathologic.
- Failure to examine the entire course of the ulnar nerve from its origin at the nerve roots of the cervical spine to the hand. Ulnar neuropathy may be due to compressive forces at one or more locations along the length of the nerve.
- Failure to recognize an occluded ulnar arterial supply to the hand.
- Failure to consider and recognize HHS, which is a treatable condition, provided that the source of trauma is eliminated.

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CHAPTER 146 Bursitis and Tendinopathy

Ryan Friedberg

BURSITIS

Bursitis is defined as the inflammation of a bursa. The term *bursa* comes from the Greek words “hide” or “wineskin” and the Latin meaning is that of a small leather sac or purse (1). Bursae are flattened sacs of synovial membrane that contain a viscid fluid that moistens the bursa wall to facilitate movement by minimizing friction between contiguous muscles, tendons, bones, ligaments, and skin (2,3).

There are more than 78 bursae on each side of the body, and are found where a tendon rubs against a bone, ligament, or other tendon (4,5). Fortunately, only a few of these bursae usually cause problems that would bring a patient to the emergency department (ED). The most common areas of bursitis seen in the ED are olecranon and prepatellar bursitis. This is likely due to their superficial locations. Other areas of bursitis seen in the ED include the subacromial, trochanteric, ischiogluteal, iliopsoas, pes anserine, and retrocalcaneal bursa (5,6).

Bursitis is usually divided into nonseptic and septic causes. The exact incidence of bursitis is unknown, but some studies suggest it is between 0.01% and 0.1% of ED visits and only 30% are infected (7–9). Approximately 80% of patients that present with bursitis are male and usually between the ages of 31 and 57 (7,10).

Nonseptic bursitis (eFigs. 146.1 and 146.2) is a sterile inflammation of the bursa that has been attributed to multiple causes including trauma, overuse, rheumatic, and idiopathic. Septic

bursitis (eFigs. 146.3 and 146.4), on the other hand, is an infection of the bursal sac usually caused from skin lesions secondary to trauma, but other causes include iatrogenic (needle aspiration) and idiopathic. Hematogenous seeding is a rare cause of septic bursitis (11). *Staphylococcus aureus* is the most common organism found in septic bursitis occurring in 72% to 92% of cases, but rare organisms such as *Cryptococcus neoformans* and *Aspergillus terreus* have been reported in patients that are immunocompromised or have systemic illness (12).

eFIGURE 146.1 AP View of Nonseptic Olecranon Bursitis

eFIGURE 146.2 Lateral View of Nonseptic Olecranon Bursitis

eFIGURE 146.3 AP view of septic Prepatellar Bursitis

eFIGURE 146.4 Lateral View of Septic Prepatellar Bursitis

CLINICAL PRESENTATION

Patients most commonly at risk for developing bursitis include laborers such as miners, gardeners, construction workers, and mechanics, in whom repetitive knee or elbow trauma is common (9). It is also common in athletes such as wrestlers, hockey players, rugby players, and football players where trauma to the knees and elbows are very common. Patients with bursitis, whether septic or nonseptic, present with a few common features. These include localized swelling and fluctuance of the bursa and usually painless passive range of motion of the elbow or the knee joint. Pain, although present in almost all septic bursitis patients, is also seen in about 45% of nonseptic bursitis patients. If generalized joint swelling, inflammation, and restricted range of motion are present, septic arthritis (and hence the need for an arthrocentesis) should be considered in the differential diagnosis (9).

Some features that help to differentiate a septic bursitis from a traumatic nonseptic bursitis include local pain, redness, warmth, and fever.

The most common type of bursitis seen in the ED is olecranon bursitis. This is the only bursa of the elbow joint and is on the extensor aspect over the olecranon process (9). In some outpatient series, it is more common than prepatellar bursitis by a ratio of 4:1 (13). This has been ascribed to the higher frequency of pressure damage and injury to the elbow compared to the knee.

DIFFERENTIAL DIAGNOSIS

Included in the differential diagnosis of bursitis is the consideration of arthritis (septic versus nonseptic), trauma, crystal-induced disease (such as gout, calcium pyrophospate dihydrate crystals), rheumatoid arthritis, and arthritis associated with such conditions as uremia, scleroderma, ankylosing spondylitis, pancreatitis, and SLE (6,9,14). An overlying cellulitis is also in the differential diagnosis (9). Although much less common, other bursae that have been noted to be septic include the trochanteric and subacromial bursae. Bacterial

endocarditis has been noted to be associated with trochanteric bursitis (15).

ED EVALUATION

Differentiation between septic and nonseptic bursitis is important. Historical findings are not particularly helpful in attempting to differentiate between aseptic and septic olecranon and prepatellar bursitis. A history of trauma may be seen with equal frequency in septic and nonseptic cases of bursitis (6,9). A prior history of bursitis that reflected past injury or an underlying rheumatic disease also was not found helpful in distinguishing between the two. However, the duration of symptoms before presentation is generally shorter in the patient with septic bursitis (14).

Although the gold standard for diagnosis of a septic bursitis is a culture-positive aspirate, physical findings are often helpful in the differentiation between septic and nonseptic bursitis (14). Fever is very specific to septic bursitis and almost never associated with nonseptic bursitis (6,13,15). An abrasion or laceration may be present in about half of patients with septic bursitis (9). Tenderness to touch, peribursal soft tissue inflammation, and overlying skin lesions are more commonly seen in infected bursae than in noninfected bursae. Elevation of surface temperature overlying the bursa of $>2.2^{\circ}C$ when compared to unaffected side has also shown to be very specific and sensitive in determining a septic bursa (16). Peribursal cellulitis is not uncommon in septic bursitis, and has been described at times as “so severe as to obscure the underlying bursal pathology” (6). Occasionally a concomitant effusion in a joint or tissue space adjacent to the bursa has been seen in septic bursitis (6,9). In nonseptic bursitis, a nontender bursal effusion (traumatic or idiopathic) may be present, although almost half have mild bursal tenderness.

Patients with crystal-induced bursitis show signs of acute bursal inflammation. Some may have a low-grade fever and a concurrent gouty arthritis (17,18). There have been reports of concurrent septic bursitis in patients with gouty bursitis (9).

Once the clinical diagnosis of bursitis of the olecranon or prepatellar bursa is made, aspiration and analysis of the bursal fluid may reveal the cause of inflammation (13). Although fluid analysis is the gold standard for diagnosing septic arthritis, the need to aspirate every olecranon or prepatellar bursa as part of the initial management has become controversial. Many have stated that bursal aspiration is a necessary part of the initial workup for bursitis to appropriately direct the therapy (8,9,14,19,20). The aspiration is diagnostic and can also be therapeutic. The controversy lies in the concern for the complications arising from the aspiration. The two most serious complications are infecting a nonseptic bursitis and creating a draining fistula or tract that will not heal and may become infected. Thus, some authors suggest forgoing aspiration and treating only with rest, compression, and NSAIDs if a nonseptic bursitis is suspected (6,7,14). However, the bursa should be aspirated if there is any suspicion for infection and appropriate antibiotics should be administered. When determining ED management, one should consider discussing the need to aspirate with the specialists providing subsequent treatment so the care remains consistent.

It has been recommended that if there is suspicion of an infection in an adjacent joint, any fluid collection should be analyzed when septic bursitis is diagnosed so that a septic effusion can be differentiated from a “sympathetic” effusion (6). Aspiration should be performed through skin that is not affected by cellulitis, if at all possible (6).

When aspirating a bursa, an aseptic lateral approach to the bursa using an 18- to 22-gauge needle has been described (9). It has been recommended that aspiration from the extensor side of the elbow or knee should not be done because of the potential of a higher risk of chronic fluid drainage (9). Sufficient fluid should be aspirated so as to drain the potentially infected bursa and obtain appropriate studies. The aspirate should include a white blood cell (WBC) count with differential, crystal evaluation, and culture and sensitivities (8). It has been suggested that fluid glucose and lactic acid levels be measured, since low glucose and elevated lactic acid levels may be

found in the presence of bacterial infection, but these are neither sensitive nor specific (6).

The appearance of the aspirate in septic bursitis may be purulent, straw colored, or serosanguinous. In the nonseptic bursa, the aspirate may range in appearance from straw colored to bloody (9). Although the presence of organisms on Gram stain or culture is diagnostic for septic bursitis, the WBC count is helpful in distinguishing septic from nonseptic bursitis. The Gram stain is not positive. In a nonseptic bursa, the leukocyte count is usually less than 1,500 per μL, with a predominance of mononuclear cells. It is uncommon to be more than 10,000 WBCs per μL (9). Septic bursitis is more likely to present with a higher WBC count with a predominance of polymorphonuclear cells, but a low WBC count does not rule out infection (9). Gram stains of culture-proven septic bursitis have been reported to be negative in about 30% of cases and hence cannot be used alone to exclude a septic bursitis.

Routine cultures should be done of the aspirate. Some series indicate that *S. aureus* is found in 80% to 100% of positive cultures; *Streptococcus* (group A β-hemolytic *Streptococcus* most commonly) is seen in less than 10%. *Staphylococcus epidermidis* has been cultured as well. Anaerobes, mycobacteria, fungi, *Haemophilus influenza,* and other gram-positive and gram-negative organisms have been found infrequently (6,9,20,21).

Crystal-induced bursitis, most commonly associated with gout, should reveal negatively birefringent urate crystals. Olecranon bursitis caused by calcium pyrophosphate dihydrate crystals has been reported as well. The appearance of the fluid may range from straw colored to bloody. Cell counts overlap septic and other nonseptic etiologies, ranging from 1,000 to 6,000 per μL, and concomitant gouty and septic bursitis have been reported (9). A recently injected bursal sac may contain the birefringent crystals of a long-acting steroid preparation (6).

Depending upon the history, radiographs may be indicated. Soft tissue abnormalities, such as calcifications, swelling, or gas, may be seen. Bony disruption as a result of trauma, foreign body, and other possible etiologies or associated abnormalities should be considered.

Although not common, an associated osteomyelitis has been described, and was associated with a longer delay to diagnosis from onset of symptoms (>3 weeks). Ultrasonography can be done to confirm a fluid collection, possibly detect loose bodies, rheumatoid nodules, as well as gout tophi, but cannot differentiate between septic and nonseptic bursitis (11). Computed tomography (CT) or magnetic resonance imaging (MRI) may also be indicated in specific circumstances (6,15).

KEY TESTING

- If septic bursitis is suspected, aspirate fluid for cell count, crystals, Gram stain, and culture.

ED MANAGEMENT

An inflamed olecranon or prepatellar bursa associated with a positive aspirate warrants appropriate antibiotic treatment. As discussed earlier, sometimes the determination of a "positive aspirate" is difficult to discern prior to the results of the culture due to the significant rate of false negative Gram stains and the significant overlap of cell counts in septic and nonseptic bursitis. In cases where the Gram stain is negative and the cell count is indeterminate it is recommended to start antibiotic treatment until the culture results are available. Penicillin antibiotics have been shown to achieve effective bursal concentrations when given either intravenously or orally. A 14-day course should be given. Other effective antibiotics include cefazolin IV and clindamycin PO (7). The presence of a bursal infection for more than 2 weeks before the initiation of antibiotic treatment is associated with persistently positive cultures on serial aspirations, and thus may require more prolonged therapy. Patients with a history of bursitis (septic or nonseptic), rheumatoid nodules, gouty tophi, immunocompromised with severe infection, or septic bursitis due to unusual organisms may also require a prolonged course of antibiotics (9). Empiric antibiotic therapy should include coverage for both *S. aureus* and *Streptococcus* species. Close follow-up and possible repeated

aspiration may be necessary (9). If there is no improvement with antibiotics and aspiration, bursectomy may be indicated. The determination to perform a bursectomy is usually reserved for critically ill patients, severe soft tissue complications, immunocompromised patients, refractory cases, or chronic/recurrent cases (11).

Supportive measures such as warm soaks, wound care for associated lesions, and protection of the bursa from further trauma are important. Some cases of bursitis may require surgical excision and drainage, and recovery from septic bursitis may take months (8,12).

Treatment of acute nonseptic bursitis (traumatic or idiopathic) has included initial aspiration, the utilization of compression dressings, and administration of nonsteroidal anti-inflammatory agents (9). Although steroid injections into the nonseptic bursa has been suggested by some (9), it seems prudent in the ED to await the results of cultures and arrange for follow-up rather than to initiate long-term therapy in the ED, especially in the face of a possible septic bursitis. In one series, complications of intrabursal steroid injections included skin atrophy over the bursa (20%), chronic pain associated with pressure applied to the elbow (30%), and the development of a septic bursitis (10%) (9,22). Since all patients with bursitis need close follow-up and there is some controversy as to the initial management (to aspirate or not), it is recommended that the initial management be discussed with the physician who will be following the patient.

Although controversial, it seems reasonable that for patients in whom the suspicion of septic bursitis is very low, aspiration may be avoided in favor of conservative therapy consisting of rest, compression, NSAIDs, and close follow-up. If these methods prove unsuccessful, one should consider aspiration with or without steroid injection. There have been no conclusive studies evaluating the risks and benefits of conservative management of nonseptic bursitis comparing rest, compression and NSAIDs versus aspiration.

Treatment of nonseptic bursitis in other areas of the body including the subacromial and trochanteric bursa can be managed

the same way as olecranon and prepatellar bursitis. It should be noted that complications from cortisone injection such as skin atrophy and the development of a septic bursitis are much less in the subacromial or trochanteric bursa due to the fact that they are not as superficial as the olecranon or prepatellar bursa. In the hands of a properly trained physician, a bursal injection of a steroid and lidocaine or bupivicane mixture can hasten relief, and can thus be another option in addition to NSAIDs and rest (23).

CRITICAL INTERVENTIONS

- Initiate antibiotic therapy for patients with bacterial infection

DISPOSITION

As oral antibiotics seem to provide good bursal coverage in septic bursitis, patients with a noncomplicated olecranon or prepatellar septic bursitis, and without significant comorbidity, may be discharged with appropriate follow-up. Some authors recommend at least one dose of IV antibiotics in the ED followed by outpatient antibiotics (7). It has been recommended that those with a purulent aspirate should be aspirated at 1- to 3-day intervals as long as the effusion persists (9).

Those with severe septic bursitis, purulent drainage, or other underlying medical problems should be considered for hospital admission and treatment with intravenous antibiotics. Indications for inpatient therapy include the presence of a high fever, severe bursal infection (intense peribursal cellulitis or wound infection), or systemic toxicity (9).

Common Pitfalls

- Failure to distinguish between a septic and nonseptic bursitis
- Misdiagnosis of septic arthritis as bursitis
- Failure to discern underlying bony or soft tissue pathology causing persistent symptoms
- Failure to arrange appropriate follow-up

TENDINOPATHY

Tendons are structures interposed between muscle and bone that transmit the force created within the muscle to the bone, making joint movement possible (24). They consist of collagen bundles that provide tensile strength and an extracellular matrix that, among other duties, provides structural support. The tendon is covered by the epitenon, a loose connective tissue that contains the blood, lymphatic, and nerve supply. The epitenon is surrounded by the paratenon, and the two are sometimes called the peritendon (25).

Tendinopathies have been in the past referred as “tendonitis,” which infers inflammation of the tendon. Through histopathologic studies of the disease process, it has been shown that most “tendonitis” is actually a degenerative process going on within the tendon and not an inflammatory one (25,27). Thus, the term “tendonitis” is often a misnomer, and the terms tendinopathy or tendinosis should be used. It is possible that there is an acute inflammatory reaction that occurs at the initial stages of the degenerative process, but if so, it is likely to last upto only several days and most of the pain that people present to the ED with is likely due to more chronic symptoms secondary to degenerative changes within the tendon (26).

As a rule, a history of overuse is common in many tendinopathies, and the osteotendinous junction is the most common site (26,28). This is possibly due to the fact that tendons are relatively hypovascular proximal to the tendon insertion (29). This hypovascularity may predispose the tendon to hypoxic degeneration and has been implicated in the etiology of tendinopathies (26). Participation in athletics and occupational duties that require repetitive motions have been implicated in overuse syndromes (tendinopathies) which likely stem from cumulative, repetitive microtrauma that causes degenerative tissue damage (30). Some relatively common tendinopathies discussed that may present to the ED include those of the *rotator cuff* (both noncalcific and calcific), the *biceps tendon,* the *extensor carpi radialis brevis (ECRB) tendon (lateral elbow),* the *patellar tendon,* and the *Achilles tendon* (31).

KEY TESTING

- X-rays: Can diagnose calcific tendinopathies and rule out underlying bone abnormalities.
- Ultrasound: Ultrasound has proven to be very effective in diagnosing tendinopathies.
- Physical exam: If unable to reproduce symptoms during physical exam either with palpation or provocative maneuvers then one must consider other etiologies of the pain.

CLINICAL PRESENTATION

The classic presentation of a patient presenting with a painful tendon is one of increasing pain at the site of the tendon, and often a history of an increase in the use (hence, "overuse") of the attached muscle. The pain is often related to the load. An early tendinopathy may be noted to cause discomfort early in the activity, diminish with continued activity, and then recur after the activity if it has been prolonged. Subsequent episodes may be of increased severity (30).

The pain is usually well localized and has been described as "sharp" or "severe" during the early stages, progressing to a "dull ache" in some patients. The pain usually does not radiate and can be reproduced with movement against resistance of the attached muscle. Exacerbation is caused by activity that increases the load on the tendon, and factors that relieve the discomfort may include relative rest, ice, NSAIDs, or other analgesic medications (32).

Associated systemic diseases that may cause a tendinopathy include an underlying spondyloarthropathy (e.g., psoriasis) as well as a tendinopathy related to a sexually transmitted disease (e.g., gonococcemia) or treatment with a fluoroquinolone (31,32).

Rotator Cuff Tendinopathy

Rotator cuff tendinopathy is the most common manifestation of what has been described as the subacromial pain syndrome (SPS) (36). The rotator cuff consists of a set of four muscles (supraspinatus,

infraspinatus, teres minor, and subscapularis) which, with the deltoid muscle, enables the arm to be positioned in the overhead position. The rotator cuff muscles, anchored on the scapula, pass beneath the coracoacromial arch. Diminished space as a result of anatomy, swelling, or trauma may cause the classic presentation of rotator cuff tendinopathy by causing impingement of the supraspinatus tendon against the anterior inferior aspect of the acromion or the coracoacromial ligament. An external rotator of the humerus as well, the supraspinatus tendon, assists the deltoid in abducting the arm, with its greatest contribution being the initiation of abduction (36). The impingement injury has three stages. The first is edema and hemorrhage. As impingement becomes repetitive, fibrosis and thickening of the subacromial bursa with tendinopathy in the supraspinatus occurs. The third stage represents a tear of the tendon, either partial or complete (37).

The clinical presentation of rotator cuff tendinopathy (or tear) includes pain, weakness, and decreased range of motion. Pain is noted in the anterior, superior, and lateral aspects of the shoulder. Acute tendinopathy may be associated with mild pain when attempting to do overhead activities. As the tendinopathy becomes more persistent, the pain may occur at rest and increase with overhead activities. As there is progression to a partial- or full-thickness tear, there may be persistent pain at rest and pain at night. There may be weakness and limited active range of motion (37).

With *calcific tendinopathy,* deposition of calcium hydroxyapatite crystals in the tendon is seen through ultrasound or radiographically. Bilateral involvement is not uncommon (38). However, up to 20% of adults with no shoulder pain may have evidence of calcification of the rotator cuff tendon (38,39). Patients may complain of variable degrees of pain, either at rest or on movement. Discomfort at night and a “catching” on movement have been described (38). Pathophysiologically, the rotator cuff tendon goes through several stages, beginning with an asymptomatic fibrocartilaginous transformation, which is followed by the development of calcification within the cuff. The next stage (resorptive) is described as the most incapacitating as there is

formation of crystals that may cause severe pain and restriction of movement. Some patients may have systemic symptoms including fever and malaise, and may have an elevated erythrocyte sedimentation rate and neutrophilia. In such cases, the differential diagnosis includes gout and a septic joint. This stage may last for 2 weeks. The final stage involves healing and repair of the rotator cuff, associated with some residual pain and restriction of movement. Specific tenderness over the greater tuberosity and symptoms similar to the impingement syndrome may be seen (39).

Biceps Tendinopathy

A similar tendinopathy to that of the rotator cuff, especially seen in those with overhead activities and impingement, is that of the biceps tendon. It may occur either with rotator cuff symptoms or independently. Most cases of bicipital tendinopathy are believed to be secondary to impingement (40). Patients may have anterior shoulder pain (at the bicipital groove) that is exacerbated with supination and pronation, and on palpation have pain at the bicipital groove.

Lateral Elbow Tendinopathy (Tennis Elbow)

Tennis elbow is reflective of tendon overuse and failed healing. Initial signs and symptoms include activity-related discomfort followed by pain at rest after pathologic changes become more extensive (28). Palpable tenderness over the lateral elbow (lateral epicondyle) may be present in the early stages. Pain of the lateral elbow caused by extensor involvement is not uncommon, often seen in those who play racquet sports (tennis elbow). This is seen with eccentric overuse of the forearm extensors (e.g., backhand) (41). Pain with manual stress testing including extension of the wrist and supination of the forearm usually confirms the site of the lesion (28). Tennis elbow has been described as primarily involving the ECRB and secondarily the extensor digitorum communis (28,41). Pain with extension of the middle finger against resistance may cause pain over the insertion of the ECRB over the lateral elbow.

Patellar Tendinopathy

The knee pain of patellar tendinopathy may have an insidious onset, and is often ascribed to an activity involving jumping, or an episode of exercise that is related to a heavy training session. The patient complains of pain usually localized to an area over the anterior knee region, often complaining of tenderness at the inferior pole of the patella. Pain is often exacerbated by climbing stairs and prolonged sitting. As is not uncommon early in the course of a tendinopathy, discomfort may ease completely with exercise, progressing to the point of discomfort at rest (43).

Achilles Tendinopathy

Achilles tendinopathy is common among adult runners, with a higher incidence as age increases. The etiology is usually multifactorial (i.e., overuse, improper technique, anatomic misalignment, improper footwear, and weakness) (26). Pain is usually proximal to the insertion at the calcaneus, but can extend up to the musculotendinous junction. Physical examination often reveals a thickened, tender tendon.

DIFFERENTIAL DIAGNOSIS

Depending upon the location of pain, the differential diagnosis of various tendinopathies should include fracture, bursitis, arthritis, muscle strain, ligamentous sprains, and referred pain. Apparent rotator cuff symptoms may represent pain referred from the cervical spine, pain from the AC joint, osteolysis of the distal clavicle, or other shoulder pathology (e.g., instability, labral tear, etc.). Other potential etiologies to be considered are referred cardiac pain or intrabdominal injury such as gall bladder disease or splenic injury.

The differential diagnosis of *tennis elbow* also includes posterior interosseus nerve entrapment (motor component of the radial nerve in the forearm). The clinical manifestations of this neuropraxia include diffuse pain and tenderness along the track of the radial nerve in the extensor mass of the proximal forearm (28). Synovitis, plica, chondromalacia, and adolescent osteochondral defect (OCD)

are also in the differential diagnosis. Lateral elbow discomfort may also be associated with referred pain from the cervical spine (28,31).

Patellar tendinopathy must be differentiated from patellofemoral pain syndrome, especially in the athlete who participates in jumping sports. However, the clinical features are generally distinctive (43). Lesions of the quadriceps (e.g., tear), patellar lesions, and the possibility of rupture may also be considered.

ED EVALUATION

A thorough history and directed physical examination is important in the evaluation of the patient who presents to the ED with a tendinopathy. Imaging of tendinopathies may be accomplished with the use of radiographs, diagnostic ultrasound, and MRI (31,44). Radiographs can pick up calcific tendinopathies as well as evaluate for bony abnormalities (i.e., hooked acromium) that can predispose one to developing a tendinopathy. The use of bedside ultrasound has become very common among ED physicians, and can be very helpful in confirming the diagnosis of a tendinopathy. The use of ultrasound for diagnosis of tendinosis has proven to be a specific, but not sensitive test (33–35). The use of MRI to evaluate for tendinosis is much more sensitive and specific, but since a tendinopathy is not a true emergency, MRI should not be part of the initial ED evaluation. Other imaging techniques as indicated (e.g., radiography, CT, bone scan) may be useful in ruling out other possibilities in the differential diagnosis.

In *rotator cuff tendinopathy,* physical examination may reveal signs of impingement or a tear. The supraspinatus, the most common rotator cuff component exhibiting a tendinopathy, may be examined by resistance testing. In an attempt to isolate the supraspinatus, the arms are abducted 90° in the scapular plane (30° anterior to the coronal plane). The arms are internally rotated so that the thumbs point downward. A downward force is placed on the arms, while the patient attempts to resist by maintaining the arms parallel to the floor. An inability to resist the force is an indication of isolated

supraspinatus weakness (37). With advanced impingement and a full thickness rotator cuff tear, the patient may be unable to abduct the arm, and on examination may be unable to maintain the arm in an abducted position after the examiner places it there. This is the drop arm sign (36).

The impingement sign described by Neer consists of forward flexing the fully internally rotated arm, causing the greater tuberosity of the humerus to impinge upon the anterior and inferior surface of the acromium. An abnormal test is indicated by pain. The examiner should fully flex the patient's shoulder to 180°. If pain is produced at the end range of the arc, it is considered to be positive. Testing of the infraspinatus and teres minor is done by having the patient place the arms to the side, flex the elbow, and attempt to externally rotate against resistance (37). With long-standing disease, range of motion may be limited. The subsequent development of adhesive capsulitis may make the diagnosis of impingement more difficult (36).

In patients with suspected *bicipital tendinopathy, speed test* is performed by having the elbow extended and the forearm supinated. The examiner then resists forward flexion of the adducted shoulder. Pain that radiates to the bicipital groove is a positive test (40). *Yergason test* is performed by having the patient flex the elbow to 90° with the arm at the side. The patient is asked to supinate forcefully against resistance. Pain referred to the bicipital groove with resisted supination of the forearm is a positive test (40).

Patients with *patellar tendinopathy* are often tender to palpation of the patellar tendon attachment at the inferior pole of the patella. Tenderness is generally elicited on the deep surface of the proximal attachment of the patellar tendon when the knee is flexed at 30° with the quadriceps muscle in total relaxation (45). Depending upon the chronicity of the condition, quadriceps wasting may be seen (43). Although mild tenderness may be a normal finding in active athletes, moderate and severe tenderness have been noted to be associated with ultrasonographic evidence of tendinopathy. Pain may also be reproduced with the decline squat test, which places a

greater load on the patellar tendon than does a squat on level ground (43).

Lateral epicondylitis (tennis elbow) usually presents with reproducible pain over the extensor tendons of the forearm as they originate from the lateral epicondyle. Extension of the wrist and supination of the forearm against resistance often reproduces the pain. If a patient presents with pain over the medial epicondyle and pain with wrist flexion and pronation, one must think of medial epicondylitis (golfer's elbow) as a leading diagnosis.

Achilles tendinopathy is often easy to diagnose as the Achilles tendon is usually easy to palpate. Patients usually present with posterior heel pain, just proximal to the insertion. Often times, one can appreciate a thickened and tender tendon with palpable nodules (26).

Diagnostic imaging in the ED, if indicated, may include radiographs of the affected location. A routine shoulder series should include an anteroposterior (AP) view with both internal and external rotation of the humerus. An axillary view will permit better visualization of the glenohumeral joint, the glenoid margin, and the acromion. A scapular Y-view assesses the anterior slope of the acromion (37). Ultrasonography and MRI have been utilized in the evaluation of the rotator cuff (37). The diagnosis of *calcific tendinopathy* is confirmed by radiographs that show calcium restricted to the tendon without affecting the bone. Patients with *bicipital tendinopathy* may show signs of impingement or spurs in the bicipital groove (40). Up to 20% of patients with *lateral elbow tendinopathy* may exhibit tendon calcification or a reactive exostosis at the tip of the lateral epicondyle (42). Like with the other tendinopathies, radiographs for Achilles tendinopathy can yield calcifications in the tendon as well as spurring off the calcaneus.

ED MANAGEMENT

Treatment of the tendinopathy necessitates a long-term plan which usually should include a supervised program of physical therapy. A tendinopathy may take from weeks to months to heal. Depending

upon the circumstances, protection, rest, ice, compression, elevation, and medication have been advised (41). In the ED, along with rest from the inciting activity, the patient may be prescribed an NSAID for pain relief. The efficacy of NSAIDs as a treatment for "inflammation" in the tendinopathies has been questioned, given the paucity of data for the occurrence of inflammation seen. In fact, the analgesic effect of NSAIDs may permit patients to ignore the early symptoms of tendinopathy (31). Some authors have suggested that NSAIDs could benefit patients with tendinosis via alternate mechanisms such as accelerated formation of cross-linkages between collagen fibers (46,47). Cryotherapy has also been suggested as an effective modality (41,44) theoretically slowing the metabolic rate of tissue and possibly decreasing the extravasation of blood and protein from the new capillaries formed during tendinosis (26).

Some have advocated injection of a corticosteroid. However, given the potential complications of steroid injections (including the possible injection of steroid into the tendon and hence a loss of tensile strength and spontaneous rupture), it seems prudent to pursue other treatment options as the initial management (relative rest, ice, physical therapy). If these other treatments fail, then corticosteroid injection could be considered. Thus, it is not advocated for corticosteroid injection to be part of the initial ED management of a tendinopathy, and that it is necessary for the ED physician to arrange appropriate follow-up for these patients. Should nonoperative treatment fail, surgical options may be indicated (36,37).

Treatment of *calcific tendinopathy* includes control of pain and maintenance of function. The acute phase may require rest of the affected arm in a sling (beware, however, of adhesive capsulitis, i.e., "frozen shoulder"). Pain may be controlled with aspirin, NSAIDs, acetaminophen or ice (38). Corticosteroid injection is controversial in the acute phase, as it has been argued that it may inhibit the resorptive process. Others have advocated its use, especially when the rotator cuff impinges on the undersurface of the acromium as a result of inflammation (38). Fluoroscopically guided needle lavage in the resorptive phase, performed in the operating room or

radiology suite, has been noted to be effective (39). The use of ultrasound as well as extracorporeal shock wave therapy (ESWT) have also been studied as therapeutic modalities (38,39). Arthroscopic surgery may also be required (39).

Load reduction and relative rest are keys to management of a *patellar tendinopathy*. Complete immobilization is contraindicated as the tensile load stimulates collagen production and directs the alignment. Cryotherapy (i.e., ice) may also be effective in the treatment of patellar tendinopathy.

Relative rest, NSAIDs, and ice are also mainstay treatments for the initial management of lateral epicondylitis and Achilles tendinopathy.

For all patients suffering from tendinopathies, appropriate follow-up should be recommended. There are many different types of treatment options that have been studied with varying degrees of success. These options are usually not prescribed by the ED physician, but rather by the specialist or the patient's primary physician. They include physical therapy focusing on eccentric muscle strengthening as well as the use of modalities such as ultrasound, iontophoresis and phonophoresis, deep tissue massage, ESWT, orthotics and braces, and corticosteroid injection (26). If nonoperative treatment fails, surgery can prove very successful in certain cases and usually involves debridement of the unhealthy tendon.

CRITICAL INTERVENTIONS

- Advise initial conservative therapy for patients with a tendinopathy, including rest, ice, and an NSAID.
- Identify patients with calcific tendinopathy, as they are at risk for capsulitis.

DISPOSITION

Given the potential chronicity of a tendinopathy, the need for appropriate patient education, physical therapy, and the potential

need for surgical intervention, it is important to arrange appropriate outpatient follow-up.

Common Pitfalls

- Underestimation of the potentially long time required for healing.
- Failure to consider other entities that may present with similar findings (e.g., MI, splenic rupture, stress fracture).
- Discharge without an appropriate follow-up plan.
- Excessive or prolonged splinting or bracing (e.g., shoulder sling, knee immobilizer), which can lead to capsulitis of the shoulder or stiffness of the knee.

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CHAPTER 147
Hand Infections

Carl R. Chudnofsky and Melanie Loewenthal

ESSENTIAL ANATOMY

The nail plate inserts into a depression on the dorsum of the finger called the *proximal nail fold,* which divides the proximal nail fold into superficial and deep epithelial surfaces called the *dorsal roof* and *ventral floor,* respectively. The eponychium, commonly called the *cuticle,* is a horny layer extension of the proximal nail fold that extends a short distance onto the dorsum of the nail. It seals the potential space between the nail plate and the proximal nail fold. Laterally, the proximal nail fold is continuous on either side with the lateral nail folds or paronychium. The soft tissue under the distal free edge of the nail is called the hyponychium (Fig. 147.1).

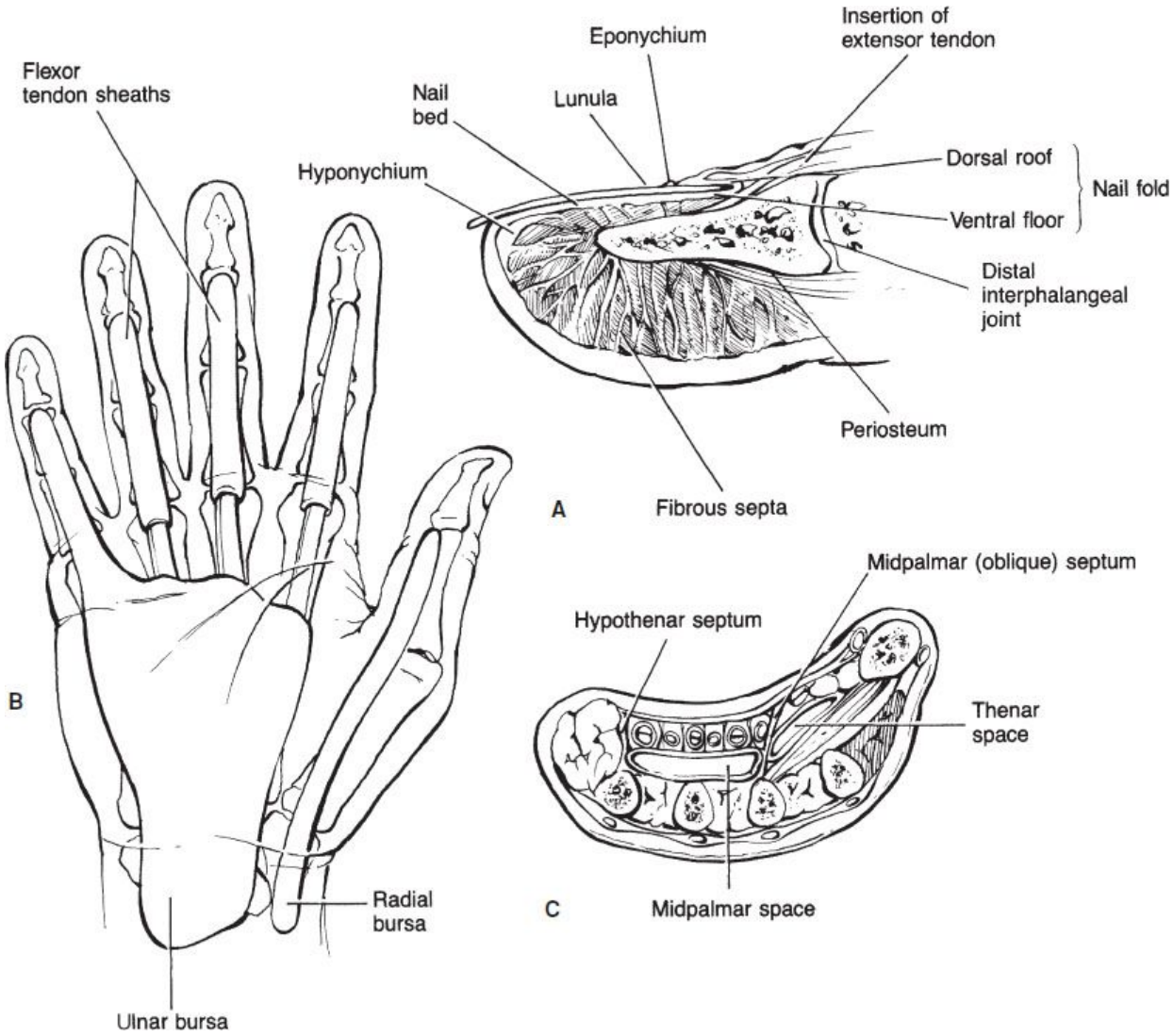

FIGURE 147.1 Anatomy. **A:** Fingertip and nail bed. **B:** Flexor tendon sheaths. **C:** Deep palmar spaces.

The distal pulp space of a finger or thumb is composed of fat globules that are divided into small fascial compartments by 15 to 20 vertical fibrous septa. The presence of these compartments has a substantial impact on the pathophysiology and management of pulp space infections (see “Felon”).

The flexor tendons are surrounded by a tendon sheath that is composed of an outer fibrous sheath and an inner synovial sheath. The inner synovial sheath has a visceral and parietal layer with a potential space between them. The tendon sheaths of the index, middle, and ring fingers extend from the midpalmar crease to just

beyond the distal interphalangeal joints. The tendon sheath of the flexor pollicis longus tendon begins at the base of the distal phalanx of the thumb and extends to the pronator quadratus muscle in the wrist. Between the base of the thumb metacarpal and the wrist, the tendon sheath of the flexor pollicis longus tendon is called the *radial bursa.* The tendon sheath surrounding the flexor tendons of the little finger begin just distal to the distal interphalangeal joint and, like the tendon sheath of the flexor pollicis longus tendon, ends at the pronator quadratus muscle in the wrist. The ulnar bursa is that part of the tendon sheath between the fifth metacarpal and the pronator quadratus muscle (Fig. 147.1). The radial and ulnar bursae communicate with each other in up to 80% of patients (1).

The hand contains several fascial spaces that are potential sites of infection. The most frequently infected spaces are the deep palmar spaces, which include the thenar space, midpalmar space, hypothenar space, Parona's space, and the web spaces. The *thenar space* is bounded on its ulnar side by the vertical septum between the third metacarpal and the long finger profundus and, radially, by the lateral edge of the adductor pollicis. The adductor pollicis also forms the dorsal roof of the compartment. The *midpalmar space* lies deep into the flexor tendons. Radially, it is bordered by the vertical septum between the third metacarpal and the long finger profundus and ulnarly by the hypothenar muscles. The dorsal roof is formed by the fascia over lying the second and the third palmar interossei and the third and fourth metacarpals. The *hypothenar space* contains the hypothenar muscles. It is bordered radially by a fibrous septum from the fifth metacarpal to the palmar fascia. *Parona's space* communicates with the hand via the carpal tunnel and is responsible for allowing infections of the hand to propagate into the forearm. This space is bordered palmarly by the flexor tendons, dorsally by the fascia overlying the pronator quadrates, radially by the flexor carpi radialis, and ulnarly by the flexor carpi ulnaris.

The majority of hand infections are caused by *Staphylococcus aureus* and *Streptococcus* species. The prevalence of community-acquired MRSA (CA-MRSA) has continued to rise in recent years, leading to an increase in CA-MRSA hand infections (2). In fact,

multiple studies since 2007 have found that the majority of hand infections are now caused by CA-MRSA (3–8). It is also important to note that intravenous drug abuse continues to be the most significant risk factor for CA-MRSA hand infections; other risk factors include infections of the digital pulp space (i.e., a Felon) and a history of a prior hand infection (2,9).

Polymicrobial infections are also increasingly common, with a prevalence reported as high 19% (10). Diabetics, patients with farm injuries, bite wounds, immunocompromised hosts and patients with a history of intravenous drug abuse are at particular risk (1,10). Anaerobes are noted in approximately 30% of all hand infections and in 40% of infections secondary to human bite or clenched-fist injuries and intravenous drug abuse (11). Gram-negative organisms are rare in normal hosts but are common in patients with diabetes mellitus or a depressed immune system (12).

Chronic hand infections may be caused by atypical mycobacteria, particularly *Mycobacterium marinum,* a common cause of hand infections occurring in aquatic environments. Sporotrichosis is a subcutaneous infection caused by *Sporothrix schenckii* (13). It usually involves the upper extremity, and is the most common subcutaneous fungal infection. Immunocompromised patients may be infected with a variety of fungi, including *Candida albicans, Coccidioides immitis, Cryptococcus,* and *Aspergillus* (14–16).

A careful and detailed history and physical examination are essential for the diagnosis and management of hand infections. A history of trauma, especially penetrating trauma, is frequently present in patients with a hand infection. The type of trauma and the setting in which that trauma has occurred can provide valuable clues to the causative organism. Cat bites are commonly infected with *Pasteurella multocida,* and infected human bite wounds or clenched-fist injuries are frequently caused by *Eikenella corrodens* and other oral flora (11). The progression of symptoms may also be helpful in determining the type of bacteria present. Streptococcal infections evolve over 24 to 48 hours and are more often associated with cellulitis and lymphangitis. In contrast, *S. aureus* is more likely to

cause a suppurative infection that develops over 3 to 6 days. Chronic infections are more often due to fungi or atypical mycobacteria (1).

Associated symptoms may aid in gauging the severity of infection and the choice of initial antimicrobial therapy. For example, a urethral or endocervical discharge in a patient with a suspected flexor tenosynovitis suggests disseminated gonorrhea. Finally, the presence of underlying medical problems (e.g., diabetes mellitus, cancer, acquired immunodeficiency syndrome [AIDS]), intravenous drug abuse, and the use of certain medications, particularly immunosuppressive agents (e.g., steroids), frequently have a significant impact on the diagnosis, treatment, and microbiology of hand infections.

The position of the hand and fingers at rest and the presence of any wounds should be noted. The location and nature of swelling, fluctuance, erythema, warmth, or tenderness should be carefully documented. The hand and individual digits should be put through a full range of motion. A thorough and well-documented neurovascular assessment is essential.

PARONYCHIA

A paronychia is an infection involving the lateral nail fold (paronychium). It is the most common infection of the hand (17). It results from mechanical separation of the eponychium from the nail plate with subsequent invasion of bacteria or fungi. Common risk factors for a paronychia include hangnails, manicures, and nail biting (1). Individuals whose hands are repeatedly submerged in water (e.g., dishwashers) seem to be particularly susceptible (18). Extension of the infection to involve the adjacent eponychium and proximal nail fold is called an *eponychia.*

The *clinical presentation* of an acute paronychia includes pain, swelling, and redness along the lateral nail fold in the area adjacent to the eponychium. If ignored or untreated, it may extend to involve the eponychium and proximal nail fold (i.e., eponychia) or, rarely, to the lateral nail fold on the opposite side (i.e., run-around infection). The involved tissue is usually very tender. Fluctuance is generally present but may be absent early in the course of the infection. In

severe infections, pus may extend beneath the nail; large amounts of subungual pus may result in a floating nail.

A chronic paronychia is a more indolent infection, often involving mixed flora or fungal organisms, especially *C. albicans.* However, it is not clear whether Candida plays an infectious role or is a frequent colonizer in an inflammatory process (18). Individuals whose hands are repeatedly exposed to water containing irritants or alkalis (e.g., dishwashers, bartenders) and those with diabetes seem to be most at risk. Patients usually complain of a waxing and waning infection with periods of acute exacerbation (1). Pain and tenderness are usually less severe in comparison to an acute paronychia.

The *differential diagnosis* for paronychia includes herpetic whitlow, a felon, and certain malignancies such as squamous cell carcinoma of the nail, malignant melanoma, and metastases from malignant tumors (19,20). Psoriasis and Reiter syndrome involving the proximal nail fold may also mimic a paronychia (18). Herpetic whitlow is a viral infection caused by the herpes simplex virus. It can usually be differentiated from a paronychia by careful history and physical examination. A severe paronychia may be confused with a felon. However, rather than subungual pus or fluctuance along the nail fold, patients with a felon will have tense swelling of the distal pulp space.

ED evaluation is usually limited to the history and physical examination. Radiographs may be useful in selected situations (e.g., a history of trauma, suspicion of a foreign body), but are generally not helpful. Laboratory testing is unnecessary in the majority of patients.

ED management depends on the severity of infection. If the diagnosis of an acute paronychia is made before the accumulation of pus, management includes an oral antibiotic effective against CA-MRSA, methicillin-sensitive *S. aureus,* and *Streptococcus* species (Table 147.1), along with warm soaks. Rest and elevation of the affected hand are helpful adjuncts. Once purulent drainage or fluctuance is noted, surgical drainage must be performed.

TABLE 147.1
Recommendations for Initial Antimicrobial Therapy of Hand Infections[a]

Infection	Initial Antimicrobial Therapy[b]	Comments
Felon/paronychia outpatient	Trimethoprim/sulfamethoxazole one DS tablet bid for 10 d	Clindamycin 150–300 mg qid for 10 d is also considered a first-line agent
Severe infections[c]	Vancomycin 1 g IV or Clindamycin 300–600 mg IV	Ceftriaxone 1 g IV is given for flexor tenosynovitis due to disseminated gonorrhea.
Diabetic/immunocompromised patients	Vancomycin 1 g IV and Piperacillin/tazobactam 3.375 g or aztreonam 1–2 g IV	High incidence of gram-negative organisms
Intravenous drug abuser	Vancomycin 1 g IV	High incidence of methicillin-resistant *Staphylococcus aureus*
Herpetic whitlow	None	Acyclovir for suppression of recurrent attacks and for severe infection in immunocompromised patients

[a]Agents or a combination of agents with similar coverage may be substituted. Alternatives for penicillin- and/or cephalosporin-allergic patients are discussed in the text.
[b]Initial antimicrobial therapy should be adjusted as the results of culture and sensitivity tests become available.
[c]Flexor tenosynovitis, web space abscess, and palmer space infection.

A digital block provides adequate anesthesia for drainage. Prior to drainage, clean the affected digit with povidone–iodine or a similar agent and place a 1-in Penrose drain securely around the proximal portion of the digit to maintain hemostasis.

To drain superficial infections, insert a no. 11 blade between the nail and eponychium lifting the eponychium away from the nail to drain the pus (Fig. 147.2). If necessary, the blade can then be swept around to incise the lateral nail fold. Make the incision tangential to the dorsolateral curve of the nail, with the blade directed away from

the nail bed and nail matrix to avoid injury to these structures. After drainage, insert a small gauze wick between the eponychium and nail to facilitate continued drainage.

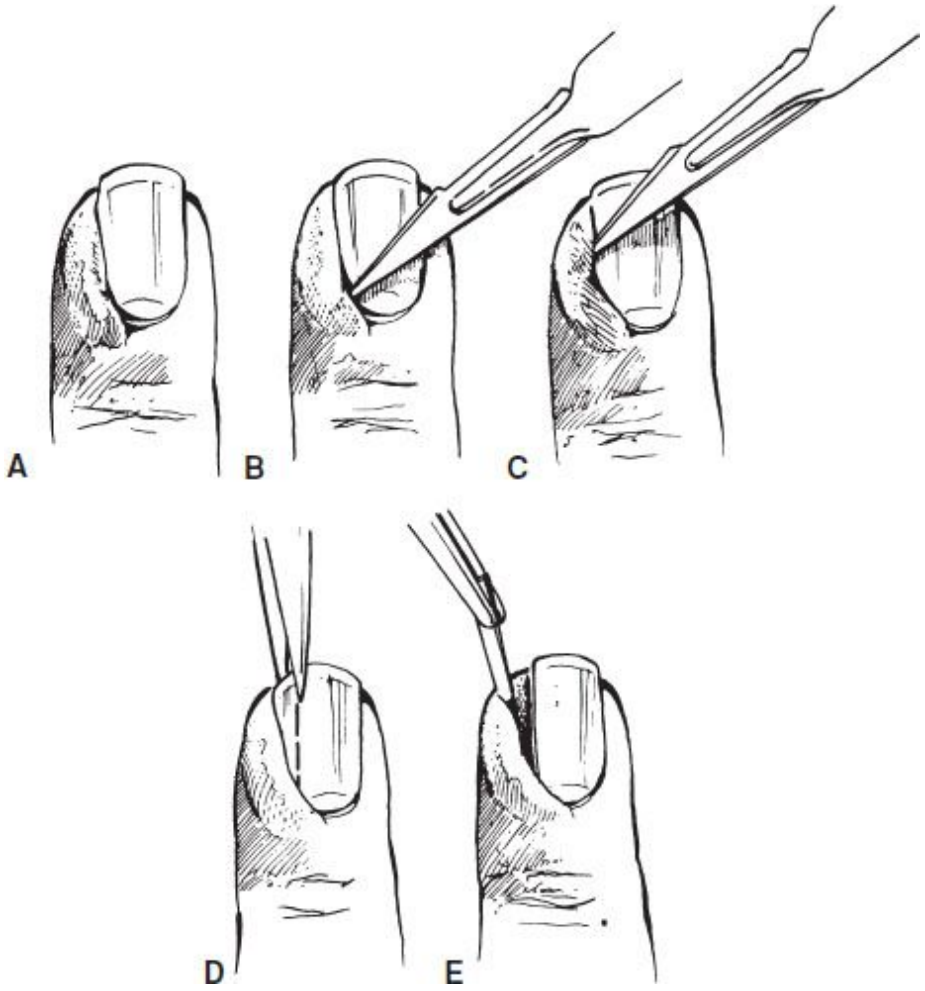

FIGURE 147.2 Drainage of a paronychia. **A:** Superficial paronychia. **B:** Elevation of the eponychia using a no. 11 blade. **C:** If necessary, the lateral nail fold may be incised to achieve adequate drainage. **D:** A more extensive paronychia with pus extending under the adjacent portion of the nail. **E:** Removal of the adjacent one-fourth of the nail to drain the subungual pus. If removal of the nail does not allow complete drainage, the lateral nail fold may be incised as in **(C)**.

If pus is present under the adjacent portion of the nail, remove one-fourth of the nail on that side to allow adequate drainage to occur (see Fig. 147.2). First separate the portion of nail to be

removed from the underlying nail bed by inserting a small hemostat or iris scissors beneath the distal free edge of the nail and gently open and close the instrument while working it proximally toward the eponychium. Once the nail is separated, use iris scissors to cut longitudinally along the nail from the distal edge to the eponychium. Finally, gently remove the nail with the aid of a Kelly clamp. If this does not allow complete drainage of pus, make an incision into the lateral nail fold as previously described and insert a gauze wick to promote continued drainage. If pus is discovered under the dorsal roof of the proximal nail fold or beneath the nail in the nail fold or if the patient presents with a floating nail, drainage requires removal of the proximal one-third of the nail.

If the infection involves the eponychium and one lateral nail fold (in addition to pus under the dorsal roof or nail root), Siegel and Gelberman (21) recommend making a single incision starting at the midpoint of the lateral nail fold and extending it proximally to the base of the nail. Bluntly elevate the eponychial tissue and lateral nail fold from the nail and remove the proximal one-third of the nail using an iris scissors (Fig. 147.3). If a run-around infection is present, make an incision in each lateral nail fold as just described. Gently elevate the entire eponychium as a flap to expose the underlying nail root, and excise the proximal one-third of the nail using iris scissors.

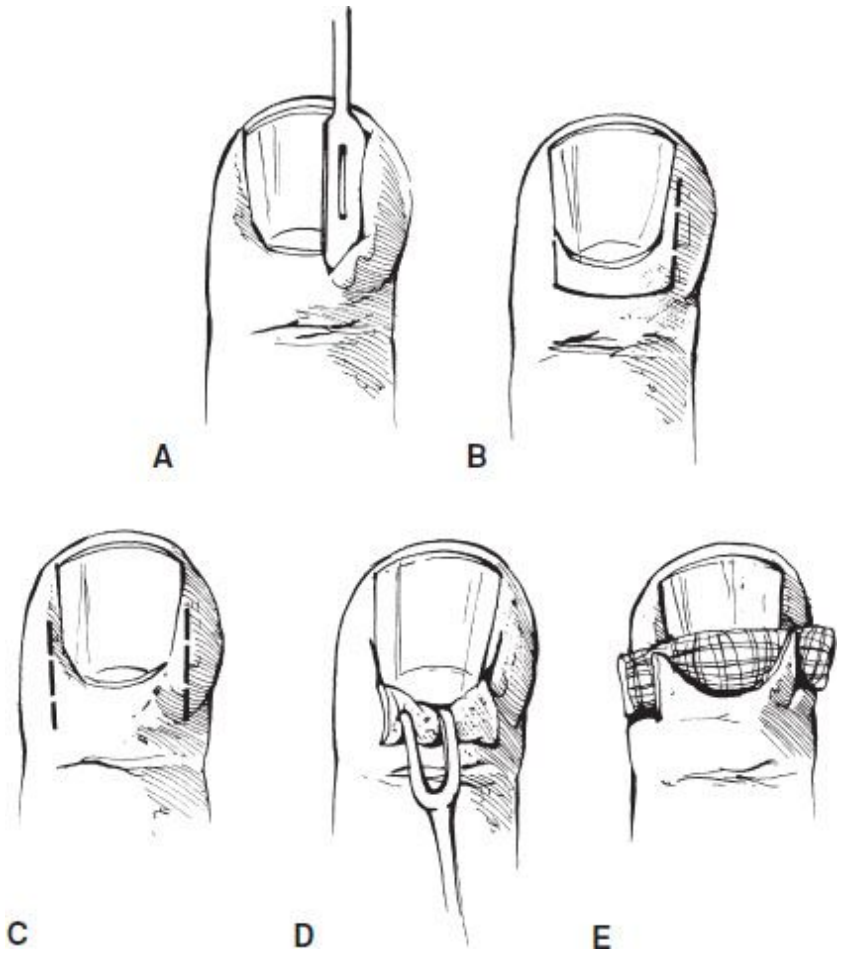

FIGURE 147.3 Drainage of a paronychia associated with a floating nail or with pus beneath either the dorsal roof of the proximal nail fold or the nail within the proximal nail fold. **A:** Elevation of the eponychial fold with a flat probe to expose the base of the nail for excision of a floating nail. **B:** Placement of an incision to drain the eponychium and lateral nail fold and to elevate the eponychial fold for excision of the proximal one third of the nail. **C–E:** Incisions and procedure for elevating the entire eponychial fold for excision of the proximal one-third of the nail. A gauze pack prevents premature closure of the cavity. (Redrawn from Neviaser RJ. Infections. In: Green DP, ed. *Operative Hand Surgery*, 3rd ed. New York, NY: Churchill Livingstone; 1993:1023.)

Some authors are reluctant to incise the eponychium for fear that the eponychial tissue will not heal primarily in the face of infection and that the incision may result in a notch or square corner in the

eponychium (22). Unfortunately, there are few scientific data regarding the optimal approach. If a floating nail is present, incision of the eponychial tissue is probably unnecessary because removal of the nail can be easily performed by pushing back the lateral nail fold and excising the loose nail (Fig. 147.3). Regardless of which technique is used, after removal of the proximal portion of the nail, insert a gauze wick between the eponychium and exposed nail to prevent adhesion of the eponychium to the nail bed and to facilitate continued drainage.

The treatment of a chronic paronychia is much more difficult. Reducing exposure to moist environments and chemical irritatants is clearly beneficial. Initial treatment with a combination of antifungals and topical steroids (e.g., 3% clioquinol in triamcinolone–nystatin mixture) should be considered, but frequently, surgical debridement with nail plate removal is needed (1).

The majority of patients with a paronychia may be discharged from the ED. Instruct the patient to keep the affected digit clean and dry and to elevate the hand to reduce pain and swelling. Patients with a small superficial paronychia should remove the gauze packing after 24 hours and begin warm soaks. Larger, more extensive infections should be checked at 48 hours. If the infection appears to be healing, remove the packing material and start the patient on warm soaks. An oral antibiotic should be prescribed (Table 147.1). The need for admission is rare, but should be considered for those patients who have an extensive surrounding cellulitis or lymphangitis, particularly in high-risk individuals (e.g., diabetics, immunocompromised patients). Consultation with a hand surgeon is recommended for high-risk patients with a severe infection.

Common Pitfalls

- Failing to recognize the need for surgical drainage. If the presence of pus is suspected, drainage should be performed.
- Failing to remove the adjacent portion of the nail when subungual pus is present. This may result in inadequate drainage.
- Failing to place a wick between the eponychium and nail plate after drainage. This may result in reaccumulation of pus and, if

the proximal portion of the nail was removed, adhesions between the eponychium and underlying nail bed.

FELON

A felon is an infection of the distal pulp space of a finger or thumb. It occurs more commonly in the right hand, with the thumb and index finger most frequently affected. The infection frequently results from a puncture wound to the tip of the digit. A subcutaneous abscess rapidly forms in the pulp space, breaking down the fibrous septa as it expands. Because the fibrous septa create a closed space within the fingertip, pressure from the expanding abscess and associated edema can lead to ischemia of the pulp space and, ultimately, slough of the tactile portion of the finger pad.

The *clinical presentation* of a felon typically includes a red, swollen, and painful fingertip. There is a history of penetrating trauma in approximately two-thirds of cases (17). Early in the course of the infection, the patient complains of an aching pain that increases when pressure is applied to the fingertip. The pain rapidly becomes severe and throbbing. Systemic signs and symptoms are rare. On examination, the fingertip is extremely tender, and there is erythema and swelling of the distal pulp space. As a rule, the swelling does not extend proximal to the distal interphalangeal joint. Fluctuance is generally present within 48 hours. In some cases, the abscess will point, whereas in others there will be a more diffuse collection of pus. In advanced cases, there may be necrosis of the tactile portion of the finger pad. Other complications of an untreated felon include necrosis of the distal phalanx secondary to osteomyelitis, pyogenic arthritis of the distal interphalangeal joint and, rarely, a flexor tenosynovitis from proximal extension (17).

The *differential diagnosis* of a felon includes cellulitis of the fingertip, a severe run-around infection, and herpetic whitlow. In cellulitis of the fingertip, fluctuance is usually absent, and pain, tenderness, and swelling are less severe. In addition, unlike a felon, cellulitis will often spread proximal to the distal interphalangeal joint. Patients with a severe run-around infection have fluctuance of the eponychium and both lateral nail folds. In contrast, the

fluctuance associated with a felon is much greater in the distal pulp space. Patients with herpetic whitlow usually complain of dysesthesia or a burning sensation of the distal phalanx. Despite associated erythema and swelling, however, the distal pulp space usually remains soft.

The diagnosis of a felon is made clinically following a detailed history and physical examination. Radiographs of the affected digit may be needed in patients with a history of trauma or to assess for the presence of a foreign body or osteomyelitis. Laboratory tests may be helpful in patients with comorbidities (e.g., diabetes) or clinical toxicity but are otherwise unnecessary. Wound cultures may be helpful in immunocompromised patients.

ED management depends upon the extent of infection. If the patient presents in the early stages of the infection, before the onset of fluctuance, management includes immobilization, elevation, warm soaks, and an oral antibiotic effective against *CA-MRSA,* methicillin-sensitive *S. aureus* and *Streptococcus* species (Table 147.1). Surgical drainage is indicated when there is fluctuance present or if associated swelling threatens to interrupt blood flow to the distal pulp space. Although the presence of pus may be difficult to assess in some patients, it is usually present if the process has been going on for more than 48 hours.

The goal of surgical intervention is to provide adequate drainage without creating a disabling scar or unstable fat pad, injuring the digital artery and nerve, or violating the flexor tendon sheath, causing an iatrogenic flexor tenosynovitis. A variety of surgical approaches have been suggested, but many are associated with a high incidence of complications and are no longer recommended. At the present time, the *unilateral longitudinal* approach is the technique most often used (1) (Fig. 147.4).

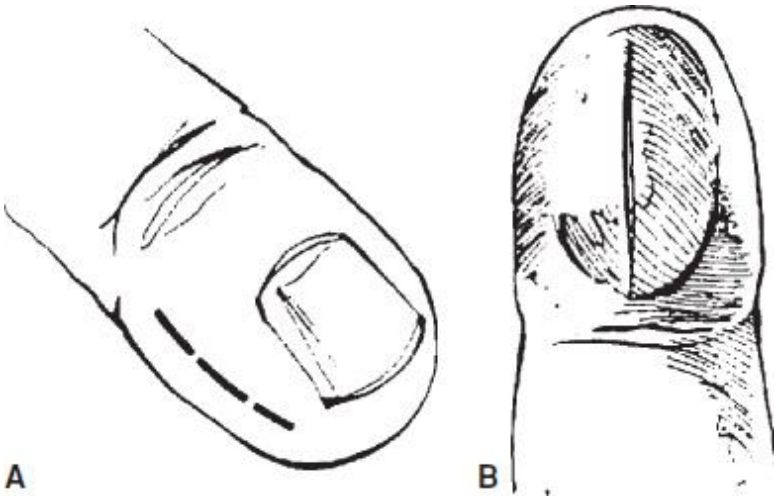

FIGURE 147.4 Incisions for drainage of felons. **A:** Unilateral longitudinal approach. Make the incision dorsal to the neurovascular bundle to prevent permanent sensory loss or ischemia of the distal fat pad. **B:** Midline longitudinal incision (recommended for patients with a draining sinus or pointing abscess on the volar surface of the fingertip). Do not let the incision cross the distal flexion crease as this may result in a disabling scar. (Redrawn from Neviaser RJ. Infections. In: Green DP, ed. *Operative Hand Surgery,* 3rd ed. New York, NY: Churchill Livingstone; 1993:1025.)

After a digital block, place a tourniquet (sterile Penrose drain) around the proximal portion of the digit as described previously. Make a unilateral longitudinal incision dorsal to the neurovascular bundle on the ulnar side of the index, long, and ring fingers and on the radial side of the thumb and little finger. Start the incision approximately 0.5 cm distal to the distal flexion crease and extend it in a straight line to a point in line with the beginning of the hyponychium. Carefully insert the blade deeper and deeper until the abscess is entered and then enlarge the opening of the cavity using a small Kelly clamp until complete evacuation is achieved. Avoid blunt rupture of all the fibrous septa because it may result in an unstable fat pad. Irrigate the cavity with saline and pack the wound with 0.25-in gauze packing. After the procedure, cover the wound with gauze and place the patient in a splint or bulky dressing that protects the finger and limits movement.

For patients with a draining sinus or pointing abscess on the volar surface of the fingertip, a midline longitudinal incision is recommended (Fig. 147.4) (17). Because the abscess cavity lies directly under the draining sinus or area of pointing, a midline longitudinal incision made directly through this area produces excellent drainage with few complications. For these patients, make the incision through the sinus (or over the area of pointing) starting 0.5 cm distal to the distal flexion crease and extend it to the beginning of the hyponychium. Do not let the incision cross the distal flexion crease as this may result in a disabling scar. After drainage and irrigation, pack the wound with 0.25-in gauze and then dress and splint the finger as described previously.

Most patients with a felon may be discharged from the ED. Instruct the patient to keep the affected digit clean and dry and to elevate the hand to reduce pain and swelling and facilitate healing. Prior to discharge, provide prescriptions for an analgesic and an appropriate oral antibiotic (Table 147.1). It is prudent to reevaluate in 48 hours. If the wound is healing well, remove the gauze packing and start warm soaks. Patients who develop pyogenic arthritis, flexor tenosynovitis, osteomyelitis, or an ischemic digit require immediate consultation with a hand surgeon, along with admission for more aggressive management.

Common Pitfalls

- Failing to recognize the need for surgical drainage.
- Improperly placed incisions. A volar incision that crosses the distal flexion crease may cause a disabling scar, whereas a lateral incision not made dorsal to the neurovascular bundle may result in permanent sensory loss or ischemia of the distal fat pad.
- Blunt rupture of all the fibrous septa is not recommended because it may results in an unstable fat pad.

HERPETIC WHITLOW

Herpetic whitlow is a viral infection of the fingertip caused by type 1 and type 2 herpes simplex viruses. This infection is spread by direct

contact with infected individuals. The disease most often affects adults with genital herpes and patients of all ages with herpetic gingivostomatitis (23). It is considered an occupational hazard for individuals who handle oral–tracheal secretions, including dentists, dental hygienists, anesthesiologists, nurses, and other healthcare providers (1). Herpetic whitlow has also been described in patients after human bites (24) and a very aggressive and destructive form of the disease may affect patients with AIDS (25,26). The infection most often affects the distal pulp space and, occasionally, the proximal and lateral nail folds (23). The fingers are affected more often than the thumb. Herpetic whitlow is self-limited and usually resolves in 2 to 3 weeks. Rare complications include systemic viremia, ocular infection, nail dystrophy, nail loss, scarring, and localized hyperesthesia or hypoesthesia (27). About 20% to 50% of patients experience recurrent infections that tend to be less severe than the original (27).

Patients with herpetic whitlow typically describe a prodrome of throbbing pain and dysesthesia or burning sensation of the distal phalanx. This is usually followed by swelling and erythema. Despite associated swelling, however, the distal pulp space usually remains soft. This helps to differentiate herpetic whitlow from a felon, in which there is tense swelling of the distal pulp space. One or more small vesicles then appear and often coalesce to form bullae. Some patients may also have associated fever, lymphadenopathy, lymphangitis, and constitutional symptoms (27).

On examination, tenderness is present but is usually much less severe than that seen with bacterial infections. The vesicles may contain fluid that is clear, turbid, or occasionally hemorrhagic but not purulent. If purulence is present, it suggests the possibility of a secondary bacterial infection. After 10 days, the vesicles or bullae will begin to crust over and, shortly after this, the area peels away to reveal normal skin.

The diagnosis of herpetic whitlow is clinical. If uncertainty exists, the diagnosis can often be confirmed by a Tzanck smear or viral culture. Perform a Tzanck smear by first unroofing a vesicle and scraping the base with a wooden applicator. Spread the scrapings on

a slide and air dry or fix with ethyl alcohol. Finally, stain the slide with Giemsa or Wright stain or with methylene blue and examine for the presence of multinucleated giant cells (27). If the Tzanck smear is negative or cannot be performed, a culture can be obtained. This is more sensitive than a Tzanck smear, but results take up to 48 hours. Additional tests include serum antibody titers and lesion specimen antigen detection (27).

The *ED management* of herpetic whitlow should include immobilization, elevation, and analgesia. Cover the digit with a dry dressing to reduce the spread of infection. The use of acyclovir (200 mg, 3 to 4 times daily) has been shown to prevent or greatly decrease recurrence rates in cases of culture-proven herpetic whitlow (28). It is also indicated for severe infections in immunocompromised patients (28). Topical acyclovir has not been shown to be effective in the treatment of herpetic whitlow. Incision and drainage are contraindicated because it can result in secondary bacterial infection.

Patients with herpetic whitlow may be discharged from the ED with follow-up in 7 to 10 days with their primary care physician or a hand specialist. Discharge instructions should include recommendation to return to the ED for any signs of secondary bacterial infection. If there is a suspicion of an associated bacterial infection on initial presentation, consultation with a hand surgeon is recommended.

Common Pitfalls

- Misdiagnosing herpetic whitlow as a felon or paronychia requiring incision and drainage. Surgical intervention causes unnecessary discomfort and may lead to secondary bacterial infection.

FLEXOR TENOSYNOVITIS

Flexor tenosynovitis is an infection of the digital flexor tendon sheaths of the upper extremity. This infection can be one of the most devastating hand infections encountered in clinical practice. It is most commonly caused by a penetrating injury, particularly at the distal and proximal flexion creases where the tendon sheaths are

more superficial. It may also result from direct extension of a neighboring infection and, rarely, by hematogenous or lymphatic spread. The thumb, index finger, and middle fingers are the digits most commonly involved, and the right hand is affected about twice as often as the left hand. If the disorder is not recognized and treated early, purulence within the tendon sheath can destroy the delicate gliding mechanism. Persistent infection leads to the formation of adhesions, resulting in severe limitation of movement. If allowed to continue, the infection will eventually destroy the blood supply to the tendon, producing tendon necrosis. Risk factors associated with poor outcomes include age greater than 43 years; the presence of diabetes mellitus, peripheral vascular disease, or renal failure; the presence of subcutaneous purulence; digital ischemia; and polymicrobial infections (29).

The *clinical presentation* of flexor tenosynovitis is one of severe pain, swelling, and limited motion of the affected digit. There is a history of penetrating trauma in approximately 90% of cases (30). Kanavel (31) described four cardinal signs of flexor tenosynovitis: (a) tenderness over the course of the tendon sheath, (b) symmetric swelling of the entire digit, (c) a flexed position of the finger at rest, and (d) excruciating pain on passive extension of the finger. The latter is the most valuable of these signs and may be the only one present very early in the disease process (32). It is also important to note that not all of these findings need be present to make the diagnosis; clinicians should have a high level of suspicion if even only one of these signs is present. Moreover, patients with medical comorbidities such as diabetes mellitus or IV drug use or those with compromised immune systems may not exhibit Kanavel signs as dramatically as those with healthy immune systems (30).

In established infections, swelling frequently involves the dorsum of the hand. This is most often due to lymphatic drainage from the affected digit rather than from extension of infection. Dorsal swelling is usually less than that seen with a thenar or midpalmar space infection. If the patient does not seek medical treatment early, the infection may spread to one of the deep palmar spaces, especially the thenar space and midpalmar space, or to adjacent bone or joints,

causing an associated osteomyelitis or septic arthritis, respectively. Infection of the tendon sheath of the little finger or thumb may extend to involve the ulnar bursa and radial bursa, respectively, with resulting pain and tenderness in the palm and wrist. When this occurs, the entire hand becomes swollen, particularly the dorsum (1).

The *differential diagnosis* of flexor tenosynovitis includes a palmar space infection, cellulitis, osteomyelitis, and septic arthritis. However, the diagnosis of flexor tenosynovitis can usually be made if a detailed physical examination is performed, with emphasis on identifying the four cardinal signs of Kanavel. The finding of excruciating pain on passive extension of the digit is particularly helpful because it is often present early in patients with flexor tenosynovitis and is generally not seen with other hand infections.

The *ED evaluation* should include radiographs of the affected digit to look for a foreign body and osteomyelitis. A complete blood cell count and blood cultures may be helpful in those individuals with systemic involvement. Urethral or endocervical cultures for *Neisseria gonorrhoeae* may be helpful in the appropriate clinical setting. Other tests should be guided by the patient's presenting complaints, underlying medical problems, and the need for operative intervention.

The *ED management* of flexor tenosynovitis includes elevation and immobilization of the affected hand, initiation of intravenous antimicrobial therapy, relief of pain, and consultation with a hand surgeon. Initial antimicrobial therapy should be broad-spectrum, aimed at both gram-positive aerobic bacteria (including CA-MRSA) and anaerobic organisms (Table 147.1). Current recommendations in immunocompetent patients include IV vancomycin or IV clindamycin as first-line agents (30). Piperacillin/tazobactam or aztreonam should be added for suspected gram-negative infection (i.e., infection in a diabetic or immunocompromised patient) (30). Patients who present with flexor tenosynovitis secondary to a human bite need coverage for *Eikenella,* which is resistant to clindamycin, cephalexin, metronidazole, and erythromycin. Fortunately, penicillin G, ampicillin, amoxicillin/clavulanate, trimethoprim/sulfamethoxazole and most fluoroquinolones provide acceptable coverage for *Eikenella*

(11). Patients who present with infections following a cat bite have a high incidence of Pasteurella multocida, which is generally sensitive to amoxicillin/clavulanate (this also covers methicillin-sensitive *S. aureus*), cefuroxime axetil, doxycycline, and penicillin G (11). Patients with evidence of disseminated gonorrhea should receive intravenous ceftriaxone.

All patients with suspected flexor tenosynovitis require consultation with a hand surgeon and admission to the hospital. If the patient presents within the first 24 to 48 hours, conservative therapy with continued elevation and immobilization, intravenous antimicrobial agents, and close observation may be attempted. If the patient's condition is not markedly improved within 12 to 24 hours, surgical drainage is indicated (30). The choice of conservative versus operative management should be left to the consulting surgeon.

Common Pitfalls

- Failing to suspect the diagnosis on initial presentation. A careful history and physical examination, with close attention to the cardinal signs of flexor tenosynovitis and a low threshold for consultation, will help avoid a delay in diagnosis.
- Misdiagnosing early flexor tenosynovitis as simple cellulitis.
- Failing to admit a patient with flexor tenosynovitis.

WEB SPACE (COLLAR BUTTON) ABSCESS

A web space abscess usually results from a break in the skin surrounding an infected palmar blister. Consequently, it is seen most often in individuals who do manual labor. Patients present with significant volar infection and dorsal web space swelling. If left untreated, the infection spreads dorsally to the dorsal subcutaneous space and deep into the palmar web space creating an hourglass configuration reminiscent of old collar buttons. As a result, a web space abscess is also known as a *collar button abscess.* Rarely, an untreated infection in the web space between the index and middle fingers will spread medially to involve the other two web spaces.

The *clinical presentation* includes pain and swelling of the involved web space and surrounding palm. Systemic signs and symptoms are unusual in uncomplicated infections. Examination reveals tenderness and swelling of the affected web space. Anteroposterior pressure over the web space elicits severe discomfort. Swelling may be more prominent on either the palmar or the dorsal aspect, depending on the nature of the infection. Because of pus and swelling, the fingers adjacent to the affected web space are held abducted at rest. Untreated infections may spread to involve the tendon sheath or palmar space, or dissect distally along the course of the lumbricals, leading to tissue slough. Rarely, the infection will spread to involve the dorsal subaponeurotic space. If this occurs, patients will have pain, tenderness, and fluctuance involving the dorsum of the hand.

The *differential diagnosis* includes a dorsal subcutaneous space infection, an infected palmar blister, and a deep palmar space infection. As with other infections of the hand, a careful history and physical examination will lead to the correct diagnosis. In a dorsal subcutaneous space infection, the fingers are not held abducted at rest, and palmar tenderness is minimal or absent. Although infection of a palmar blister usually precedes a web space abscess, pain and tenderness are mild in comparison and are localized over the blister, not the web space. Furthermore, swelling is usually minimal and, when present, does not involve the dorsum of the hand. The findings associated with a deep palmar space infection vary with the involved space and are discussed in the next section.

The diagnosis of a web space abscess is made clinically. Radiographs of the affected hand are recommended if a foreign body or osteomyelitis is suspected but are otherwise unnecessary. Laboratory testing may be helpful in those individuals with systemic involvement or significant comorbidities or as needed prior to surgery.

ED management includes elevation of the affected hand, parenteral opiate analgesics, and initiation of antimicrobial therapy, (Table 147.1). Patients with suspected web space infection require consultation with a hand surgeon and admission to the hospital. Definitive management requires drainage in the operating suite.

Common Pitfalls

- Incorrectly diagnosing a primary dorsal space infection because of the presence of dorsal edema.
- Failing to recognize palmar involvement when dorsal edema is more prominent.
- Failing to recognize web space involvement in a patient with an obviously infected palmar blister.
- Failing to request hand surgery consultation.

PALMAR SPACE INFECTIONS

The palm contains four fascial spaces that are important sites of infection: the thenar space, the midpalmar space, the hypothenar space, and Parona's space. These compartments may become infected from direct penetrating trauma, from contiguous infection, such as a tenosynovitis or osteomyelitis or, rarely, from hematogenous seeding. Deep-space infections may be associated with significant morbidity and permanent loss of function; thus, prompt diagnosis and treatment are essential.

The *clinical presentation* of patients with a palmar space infection depends on which space is involved. However, any patient, regardless of the space involved, may present with fever, chills, and other manifestations of a serious infection.

A *thenar space* infection causes severe pain and tenderness and tense swelling of the thenar eminence. Because lymphatic drainage from the palm is directed dorsally, there is usually marked dorsal edema, as well. However, there is little, if any, tenderness over the dorsum of the hand. Fluctuance is often present in the web space between the thumb and index finger. The thumb is held abducted and flexed; passive adduction produces severe pain.

In contrast, patients with a *midpalmar space* infection have pain and tenderness over the central palm. There is marked fluctuance and swelling of the midpalmar space, resulting in a loss of normal palm concavity. In severe infections, there is frequently a bulge or convexity of the palm, a finding considered by Mann (33) to be almost pathognomonic of a midpalmar space infection. As with other

serious hand infections, there is also edema over the dorsum of the hand but no tenderness, erythema, or fluctuance. Motion of the middle and ring fingers is painful and limited.

Infection of the *hypothenar space* is rare. There are pain and fullness over the hypothenar eminence, with a noticeable lack of swelling in the palm and fingers.

Isolated infections in *Parona's space* are also rare; infections here are usually associated with tenosynovitis or other deep space infections that have propagated into the forearm. Patients will have pain with finger flexion and may present with an acute carpal tunnel syndrome (1).

The *differential diagnosis* of a palmar space infection includes a cellulitis or superficial abscess of the palm, a web space infection, and flexor tenosynovitis. Both a cellulitis and a superficial (subcutaneous) abscess of the palm produce pain and tenderness that may not be localized to a particular space. Moreover, unless there is digital involvement, movement of the fingers or thumb causes little, if any, discomfort.

ED evaluation should include radiographs to look for foreign body, osteomyelitis, or gas in the tissues. A complete blood count and blood cultures may be helpful in those individuals with systemic involvement.

The *ED management* of palmar space infection includes elevation and immobilization of the affected hand, parenteral opiate analgesics, and initiation of antimicrobial therapy (Table 147.1). All patients with a suspected palmar space infection require consultation with a hand surgeon and admission to the hospital. Definitive management requires drainage in the operating suite.

Common Pitfalls

- Failing to appreciate the presence of a serious palmar space infection.
- Misinterpreting the presence of dorsal edema as a dorsal cellulitis.
- Failing to request hand surgery consultation.

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CHAPTER 148

Low Back Pain

David Della-Giustina

Low back pain is a common complaint that affects up to 90% of the population at some point in their lives. Approximately 7.6% of all US adults report at least one episode of severe acute low back pain within a 1-year period (1). Up to 85% of patients with low back pain will have no definite etiology determined for their symptoms (1,2). Fortunately, despite the lack of a definite etiology, almost 85% to 90% of patients will have resolution of their symptoms within 1 month (1,3). In approaching the patient with back pain, patients may be categorized into four groups: (a) nonspecific back pain, (b) back pain with radiculopathy, (c) back pain associated with another specific spinal cause, and (d) back pain in children (1). By far, the majority of patients with back pain presenting to the emergency department (ED) fall into the first category.

CLINICAL PRESENTATION

The clinical presentation of the patient with back pain ranges from the patient with mild pain who requires a work excuse to the patient with the severe, unrelenting pain of an epidural abscess. It is more important that one provides a thorough evaluation of each patient, focusing on the red flags found in the history and physical examination that raise suspicion for serious disease, rather than recognizing a particular classic presentation for the various diseases (Table 148.1).

TABLE 148.1
Red Flags in the History and Physical Examination

History
Pain longer than 6 wk
Age <18 or >50 yr
History of trauma
Radicular pain below the knee
Neurologic complaints (paresthesias, anesthesia, weakness)
Incontinence of bowel or bladder
Night pain
Unrelenting pain despite rest and analgesics
Fever, chills, and night sweats
History of injection drug use
History of cancer
Physical Examination
Fever
Patient writhing in pain
Point vertebral tenderness
Neurologic deficits
Positive straight leg raise

Sciatica is a broad term that is defined as a radicular pain into the leg in the distribution of a lumbosacral nerve root (see back cover), which is often accompanied by a neurosensory or motor deficit (1,4). Back pain with radiculopathy, which is a better description than sciatica, only affects 1% of patients with low back pain (4). Although there are many etiologies for back pain with radiculopathy, it most commonly occurs as a result of a herniated disc. Generally, these patients have a more protracted course than nonspecific back pain patients, with only 50% of patients with sciatica recovering within 1 month. However, of all back pain patients with radiculopathy, only 5% to 10% will require surgery (1,2,4).

Children are in a separate category, because back pain is an unusual condition in children and is much more likely to be pathologic rather than nonspecific. The differential diagnosis for the child with back pain is different from that of the adult, and it varies further based on the age of the child. Because of the higher potential for serious disease, one should approach the child with back pain more aggressively.

DIFFERENTIAL DIAGNOSIS

Adults with Nonspecific Back Pain

The majority of patients seen in the ED for acute low back pain have symptoms that fall into the category of nonspecific back pain (Fig. 148.1). This syndrome is known by many other names such as idiopathic back pain, mechanical back pain, back sprain/strain and lumbago. Essentially, it is an episode of acute low back pain without associated radiculopathy or neurologic deficits.

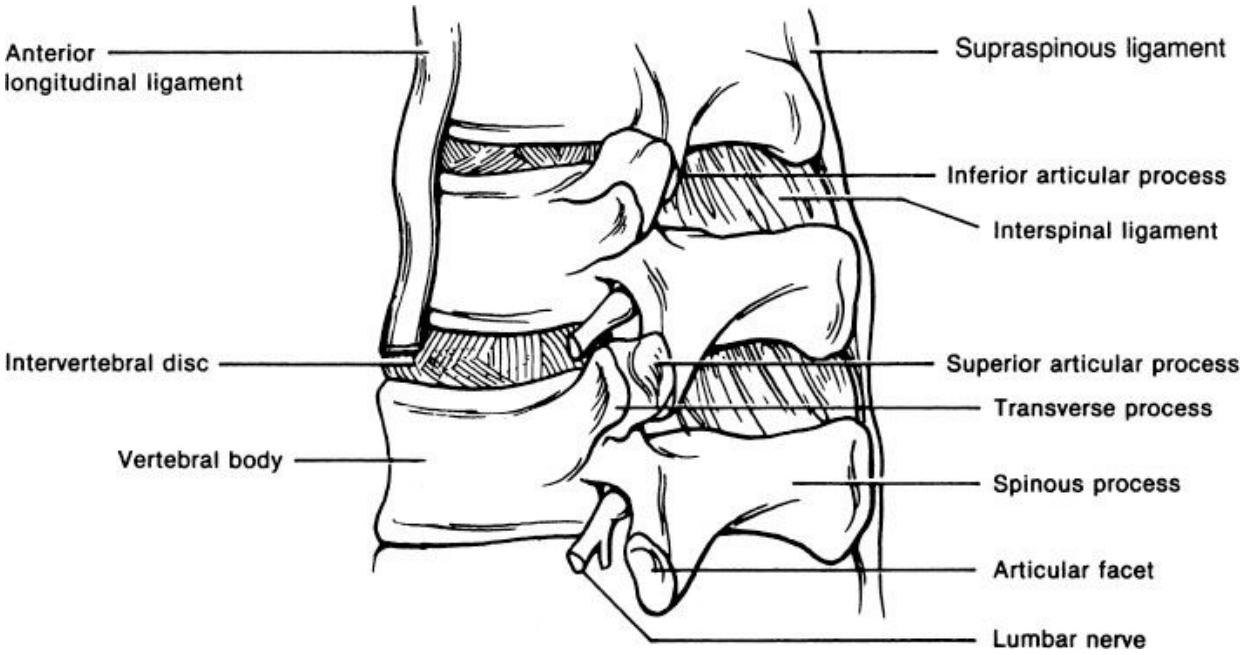

FIGURE 148.1 Normal anatomy of the lumbar spine.

The patient typically complains of mild-to-moderate pain in the lumbar area, which may radiate to the buttocks or thigh, is worsened by activity and is relieved with rest. The inciting incident is usually unremarkable, varying from an unusual posture for a period of time to lifting a heavy object. Physical examination typically reveals mild paraspinal tenderness, negative straight leg raise testing, normal neurologic examination, and no other significant findings. The investigation of red flags, if any, from the history and physical examination is negative. Because 85% to 90% of these patients will have a spontaneous resolution of their symptoms within 4 weeks,

there is no need to perform diagnostic testing unless red flags are uncovered. This saves the patient unnecessary pain, expense and radiation exposure.

Spinal Infection

Vertebral osteomyelitis and spinal epidural abscess are uncommon etiologies for back pain. However, because of the potential morbidity and mortality that result from missed infection and due to the fact that the incidence of these infections is increasing, one must remain vigilant concerning these possibilities (5,6). These infections occur more commonly in injection drug users, the immunocompromised, diabetics, elderly, those who have an ongoing or recent infection and those who have had spinal surgery (5,6). These infections frequently occur secondary to hematogenous spread of *Staphylococcus aureus.* Patients with spinal infection typically present with moderate-to-severe back pain accompanied by fever, chills, unrelenting pain, night sweats, and weight loss. With epidural abscess, the patient may have associated radicular pain and neurologic symptoms. Some patients with epidural abscess may present with sepsis. However, one cannot rely on the presence of a fever, unrelenting pain or neurologic deficit to rule in this disease (5,6). In evaluating patients for suspected spinal infection, the peripheral white blood cell (WBC) count may be elevated or normal, but the erythrocyte sedimentation rate (ESR) and C-reactive protein are almost always elevated with the one caveat that the more severely immunocompromised may not demonstrate this elevation (5–7). One should always consider back pain, especially thoracic back pain, in a patient who is an injection drug user as a spinal infection until proven otherwise.

Radiculopathy

Back pain with radiculopathy is a set of symptoms caused by compression or irritation of the lumbosacral nerve roots that form the sciatic nerve (L4 to L5, S1 to S3). Symptoms include unilateral pain in the back, buttocks, posterior leg, and foot, as well as tingling and weakness. The differential diagnosis includes any cause of

compression or inflammation of the spinal nerve roots, cauda equina, and spinal cord. The major cause of sciatica is herniated disc. However, in the ED, one should consider other etiologies, including spinal stenosis and compression of the cauda equina or spinal cord by tumor, infection, or hematoma.

Herniated Disc

Although radiculopathy is seen in only 1% of patients with low back pain, it is a common presentation of a symptomatic herniated disc. Ninety-five percent of herniated discs involve either the L4 to 5 or L5 to S1 intervertebral discs (1,2,4). Herniated disc most commonly occurs in patients during their fourth or fifth decades of life. Patients often complain of weeks of nonradicular low back pain preceding the onset of the radicular symptoms. The radicular symptoms are the hallmark of the nerve root compression and usually become the prominent symptom, with a diminution of the back pain. Clinically, the diagnosis of herniated disc is made by localizing the pain to an isolated nerve root and demonstrating neurologic dysfunction in the distribution of that nerve root (see back cover). If a diagnosis of herniated disc is entertained, one should ensure that only one nerve root is involved. The involvement of multiple nerve roots is cause for concern for a larger central disc herniation or a spinal mass.

Epidural Compression Syndrome

Epidural compression syndrome is a collective term encompassing spinal cord compression, cauda equina syndrome, and conus medullaris syndrome. This term is commonly used to group these syndromes together for two reasons. First, the presentation for these syndromes is similar, except for the level of the neurologic deficit. Secondly, the initial evaluation and management of these syndromes is similar, until the actual diagnosis is known. This syndrome may be caused by compression of the cauda equina or spinal cord by tumor, large central disc herniation, infection, or hematoma. The patient usually presents with minimal-to- moderate back pain with bilateral neurologic deficits and incontinence. The most common sensory

deficit found in cauda equina syndrome occurs over the buttocks, perineum, and posterior-superior thighs in the "saddle" distribution (8). Urinary retention is the most consistent finding in cauda equina syndrome (sensitivity 90%) (1,8). This finding proves useful in evaluating the patient with a benign history and physical examination but who complains of urinary incontinence. By evaluating a postvoid residual, a negative test (no urinary retention) makes it extremely unlikely that the patient has incontinence because of epidural compression. All patients with suspected epidural compression require emergent magnetic resonance imaging (MRI) imaging and neurosurgery consultation.

Spinal Stenosis

Spinal stenosis is a narrowing of the spinal canal that may occur at single or multiple levels and is associated with radiculopathy or claudication (9,10). Generally, spinal stenosis is a cause of chronic back pain, but it has associated flares of acute pain. The symptoms, which usually begin in the sixth decade, include low back pain that is aggravated by prolonged standing and spinal extension and relieved by rest and forward flexion. The classic symptom for spinal stenosis is pseudoclaudication, although this is seen in only 60% of patients. Pseudoclaudication is pain of the lateral legs that occurs with walking and is relieved with rest. This pain is termed *pseudoclaudication* because it is caused by neurologic compression associated with the upright position rather than muscle ischemia because of arterial insufficiency. The more appropriate term for this symptom now is neurogenic claudication (9,10).

Back Pain in Children

Children rarely present to the ED with complaints of back pain. When they do, one must perform a more thorough diagnostic evaluation, as there is a much higher probability of a serious treatable disorder. If the pain is associated with a recent increase in physical activity or involvement in sports such as football, dance and gymnastics, then one should consider spondylolysis or

spondylolisthesis as the cause of the pain. Other etiologies to consider in the child younger than age 10 are discitis, tumor, and osteomyelitis. Etiologies for children age 10 years and older include spondylolysis, spondylolisthesis, Scheuermann disease, tumor, vertebral osteomyelitis, herniated disc, and ankylosing spondylitis.

ED EVALUATION

The ED evaluation must concentrate on the identification of red flags in the history and physical examination (Table 148.1). The presence of red flags should alert the clinician that serious pathology might be present and a more aggressive diagnostic evaluation is indicated. The absence of red flags means that it is unlikely that the patient has significant disease, and no diagnostic tests are required. Therefore, the majority of patients with back pain encountered in the ED require no diagnostic testing.

Children without an obvious etiology for their back pain should be evaluated with a complete blood count (CBC), ESR, urinalysis (UA), and plain spinal radiography.

History

Back pain may be divided into three categories based on the duration of the symptoms: acute (<6 weeks), subacute (between 6 and 12 weeks), and chronic (>12 weeks). Pain that is subacute or chronic is a red flag because 85% to 90% of back pain episodes resolve within 4 to 6 weeks. Patients with persistent back pain for more than 6 weeks require further diagnostic evaluation.

Patients older than 50 years or younger than 18 years raise a red flag because of the higher probability of significant pathology, such as tumor or infection. Those patients younger than age 18 years have a higher likelihood of congenital and bony abnormalities, such as spondylolysis and spondylolisthesis. In patients older than age 50 years, causes such as neoplasia, fracture, or referred pain from vascular disease, pancreatitis, and other intra-abdominal or retroperitoneal processes are more common.

A history of trauma suggests fracture and is usually a readily available historical clue. In an otherwise healthy patient, a major mechanism (motor vehicle crash or a fall from a significant height) is required to cause vertebral fracture. However, one must consider that the patient with osteoporosis may sustain a vertebral fracture from even minimal trauma.

A history of radicular pain suggests nerve root compression. Patients with radiculopathy commonly complain more of the leg symptoms than the back pain. In addition to the radicular symptoms, one must inquire about neurologic deficits such as weakness, paresthesias, anesthesia, gait disturbances, and bowel and bladder incontinence. Any neurologic deficit raises a red flag for compression of at least a single spinal nerve root but may signal compression of the cauda equina or spinal cord. Bilateral or rapidly progressive symptoms or urinary or fecal incontinence are especially worrisome and suggest epidural compression.

The typical description for a benign etiology of back pain is that of a dull, aching pain, which usually worsens with movement but improves with rest. Atypical pain features, such as night pain or unrelenting pain despite rest raise red flags for infection and tumor. Features suggestive of disc herniation include pain that is worsened with prolonged sitting, sneezing, coughing, or the performance of the Valsalva maneuver (2,11). Finally, bilateral sciatica pain that worsens with activities such as prolonged standing, walking, and back extension and is relieved by rest and forward flexion is consistent with spinal stenosis (9,10).

Constitutional symptoms such as fever, chills, night sweats, malaise and an undesired weight loss are red flags that suggest infection or malignancy. The significance of these symptoms is increased if the patient has additional infectious risk factors such as injection drug use, immunocompromise, recent or ongoing bacterial infection, or a recent genitourinary or gastrointestinal procedure.

A history of cancer raises suspicion for spinal metastases. Back pain is the initial symptom of spinal metastases in 83% to 96% of these cases (1,12). Malignancies at a high risk to metastasize to the

spine include breast, lung, thyroid, kidney, prostate, myeloma, lymphoma, and sarcoma.

Physical Examination

The physical examination is directed toward verifying neurologic complaints, identifying neurologic deficits and uncovering red flags (Table 148.1). The presence of fever raises a concern for spinal infection. However, the presence of fever is insensitive, ranging from 27% for tuberculosis osteomyelitis to 50% for pyogenic osteomyelitis and 83% for spinal epidural abscess (8). Patients with pyelonephritis may also present with fever and back pain, though the more dangerous spinal epidural abscess must first be excluded, particularly in the injection drug user or immunocompromised patient. All patients with back pain require an abdominal examination to evaluate for bruits, masses, tenderness, or an enlarged and pulsatile aorta consistent with an aortic aneurysm. Many abdominal disorders present with referred back pain.

In children, one should specifically evaluate for the presence of birthmarks, such as café au lait spots (indicative of neurofibromatosis), as well as midline skin abnormalities of the back that may indicate underlying developmental spinal abnormalities.

Examination of the back should include a search for evidence of underlying infection or trauma. Inspect the back, looking for contusion or swelling consistent with trauma and erythema, warmth or drainage consistent with infection. Point tenderness to percussion of the vertebral bodies is found with bacterial infection with a sensitivity of 86%, but is nonspecific (8). Straight leg raise testing is performed to evaluate for evidence of a herniated disc with nerve root compression. A positive test produces a radicular pain that radiates below the knee. Reproduction of the patient's back pain is not a positive test (1,2,8). A positive straight leg raise test is 80% sensitive for a L4–5 or L5–S1 herniated disc. Radicular pain in the affected leg when elevating the asymptomatic leg (positive crossed straight leg raise test) is highly specific, though insensitive, for nerve root compression by a herniated disc (1,2,8).

The neurologic examination is the most important part of the physical examination. The examination should evaluate lower extremity strength, sensation, and reflexes (see back cover). Rectal examination does not need to be performed on all patients with back pain; however, it should be performed on those patients with red flags or neurologic findings.

Laboratory Testing

If the patient has red flags for infection or tumor, one should obtain a CBC, UA, and an ESR. With infection, the WBC count may be normal or elevated, but the ESR is usually elevated although it is nonspecific. C-reactive protein (CRP) is another nonspecific marker of inflammation and may be elevated like the ESR, though its utility in this setting is not clear. The UA can be positive in infection, if it is the source of hematogenous spread, but it is usually normal.

Imaging Studies

Plain spinal radiographs should always be obtained in children or in adults when there is concern of fracture, and should be considered as an initial imaging study for those with suspected spinal infection, tumor, or neurologic dysfunction. In adults, only anteroposterior (AP) and lateral views of the lumbar spine are necessary. Oblique views and a cone-down view of L5–S1 add minimal information and more than double the radiation exposure (4). In children, the oblique views should be obtained after reviewing the AP and lateral views because these additional views may demonstrate spondylolysis or spondylolisthesis, which are common problems in children. It is not necessary, however, to obtain plain radiographs in the majority of patients, who have nonspecific back pain or suspected disc herniation.

MRI is the imaging study of choice for patients with suspected epidural compression syndrome, spinal infection, spinal metastases, herniated disc, and spinal hematoma (13). MRI provides the best resolution of the spinal cord, spinal canal, and disc disease. In cases of suspected epidural compression due to tumor, infection or

hematoma, the entire spine should be imaged for two reasons. First, there is a risk of false localization to a spinal level on physical examination. Second, in metastatic spinal cord compression, there is a 10% risk of asymptomatic metastases distant from the affected site that may alter the treatment regimen. Although MRI is the gold standard for disc herniation, it is not necessary to order an emergent study from the ED in the absence of signs or symptoms of epidural compression. For suspected herniated disc, an outpatient MRI is appropriate for those who fail to respond to 4 to 6 weeks of conservative management.

Computed tomography (CT) scanning is superior to MRI in evaluating the bony architecture of the spine, especially in the assessment of a vertebral fracture. However, CT is inadequate for imaging the spinal cord and the spinal canal surrounding the spinal cord. When used in conjunction with myelography (CT-myelogram), CT scanning approaches the accuracy of MRI and should be considered the imaging method of choice in the patient who is unable to undergo an MRI.

KEY TESTING

- CBC and ESR for suspected tumor or spinal infection
- Plain films or CT for suspected fracture
- MRI for suspected epidural compression, spinal infection, or metastases

ED MANAGEMENT

The treatment of patients with nonspecific low back pain should focus on the areas of activity modification, analgesia, and other modalities. In terms of activity modification, patients should continue their routine daily activities as tolerated, using pain as the limiting factor. Routine activity has been demonstrated to allow more rapid recovery than either bed rest or back mobilizing exercise (1,14).

Appropriate analgesia is paramount in treating the patient with nonspecific back pain. The primary treatment regimen should

involve acetaminophen alone or in combination with a nonsteroidal anti-inflammatory drug (NSAID). When employing NSAIDs, one must consider that no single NSAID has been shown as being most effective (1,2,15–17). Thus, one should initiate therapy with a less expensive agent such as ibuprofen, naproxen, or indomethacin. The use of the injectable NSAID ketorolac should be reserved for the patient who is unable to tolerate an oral NSAID. Additionally, NSAIDs should be used with caution in patients at risk of adverse effects, such as the elderly and those with peptic ulcer disease or renal disease.

Muscle relaxants, such as cyclobenzaprine (Flexeril), are often efficacious in treating nonspecific back pain, but clinical trials have not clearly identified which patients benefit from them. Side effects, especially sedation, are common (1,2,15–17). There is no good evidence that the addition of a muscle relaxant to a NSAID provides any additional benefit over NSAIDs alone (17).

Opioid analgesics should also be prescribed for patients with moderate-to-severe back pain. The prescriptions for these medications are best limited to 1 to 2 weeks' duration because of the risk of sedation, addiction, and constipation. Patients should be warned not to use acetaminophen when they are treated with an acetaminophen–opiate combination. There is no proven benefit to the use of oral steroids in the treatment of the patient with acute low back pain (1,16,18).

Manipulation is a controversial area of treatment. Although safe and recommended as effective by the 1995 Agency for Health Care Policy and Research (AHCPR) guidelines, more recent literature shows it is no more effective than exercises and only minimally more effective in improving patient satisfaction with care than giving the patient an instructional booklet (1,3,19,20). Other physical modalities, such as traction, transcutaneous electrical nerve stimulation (TENS) units, diathermy, and ultrasound, appear to be ineffective (1,3).

The treatment regimen for herniated disc mirrors that for nonspecific low back pain, including the use of routine activity as

opposed to bed rest (17), with the exception that manipulation should be used with extreme caution.

The patient with suspected epidural compression requires emergent advanced imaging, specialty consultation, and should be considered for treatment with dexamethasone. The acute use of steroids in the patient with epidural compression from disc herniation and epidural abscess is controversial and there is no definitive answer. For the patient with potentially metastatic disease, a wide range of dosing for dexamethasone (10 to 100 mg IV) has been suggested (21–23). The current recommended approach is to administer 10 to 16 mg of dexamethasone IV to the patient with known cancer and signs of epidural compression (12,21). One should not delay steroid administration while awaiting definitive confirmation by imaging studies. For patients with spinal cord compression due to neoplasm, emergent radiation therapy is also recommended.

In the patient with suspected spinal infection obtain at least two sets of blood cultures, as these are frequently positive. One should discuss the need for antibiotics in the ED with the consultant prior to administration, because these patients may require open or needle guided biopsy with culture of the site. The administration of antibiotics may obscure the culture results. However, patients with paralysis or sepsis because of infection require antibiotics and one should not delay their administration. Empiric antibiotic therapy should be directed against methicillin-resistant *S. aureus* (MRSA), such as parenteral vancomycin, in addition to a third- or fourth-generation cephalosporin due to the potential of a gram-negative bacilli infection (5).

CRITICAL INTERVENTIONS

- Administer dexamethasone in suspected epidural compression due to tumor.
- Administer antibiotics that cover MRSA and gram-negative bacilli in patients with suspected spinal infection.

DISPOSITION

Patients with nonspecific low back pain and back pain with radiculopathy can be discharged home with primary care physician follow-up in 2 to 4 weeks. They should be treated with acetaminophen and NSAIDs, unless contraindicated. Most patients may benefit from a short course (1 to 2 weeks) of opiate analgesia, such as hydrocodone or oxycodone. If patients have a deficit in a single nerve root consistent with a herniated disc, the primary care physician should see the patient within 7 to 10 days. All patients suspected of having an epidural compression syndrome require emergent MRI and consultation in the ED by a spine surgeon. If known or suspected metastatic disease is present, an oncologist should also be consulted. All patients with suspected spinal infection require emergent MRI.

Transfer to another facility is necessary in the patient with suspected spinal infection or epidural compression syndrome, if the facility evaluating the patient is unable to obtain an appropriate imaging study (MRI or CT myelogram) or lacks the appropriate specialists. In patients with suspected epidural compression syndrome due to tumor, steroids should be administered before the transfer.

Common Pitfalls

- Failure to consider a ruptured abdominal aortic aneurysm in the patient older than age 55 years with acute low back pain.
- Overutilization of diagnostic tests in the patient with low back pain and no “red flags.”
- Underutilization of testing in children with back pain, who have a much higher incidence of serious etiologies than adults.
- Failure to consider spinal infection in the immunocompromised patient or the injection drug user with back pain, especially when fever is present.
- Overutilization of MRI in patients with suspected herniated disc. Such patients do not require imaging with MRI unless they fail to improve within 4 to 6 weeks, and it is not required in the ED.

- Failure to administer dexamethasone and order emergent imaging and consultation in patients with suspected epidural compression syndrome.

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CHAPTER 149

Foot Disorders

Valerie Dobiesz and Carissa Tyo

Foot pain is a common complaint in the emergency department (ED), and foot disorders can be extremely debilitating. Foot injuries rank second only to knee injuries as the most common injuries associated with sports. Nontraumatic causes of foot pain are usually chronic or subacute in nature. In the vast majority of cases, overuse conditions or improperly fitting shoes are the causes. The emergency physician can often provide symptomatic relief and definitive care. Special attention needs to be given to diabetic patients with foot disorders, as they are at high risk for serious complications.

The vast majority of foot disorders can be diagnosed easily without further testing and can be successfully treated on an outpatient basis. Patients should be referred to a primary care physician, a podiatrist, or an orthopedic surgeon for definitive care and follow-up.

TINEA PEDIS

Tinea pedis is a dermatophyte infection of the soles of the feet, the interdigital spaces, and is often accompanied by onychomycosis (tinea unguium). Superficial mycotic infections are present in 20% to 25% of the world's population and the most common fungal infections of the skin are on the feet (1). Males are more commonly affected, and the incidence increases with age. Occlusive footwear, because it causes moisture and warmth between the toes, and hyperhidrosis predispose to this condition; communal activities such

as swimming and bathing promote its spread. The infection can be acute or chronic and both types are contagious, typically caused by the shedding of skin scales containing hyphal elements. The most frequent dermatophyte involved is *Trichophyton rubrum* (1).

There are four types of tinea pedis. The interdigital type involves maceration and desquamation in the lateral toe spaces, the vesicular type manifests as episodes of unilateral acute vesiculation on the soles, the chronic hyperkeratotic or moccasin type causes dry pruritic erythema with diffuse scaling over the soles, and the ulcerative type presents with vesiculopustular lesions and secondary bacterial infection. Symptoms include extreme itching, burning, and irritation on the soles of the foot and between the toes.

ED management includes a variety of topical antimycotic agents, such as imidazoles, pyridines, allylamines, and benzylamines. These agents should be used twice daily for 1 to 6 weeks depending on the agent used. Widespread infections, cases involving the nails (onychomycosis), cases in patients with immunocompromised states or diabetes, or failed topical therapy are treated with systemic antimycotics such as itraconazole, terbinafine, fluconazole, or the imidazoles. Care should be exercised to observe for signs of opportunistic bacterial superinfection through the disrupted dermal barrier.

PARONYCHIA

Paronychia are soft tissue infections arising along the perionychium and may be acute or chronic in nature. They tend to follow the course of the nail margin and on occasion extend under the nail bed itself. These infections tend to arise acutely after local trauma including nail cutting, hangnail, and nail-biting, though obviously less common on the foot. Small breaks in the skin allow for the entrance of the infecting organism. Symptoms start with local erythema, pain, and swelling. This may then progress to suppurative infection with local abscess formation and, in severe cases, cellulitis and eventually osteomyelitis. In acute infections, the organism is typically *Staphylococcus aureus* and less commonly *Streptococcus* or

Pseudomonas species. In diabetic patients, the infection may be due to mixed flora. Chronic infections due to *Candida* often arise from chronic exposure of the feet to moisture.

ED management options are described in detail in Chapter 147.

PLANTAR WARTS (VERRUCA VULGARIS)

Plantar warts are hyperkeratotic lesions on the plantar surface of the foot caused by the human papillomavirus (HPV) through direct skin contact and are generally self-limited. Each subtype of HPV shows a preference for certain areas of the body, with subtypes 1, 2, 4, 27, and 57 most commonly associated with plantar warts (2,3). They tend to grow endophytically (into the deeper layers of skin) on pressure areas of the feet such as bony prominences or the heel or ball of the foot and may be painful when the patient puts weight on them. Children, especially teens, are more susceptible to infection than adults. Warts are firm and flat with well-defined boundaries and may be brown or gray, with the center containing one or more pinpoints of black representing thrombosed capillaries. Callus formation over the wart is common. Distinguishing warts from calluses may be difficult. Warts occur at any site, whereas calluses appear only on pressure areas. Pinching around the lesion and producing pain supports an underlying wart. If the hyperkeratotic area is scraped, the underlying wart typically bleeds and has a spotted appearance, representing thrombosed vessels.

ED management consists of application of pressure-relieving dressing and administration of analgesics, topical keratolytic agents solutions such as salicylic acid, cantharidin, or dichloroacetic acid, or duct tape occlusion therapy for a maximum of 2 months (4–6). Refractory warts may require cryotherapy with liquid nitrogen, laser, or surgical excision. HPV vaccine may have a role in the treatment of recalcitrant warts (7).

SUBUNGUAL HEMATOMA

Painful and black toenails are often a result of acute trauma or repeated minor trauma from improper footwear, resulting from the

toenails' rubbing on the undersurface of the shoe or the foot sliding forward to jam the toes. If the symptoms are acute, the treatment is drainage of the hematoma with nail trephination, which can be done using a heated paper clip, an 18-gauge needle, or an electrocautery device. To prevent recurrence, the patient can be instructed to use a metatarsal pad under the metatarsal heads or a tongue pad underneath the tongue of the shoe, and instructed to wear shoes with an adequate toe-box.

ONYCHOCRYPTOSIS (INGROWN TOENAIL)

Ingrown toenails are often the result of poorly fitting shoes, abnormal nail growth, or poor nail cutting. A sharp edge of the nail pierces the epidermis of the sulcus and penetrates the dermal tissues. The hallux or great toe of male adolescents is most often involved. Symptoms include pain, swelling, erythema, and purulent drainage of the affected toe. Patients may develop granulation tissue along the nail margin owing to chronic inflammation. Warm soaks are helpful in mild cases, whereas partial resection of the nail (generally a narrow longitudinal strip) may be needed for more severe cases. In the presence of infection, the ED management options are those described for a paronychia (Chapter 147). More definitive treatment should be carried out by a podiatrist or surgeon.

BLISTERS, CALLUSES, AND CORNS

Excessive localized pressure or friction between the foot and improperly fitted shoes or from constant sliding of the foot inside a shoe can result in blisters, calluses, and corns. *Blisters* result from shearing forces, causing fluid to accumulate within the layers of the skin. In one study of endurance sports, blisters were the most common reason for medical attention, accounting for 53% of medical encounters during an adventure race (8). The treatment of blisters is geared toward prevention, with local treatment of hotspots using padding and lubrication to prevent friction over the affected areas. Comfortable, well-fitting shoes and thick padded

socks may help to prevent blister formation and should be considered high priority for management. Once formed, the treatment of blisters is controversial and depends on the needs of the patient. In sports, the patient often desires a rapid return to activity, which may be facilitated by drainage and bandaging of the sites. This drainage may be done with a sterile sharp tool such as a scalpel or needle. The overlying skin should be left intact and a dressing applied. As an open wound, the area should be monitored closely for signs of infection. Infected blisters must be debrided, and antibiotics may be indicated if signs of local cellulitis are present. If the patient does not need to reenter activity, blisters may be left intact and observed for signs of infection.

Calluses develop from excessive pressure, causing hypertrophy of the squamous cell layer of the epidermis on skin that is normally thick, such as the sole. A callus is painless and may be diffuse or localized. Treatment includes regular debridement with a callus file, pumice stone, or scalpel.

A *corn* (Helomata or clavi) is a painful conical thickening of skin with recurrent pressure; the apex of the cone points inward and causes pain. Corns usually occur over bony prominences such as the fourth or fifth toe. When they occur in moist areas, such as between the toes, they are called *soft corns.* Treatment is aimed at prevention with appropriate footwear and padding proximal to the lesions to relieve pressure. These lesions should be aggressively pursued and treated in diabetic patients because of the risk of infection and long-term sequelae.

PIEZOGENIC PEDAL PAPULES

First described in 1968, piezogenic pedal papules are small (2 to 5 mm), white to yellow, and located along the medial or posterolateral aspect of the heel. They tend to be bilateral and are associated with weight bearing. Thought to arise from local pressure, these papules form in long-distance runners with a predisposition to women and children. They arise from a herniation of subcutaneous fat through the collagen matrix of the reticular

dermis of the foot. They may be either symptomatic or asymptomatic and may improve or resolve with elevation of the feet (9). Although no satisfactory medical or surgical treatment exists, heel cups may provide some relief.

BROMHIDROSIS

Malodor of the feet is caused by keratin decomposition in the presence of hyperhidrosis or excessive production of sweat. A corynebacterial overgrowth or fungal colonization may occur, worsening the condition. Treatment includes measures to reduce sweat production and to control secondary infection. Use of talcum powder, spray deodorants, and absorbent insoles may be helpful.

METATARSAL STRESS FRACTURES

Stress fractures are the result of repetitive loading forces, causing the bone to fatigue and eventually fracture. Metatarsal bones are a common site of stress fracture. The most common metatarsal stress fracture occurs at the neck of the second metatarsal and is commonly described in military recruits (march fracture). It is more common in patients with Morton syndrome (the first ray shorter than the second) (10).

Symptoms include localized pain that is worsened by activity or weight bearing and is relieved with rest. Plain x-rays typically do not reveal stress fractures until 10 to 14 days after they occur. Bone scan or magnetic resonance imaging (MRI) may be diagnostic but are not practical or necessary in the ED setting. The condition is treated conservatively by having the patient avoid weight bearing on the site for 4 to 6 weeks, applying ice, and administering nonsteroidal anti-inflammatory drugs (NSAIDs).

BUNIONS (HALLUX VALGUS)

Bunions are inflammation at the first metatarsophalangeal (MTP) joint. Inflammation at the base of the little toe is called a *bunionette* (tailor's bunion). This condition is more common in females in a 10:1 ratio. The hallux valgus deformity consists of lateral deviation

of the hallux and medial deviation of the first metatarsal. The etiology of both is unclear, but hereditary biomechanical abnormalities and improperly fitting shoes may be factors. Symptoms of bunions are pain and erythema at the MTP joint. ED management is focused on analgesia with NSAIDs, bunion pads, ice, and patient education on proper shoes with a wide toe box and no high heels. In severe cases, surgical correction is indicated.

TOE DEFORMITIES (MALLET/HAMMER/CLAW TOES)

Mallet toes are flexion contractures of the distal interphalangeal joint, most commonly of the second digit. Although the exact etiology is uncertain, ill-fitting shoes are believed to contribute. Mallet toes are more common in diabetic patients and may lead to the formation of calluses and corns of the abnormally flexed toe, leading to a risk of infection owing to friction and ultimately ulceration at the pressure points.

Like mallet toes, hammertoes arise from an abnormal flexion contracture in the toe. However, this deformity arises in the proximal interphalangeal joint. Ill-fitting shoes are also believed to contribute to this deformity, with similar attendant problems arising from pressure points along the deformed toes.

Claw toes are also deformities of the toes but tend to arise because of neuromuscular diseases and affect all minor toes equally often. They tend to be associated with extension of the MTP joint and occasionally with flexion of the distal interphalangeal joint. As with mallet and hammertoes, complications arise from abnormal distribution of pressures on the feet.

Treatment of toe deformities starts with local padding and support, with use of well-fitting shoes. Surgical correction may be indicated in some case. Diabetics, in particular, should be referred for podiatric or orthopedic consultation.

CALCANEAL STRESS FRACTURES

Repetitive stress on the calcaneus may over time result in a stress fracture. Patients typically present with insidious onset of heel pain

aggravated by weight-bearing activities. On examination, there is localized tenderness over the medial or lateral aspects of the calcaneus, and pain is elicited by squeezing the calcaneus from both sides, the heel "squeeze" test. It may initially be confused with plantar fasciitis. Radiographs are typically normal initially or show a typical sclerotic appearance on the lateral view parallel with the posterior margin of the calcaneus. Treatment is conservative with rest, administration of NSAIDs, and advising the patient not to put weight on the site.

TARSAL TUNNEL SYNDROME

Tarsal tunnel syndrome (TTS) is a compressive neuropathy of the posterior tibial nerve arising from constriction as the nerve passes through the tarsal tunnel. Symptoms include burning and paresthesias to the heel which may radiate down to the toes or shoot back up the leg. Similar to carpal tunnel syndrome, the condition arises from the increased pressure within the tarsal tunnel contributing to neuropathic dysfunction of the posterior tibial nerve. In addition to paresthesias and pain, the patient may also have numbness, hot/cold sensations, or electric shock sensations down the foot.

The causes of TTS are varied and may arise from pathology in any of the components and contents of the tarsal tunnel. Approximately 50% of the time, the etiology is idiopathic. For the other 50%, a cause may be discernible (11). Bone spurs, ganglion cysts, varicose veins, local inflammation, or acute bony injury are a few examples of potential causes. Treatment depends largely on the etiology of the compression and may include steroid injection, immobilization, and ultimately surgical decompression.

Diagnosis can be made by performing at Tinel sign over the tarsal tunnel. The physician taps over the region just posterior and inferior to the medial malleolus to assess for worsening paresthesia to the foot. Imaging may be useful to assess for potential etiologies. X-rays may elucidate fractures or bone spurs, ultrasound may clarify vascular malformations or varicosities, MRI can demonstrate local

inflammatory problems as well as cystic or mass lesions. However, imaging may be deferred to the primary care setting.

ED management may include offloading strategies with crutches or walkers, compression wraps, rest, anti-inflammatories, and consideration of referral for physical therapy. Patients should be directed to follow up with a primary care physician, podiatrist, or orthopedist.

ACHILLES TENDONITIS

Achilles tendonitis or tendonopathy is caused by overuse and is seen most commonly in middle-aged or older recreational athletes, especially with recent changes in activity level, training duration, running surface, or footwear. High body mass index has also been implicated as playing a role in the development of this condition (12). Inflammation or tissue degeneration and disorganization of the tendon results in pain 2 to 6 cm above the tendon insertion (13). Tenderness anterior to the tendon is more consistent with retrocalcaneal bursitis. Treatment includes rest, ice, heel lifts, eccentric exercises, NSAIDs, low-energy shock wave therapy, and, rarely, injection, laser therapy and surgery (13).

RETROCALCANEAL BURSITIS

Retrocalcaneal bursitis is an inflammation of the bursa that lies between the Achilles tendon and the posterior border of the calcaneus. Symptoms begin early in activity and are exacerbated by dorsiflexion of the foot. Tenderness is just anterior to the Achilles tendon (deep) and posterior to the calcaneus. Hind foot swelling is often present. The treatment is rest and administration of NSAIDs. The patient is instructed on stretching exercises and use of a heel lift. This condition can also be treated with steroid and local anesthetic injections.

PLANTAR FASCIITIS

The plantar fascia is a band of connective tissue on the plantar surface of the foot that extends from the calcaneal tuberosity to the

metatarsal heads. Plantar fasciitis is the most common cause of inferior heel pain and the etiology is not clearly understood but felt to be multifactorial in origin (14). Irritation and microtears due to overuse and repetitive heel strikes cause degeneration of the fascia, resulting in heel pain. The pain occurs often in the morning or with prolonged sitting. It is believed to be a degenerative process without inflammation. This entity accounts for 10% of running injuries and primarily afflicts the middle-aged, the elderly, and athletes. Physical examination findings include (a) point tenderness over the medial calcaneal tuberosity, (b) reproduction of pain with passive dorsiflexion of the ankle or toes, or (c) heel pain with standing on the toes.

ED management is focused on relaxing the tension on the fascia and includes rest, ice, stretching exercises, arch support, avoidance of aggravating activities, use of orthotics, administration of NSAIDs, dorsiflexion night splints, advising the patient to wear proper shoes, ultrasonic shockwave therapy, and rarely surgery (14–16).

MORTON&RSQUO;S INTERDIGITAL NEUROMA

Morton's neuroma is a common source of forefoot pain due to a degenerative neuropathy from repetitive trauma compressing the interdigital nerve, most often between the third and fourth metatarsal heads. It is seen in patients who are runners, dancers, and basketball players, and in those who have to stand for long periods of time or wear high-heeled shoes. Symptoms are sharp, stabbing pain and paresthesia between the toes.

The diagnosis is made clinically by pinching between the metatarsal heads and simultaneously using the other hand to compress the forefoot with pressure on the first and fifth metatarsal heads. This maneuver will elicit pain and possibly a palpable mass or an audible click, known as *Mulder click*. Treatment includes ice in acute cases, orthotics, rest, steroid injections, and possible surgical excision (17).

Common Pitfalls

- Failure to aggressively manage diabetic patients with foot disorders. The risk of complications is high if such patients are inadequately treated.
- Failure to recognize metatarsal stress fractures, which are common and may not be visualized radiographically in the acute setting. Suspected stress fractures are treated with avoidance of weight bearing.
- Failure to distinguish between plantar warts and calluses.

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CHAPTER 150 Monoarticular Arthritis

Alan C. Heffner

Acute joint pain is a common emergency condition that carries a broad differential diagnosis. Trauma and crystal disease are the most common causes, while bacterial infection carries the greatest potential for morbidity and mortality. Arthrocentesis and synovial fluid analysis are key steps in the evaluation of acute monoarticular arthritis.

CLINICAL PRESENTATION

Acute arthritis typically presents with joint pain and swelling. The onset and severity of inflammation varies greatly depending on etiology and host factors such as age, comorbid disease, and immunocompetence. This chapter focuses on the most important types of monoarticular arthritis including crystal and infective arthropathies. Septic arthritis is divided into gonococcal and nongonococcal disease, reflecting the varied pathogenesis and management of these diseases.

Gonococcal Arthritis

Neisseria gonorrhoeae remains a common cause of septic arthritis in young, healthy, sexually active adults in the United States. Disseminated gonococcal infection (DGI) should be suspected in any sexually active patient with joint complaints. Women are more frequently affected than men and are predisposed to systemic spread during pregnancy and the perimenstrual period. DGI presents in two distinct patterns. The first is an acute suppurative monoarthritis

involving the knee, wrist, or ankle that occurs in 40% of DGI patients. Polyarthralgias may precede localization to a single joint. The second pattern is the gonococcal arthritis–dermatitis syndrome. Hematogenous spread of bacteria and immune complexes underlie the triad of *dermatitis, tenosynovitis,* and *migratory polyarthritis.* The classic skin lesions are scattered small painless erythematous macules or petechiae, which evolve into pustular to necrotic lesions on an erythematous base. Transient painful extensor tenosynovitis often involves the wrists, hands, and ankles but asymmetric migratory extremity polyarthralgias are the most common. Toxicity varies greatly in DGI. Patients can experience only mild constitutional symptoms and fever is often absent. Symptoms of primary genital infection may be absent.

Nongonococcal Septic Arthritis

Nongonococcal septic arthritis is a medical emergency due to the potential for rapid joint destruction and clinical sepsis. Permanent joint damage complicates 40% of septic joints and overall mortality is 15% but reaches as high as 50% in some subgroups (1,2). Large weight-bearing joints such as the knee and hip are most commonly involved, with the shoulder, ankle, elbow, and wrist occurring with decreasing frequency. Any articular surface may be affected including sternoclavicular, acromioclavicular, and sacroiliac joints.

Pathogenesis of nongonococcal septic arthritis involves one of four mechanisms: hematogenous seeding, contiguous spread, direct traumatic implantation, or postoperative invasion of prosthetic hardware. Hematogenous seeding of the vascular synovium is the most common source of septic arthritis. Bacteremia may stem from IV drug use, indwelling vascular access, recent invasive procedures, and distant active or recent infection. Contiguous spread into a joint occurs from adjacent cellulitis, tenosynovitis, osteomyelitis, or abscess. Examples include diabetic foot infections and pediatric metaphyseal osteomyelitis. Direct joint inoculation occurs with trauma or iatrogenically; the clenched fist “fight bite” injury and cat bites to the hand and wrist are commonly overlooked injuries.

Local factors such as antecedent arthritis, joint surgery or trauma, intra-articular steroid injections, and prosthetics predispose patients to septic arthritis. The risk of septic arthritis is severalfold higher in patients with underlying rheumatoid arthritis (1,3). Infections complicate up to 2% of prosthetic joint procedures, with revision arthroplasty carrying even greater risk. Pain localized to a prosthetic joint may signify mechanical loosening, prosthesis failure, or joint infection. Crystal-induced arthritis is rare in prosthetic joints.

Nongonococcal septic arthritis classically presents with rapidly progressive joint pain and swelling. Chronic illness and immunocompromise increase the risk of septic arthritis but also moderate the presenting symptoms. Insidious clinical progression in the absence of systemic toxicity is common in this group. Polyarticular involvement occurs in 10% to 20% of patients (4).

Gram-positive cocci remain the major nongonococcal pathogens in adults. *Staphylococcus aureus* is the most common causal organism, followed by streptococci including *Streptococcus pneumoniae.* Gram-negative bacilli including *Pseudomonas aeruginosa* cause 20% of infections and occur predominantly in immunocompromised patients and IV drug users. Anaerobes are isolated in a minority of cases but are more common with penetrating trauma. Inoculation of oral flora occurs in penetrating bite wounds. Mycobacterial and fungal arthritis are uncommon but important considerations in immunocompromised patients and those presenting with subacute progressive pain of the spine or weight-bearing joints.

Crystal-Induced Monoarthritis

Crystal-induced acute arthropathy is more common than septic arthritis and represents the most important mimic of infection. Gout and pseudogout may be clinically indistinguishable from septic arthritis. In both disorders, patients may demonstrate systemic symptoms, including fever.

Gout develops when monosodium urate (MSU) crystals precipitate within joints and trigger an acute inflammatory reaction. The

typical presentation is a middle-aged man with severe joint pain, swelling, redness, and warmth that evolves rapidly over hours to days. The initial attack is monoarticular in 85% of cases. Although any joint may be affected, the first metatarsophalangeal (MTP) joint (podagra) is involved in 60% of cases, followed by ankle, midfoot, and knee. Left untreated, gout follows a course of increasingly frequent attacks separated by shorter intercritical periods. Recurrent exacerbations cause chronic arthritic changes with bony erosions resembling rheumatoid arthritis or degenerative joint disease. Noninflammatory soft tissue tophaceous deposits may develop in the Achilles tendon or extensor surface of the fingers, forearms, or elbows. Common precipitants of acute attacks include increased purine intake, enhanced cellular breakdown (i.e., chemotherapy), alcohol, and joint trauma. In contrast to the classic presentation, older men and postmenopausal women may present with subacute to chronic polyarticular synovitis involving the small joints of the hands and feet. This presentation, resembling rheumatoid arthritis, is strongly associated with diuretic use and renal insufficiency.

Pseudogout is the result of calcium pyrophosphate dihydrate (CPPD) crystal deposition and manifests three common clinical courses: (1) asymptomatic radiographic stippling of articular cartilage (chondrocalcinosis), (2) acute attacks of mono- or oligoarticular inflammatory arthritis (pseudogout), and (3) progressive degenerative joint changes similar to osteoarthritis. Pseudogout usually develops after age 50 and may involve single or multiple joints, especially the knees, wrists, ankles, and elbows. Acute attacks may exhibit abrupt onset and marked discomfort, clinically indistinguishable from gout or septic arthritis. More commonly, the exacerbations evolve over days. Systemic illnesses including surgery or trauma are common triggers. Most cases are idiopathic, but CPPD deposition is associated with hyperparathyroidism and hemochromatosis.

DIFFERENTIAL DIAGNOSIS

Acute monoarthritis occurs with inflammatory, infectious, ischemic, neoplastic, traumatic, mechanical, or hemorrhagic processes (Table 150.1). The major diseases to consider include septic arthritis, crystal arthropathy, and trauma, but many disorders may produce pain, swelling, and erythema in or around a joint.

TABLE 150.1
Differential Diagnosis of Acute Monoarticular Arthritis

Infectious

Gonococcal

Nongonococcal

Mycobacterial (*M. tb* and atypical)

Spirochete (Lyme, syphilis)

Fungal

Peri- and postinfectious viral: HIV, hepatitis B, rubella, parvovirus, others

Crystal-Induced

Gout (MSU)

Pseudogout (CPPD)

Calcium apatite

Traumatic

Fracture

Ligamentous injury

Overuse injury

Ischemic

Avascular necrosis

Vasoocclusive crisis

Decompression illness

Spontaneous osteonecrosis

Hemorrhagic

Posttraumatic

Hemophilia

Systemic anticoagulation

Neoplastic

Metastasis

Osteochondroma

Osteoid osteoma

Pigmented villonodular synovitis

Systemic Disease

Remote infection, infectious endocarditis

Rheumatic fever

Seronegative spondyloarthropathies (Ankylosing spondylitis, enteropathic, psoriatic and reactive arthritis)

Reiter syndrome, Behcet disease

Rheumatoid arthritis, Systemic lupus erythematosus

Sarcoidosis, amyloidosis

Serum sickness

Periarticular conditions such as cellulitis, tendonitis, and bursitis must be distinguished from intra-articular pathology. Enthesitis is localized to tendinous insertions to bone. Bursitis results in pain and swelling overlying bony prominences. Most cases are noninfectious but septic bursitis may occur in the setting of local trauma; the olecranon and prepatellar bursas are the most commonly infected.

A variety of classically polyarticular inflammatory conditions including *rheumatoid arthritis, seronegative spondyloarthropathy, systemic lupus erythematosus,* and *postinfectious arthritis* may present with acute monoarticular symptoms. The seronegative arthritides, characterized by the absence of rheumatoid factor, include *ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis* (associated with inflammatory bowel disease), and reactive arthritis (such as *Reiter syndrome*). Sterile postinfectious arthritis may be triggered by preceding or coincident infection with a variety of agents including Group A streptococci, HIV, parvovirus, hepatitis B, and rubella. Serum sickness and endocarditis are additional considerations.

Lyme disease manifests musculoskeletal features ranging from acute episodic arthralgia to chronic mono- or oligoarticular arthritis. Knee involvement is common. A history of tick exposure, travel to an endemic region, or erythema migrans rash is helpful but not always present.

Vascular compromise may lead to bone infarction and osteonecrosis. The weight-bearing surface of the femoral head and medial condyle of the knee are common locations. Patients complain of severe pain in the absence of trauma. Precipitants include sickle cell vasoocclusive disease, vasculitis, decompression illness, posttraumatic injury (i.e., hip dislocation), and corticosteroid-induced avascular necrosis.

Traumatic joint injuries are common. Development of an immediate joint effusion after injury suggests hemarthrosis due to ligamentous disruption or osteochondral fracture. Hemarthrosis may occur spontaneously or after minor trauma in the setting of coagulopathy due to anticoagulation or hemophilia. Osteoarthritis is a chronic, slowly progressive disease affecting weight-bearing joints.

Acute exacerbations may coincide with new or worsening effusion following overuse or minor trauma. Neoplastic lesions present with pain or pathologic fracture.

Children who present with a limp or refusal to walk may have septic arthritis or *acute transient synovitis*. Transient synovitis is the most common cause of hip pain in children 3 to 10 years of age. This self-limited inflammatory condition typically presents 1 to 3 weeks after a viral illness. There is considerable overlap in the clinical presentation of septic arthritis and transient synovitis. Consider slipped capital femoral epiphysis (SCFE) in a portly pubescent child and *Legg–Calve–Perthes disease* (aseptic necrosis of the femoral head) in young school-age children (see Chapter 242).

ED EVALUATION

Septic arthritis poses risk of joint destruction and even death if treatment is delayed. For this reason, the emergency evaluation of any joint complaint focuses on excluding infection. Assessment centers on history, physical examination, and arthrocentesis when indicated. Serum inflammatory markers are rarely informative and may mislead the physician if used as a substitute for arthrocentesis.

The temporal course, duration of symptoms, and history of similar joint symptoms should be clarified; acute and acute-on-chronic presentations deserve special attention. A history of recurrent monoarthritis or typical podagra suggests crystal-induced or other noninfectious arthritis. However, acute symptoms in patients with pre-existing arthritis deserve special attention, as antecedent joint pathology predisposes to infection (3,4). Atypical or marked exacerbations of chronic arthritis also warrant a high suspicion for superimposed infection. Acute worsening should not be attributed to progression of disease until infection is excluded. Rheumatoid arthritis carries a 10-fold higher incidence of septic arthritis and greater mortality compared to the general population; delayed diagnosis contributes to this poor outcome.

The degree and distribution of joint involvement separates arthritis into mono-, oligo- (less than three joints), and polyarthritis

patterns. Unless prompted, patients may complain only of a single painful joint, to the exclusion of other symptoms. Constitutional symptoms and morning stiffness are classically associated with rheumatic diseases.

A focused history should include comorbid diseases, especially immunosuppression. Immunomodulating drugs and antibiotics blunt the clinical presentation of acute infection. Potential septic sources include recent infection, invasive procedures, IV drug use, sexually transmitted diseases (STDs), and tick exposure. Genital ulcerations or discharge occur with gonococcal disease or Reiter syndrome. Rash, oral ulcers, uveitis, urethritis, and diarrhea suggest reactive arthritis. Medications should be reviewed with attention to precipitants of crystal arthropathy, such as diuretics. Infection following intra-articular injection is uncommon (2,5). Recent trauma suggests a fracture or musculotendinous injury but even minor trauma can precipitate gout. Penetrating injuries may introduce infection.

Examination begins with general assessment of toxicity and hemodynamic stability. Sepsis and shock may complicate infectious arthritis. Systemic findings including fever are not reliable to confirm or exclude septic arthritis. Fever is absent in up to 50% of patients with septic arthritis (6). Extra-articular sources of infection including cellulitis, pneumonia, genitourinary infection, and indwelling vascular access should be investigated as potential sources of bacteremic joint seeding. Cellulitis overlying a joint prosthesis increases the risk for joint involvement (7). Skin examination for disseminated gonococcal lesions is important. Oral ulcers may be present in Behcet syndrome, Reiter syndrome, and systemic lupus erythematosus. Oral thrush suggests immunosuppression. Infectious endocarditis commonly manifests with musculoskeletal symptoms and should be considered in any patient with a murmur and arthritis. Acute rheumatic fever and systemic lupus may also present this clinical picture.

Examine all joints to classify the number, degree, and symmetry of joint involvement. Resting position provides important clues to intra-articular pathology. The inflamed hip is often flexed and

externally rotated. An irritable knee is held in mild flexion. Testing active and passive range of motion distinguishes intra-articular from periarticular conditions such as bursitis, tendonitis, strain/sprain, and cellulitis. Pain on gentle motion, whether active or passive, is the hallmark of joint inflammation. *Patients with intra-articular pathology typically experience pain with any range of motion.* Refusal to move is common in severely inflamed joints. In contrast, periarticular conditions produce focal inflammation and localized tenderness without the same limited passive movement. Deep axial joints are difficult to evaluate. Pain localized to the sacroiliac joint may be exacerbated with the FABER maneuver (placing the hip into forced flexion, abduction, and external rotation).

The etiology of acute monoarthritis is difficult to diagnose by history and examination alone (6). Synovial fluid analysis is the diagnostic cornerstone for acute arthritis discrimination. Arthrocentesis should be performed in all cases of acute monoarticular arthritis, with the possible exception of classic recurrent gout. The emergency physician can safely aspirate most peripheral joints, but deep joints such as the hip and sacroiliac may require specialist consultation and fluoroscopic or ultrasound guidance. Orthopedic consultation is advisable before arthrocentesis of prosthetic joints.

Synovial fluid samples should be analyzed for cell count with differential, Gram stain, culture, and light microscopy for crystals. These tests require a minimum of 2 mL of fluid. *Culture and light microscopy for crystals are the most informative tests if fluid is limited* (8). Synovial fluid chemistries including lactate dehydrogenase (LDH), glucose, protein, and lactate are rarely helpful and may be misleading.

Synovial fluid leukocyte count distinguishes inflammatory versus noninflammatory effusions. Normal synovial fluid is clear, straw-colored, and highly viscous, with <200 WBC/mm^3. Leukocyte counts $<2{,}000$ WBC/mm^3 are considered noninflammatory and occur in osteoarthritis and chronic or inactive inflammatory diseases. More than 2,000 WBC/mm^3 indicates an inflammatory process. The synovial fluid of septic arthritis is classically opaque to

purulent with leukocyte counts >50,000 WBC/mm^3. However, the synovial leukocyte count must be interpreted with caution. The likelihood of infection increases with progressively greater synovial WBC count, but 40% of patients with nongonococcal infection have <50,000 WBC/mm^3 (9,10). Early infection, prior antibiotics, and immunocompromise (including immunosuppression) contribute to low leukocyte counts in the setting of infection. Predominance of polymorphonuclear cells (especially >90%) also suggests infection (6). Elevated leukocyte count is not specific for infection; rheumatoid and crystal arthropathy may induce vigorous inflammatory responses.

Gram stain may confirm infection but a negative stain does not exclude infection as it is diagnostic in less than 50% of cases. *Culture should be performed on all diagnostic synovial aspirates.* Synovial fluid culture is also imperfect. Direct inoculation of joint fluid into blood culture bottles and onto chocolate agar medium enhances organism yield. Potential sources of primary infection (i.e., blood and urine) should be cultured. Suspected DGI cases also warrant genital tract, oropharynx, rectum, and skin lesion cultures. Infection in these locations may be asymptomatic. Fungal and mycobacterial cultures are warranted in patients at risk.

Polarized light microscopy is the gold standard for crystal identification. MSU appears as needle-shaped or elongated crystals exhibiting brilliant negative birefringence. The rhomboid or rod-shaped crystals of CPPD are more difficult to visualize under white light and display weak positive birefringence. Differentiating intracellular and extracellular crystal formations is not diagnostically helpful. Because of interobserver variability, repeat examination is warranted when initial microscopy is inconclusive and clinical suspicion of crystal disease remains high (8). Septic arthritis is generally excluded by confirmation of an alternative diagnosis such as crystal arthropathy. Although rare, concomitant septic and crystal arthritis is described in 1.5% of cases (11–13).

Blood tests rarely aid in the diagnosis of acute monoarthritis (6). Inflammatory markers including WBC count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and

procalcitonin do not discriminate infective arthritis (7). Peripheral leukocytosis is present in half of patients with septic arthritis, and patients with acute gout can have significant leukocytosis (9). Acute-phase reactants such as ESR and CRP are common in bacterial arthritis but also rise in noninfectious disease. Serial acute-phase reactants are sometimes used to follow therapeutic response in established infection. Serum uric acid levels are likewise discouraged, as they do not correlate with acute gout symptoms (5). *In short, blood tests are often unhelpful or misleading in attempts to exclude septic arthritis.*

Radiography yields little in the evaluation of acute nontraumatic monoarthritis. Plain films are commonly normal or reveal nonspecific soft tissue swelling or joint effusion in the setting of inflammation. Joint space narrowing, periarticular osteoporosis, and erosive osteomyelitis caused by infection occur over days to weeks. Neonates rarely manifest joint dislocation or subluxation in the setting of infection. Chronic or recurrent gout may induce joint space narrowing and juxta-articular bony erosions with overhanging edges. Linear stippling and punctate densities of articular cartilage such as the menisci or triangular ligament of the radioulnar joint identifies chondrocalcinosis of CPPD but does not exclude other disease. Prosthetic loosening may be evident on plain films but does not differentiate mechanical failure from infection. Radiographs in patients with subacute to chronic symptoms should be scrutinized for fracture, foreign body, avascular necrosis, loose joint bodies, chronic joint changes, osteomyelitis, tumor, Paget disease, and osteochondritis desiccans among other processes.

Advanced imaging with ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) can differentiate articular from periarticular soft tissue processes and is sensitive for joint effusions. This is particularly helpful in difficult-to-examine joints such as the hip, sternoclavicular, and sacroiliac joints. Unfortunately, these techniques do not distinguish infected from sterile joint fluid.

KEY TESTING

- Arthrocentesis, with synovial fluid analysis for:
- Cell count with differential, Gram stain, culture, light microscopy for crystals
- If the synovial fluid sample is limited, culture and light microscopy for crystals are the most helpful tests.

ED MANAGEMENT

Gonococcal Arthritis

Initial therapy for disseminated gonococcal disease is a parenteral third-generation cephalosporin; alternative regimens include spectinomycin. Empiric therapy for concurrent chlamydia infection is also required.

Septic Arthritis

Rapid diagnosis and therapy is important to prevent joint and systemic morbidity of septic arthritis. Treatment requires appropriate antibiotics and surgical source control in most cases. As with any infectious process, begin antibiotics immediately after appropriate culture collection if the diagnosis is highly suspected. Antibiotic selection is based on the clinical probability of a specific pathogen as determined by patient presentation, age, comorbid risks, and Gram stain. Empiric broad-spectrum parenteral antibiotics are indicated in most situations (Table 150.2). Although primary pathogens are somewhat dissimilar, combination therapy with vancomycin and a third-generation cephalosporin are appropriate for most adults and children. The growing incidence of methicillin-resistant *S. aureus* (MRSA) warrants empiric coverage for this agent (14). Patients with gram-negative bacilli identified on stain and those at high risk for these pathogens warrant broadened empiric coverage. Intra-articular antibiotics provide no additional value for septic arthritis and carry the risk of chemical synovitis. Removal of infection and inflammatory debris is an essential component of treatment. Closed needle aspiration versus open surgical drainage of septic joints is controversial and should be left to the discretion of

the orthopedic consultant. Adjunctive systemic steroids to reduce the inflammatory response following infection control remains under investigation.

TABLE 150.2
Treatment of Monoarticular Arthritis[a]

Type	Example Regimen (Pediatric Dose)	Alternative Regimen
Infectious		
Empiric and non-GC	Vancomycin (20 mg/mg or 2 g max dose) q8–12h IV *and* Third-generation cephalosporin Ceftriaxone 2 g qd (50 mg/kg qd) Cefotaxime 2 g q8h (50 mg/kg) Ceftazidine 2 g q8h (50 mg/kg) Patients at risk for gram-negative organisms warrant broadened empiric coverage for these organisms	Linezolid 600 mg IV q12h Levofloxacin 750 mg IV 24h
Isolated GC	Ceftriaxone 1 g qd Cefotaxime 1 g q8h Ceftizoxime 1 g q8h Treat empirically for concurrent chlamydia[a]	Spectinomycin 2 g IV q12h
Crystal-Induced	NSAID Naproxen 500 mg PO bid for 5 d Indomethacin 50 mg PO tid. for 3 d and taper over 4–7 d (or comparable NSAID) Acetaminophen and narcotic analgesics as needed	Corticosteroids Prednisone 30 mg PO qd for 5 d Methylprednisolone 40–60 mg IV q8–12h Triamcinolone 60 mg IM Methylprednisolone 5–40 mg IA Colchicine 0.6 mg PO q1h for up to three doses
Traumatic	Joint aspiration for tense effusion Rest, ice, compression, elevation (RICE) Orthopaedic follow-up as needed	
Hemorrhagic	Correct coagulopathy RICE	
Inflammatory	Naproxen 500 mg PO bid (or comparable NSAID) High-dose ASA for RA Acetaminophen and narcotic analgesics as needed	

[a]See text for details.
ASA, acetylsalicyclic acid; IM, intramuscular; RA, rheumatoid arthritis; PO, per os (by mouth).

Crystal-Induced Arthritis

Although acute crystal-induced arthritis is generally self-limited, treatment relieves discomfort and prevents progressive joint destruction (Table 150.2). Nonsteroidal anti-inflammatory drugs (NSAIDs) are the historic treatment of choice for most patients. High initial dosing typically provides marked relief within 24 hours and may be tapered as symptoms improve to reduce potential adverse effects. The usefulness of NSAIDs is limited by their side effects including gastropathy, renal dysfunction, and interaction with warfarin.

Systemic corticosteroids are an important alternative. Comparable efficacy and safety in acute gout supports first-line use of glucocorticoid therapy, especially for patients with contraindication or suboptimal response to NSAID therapy (15–17). Oral, IV, and intramuscular options are available. Intra-articular steroids are very effective for crystal disease but their use requires the confident exclusion of infection. The appropriate intra-articular steroid dose is dependent on joint size; 20 to 40 mg of methylprednisolone acetate is adequate for larger joints such as the knee, whereas 5 to 10 mg is appropriate for smaller joints.

The leukocyte inhibitor colchicine provides dramatic relief of gout if utilized within 24 hours of onset but use has declined due to its narrow therapeutic window and higher risk of adverse effects. While traditional dosing was higher, a newer, more conservative recommendation is to administer 0.6 mg/hr up to three doses (1.8 mg total). Patients should not take additional colchicine for 7 days following an oral load. IV colchicine carries increased risk of systemic toxicity and is not recommended. Elderly patients and those with renal and hepatic dysfunction are not candidates for colchicine.

Serum urate-lowering agents such as allopurinol and probenecid are contraindicated in the setting of acute or resolving gout. The resultant change in serum urate may exacerbate or prolong an attack. Joint rest and cold applications provide symptomatic relief.

Warm compresses exacerbate joint inflammation and should be avoided. Acetaminophen and narcotic analgesics provide additional relief if needed.

CRITICAL INTERVENTIONS

- Initiate early parenteral antibiotic therapy for patients with septic arthritis.

DISPOSITION

Gonococcal arthritis is typically responsive to antibiotics and may not require surgical drainage. Reliable nontoxic patients with gonococcal disease of nonweight-bearing joints may be treated as outpatients with daily parenteral therapy and close monitoring. Clinical improvement should occur within 48 hours at which time patients may be transitioned to oral therapy. Counseling includes discussion of STDs, birth control, partner counseling, and referral for HIV and syphilis testing. Patients with nongonococcal or undifferentiated septic arthritis require hospitalization. Most patients with acute gout can be successfully treated as outpatients. Precipitating factors such as alcohol use, purine-rich foods, and diuretics should be addressed.

Common Pitfalls

- Failure to consider infection in patients with acute worsening of pre-existing arthritis.
- Failure to obtain synovial fluid for analysis.
- Excluding septic arthritis based on absence of fever or normal serum inflammatory markers.
- Ordering protein and glucose on synovial fluid.
- Failure to perform culture on all diagnostic synovial fluid specimens.
- Inadequate empiric antibiotic selection in cases of suspected infection.
- Failure to recognize the migratory polyarthritis and tenosynovitis of disseminated gonorrhea.

- Diagnosing or excluding gout based on the serum urate level.
- Prescribing serum urate–lowering agents during an acute gout attack.

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CHAPTER 151

Polyarticular Arthritis

Richard S. Hartoch

Polyarticular arthritis presents as an acute or chronic inflammatory synovitis (synovial warmth, swelling, and tenderness) developing at a minimum of two joints. The emergency physician encounters polyarthritis in two contexts: the patient without a known rheumatologic disease who presents with multiple painful joints, and the patient with complications of a previously diagnosed condition, most commonly rheumatoid arthritis (RA).

CLINICAL PRESENTATION

Many polyarthritis syndromes have a gradual onset and may defy precise diagnosis despite extensive initial workup. Symptoms of early hepatitis C, systemic lupus erythematosus (SLE), RA, and other collagen–vascular diseases overlap and laboratory test results may be equivocal. A definitive diagnosis may not readily be made on a single emergency department (ED) visit. Although the syndromes share arthritis as a common feature, all have associated symptoms that are helpful in evaluation (Table 151.1). A thorough history and physical examination may be the most important tools in establishing a diagnosis.

TABLE 151.1
Polyarticular Arthritis: Clinical Features

Rheumatoid Arthritis

Symmetric, additive involvement initially of small joints, especially MCP, PIP, and wrists

Morning stiffness, positive rheumatoid factor in 75%

Acute Rheumatic Fever

Migratory polyarthritis, carditis, erythema marginatum, subcutaneous nodules, chorea

Gonococcal Arthritis

Tenosynovitis, characteristic rash

Lyme Disease

Brief, recurrent; involves knees, preceded by characteristic rash

Erythema chronicum migrans, cardiac and neurologic involvement, Bell palsy

Reactive Arthritis (formerly Reiter Syndrome)

Asymmetric involvement of lower extremities

Urethritis, conjunctivitis, skin lesions

Viral Arthritis

Symmetric involvement of fingers, wrists, and knees

Serum Sickness

Migratory involvement of large and small joints; associated rash

Systemic Lupus Erythematosus

Multiple organ system involvement

Symmetric evanescent involvement of any joint

Serologic markers—ANA (sensitive), anti-dsDNA (diagnostic)

Osteoarthritis

Lower extremity involvement

Heberden nodes

Lack of inflammatory signs

Ankylosing Spondylitis

Insidious involvement of spine (occasionally hips and shoulders)

Uveitis in 25%; HLA-B27 positive (90%)

Colitic Arthritis

Large joints

Parallels course of ulcerative colitis or regional enteritis

Psoriatic Arthritis

Distal interphalangeal joint involvement

Symmetric or asymmetric

Skin disease begins first; 80% have pitting of nails

Rheumatoid Arthritis

The most commonly encountered etiology of polyarthritis is RA, characterized by symmetric joint inflammation, constitutional symptoms, and in some cases, extra-articular organ involvement. The disorder ranges in severity from a mild nonprogressive arthritis to a fulminant, sometimes fatal, illness with destruction of joints and serious systemic involvement. Early recognition and initiation of appropriate therapy generally results in an improved outcome. A majority of patients who have been newly diagnosed with RA will experience remission if aggressively treated by a rheumatologist.

The onset of RA may be acute or insidious. Inflammation in multiple joints in almost any combination may be present, although symmetric inflammation of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints and wrists is most common. The vast majority of RA patients will complain of pain when their four MCP joints are gently squeezed together. RA virtually never affects the thoracic or lumbar spine. Systemic manifestations include malaise, anorexia, fever, myalgias, and weight loss. In some patients, especially those with high titers of rheumatoid factor and more severe joint disease, there is systemic organ involvement, most commonly lungs and heart.

Acute Rheumatic Fever

Although the incidence of acute rheumatic fever (ARF) has dramatically declined over the past 40 years, recent reports have described episodic outbreaks. The diagnosis of ARF mandates fulfillment of the modified Jones criteria (Table 151.2). Arthritis, the most common finding in ARF, is seen in more than 75% of first attacks. It is typically migratory and most often first affects the large joints of the lower extremities, knees, and ankles, followed by wrists and elbows. Each joint is inflamed for up to 1 week. Carditis, clinically seen in 40% to 50% of acute cases, is the most serious finding. Recent echocardiographic studies have revealed that the carditis is often subclinical and present to varying degrees of severity in virtually all patients with ARF. The patient may present

with pleuritic chest discomfort, a new murmur (usually mitral regurgitation), cardiomegaly, and possibly congestive heart failure. Chorea occurs in 5% of cases. It develops several months after streptococcal infection and is characterized by emotional disturbances, weakness, and sudden involuntary movements that cease with sleep. *Erythema marginatum* (5% of cases) begins as a macule that extends outward with central clearing. It may resemble erythema chronicum migrans, the rash of Lyme disease (LD). It is not painful or pruritic. It usually fades within hours but may recur. Subcutaneous nodules, seen in <10% of patients, are firm, painless, and of variable size (2 to 10 mm). They are most commonly seen over the extensor joint surfaces or bony prominences.

TABLE 151.2
Modified Jones Criteria for Diagnosis of Acute Rheumatic Fever

Major Criteria	Minor Criteria
Carditis	History of acute rheumatic fever
Polyarthritis	Fever
Chorea	Arthralgia
Erythema marginatum	Elevated sedimentation rate
Subcutaneous nodules	Prolonged PR interval

Note: The diagnosis of acute rheumatic fever requires two of the major criteria or one of the major criteria and two of the minor criteria plus evidence of recent group A streptococcal pharyngitis (positive culture or increased ASO titer).

Poststreptococcal reactive arthritis (PSRA) is a clinical syndrome with insufficient Jones criteria to be called ARF. Consider obtaining an antistreptolysin O (ASO) titer. Treat strep pharyngitis with antibiotic and arthritis with nonsteroidal anti-inflammatory drugs (NSAIDs). Prednisone may be indicated in severe cases.

Gonococcal Arthritis

Gonococcal arthritis (GA), although infrequently seen, is still the most common bacterial arthritis among healthy young people. It develops in 1% to 3% of patients with untreated gonococcal infection. Disseminated gonococcal infection (DGI) is characterized

by a clinical triad: dermatitis, tenosynovitis, and migratory polyarthritis. Joint involvement is predominantly asymmetric, often affecting the knee, ankle, elbow, and wrist. A painless, nonpruritic skin rash consisting of scattered papules or vesicles with a hemorrhagic or necrotic center is seen in roughly 50% of patients. HIV patients are infected in unusual joints (hip and sternoclavicular) and may develop a more aggressive course.

Lyme Disease

LD is caused by the spirochete *Borrelia burgdorferi,* transmitted by the bite of the deer tick, *Ixodes scapularis* (formerly *I. dammini*). A characteristic rash, erythema chronicum migrans, develops in 60% of patients. It starts as a single red macule that expands to form a large annular lesion with a red outer border and central clearing. Two weeks to 2 years after the initial skin lesion, 60% of patients develop an acute arthritis, typically asymmetric oligo- or monoarticular, involving large joints, most commonly the knee. About 10% of patients develop cardiac abnormalities, most often atrioventricular (AV) block. Although cardiac involvement is transient, some patients require temporary pacemakers. Approximately 10% of patients develop significant neurologic abnormalities, including meningitis, encephalitis, and cranial neuropathies, particularly facial nerve paralysis.

Reactive Arthritis

Reactive arthritis (formerly Reiter syndrome) may occur as a polyarthritis in young, often human leukocyte antigen (HLA) B-27–positive men. It classically presents as a triad of nongonococcal urethritis, asymmetric polyarthritis, and conjunctivitis. The arthritis is usually acute in onset, involving the large joints of the lower extremities, particularly the knees and ankles. Urethritis usually precedes the development of arthritis, although it may be asymptomatic and suggested only by the finding of white blood cells on microscopic examination of first-voided, morning urine. Conjunctivitis occurs in 30% of patients and iritis in 10%. Two

distinctive skin lesions are occasionally seen. *Keratoderma blennorrhagica* (15% of patients), scaling lesions on the palms and soles that begin as erythematous macules, may progress to lesions indistinguishable from those of psoriasis. *Circinate balanitis* (25% of patients) produce painless superficial ulcers of the glans penis. Reactive arthritis may be triggered by intestinal infections (*Salmonella, Shigella,* or *Campylobacter*) or sexually transmitted diseases (*Gonorrhea* or *Chlamydia*).

Viral Arthritis/Postinfectious Arthritis

Transient nondestructive arthritis has been associated with viral infection, the best documented being hepatitis A, B, and C and rubella. The arthritis of hepatitis is believed to be due to the deposition of circulating immune complexes in affected joints. It typically occurs during the prodrome of the illness before the appearance of jaundice. Liver enzymes are usually elevated, and HBsAg or anti-HBc may be positive. The most common presentation is that of a symmetric polyarthritis potentially involving the hand, wrist, elbow, and ankle. It can be painful with prominent morning stiffness but seldom lasts more than 3 weeks. The presentation of hepatitis C may easily be mistaken for RA.

Parvovirus has been implicated as the etiologic agent in an acutely painful polyarthritis involving hands, wrists, elbows, knees, and shoulders. Parvovirus, perhaps better known for its causative role in erythema infectiosum (fifth disease in children), may be detected by elevated IgM titers. The arthritis, often seen in patients who work with children, persists for several weeks and is generally responsive to NSAID therapy. Polyarthritis syndromes have also been described in association with enteric infections (*Yersinia, Shigella, Salmonella, Clostridium difficile*), respiratory infection (mycoplasma), and α-viruses outside US.

Serum Sickness

Serum sickness, typically occurring 6 to 10 days after an antigenic stimulus, presents with the abrupt onset of fever, lymphadenopathy,

and arthritis especially involving knees, ankles, shoulders, and wrists. Urticaria or angioedema may also develop. A more severe reaction tends to result after subsequent exposure to the same antigen. Penicillin is the most commonly implicated causal agent, but many other drugs including other α-lactams, ciprofloxacin, levoquin, angiotensin-converting enzyme inhibitors, and allopurinol have been implicated as well.

HIV Arthritis

Several polyarthritis syndromes have been described in association with HIV infection. A painful, asymmetric, oligoarticular arthritis affecting the knees and ankles has been widely reported. Also seen are seronegative spondyloarthritis and lupus-like syndromes. These polyarthritides may occur at any stage of HIV infection and have been reported to develop months or years before the actual diagnosis of HIV. Because of impaired immunity, HIV patients are at risk for pyogenic joint infections. *Streptococcus* and *Staphylococcus* sp predominate, but opportunistic pathogens may be involved.

DIFFERENTIAL DIAGNOSIS

There are numerous disorders that produce polyarticular arthritis, including RA, acute rheumatic fever, GA, LD, gout, postviral arthritis, septic arthritis, serum sickness, SLE, osteoarthritis, ankylosing spondylitis, ulcerative colitis, regional enteritis (Crohn disease), and psoriatic arthritis. Clinical features that may be helpful in distinguishing the disorders are listed in Table 151.1. Inflammation in the periarticular soft tissues (tendons, bursae, etc.) can cause swelling and limitation of motion, simulating joint disease. Arthritis generally affects both active and passive motion equally, whereas acute tendinitis or bursitis limits active motion significantly more than passive ranging.

ED EVALUATION

Sudden onset of joint pain (developing over several hours, rather than days) strongly suggests gout or infection. The most critical

joint disorder to consider and diagnose immediately is septic arthritis, which can cause rapid destruction and systemic illness. Although the classic presentation is single joint involvement in a febrile patient, 15% of cases of septic arthritis are polyarticular and 20% are afebrile. Patients with underlying joint disease, diabetes, alcoholism, and malignancy are at particular risk for polyarticular infection. These patients are often bacteremic and have inpatient mortality rates exceeding that of myocardial infarction.

The persistence of symptoms for over 4 to 6 weeks suggests a systemic rheumatologic disease. Symmetric joint involvement is seen in RA, hepatitis C, and SLE. Asymmetric joint involvement is typical of the seronegative arthritides (e.g., reactive arthritis and psoriatic arthritis). Migratory involvement (leaving one joint before involving another) is characteristic of acute rheumatic fever. A family history of arthritis supports a diagnosis of RA or one of the seronegative spondyloarthropathies. Thiazide and loop diuretics, alcohol, high protein intake, low-dairy diets, and obesity are linked with the development of gout, which may be polyarticular in presentation. Hydralazine, procainamide, isoniazid, phenytoin, and several tumor necrosis factor (TNF) inhibitors can induce a lupus-like reaction.

To assess patterns of involvement and chronicity, all joints should be examined, not just those that are symptomatic. A relatively rapid assessment can survey up to 60 joints. Several acute polyarthritides are associated with a characteristic rash. Subcutaneous nodules are seen in 35% of patients with RA and $<10\%$ of those with ARF. Psoriatic arthritis may be associated with pitting of the nails and the typical papulosquamous eruption. A general physical examination may note such important findings as a pleural effusion in SLE and RA or clinical signs of liver dysfunction in arthritis associated with hepatitis. A pelvic examination should be performed on all women with unexplained arthritis to rule out *Neisseria gonorrhoeae.* Generalized lymphadenopathy or thrush may suggest HIV.

The most important laboratory test is examination of the joint fluid. Usually obtained studies include white cell count with differential, Gram stain and culture, and examination for crystals.

Specific diagnostic tests (e.g., antinuclear antibody, rheumatoid factor, Lyme titer, HIV, hepatitis screen) are seldom available on an emergency basis. They should be ordered in appropriate patients for use in subsequent evaluation. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can be elevated in any inflammatory condition. Such tests are generally of only marginal diagnostic assistance but may be useful in monitoring disease activity in patients with chronic arthritis. The diagnosis of ARF, which should be especially considered in children and young adults, requires laboratory confirmation of recent group A streptococcal infection. In patients with GA, arthrocentesis cultures are positive in only half of affected joints. Higher yield for positive culture may be obtained from the mucosal surface of initial infectious contact (throat, cervix, urethra, or rectum). Polymerase chain reaction (PCR) may be useful in identifying gonococcal infection from a joint that is culture-negative.

Radiographs are of limited utility in the evaluation of the patient with nontraumatic joint pain. Radiographically visible inflammatory changes (such as symmetric erosions of the wrist and MCP joints in RA) occur late in the course of disease. A normal radiograph does not rule out a diagnosis of arthritis.

Recent RA literature repeatedly stresses the importance of early diagnosis and prompt referral of suspected cases to a rheumatologist. Proper treatment, which involves the *very* early usage of disease-modifying antirheumatic drugs (DMARDs), yields a markedly improved long-term outcome. Delay of as little as 3 months in initiating therapy has been shown to result in significantly increased joint damage at 5 years. The diagnosis of RA is based largely on a high index of suspicion, a careful history, and directed physical examination. Rheumatoid factor, although not a specific marker for RA, is present in the serum of 75% of patients. Clinical criteria established by the American Rheumatism Association include prolonged morning stiffness, symmetric joint involvement, chronicity, rheumatoid nodules, and radiographs revealing erosions. Recent studies reveal that the characteristic bone erosions may be visualized by ultrasound and magnetic resonance

imaging (MRI) significantly earlier than by conventional radiography.

KEY TESTING

- Arthrocentesis with joint fluid analysis to exclude septic joint

ED MANAGEMENT

The management of polyarthritis depends on the correct diagnosis. Septic arthritis must be managed as an inpatient with IV antibiotics, orthopedic consultation, and discovery of the source of possible bacteremia. Suspected RA mandates *prompt* rheumatologic consultation for rapid initiation of DMARD therapy, usually methotrexate, biologic TNF inhibitors, biologic non-TNF inhibitors, or other agents. NSAIDs are *not* effective in limiting the destructive consequences of RA.

The mainstay of treatment for general, undiagnosed polyarthritis is NSAIDs. These agents control both pain and inflammation. If one NSAID fails to control symptoms, another in a different class may be more effective. All NSAIDs should be prescribed with caution, and patients should be monitored for adverse gastrointestinal effects, renal dysfunction, edema, and cardiac complications. NSAIDs should generally be taken with food.

TNF inhibitors are newer agents used in the treatment of RA. They are generally well tolerated, but the practitioner must be alert to clinically significant, potentially life-threatening side effects. TNF has antitumor and antiviral effects and has particular activity against intracellular pathogens, notably *Mycobacterium tuberculosis.* TNF stimulates inflammatory cells to areas of infection and may be involved in the formation of granulomas which contain TB. It plays an important role in modulating the systemic inflammatory response of sepsis.

Patients receiving TNF inhibition are subject to a variety of serious infections and may present to the ED appearing “less sick” than other patients with similar conditions. Particular issues include unrecognized sepsis with various bacteria, notably *Streptococcus*

pneumoniae and *Klebsiella.* One should also consider reactivation of TB, opportunistic infections including *Listeria, Legionella,* and disseminated fungal infections. These patients with their blunted immune response may not show expected signs and symptoms of severe infection. They may have a negative PPD test for TB due to anergy.

Several disorders require more specific treatment. Patients with a first attack of ARF should be hospitalized and closely monitored for worsening carditis, arrhythmias, and valve damage. High-dose salicylates and prednisone may be useful. The patient must be monitored for the development of congestive heart failure. A course of penicillin is recommended to eradicate any remaining streptococci, and the patient may be kept on low-dose penicillin prophylaxis indefinitely thereafter.

Most patients with GA should be hospitalized. Therapy is initiated with a parenteral third-generation cephalosporin. Because of recently described increased rates of GC resistance, fluoroquinolones may not be effective. Repeated joint aspirations, arthroscopy, or surgery may be required. In most cases, dramatic clinical improvement is noted in several days, and the patient may transition to oral antibiotics. Patients should be treated concurrently for chlamydia.

The arthritis associated with LD is generally treated for at least a month with doxycycline or amoxicillin. Resistant cases are treated with IV ceftriaxone. Reactive arthritis is not curable, but treatment of the initial urethritis may prevent development of the full-blown disease. Slit-lamp examination of the anterior chamber is essential to rule out associated iritis. Arthritic inflammation is treated symptomatically with NSAIDs.

Complications of RA

RA is the most common and most serious of the chronic polyarthritides and may be associated with a number of emergent complications (Table 151.3). The emergency physician should be aware of classic acute issues arising in patients with well-established

RA. RA patients are also at risk for toxic and immunosuppressive effects of treatments.

TABLE 151.3
Complications of Rheumatoid Arthritis

Organ	Manifestations
Neurologic	Subluxation C-1, C-2 (cord compression); entrapment neuropathy (carpal tunnel); peripheral neuropathy; myositis; necrotizing vasculitis (central nervous system)
Musculoskeletal	Septic arthritis; tendon rupture; synovial cyst knee (pseudophlebitis); rheumatoid nodules
Larynx	Cricoarytenoid arthritis (airway)
Lung	Pleurisy; effusion; fibrosis
Cardiac	ACS; sudden death; pericarditis; tamponade; conduction defects; valvular (nodules)
Hematologic	Anemia; leukopenia; hyperviscosity; Felty syndrome (splenomegaly, neutropenia)
Ocular	Sjögren syndrome; episcleritis; scleritis
Blood vessels	Vasculitis (usually dermal, can be widespread)

Cardiovascular disease (CVD) is one of the most common causes of death in patients with RA and occurs at a younger age than in the general population. Chronic inflammation as seen in RA, PA, and SLE results in accelerated atherosclerosis. RA patients with an acute coronary syndrome (ACS) are more likely to present to the ED with atypical symptoms. RA may be considered an independent risk factor for coronary artery disease, and in fact several studies reveal it to be as significant as diabetes or hypertension. The increased CVD risk may be present even before clinical evidence of RA develops. Aggressive efforts to control inflammation and modify traditional cardiac risk factors are particularly vital in these patients.

Radiographic abnormalities of the cervical spine are common, particularly subluxation of C-1 on C-2. Usually these abnormalities are asymptomatic, but the appearance of neurologic symptoms or signs necessitates neurosurgical consultation. Patients may note a peculiar slipping sensation with neck movements that is associated

with either exacerbation or relief of symptoms. A patient with RA who sustains even minor cervical trauma is at risk for serious injury. The potential for cervical spine instability should be considered when intubating a patient with chronic RA, and cervical spine precautions should be observed.

Various entrapment neuropathies occur in RA, of which carpal tunnel syndrome is the most common. Patients initially complain of sensory changes over the distribution of the median nerve and a "toothache-like" pain at the wrist. The diagnosis is confirmed with electromyography and nerve conduction studies. Treatment consists of splinting the wrist and arranging consultation with a rheumatologist, orthopedist, or neurologist. Local corticosteroid injection is occasionally useful. Surgical release of median nerve entrapment is sometimes necessary. Generalized muscle wasting, weakness, and peripheral neuropathy in RA patients may also be manifestations of systemic vasculitis.

Rupture of the extensor tendons of the hand is not uncommon in advanced RA. Once one tendon ruptures, the increased strain on the remaining tendons may lead to rupture of others. Patients cannot extend the fingers actively at the MCP joints, but passive extension is still possible. Treatment is elective surgical repair.

The development of a synovial cyst behind the knee is common in RA. Synovial inflammation may result in large knee effusions, and high pressure generated during flexion of the knee may cause cyst formation in the popliteal fossa. The diagnosis is confirmed by an arthrogram or ultrasound of the knee joint. Curative treatment is difficult. Joint aspiration and local corticosteroid injection may be temporarily helpful. These cysts may rupture, dissecting into the calf. The resulting calf pain, swelling, and redness may mimic the presentation of deep vein thrombosis. Duplex sonography is helpful in distinguishing these clinical entities.

The cricoarytenoid joint is a synovial articulation and can be involved in RA. Patients may present with stridor and significant airway obstruction, dyspnea, dysphagia, painful speech, foreign-body sensation, or hoarseness. There may be tenderness over the thyroid cartilage. Laryngoscopy reveals redness and edema over the

arytenoids and abnormal bowing of the vocal cords during inspiration. Intubation may be difficult. Cricothyrotomy or tracheostomy may be necessary to secure the airway. Corticosteroids and cool humidification are useful in milder cases.

The most common type of vasculitis associated with RA involves small dermal vessels, causing relatively benign infarctions in the periungual areas of the fingers. Occasionally patients develop a necrotizing vasculitis, which can follow a fulminant course. The presenting manifestations may be large ulcerations, digital gangrene, neuropathies, mesenteric ischemia, or coronary arteritis. Patients with systemic vasculitis usually have fever, leukocytosis, high titers of rheumatoid factor, an elevated ESR, and antinuclear antibodies. They should be admitted to the hospital for initiation of high-dose corticosteroids. At times cytotoxic agents or apheresis are useful. The prognosis in patients with extensive vasculitis is poor.

Sjögren syndrome (keratoconjunctivitis sicca), sometimes associated with RA, is characterized by dry eyes and dry mouth and is caused by decreased lacrimal and salivary gland function. Patients complain of grittiness in the eyes and thick mucus beneath the eyelids. The diagnosis is made by the Schirmer test which measures tear production. Treatment consists of artificial tears, humidified air, and eye goggles to minimize tear evaporation.

Episcleritis, also associated with RA, is usually benign but should be followed by an ophthalmologist because it can lead to *scleritis.* A brief course of topical corticosteroids as prescribed by an ophthalmologist is usually beneficial. Scleritis is a more diffuse process and can cause uveitis, glaucoma, and rupture of the globe. Patients complain of a deep aching sensation and tenderness on gentle palpation of the globe. Slit-lamp examination reveals cellular exudate in the anterior chamber. Prompt ophthalmologic consultation is indicated.

Hematologic problems, including anemia, leukopenia, and hyperviscosity, occur in RA. Felty syndrome (triad of RA, splenomegaly, and neutropenia) is associated with severe disease. These patients are prone to recurrent infections and have hepatic

dysfunction and recurring cutaneous ulcers. Splenectomy is occasionally beneficial.

Pleurisy and pleural effusions are common in RA but are not usually life-threatening. Pericarditis is also common, but only rarely does pericardial tamponade or constrictive pericarditis occur.

CRITICAL INTERVENTIONS

- Consider ACS in patients with RA, PA, and SLE.
- Consult a rheumatologist as soon as possible when RA is suspected.

DISPOSITION

Septic arthritis requires emergent intervention and inpatient management. Patients with a first attack of ARF should be hospitalized. Most patients with GA should also be hospitalized for initial therapy. LD in early stages is generally treated with doxycycline on an outpatient basis. Advanced cases may require hospitalization.

Patients with RA or SLE may present with complications requiring admission, but isolated nonseptic exacerbations of joint pain are often managed successfully on an outpatient basis. Admission decisions for other causes of polyarticular arthritis are often dependent upon the certainty of diagnosis, the adequacy of pain control, and the presence or absence of other disease complications.

Common Pitfalls

- Failure to analyze synovial fluid in a patient with new joint tenderness, warmth, and swelling.
- Failure to diagnose ACS in a patient with RA who presents with atypical symptoms.
- Failure to identify sepsis or a serious opportunistic infection in a patient on TNF inhibitor therapy.
- Failure to recognize an acute septic joint in a patient with underlying chronic polyarthritis.

- Failure to consider a diagnosis of RA, resulting in delayed diagnosis and treatment.
- Failure to consider acute rheumatic fever in a child or young adult.
- Failure to consider underlying HIV infection in a person with a newly diagnosed, seronegative spondyloarthropathy or lupus-like syndrome.

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SECTION XV
Neurologic Emergencies

Section Editor: JEFFREY J. SCHAIDER

CHAPTER 152
Organic Brain Syndrome

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Patients in acute distress from mental health causes seek treatment in the emergency department (ED). EDs also provide medical evaluations prior to civil commitment for many patients in psychiatric crisis (1). The purpose is to detect the presence of medical illness complicating or causing psychiatric symptoms. Differentiating between functional (psychiatric) and organic (medical) causes of behavioral abnormalities may seem arbitrary. However, arranging the proper tests, treatments, consultants, and site of care depends on accurately making this differentiation. Several studies have documented high rates of patients receiving treatment for psychiatric illnesses that were really caused by treatable but undetected medical illness (2,3). In addition, patients with functional psychiatric syndromes such as schizophrenia often have comorbidities that go undetected or undertreated, leading to excess mortality (4).

CLINICAL PRESENTATION

The term *organic brain syndrome* (OBS) covers a range of clinical manifestations. The first two, delirium and dementia, are always presumed to be due to organic causes. Specific changes in cognitive function can help distinguish between delirium and dementia (5) (Table 152.1).

TABLE 152.1
Diagnostic Criteria for Delirium and Dementia[a]

Delirium

Definition: Disturbance of consciousness accompanied by change in cognition; not due to a pre-existing dementia

- Disturbance of consciousness:
  - Alterations in or lack of awareness of the environment
  - Reduced ability to concentrate
  - Attention: Inability to focus, sustain, or shift attention
- At least two cognitive deficits:
  - Memory deficit
  - Disorientation
  - Language disturbance
  - Perception alteration (i.e., hallucination or illusions)
- Rapid, abrupt onset over hours or days
- Organic cause:
  - Clinical evidence by history, physical, or testing, that the disturbance is due to the physiologic manifestations of a general medical condition or substance abuse or both

Dementia; often called neurocognitive disorders

Definition: Multiple cognitive deficits (especially memory) that are not due to a delirium. Consciousness is not necessarily clouded.

- Memory impairment:
  - Impaired ability to learn new information
  - Impaired ability to recall previously learned information
- At least one cognitive deficit:
  - Aphasia (language disturbance)
  - Apraxia (decreased ability to carry out motor activities despite intact motor function)
  - Agnosia (not recognizing or identifying objects despite intact sensory function)
  - Disturbed executive function (planning, organizing, sequencing, abstracting)
  - Intellectual impairments interfere with normal social or occupational function
- Organic cause:
  - The defects are caused by an underlying medical condition
  - The specific causes are important as some are correctable and some are not

[a]References 5, 6, 11, 12.

Delirium is often due to a life-threatening illness (5–10). In the elderly, it may be one of the most common disease presentations and is associated with high mortality rates (8,9,11). Delirium is defined

first by disturbed consciousness. Patients have altered awareness of the environment; difficulty in focusing, sustaining, or shifting their attention; and reduced ability to concentrate (6). Delirious patients may be hyperalert and have inappropriately fearful responses to normal stimuli. They may be hallucinating, hyperactive, or combative. There are also disturbances in at least two of the following: Perception, language, sleep cycles, memory, or psychomotor activity (6). However, the patient's limited awareness and inability to concentrate often make testing of these functions impossible (10). Delirium is also likely to resolve when the patient recovers from the underlying cause (5,11).

Dementia is now often referred to as a spectrum called neurocognitive disorders (6). It refers to the more gradual development of intellectual impairment sufficient to interfere with social and physical functioning (5,10). The hallmark finding is progressive impairment of memory. Memory deficits can be remarkable in patients who appear to function well otherwise. The diagnosis requires one additional cognitive impairment, such as loss of language, visual–spatial, or abstraction ability; impaired judgment; personality change; or reduced organizational ability (6). In contrast to delirium, consciousness is not clouded and deficits develop slowly over a more prolonged time course (5,10). The maintenance of normal consciousness and self-awareness and the slow progression can result in severe loss of function before family or providers detect the problem. In fact, it is frequently an acute precipitant such as medical illness or a change in living situation that calls attention to the long-term decline.

In addition to delirium and dementia or neurocognitive disorders, all of the major psychiatric diagnostic groups can be closely mimicked by the effects of medications or medical illnesses (7,12). Medical illness can cause clinical manifestations similar to those of psychosis, mania, depression, anxiety disorders, or even personality disorder. In some cases, a neuropsychiatric manifestation is the first symptom prompting treatment (12,13). Finally, medical illness can cause an acute worsening of behavioral symptoms in patients with

chronic existing psychiatric diseases that were previously well controlled (14).

DIFFERENTIAL DIAGNOSIS

The first challenge is to distinguish between functional psychiatric illness and OBS (7). One of the most important features in OBS is cognitive dysfunction (7,16). This may be undetectable unless actively sought (17). Most patients with functional disorders, even schizophrenic patients, have normal vital signs, motor and speech function, cognitive function, and memory (12). Thus, abnormalities in these areas cannot be assumed to reflect chronic psychiatric illness. OBS can also be distinguished from functional disorders by comparing the patient's syndrome to the standard psychiatric definitions (6). The presence of atypical features point to an organic cause (12).

It is useful to note similarities among delirium, dementia, and the more standard psychiatric diagnoses. Delirium shares features with anxiety disorder, acute psychosis, or mania (5,18). Alcohol withdrawal is a form of delirium (19). Dementia can appear similar to depression, chronic schizophrenia, or personality disorder. This same overlap in cause can assist in working through the differential diagnosis.

Many medical problems can result in compromised mental functioning and what appear to be manifestations of psychiatric disease (2,7,15,18). Table 152.2 lists the most common causes by clinical syndrome. Medications are by far the most common (7). The major life-threatening causes can be summarized as any profound disruption in blood or nutrient supply to the brain: Shock; hypoxia; sepsis; anemia; hypoglycemia; hypertensive encephalopathy; hyperthermia; fluid, electrolyte, or acid–base imbalance; carbon monoxide; intracranial infection or mass; or stroke (2,7,18). Alcohol withdrawal and Wernicke encephalopathy require emergent recognition and treatment. Infections, both neurologic and systemic, are important causes of OBS. Some infections such as viral encephalitis are seasonal (20,21). Metabolic derangements with behavioral symptoms are common in liver, renal, pulmonary,

thyroid, pituitary, and adrenal diseases (2,7,21). Trauma, illicit drugs, and toxins are common in the young (3,22). Patients with HIV infection may present with symptoms of secondary HIV mania as a first sign, and they are also more susceptible to CNS infections (13,23). Altered behavior in patients with cancer, heart disease, collagen vascular disease, or HIV infection should also prompt consideration of organic causes.

TABLE 152.2
Causes of Organic Brain Syndrome by Manifestation[a]

Organic Brain Syndrome	Causes
Delirium	
Emergency causes	Shock from any cause
	Hypoxia from any cause
	Hypoglycemia/electrolyte/acid–base imbalance
	Acute thiamine deficiency (Wernicke)
	Hyperthermia
	Thyroid storm
	Intracranial catastrophe: mass, blood, trauma, abscess, ischemia
	Carbon monoxide poisoning
	Alcohol withdrawal
	Toxic alcohols
Medications, toxins	Any drug with anticholinergic properties
	Clonidine
	Lidocaine
	Antabuse
	Caffeine/ergot
	Illicit drug intoxication
Neurologic	Subarachnoid hemorrhage
	Status seizure (petit mal, complex partial)
	Postictal syndrome
	Hypertensive encephalopathy
	Cerebral vasculitis: systemic lupus erythematosus, etc.
Endocrine	Diabetes mellitus
	Hyperthyroidism
	Addison disease
	Cushing disease (exogenous)
Metabolic, dietary	Hepatic encephalopathy
	Renal failure
	Hypomagnesemia
Infectious	Encephalitis/meningitis/brain abscess
	Sepsis
	Infective endocarditis
	Pneumonia
	Neurosyphilis
	Tuberculosis
	Typhoid fever/rheumatic fever
Miscellaneous	Alcohol or drug withdrawal syndromes
	Congestive heart failure
	Femur fractures (especially postoperative)
	Air and fat emboli syndromes
Dementia; Neurocognitive Disorders	
Medications, toxins	Beta-blockers
	Any drug with anticholinergic properties
	Methyldopa
	Clonidine
	Sedatives
Neurologic	Intracranial mass, blood, trauma, abscess
	Stroke, TIA
	Multi-infarct dementia
	Normal pressure hydrocephalus
	Chronic subdural hematoma
Endocrine	Diabetes mellitus
	Addison disease
	Cushing disease (endogenous)
	Hyperparathyroidism
	Apathetic hyperthyroidism
Metabolic, dietary	Vitamin B_{12} deficiency
	Chronic liver disease
	Hypercalcemia
	Chronic electrolyte imbalance
	Pernicious anemia
	Uremia
	Chronic thiamine deficiency (Korsakoff, beriberi)
Infectious	Neurosyphilis
	Tuberculosis (meningitis, miliary)
	HIV/AIDS
Miscellaneous	Chronic anemia
	Hypoxia
	Hypercarbia
	Depression (functional)
Anxiety Disorders	
Medications, toxins	Any drug with anticholinergic properties
	Bronchodilators
	Decongestants
	Diet pills and stimulants
	Digitalis toxicity
	Illicit drug intoxication
	Hallucinogens
	Hypotensive agents
Neurologic	Intracranial mass, blood, trauma, abscess
	Stroke, TIA
	Seizure disorder
	Essential tremor
	Postconcussion syndrome
	Cerebral vasculitis: systemic lupus erythematosus, etc.
Endocrine	Hypoglycemia
	Cushing disease
	Hyperthyroidism
	Menopause
Metabolic, dietary	Hyperkalemia
	Hypocalcemia
	Hyponatremia
	Hyperthermia
	Vitamin B_{12} or folate deficiency
	Secreting tumors (i.e., carcinoid, insulinoma, pheochromocytoma)
	Porphyria
	Caffeine
	Monosodium glutamate
Infectious	Encephalitis, meningitis
	Sepsis
	Pneumonia

Table continued on following page

Organic Brain Syndrome	Causes
Miscellaneous	Any hypoxia
	Hypovolemia
	Anemia
	Thrombotic thrombocytopenic purpura
	Hemolytic–uremic syndrome
	Myocardial infarction/arrhythmias/valvular disease
	Congestive heart failure/pulmonary edema
	Hypertension
	Anaphylaxis
	Asthma/chronic obstructive pulmonary disease
	Pneumothorax
	Pulmonary embolism
	Alcohol or drug withdrawal
	SSRI discontinuation syndrome
	Envenomation
Mania	
Medications, toxins	Corticosteroids
	Isoniazid
	H_2 blockers
	Cyclosporine
	Procyclidine
	Phencyclidine
	Cyclobenzaprine
	Bromides
	Levodopa
	Captopril
	Cocaine, amphetamines
	Nicotine
Neurologic	Intracranial mass, blood, trauma, abscess
	Stroke, TIA
	Temporal lobe seizure
	Multiple sclerosis
	Wilson disease
Endocrine	Huntington disease
	Hyperthyroid
	Cushing disease (exogenous)
	Addison disease
	Hepatic encephalopathy (early)
	Hemodialysis
Infectious	Caffeine
	Encephalitis, meningitis
	Sepsis
	Neurosyphilis
	HIV/AIDS
Miscellaneous	Influenza
	Alcohol or drug withdrawal
	SSRI discontinuation syndrome
Psychosis	
Medications, toxins	Any drug with anticholinergic properties
	Corticosteroids
	Histamine blockers
	Dilantin
	Alprazolam
	Stimulants, diet pills
	Isoniazid
	Antihypertensives
	Illicit drug intoxication
Neurologic	Intracranial mass, blood, trauma, abscess
	Stroke, TIA
	Cerebritis: systemic lupus erythematosus, etc.
	Complex partial seizure
Endocrine	Diabetes mellitus
	Hyperthyroidism
	Cushing disease (exogenous)
	Addison disease
Metabolic, dietary	Hypercalcemia
	Hypomagnesemia
	Hypoglycemia
	B_{12} deficiency
	Thiamine deficiency (Wernicke and Korsakoff)
Infectious	Acute hepatic encephalopathy
	Encephalitis, meningitis
	Neurosyphilis
	HIV/AIDS
Depression	
Medications, toxins	Beta-blockers
	Oral contraceptives
	Steroids
	Neuroleptics
	Ranitidine
	Anticholinesterases
	Benzodiazepines
	Alpha methyldopa
Neurologic	Frontal brain mass
	Stroke
	Multiple sclerosis
	Early dementia
	Epilepsy
	Tumors: pancreas, lung, prostate, brain
Endocrine	Diabetes mellitus
	Hypothyroidism, apathetic hyperthyroidism
	Addison disease
	Cushing disease (endogenous)
	Hyperparathyroidism
Metabolic, dietary	Hyponatremia
	Hypokalemia
	Hypocalcemia
	B_{12} deficiency
	Folate deficiency
	Chronic hepatic encephalopathy
	Uremia
Infectious	Neurosyphilis
	Mononucleosis
	Hepatitis
Miscellaneous	Influenza
	SSRI discontinuation syndrome

[a]References: 2, 3, 8, 9, 13, 17–19, 21, 23, 24, 26, 27, 29.

ED EVALUATION

Any patient with neuropsychiatric symptoms should receive a thorough history, physical and mental status examination (3,16,17).

Often, the history must be obtained from family or paramedics. Sometimes family members can articulate only that the patient has changed or worsened in some indefinite way. A frequent complaint in the elderly is a sudden refusal or inability to eat (1). The history should include information on medications, alcohol and drug use (including over-the-counter and herbal preparations), recent hospitalizations, surgeries, or trauma (5,12,19,24,25). Past psychiatric, endocrine, pulmonary, cardiac, renal, hepatic, malignant, and collagen vascular diseases and potential exposure to medications or toxins and risk factors for HIV infection are important history questions (2,7,13,17,23,26). Complaints such as headache, focal neurologic deficits, abdominal pain, dyspnea, fever, incontinence, nonauditory hallucinations, weight loss, cough, vomiting, or diarrhea also point to organic causes (1).

The patient's normal level of functioning and the pattern and rate of behavioral change must be ascertained. A recent abrupt change in a previously normal patient or new additional psychiatric manifestations in patients with chronic illness, are key signs of organic cause (7,8,11,27). Visual hallucinations, distortions, or illusions are also important clues to an organic etiology (12). Beware of missing new delirium occurring in a patient with chronic dementia. For example, acute worsening of chronic dementia can occur with a new stroke, pneumonia, sepsis, myocardial infarction, new medications, or metabolic, endocrine, or rheumatologic derangements. Sometimes it is not clear what precipitated the ED visit of a patient with chronic dementia. Sensitive questioning can reveal that family members no longer feel able to safely care for the patient and desire help or even nursing home placement. In other cases, the patient has had a catastrophic anger reaction that the family did not mention because they did not recognize it as a classic manifestation of dementia.

Physical examination findings indicative of an organic cause include abnormal vital signs, diaphoresis, jaundice, or pallor. Any motor disturbance such as tremor or partial complex seizure activity should be noted (12); either increased or decreased psychomotor activity levels may be seen (15). Signs of thyroid or adrenal disease

should be sought. A complete neurologic examination, including gait and tests of cognitive function, is required (7,15,16). Certain findings on mental status examination indicate an organic cause for behavioral changes. A neat, well-groomed appearance in a patient who is now disorganized indicates a very abrupt onset (17). Altered awareness of the environment, anxiety, labile mood, or rapid changes in mental status are associated with OBS, as are language abnormalities, altered speech, or disordered visual–spatial abilities. The new onset of mania in a patient older than the age of 30, or psychosis in patients older than 40, is highly unusual and should prompt testing for organic causes.

When ordering tests to detect the cause of OBS, it helps to categorize those causes as medication-related, toxicologic, neurologic, endocrine, metabolic, dietary, infectious, hepatic, renal, cardiac, or pulmonary. The specific evaluation should be guided by findings in the history, physical, and mental status examinations (7). Glucose, electrolytes, complete blood count, and renal function tests should be obtained (12). Additional useful testing may include electrocardiography, liver and thyroid function tests, toxicology, and arterial blood gases for hypoxia, CO_2 retention, and carbon monoxide exposure. A chest x-ray, urinalysis, and blood and urine cultures should be done when infection is suspected. Most patients warrant computed tomography of the head and lumbar puncture with cerebrospinal fluid cultures, including tests for tuberculosis and viral encephalitis (12). In patients with dementia, additional testing for correctable causes should include vitamin B_{12}, folate, thyroid, and syphilis testing (28).

ED MANAGEMENT

ED management generally depends on the underlying cause of OBS. The physician's first task is to rapidly identify and treat life-threats and then to take action to prevent injury (e.g., from falling out of bed or wandering away). As unsuspected alcoholism is common and the diagnosis of Wernicke encephalopathy or withdrawal can be difficult, thiamine should be given empirically and the glucose level checked early and followed up as necessary (12). Unless it is obvious

that the patient is suffering from severe alcohol withdrawal, extra caution is appropriate when initiating sedatives for behavioral control, as another condition may be causing global brain dysfunction, and there may be increased sensitivity to sedatives (11,15). Frequent reassessment is especially critical in patients with delirium, as the underlying causes are so serious and the condition can deteriorate rapidly. One-to-one observation, sedatives, or even restraints, may be necessary to ensure the patient's safety during evaluation and treatment (9,11,15).

CRITICAL INTERVENTIONS

- Rapidly search for and treat life threatening conditions.
- Distinguish between functional psychiatric illness and organic disease.
- Search for new medical illness superimposed upon a chronic dementia that can cause an acute but reversible decline or change.

DISPOSITION

Nearly all patients suffering from acute OBS need to be hospitalized for continued diagnostic evaluation and treatment or for the assurance of their physical safety (5). An exception is the patient with chronic dementia who has not had an acute decline in function but who is brought to the ED for evaluation of a long-term problem. Any medical illness superimposed upon a chronic dementia can cause an acute but reversible decline, so those with chronic dementia and acute worsening need admission. Another exception is the patient who is suffering from recreational drug or alcohol intoxication that clears in the ED. If these patients are discharged, they must go home with responsible family or friends.

Families caring for patients with progressive dementia need to be warned about the dangers of driving, cooking, or starting fires and to know that patients can wander away or can occasionally exhibit catastrophic anger reactions if they are under stress. It helps families to understand that these reactions can be a normal consequence of

dementia. Good follow-up must be ensured. Social services will be helpful in arranging home nursing care.

Psychiatric consultation may assist in the assessment of competency when the patient's judgment is in question. Some patients may try to leave the hospital once they are admitted; a recorded psychiatric competence evaluation is extremely helpful to hospital staff (9,11). Patients with acute impairment of judgment or consciousness or with cognitive deficits do not have sufficient decision-making capacity to sign themselves out of the hospital against medical advice (30). There is growing use of empiric symptom severity scores, such as the Organic Brain Syndrome Score for assessing OBS, and there are inpatient intervention programs that show promise for improvement in diagnosis and management (9,11,25,27).

Common Pitfalls

- Failing to do a complete history, physical, and mental status examination in all patients with psychiatric symptoms (3,7,16).
- Failing to note abnormal vital signs as an indicator of possible organic causes.
- Assuming that apparent psychiatric symptoms are due to functional psychiatric disorders (3,7).
- Assuming that physical complaints in a psychiatric patient are due to functional causes (1).
- Failing to detect a mild early cognitive deficit or assuming that it is due to chronic functional illness.
- Missing acute delirium that occurs in a patient with chronic dementia.
- Becoming distracted by combative or abnormal behavior and thus failing to follow through in performing a complete evaluation and frequent reassessments.

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CHAPTER 153 Headache

Benjamin W. Friedman

Head pain accounts for 2 million emergency department (ED) visits annually in the United States (1). The vast majority of headaches presenting to the ED do not threaten life or limb. Most often, they are acute manifestations of an episodic headache disorder or a self-limited, infectious or inflammatory condition readily amenable to treatment. Management of the patient with headache in the ED requires distinguishing the small fraction of patients with serious illness who require immediate diagnosis and hospitalization from the great majority in whom the clinical focus is directed toward headache-specific, short-term pain management, prophylaxis against recurrence, explanation, reassurance, and careful follow-up, while minimizing throughput time and use of healthcare resources.

CLASSIFICATION OF HEAD PAIN

The simplest means of categorizing headaches is to dichotomize into primary headaches (e.g., migraine) versus "organic" or secondary headaches. The latter are so named because they are secondary to some underlying cause (e.g., subarachnoid hemorrhage) (2).

The pain-sensitive structures of the head include the blood vessels and all extracranial structures of the head and neck. The only intracranial structures sensitive to pain are the vasculature of the brain, the dura mater, the venous sinuses, and cranial and cervical nerves. The parenchyma of the brain itself and much of its meningeal coverings are not pain sensitive.

For many years, traditional teaching held that there were three major mechanisms of head pain: Vasodilatation within the cranial

vasculature, causing a “vascular” headache; spasm of the neck and scalp muscles, causing a “muscle contraction” headache; and traction on blood vessels or inflammation around or within these and other pain-sensitive structures, causing a “traction–inflammatory” headache. More recently, traditional concepts of the etiology of headache, particularly of migraine, have given way to explanations based on animal models and neuroimaging in which abnormal release of vasoactive neuropeptides actuates nociceptive pathways. It is now clear that vasodilation is not the primary mechanism of headache. Headache is best thought of as a cranial and cervical neuropathy causing activation of secondary and tertiary nociceptive pathways within the brainstem (3).

For emergency clinicians, thorough headache management addresses the twin challenges of accurate diagnosis and effective treatment (Table 153.1). Secondary headaches, particularly malignant secondary headaches, must be considered and excluded. This often can be accomplished based on the description of the acute headache and the patient’s past headache history. For select patients, a diagnostic workup is indicated (Table 153.2). Patients with an acute exacerbation of a recurrent primary headache disorder should be treated with disease-specific therapies rather than nonspecific analgesics.

TABLE 153.1
Differential Diagnosis of Headache

Secondary Headache	Characteristic Features
Meningitis/encephalitis	Fever, altered mental status
Subarachnoid hemorrhage	Abrupt onset headache
Hypertension	Marked elevation in mean arterial pressure
Narrow-angle glaucoma	Steamy cornea, nonreactive pupil
Sinusitis	Symptoms of upper respiratory infection
Cervical artery dissection	Facial pain, Horner syndrome
Pituitary apoplexy	Bitemporal visual loss, hypotension
Cerebral venous thrombosis	Thromboembolic risk factors
Brain tumor	Not necessarily progressive and constant
Temporomandibular joint syndrome	Worsened by mastication; Tender TM joint
Low CSF pressure headache	Orthostatic
Idiopathic intracranial hypertension	Obese patients. Transient visual obscurations
Primary Headache	**Characteristic Features**
Migraine	Unilateral, throbbing, photo and phonosensitivity
Tension-type headache	Bilateral, pressure like, mild to moderate
Cluster headache	Severe, periorbital, lacrimation, rhinorrhea, conjunctival injection
Trigeminal neuralgia	Lancinating facial pain

TABLE 153.2
Ten Headaches to Worry About

1. Acute headache, characterized as "first or worst" of the patient's life
2. New-onset headache associated with fever and alteration in mental status
3. New-onset headache with vomiting unexplained by other systemic illness
4. Any headache associated with focal findings, including alterations in vision, unless focality is known to be chronic and unchanged from baseline
5. Headache associated with red eye
6. Any headache associated with papilledema
7. Single acute headache with pain on neck flexion but absent on rotation
8. Subacute headache, unremitting or progressively worsening
9. Acute or subacute headache in the elderly
10. Any headache in the immunocompromised host, especially if HIV-positive with low T cell count

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Secondary Headaches

Meningitis/Encephalitis

The headache of meningitis tends to be generalized, though it is the constellation of signs and symptoms rather than the headache itself that remains key to diagnosis (4). Alterations in mental status are typical for bacterial meningitis, as is fever. The absence of fever, neck stiffness, and altered mental status practically eliminates bacterial meningitis from the differential diagnosis, though the individual components of this triad have poor predictive ability (5). Classically, the headache of meningitis worsens with sharp, sudden head movements—so called jolt accentuation. Patients with encephalitis may present with isolated headache, but evidence of brain parenchymal involvement, such as altered mental status, seizures, or focal neurologic findings should be apparent. In the United States, patients with Lyme meningitis frequently recall the classic erythema migrans rash and often present with a concomitant seventh cranial nerve palsy, while in Europe, painful radiculopathy is more common (6). Opportunistic infections are discussed below.

Subarachnoid Hemorrhage

Headache of SAH is the prototypic “first or worst” headache of one’s life, of sudden onset, often associated with nausea, vomiting, neck stiffness, and a transient alteration of consciousness. In patients with focal findings or sustained abnormalities of consciousness, the need for a neuroimaging study is apparent. However, some patients present without focal neurologic findings. In these patients, SAH may be difficult to distinguish from a first attack of migraine.

An especially difficult challenge for the emergency physician is identification of the “sentinel leak” that precedes major hemorrhage in one-third of patients. Detection of this premonitory bleed presents an opportunity to prevent a neurologic catastrophe. Clinical decision rules may allow the clinician to risk stratify patients (7).

Hypertension

Elevated blood pressure and headache have long been linked in the public mind. The causative pathway remains uncertain. It is clear that both hypertension and headache may both be present in malignant processes such as preeclampsia, posterior reversible encephalopathy syndrome, and reversible cerebral vasoconstriction syndrome. However, most headaches in hypertensive patients are either migraine or tension type and are only rarely due to elevated blood pressure. Mild-to-moderate elevations in blood pressure are not generally believed to be a cause of headache. By in large, it is felt that only acute elevation of diastolic pressure of at least 25% above baseline or sustained diastolic elevations in excess of 130 mm Hg have the potential to cause headache (2).

Narrow-Angle Glaucoma

Ocular or periorbital pain characterizes headache caused by narrow-angle glaucoma. The diagnosis of acute glaucoma also requires diminished visual acuity, a pupil that is typically fixed in midposition, an edematous (“steamy”) cornea, perilimbal injection, and increased intraocular pressure. Vomiting may be the dominant feature, especially in the elderly, who may also present with altered mentation.

Sinusitis

Acute sinusitis presents with frontal headache or facial pain, tenderness, and fullness. The diagnosis of acute sinus headache requires symptoms of a recent or intercurrent upper respiratory infection. Specifically, patients should report rhinorrhea or nasal congestion, stuffiness or blockage, and fever. Chronic sinusitis does not cause acute headache. Migraine, too, may present with nasal congestion or rhinorrhea. Physicians should consider this latter diagnosis in all patients who presents with recurrent headaches (8).

Cervical Artery Dissection

Spontaneous dissection of the cervical arteries is an uncommon syndrome, often associated with surprisingly minor trauma. It is marked by sudden onset of headache associated with facial or neck pain and focal ischemic symptoms. The pain and its location are determined by the location of the dissection in the carotid or

vertebrobasilar system. In the carotid system, the pain is anterior and may be accompanied by monocular symptoms, Horner syndrome, and other focal findings. With dissection in the posterior circulation, the pain is occipital, and brainstem findings predominate.

Pituitary Apoplexy

Acute hemorrhage or infarction of the pituitary gland is a rare cause of sudden-onset headache that typically occurs in patients with underlying (although often not diagnosed) pituitary adenoma. This headache may be accompanied by decreased visual acuity, temporal visual field cuts, ocular palsies, and hormonal dysfunction such as acute adrenal crisis.

Cerebral Venous Thrombosis

Thrombosis of the venous system of the brain is an uncommon cause of headache that is often difficult to diagnose. The onset may be sudden or gradual. Both noncontrast head CT and spinal fluid analysis are often normal, so diagnosis is often delayed until after hospital admission. Magnetic resonance venography is useful in making the diagnosis. Risk factors include traditional thromboembolic risk factors, pregnancy and the postpartum period, trauma, and contiguous sources of infection.

Brain Tumor

Headache is the initial symptom of primary brain tumor in half of all cases, though by the time patients present to medical attention, they have often developed other signs suggestive of a malignant CNS process. Headache is an uncommon presenting symptom of a metastatic undiagnosed non-CNS malignancy. Brain tumor headache is nonspecific and cannot be used to differentiate brain tumor from benign headache etiologies. Initially brain tumor headache is often mild to moderate in intensity, relieved by over-the-counter analgesics, and diffuse. Brain tumor headache may be intermittent rather than progressive and while it may awaken the patient at night, worsen with Valsalva maneuver, or present with nausea and vomiting, it is often not associated with these signs of increased intracranial pressure (9).

Temporomandibular Joint Syndrome
Headache precipitated by chewing or jaw movements may be due to temporomandibular joint syndrome. Definitive diagnosis requires evidence of joint pathology on imaging studies, though may be suspected if physical examination reveals a tender joint (2).

Headache Associated with Low Cerebrospinal Fluid Pressure
Low cerebrospinal fluid pressure headaches occur most commonly in the setting of recent lumbar puncture or spinal anesthesia. Noniatrogenic causes of low CSF pressure headaches are increasingly recognized. Low CSF pressure headaches are characteristically orthostatic. There is worsening of pain, dizziness, and nausea when the patient is upright and improvement on lying down. Diplopia with cranial nerve palsies may be present. The history is often diagnostic. If an LP is performed, an opening CSF pressure of <30 mm H_2O strongly suggests this diagnosis.

Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)
Headache in idiopathic intracranial hypertension is associated with high CSF pressures in the absence of intracranial structural disease. This is characteristically a disease of young obese women. Because of overlapping demographics, idiopathic intracranial hypertension may be misdiagnosed as migraine. Pain is often postural and associated with pulsatile tinnitus, nausea, vomiting, and eventually progressive visual loss, which may occur rapidly. Patients may report transient visual obscurations. Papilledema is present in about 90% of patients. The diagnosis is confirmed by CSF pressures >250 mm H_2O and unremarkable neuroimaging (10).

Temporal (Giant Cell) Arteritis
Headache is the dominant complaint in temporal (giant cell) arteritis, a progressive, systemic, inflammatory disorder. The syndrome is exceedingly rare in patients younger than 50 years of age. It is accompanied by constitutional symptoms such as anorexia and weight loss. The onset is gradual, with polymyalgia, proximal weakness, masseter claudication, and periocular discomfort developing over months to years. The diagnosis is suggested by firm,

tender, temporal and occipital arteries and an elevated erythrocyte sedimentation rate (>50 mm/h), although about 25% of cases have only mild elevations of the sedimentation rate. Major complications include monocular blindness and stroke (11).

Headache in Immunocompromised HIV-Positive Patients

Headache in immunocompromised patients with HIV is often caused by a benign recurrent headache disorder. However, the clinician should consider infectious etiologies, particularly cryptococcal meningitis, which may present with no more than an indolent subacute headache that seems like a persistent tension-type headache. HIV itself may cause headache, particularly as T cell counts dwindle. The list of other opportunistic CNS infections includes mycobacteria (*Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare*), spirochetes (*Treponema pallidum*), viruses (herpes simplex, herpes zoster, cytomegalovirus, and JC virus), and protozoa (*Toxoplasma*). Noninfectious causes of headache include CNS lymphoma (primary and secondary) and adverse reaction to antiretroviral or prophylactic therapy (4).

Posttraumatic Headache

Posttraumatic headache begins within 1 week of traumatic brain injury. While if often resolves within several months, it will persist in a minority of patients as either a chronic or episodic headache. Headache is often part of a postconcussive syndrome that may include dizziness, neurocognitive impairment, depression, irritability, and emotional lability. Phenotypically, it may take the form of migraine, tension type, or cervicogenic headache. Prognosis is varied and not related to initial mechanism or severity of injury. History of pre-existing headache disorder, and psychiatric and social stressors will impact outcome (12).

Headache in Pregnancy

In general, pregnancy decreases the frequency of migraine attacks in patients with a history of migraine. This becomes more apparent in the latter two trimesters. Benign causes of headache predominate by far among women who complain of headache in pregnancy. Headache may be the presenting symptom of preeclampsia or

eclampsia. These headaches have a vascular throbbing quality. An assessment of blood pressure, proteinuria, and reflexes should occur in all patients with headache in the final trimester of pregnancy. In addition, the latter half of pregnancy and the first several weeks postpartum are considered a thrombophilic period. Clinicians should consider the diagnosis of venous sinus thrombosis for de novo headaches that present in this time period.

Acute Headache Associated with Metabolic Disorders

Of all patients presenting to the ED with headache, a little more than one-third have a systemic infection, usually associated with fever, causing their head pain. Other metabolic causes of headache include hypoglycemia, hypoxia, carbon monoxide poisoning, and hypercarbia.

Primary Headache Disorders

The two most common causes of headache visit in emergency practice are the highly prevalent primary headache disorders: Migraine and tension-type headache. The acute migraine or tension-type headache that causes the patient to visit the ED is a symptom of an underlying episodic headache disorder, which ultimately requires attentive long-term management. For these headaches a diagnostic workup is generally not needed. The goal of the emergency clinician is to reassure the patient of the benign nature of the headache, provide durable short-term relief, and assist the patient to access continuing headache care.

Migraine

Migraine affects 12% of the US population with a 3:1 female predominance. If left untreated, an acute migraine attack generally lasts between 4 and 72 hours (2). Classically described features include unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea, photophobia, and phonophobia, although not all of these features are required for diagnosis. Constitutional symptoms occur primarily during the prodrome and the “postdrome.” These include mood changes, fatigue, myalgias, food cravings, and

irritability. Neurologic symptoms occur mainly during the migraine aura (which occurs in a minority of patients) and include visual phenomena such as bright sparkling lights (scintillating scotomata), jagged lines (fortification spectra), and geometric figures. A unique characteristic of migraine visual auras is their propensity to move across the visual field and to vary in color or intensity, sometimes shifting from positive to negative phenomena (scotomata). Less common migraine auras include motor abnormalities (hemiparesis, ophthalmoplegia, aphasia), sensory dysesthesias, and brainstem disturbances (vertigo, ataxia).

Cluster Headache

In contrast to migraine, cluster headache is uncommon, affecting 0.1% of the population. Prevalence is three to four times higher in men than woman and associated with tobacco use. The first episode of cluster headache may be indistinguishable from SAH, carotid artery dissection, or acute orbital, periorbital, or ocular disease. Unilateral pain is localized to the orbital, supraorbital, and/or temporal areas. Attacks are associated with one or more of the following ipsilateral signs: Conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, and eyelid edema. Restlessness and agitation are common features. Attacks characteristically occur in clusters lasting for weeks or months, with multiple extremely painful attacks occurring several times each day (13).

Tension-Type Headache

Tension-type headache is the most common type of primary headache, with a prevalence in the general population of nearly 40% (14). The pain is typically bilateral, pressing or tightening in quality, of mild-to-moderate intensity, and does not worsen with routine physical activity. There is no nausea, but photophobia or phonophobia may be present. Tenderness of the pericranial musculature may accompany this headache (2).

Trigeminal Neuralgia

Trigeminal neuralgia is the prototypic form of facial neuralgia, characterized by repetitive, unilateral, lancinating pain in the distribution of at least one branch of the trigeminal nerve. Attacks may be triggered by some minor stimulus, such as a light touch on the face. Sensory deficits and bilateral symptoms are suggestive of a specific underlying anatomic lesion (2).

Coital Headache

Headache that occurs immediately before, during, or shortly after orgasm is termed *coital* or *orgasmic headache.* The pain is often severe and may persist for several hours. If there is no prior history of coital headache, SAH must be excluded. Reversible cerebral vasoconstriction syndrome can cause recurrent coital headaches.

Chronic Headache

Patients presenting to the ED with chronic headache (i.e., headache that has been present for months to years) are part of what has been called the "last straw" syndrome (15). Chronic headaches can be divided clinically into several different groups, each requiring a different diagnostic and therapeutic strategy. These include patients with features of chronic tension-type headache, chronic migraine (most often transformed from an episodic pattern to a chronic daily pattern), and, rarely, tumor, subdural hematoma, idiopathic intracranial hypertension, and posttraumatic headache. A comorbid association exists between headache and psychiatric disorders including depression, and anxiety disorder, but current opinion does not favor a causal relationship. Some patients with severe tension-type headache or frequent migraines overuse nonnarcotic analgesics resulting in worsening of the frequency of the underlying headache attacks.

ED EVALUATION

A meticulous history is the key to headache diagnosis. Only in unusual circumstances does the neurologic examination, laboratory

testing, or neuroimaging reveal an abnormality that was completely unsuspected after a careful history.

Headache History

Temporal Profile

Headaches should be classified into one of the following four categories.

1. Single acute: Is this a “first/worst” headache of sudden onset?
2. Recurrent acute: What are the frequency, pattern, and duration of individual headache episodes?
3. Subacute: Is the headache progressively worsening?
4. Chronic: Has there been a pattern break or is this a “last straw” visit to the ED?

Associated Symptoms

In particular, look for transient loss of consciousness at onset, nausea, vomiting, neck stiffness, unilateral lacrimation or rhinorrhea, photophobia, phonophobia, or visual changes.

Circumstances of Onset

For single acute headaches, determine exactly what the patient was doing when the headache began. For recurrent headache, identify typical precipitants.

Prodromes and Aura

Prodromes such as a shift in appetite, mood, sleep patterns, or energy level, may precede the headache by several days and suggest migraine. Visual or sensory aura, which precede the headache by no more than 1 hour and generally resolve with headache onset, defines the subtype of migraine with aura.

Location of Pain

Hemicranial, hemifacial, and unilateral ocular and periorbital pain have greater discriminating value than holocranial or bilateral pain.

Quality and Severity of Pain

Quality and severity of pain have limited value in identifying the type of headache and correlate poorly with the seriousness of

underlying disease.

Age at Onset
For many patients, migraine begins in the second decade of life, with a peak prevalence in the fourth decade of life. New-onset headache in the elderly is worrisome and deserves a thorough evaluation.

Recent Trauma
Recent history of trauma is relevant to chronic subdural hematomas and posttraumatic headaches.

Relief Measures
Headaches that are substantially relieved by lying down are usually posttraumatic or low CSF pressure headaches. Patients with migraine seek dark, quiet spaces, while those with cluster prefer to pace.

Family History
Migraine, and to a lesser extent, a predisposition to SAH are inherited.

Medical History
Ask about concurrent illnesses, medications (including oral contraceptives), hospitalizations, allergies, smoking, alcohol, drug use, and risk factors for HIV.

Occupational History
Note exposure to carbon monoxide, fumes, solvents, and other toxins.

Psychosocial History
Search especially for signs and symptoms of depression, anxiety, and stress.

Multiplicity
Many patients suffer from different kinds of headaches. To minimize confusion, it is important to determine this early and to obtain parallel but distinct histories of each headache type.

Physical Examination

General Examination

After obtaining vital signs, the remainder of the nonneurologic examination should be goal directed, including the eyes, neck, face, and scalp. Visual acuity should be checked, visual fields assessed, and the eye examined for ptosis, conjunctival injection (perilimbal vs. diffuse), corneal clouding, and pupillary size, reactivity, and equality. Any suggestion of acute glaucoma mandates measurement of intraocular pressure.

A funduscopic examination may identify signs of increased ICP. Spontaneous venous pulsations (SVPs) are lost when the ICP exceeds about 250 mm H_2O, though absence of SVPs in patients with normal ICP occurs in about 20% of the normal population. Bilateral papilledema is a highly specific indicator of increased ICP but may lag behind acute elevations of ICP by as much as 1 week (10).

The neck should be examined for pain with flexion, which indicates meningeal irritation secondary to chemical or infectious meningitis. Tension-type headache may produce tightness in the paracervical muscles with discomfort on flexion. Unlike the nuchal rigidity of meningitis, tension-type headache causes pain with chin-to-shoulder rotation of the head. Because it may take several hours for subarachnoid blood to reach the cervical area of the meninges and several more hours for it to produce a chemical meningitis, absence of nuchal rigidity early in the course of an SAH does not reliably exclude this entity. Tender areas along the spine may indicate a cervical etiology of headache.

The sinuses, temporomandibular joints, and scalp should be palpated for tenderness, paying special attention to the temporal and occipital arteries in older patients. In posttraumatic headache, hemotympanum, CSF otorrhea, infraorbital ecchymoses, posterior auricular ecchymoses, and CSF rhinorrhea indicate basilar skull fracture.

Neurologic Examination

Mental status assessment is a critically important feature of the neurologic examination that is commonly overlooked. Focality is detected most readily by pronator drift, asymmetry of cranial nerves II to VIII, and abnormalities of gait and station. In general, sensory

examination (other than cranial nerve V), assessment of reflexes, and motor testing of individual muscle groups are not efficient use of the emergency physician's time in the evaluation of the patient with headache.

Laboratory Testing

As with the physical examination, laboratory tests are usually normal. In patients with a history strongly suggestive of a particular kind of headache (e.g., migraine), no laboratory tests are necessary. An exception to this rule is the erythrocyte sedimentation rate and C-reactive protein in patients suspected of having temporal arteritis (16). In certain situations, an assessment of carboxyhemoglobin level will indicate the diagnosis.

Imaging

When a diagnosis can be made on the basis of the history and a normal clinical examination, no imaging is needed. Patients with new-onset headache often require CT or magnetic resonance imaging at the time of their ED visit. Those with subacute and chronic headache may have an imaging procedure scheduled electively.

Optimal imaging modality depends on availability. For most patients at most EDs, a noncontrast head CT can be obtained in an expedited manner, and provides valuable information about space-occupying lesions and acute bleeds. MRI is less readily available on an emergent basis, but is generally more sensitive than CT, and does not expose patients to ionizing radiation. A noncontrast head CT is the preferred test for evaluation of acute SAH, as small amounts of acute blood are more difficult to detect on the MRI. Detection of subarachnoid hemorrhage on CT is dependent on the amount of subarachnoid blood, resolution of the scanner, and skill of the interpreter and is inversely related to time interval from onset of bleeding to scan. Sensitivity of noncontrast head CT for subarachnoid blood approaches 100% if performed within 6 hours of headache onset and greater than 90% if performed with 24 hours (17). Noncontrast head CT is inadequately sensitive for subarachnoid blood beyond 24 hours.

The sensitivity of MRI is inferior to that of CT during the first 24 hours after an SAH, and improves thereafter. In addition to late identification of SAH, MRI is preferred for imaging the posterior fossa (cerebellum and brainstem), and detecting nonhemorrhagic stroke.

Digital subtraction angiography is the traditional gold standard for evaluation of aneurysms and arteriovenous malformations causing subarachnoid hemorrhage. CT angiography (CTA) can be performed rapidly, has a sensitivity of approximately 95% for the detection of aneurysms, and is playing an increasing role in the diagnostic evaluation of patients with subarachnoid hemorrhage (18). MRA has performance characteristics similar to CTA but may be less available and less feasible depending on patient condition.

Lumbar Puncture

There are two primary indications for an emergency LP in a patient with headache: Suspicion of CNS infection or substantial suspicion of subarachnoid hemorrhage. The other circumstance in which an LP is the diagnostic standard is in idiopathic intracranial hypertension.

The risk of herniation after LP in patients with increased ICP or a mass lesion is low but has not been precisely quantified. A subset of young, healthy, neurologically intact ED patients can safely undergo LP without screening CT (19). Postural headache is a common occurrence after diagnostic LP. Despite common teaching, no evidence exists from randomized trials to suggest bed rest is more effective than immediate mobilization after LP. The role of fluid supplementation in the prevention of postural puncture headache remains uncertain. Several meta-analyses have found the use of smaller diameter and atraumatic-tip needles to be associated with a lower incidence of postural puncture headache than larger and bevel-tip needles, respectively. If a beveled needle is used, the bevel should be aligned parallel to the dural fibers (i.e., pointed toward the patient's hip) (20).

KEY TESTING

- Only a minority of ED patients with headache require diagnostic evaluation. For the emergency clinician, deciding whether or not to test is equally important as deciding which test to order.
- Laboratory values, while suggestive, are rarely helpful. The exception to this is an erythrocyte sedimentation rate and C-reactive protein. When these values are normal, the diagnosis of temporal arteritis is practically excluded.
- Neuroimaging is useful to exclude disease in a minority of patients. Benefits of CT scan such as availability, rapidity of test, and sensitivity for acute blood must be weighed against risk of radiation sequelae. Benefits of MRI such as increased sensitivity for space-occupying lesions, demyelinating processes, and ischemia must be weighed against considerations such as throughput time and costs to the healthcare system.

ED MANAGEMENT AND DISPOSITION

Treatment of many of the secondary headaches mentioned above is discussed in corresponding chapters elsewhere in this text. Below, we review management and disposition of the primary headaches and select secondary headaches not discussed elsewhere.

Migraine

Table 153.3 lists parenteral therapies for acute migraine (21). Historically, emergency clinicians used opioids to treat acute migraine. A growing consensus favors the use of the disease-specific agents discussed below, rather than nonspecific analgesics, with the goals of decreasing ED recidivism, improving functionality after treatment, and preventing progression of the underlying episodic migraine disorder to a chronic persistent illness (22).

TABLE 153.3
Parenteral Therapies for Acute Migraine

Drug	Dose	Route	Repeat Dose	Comments
NSAID				
Ketorolac (Toradol)	60 mg 30 mg	IM IV	6 h	Reasonable therapy, especially for headaches without migraine or cluster features. Not as effective for migraine as DHE, antiemetic dopamine antagonists or sumatriptan
Serotonin Agonists				
Dihydroergotamine	0.5–1 mg	IM, SC or IV over 30–60 min	0.5–1 mg IM, SC or IV over 30–60 min	Less effective than sumatriptan and dopamine antagonists but less relapse than sumatriptan. Combine with antiemetic (e.g., metoclopramide or prochlorperazine) for added efficacy and tolerability. Contraindicated in cardiovascular disease and pregnancy; d/c if chest pain, worsening headache or increased blood pressure.
Sumatriptan (Imitrex)	6 mg	SC	6 mg SC in 1 h (max 12 mg per 24 h)	More rapid action than DHE; 50% rebound within 24 h; higher cost, poorly tolerated by some patients and contraindicated in those with cardiovascular risk factors
Dopamine Antagonists				
Prochlorperazine (Compazine)	10–20 mg	Slow IV infusion	10–20 mg in 1 h	May cause dystonia, akathisia (consider administration with diphenhydramine 25–50 mg IV); PR less effective than IV
Metoclopramide (Reglan)	10–20 mg	IV in 50 mL D5W over 20 min	40 mg in 1 h	Enhances gastric emptying; may cause dystonia, akathisia (consider administration with diphenhydramine 25–50 mg IV)
Droperidol	1.25–2.5 mg	Slow IV infusion	Repeat dose ok	Black box warning for QT prolongation. May cause akathisia.
Corticosteroids				
Dexamethasone	10–20 mg	IV	60 mg prednisone tapering 5 mg/d	May decrease inflammation; interval medication until prophylactic agents take effect Increasing evidence for dexamethasone as primary therapy to decrease recurrence of headache after ED discharge
Opioids				
Morphine	0.1–0.15 mg/kg	IV	Titrate against pain prn	Most of above regimens provide superior pain relief in controlled trials
Hydromorphone	1–2 mg	IV		Generally considered therapeutic option of last resort

The established efficacy and selective pharmacology of the triptans have earned this group of drugs a central role in the abortive management of migraine over the past decade. Subcutaneous sumatriptan, the putative gold standard, is highly effective if administered early after headache onset. This medication is best avoided in patients with cardiovascular risk factors and those who are pregnant. Unpleasant adverse events such as palpitations and flushing frequently accompany this medication, and headache recurrence after ED discharge occurs in nearly two-third of patients who initially experience relief. This medication should be reserved for those who have had a previous favorable experience with it.

Newer triptans offer additional dosage forms and longer half-lives, though to date, sumatriptan is the only parenteral option. ED use of oral triptans may be limited by nausea, vomiting, and delayed gastrointestinal absorption, a frequent feature of migraine attacks.

Dihydroergotamine, a more tolerable form of the original ergot alkaloid, is best administered as a slow intravenous drip following pretreatment with an antiemetic, preferably one of the antiemetics with antimigraine properties discussed below. Dihydroergotamine

should not be used in those with cardiovascular risk factors, those who are pregnant, or taking macrolide antibiotics or antiretrovirals.

The intravenous dopamine antagonists metoclopramide, droperidol, and prochlorperazine can be used as monotherapy or as adjunctive therapy in combination with other abortive agents (21). The efficacy of these agents has been established in multiple systematic reviews (21) though the therapeutic mechanism of action is not well understood. The dopamine antagonists are well tolerated and highly effective with few practical contraindications. Akathisia, which may at times be severe enough to interfere with the therapeutic plan, can be mitigated with the coadministration of 25 to 50 mg of intravenous diphenhydramine.

Parenteral nonsteroidal anti-inflammatory drugs or salicylates may be used as primary or adjunctive therapy for acute migraine. Caution should be exercised in patients who have taken substantial doses of over-the-counter medication prior to ED presentation, which is not uncommon.

Corticosteroids such as dexamethasone decrease the frequency of headache recurrence after ED discharge, though with a number-needed-to-treat of 10, this class of medication may not be appropriate for every patient (21). Unfortunately, there is no evidence to guide optimal dosage and duration of therapy with corticosteroids. There is a belief that patients who present with status migrainosus (unremitting migraine for greater than 72 hours) are best served by a course of corticosteroids lasting at least several days.

Cluster

High-flow 100% oxygen is highly effective for cluster headache and should be administered as soon as the patient with cluster headache enters the ED (13). Dihydroergotamine (DHE) and sumatriptan are also effective in the ED management of cluster. However, concerns about coronary vasospasm limit the use of these drugs in patients with any cardiovascular risk factors. Limited evidence suggests the dopamine antagonists may be effective as well. On discharge, patients with an exacerbation of cluster should receive verapamil, starting at 80 mg tid, if there are no contraindications. A tapering

course of steroids should be prescribed, and close follow-up arranged (13).

Tension-Type Headache

Many patients with tension-type headache can be managed with oral analgesics, such as nonsteroidal medication, aspirin, or acetaminophen. Those who require parenteral medication will often respond to migraine medications. The parenteral dopamine antagonists are highly effective for tension-type headache. Subcutaneous sumatriptan should be reserved for those patients with tension-type headache who have previously experienced migraine headache.

Trigeminal Neuralgia

Trigeminal neuralgia syndrome responds best to carbamazepine, which has a number-needed-to-treat of less than two (23). Oxcarbazepine or baclofen may be used as second-line agents. Nonsteroidals or opioids may be necessary until other medications take effect. Facial nerve blocks with long-acting local anesthetics will provide immediate but short-lived relief in selected patients. All patients should be referred to specialty care for a diagnostic workup, which may reveal an anatomic cause such as multiple sclerosis, tumor, or neurovascular compression.

Coital Headache

Once subarachnoid hemorrhage has been excluded, coital headache patients require explanation, reassurance, and referral. It is reasonable to offer the patient a therapeutic trial of indomethacin 50 mg PO, taken 1 hour before intercourse.

Posttraumatic Headache

Once the diagnosis has been confirmed by a normal CT or MRI, posttraumatic headache patients should be educated and reassured. Confirmation that this is indeed “real” and that it will improve with

time is an important therapeutic intervention. Patients should be referred to a neurologist.

Headache Associated with Low Cerebrospinal Fluid Pressure

Traditional management of post-LP headache includes fluid replacement and bed rest. Other treatments include administration of intravenous caffeine and performance of an epidural blood patch, although a solid evidence base for these practices is lacking (24). Unless individuals are incapacitated by the headache, they can generally be managed as outpatients.

Idiopathic Intracranial Hypertension

Acute symptoms can be relieved with lumbar puncture, with the goal of removing enough CSF to normalize pressure. Acute headache may be relieved with migraine medication. Control of pain does not treat the underlying threat to the patient's vision. Patient should be prescribed acetazolamide and referred for specialty care. Modest reduction in weight may improve prognosis. If acuity worsens in spite of maximal medical management, an optic sheath decompression or ventricular shunt will be needed (10).

Temporal Arteritis

An erythrocyte sedimentation rate and C-reactive protein should be used to exclude temporal arteritis in patients older than 50 who present with new-onset headache. Because untreated patients are at risk of blindness, all patients with the working diagnosis of temporal arteritis should immediately receive corticosteroids and be referred for temporal artery biopsy.

Headache in Immunocompromised HIV Patients

Immunocompromised HIV-positive patients presenting with headache are at high risk for opportunistic infections. Emergency clinicians should have a low threshold for initiating a diagnostic

workup, including neuroimaging to look for mass lesions, lumbar puncture to evaluate for meningitis, and a serum cryptococcal antigen, which is highly sensitive for cryptococcal meningitis (4).

Chronic Headache

Individuals with chronic headache are among the most challenging to manage in a busy ED because their underlying pain disorder cannot be solved from the acute setting. Though tempting to treat the acute pain with parenteral opioids, this course of action will not improve the patient's long-term course. Within the heterogeneous group of patients with chronic headache, one must try to identify treatable subsets, such as those with medication overuse headache and untreated psychiatric comorbidities, and make the appropriate referrals. Comprehensive headache management programs with a multidisciplinary approach and individualized treatment plan have demonstrated some benefit in a select group of frequent ED users with chronic headache who are motivated to attend specialized headache classes (25). In general, patients with chronic headache, including chronic tension-type headache, chronic migraine, and medication overuse headache can benefit most from the expertise of a headache or pain specialist.

CRITICAL INTERVENTIONS

- Consider full headache differential diagnosis in all patients who present to ED with headache.
- Perform head CT and LP for patients who present with acute onset of "worst headache" to exclude subarachnoid hemorrhage.
- Administer antibiotics promptly in suspected bacterial meningitis.
- Treat pain appropriately and promptly.
- Help patients access suitable outpatient care.

Common Pitfalls

- Failure to diagnose the sentinel leak of SAH until a major bleed occurs subsequently.
- Misdiagnosis of migraine as hypertension or chronic sinusitis.

- Failure to diagnose and initiate treatment in patients with ongoing cluster headache because the acute headache has resolved prior to evaluation by the emergency clinician.
- Failure to diagnose and treat migraine appropriately either because a large tension-type component is present or because the headache is not hemicranial.
- Presuming that response to specific medications necessarily defines the etiology of a headache. The headache of brain tumors, aneurysms, and SAH may respond to a migraine regimen.

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CHAPTER 154

Subarachnoid Hemorrhage

Jonathan A. Edlow

Headache is a common presenting complaint in patients presenting to the emergency department (ED). Subarachnoid hemorrhage (SAH), which comprises less than 1% of ED headaches, is a true medical emergency in that effective time-dependent treatment exists (1,2). Deciding which patients to evaluate for SAH and the components of that evaluation is therefore a critical issue for emergency physicians. The classic presentation of a thunderclap headache in a patient with a stiff neck and an abnormal mental status presents little difficulty; however approximately 40% of patients present awake, alert, and neurologically intact. Misdiagnosis in this group results in worse outcomes (1,2).

This chapter is limited to atraumatic SAH, the most common cause of which is a ruptured cerebral aneurysm or arteriovenous malformation (AVM). Approximately 2% of the general population harbors cerebral aneurysms and yet the incidence of SAH is ~8 to 10 per 100,000 (2,3). Therefore, the vast majority of aneurysms never rupture. The fact that the vast majority of aneurysms are incidental has important diagnostic implications for emergency physicians (4).

Although most unruptured aneurysms are asymptomatic, they can present with mass lesion (classically the pupil-involving third nerve palsy), headache, seizure, and cerebral ischemia. Presentation of an unruptured aneurysm as isolated thunderclap headache without SAH is rare. Aneurysmal rupture is associated with a surge in intracranial pressure (ICP) that can lead to decreased cerebral perfusion resulting in syncope, any neurologic deficit or in some cases, sudden death.

Mortality rates on the first day and first month are 12% and 40% respectively (1–3).

Blood from a ruptured aneurysm is nearly always found at the base of the brain in the basal cisterns. Emergency physicians should be aware of two other patterns (Fig. 154.1A–C). The first is a perimesencephalic SAH, in which the blood is localized to the prepontine cistern. These bleeds are nonaneurysmal and are thought to be due to venous bleeding. Angiography is negative and patient outcomes are excellent (5). The second type is the convexal SAH in which the blood is found in the subarachnoid space high up on the hemispheres. These bleeds are also nonaneurysmal and are usually due to amyloid angiopathy, reversible cerebral vasoconstriction syndrome (RCVS), or hypertension (6). The outcomes are a function of the underlying condition more than the SAH by itself (6).

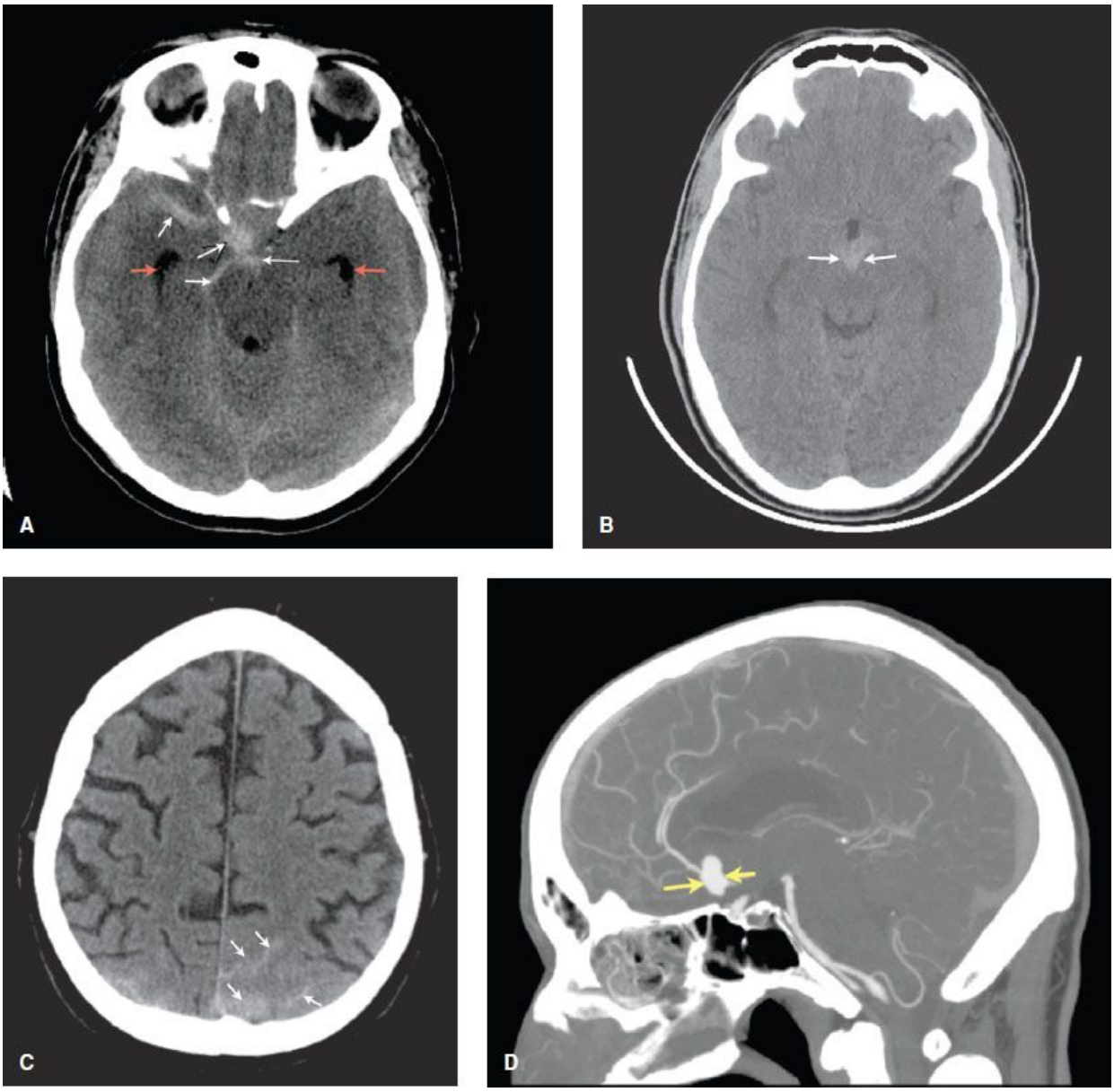

FIGURE 154.1 **A:** *White arrows* show subarachnoid blood in the basal cisterns, the typical location for a patient with an aneurysmal SAH. The *red arrows* show mild early hydrocephalus. **B:** *White arrows* show blood in the interpeduncular cistern (blood was also present in the prepontine cistern) in a patient with a perimesencephalic hemorrhage. He had a negative angiogram. **C:** *Arrows* show blood in the subarachnoid space high on the convexities in a patient with a bleed due to amyloid angiopathy. This location is also typical for reversible cerebral vasoconstriction bleeds. **D:** This is a sagittal cut of source image from a CT angiogram showing an aneurysm of the

anterior communicating artery *(yellow arrows),* a very common location for an aneurysm.

Both the American Heart Association (AHA, 2012) and the European Stroke Organization (ESO, 2013) have published recent evidence-based guidelines on SAH including detailed recommendations about the management beyond the ED phase of care (3,7).

CLINICAL PRESENTATION

There is a wide spectrum of presentations ranging from a nonacute onset headache in a neurologically intact patient to sudden death. This "bell-shaped curve" range of presentations is important for emergency physicians to know. On the right side of the curve are ill patients with an abnormal mental status and other clear-cut focal neurologic deficits. Although the specific diagnosis may not be immediately obvious, the fact that they require diagnostic testing is clear. Computed tomography (CT) of the brain is almost always an initial part of that workup and will usually reveal the problem in severely affected SAH patients. In the middle of the bell-shaped curve are patients presenting with the classic abrupt onset of a severe, unusual headache. Often, they will have had syncope at onset, be vomiting, or have prominent neck pain or stiffness. In this group too, the need for a diagnostic evaluation for SAH is clear.

Importantly however, physicians must understand the left-hand side of the curve. These patients complain of various less typical (but well described in the literature) symptoms. The headache of SAH usually is abrupt in onset, severe in intensity, and unlike other prior headaches in quality; however any of these aspects may be absent in an individual patient. Of this latter group, physicians ultimately must use their clinical judgment to decide which patients need a workup for SAH. This clinical judgment must be informed by knowledge of the range of presentations.

These presentations include abrupt onset isolated neck pain (suggesting neck strain or cervical arthritis), neck pain and low-grade fever or meningismus (viral syndrome or viral meningitis), retro-

orbital headache (sinusitis), headache with an elevated blood pressure, chest pain or an abnormal electrocardiogram (hypertensive emergency, Takosubo's cardiomyopathy, or other cardiac cause), and prominent vomiting (gastrointestinal conditions) and headache with confusion or mildly altered level of consciousness (intoxication or psychiatric diagnosis) (1,2,8–10). The severity of the SAH is often conveyed by using a clinical severity score (Table 154.1).

TABLE 154.1
Common Grading Scales Used in SAH Patients

(A) Hunt and Hess Severity Scale

Grade 1—asymptomatic, mild headache

Grade 2—moderate-to-severe headache, nuchal rigidity, no focal deficit other than cranial nerve palsy

Grade 3—mild mental status change (drowsy or confused), mild focal neurologic deficit

Grade 4—stupor or moderate-to-severe hemiparesis

Grade 5—comatose or decerebrate rigidity

(B) World Federation of Neurologic Surgeons

Grade 1—GCS 15, no motor deficit

Grade 2—GCS 13–14, no motor deficit

Grade 3—GCS 13–14, motor deficit present

Grade 4—GCS 7–12, motor deficit may be present or absent

Grade 5—GCS 3–6, motor deficit may be present or absent

(C) Fisher Scale (CT Appearance)

Group 1—no blood

Group 2—diffuse deposits of SAH blood, no clots, no layers of blood >1 mm

Group 3—local clots or vertical layers of blood ≥1 mm thickness

Group 4—diffuse or no SAH, but intracerebral or intraventricular clot

One misconception is that the onset of symptoms is always with strenuous activity. In fact, onset during sleep or quiet activity is common (1,2). The headache may not be "worst of life." As a general rule, one must consider the likelihood of other possibilities in the differential diagnosis, understanding that one cannot confidently make a diagnosis of migraine or tension-type headache after a first

ever headache. Although patients often use the term “sinusitis,” this is an unusual cause of an acute severe headache (9).

Historically, misdiagnosis of SAH is reported to occur ~20% of cases (1,2). Even in the modern era of near-universal CT access in EDs and educational focus on misdiagnosis of SAH, the rate of misdiagnosis of SAH in the ED remains 5% to 7% (2,10,11).

Based on a prospective cohort study of nearly thunderclap headache patients presenting to six Canadian EDs, a sensitive clinical decision rule has been proposed (12). Of the 2000 patients, 130 (6.5%) had SAH, making the study population representative of the spectrum seen in practice. Using recursive partitioning, they developed three clinical decision rules all of which were 100% sensitive for SAH that would have reduced the rates of investigations from 83% (baseline) to between 64% and 74% (12). The one rule that did not include the variable “arrival by ambulance” identified all SAH patients (all had at least one of the four).

- Age >40 years
- Complaint of neck pain or stiffness
- Witnessed loss of consciousness
- Onset with exertion

This clinical rule validated well in an independent population of patients although it was used somewhat differently in the second study (13).

The concept of warning bleeds is also important to consider. Some patients with SAH will have had a severe unusual headache in the days to weeks prior to being diagnosed with their SAH. These headaches have been called warning (or sentinel) bleed (or headache). Evidence suggests that these are actually small SAHs that were either not recognized by the patient or by the physician and so no evaluation (or an incomplete evaluation) was done. In a pooled analysis of 813 patients with thunderclap headache who had a negative CT and LP, none were subsequently diagnosed with SAH or died suddenly during follow-up (14). This suggests the standard workup will correctly diagnose warning bleeds.

One final point should be made regarding which patients to evaluate for SAH is the patients’ response to analgesics administered

for their headache. Because there is a final common pathway for pain sensation in the head, a patient's favorable response to any analgesic, narcotic or otherwise, including triptans, should ***not*** be used to make diagnostic inferences. The headache of patients with serious causes including SAH can improve or resolve with various analgesics including triptans.

DIFFERENTIAL DIAGNOSIS

Even among patients presenting with a thunderclap headache, only ~10% will have an SAH, most commonly from a ruptured aneurysm or AVM (2). The majority of patients with thunderclap headache have migraine and tension-type headache. A very small but important minority will have far less common but serious and treatable causes such as arterial dissection, cerebral venous sinus thrombosis (CVST), RCVS, pituitary apoplexy, and other vasculopathies.

The presence of multiple thunderclap headaches in a neurologically intact patient is nearly pathognomonic for RCVS (15). Table 154.2 shows the differential diagnosis of important treatable and serious causes of headache, of thunderclap headache, and of the vascular lesions responsible for nontraumatic SAH. Table 154.3 summarizes reasons for misdiagnosis.

TABLE 154.2
Differential Diagnoses Relevant to Patients with SAH

List of "Cannot Miss" Causes of Acute Severe Headache

- Subarachnoid hemorrhage
- Meningitis, encephalitis, and brain abscess
- Cerebral venous sinus thrombosis
- Cervical artery dissection
- Pituitary apoplexy
- Spontaneous intracranial hypotension
- Idiopathic intracranial hypertension (pseudotumor)
- Acute ischemic or hemorrhagic stroke
- Reversible cerebral vasoconstriction syndrome
- Acute narrow-angle closure glaucoma
- Temporal arteritis
- Mass lesion
  - Tumor
  - Abscess
  - Parameningeal infection
  - Intracranial hematoma
  - Colloid cyst of the third ventricle

Differential Diagnosis of Thunderclap Headache

- Subarachnoid hemorrhage
- Cerebral venous sinus thrombosis
- Cervical artery dissection
- Pituitary apoplexy
- Reversible cerebral vasoconstriction syndrome
- Hypertensive crisis
- Acute ischemic or hemorrhagic stroke
- Benign (primary) thunderclap headache (sometimes associated with orgasm, hot bath, cough, or exertion)
- Colloid cyst of the third ventricle
- Idiopathic intracranial hypotension
- Acute expansion of an unruptured aneurysm
- Intracranial infection (rarely)
- Acute sinusitis (rarely)
- Takasubo's cardiomyopathy (rarely)

Differential Diagnosis of Nontraumatic SAH

- Aneurysmal or arteriovenous malformation
- Perimesencephalic SAH
- Due to other specific vascular lesion (such as moyamoya)
- Convexal SAH
  - Amyloid angiopathy
  - Reversible cerebral vasoconstriction syndrome
  - Hypertensive crisis

TABLE 154.3
Reasons for Misdiagnosis of SAH

Failure to Know the Spectrum of Presentations of Subarachnoid Hemorrhage:

Not evaluating patients with unusual (for the patient) headaches

- Is the onset abrupt?
- Is the quality different from prior headaches?
- Is the severity greater than prior headaches?
- Are there associated symptoms that have been absent with prior headaches (such as vomiting, diplopia, syncope, or seizure)?

Failure to Appreciate that the Headache Can Improve Spontaneously or with Nonnarcotic Analgesics

Overreliance on the classic presentation with misdiagnosis of:

- Viral syndrome, viral meningitis and gastroenteritis
- Migraine and tension-type headache
- Sinus-related headache
- Neck pain (rarely, back pain)
- Psychiatric diagnoses

Focus on the secondary head injury (resulting from syncope and fall or car crash)

Focus on the electrocardiographic abnormalities

Focus on the elevated blood pressure

Lack of knowledge of presentations of the unruptured aneurysm

Failure to Understand the Limitations of Computerized Tomographic (CT) Scans:

CT scans are less sensitive with increasing time from onset of headache

CT scan can be falsely negative with small volume bleeds (spectrum bias)

Interpretation factors (expertise of physician reading the scan)

Technical factors (Have thin cuts been taken at the base of the brain? Is there motion artifact?)

CT can be falsely negative for blood at hematocrit level of less than 30%

Failure to Perform Lumbar Puncture and Correctly Interpret Cerebrospinal Fluid Findings:

Failure to do lumbar puncture in patients with negative, equivocal, or suboptimal CT scans

Failure to recognize that xanthochromia may be absent very early (<12 h) and very late (>2 wks)

Failure to understand the performance characteristics of xanthochromia measurement

Failure to properly distinguish traumatic tap from true subarachnoid hemorrhage

ED EVALUATION

For decades, the standard ED evaluation has been CT followed by lumbar puncture (LP) if the CT is nondiagnostic. As of mid-2013, in guidelines published by ACEP, the AHA and the ESO, this recommendation stands (3,7,16). Large studies confirm the safety and the sensitivity of this protocol (14,17).

A key point is to realize that the sensitivity of CT and LP changes with the time elapsed from the onset of the bleed and the performance of the test (1,2,8). CT is an excellent test early but the sensitivity degrades rapidly with time. LP and cerebrospinal fluid (CSF) analysis shows blood early in the course of a SAH. Increasing numbers of RBCs in the fourth tube and low percent change in RBCs from tube 1 to tube 4 are the most useful to predict SAH (18,19). Xanthochromia (the yellow color of CSF due to hemoglobin breakdown) takes time to develop but is usually present for up to 2 weeks after the bleed. Nearly all North American hospital laboratories use visual inspection for xanthochromia (20). Studies support the notion that measuring xanthochromia by visual inspection is a valuable method and that spectrophotometry, while more sensitive, lacks specificity (21,22).

Newer data about older techniques (early CT) and greater availability and data about newer techniques—CT angiography (CTA), magnetic resonance imaging (MRI), and MR angiography (MRA)—are beginning to impact the diagnostic paradigm for SAH (Fig. 154.1D). Each of these testing strategies has both advantages and limitations compared to the time-honored CT followed by LP (Table 154.4). Although official guidelines do not reflect it, the preponderance of data suggest that a normal CT performed within 6 hours of headache onset and interpreted by an experienced attending level radiologist excludes SAH with close to 100% sensitivity and that LP is no longer required in this setting (23–25).

TABLE 154.4
Diagnostic Strategies

Diagnostic Strategy	Advantages	Disadvantages
CT + LP	Time-honored method Very sensitive to SAH (CT has excellent sensitivity early; LP has excellent sensitivity later) Recommended by all current guidelines	Traumatic tap occurs in ~20% of LPs and can confuse the diagnosis No standard number of RBCs Different methods to detect xanthochromia
LP first	Forces the LP, which is otherwise not done in many cases in routine practice Will diagnose other causes that cause abnormal CSF	May miss pathology only visible on CT and which is associated with normal CSF Risk of herniation if patients are not carefully examined and selected
CT only (no LP if <6 h)	Avoids a painful, invasive procedure Saves time	Will miss some diagnoses that are only diagnosable by CSF examination May miss as much as 4/1,000 true SAHs
CT + CTA	Rapid Accurately diagnoses aneurysms	Additional radiation exposure Adverse reactions to contrast media Will diagnose incidental aneurysms
MRI	MRI is sensitive for acute blood MRI is also very sensitive for chronic blood, helping to diagnose older bleeds	Expense and availability If not followed by LP, the issue of spectrum bias still occurs (in which a bleed is too small to be positive, same as with CT) Radiologists are less familiar with technique and correct sequences must be obtained
MRI + MRA	Same as above Accurately diagnoses aneurysms	Same as above Will diagnose incidental aneurysms

CT, computed tomography (noncontrast); LP, lumbar puncture; SAH, subarachnoid hemorrhage; RBCs, red blood cells; CSF, cerebrospinal fluid; CTA, CT angiography; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography.

A recent study reported instances of CT-negative LP-positive patients (CT done within 6 hours) but the data as reported make it unclear how many of their "SAH" patients truly had SAH nor how many patients in the early presenting group had positive CT scans. Another study of early CT-negative patients found no patients with aneurysmal SAH among those presenting early (26).

For the strategies that include an angiogram, it is important to recognize that many of these aneurysms will be incidental. Approximately 2% of the general population has cerebral aneurysms. Since most patients with SAH have a positive CT, a "positive" CTA in a CT-negative patient makes it even more likely that the aneurysm is incidental. A CTA or MRA that diagnoses (what is actually) an incidental lesion can lead to an unnecessary procedure on the one hand, or a lot of anxiety and subsequent imaging on the other (4). For CTA, there are also considerations of radiation and dye complications (4).

Whatever diagnostic algorithm is used, one must factor in time from headache onset and understand the limitations of the tests.

KEY TESTING

- Noncontrast brain CT
- LP if CT is nondiagnostic
- Consider other testing algorithms; however each has limitations that must be explicitly addressed (Table 154.4)

ED MANAGEMENT

As always, initial attention to airway, breathing and circulation takes priority. Most patients with SAH do not require intubation. If an SAH patient needs airway control, standard rapid sequence intubation is used. For patients being transferred to another facility, one must consider the possible need for airway control over the duration of time of the transfer.

With regard to blood pressure control, the data are poor quality in terms of a specific target blood pressure. The 2012 AHA recommends that the systolic blood pressure be kept at less than 160 mm Hg and

the 2013 European ESO recommends that the systolic pressure be kept below 180 mm Hg. However many practitioners aim for a lower number. Both the AHA and ESO caution that the data are poor and that more important than a specific one-size-fits-all pressure, the clinicians must balance issues such as cerebral perfusion, risk of rebleeding, premorbid blood pressure, and other factors. Whatever target is used, use an antihypertensive intravenous easy-to-titrate drug such as nicardipine, esmolol, or labetalol.

With the ABCs covered, and the causative vascular lesion defined as above, there are a number of other issues that the emergency physician must consider. Pain and anxiety should be treated. Patients should be placed on telemetry and have a 12-lead electrocardiogram. Intravenous access should be established and blood should be sent for testing to the laboratory for routine hematologic and chemistry tests as well as tests of clotting and troponins. Other management issues should all be discussed and resolved with the accepting neurovascular specialist. These include treatment of seizures and hydrocephalus, vasospasm prophylaxis, the timing and choice of cerebrovascular imaging, and administration of short-term antifibrinolytics (Table 154.5).

TABLE 154.5
Treatment Approach

1. Airway management if indicated
2. Specialist consultation and arranging an angiogram
3. Arrangement for transfer to a neurovascular center
4. Management of hypertension
5. Volume status and intravenous fluids
6. Seizure treatment
7. Acute treatment of hydrocephalus, extra-axial or intracerebral hematomas
8. Nimodipine administration for vasospasm prophylaxis
9. Discuss short-term antifibrinolytics to prevent rebleeding
10. Cardiac telemetry
11. Analgesia
12. Treatment of elevated ICP

When SAH is diagnosed, rapidly consult with a cerebrovascular expert. This discussion should consider the points above on a case-by-case basis.

If a patient with SAH deteriorates while still in the ED, repeat the CT. There may be little to do for a massive rebleed or large territorial cerebral infarction from vasospasm; however, in some cases, acute hydrocephalus or a space-occupying bleed may be amenable to surgical intervention. In cases in which the CT is unchanged, consider nonconvulsive status epilepticus, cerebral hypoperfusion from overly aggressive lowering of the blood pressure or side effects of analgesics or anxiolytics.

Controversies

- Avoiding LP in the evaluation of SAH in patients who present typically with thunderclap headache and have a noncontrast CT scan performed within 6 hours of headache onset that is read as negative by an attending radiologist
- Ideal level of blood pressure control is unclear
- Seizures should be treated; however, prophylactic anticonvulsants are not indicated
- Administration of short-term antifibrinolytics (after diagnosis but before definitive treatment) to prevent early rebleeding may be considered

CRITICAL INTERVENTIONS

- Control airway using standard rapid sequence technique if clinically indicated
- Whatever diagnostic algorithm is used, follow it to its completion
- When controlling blood pressure, factor in premorbid blood pressure and current cerebral perfusion pressure
- Repeat CT scan for SAH patients who deteriorate while in the ED to identify a reversible cause
- Patients with SAH should be admitted to a facility with experience in SAH

DISPOSITION

Patients with SAH should be admitted to an ICU. Based on data over the past decade, the AHA recommends that patients with aneurysmal

SAH be treated in a high-volume center (defined as one that manages >35 cases per year) (3). The improved outcomes likely result not only from the technical expertise of the interventionalist and/or surgeon, but also the multidisciplinary neurointensive care that is available. Increasing numbers of SAH patients are being treated by endovascular coiling.

Common Pitfalls

- Failure to consider SAH in a patient with headache because they "do not appear ill" or "have a normal level of consciousness and neurologic examination," that is, failure to understand the spectrum of presentations
- Failure to fully workup patients with thunderclap headache for SAH
- Assuming that a patient with a severe headache whose pain has improved with analgesics does not have a serious cause of headache
- Failure to understand the limitations of CT, LP, and MRI, especially with regard to "timing" of the test compared to the onset of symptoms
- Failure to refer a patient with an SAH to a high-volume neurovascular center where patient outcomes are demonstrably better

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CHAPTER 155 Cerebrovascular Disease

Phillip A. Scott

The term *stroke* refers to the sudden onset of a neurologic deficit caused by an acute vascular lesion of the brain that is hemorrhagic, embolic, thrombotic, or aneurysmal in nature. *Cerebrovascular disease* is a broader term, encompassing stroke and other vascular causes of central nervous system dysfunction.

ISCHEMIC CEREBROVASCULAR DISEASE

Ischemic neurologic deficits are commonly categorized by their time course. A transient deficit, not accompanied by tissue infarction, is considered a *transient ischemic attack* (TIA), with the majority resolving within 60 minutes of onset (1). By extension, the presence of cellular loss on advanced imaging, typically accompanied by persistent clinical signs, defines infarction—that is, *stroke.* Other classification systems define stroke syndromes by probable cause or anatomic location.

Risk Factors

Not surprisingly, risk factors for ischemic cerebrovascular disease parallel those for atherosclerotic heart disease. Hypertension, diabetes, and coronary artery disease substantially increase the risk of stroke. Left ventricular hypertrophy, atrial fibrillation, and acute myocardial infarction (AMI) are also independent risk factors for ischemic stroke.

There are significant associations of ischemic cerebrovascular disease with age, gender, and race. The incidence of all strokes

increases with age, doubling with each decade of life. There is a slightly higher risk in men as compared with women, and black men and women have an overall age- and sex-adjusted stroke incidence rate 1.5 times higher than whites.

Medical conditions predisposing to stroke include a history of migraine headaches, elevated fibrinogen levels or hematocrit (causing increased blood viscosity), and advanced age with elevated total serum cholesterol levels.

Environmental risk factors for ischemic cerebrovascular disease include smoking and heavy alcohol consumption. Women taking oral contraceptives, particularly high-estrogen formulations, are also at increased risk for stroke. This risk is more pronounced in female smokers older than 35 years of age and in those with other cardiovascular risk factors.

Finally, patients with a history of ischemic stroke represent a high-risk population, with 1- and 5-year recurrence rates among survivors of 10% and 20%, respectively.

TRANSIENT ISCHEMIC ATTACK

There is a higher risk of early stroke following TIA than previously thought. Ten percent to 15% of patients with TIA have a stroke within 3 months, with half experiencing a stroke within 48 hours of the initial TIA (1).

TIAs may result from plaque ulceration or embolism of platelet aggregates from extracranial or intracranial atherosclerosis. After impeding local blood flow, these emboli break up, accounting for the transient nature of the episode. Other sources of emboli include prosthetic heart valves and infective or marantic vegetations on valve leaflets. Small vessel disease in penetrating cerebral arteries may actually be the most common cause of TIAs and that these “lacunar” TIAs may represent a subgroup with a better prognosis than TIAs with cortical symptoms. Hypotension and mechanical kinking of the extracranial vessels are less common causes of TIAs. Cardiac dysrhythmias are an important potential etiology for the emergency physician to consider.

CLINICAL PRESENTATION

Carotid artery syndrome results from transient disruption of the anterior circulation of one cerebral hemisphere or of the retina. Hemispheric ischemia results in an abrupt onset of contralateral monoparesis or hemiparesis, numbness, tingling, aphasia, or hemianopia. Occlusion of the ophthalmic branch of the internal carotid artery results in retinal ischemia, causing temporary monocular blindness (amaurosis fugax). The patient complains of a "fog," "mist," "cloud," or "shade being drawn" over the visual field of one eye. Funduscopic examination of the involved eye may reveal cholesterol crystals (Hollenhorst plaques) in the retinal vessels.

Transient ischemia involving the posterior circulation (the brainstem or occipital lobes) is termed *vertebrobasilar artery syndrome.* Interruption of brainstem circulation may result in symptoms of vertigo, dizziness, ataxia, nausea, or vomiting secondary to involvement of the vestibular nuclei. Dysarthria, dysphagia, and perioral numbness may also occur. Occipital lobe ischemia results in blurred or dim vision or total cortical blindness. Diplopia may result from loss of conjugate gaze.

Basilar artery TIAs may cause *drop attacks*—brief paretic spells resulting in the patient's dropping to his or her knees. There is no loss of consciousness, distinguishing it from true syncope, and the patient attempts to rise immediately after falling.

Transient global amnesia (see Chapter 157, "Transient Global Amnesia") is thought to be caused by ischemia of the temporal lobes or thalamic area supplied by the posterior cerebral arteries. These episodes affect men more frequently than women and are characterized by a rapid development of retrograde memory loss and confusion, with preservation of self-identity. The length of retrograde amnesia gradually shortens until only the period during the attack remains lost.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of TIAs includes transient deficits secondary to mass lesions from either tumor or hemorrhage (these patients often have a residual neurologic deficit detectable on

examination); infection (as with focal abscess, septic emboli, meningitis, or encephalitis); seizure with a subsequent Todd paralysis; complicated migraine; exacerbation of multiple sclerosis; hypoglycemia; and syncope from any cause, particularly cardiac dysrhythmias.

ED EVALUATION

Clinical investigation of a TIA is directed toward identifying whether the deficit involves the anterior or posterior circulation, establishing the source of the TIA, and ruling out other causes of focal deficits. A detailed history often provides the most significant information. The patient may not be aware of any deficits, and the family should be questioned, if possible, along with the patient. The onset and course of symptoms should be carefully elicited. Were there any prior episodes? If so, how many? Were the events in the same or differing vascular distributions?

The neurologic examination in patients with TIAs is often unremarkable, but a thorough assessment is essential. Orthostatic blood pressures should be measured in patients with vertebrobasilar TIAs, because symptoms are often related to postural changes. Auscultation for cervical and subclavian bruits should be performed, as should evaluation for cardiac dysrhythmias, murmurs, and left ventricular dysfunction.

Determination of the $ABCD^2$ score may assist in predicting short-term risk of stroke in patients presenting with TIA. Patients are assessed on points based on age $\leq$60 years (1 point); blood pressure $\leq$140/90 mm Hg on initial evaluation (1 point); clinical symptoms of weakness (2 points) or speech impairment without weakness (1 point); duration 10 to 59 minutes (1 point) or $\leq$60 minutes (2 points); and diabetes (1 point). The 48-hour risk of stroke was 0% for scores of 0–1, 1.3% for 2–3, 4.1% for 4–5, and 8.1% for 6–7 (2).

KEY TESTING

Laboratory Testing	• CBC with platelets • Chemistry panel with glucose • Prothrombin time and partial thromboplastin time • Consider erythrocyte sedimentation rate and C-reactive protein if vasculitis suspected • Consider specialized coagulation testing in younger patients with TIAs
Cardiac Evaluation	• EKG • Consider prolonged cardiac monitoring in patients with unclear TIA origin • Consider echocardiography in patients where no other cause has been identified
Neuroimaging Options	• CT • MRI with diffusion-weighted imaging (DWI)
Vascular Imaging Options	• Carotid ultrasound • CT angiography • MR angiography

ED MANAGEMENT

Medical therapy is indicated for patients with posterior circulation TIAs, patients with anterior circulation TIAs who have <50% stenosis on carotid duplex scanning, and patients who are not candidates for carotid endarterectomy. Medical treatment options are limited to antiplatelet therapy and anticoagulation.

Acceptable options for initial antiplatelet therapy in patients with TIA include the following:

- Aspirin (50 to 325 mg/d) monotherapy
- Extended-release dipyridamole combined with aspirin (Aggrenox)
- Clopidogrel (Plavix) monotherapy (75 mg/d)
- Clopidogrel (300-mg loading dose) combined with aspirin (75 mg)

Antiplatelet therapy with aspirin (50 to 325 mg/d) reduces the incidence of nonfatal stroke, nonfatal myocardial infarction, and death from all vascular causes in patients with TIAs. Because the lower dosages require several days to achieve maximal platelet inhibition, therapy in the early setting should be initiated with 300

to 325 mg/d. The combination of dipyridamole plus aspirin (Aggrenox) was modestly better than aspirin alone; however, a number of patients discontinue combination therapy owing to medication intolerance (3,4).

Clopidogrel is an ADP-inhibitor and also acceptable as monotherapy for patients with TIA. Its role as a primary or secondary agent in the treatment of TIA is debated, given its cost and the small (0.5%) absolute improvement in reducing risk for the combined end point of stroke, AMI, and vascular death in patients with atherosclerotic vascular disease compared to aspirin alone (5). The combination of clopidogrel with aspirin was superior to aspirin alone in preventing recurrent stroke in patients with TIA or minor stroke (8.2% vs. 11.7%) in a large Chinese study (6). A companion trial is currently underway in the United States (7).

The use of anticoagulation in patients experiencing noncardioembolic TIA lacks a rigorous scientific basis. Though heparin has traditionally been used in select patients with TIA, no prospective randomized study of significant size has demonstrated a clear benefit and its use cannot be recommended on the basis of existing data. If used at all, it should be reserved for “high-risk” patients such as those with crescendo TIAs, vertebrobasilar TIA, recurrent TIA while receiving maximum antiplatelet therapy, high-grade carotid stenosis, or a suspected cardiac source for emboli. Neurologic consultation is recommended prior to initiation.

Adjusted-dose oral anticoagulation with warfarin has been the predominant treatment for stroke prevention in patients with a cardioembolic TIA due to atrial fibrillation. A target international normalized ratio (INR) of 2 to 3 is recommended. The efficacy of aspirin is considerably less than warfarin in this population and is recommended as an alternative for those with contraindications to oral anticoagulation. Newer oral anticoagulants inhibiting thrombin or factor Xa have demonstrated improved stroke prevention with comparable safety to warfarin. The lack of an available antidote has raised concern over their use. Anticoagulant therapy may be appropriate for patients with other sources of cardiogenic emboli

who have a TIA; however, randomized clinical trials have not been performed in these specific patient populations.

A subset of patients with TIA has surgically correctable carotid stenosis and represent an important group for the emergency physician to identify. Those with ≥50% carotid stenosis are potential candidates for endarterectomy and should receive medical therapy in the ED pending a decision on vascular intervention.

CRITICAL INTERVENTIONS

- Initiate antiplatelet therapy for patients with TIA.
- Identify and refer patients with surgical or endovascular correctable carotid stenosis.

DISPOSITION

Patients who have a new anterior circulation TIA and are potential surgical candidates should not be discharged without arranging expeditious evaluation of the carotid arteries. If duplex scanning is not immediately available, the patient should be started on antiplatelet therapy and carotid duplex scanning performed as soon as possible, with subsequent vascular consultation for patients determined to have stenosis of 50% or more.

Because of the increased short-term risk of stroke, it may be optimal to admit patients with TIA to an inpatient or observation bed. Current guidelines state it is reasonable to hospitalize patients with TIA if they present within 72 hours of the event and have either an $ABCD^2$ score ≤3; $ABCD^2$ score of 0–2 and inability to complete diagnostic workup as outpatient within 2 days; or an $ABCD^2$ score of 0–2 and other evidence indicating the event was caused by focal ischemia (2). The clinical utility of the $ABCD^2$ score in the emergency department setting, however, has been questioned owing to its low sensitivity and specificity (8). Admission and neurologic consultation should be considered for high-risk patients. Standard protocols for patients with TIAs should be jointly developed with neurologic specialists in each institution. Active collaboration can

ensure the provision of efficient and consistent patient care and facilitate future modifications as new data become available.

Common Pitfalls

- Discharging patients with anterior circulation TIAs before determining whether there is a potentially surgically correctable carotid lesion. This carries a high medicolegal risk.
- Failure to obtain consultation in high-risk patients: Those with crescendo TIAs, vertebrobasilar TIA, recurrent TIA on maximal antiplatelet therapy, high-grade carotid artery stenosis, or presumed cardioembolic source.
- Failing to discuss signs and symptoms of stroke with the patient and emphasizing the need to immediately return for recurrent symptoms.

ISCHEMIC STROKE

Ischemic strokes have traditionally been classified by clinical presentation, time course of onset, progression of deficits, accompanying symptoms, and risk factor profiles. The clinical description of the deficit identifies the extent and location of the stroke and allows accurate communication regarding patient status. The time course and progression of symptoms suggest certain etiologies; for example, prolonged, "stuttering" deficits indicate a thrombotic phenomenon, whereas an abrupt onset of the maximal deficit suggests an embolic event. Associated symptoms may suggest other causes for neurologic deficits (e.g., a seizure preceding a Todd paralysis or chest pain preceding an ischemic stroke of cardioembolic origin). Consideration of cerebrovascular risk factors helps to classify the stroke as lacunar, embolic, thrombotic, extracranial, or intracranial.

CLINICAL PRESENTATION

Anterior Cerebral Artery Syndrome

Patients with infarction in the territory of the anterior cerebral artery present with hemiparesis involving the leg more than the face or

arm. Urinary incontinence and primitive reflexes (grasp and suck) are often present. The patient may perseverate with speech or motor movements and respond slowly to questions. If both anterior cerebral arteries originate from a common trunk, a bilateral parasagittal infarct may occur, with paraplegia and speechlessness (anarthria).

Middle Cerebral Artery Syndrome

Infarction in the distribution of the middle cerebral artery is the most common of the stroke syndromes. Patients with infarcts of the middle cerebral artery present with weakness of the face and arm greater than that of the leg, often with corresponding cortical sensory loss. The presence of aphasia localizes the lesion to the dominant hemisphere. Inattention, extinction on double simultaneous sensory or visual testing, neglect, or constructional or dressing apraxia indicates nondominant hemisphere involvement. Homonymous hemianopia and conjugate eye deviation toward the side of the infarct may also be found. All of these findings are present in the patient with a proximal trunk occlusion and variably present when branches of the middle cerebral artery are involved.

Posterior Cerebral Artery Syndrome

Infarcts in the posterior cerebral artery territory present with homonymous hemianopia secondary to visual cortex involvement. The patient is often unaware of the deficit until formally tested. Motor involvement is minimal, but sensory loss, including both light touch and pinprick, may be severe. There is no aphasia or disruption of nondominant hemisphere functions. Small branches of the posterior cerebral artery anastomose with branches of the anterior and middle cerebral arteries in border zones between the arterial distributions. These areas are at risk for *watershed infarcts* during periods of decreased blood flow.

Vertebrobasilar Artery Syndrome

The classic sign of brainstem stroke is the presence of crossed symptoms: Ipsilateral cranial nerve palsy and contralateral

hemiplegia. One of the most common strokes in this region is due to occlusion of the vertebral or posterior-inferior cerebellar artery, resulting in the *lateral medullary (Wallenberg) syndrome.* Patients may present with ipsilateral facial pain (described as a sharp or stabbing sensation to the face or eye), vertigo, headache, limb ataxia, Horner syndrome, and weakness of the soft palate, with dysphagia and dysphonia. Contralateral symptoms include loss of pinprick and temperature sensation in the arm and leg. Other brainstem syndromes may result in deafness, nausea, vomiting, vertigo, and diplopia.

Cerebellar Infarction

A subset of posterior circulation strokes involves the cerebellum. The most common initial symptom is the sudden inability to walk or stand. This may be followed by complaints of headache, nausea, vomiting, central vertigo, and, possibly, a stiff neck. Cranial nerve findings may also be present. Although the initial CT scan is often unremarkable, one-third of patients develop significant posterior fossa edema. In this confined space, edema produces pressure on the brainstem, causing a decrease in the level of consciousness, typically after a stable period of 6 to 12 hours. Pathologic respiratory patterns and pupillary dilation are late findings, indicating impending herniation. Recognition of cerebellar infarction is critical, and frequent neurologic assessment is imperative. Repeat CT scanning or magnetic resonance imaging (MRI) is indicated for patients with a declining level of consciousness. Surgical decompression and/or medical treatment of elevated intracranial pressure (ICP) may be lifesaving.

Lacunar Syndromes

Lacunar infarcts cause several distinct stroke syndromes. Lacunes are found almost exclusively in the basal ganglia, internal capsule, thalamus, and brainstem and are associated with hypertensive arteriopathy. Approximately 20% of patients with lacunar infarctions have had a prior TIA, and the onset of symptoms is often surprisingly

gradual (>36 hours in up to 30% of patients). Deficits often improve with time, and treatment is aimed at control of hypertension after the acute episode resolves. An evaluation for embolic sources should also be undertaken. Lacunar strokes are classified by clinical presentation.

The most frequent lacunar syndrome, *pure motor stroke,* causes paresis/paralysis of the face, arm, and leg. It is easily diagnosed when the deficit involves all three areas equally but may also present as a partial deficit. The location of the lacune may be in the internal capsule or pons. Cortical sensory deficits are notably absent.

Pure sensory stroke is the result of infarction of the ventral posterior nuclei of the thalamus and results in sensory loss in the face, arm, and leg. The patient may also complain of paresthesias involving the affected side. There is no hemiplegia or other cortical sign.

Patients with *clumsy hand–dysarthria syndrome* present with slurred speech and weakness and ataxia of the upper limb. Facial weakness may also be present. The syndrome is most commonly associated with lesions of the anterior limb and genu of the internal capsule and typically has a good functional outcome.

DIFFERENTIAL DIAGNOSIS

Table 155.1 lists conditions that may mimic ischemic stroke and is divided into structural and nonstructural diseases. Neuroimaging is used initially to evaluate these possibilities and to rule out structural causes of neurologic deficits.

TABLE 155.1
Differential Diagnosis of Ischemic Stroke

Structural Causes	Nonstructural Causes
Intracerebral hemorrhage	Meningitis
Epidural hematoma	Encephalitis
Subdural hematoma	Hypertensive encephalopathy
Intracranial tumor	Wernicke encephalopathy
Intracranial abscess	Hypoglycemia
	Complicated (hemiplegic) migraine
	Todd postictal paralysis
	Peripheral nerve palsy (Bell palsy)
	Labyrinthitis
	Ménière's disease
	Demyelinating disease (multiple sclerosis)
	Drug toxicity (phenytoin, lithium)

Diseases presenting with features similar to posterior circulation strokes can be difficult to distinguish from stroke. Wernicke encephalopathy presents as the triad of ophthalmoplegia, ataxia, and confusion and is found typically in chronic alcoholics. Ménière's disease, with its characteristic triad of vertigo, tinnitus, and deafness, occurs in patients between the ages of 30 and 60 and is paroxysmal in nature. Gross ataxia and other cranial nerve deficits should be absent. Multiple sclerosis typically presents in the third to fourth decades of life and has variable symptoms, depending on the location of demyelination. Symptoms of phenytoin and carbamazepine toxicity include sedation, nystagmus, vertigo, ataxia, and nausea. Central nervous system symptoms of acute lithium toxicity include confusion, hyperreflexia, tremors, and cranial nerve deficits; dysarthria also may be a prominent feature.

Special consideration should be given to stroke patients younger than 50 years of age or those who have pre-existing heart disease, hematologic disorders, or vasculitis. These patients typically fall into the cardioembolic, other, or unknown subtype classifications and may have reversible etiologies or other contributing disease states that should be identified as rapidly as possible. Conditions associated with each of these groups are listed in Table 155.2.

TABLE 155.2
Differential Diagnosis of Special Patient Groups with Ischemic Stroke

Condition	Comments
Young Adults with Stroke	
Arterial dissection	Age between 15 and 50 Accounts for 20% of strokes in the young, often preceded by minor trauma
Cardioembolism	Mitral valve prolapse, patent foramen ovale with paradoxical emboli, rheumatic heart disease
Premature atherosclerosis	Hyperlipidemia
Migrainous stroke	Female predominance
Air embolism	Scuba diving, medical procedures
Substance abuse	Heroin, cocaine, amphetamines, LSD
Pre-Existing Cardiac Disease	
Ischemic heart disease	Peripheral emboli from mural thrombus
Dysrhythmias	Atrial fibrillation, ventricular tachycardia, sick sinus syndrome, etc.
Valvular heart disease	Rheumatic heart disease, prosthetic valves
Dilated cardiomyopathies	Peripheral emboli from mural thrombus
Endocarditis	Associated fever and murmur
Hematologic Disorders	
Hyperviscosity syndromes	Cancer, myeloproliferative diseases, dysproteinemia, thalassemia, sickle cell disease, polycythemia
Coagulopathies	Disseminated intravascular coagulation, protein C or S deficiencies, antithrombin III deficiency, antiphospholipid antibody syndrome
Thrombotic thrombocytopenic purpura	Rare disorder with fever, microangiopathic hemolytic anemia, thrombocytopenia, neurologic and renal impairment
Vascular Disorders	
Infectious vasculitis	Herpes zoster, human immunodeficiency virus infection, syphilis, tuberculosis, aspergillosis
Noninfectious vasculitis	
Necrotizing	Polyarteritis nodosa
Nonnecrotizing	Giant cell arteritis (patients >age 50; females > males), Takayasu arteritis
Cerebral venous thrombosis	Presents with headache and papilledema; magnetic resonance imaging is diagnostic

ED EVALUATION

Like myocardial infarction, stroke is an acute disease necessitating early identification and treatment. Prehospital personnel should obtain information surrounding the onset of symptoms, and particularly noting the time deficits started ("last seen normal" time). Patients found lying immobile for prolonged periods are at risk for decubitus ulcers, dehydration, hypothermia or hyperthermia, and rhabdomyolysis. Intravenous access should be obtained and a fingerstick glucose level determined. In the prehospital phase, it is unusual for patients with ischemic stroke to have an altered level of consciousness; an altered sensorium suggests other etiologies. Glucose-containing solutions and routine administration of dextrose (D_{50}) should be avoided unless hypoglycemia is documented or strongly suspected. Narcan is generally not required unless there are historic features or pinpoint pupils, suggesting opiate ingestion.

On arrival in the ED, stroke patients require a monitored bed and rapid assessment of airway, breathing, and circulatory status. Complete vital signs should be obtained, including a core temperature. A focused physical examination should be performed, including a search for evidence of head trauma. The neck should be examined for meningeal signs present with either infection or subarachnoid hemorrhage (SAH). Auscultation for carotid bruits, particularly on the side opposite a clinical deficit, should be performed. The heart is examined for rate, regularity, and murmurs, searching for conditions predisposing to stroke, such as atrial fibrillation and mitral valvular disease. The extremities should be assessed for evidence of peripheral vascular disease or emboli and the skin examined for needle tracks or evidence of petechiae or ecchymosis, suggesting endocarditis, sepsis, or coagulopathy.

The neurologic examination should include a brief assessment of mental status, including level of consciousness, language, memory, and interpretation. A careful eye examination should follow, with testing of both visual acuity and visual fields. Pupillary size, reactivity, and extraocular movements provide information on brainstem function and cranial nerves III, IV, and VI. Anisocoria suggests a third nerve palsy, potentially from elevated ICP, and

should be investigated with a “swinging flashlight” test. Conjugate eye deviation toward the normal arm and leg suggests a hemispheric lesion, whereas deviation toward the paretic arm or leg suggests a brainstem lesion. Funduscopic examination of the retina may reveal papilledema, hypertensive changes, Hollenhorst plaques, diabetic changes, or Roth spots suggestive of specific stroke etiologies. Cranial nerves V and VII through XII may quickly be assessed by examining facial and corneal sensation; smiling symmetry, eyebrow raising, and forehead wrinkling; gross auditory acuity; gag reflex; shoulder shrug (trapezius strength); head rotation against resistance (sternocleidomastoid strength); and tongue protrusion, respectively.

Motor strength and tone should be assessed in both proximal and distal muscle groups. Pronator drift is a sensitive indicator of upper extremity weakness.

The sensory examination is the most subjective part of the neurologic examination and should be interpreted in view of the patient’s ability to cooperate and the overall examination. Double simultaneous extinction is tested at this time, particularly if visual field deficits were identified. The ability of a patient to identify, by touch, common objects such as keys or pens (stereognosis) and to identify a number drawn on the skin surface (graphesthesia) is an easy test of sensory function done in the ED.

Cerebellar function can be assessed by finger-to-nose and heel-to-shin tests; these are particularly useful with the bedridden patient. Important reflex arcs to test include the biceps (C5, C6), triceps (C6, C7, C8), patellar (L2, L3, L4), and Achilles (L5, S1), and pathologic reflexes. Asymmetry of deep tendon reflexes or a unilateral Babinski sign may indicate corticospinal tract lesions.

Assessment of station and gait is one of the most revealing parts of the neurologic examination. Subtle weakness, ataxia, rigidity, and sensory defects can be identified by observation of the gait, toe walking, heel walking, tandem walking, and Romberg tests.

KEY TESTING

All patients:

- Noncontrast brain CT or brain MRI

- Blood glucose
- Oxygen saturation
- Serum electrolytes/renal function tests
- Complete blood count, including platelet count
- Cardiac enzymes
- Coagulation studies (prothrombin time/INR/activated partial thromboplastin time)
- EKG

Selected patients:

- Thrombin time and/or ecarin clotting time if patient suspected of taking direct thrombin inhibitors or factor Xa inhibitors
- Liver function tests
- Toxicology screens
- Blood–alcohol level
- Blood cultures (if febrile, or infectious etiology suspected)
- Serum creatine phosphokinase and/or urine myoglobin (if rhabdomyolysis suspected)
- Pregnancy test
- Arterial blood gas
- Chest x-ray (if pulmonary disease suspected)
- Lumbar puncture (if SAH is suspected and CT scan is negative)
- Electroencephalogram (if seizures suspected)

Noncontrast CT imaging will provide the information necessary for most emergent treatment decisions. An ischemic stroke does not become hypodense for 6 to 72 hours after vessel occlusion and is often not visible on initial CT evaluation. If CT scanning is unavailable, the patient should be stabilized and transferred as rapidly as possible to a facility with CT capability.

Multimodal CT (combining noncontrast brain CT with CT angiography and/or CT perfusion mapping) provides further vascular and tissue information and can enhance both diagnostic and management decisions. Disadvantages include an increased time to image acquisition and interpretation, the use of iodinated contrast, and additional radiation exposure. Multimodal MRI also provides enhanced information but typically plays a more limited role in the

acute evaluation of most patients with stroke. Limitations include availability, patient cooperation, and contraindications to the procedure because of metallic foreign bodies or devices. Though their exact role in acute stroke care has yet to be defined, computed tomography angiography and magnetic resonance arteriography (MRA) may be of particular benefit in evaluating the patient with suspected carotid or vertebrobasilar artery dissection.

ED MANAGEMENT

The primary goal of acute stroke management is to reverse the clinical deficit by reestablishing cerebral blood flow, if possible. Patients who present within 3 hours of symptom onset are the most likely to benefit from intravenous recombinant tissue plasminogen activator (r-TPA, alteplase) and eligible patients should be treated (9,10). Data also support the use of intravenous r-TPA in selected patients who can be treated within 4.5 hours of symptom onset, though this indication does not have FDA approval (11).

Intravenous Thrombolytic Therapy

The American College of Emergency Physicians, American Academy of Neurology, and American Heart Association support the use of r-TPA (alteplase) in eligible patients. The NIH/NINDS Stroke Study found that r-TPA-treated stroke patients were at least 30% more likely to have minimal or no disability 3 months after the event, compared with those who received placebo (absolute increase in favorable outcome, 11% to 13%). Although treated patients had a symptomatic intracranial hemorrhage rate of 6.4% (vs. 0.6% for placebo), there was no significant difference in mortality at 3 months (17% r-TPA, 21% placebo) (12). Post hoc analyses do not support withholding therapy from any patient on the basis of suspected stroke subtype, age, clinical deficit, or CT findings of early ischemic changes.

Data also demonstrate the safety of community delivery of r-TPA in stroke. In a study of Michigan community hospitals, 557 stroke patients received intravenous r-TPA in the emergency department.

The symptomatic intracerebral hemorrhage (ICH) rate was equivalent to the NINDS study (12).

The development of treatment guidelines for stroke may improve patient selection and speed the delivery of thrombolytics to appropriate patients. The National Institutes of Health recommends a target "door-to-needle" time for eligible r-TPA patients of 60 minutes.

Table 155.3 outlines inclusion and exclusion criteria for the use of intravenous r-TPA in acute stroke. Eligible patients should be treated with 0.9 mg/kg of r-TPA (maximum dose, 90 mg), with 10% given as a bolus over 1 to 2 minutes and the remainder given over 60 minutes via infusion pump. Administration of r-TPA between 3 and 4.5 hours after stroke onset may be considered for patients meeting the additional criteria listed in Table 155.3 (11). Table 155.4 presents posttreatment blood pressure control guidelines. An algorithm for the management of suspected intracranial hemorrhage secondary to thrombolytic therapy is shown in Figure 155.1.

TABLE 155.3
Intravenous r-TPA in Ischemic Stroke: Inclusion and Exclusion Criteria

Inclusion Criteria

1. Age 18 or older
2. Clinical diagnosis of ischemic stroke
3. Time of onset well established to be <180 min before treatment would begin. *"Time of onset" of stroke is defined as that point at which a change in the baseline neurologic function occurred. If that time is not known (e.g., the patient awakens from sleep with new symptoms), the last time the patient was observed to be neurologically intact* must *be considered to be the time of onset.*

Exclusion Criteria

1. Significant head trauma in prior 3 months
2. History of prior stroke within 3 months
3. Symptoms suggestive of subarachnoid hemorrhage
4. Arterial puncture at noncompressible site in prior 7 days
5. History of prior intracranial hemorrhage
6. Intracranial neoplasm, arteriovenous malformation, or aneurysm
7. Recent intracranial or spinal surgery
8. Recent lumbar puncture (within previous 7 days)
9. Elevated blood pressure (systolic > 185 mm Hg or diastolic > 110 mm Hg)[a]
10. Blood glucose concentration < 50 mg/dL (2.7 mmol/L)
11. CT demonstrates multilobar infarction (hypodensity involving >1/3 of the cerebral hemisphere)
12. Active internal bleeding
13. Acute bleeding diathesis, including but not limited to:
14. Platelet count <100,000/mm^3
15. Heparin administered within 48 h with an abnormal activated partial thromboplastin time (aPTT)[b]
16. Current use of anticoagulant with INR >1.7 or PT >15 s[b]
17. Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, ECT [ecarin clotting time], TT [thrombin time], or factor Xa activity assay)

Relative Exclusion Criteria

Experience indicates under some circumstances patients may receive fibrinolytic therapy despite having relative contraindications. Consider risk to benefit carefully if any of these relative contraindications are present as well as consulting a stroke specialist.

1. Only minor or rapidly improving stroke symptoms
2. Pregnancy
3. Seizure at onset with postictal residual neurologic impairment
4. Major surgery or serious trauma within previous 14 d
5. Recent gastrointestinal or urinary tract hemorrhage (within previous 21 d)
6. Recent acute myocardial infarction (within previous 3 mos)

Additional Exclusion Criteria for Treatment between 3 and 4.5 h of onset

1. Age >80 yrs
2. Severe stroke (NIHSS >25)
3. Taking oral anticoagulant, regardless of INR
4. History of both diabetes and a prior stroke

[a]Hypertension may be treated with labetalol 10–20 mg IV over 1–2 min (may repeat × 1) or nicardipine infusion and TPA initiated if reduction to above levels occurs. More aggressive treatment to reduce blood pressure excludes the patient from treatment with TPA.

[b]In patients without a history of recent oral anticoagulants or heparin use treatment with r-TPA can be initiated before the availability of coagulation study results, but should be discontinued if either the PT is >15 s or INR >1.7 or the PTT is elevated.

Adapted from: Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke r-TPA Stroke Study Group. *N Engl J Med*. 1995;333(24):1581–1587; Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(3):870–947; Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359(13):1317–1329.

TABLE 155.4
Post r-TPA Blood Pressure Management in Acute Stroke

1. Monitor BP every 15 min
2. If systolic BP is 180–230 mm Hg or diastolic BP 105–120 mm Hg, give labetalol 10 mg IV over 1–2 min followed by an infusion at a rate of 2–8 mg/min; or
3. Nicardipine 5 mg/h IV, titrate to effect by increasing/decreasing 2.5 mg/h every 5–15 min, maximum 15 mg/h
4. If blood pressure not controlled, consider sodium nitroprusside infusion

Adapted from: Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(3):870–947.

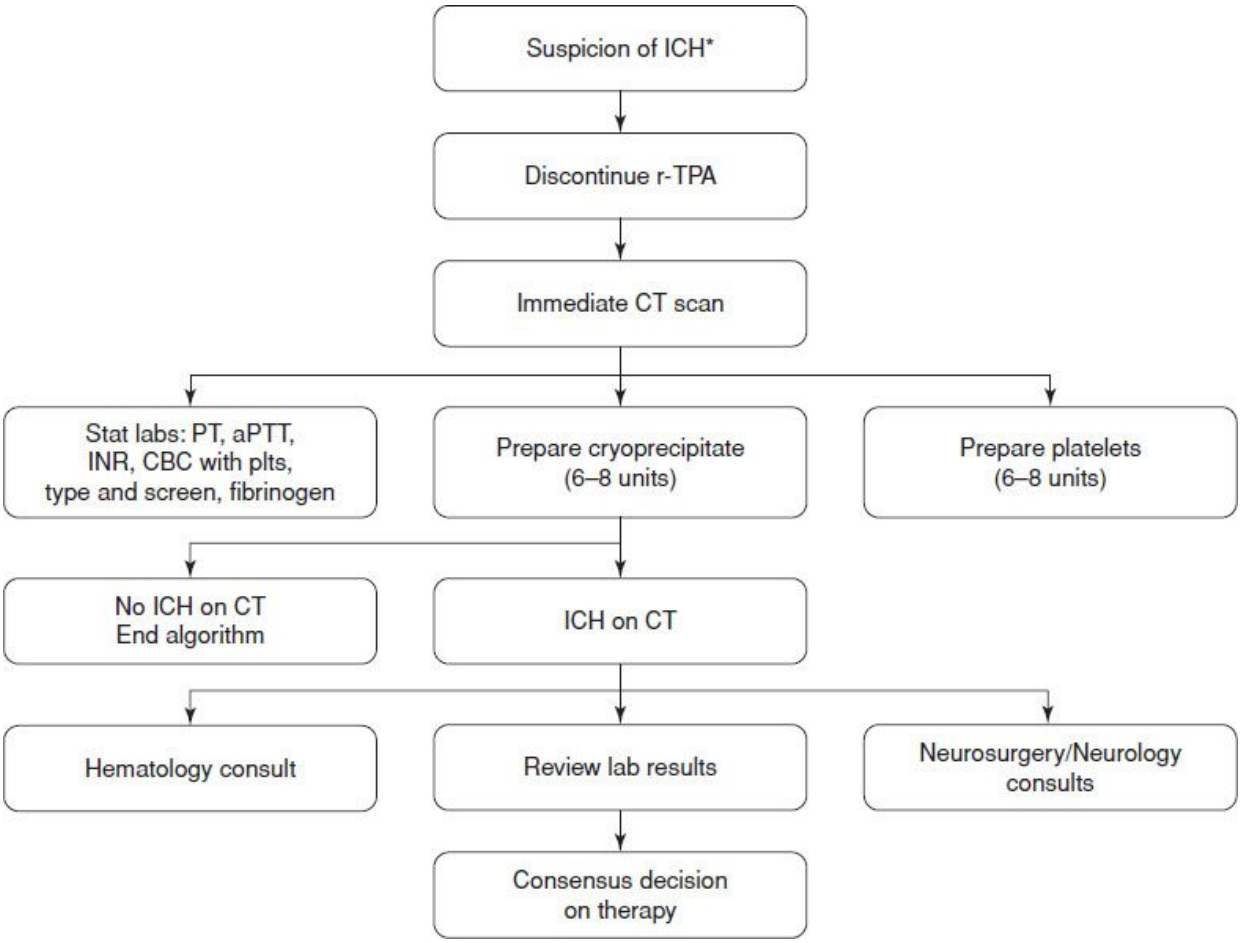

FIGURE 155.1 Management of suspected intracranial hemorrhage after r-TPA use. *Symptoms include neurologic deterioration, headache, acute hypertension, nausea, vomiting.

The development of institution-specific evaluation and treatment guidelines is recommended to identify local responsibilities concerning thrombolytic delivery and posttreatment care and disposition. A multidisciplinary approach will deliver the highest level of care in a time-critical setting.

Endovascular Therapy

Intra-arterial thrombolysis or mechanical reperfusion are potential considerations for patients who are ineligible for intravenous thrombolytic therapy (due to late presentation >4.5 hours from symptom onset or other reasons) presenting within 6 to 8 hours of

symptom onset (13,14). Their exact role, however, is unclear. Two recent trials found no clinical improvement using endovascular therapy compared to standard intravenous r-TPA alone (15,16). The use of advance neuroimaging to select stroke patients with favorable penumbral patterns for mechanical embolectomy using the Merci Retriever or Penumbra System also failed to demonstrate superiority of those devices over standard treatment (17). Technology in this area is rapidly advancing and decisions regarding endovascular treatment should be made with qualified specialists, preferably within the context of a clinical trial.

In patients who are ineligible for reperfusion strategies, no acute intervention has proven effective in improving functional outcome. The objective of treatment is then to limit infarct extension and recurrence. Current approaches to preventing or minimizing infarct extension include maintenance of adequate cardiac output to preserve cerebral blood flow, regulation of core temperature, and control of the blood glucose level. Strategies to prevent recurrent infarction focus on antiplatelet and anticoagulation therapy.

Hypertension Management

Acute elevations of blood pressure typically decline, without treatment, within a few days to prestroke levels. Because the benefit of blood pressure control is unproved, it is reasonable to avoid treating hypertension in the absence of specific indications such as thrombolytic therapy for acute stroke, AMI, hypertensive encephalopathy, arterial dissection, and hemorrhagic transformation. Although no data exist to define the point of treatment for severe isolated hypertension in stroke, there is consensus that antihypertensive agents should be withheld unless the blood pressure exceeds 220/120 mm Hg.

In stroke patients who are not eligible for r-TPA and who require antihypertensive therapy, the goal is a gradual reduction of blood pressure by about 15%. No data are available to guide selection of medications for the lowering of blood pressure in this setting. Reasonable initial agents include labetalol, 10 to 20 mg IV over 1 to 2 minutes, repeated or doubled every 10 minutes (maximum dose,

300 mg) or nicardipine, 5 mg/h IV infusion as initial dose; titrated to desired effect by increasing 2.5 mg/h every 5 minutes to maximum of 15 mg/h. For patients with DBP >140 mm Hg, consider a sodium nitroprusside infusion, 0.5 μg/kg/min IV as initial dose with continuous blood pressure monitoring and titration. The use of antihypertensive agents requires frequent neurologic checks so that treatment may be discontinued if there is neurologic deterioration (10).

Volume Management

Maintenance of intravascular volume is important in optimizing cardiac output in stroke patients. These patients are often unable to maintain adequate oral intake, and up to one-third may be significantly hypovolemic. Volume deficits should be corrected as rapidly as possible and followed by maintenance fluids. Avoidance of hypoosmolar solution is recommended to prevent exacerbation of cerebral edema. Aggressive hypervolemic therapy to increase cerebral blood flow should be avoided because it does not improve outcome and may contribute to cerebral edema. Hemodilution has also not been proven to alter stroke outcome and cannot be recommended.

Temperature Regulation

Temperature regulation of the ischemic stroke patient is often neglected in the ED. Experimentally, hypothermia has a protective effect on ischemic neurons, whereas hyperthermia may worsen damage by increasing cellular metabolic demand. Fever is not uncommon in stroke patients and should be promptly treated.

Glucose Regulation

Because the optimal glucose level after stroke is unknown, it is reasonable to treat excessive levels (possibly beginning at levels of 140 to 180 mg/dL) with insulin. Close monitoring of glucose levels with adjustment of therapy is recommended (10). Hypoglycemia should be promptly corrected.

Anticoagulation

In patients with ischemic stroke, early anticoagulation has no proven benefit and is associated with an increased risk of serious bleeding complications and hemorrhagic transformation of the infarct. No well controlled, randomized, clinical trial has demonstrated a benefit from anticoagulation even in potentially high-risk groups: Patients with intracardiac or intra-arterial thrombi, vertebrobasilar disease, or arterial dissection. Therefore, emergent anticoagulation to improve neurologic outcome or prevent early recurrent stroke is not recommended (10). Given the lack of evidence and the potential risks, consultation is recommended prior to anticoagulation initiation in stroke. All anticoagulants should be withheld for 24 hours after the use of r-TPA in acute stroke.

Antiplatelet Therapy

Antiplatelet therapy is a cornerstone of stroke management and reflects the central role of platelet activation in clot formation. The use of aspirin in patients with a previous mild stroke or TIA results in a 20% reduction in stroke risk. In patients treated within 48 hours of stroke onset with 300 mg of aspirin daily, there was a statistically significant reduction in recurrent ischemic stroke at 14 days, with no increase in risk of hemorrhagic stroke (18). Initiation of aspirin therapy (initial dose 325 mg) is recommended in patients who are not treated with thrombolytic therapy and do not have aspirin sensitivities or swallowing difficulty. The combination of clopidogrel (Plavix) and aspirin proved superior to aspirin alone in reducing the 90-day incidence of stroke (8.2% vs. 11.7%) in a Chinese study of patients with acute TIA or minor stroke (NIH stroke scale <3) (6) (Fig. 155.2). Data on non-Chinese populations is not yet available.

UPMC | *Stroke Institute*

NIH STROKE SCALE

Name _____

1A. LEVEL OF CONSCIOUSNESS:	1B. LOC QUESTIONS:	1C. LOC COMMANDS:
	Ask the month and his/her age.	Open and close the eyes. Open and close the non-paretic hand.
0 = Alert 1 = Not alert, but arousable 2 = Not alert, obtunded. 3 = coma.	0 = Answers both correctly. 1 = Answers one correctly. 2 = Answers neither correctly.	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.
2. BEST GAZE (HORIZONTAL):	**3. VISUAL FIELDS:**	**4. FACIAL PALSY:**
0 = Normal. 1 = Partial gaze palsy. 2 = Forced deviation, or total gaze paresis	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia	0 = Normal 1 = Minor paralysis 2 = Partial paralysis (total or near total paralysis of lower face). 3 = Complete paralysis of upper and lower face
5. MOTOR ARM:	**6. MOTOR LEG:**	**7. LIMB ATAXIA:**
Right Arm extended with palms down 90 degrees (if sitting) or 45 degrees (if supine) for 10 seconds. 0 = No drift. 1 = Drift. Limb drifts down from position, and does not hit bed or support in 10 sec. 2 = Some effort against gravity. 3 = No effort against gravity. 4 = No movement. ***Left***	***Right*** Leg extended at 30 degrees always tested supine for 5 seconds. 0 = No drift. 1 = Drift. Limb drifts down from position, and does not hit bed or support in 5 sec. 2 = Some effort against gravity. 3 = No effort against gravity. 4 = No movement. ***Left***	The finger–nose–finger and heel–shin tests. 0 = Absent. 1 = Present in one limb. 2 = Present in two limbs.
8. SENSORY:	**9. BEST LANGUAGE:**	**10. DYSARTHRIA:**
to pinprick or noxious stimuli 0 = Normal. 1 = Mild to moderate sensory loss. 2 = Severe to total sensory loss.	0 = No aphasia, normal. 1 = Mild to moderate aphasia. 2 = Severe aphasia. 3 = Mute, global aphasia, coma.	0 = Normal. 1 = Mild to moderate;. 2 = Severe (including mute/anarthric due to aphasia). Do not score if intubated.
11. EXTINCTION AND INATTENTION:		
0 = No abnormality. 1 = Present. 2 = Profound (2 modalities).		**TOTAL SCORE:**

Date _____ Time _____

Examiner _____ Signature _____

SYS326310 JKW/AL CP SM 01/08

FIGURE 155.2 NIH Stroke Scale. (Courtesy of UPMC Stroke Institute with permission.)

CRITICAL INTERVENTIONS

- Obtain an emergent CT scan.
- Initiate aspirin therapy for nonhemorrhagic ischemic strokes that are not eligible for TPA and do not have swallowing difficulties.
- Identify patients eligible for thrombolytic therapy and expedite their diagnostic evaluation and treatment.
- Correct hyperthermia.

DISPOSITION

Factors influencing disposition in the patient with ischemic stroke include infarct location, time of symptom onset, infarct size, stroke etiology, concurrent medical conditions, and social resources available to the patient. The vast majority of stroke patients are admitted to the hospital, often to a specialized unit or floor skilled in the care of patients with neurologic deficits. Cardiac monitoring is recommended to assess for atrial fibrillation and other arrhythmias.

Patients with minor, completed strokes are potential candidates for evaluation in an ED clinical decision unit. Predefined protocols for neurologic consultation, subsequent neurologic and vascular imaging, and initiation of therapy to prevent recurrent stroke in this setting speed patient care and reduce length of hospital stay.

Common Pitfalls

- Failure to perform a complete history and physical examination, particularly in uncooperative elderly patients. The history and physical examination are the basis for determining the extent of a stroke and its etiology.
- Failure to consider unusual etiologies of stroke, such as arterial dissection and emboli, in younger patients with new neurologic deficits.
- Misdiagnosis of cerebellar stroke as alcohol or drug intoxication, labyrinthitis, benign positional vertigo, or severe gastroenteritis,

and failure to obtain neurosurgical consultation.
- Failure to optimize cardiac output and to treat temperature elevations in the ED.
- Overly aggressive blood pressure management. Reduction of blood pressure may reduce cerebral blood flow and lead to extension of an ischemic stroke.
- Initiation of anticoagulation in patients with acute stroke prior to consultation.

Patients treated with r-TPA and those with impaired gag or swallowing reflexes or mental status changes should be admitted to the intensive care unit or a specialized stroke unit. Similar admission is also indicated for patients with cerebellar strokes and should be considered for patients with large hemispheric strokes who are at risk for the development of cerebral edema.

Stroke patients are often cared for in the inpatient setting without neurologic consultation. Neurologic consultation in the ED is indicated when the diagnosis is unclear or when further evaluation is required (e.g., arterial dissection, migrainous infarct, unusual hematologic conditions). Patients with cerebellar infarction should have neurosurgical consultation, because decompressive craniectomy may be lifesaving in selected patients.

HEMORRHAGIC CEREBROVASCULAR DISEASE

ICH, defined as hemorrhage directly into the brain parenchyma, affects 10% to 15% of all stroke patients. Major risk factors for intracranial hemorrhage include advanced age, hypertension, and race. Blacks have a higher incidence of ICH than do whites; other risk factors include cigarette smoking and alcohol use.

The most common site for ICH is the putamen, which accounts for 35% to 50% of all hemorrhages. Next in frequency are the subcortical white matter (30%), the cerebellum (16%), the thalamus (10% to 15%), and the pons (5% to 12%) (11). Pathologically, these are areas of the brain supplied by small arteries that are 50 to 200 μm in size.

CLINICAL PRESENTATION

The onset of ICH is usually heralded by a sudden headache, vomiting, and neurologic deficit. Many patients exhibit a decreased level of consciousness owing to ICP. ICH often occurs during activity and only rarely has its onset during sleep. In one-third of cases, clinical deficits are maximal at onset. In the remaining two-thirds, the symptoms follow a steadily progressive course over the first 30 minutes. Coma is a poor prognostic sign and is associated with larger hemorrhages and ventricular extension. Headache and vomiting are typically absent in ischemic strokes and thus are of help in identifying patients with ICH. Early seizures are uncommon in ICH involving the putamen, thalamus, and pons but may be present in up to one-third of patients with subcortical white matter ("lobar") hemorrhages. Hypertension is noted in more than 90% of patients with ICH.

The clinical deficits are related to the location and size of the hemorrhage. Putaminal hemorrhages cause a dense contralateral hemiplegia with sensory loss and homonymous hemianopia. The eyes show conjugate deviation away from the paralyzed side, which may overcome with caloric testing or doll's-eye reflex testing. Thalamic hemorrhages cause similar motor and sensory findings but may also cause conjugate downward gaze with pinpoint, unresponsive pupils. Deficits from a lobar hemorrhage depend on the size and location of the hemorrhage. Pontine hemorrhage typically causes a severe occipital headache, followed rapidly by a decreased level of consciousness; coma is present in 80% of patients. Patients may become hyperthermic and may have severe neurologic deficits. These include quadriplegia, loss of corneal reflexes, and pinpoint pupils with absent horizontal eye movements on caloric or doll's-eye reflex testing. Cerebellar hemorrhage causes extremity and truncal ataxia and an inability to walk. These symptoms are commonly accompanied by vomiting, disequilibrium, and headache. An ipsilateral gaze palsy may also be present. Patients with cerebellar hemorrhage may initially appear stable but can deteriorate rapidly to coma and death.

DIFFERENTIAL DIAGNOSIS

The presence of intracerebral blood on head CT should not automatically be ascribed to a hypertensive hemorrhage. Various nonhypertensive causes of ICH include arteriovenous malformation, berry aneurysm, sympathomimetic drug use, intracranial tumor, use of anticoagulant and thrombolytic agents, hematologic disorders (e.g., leukemia, thrombotic thrombocytopenic purpura, hemophilia), cerebral vasculitis, and mycotic aneurysm.

ED EVALUATION

The evaluation of patients with suspected ICH is similar to that for ischemic stroke. However, patients with ICH may exhibit rapid neurologic deterioration and a decreased level of consciousness, necessitating acute airway intervention. Vital signs should be monitored closely, and frequent neurologic assessments are required. A general physical examination should be completed in addition to a rapid and thorough neurologic examination. Use of structured examination tools including the NIH Stroke Scale (Fig. 155.2) can provide easy quantification of deficits to allow serial comparisons over time and enhance communication between medical providers. The Glasgow Coma Score is a good predictor of long-term outcome.

KEY TESTING

- Additional investigations in the patient with suspected or confirmed ICH are identical to the Key Testing recommended for Ischemic Stroke.
- Laboratory data should be obtained to help identify possible contributing causes, such as coagulopathy, thrombocytopenia, or platelet dysfunction.
- Toxicologic screening is indicated for patients with atypical presentations and for younger patients without a history of hypertension.

ED MANAGEMENT

The goals of emergency care for ICH are rapid diagnosis, management of the airway, correction of coagulation deficiencies, control of ICP, and early neurosurgical consultation. Oxygen should be administered to maintain oxygen saturation as needed. Intubation is indicated for airway protection or hyperventilation to reduce ICP. Rapid sequence intubation with paralytic agents may be necessary to obtain adequate CT images in a combative patient.

Patients on warfarin should have their warfarin held, undergo replacement of vitamin K–dependent factors to correct the INR, and receive intravenous vitamin K. Prothrombin complex concentrates (PCCs) have not demonstrated improved clinical outcomes compared to traditional fresh frozen plasma (FFP) but have advantages of speed of administration, smaller volume, and reduces risk of infectious disease transmission, and are increasingly recommended for warfarin reversal. Recombinant factor VIIa can limit the extent of hematoma expansion in noncoagulopathic ICH patients but increases the risk of thromboembolic events and has no clear clinical benefit (19). It does not replace all clotting factors and is not recommended as the sole reversal agent for warfarin-associated hemorrhage (20).

Recommendations for the optimum reversal strategy of newer oral direct thrombin inhibitors and factor Xa inhibitors are problematic, as no direct antidote is available and only limited data exists on effective reversal strategies. The best data at this time suggest that PCCs might be useful. Emergent consultation with local coagulation specialists is reasonable in this rapidly changing area.

Hyperglycemia should be avoided, and maintenance of normoglycemia is recommended.

Prophylactic anticonvulsant medication should not be used, though patients with clinical seizures or evidence of seizure on EEG should be treated with antiepileptic drugs (20).

Management of hypertension in the patient with ICH is also rapidly evolving. Data from the international INTERACT2 trial demonstrated safety in targeting acute blood pressure reduction to 140 mm Hg—with a trend toward reducing death or severe disability —in patients with spontaneous ICH with elevated systolic blood pressures (21). A North American trial (ATACH II) is currently

underway. Useful antihypertensive agents in the setting of ICH include nitroprusside, esmolol, labetalol, nicardipine, enalapril, hydralazine, and nitroglycerine.

Data regarding ICP control in patients with ICH is very limited. ICH patients with a GCS score of ≤ 8, clinical evidence of herniation, or those with significant intraventricular hemorrhage or hydrocephalus might be considered for ICP monitoring and treatment. Elevations in ICP, defined as readings ≤ 20 mm Hg for 5 minutes, may present as a decreasing level of consciousness and/or neurologic deterioration. Initial management options include elevation of the head (30 degrees), osmotherapy, and hyperventilation. Osmotherapy options include mannitol (20% solution; 1 g/kg bolus) and hypertonic saline (250 cc of 7.5% saline). Target serum osmolality has been recommended to be 300 to 320 mOsm/kg, although definitive data are lacking (20).

Reduction of the pCO_2 to 30 to 35 mm Hg lowers ICP by 25% to 30% in most patients, though peak ICP reduction may be delayed up to 30 minutes after the pCO_2 is changed. Because hypocarbia causes cerebral vasoconstriction, overaggressive reduction in pCO_2 may reduce cerebral blood flow below critical values and should thus be avoided.

In general, ICP monitoring is indicated in patients whose condition is thought to be deteriorating owing to increases in ICP. Other patients may warrant ICP monitors, however, particularly those with intraventricular hemorrhage. Placement of an intraventricular catheter offers the potential for direct removal of cerebrospinal fluid and reduction of ICP.

Neurosurgical consultation should be obtained early and, if unavailable, the patient should be stabilized and transferred. The indications for hematoma evacuation depend on many factors, including patient age, hemorrhage location and size, and surgical accessibility. Patients who present initially with coma or loss of brainstem function generally do not benefit from surgical evacuation, whereas those who experience progressive deterioration after a lobar hemorrhage are often operated on. In patients with cerebellar hemorrhage, surgical evacuation as soon as possible is recommended

for patients who are deteriorating neurologically or have brainstem compression and/or hydrocephalus.

CRITICAL INTERVENTIONS

- Protect the airway.
- Correction of abnormal coagulation.
- Manage elevated ICP.
- Obtain neurosurgical consultation.

DISPOSITION

All patients with ICH should be admitted for close observation and monitoring. Typically, intensive care unit monitoring is required. If neurosurgical treatment capabilities are not available locally, arrangements should be made to transfer the patient.

Common Pitfalls

- Failure to diagnose cerebellar hemorrhage. Patients may be misdiagnosed with acute viral syndrome, labyrinthitis, or intoxication. Surgical intervention may be lifesaving.
- Delay in transport. Patients with ICH require early neurosurgical consultation and should be transported to an appropriate facility if immediate neurosurgical attention is not otherwise available.

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CHAPTER 156

Seizures

Andy Jagoda

Seizures are both a primary problem and a result of an underlying disorder. They account for an estimated 1% to 2% of emergency department (ED) visits. Two to 4 million Americans have epilepsy, a condition of recurrent unprovoked seizures.

Seizures result from excessive and disorderly neuronal discharge in the cerebral cortex. Epilepsy is a condition of unprovoked seizures, whereas an underlying pathologic process provokes other seizures. The clinical manifestations of a seizure reflect the area of the brain in which neurons are discharging abnormally. Seizure discharges and symptoms may be focal or may be generalized to both hemispheres. The clinical spectrum of seizures includes focal or generalized motor activity, altered mental status, sensory or psychic experiences, or autonomic disturbances.

Ictus refers to the period during which a seizure occurs. An aura, or "warning," represents the beginning of a partial seizure, which can remain focal or can spread into a generalized event; a corollary is that patients with a primary generalized seizure (affecting both hemispheres without a focus) disorder do not have an aura. The period after a seizure but before the patient returns to baseline mental status is called the postictal period.

An acute symptomatic seizure, also referred to as a provoked seizure, is a seizure that occurs within 7 days of an acute CNS or systemic event, for example, stroke, hypoglycemia, head trauma. A remote symptomatic seizure is a seizure that occurs more than 7 days from an inciting event.

Status epilepticus (SE) is broadly defined as prolonged seizure activity with a high morbidity and mortality. Time definitions are changing for SE: It had been defined as seizures that last >30 minutes or in which there are recurrent seizures without a return to baseline mental status between events. Currently some researchers define SE as a seizure that lasts 5 to 10 minutes or two seizures without full recovery between them (1,2). The longer a seizure lasts the more neuron injury occurs, and the more difficult it is to stop the seizure activity. There are a projected 125,000 to 200,000 cases of SE each year in the United States, with an overall mortality of 22%. There is a bimodal distribution of cases, with the highest incidence occurring in the first year of life and after the age of 60 years. More than one-half of patients presenting to the ED in SE have no prior seizure history.

CLINICAL PRESENTATION

The classification of seizures (Table 156.1) is based on the behavioral, electrophysiologic, and clinical features of the event rather than on pathophysiologic mechanisms or anatomic localization. Seizures can be broadly divided into primary generalized seizures and partial seizures (also called focal seizures). Primary generalized seizures do not have an inciting focus but begin bilaterally in both hemispheres of the cerebral cortex. Partial seizures begin in a localized area of the brain; they may remain focal but can also spread to incorporate both hemispheres, in which case, the seizure is termed *secondary generalized.* Among the types of new onset seizures in adults, partial seizures are more common than primary generalized seizures (3).

TABLE 156.1
Classification of Seizures

Partial Seizures

A. Simple partial
   1. Motor
   2. Somatosensory
   3. Autonomic
   4. Psychic
B. Complex partial
C. Secondary generalized

Generalized Seizures

A. Nonconvulsive (absence)
B. Convulsive
   1. Tonic clonic
   2. Clonic
   3. Tonic
   4. Myoclonic
   5. Atonic

Status Epilepticus

A. Convulsive generalized
B. Convulsive focal
C. Nonconvulsive

There are six types of generalized seizures (Table 156.1); five have convulsive activity, and one has nonconvulsive activity (absence seizure). All primary generalized seizures, except myoclonic seizures, are associated with an altered level of consciousness. Generalized convulsive seizures classically begin as myoclonic jerks followed by loss of consciousness and sustained generalized skeletal muscle contractions. The seizure activity lasts 90 to 120 seconds and may be associated with urinary incontinence and tongue biting. The convulsive seizure is followed by the postictal state characterized by a brief period of confusion and somnolence. It is not possible to have a bilateral tonic–clonic event with preservation of mental status. This fact can be helpful at times in distinguishing neurogenic seizures from psychogenic seizures.

Absence seizures are primary generalized events causing an alteration in mental status without significant motor activity. Patients have short episodes of sudden immobility and a blank stare. Absence seizures are more frequent between the ages of 5 and 10 years and are infrequent after the midteens. The average duration is 10 seconds, and there is rarely a postictal period.

Partial seizures are subdivided according to associated impairment of consciousness. Simple partial seizures have brief sensory or motor manifestations with no impairment of consciousness and are categorized according to clinical presentation (Table 156.1). Partial seizures that cause an impairment of consciousness are termed

complex partial seizures. These seizures have been known as temporal lobe or psychomotor seizures and are characterized by mental and psychological symptoms including changes in effect, confusion, or hallucinations. Partial seizures that evolve to generalized seizures are associated with altered consciousness just as other generalized seizures.

When a patient arrives to the ED with a generalized seizure or postictal, it can be difficult to differentiate between a primary generalized seizure and a secondary generalized partial seizure. A careful history can elicit a preceding symptom such as an aura, focal movement abnormality, or even staring behavior leading to a diagnosis of partial seizure that has generalized. A focal finding on computed tomography (CT) scan suggests a partial seizure that has secondarily generalized.

Seizures may have harmful secondary traumatic or metabolic consequences. Seizures may result in a fall or a motor vehicle accident. The convulsive movements of a seizure may result in injury from direct trauma to head, trunk, or limbs. There is typically a period of transient apnea and hypoxia, the duration of which varies with the duration of seizure activity. There is an increase in blood pressure, serum lactate and serum glucose levels, and white blood cell (WBC) count without a left shift. Body temperature is frequently elevated. Lactic acidosis occurs within 60 seconds of a convulsive event and normalizes within 1 hour. A transient cerebrospinal fluid pleocytosis of up to 20 WBC/μL has been reported to occur in 2% to 23% of seizure patients (Table 156.2).

TABLE 156.2
Physiologic and Systemic Consequences of Convulsive Seizures

Physiologic	Systemic
Hyperthermia	Central nervous system edema
Acidosis	Pulmonary edema
Hypoglycemia/hyperglycemia	Hypertension followed by hypotension
Hypoxia	Dysrhythmias
Acidosis	Rhabdomyolysis
Leukocytosis	Disseminated intravascular coagulation
Cerebrospinal fluid pleocytosis	Fractures/dislocations

DIFFERENTIAL DIAGNOSIS

Seizure Mimics

Some nonseizure conditions can mimic seizures. Such conditions include syncope, dysrhythmia, migraine, vertigo, sleep disorders, decerebrate posturing, drug reactions, tetanus, strychnine poisoning, and psychogenic events. Other, less common, seizure mimics include narcolepsy, hyperventilation syndrome, and dystonic reactions. A detailed history and physical can usually differentiate among these conditions.

Syncope can be associated with occasional twitching movements, which can be misdiagnosed as a seizure and can be called convulsive syncope. Full tonic–clonic movements, tongue biting, and postictal amnesia have not been commonly described in convulsive syncope. When put in the context of when and where the event occurred, the length of event, and the type of movements, convulsive syncope can usually be reliably differentiated from seizure.

Migraine with an aura can be confused with nonconvulsive seizures. This is compounded by the finding that many migraine patients have abnormal electroencephalograms (EEGs). Basilar migraine can result in loss of consciousness, making the differentiation even more difficult.

Psychogenic seizures, referred to as pseudoseizures, are functional events with a clinical presentation mimicking neurogenic seizures, with no corresponding alteration in EEG activity. These events are often conversion reactions and not under the patient's conscious control. Up to 30% of patients referred to epilepsy clinics are diagnosed with psychogenic seizures with a mean delay from onset

of events to diagnosis of 7.2 years (4). Psychogenic seizures often last longer than neurogenic events, and there usually is not a postictal period. Patients can often recall events during the seizure, have not been incontinent, and do not incur physical injury. Psychogenic seizures are classically manifested by forward-thrusting pelvic movements and head turning from side to side (4). Several maneuvers and tests are useful in diagnosing psychogenic seizures. These patients often avoid or resist noxious stimuli. These patients may display gaze aversion and look away from an examiner, regardless of position. On laboratory testing, psychogenic seizure patients do not have a metabolic acidosis, which is nearly universal with generalized convulsive seizures. Though not helpful in the ED setting, there is not a postictal increase in serum prolactin levels.

Seizure Etiologies

Emergency physicians encounter a number of clinical scenarios involving both acute and remote symptomatic seizures. The medical causes of new seizures may be the result of acute or progressive neurologic insults or systemic stressors, and the evaluation of the patient with seizures must always look for those potentially reversible or treatable causes (Table 156.3). The two most commonly identified etiologic antecedents to seizures are neurologic injury from birth (8%) and cerebrovascular disease (11%) (3). Other identified etiologies of secondary seizures include trauma (5.5%), neoplasm (4%), degenerative disease (3.5%), and infection (2.5%). In the elderly, the cause of seizure is more likely to be vascular (stroke), degenerative, or neoplastic than the causes in the young (5).

TABLE 156.3
Etiology of Seizures

I. Idiopathic
II. Structural
    A. Degenerative disease (e.g., multiple sclerosis, tuberous sclerosis)
    B. Neoplasm
    C. Scar from birth trauma, other trauma, anoxic damage
III. Infection: Bacterial, Viral, Parasitic, Syphilitic
    A. Meningitis
    B. Encephalitis
    C. Abscess
IV. Metabolic
    A. Hypoglycemia
    B. Hyperosmolar states
    C. Hyponatremia
    D. Hypocalcemia
    E. Hypomagnesemia
    F. Hypoxia
    G. Uremia
    H. Thyroid disease
    I. Nutritional deficiency
V. Toxin
    A. Drug withdrawal
        1. Alcohol
        2. Benzodiazepine
        3. Antiepileptic drug
    B. Drug overdose
        1. Isoniazid
        2. Tricyclic antidepressant
        3. Anticholinergics, including antihistamines
        4. Salicylates
        5. Theophylline
        6. γ-hydroxybutyrate
        7. Cocaine and related stimulants
VI. Vascular
    A. Subdural hematoma
    B. Epidural hematoma
    C. Intraparenchymal hemorrhage
    D. Stroke
    E. Subarachnoid hemorrhage
    F. Arteriovenous malformation
VII. Eclampsia

Metabolic and toxin-related etiologies must always be considered in the differential diagnosis and are often the most reversible. Hypoglycemia is the most common metabolic cause of seizures; hyponatremia, hypocalcemia, and hypomagnesemia are much less common (6). Interestingly, the metabolic encephalopathies, such as nonketotic hyperglycemia and uremia, can cause both focal and generalized seizures. Alcohol is the toxin most commonly associated with seizures, followed by tricyclic antidepressants, anticholinergics, cocaine, amphetamines, antihistamines, theophylline, and isoniazid. Drug withdrawal, including noncompliance with anticonvulsant medications in patients with a known seizure disorder, is a leading cause of recurrent seizures.

Acute central nervous system (CNS) infections are responsible for 4% to 12% of acute isolated seizures and up to 28% of cases of refractory SE.

A number of physiologic and psychological stressors can activate seizure disorders. These stressors include fatigue, sleep deprivation, hyperventilation, photic stimulation, emotional stress, and menstruation. In rare cases, seizures can be triggered by colors, objects, music, and voices. Pregnancy can also result in the onset of a seizure disorder, which is separate from eclamptic seizures.

ED EVALUATION

History and Physical Examination

The history must include a description of the event and an indication of the frequency, pattern, and duration of recent or previous seizures. Every attempt should be made to interview observers and emergency medical services (EMS) to obtain a clear description of the seizure to avoid misdiagnosing nonseizure events. One should ask the patient or EMS personnel about incontinence, loss of consciousness, and injury and determine whether there was an aura or a postictal period. Inciting factors such as medication noncompliance, infection, pregnancy, sleep deprivation, alcohol use, or other drug or medication use should be identified. A history of head trauma,

headaches, diabetes, cancer, cerebrovascular disease, electrolyte imbalances, or infections can prove vital to making a diagnosis.

The physical examination begins with the vital signs, which can provide important red flags of underlying pathology. Signs of trauma should be sought, and a careful neurologic examination performed. Both unilateral and bilateral pupillary dilation as a result of seizure has been reported. Postictal patients often have hyperreflexia, upgoing toes, evidence of incontinence, or a tongue laceration. A focal deficit can represent a metabolic derangement such as hypoglycemia, an old or a new CNS lesion, or a Todd paralysis secondary to the seizure. Todd paralysis can be manifested as either a motor or a sensory deficit. Although it typically resolves within hours of seizure, neuroimaging may be necessary to differentiate a Todd paralysis from other causes of acute focal neurologic dysfunction.

Postictal confusion is common but almost always resolves in a few hours. Other causes of altered mental status must be strongly considered in patients whose mental status remains impaired or when family or friends note an abnormally longer than normal postictal phase or unusual behavior manifestations. It is estimated that approximately 15% of patients treated for convulsive SE continue to be in nonconvulsive status after their motor activity is controlled; this unrecognized status may be a factor in the high mortality associated with SE and suggests the need for EEG monitoring if there is a prolonged “postictal” period (7). Causes of altered mental status in patients who have had a seizure are listed in Table 156.4.

TABLE 156.4
Causes of Altered Mental Status in Patients Who Have Had a Seizure

Postictal state
Persistent nonconvulsive seizures
Metabolic abnormality
Hyperosmolar state
Central nervous system infection
Central nervous system vascular event
Drug effect
Psychiatric dysfunction

Laboratory Testing

Laboratory testing in postictal patients often demonstrates a metabolic acidosis or an elevated serum–creatine phosphokinase level. These findings can be helpful and should be sought, but, unfortunately, they are time and patient dependent and their absence does not rule out the possibility that a seizure occurred.

Of all laboratory tests, serum glucose determination followed by a serum sodium determination has been found to be the most valuable in diagnosing an unsuspected etiology of seizure (8). The decision to measure other electrolytes, creatinine, blood urea nitrogen, calcium, and magnesium is based on the individual patient assessment; generally, these tests are of limited value in patients with no underlying medical problems who have returned to baseline. An arterial blood gas analysis is indicated when hypoxia or an underlying acidosis is suspected. A pregnancy test should be obtained in all women of childbearing age (6). Serum antiepileptic drug (AED) levels should be checked in patients taking such medications and in those who have had a seizure or when a history cannot be obtained (Table 156.5). Such therapeutic ranges are available for phenytoin, carbamazepine, valproate, and phenobarbital. Serum levels of most of the newer AEDs cannot be measured rapidly in most hospitals.

TABLE 156.5
Drugs Used in the Treatment of Epilepsy

Drug	Trade Name	Route	Seizure Type	Loading Dose (mg/kg)	Daily Dose for Adults (mg)	Therapeutic Range (μg/mL)
Phenytoin	Dilantin	PO, IV	P, GC	20	300–400	10–20
Fosphenytoin	Cerebyx	IV, IM	P, GC	20	—	10–20
Carbamazepine[a]	Tegretol	PO	P, GC	—	800–1,600	6–12
Valproate[b]	Depakene	PO	All	—	1,000–3,000	50–120
Divalproex sodium	Depakote	PO	All	—	1,000–4,800	50–120
	Depacon	IV	All	10–20	—	50–120
Phenobarbital		PO, IV, IM	P, GC	10–20	90–150	15–35
Levetiracetam	Keppra	PO, IV	P, GC	—	500–1500	
Primidone	Mysoline	PO	P, GC	—	750–1,250	6–12
Clonazepam	Klonopin	PO	A, M	—	1.5–20	0.02–0.08
Ethosuximide[c]	Zarontin	PO	A	—	750–1,250	40–100
Lamotrigine	Lamictal	PO	All	—	200–600	—
Felbamate[d]	Felbatol	PO	P, GC	—	1,800–4,800	—
Gabapentin[e]	Neurontin	PO	P, GC	—	900–3,600	—
Topiramate	Topamax	PO	P, GC	—	200–600	—
Tiagabine		PO	P, GC	—	32–48	—
Diazepam[f]	Diastat	Rectal	All	0.2–0.5	—	—

PO, orally; IV, intravenous; P, partial seizure; GC, generalized seizure; IM, intramuscular; A, absence seizure; M, myoclonic seizure.
[a]Drug of choice for partial seizures, with or without secondary generalization.
[b]Drug of choice for primary generalized tonic–clonic seizures.
[c]Drug of choice for absence seizures.
[d]Associated with aplastic anemia in 1 in 5,000 patients; hepatic failure in 1 in 30,000.
[e]Only anticonvulsant that is renally metabolized; recommended in patients with multiple medical problems.
[f]Used primarily in children to control clusters of breakthrough seizures.

Alcohol is by far the most common drug of abuse associated with seizures, followed by cocaine. Serum alcohol, salicylate, lithium, and theophylline levels and urine drug–screening tests should be ordered based on clinical suspicion. Since patients with epilepsy can have other medical problems (e.g., depression), other possibilities (e.g., tricyclic overdose) should not be overlooked and an electrocardiogram (ECG) considered.

Patients who have had a seizure but who are not immunocompromised and who do not have an abnormal mental status, fever, or meningeal signs do not require a lumbar puncture as part of their ED evaluation. However, seizures, especially SE, are associated with hyperthermia, leukocytosis, and altered mental status, thus often forcing consideration of encephalitis. It is also important to note that, as mentioned previously, seizures can cause cerebrospinal fluid pleocytosis, further confusing the issue occasionally. It is recommended that antibiotics and/or antivirals, once started, be continued until cerebrospinal fluid culture results are available.

Neuroimaging and Electroencephalography

CT scanning of the head is indicated in the ED when an acute intracranial event, such as subdural or subarachnoid hemorrhage, is suspected. Patients with acute trauma, a past history of malignancy, or with an abnormal neurologic examination are most likely to have an abnormal imaging study. Special populations, including immunocompromised hosts, the elderly, and immigrants from countries where cysticercosis is endemic are candidates for neuroimaging.

All patients who have had a first-time seizure will need an imaging study but not necessarily an emergent CT scan obtained during the ED stay. If the patient has a normal mental status and neurologic examination and is judged to be reliable for follow-up, it is reasonable, after consultation with a neurologist, to arrange for outpatient magnetic resonance imaging (MRI). MRI is superior to CT scanning in identifying structural epileptogenic abnormalities (9).

EEG monitoring is not a standard practice in the ED, yet there are clear indications for its use on an emergent basis (6). Any patient with altered mental status in whom nonconvulsive SE is suspected requires an emergent EEG. An emergent EEG is also indicated in patients with refractory SE who have been managed with paralysis or intravenous (IV) agents.

Additional laboratory and radiographic testing may be indicated to identify underlying complicating factors, such as cardiac dysrhythmia, urinary tract infection, sepsis, or pulmonary disease.

KEY TESTING

- Serum glucose
- Serum AED levels
- Electrolytes, creatinine, blood urea nitrogen, calcium, and magnesium (limited value in patients who have returned to baseline state)
- Urine/serum drug screen if suspected overdose
- CT or MRI of brain if suspected intracranial event. First-time seizure may have imaging in ED or as outpatient.

ED MANAGEMENT

Prehospital Concerns

In most cases, prehospital personnel will arrive at least 5 minutes after the onset of seizure activity, so patients who are still seizing on EMS arrival are best managed as presumed SE. If a patient is found convulsing or remains confused or unresponsive, the patient's blood sugar should be measured, or, if this test is not available, dextrose (D_{50} or D_{25} in children) should be administered. A randomized, double-blind out-of-hospital trial comparing IV lorazepam, diazepam, and placebo demonstrated benefit and safety of paramedic administered benzodiazepines in the management of SE in the field (10).

When IV access is not immediately available, rectal diazepam is an option, especially in children. Many parents of children with epilepsy have rectal diazepam on hand to be given, should their child have a seizure. Intramuscular (IM) injection of midazolam is also an option when IV access has not been established. A randomized double-blind noninferiority trial demonstrated that IM midazolam is as least as safe and effective as IV lorazepam for children and adults (11).

Patients with a known seizure disorder who experience a typical event and are asymptomatic afterward do not necessarily require transport to the hospital, if they have the capacity to refuse transport. Prehospital personnel should advise these patients to contact their primary care provider as soon as possible.

First-Time Seizures

Patients who have had a single, unprovoked seizure have about a 35% risk of recurrence within the next 5 years; the risk of recurrences increases to approximately 75% after two or three seizures (12). When a cause of the seizure is identified, management is based on the underlying pathology. When no cause can be identified, a risk–benefit analysis regarding initiation of antiepileptic therapy must be performed. There are significant psychological and social consequences of a diagnosis of epilepsy (i.e., individual state limitations on driving cars), as well as potential dangers from the

chronic use of antiepileptic medications. Thus, one must be cautious when labeling patients as epileptic and instituting treatment from the ED.

For most first-time seizures, if a head CT was not indicated or if one is done that is negative, the patient can be discharged with very close follow-up by a primary care physician or neurologist (6). If such follow-up cannot be assured, a neurologist should ideally see the patient prior to discharge.

If there is a structural cause noted on CT scan that does not need emergent intervention—such as calcification suggestive of cysticercosis or a remote ischemic lesion—initiation of antiepileptic medications (AED) should be considered in consultation with a neurologist. Similarly, in the case of a patient who has had prior seizures but is not on any medications, an AED should be considered.

The choice of drug is based upon the type of seizure and the ease of achieving therapeutic serum levels. First-line medications that are effective for both primary generalized seizures and partial seizures with or without secondary generalization are carbamazepine, phenytoin, and valproate. Phenytoins and valproate are available for IV loading while oral carbamazepine may take days to reach therapeutic levels.

IV phenytoin loading, 15 to 20 mg/kg, can be accomplished quickly and leads to therapeutic blood levels within 1 hour of the infusion's completion. IV phenytoin has a pH ~2, and loading can be associated with local site irritation and even necrosis if extravasation occurs. Confusion, ataxia, and hypotension—caused primarily by the diluent propylene glycol—are dose- and rate-related effects. Infusions should not be run faster than 50 mg/min in adults. Fosphenytoin is a water-soluble disodium phosphate ester of phenytoin, which does not need a propylene glycol vehicle and has a more physiologic pH than does phenytoin. Fosphenytoin has fewer side effects than phenytoin, though too rapid an infusion can still cause hypotension, ataxia, and confusion. Fosphenytoin is measured in phenytoin equivalents (PE); its dosing is the same 20 mg (PE) as phenytoin though it can be given at up to 150 mg (PE)/min. Fosphenytoin can also be given safely by the IM route, with 100% bioavailability and therapeutic

serum levels within 1 hour of a loading dose, although this requires a large volume IM injection 10 mL/500 PE. Oral phenytoin loading is another option, although it takes up to 6 hours for serum therapeutic levels to be reached (6). A daily maintenance dose of 300 mg can be given at bedtime, although, in some patients, divided dosing can provide better seizure control by minimizing variations in the blood level.

Recurrence of Seizures in Patients with Known Seizure Disorder

Noncompliance with anticonvulsant medication is, by far, the most common cause of seizure recurrence in a patient with a known seizure disorder. A patient who has been on phenytoin, but has a subtherapeutic level, should be given supplemental IV phenytoin or fosphenytoin to raise serum levels into the therapeutic range. IM fosphenytoin is another option that eliminates the need for infusion pumps and cardiac monitoring. The patient can then be discharged with instructions to resume oral dosing within 12 hours. Likewise, patients with subtherapeutic valproic acid levels can be supplemented with IV valproic acid administered at 20 mg/min and discharged on their oral regimen. Levetiracetam is also available in an IV formulation; however, because serum drug levels are not readily available, dosing augmentation must be done empirically.

Patients who have seizures despite therapeutic anticonvulsant levels must be evaluated carefully for precipitating factors such as infection, new anatomic lesions, or new medications. Decisions to increase the drug dose should be made only after communication with the patient's primary care physician. A second anticonvulsant is generally only added once a patient has failed monotherapy taken to maximum doses.

The evaluation of pregnant patients with new onset seizures should follow the same principle as in other patients. However, if no etiology is identified, anticonvulsants should be withheld, pending a neurology consult. Eclampsia is an additional consideration in

patients at more than 20 weeks' gestation (see Chapter 140, Hypertensive Disorders of Pregnancy).

Noncompliance and sleep deprivation are the two most common causes of seizure recurrence in pregnant patients with epilepsy (13). Active seizures should be treated pharmacologically, just as in the nonpregnant patient, because the risks to the fetus of seizure-related hypoxia and acidosis are greater than the potential teratogenicity of anticonvulsant medications. Phenytoin and phenobarbital have similar teratogenetic profiles; carbamazepine is probably the safest of the anticonvulsants to use in pregnancy. Beyond 24 weeks' gestation, fetal monitoring should be provided during and after a seizure.

Alcohol-Related Seizures

Alcohol-related seizures deserve special mention because alcohol use is frequently involved in patients presenting to EDs with seizures. Alcohol-withdrawal seizures classically occur 6 to 48 hours after a significant reduction in the serum alcohol level, but they have also been associated with rising blood ethanol levels in some patients. Alcohol-related seizures are temporally associated with alcohol use but are not necessarily solely the result of the alcohol. Alcoholics are susceptible to cerebrovascular insults, trauma, metabolic disorders, and infections and are thus at increased risk for seizures. Management of the alcoholic who has had a seizure focuses on determining whether the event was a withdrawal seizure or because of another etiology. Patients with a first-time alcohol-related seizure should be evaluated fully in the same manner as any other patient.

The diagnosis of alcohol-withdrawal seizures is based on the history, and the clinician must always consider the possibility that another etiology is responsible. There is no good evidence to support the use of phenytoin either acutely or chronically in the management of alcohol-withdrawal seizures. Benzodiazepines alone are sufficient to prevent successive withdrawal seizures in the acute setting. Patients who have had one alcohol-withdrawal seizure should be treated with lorazepam 2 mg IV. Following this, if the patients have been observed to remain seizure-free and at baseline mental status

for 6 hours with no evidence of withdrawal, they can be discharged if a suitable environment is available (14).

Psychogenic Seizures

Psychogenic seizures should be suspected in patients who are refractory to anticonvulsants and whose clinical presentation is atypical. The diagnosis is suspected particularly when a convulsing patient does not have a metabolic acidosis, and it can be confirmed, when possible, by demonstrating that an abnormal EEG does not accompany the clinical convulsion. Management of psychogenic seizures is dependent on making the correct diagnosis; although this sounds obvious, the anxiety associated with evaluating a convulsing patient often leads to the initiation of pharmacologic interventions before an adequate assessment is performed (15). The key to management is avoiding iatrogenic harm by aggressive pharmacologic interventions or supportive measures such as intubation. Long-term management usually involves a comprehensive evaluation in an epilepsy monitoring unit, with a coordinated approach involving both an epileptologist and a psychiatrist.

Status Epilepticus

The management of convulsive SE involves expedited and simultaneous maintenance of the patient's airway, breathing, and circulation; diagnostic testing; and pharmacologic intervention (Fig. 156.1). The definition of SE has changed in recent years to reflect the importance of rapid therapeutic intervention. Many researchers consider 5 minutes of continuous seizure activity to be SE. The term "impending status" has been suggested for any seizure lasting >5 minutes because videotape studies show that the mean duration of seizures is 1 minute $\pm$ 12 seconds. This average would make a seizure of 5 minutes duration "18 to 20 standard deviations away from the norm of a single seizure, indicating that something distinctly unusual and severe is happening" (16).

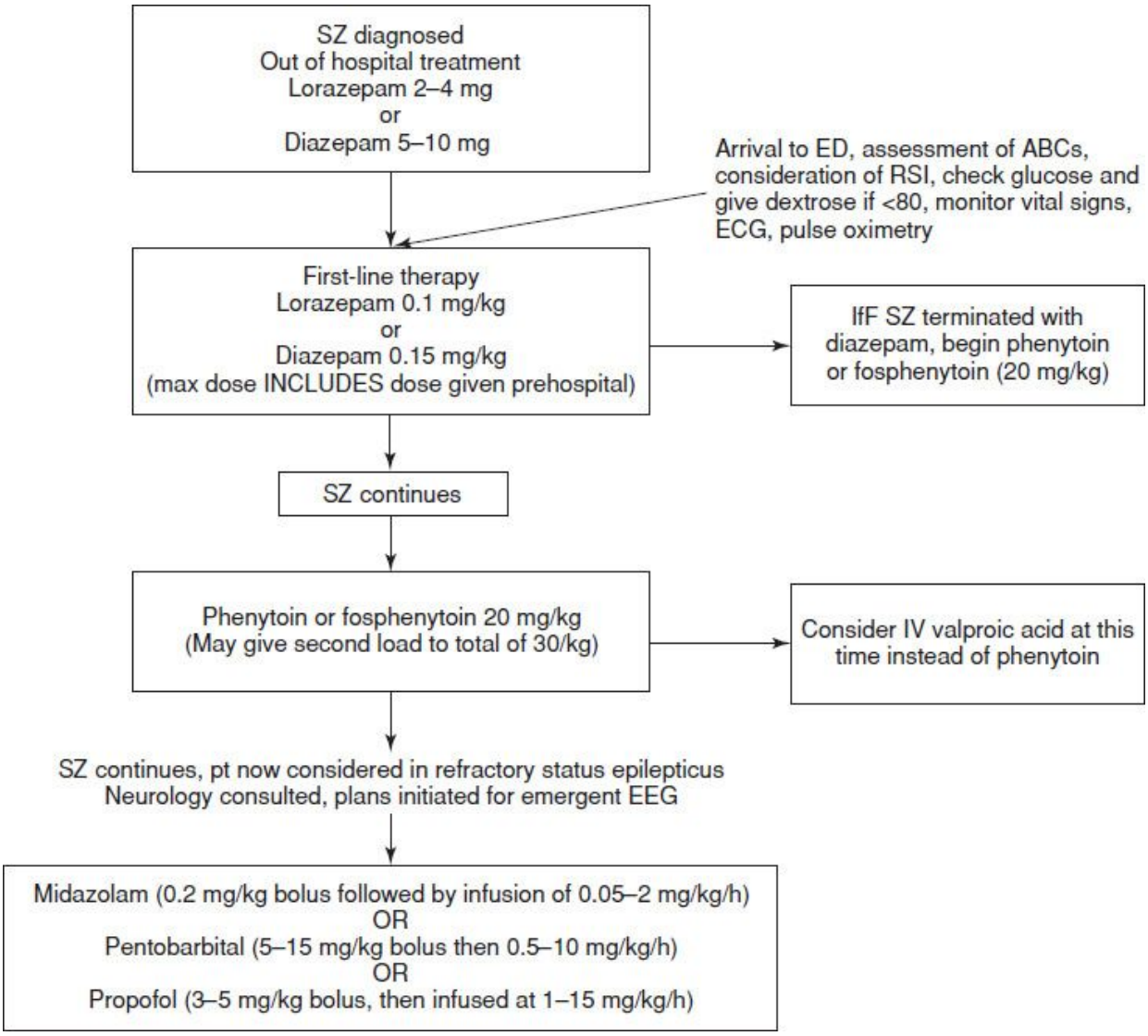

FIGURE 156.1 Approach to patient in status epilepticus. (Modified from Shearer P, Park D. Seizures and status epilepticus. *Ann Emerg Med.* 2002;39:190–192.)

SE occurs more frequently in patients with an underlying neurologic insult, either old or new, and most patients do not have a prior history of epilepsy. A population-based study reported the causes of SE as low AED levels in patients with known seizures (34%), remote symptomatic causes (24%), cerebrovascular accidents (22%), anoxia or hypoxia (~0%), metabolic causes (~0%), and alcohol and drug withdrawal (~0%) (17). Morbidity and mortality in SE is related to the etiology, duration, and systemic consequences

of the inciting event and the seizure. First-line agents for SE are the benzodiazepines (midazolam, lorazepam, or diazepam). IV phenytoin, fosphenytoin, valproic acid, and possibly levetiracetam are second-line agents. Patients who continue to seize despite aggressive use of these agents are considered to be in refractory SE and require treatment with IV anesthetic dose of midazolam, propofol, or pentobarbital. Refractory SE almost always indicates the presence of an underlying CNS disorder (18).

Airway support needs to be aggressive with continuous pulse oximetry. Patients should be intubated at any sign of hypoxia or loss of protective gag reflex. IV access should be secured using a nondextrose-containing solution because phenytoin precipitates if it is inadvertently administered with dextrose (dextrose will not precipitate fosphenytoin). Fluids should be run at keep-open rates unless the patient is hypotensive, because SE can be associated with both cerebral and pulmonary edema. When patients are intubated, short-acting paralytic agents should be used as continued motor activity, will be masked by long-acting agents lulling a clinician into a false sense of security. If prolonged paralysis is needed to carry out a procedure, a bedside EEG should be arranged.

The blood glucose level should be checked immediately by bedside testing. Blood should be tested for electrolytes, magnesium, phosphate, calcium, liver and renal function, hematocrit, WBC count, platelet count, AED levels, toxic drug screen (particularly salicylates), and alcohol. The urine should be checked for evidence of rhabdomyolysis, and a pregnancy test should be done on all women of childbearing age. The family and EMS should be questioned about the possibility of isoniazid or other drug overdose.

Patients in SE should be placed on a cardiac monitor, and an ECG should be done. A nasogastric tube should be inserted to prevent gastric distention, and a Foley catheter should be placed to help monitor volume status. A head CT scan should be done at some point in all patients. Consideration should be given to performing a lumbar puncture, if no source of the seizure activity is found.

The pharmacologic management of SE begins while the patient is being stabilized and diagnostic testing is being performed.

Hypoglycemia is treated immediately with thiamine and dextrose. Antibiotics should be given very early in the management of any patient in whom meningitis, encephalitis, or sepsis is suspected.

The benzodiazepines diazepam and lorazepam are considered the first-line drugs in the management of SE. Lorazepam (0.1 mg/kg IV, up to 10 mg) or diazepam (0.15 mg/kg IV, up to 20 mg) will stop seizures in the majority of cases. Both drugs are efficacious, but lorazepam is preferred because its anticonvulsant action lasts up to 12 hours. Diazepam has a greater volume of distribution, and, although it rapidly enters the CNS, it quickly redistributes and the CNS effect may only last 20 minutes. Consequently, if lorazepam terminates the seizure activity, no additional anticonvulsant needs to be immediately given. However, a long-lasting anticonvulsant such as phenytoin must be added when diazepam is used, or the patient will be at higher risk of seizure recurrence. The Veterans Affairs (VA) Cooperative Study compared four IV treatment regimens for convulsive SE: Diazepam followed by phenytoin, lorazepam alone, phenytoin alone, and phenobarbital alone. This well-designed, randomized, double-blind study found no outcome difference between the four treatments, although lorazepam was more effective when compared directly with phenytoin alone. The authors recommended lorazepam as the first-line agent in generalized convulsive status (2).

When seizures persist despite a full loading dose of a benzodiazepine, either valproic acid (20 mg/kg over 5 to 20 minutes), or a phenytoin is recommended (20 mg/kg of phenytoin or fosphenytoin equivalents at a rate of 50 mg/min or 150 mg/min, respectively). There is a growing body of literature supporting the early use of valproic acid instead of a phenytoin due to its efficacy and its favorable side effect profile (19,20). There is some, but limited, evidence to support IV levetiracetam as a second-line agent in treating SE. Unlike most of the agents used in treating status, levetiracetam has no hepatic metabolism, is renally excreted, and can be rapidly loaded making it an attractive agent in select cases (21).

SE that does not terminate after a benzodiazepine and a second-line agent is usually the result of a significant underlying CNS lesion.

The patient is considered to be in refractory SE and should be treated with anesthetic doses of midazolam, pentobarbital, or propofol. Studies have not shown one drug to be better than the others (22). The choice of drug for refractory SE is made on the basis of accessibility, familiarity with use, the potential role of side effects of each drug, and consideration of the preference of the admitting neurocritical care service. Underdosing and delay in starting any drug are the main pitfalls.

Midazolam is given as a loading dose of 0.2 mg/kg and is followed by an infusion of 0.05 to 2 mg/kg/h (23). Propofol provides almost immediate suppression of seizure activity after a bolus infusion (24). It is rapidly metabolized and can be titrated easily. Propofol is given as a bolus of 3 to 5 mg/kg followed by an infusion at 1 to 15 mg/kg/h. The propofol infusion syndrome of hypotension, lipidemia, rhabdomyolysis, and metabolic acidosis limits the prolonged infusion of propofol in both adults and children (25). Pentobarbital is given as 5 to 15 mg/kg at 25 mg/min, followed by 0.5 to 10 mg/kg/h as an infusion (26). Besides requiring ventilatory support, these patients are at significant risk for hypotension and therefore require hemodynamic monitoring. Hypotension should be treated with fluids and vasopressors as needed. EEG monitoring should be instituted to evaluate for continued seizure activity (27). Pentobarbital has the longest duration of action of the three agents, making it more difficult to remove when evaluating seizure suppression (28).

Many other IV and inhalational drugs have been tried in the management of refractory SE, but no controlled trials support their use (29). These drugs include inhalational anesthetics, continuous infusions of ketamine, IV lidocaine, and rectal chloral hydrate. Current recommendations would support use of these drugs only if all other measures fail.

Subtle Status Epilepticus

Subtle status occurs when the clinical manifestations of convulsive SE diminish and become less overt but the condition persists; mortality is very high in this group especially if it goes unrecognized.

Continuous EEG monitoring should thus be considered in all SE patients (2).

Nonconvulsive Status Epilepticus

Nonconvulsive SE presents as altered mental status ranging from a mild behavioral alteration noticeable only to family or friends to frank coma (30–32). Other manifestations may include speech arrest, cognitive deficits, delusions, paranoia, hallucinations, or psychosis. Because, by definition, there is rarely a significant motor component, the diagnosis is often missed, and there are many case reports of these patients initially being diagnosed with a psychiatric illness. Nonconvulsive SE has been reported in every age group, can be the initial presentation of a seizure disorder, and has been reported to last as long as 8 weeks.

The diagnosis should be suspected in patients with a seizure history who present with a prolonged postictal period or an unusual behavior pattern. Nonconvulsive SE should also be considered in patients without a seizure history who present with altered mental status of undetermined etiology. The diagnosis is made by EEG. Treatment is the same as for convulsive SE, beginning with lorazepam, 2 mg/min, until the EEG normalizes or a total of 10 mg is administered. This treatment should be followed by phenytoin loading, although it is questionable whether phenytoin is effective in absence status.

CRITICAL INTERVENTIONS

- Check a rapid glucose in patients with seizures or refractory SE.
- Protect actively seizing patients from injury.
- Administer rapid, aggressive benzodiazepine therapy for SE.
- Provide aggressive airway support for patients in SE, and intubate if there are signs of hypoxia or a loss of protective gag reflex.
- Establish a departmental protocol for management of SE.

DISPOSITION

The disposition of patients who have had a seizure depends on the etiology of the event and, often, on the socioeconomic environment to which the patient will return (33). Of prime importance is communication with the primary care provider who will be responsible for following up on the patient's diagnostic tests and medications.

Hospital admission should be considered when the cause of a seizure is unclear, when seizure recurrence has not been controlled, when the seizure is secondary to a treatable underlying illness, or when there is concern that the patient will not receive timely outpatient evaluation. All patients who have been in SE should be admitted, usually to an intensive care setting.

Common Pitfalls

- Improper infusion of phenytoin
- Assumption that altered mental status is because of a postictal state and failure to consider other possible etiologies such as subtle status or nonconvulsive status
- Failure to have and to activate an SE protocol

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CHAPTER 157

Transient Global Amnesia

Richard M. Kaplan and Michael S. Joo

Transient global amnesia (TGA) is a distinct clinical entity characterized by abrupt transient memory loss regarding recent events, along with an inability to form new memories and retain new information. TGA has been reported to have a frequency of 5 to 32 episodes per 100,000 people annually (1–3). TGA may be due to transient ischemia of the vertebrobasilar and posterior cerebral circulation with medial temporal lobe dysfunction. Other possible explanations for TGA include spreading cortical depression (possibly related to migraine) or jugular valve incompetence with retrograde transmission of high venous pressures to the cerebral venous system. Patients without jugular vein incompetence may have vascular causes other than congestion (4–9). Current research has investigated the role of the hippocampal CA1 neuron which may be critical as a relay in the hippocampal-parietal network. The CA1 neuron is vulnerable to metabolic and oxidative stress, and may be involved in impairment of memory formation (10).

CLINICAL PRESENTATION

TGA may last from less than 1 hour to 24 hours. Melo (11) reported that 16 of 103 (16%) of TGA patients sustained an episode that lasted for 1 hour or less. Most episodes last from 1 to 10 hours. TGA seems to occur mainly in the morning, and the average duration is about 6 hours (3,7,8,12). Patients are usually older than 50 years of age and are disoriented to time and place, but not to self. Phrases and questions are commonly repeated, and patients have difficulty

making sense of their immediate circumstances. The patient remains attentive, follows commands, and may be able to perform simple cognitive tests, but the responses are forgotten moments later. Motor skills, speech, language, personality, and judgment remain intact. Upon recovery, the patient has complete amnesia to the events that occurred during the TGA episode (1,7,8,13).

It is imperative to obtain an accurate history regarding the specific symptoms. TGA may be associated with emotional or stressful events, sexual activity, physical exertion, exposure to pain or extremes in temperature, or medical procedures (3,5,8,11,12). If a patient's disorientation causes anxiety, this, in turn, may lead to hyperventilation, palpitation, dizziness, nausea, presyncope, paresthesias, or a choking sensation (8).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of TGA includes psychogenic amnesia, complex partial seizures, central nervous system (CNS) infarction, tumor or bleed, cerebrovascular insufficiency of the posterior circulation, migraine, toxin or drug effect, head injury, metabolic abnormality, or high altitudes. Stressful events and anxiety disorders may be associated with an acute onset of psychogenic or hysterical amnesia. Unlike complex partial seizures, TGA usually lasts for hours, and patients do not experience a warning, aura, postictal symptoms, or incontinence. When electroencephalographic (EEG) testing is performed during a TGA episode, brain wave slowing without epileptiform patterns may be observed (14).

Cerebrovascular insufficiency in memory-related areas of the brain, due to a transient ischemic attack (TIA) or other hemodynamic compromise, could theoretically lead to transient memory loss. The vertebrobasilar and posterior cerebral arteries supply the temporal lobes, hippocampus, and thalamic nucleus (12). Case studies have reported that TGA may be an early warning sign of heparin-induced thrombocytopenia and antiphospholipid syndrome (15,16).

TGA may be confused with migraine, but a migraine typically presents with a prodrome and unilateral head pain associated with nausea (17). Hypoglycemia, hyperglycemia, uremia, and hypocalcemia may be associated with a change in mental status or a near-syncopal or seizure-like event that may be confused with TGA. Routine laboratory studies may help with the diagnosis. Illicit or prescription drugs may cause confusion or delirium. Specifically, there are cases describing an association between sildenafil (Viagra) and apparent TGA (18). Toxins such as solvents or heavy metals, as well as drug withdrawal, may cause similar symptoms.

Several cases have been reported of young healthy climbers at very high altitudes who experienced TGA. There were no injuries, neurologic abnormalities, or symptoms related to hypoxia. Upon partial descent from altitude, their symptoms resolved completely, and they were later able to tolerate higher altitudes (19). Head trauma may also lead to retrograde amnesia (difficulty recalling events from the immediate past) and anterograde amnesia (inability to learn new information after the injury) (17).

ED EVALUATION

The diagnosis of TGA is made by taking a thorough history. This involves speaking with a reliable witness to the preceding events. The physical examination, including a complete neurologic examination, is normal. Laboratory investigation should include electrolytes and a complete blood count. A computed tomography (CT) scan of the brain is usually obtained in patients with TGA, but it is of questionable utility. No clear relationship has been documented between any brain CT findings and TGA. Landi (20) documented a case of TGA due to a left temporal hemorrhage. Zorzon (21) reviewed 50 head CTs from patients diagnosed with TGA and observed one left occipital and one right temporal infarction. It was not clear from the study as to the “age” of the infarcts. Pai (12) noted that of 17 patients with TGA, two CT abnormalities were noted, an old left and right thalamic infarct.

Additional studies may include magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) (22), single-photon emission CT (SPECT), PET imaging, and EEGs. MRI and SPECT studies performed during TGA episodes have shown temporal lobe changes (2,23,24). If MRI with DWI is performed too early in the course of disease, a negative study may be obtained (2). An MRI with DWI (25) has documented TGA with an acute infarction of the retrosplenium of the corpus callosum; the retrosplenial cortex is thought to allow for "memory" connections between the anterior thalamus and the medial temporal structures. Increased time lapse from symptom onset to MRI with DWI within the first 24 hours and increased field strength may increase detection rates (22). Recent studies involving PET imaging 2 hours after onset of symptoms of TGA revealed hypometabolism in the left hippocampus that correlated with findings of small nodular hyperintensities in the same region on MRI with DWI at 48 hours (26).

SPECT has demonstrated a decrease in blood flow to the thalamus (27) and ischemia in brain regions supplied by the posterior cerebral arteries that included the medial left temporal lobe and left thalamus (28). Pai (12) documented that the left temporal region was the most common site of dysfunction on EEG and SPECT. SPECT has shown a possible temporal relationship to areas of hypoperfusion. In the acute phase, significant hypoperfusion was seen in the right precentral, cingulate, and medial frontal gyri. At 1 month, significant hypoperfusion was seen in the right precentral and cingulate gyri, and the left postcentral gyrus, with resolution of changes at 1 year (29).

ED MANAGEMENT

TGA is a benign condition with a good prognosis. Although a vascular etiology has not been identified, daily aspirin therapy is suggested. When the diagnosis has been made, the patient and family require reassurance regarding the benign nature of TGA.

Patients with TGA do not appear to have a higher incidence of cardiovascular risk factors. TGA patients are at a very low risk of

subsequent stroke or myocardial infarction (MI). Additional TGA episodes occur in about 3.5% to 15% of patients at 3 to 7 years (3,7,8,11,30).

CRITICAL INTERVENTIONS

- Obtain an accurate and detailed history reported by a reliable observer.
- Perform a thorough neurologic examination.
- Rule out a CVA.
- Reassure the patient and the patient's family.

DISPOSITION

The typical patient with TGA has an uncomplicated course and a complete recovery. This is supported by imaging studies (29). If the diagnosis is clear and the episode has resolved, the patient may be discharged with family or friends. If symptoms persist or if there is any question about the diagnosis, the patient should be admitted to the hospital. A neurology consultation may be considered along with a further workup that may include an MRI and/or an EEG.

Common Pitfall

- Failure to consider the diagnosis.

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CHAPTER 158

Peripheral Neuropathies

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The peripheral nervous system begins within the spinal canal with the ventral and dorsal nerve roots. These merge to form the spinal nerves, which then supply the visceral nerves, nerve plexuses, and peripheral nerves. Several generalizations can be made about the findings attributed to each of these areas. Lesions affecting the dorsal (afferent) roots produce pain, sensory loss, and decreased reflexes, but muscle strength is preserved. Ventral (efferent) root lesions produce muscle weakness, spasm, and autonomic symptoms without pain. A combination of all these symptoms occurs when spinal nerves are affected. Disorders affecting the visceral fibers will produce autonomic symptoms, which include extreme fluctuations in cardiac rhythm, blood pressure, gastrointestinal (GI) motility, urogenital function, sweating, and salivation.

Peripheral neuropathies are confusing entities; nevertheless, only 13% to 25% of patients undergoing intensive evaluation fail to have a diagnosis made (1,2). Emergency physicians evaluating patients complaining of symptoms consistent with peripheral neuropathy should determine the chronicity, pattern, and symmetry of symptoms to establish a working differential diagnosis (1,3,4). In general, peripheral neuropathies can be divided into several basic categories: polyneuropathy, plexopathy, radiculopathy, and mononeuropathy.

ACUTE POLYNEUROPATHY

Polyneuropathy results from the simultaneous dysfunction of multiple peripheral nerves. Symptoms include diffuse motor and/or sensory loss, with variable autonomic dysfunction. Polyneuropathies that develop over several days to 2 to 4 weeks are considered acute. Of these, Guillain–Barré syndrome (GBS) is the most common (4–6).

CLINICAL PRESENTATION

GBS, also known as acute inflammatory demyelinating polyradiculoneuropathy (AIDP), is a worldwide, nonseasonal, acute polyneuropathy that affects all ages, with a yearly incidence of 0.4 to 2.0 cases per 100,000 population (4,5,7,8). Pathologic examination reveals inflammation and segmental demyelination as the primary defect in about 90% of cases in North America and Europe (4,5,7,9). Primary axonal degeneration presenting as acute motor axonal neuropathy (AMAN) or acute motor and sensory axonal neuropathy (AMSAN) occurs in only 10% of cases in this region (7,9), but accounts for 30% to 65% of cases in China, Japan, Bangladesh, and Central and South America (5,9).

In classic GBS (AIDP), patients experience a prodromal event such as an upper respiratory tract infection, gastroenteritis surgery, vaccination, or infection with agents such as *Mycoplasma,* the herpes viruses, CMV, EBV, hepatitis B and C, and HIV. Overall, *Campylobacter jejuni* infection is the most commonly identified pathogen associated with GBS (4,5,8). In 1 to 3 weeks patients develop the onset of distal paresthesias and a symmetric ascending motor paralysis that progresses to its peak over 10 to 14 days. Motor weakness is both proximal and distal, with legs being involved prior to the arms and trunk. Additional findings include hyporeflexia or areflexia within 7 to 10 days of symptom onset, mild sensory losses, cranial nerve palsies (facial diplegia occurs in 50% of cases) (4), and autonomic dysfunction. Bowel and bladder disturbances are uncommon (15%) and brief in duration (4). Patients are afebrile and mental status is unaffected. It is not unusual for patients to initially present with low back, hip, and thigh pain that is confused with disc disease or lumbar strain.

The axonal variants of GBS (AMAN and AMSAN) tend to present in a more acute manner than AIDP and tend to have a worse prognosis (4). They also have a stronger association with preceding *C. jejuni* infection. The Miller-Fisher variant of GBS presents with ophthalmoplegia, ataxia, and areflexia. Other less common variants include pure sensory GBS, pure pandysautonomia, and pharyngeal–cervical–brachial GBS. These variants may make diagnosis difficult; however, when considering the differential diagnosis of classic GBS, marked or persistent asymmetry of weakness, lack of facial and respiratory muscle weakness in a patient with generalized paralysis, prolonged incontinence, a sharp sensory level, or fever strongly suggest an alternative diagnosis (7).

DIFFERENTIAL DIAGNOSIS

Tick Paralysis

Tick paralysis typically affects children in the spring and summer months. An acute ascending motor paralysis nearly identical to GBS results from a toxin present in the saliva of ticks (usually *Dermacentor* in the United States) that have been attached to a human host for a period of 5 to 7 days. Unlike GBS, sensory loss and CSF abnormalities are not seen in tick paralysis (10). The diagnosis is made when the offending tick is located, and treatment consists of its removal and supportive care. Symptoms begin to improve within hours of tick removal and generally resolve completely within 2 to 3 days. *Ixodes holocyclus,* a tick species found in Australia, is associated with paralysis that can progress despite tick removal. For this species, a hyperimmune serum has been developed (1,10).

Botulism

Exposure to botulinum toxin, which inhibits the release of acetylcholine at neuromuscular junctions, usually results from the ingestion of improperly canned foods, GI tract colonization in young infants fed raw honey, or rarely, from cutaneous infection with *Clostridium botulinum.* The toxin is a potential weapon of mass terror, and exposure may be via ingestion or inhalation. Initial

symptoms of botulism begin hours to several days after exposure and include nausea, vomiting, and dry mouth in patients who have ingested the toxin. Neurologic symptoms begin with cranial nerve palsies with prominent ocular findings (e.g., blurred vision, dilated pupils, diplopia). These are rapidly followed by symmetric, descending motor weakness and autonomic dysfunction. Sensation and mental status are not affected and fever is absent. Treatment consists of antitoxin therapy (available through the Centers for Disease Control [CDC]) and supportive care (1,10).

Poliomyelitis-Like Syndromes

In the United States, poliomyelitis is rare and nearly all cases are imported or related to the use of the live attenuated oral vaccine. Patients with polio first develop an acute viral illness with fever, headache, meningeal signs, muscle pain, and tenderness. These symptoms are present 1 to 2 days before weakness develops. Polio paralysis is more proximal than distal, legs are involved more than arms, and classically, involvement is asymmetric. Sensory loss is extremely rare, and its presence should raise the suspicion of other diagnoses. The most serious complication of polio is respiratory muscle paralysis. Progression of paralysis abates when patients become afebrile. A similar paralytic syndrome may occur following infection with other nonpolio enteroviruses or with the West Nile virus, a flavivirus introduced into the United States in 1999 (1,10,11).

Diphtheria

Diphtheria begins as a pharyngeal infection caused by an exotoxin-producing *Corynebacterium diphtheriae*. Subsequent toxicity, both cardiac and neurologic, correlates with the severity of the pharyngeal disease. Paralysis of local pharyngeal muscles, followed by cranial nerve palsies, occurs in the first or second week of infection. Cardiac toxicity begins 1 to 2 weeks after the onset of illness. The polyneuropathy, which is mainly motor, does not develop for 5 to 8 weeks. Weakness may begin in all extremities

simultaneously, or it may first appear in proximal muscles and then spread distally. Occasionally, the primary site of infection is a skin wound, in which case sensorimotor changes are first noted near the infected wound. Treatment of diphtheria involves use of antitoxin within the first 48 hours of acute infection. Treatment of the neuropathy consists of supportive care (4,10).

Acute Intermittent Porphyria

In this disorder, stimulation of an enzymatically deficient heme synthesis pathway results in the buildup of neurotoxic precursors. An acute attack classically begins with severe abdominal pain, which is followed by tachycardia, hypertension, and mental status changes. Seizures may occur. Within days, a sensorimotor polyneuropathy that can be symmetric or asymmetric, and ascending or descending, may develop and can progress to respiratory failure and death. Treatment consists of intravenous glucose and hematin to shut down the defective pathway, β-blockers to control hypertension, and supportive care (1,4).

Heavy Metals/Toxins

Most neuropathies due to heavy metal poisoning are subacute or chronic. Acute presentations are associated with thallium, massive arsenic, and organophosphate exposure. Thallium ingestion produces abdominal pain, vomiting, and diarrhea, followed by painful paresthesias and the rapid onset of diffuse motor weakness. Differentiation from GBS is often made 1 to 2 weeks after the onset of symptoms, when thallium-induced alopecia becomes apparent. Acute arsenic polyneuropathy, which is also clinically similar to GBS, begins 8 to 20 days after a large exposure and is associated with GI symptoms, renal failure, hepatic failure, and mental status changes. Organophosphates initially produce a cholinergic syndrome, but in 2 to 5 weeks a predominantly motor, distal symmetrical polyneuropathy may develop (4).

Others

Acute polyneuropathy may develop as a complication of critical illness, uremia and dialysis, malignancy, nutritional deficiencies, collagen vascular disease, infectious agents, or a host of toxins and drugs. These should be considered in patients with a presumptive diagnosis of GBS.

Neurologic and muscular disorders that produce weakness and must be differentiated from GBS include myelopathy, transverse myelitis, lumbar disc disease, myasthenia gravis, and acute myopathy. Within this category, cervical myelopathy deserves added attention. It presents with an ascending paraplegia or quadriplegia and a sensory level. Unlike GBS, it is associated with localized neck pain or tenderness, hyperreflexia (unless spinal shock is present), pathologic reflexes (e.g., Hoffman sign), and loss of sphincter tone. Respiratory compromise is not seen unless the cord is involved above the C5 level. Active or passive neck motion may exacerbate symptoms. Acute myelopathy is usually the result of trauma. Subacute myelopathy is seen with neoplasm, subdural, or epidural abscess, disc herniation, and hematoma; however, these etiologies may present with acute onset of symptoms, especially if the vascular supply to the cord is compromised. Patients who have symptoms suggestive of a myelopathy must undergo rapid imaging with a magnetic resonance imaging (MRI) or computed tomography (CT) myelogram as correct diagnosis, and intervention may prevent permanent deficits.

Metabolic disorders such as acute hypophosphatemia, hypokalemia, hypermagnesemia, hyperkalemia, and periodic paralysis may produce severe generalized weakness that may mimic GBS. Hysteria and malingering should also be considered in the differential diagnosis.

ED EVALUATION AND MANAGEMENT

Patients presenting with the acute onset of weakness warrant rapid assessment of airway, ventilatory capacity, and cardiovascular status. Following stabilization, history and physical examination, including a detailed neurologic examination, are the principal

methods of emergency department (ED) evaluation. The emergency physician should obtain a complete blood count, serum electrolytes, calcium, magnesium, phosphate, glucose, blood urea nitrogen, creatinine, chest radiograph, and electrocardiogram on all patients.

Additional studies might be obtained by the emergency physician if clinical evaluation raises the suspicion of a specific disease process. Otherwise, additional testing should be left to the consulting neurologist following characterization of the neuropathy by nerve conduction studies and electromyography (3).

Patients suspected of having GBS should undergo lumbar puncture. The characteristic findings are normal pressure and albuminocytologic dissociation (elevated protein levels with fewer than 10 mononuclear cells/μL). Cerebrospinal fluid changes may be delayed 1 to 2 weeks after the onset of symptoms. An increased cell count should raise the suspicion for HIV, West Nile virus, or Lyme disease as the precipitating event (1,4).

Baseline measurements of pulmonary function are important, because 25% to 33% of patients with GBS eventually require mechanical ventilation (1,4,5,9). Forced vital capacity (FVC) or negative inspiratory force (NIF) should be tested in the ED. A brief bedside test is to have the patient take a single deep inspiration and then quickly count for as long as possible; the ability to count to 20 correlates with an FVC of 1.5 L (4). FVC of $<$15 to 20 mL/kg or an IF of $<$20 to 30 cm H_2O are indications of imminent respiratory failure and the need to initiate mechanical ventilation (1,4,5,12). Patients who remain in the ED for several hours should have serial pulmonary function testing. Bulbar muscle strength should also be followed, as intubation may be required to maintain a patent airway and prevent aspiration. Frequent vital signs and continuous cardiac monitoring are essential to identify life-threatening cardiovascular autonomic dysfunction. Blood-pressure fluctuations should be treated, as needed, with fluids and short-acting agents.

DISPOSITION

Every patient with an acute polyneuropathy should be evaluated by a neurologist. Admission to the hospital for further diagnostic studies and continued monitoring of vital signs and respiratory status is required. Whether an intensive care unit (ICU) is necessary for all patients is controversial. Any patient with significant respiratory impairment, inability to protect the airway, or autonomic instability should be admitted to an ICU. Several clinical findings have been associated with a high rate of mechanical ventilation: FVC <20 mL/kg, NIF <30 cm H_2O, EF (expiratory force) <40 cm H_2O, more than a 30% reduction in FVC from baseline, <7 days from symptom onset to hospital admission, and the inability to cough, stand, or lift the elbows or head off the bed (12,13). The presence of any of these should prompt an ICU admission. For all other patients, the admission destination depends on the adequacy of monitoring in other settings. Patients with severe or rapidly progressive GBS benefit from early plasma exchange or immune globulin therapy (1,3,4,5,9); therefore, these patients should be transferred to a facility capable of providing such therapies.

Although the majority of patients with GBS recover completely or with minimal deficits, it should be noted that GBS has a 3% to 5% mortality (4,5). Ten percent to 20% of patients will have severe persistent deficits (3,4,5,9). In addition, 5% to 10% will have recurrent episodes of acute peripheral neuropathy (4,14).

Common Pitfalls

- Mistaking the low back pain of GBS for disc disease or back strain.
- Mistaking the symptoms of cervical myelopathy or other spinal cord pathology for GBS.
- Failing to admit patients with minimal, but suggestive, symptomatology.
- Inadequately monitoring for respiratory and autonomic dysfunctions.

- Ascribing the symmetric weakness of GBS or other acute polyneuropathies to a psychiatric disorder.
- Failing to recognize variant presentations of GBS.

SUBACUTE POLYNEUROPATHY

CLINICAL PRESENTATION

Polyneuropathy that develops over a period of several weeks to months is said to be subacute; however, the distinction between subacute polyneuropathy (SPN) and acute polyneuropathy is not always clear. SPN may be symmetric or asymmetric. Symmetric disease generally begins with distal sensorimotor losses and tends to produce marked sensory impairment. Asymmetric SPN is frequently the result of neuronal ischemia; nerves are randomly affected, producing patchy sensorimotor losses.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of SPN includes subacute or chronic inflammatory demyelinating polyneuropathy (CIDP), mononeuritis multiplex, and other neuromuscular diseases that produce subacute weakness such as myelopathy, myasthenia gravis, amyotrophic lateral sclerosis, Parkinson disease, and depression. However, perhaps more important to consider are the numerous toxic, nutritional, and systemic disorders that can result in SPN.

The etiologies for *symmetric* SPN include diabetes mellitus, alcoholism, nutritional deficiencies, uremia, amyloidosis, heavy-metal intoxication, industrial solvents (e.g., glue sniffing), paraneoplastic syndromes, and a multitude of toxins and medications. Collagen vascular disease, autoimmune diseases, and infections such as Lyme disease and HIV are much less common causes.

The etiologies of *asymmetric* SPN include diabetes mellitus (e.g., diabetic amyotrophy), collagen vascular and autoimmune diseases, peripheral vascular disease, sarcoidosis, neoplastic disease, paraproteinemia, leprosy, Lyme disease, and HIV infection.

ED Evaluation and Management

History and physical examination are the principal methods of evaluation. Key historic elements to elicit are a history of neuromuscular or systemic disease, medications (prescription and nonprescription), and potential infectious or toxic exposure. Laboratory studies should include complete blood count, serum electrolytes, calcium, magnesium, phosphate, glucose, blood urea nitrogen, creatinine, and a screening chest radiograph. As with acute neuropathies, further studies should be obtained only if a specific etiology is suspected following initial evaluation (3).

If a medication is suspected as the etiology, it should be discontinued or changed after consultation with the primary care physician. Short-term follow-up should be arranged.

DISPOSITION

Most patients with SPN may be referred to their primary care physician for outpatient evaluation and referral to a neurologist. A recent review found that optimal, evidence-based, outpatient diagnostic tests are often not done (15); therefore, it may be of value to discuss these with the patient's provider or mention them in discharge recommendations. These tests are as follows: glucose tolerance test, serum B_{12} with metabolites, and serum protein electrophoresis (2).

Common Pitfall

- Attributing SPN to a chronic medical condition, thus overlooking potentially treatable causes such as nutritional deficiencies, medication exposure, toxin exposure, infection, or vasculitis.

PLEXOPATHY AND RADICULOPATHY

CLINICAL PRESENTATION

A plexopathy is a disorder that affects the brachial or lumbosacral plexus. Symptoms include pain and mixed motor and sensory

deficits in a pattern that cannot be attributed to individual peripheral nerves or nerve roots.

Acute or subacute plexopathies are associated with local trauma (e.g., shoulder dislocation), compression (e.g., retroperitoneal hematoma or abdominal aortic aneurysm), vascular disease (usually due to diabetes or collagen vascular disease), infection (e.g., Lyme disease), or they may be idiopathic. Idiopathic lumbosacral plexopathy is uncommon (16), but acute idiopathic brachial plexopathy (Parsonage–Turner syndrome) though rare is well described (4,17). It is seen most commonly in young adults with a slight male predominance, and there appears to be some association with recent viral illnesses and immunizations (1,17). Symptoms of brachial plexopathy begin with the sudden onset of severe shoulder pain that may extend into the neck and upper arm. Less commonly, the lower plexus cords may be affected, producing symptoms in the forearm and hand. Within days to weeks, motor weakness and sensory loss develop, usually coinciding with resolution of pain (11,17). About 90% of patients recover good neurologic function by 3 years (17). There is recent evidence to suggest that this syndrome is heterogeneous, including both plexopathy and multiple mononeuropathies (17,18). Chronic plexopathy is associated with infections, vascular disease, collagen vascular disease, tumor, infiltrative processes, and radiation therapy.

In contrast to plexopathy, a radiculopathy affects spinal nerve roots or spinal nerves. Symptoms include pain and sensorimotor deficits in a pattern consistent with the involved nerve root (e.g., lancinating pain along the L-5 nerve root dermatome). Frequently, several adjacent roots are affected, making differentiation from a plexopathy or multiple mononeuropathies clinically impossible. The etiologies of radiculopathy include all those of a plexopathy, as well as specific spinal canal or cord disorders such as herniated disc, spinal stenosis, and epidural tumor, abscess, hematoma, granuloma, and infection (1,4).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of plexopathy includes polyneuropathy, multiple mononeuropathies, and spinal cord and nerve root disorders. Brachial plexopathy can easily be confused with cervical radiculopathy, and lumbosacral plexopathy with lumbosacral radiculopathy. The pain of idiopathic brachial plexopathy tends to resolve as motor symptoms develop, unlike the persistent pain of cervical radiculopathy. In addition, pain from cervical radiculopathy increases with neck movement, coughing, and sneezing, whereas brachial plexopathy pain does not. Pain from both lumbosacral plexopathy and lumbosacral radiculopathy is persistent; however, back pain is not a prominent feature of lumbosacral plexopathy (16).

Thoracic outlet syndrome can mimic brachial plexopathy by producing pain and weakness in the arm. Other local joint or tendon disorders, muscular disorders, and amyotrophic lateral sclerosis may also mimic plexopathy but can usually be differentiated by their lack of sensory abnormalities. Abdominal or retroperitoneal processes may cause irritation and pain in a distribution consistent with either a radiculopathy or plexopathy.

ED EVALUATION AND MANAGEMENT

The history and physical examination, including a detailed neurologic examination, are essential in management decisions. Motor findings are more reliable than sensory findings when evaluating the upper extremity (14). The pattern of muscle weakness is unique for each nerve root (C5–T1) and peripheral nerve. In the lower extremity, the sensory examination is more reliable than the motor examination when evaluating root disorders (14). The lower extremity sensory examination reveals root dermatomes that run horizontally or diagonally across the anterior leg, whereas the peripheral nerve dermatomes run vertically. A plexopathy will produce a pattern of muscle and sensory deficits that are a blend of both root and peripheral nerve pathology. Patten's *Neurological Differential Diagnosis* provides a detailed review of the complex clinical examination findings that will help

differentiate spinal nerve root versus plexus versus peripheral nerve disorders (14).

Patients with symptoms of *acute brachial plexopathy* should have cervical spine, chest, and shoulder radiographs. Laboratory studies such as complete blood cell count, serum electrolytes, glucose, blood urea nitrogen, creatinine, and sedimentation rate should be obtained if the history or physical examination suggests infection, diabetes, or collagen vascular disease.

Acute lumbosacral plexopathy generally occurs secondary to another disease process. A complete blood cell count, serum electrolytes, glucose, blood urea nitrogen, creatinine, erythrocyte sedimentation rate, and lumbosacral films are appropriate. An abdominal ultrasound or CT is indicated if an aortic aneurysm or other retroperitoneal pathology (e.g., bleed, tumor) is suspected. A determination of postvoid residual urine volume will aid in defining the extent of the neurologic deficit.

The approach to an *acute radiculopathy* is dictated by the history and physical examination. Whereas an evaluation consistent with an acute herniated disc and no objective neurologic deficits may require only conservative management with analgesia, muscle relaxants, limited activity, and close follow-up, the presence of objective deficits or another etiology will require an aggressive evaluation, including blood testing, a determination of postvoid residual urine volume, spinal imaging, and consultation.

In patients with chronic symptoms, minimal immediate diagnostic workup is necessary. A chest and neck radiograph or lumbosacral films are reasonable screening tools for such patients.

DISPOSITION

Acute symptoms resulting from plexopathies are often difficult to distinguish from root and spinal cord disorders (4); therefore, they generally require urgent neurosurgical consultation. Spinal CT, MRI, or myelography may be required to determine the correct diagnosis, and hospital admission to complete such testing is recommended.

Outpatient follow-up is appropriate for patients with chronic symptoms.

Common Pitfalls

- Attributing symptoms to mononeuropathy, and thereby failing to proceed with the appropriate diagnostic evaluation required for plexopathies and radiculopathies.
- Failing to consider potentially catastrophic etiologies for acute plexopathies (e.g., abdominal aneurysm).
- Failing to consider potentially catastrophic etiologies for acute radiculopathies (e.g., spinal epidural abscess or acute cord compression).

MONONEUROPATHY

CLINICAL PRESENTATION

Mononeuropathies produce variable symptoms of pain and sensorimotor loss in the distribution of a single peripheral nerve. Nerve compression (e.g., Saturday night palsy and meralgia paresthetica) and nerve entrapment (e.g., carpal tunnel syndrome) are the most frequently encountered etiologies for mononeuropathies seen in the ED. Entrapment syndromes have been associated with repetitive activity, pregnancy, rheumatoid arthritis, osteoarthritis, gout, hypothyroidism, acromegaly, amyloidosis, multiple myeloma, collagen vascular disease, and local tumors (5,15). Other causes of mononeuropathies are trauma, diabetes mellitus, peripheral vascular disease, collagen vascular disease, infection, granulomatous disease, infiltrative disorders, neoplasia, radiation therapy, and primary nerve tumors.

A unique form of mononeuropathy is mononeuritis multiplex. This entity involves the simultaneous or near-simultaneous dysfunction of two or more peripheral nerves. It may result from diabetes, multiple pressure palsies, infections (e.g., leprosy, Lyme disease, HIV infection), infiltrative or neoplastic disease, vascular disease, or collagen vascular disease (1). Overall, greater than 50%

of cases result from systemic vasculitis of the vasa nervorum (4). Abrupt onset of mononeuritis multiplex in patients with a collagen vascular disease or other vasculitis generally indicates an acute necrotizing vasculitis that requires aggressive treatment (14).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a mononeuropathy includes radiculopathy, plexopathy, polyneuropathy, local joint or muscular disorders, hysteria, and malingering.

ED EVALUATION AND MANAGEMENT

The evaluation of a mononeuropathy should focus on the nature of the deficit and historical factors such as duration, any traumatic injury, occupational factors (e.g., repetitive activity), or symptoms suggestive of diabetes, collagen vascular disease or vasculitis. The physical examination should determine whether the deficit fits the distribution of a single peripheral nerve. Provocative symptoms (e.g., Tinel sign and Phalen sign) may help elicit symptoms that are only episodic. Palpation along the course of the nerve may reveal areas of compression. Evidence of systemic disease should also be sought.

Complete blood cell count, electrolytes, blood glucose, erythrocyte sedimentation rate, antinuclear antibody testing, thyroid function tests, and serum protein electrophoresis are indicated only if a systemic disorder is suspected. Radiographs may be helpful in cases associated with trauma or when bone abnormalities are a possible cause of entrapment.

Identified etiologies, such as diabetes or repetitive activities, should be addressed. Patients with symptoms consistent with carpal tunnel syndrome may benefit from use of wrist cock-up splints.

DISPOSITION

Most patients with a mononeuropathy can be discharged with outpatient follow-up. Patients in whom the etiology is unclear should be referred to their primary care physician or a neurologist

for further testing, which may include nerve conduction studies and electromyography.

Urgent evaluation by a plastic surgeon, orthopedic surgeon, or neurosurgeon is indicated for posttraumatic mononeuropathy. Hospital admission is indicated for acute mononeuropathy multiplex in patients with known or suspected collagen vascular disease or vasculitis because this disorder usually indicates an acute necrotizing vasculitis, which requires aggressive steroid or other immunosuppressive therapy (15,19).

Common Pitfalls

- Failing to differentiate a mononeuropathy from a polyneuropathy, plexopathy, or radiculopathy.
- Failing to detect systemic signs of collagen vascular disease or other vasculitic disorder in patients with mononeuropathy multiplex.

KEY TESTING

Polyneuropathy:

- Acute onset: CBC, serum electrolyte, calcium, magnesium, phosphate, glucose, BUN, creatinine, lumbar puncture, CXR, EKG and pulmonary function testing
- Subacute onset: CBC, serum electrolyte, calcium, magnesium, phosphate, glucose, BUN, creatinine, lumbar puncture, CXR

Plexopathy:

- Acute Brachial Plexopathy: CXR, shoulder radiograph, cervical spine imaging
- Acute Lumbar Plexopathy: CBC, serum electrolyte, glucose, BUN, creatinine, ESR, lumbosacral spine imaging, postvoid residual urine volume

For All Peripheral Neuropathies:

- Testing done if clinical evaluation raises the suspicion of a specific disease process
- May include: MRI, CT scan, abdominal ultrasound, toxicology studies, thyroid studies, ESR, collagen vascular evaluation

CRITICAL INTERVENTIONS

- Perform rapid assessment of airway and ventilatory capacity, including measurements of pulmonary function, for patients with suspected GBS; repeat periodically and intubate when indicated.
- Perform lumbar puncture on patients suspected of having GBS.
- Recognize neurologic distribution (ascending vs. descending, proximal vs. distal, symmetric vs. asymmetric).
- Always consider and evaluate for the catastrophic causes of any acute radiculopathy or plexopathy.
- Admit patients with acute mononeuropathy multiplex and known or suspected collagen vascular disease or vasculitis.
- Elicit symptom onset, evolution of symptoms and prodromal illness or symptoms. Pay particular attention to medications and potential environmental, toxic or occupational exposures.

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CHAPTER 159

Bell's Palsy and Trigeminal Neuralgia

Ross P. Berkeley

BELL&RSQUO;S PALSY

Bell's palsy is an acute, unilateral facial nerve (cranial nerve VII) neuropathy that causes peripheral weakness or paralysis of the muscles of facial expression. Named after Sir Charles Bell (1774 to 1842), the Scottish surgeon and anatomist who described the innervation of the facial muscles, this is the most common disorder affecting the facial nerve, with an annual incidence of approximately 15 to 30 per 100,000 persons. Bell's palsy is an idiopathic disorder equally affecting males and females, with a peak incidence in the second through fourth decades; there is no apparent predilection for one side of the face over the other (1–3). There is an increased prevalence during pregnancy, most commonly in the third trimester and the early postpartum period, compared with nonpregnant women of the same age. Case series have suggested that the onset of Bell's palsy during pregnancy may be associated with the development of preeclampsia (4,5). Additionally, there is an increased prevalence in patients with diabetes (6).

The pathophysiology of Bell's palsy is a subject of considerable debate, but edema of the facial nerve is suspected. Postulated etiologies include inflammation leading to compression of the facial nerve at the narrowest portion of its path through the temporal bone, the meatal foramen, possibly complicated by ischemic neuropathy and demyelination. Significant attention has been given

to herpes simplex virus type 1 as a possible etiologic agent, as it has been detected in the endoneurial fluid of the facial nerve of patients with Bell's palsy who have undergone surgical decompression, but its role in the pathogenesis of Bell's palsy has not been established (1,7,8). Genetics may play a role, as between 4% and 8% of patients with Bell's palsy have an associated family history (2,8).

CLINICAL PRESENTATION

Patients with Bell's palsy often report the rapid progression of facial weakness or paralysis, usually over hours or days, and frequently believe they may have had a stroke. There is typically drooping of the corner of the mouth, loss of the nasolabial fold, and difficulty closing the eye in patients with significant facial paresis. An observer may note upward movement of the eye on attempted closure of the affected eyelid (*Bell's phenomenon*). Although tear production tends to decrease, patients may experience tearing secondary to loss of lid control. Inability to completely close the eyelid, along with decreased lubrication, commonly causes eye irritation. Patients may note alteration or loss of taste (*ageusia*) in the anterior two-thirds of the tongue and may complain of abnormal sensitivity to sounds (*hyperacusis*) secondary to paresis of the stapedius muscle. Although some patients complain of subjective numbness on the affected side, sensation is preserved in Bell's palsy (3,9).

A facial palsy is readily evident on physical examination. It is critical, however, to distinguish a central from a peripheral facial nerve deficit. Since the muscles of the forehead are innervated by both cerebral hemispheres, a supranuclear (central) seventh cranial nerve palsy spares the function of the forehead. A patient with a unilateral central lesion, such as a cortical ischemic stroke, should therefore be able to wrinkle the forehead when asked to elevate the eyebrows, although the lower two-thirds of the face will be weak. With the peripheral facial nerve deficit seen in Bell's palsy, however, the entire face on the affected side will be weak, including the muscles of the forehead. As Bell's palsy is an isolated peripheral

neuropathy, any historical or physical examination evidence of central nervous system (CNS) involvement, or the presence of other neurologic and/or systemic findings, should prompt further evaluation and a thorough workup.

DIFFERENTIAL DIAGNOSIS

Bell's palsy is defined, in part, by its idiopathic nature and unilateral peripheral facial nerve involvement. It is a diagnosis of exclusion, and a comprehensive history, along with a diligent physical examination, is essential to exclude other potentially treatable or serious causes of facial nerve paralysis.

Lyme disease (see Chapter 185), caused by the tick-borne spirochete *Borrelia burgdorferi,* may cause a unilateral or bilateral facial nerve palsy. Evidence suggestive of Lyme disease may include a history of a tick bite, a rash consistent with erythema chronicum migrans (an expanding erythematous ring-like rash with partial central clearing), and arthralgias. Painless swelling and erythema of the face preceding the palsy may help distinguish a facial palsy caused by Lyme disease from a simple Bell's palsy (10). Serologic tests for the diagnosis of Lyme disease, such as immunoglobulin titers, may be misleading, and results are not generally available during an emergency department (ED) visit. In endemic areas, Lyme disease may be responsible for a significant proportion of cases of facial nerve paralysis (11), which may be mistakenly diagnosed as Bell's palsy; more than 50% of cases of pediatric facial paralysis are due to Lyme disease (8). As there may not be a known history of tick bite in many cases and because a large portion of patients fail to manifest an erythema chronicum migrans rash, the diagnosis of Bell's palsy should be called into question in such regions.

Ramsay Hunt syndrome (herpes zoster oticus) is the second most commonly identified cause of unilateral facial nerve palsy. It is classically accompanied by a painful vesicular rash in the external auditory canal, the anterior two-thirds of the tongue, or the soft palate. In some cases, however, vesicles may be absent or have a delayed appearance, termed *zoster sine herpete;* the presence of

dermatomal pain and dysesthesia should arouse suspicion of this entity (12). Involvement of the vestibulocochlear nerve (cranial nerve VIII) may result in hearing loss, tinnitus, or vertigo in up to 75% of cases (2). Ramsay Hunt syndrome is strongly suspected to be due to the reactivation of latent varicella virus in the geniculate ganglion in previously infected patients. Ramsay Hunt syndrome tends to present with more severe facial paralysis as compared with Bell's palsy, and the syndrome has a much lower rate of complete recovery (8). Early treatment with steroids and acyclovir within the first 72 hours is typically recommended.

Human immunodeficiency virus type 1 (HIV-1) is a neurotropic virus and may cause a facial palsy that is clinically indistinguishable from Bell's palsy during the period of acute seroconversion (13). In the later stages of HIV infection, a facial palsy is generally associated with advanced immunocompromise and is more commonly the result of opportunistic CNS infection or lymphoma. Mononeuritis multiplex can be associated with early HIV infection and may present with facial paralysis but, by definition, this vasculitic syndrome involves two or more distinct peripheral nerve regions. Milder cases of this syndrome may resolve spontaneously, although more severe cases may require use of intravenous immunoglobulin or steroids (14).

An acoustic neuroma, also known as a *vestibular schwannoma,* is a slow-growing benign tumor arising in the cerebellopontine angle. Patients typically present with progressive unilateral hearing loss over a prolonged period of time, as well as tinnitus, vertigo, and dysequilibrium. Unilateral facial weakness may occur as a result of facial nerve compression by the enlarging mass. A contrast-enhanced computed tomography (CT) with fine cuts through the skull base can be used as an initial screening test; however, magnetic resonance imaging (MRI) is the diagnostic modality of choice. Treatment may include surgical skull base excision or stereotactic radiosurgery to slow growth or treat postoperative residual tumor. Other causes of facial nerve compression include cholesteatoma, meningioma, and arteriovenous malformation (AVM).

Melkersson–Rosenthal syndrome is a rare disorder of unclear etiology, associated with recurrent episodes of facial palsy, orofacial edema leading to the development of lip scarring, and a fissured tongue. A partial palsy involving only one or two branches of the facial nerve should arouse suspicion of a parotid gland mass. Appropriate history and physical examination should readily identify facial nerve paresis caused by acute and chronic otitis media or mastoiditis. Other potential infectious etiologies include Epstein–Barr virus, cytomegalovirus, mumps, tuberculosis, and leprosy. A pontine lesion or infarction may cause facial weakness, as may multiple sclerosis, but there should be other commonly associated features to differentiate from Bell's palsy. Peripheral facial nerve palsies may also be caused by temporal bone trauma, amyloidosis, and Sjögren syndrome. Guillain–Barré syndrome and sarcoidosis may also cause a bilateral peripheral facial nerve palsy (1,3).

ED EVALUATION

A careful evaluation of the eye for corneal abrasions, including fluorescein staining with examination under a Wood's lamp, is warranted in patients with a complaint of visual disturbance or eye irritation, an inability to fully close the eyelid, or conjunctival injection. The external auditory canal and oropharynx should be inspected for vesicles, which are a defining feature of Ramsay Hunt syndrome. A thorough neurologic examination should be performed to confirm that facial weakness is not of central origin.

In the absence of other neurologic or systemic findings, a diligent history and physical examination demonstrating acute unilateral peripheral facial weakness permits a clinical impression of Bell's palsy, and further diagnostic evaluation (e.g., extensive laboratory work) is unnecessary. Diagnostic imaging is indicated only if there are atypical signs or symptoms, or if a patient recently diagnosed with Bell's palsy has no improvement after 3 or more weeks. In such cases, a CT of the head with fine cuts through the skull base is an appropriate screening examination. An MRI with and without

enhancement may be useful as a subsequent diagnostic modality, but this is rarely necessary during an ED evaluation.

KEY TESTING

- Careful ophthalmologic examination including evaluation for corneal abrasion
- Thorough neurologic examination

ED MANAGEMENT

ED management begins with reassurance to alleviate patient concerns regarding stroke or brain mass, along with a discussion of the overall prognosis and potential complications of Bell's palsy. Approximately 70% to 85% of patients with Bell's palsy can be expected to spontaneously recover normal facial function (Table 159.1), often within 3 months, although full recovery may take up to 9 months (2,15). The maximal extent of facial paresis is a key prognostic indicator: 94% of those with partial paresis experience spontaneous and complete recovery, whereas only 61% of patients with complete paralysis can expect a return of normal function. Younger patients have a significantly more favorable prognosis than those older than age 60. The disorder carries an approximately 7% to 8% recurrence rate of facial nerve paresis on either side (2,3).

TABLE 159.1
Poor Prognostic Indicators of Potential for Full Recovery

Complete facial paralysis
Age >60 yrs
Diabetes
Postauricular pain
Lack of signs of remission within first 2 wks of symptom onset

Patients should be educated regarding eye protection, including wearing glasses if there is incomplete closure of the lid, and advised to apply a lubricant eye ointment or tape the eyelid closed at bedtime to prevent corneal abrasions. Artificial tears should be

recommended to maintain eye lubrication during the daytime, especially when lacrimal gland function is compromised.

Although the majority of patients with Bell's palsy will spontaneously improve, the focus of pharmacologic treatment is to decrease the risk of development of long-term complications, some of which can be significant (Table 159.2). In a 2012 guideline update based on analysis of two Class I studies, the American Academy of Neurology recommends oral corticosteroids to increase the probability of complete facial nerve functional recovery, with a number needed to treat of 6 to 8. A course of oral prednisolone at 25 mg twice daily for 10 days, or at 60 mg daily for 5 days followed by a 5-day taper, can be considered (15–17). Steroids should ideally be started within the first 3 days of symptom onset; despite a lack of compelling evidence, such treatment may be considered for patients presenting as far out as 7 days (18). Although there is a paucity of evidence supporting a definitive therapeutic effect, antiviral agents may potentially confer an incremental benefit in recovery from Bell's palsy, and can be considered as an adjuvant therapy to steroids (16).

TABLE 159.2
Potential Long-Term Sequelae of Bell's Palsy

Partial or complete unilateral facial weakness and asymmetry
Recurrent corneal abrasions, corneal ulceration, and exposure keratitis
Hemifacial spasm
Hyperacusis: due to paresis of the stapedius muscle
Dysgeusia: impairment of taste; or *ageusia:* loss of taste
Motor synkinesis: involuntary facial movements accompanying purposeful movement of other muscle groups; due to aberrant facial nerve regeneration
Crocodile tear syndrome (gusto-lacrimation): spontaneous unilateral tearing in response to salivation, due to autonomic synkinesis; rare

CRITICAL INTERVENTIONS

- Differentiate between central and peripheral cranial nerve VII palsy.

- Rule out other causes of facial nerve deficit.
- Perform a thorough ophthalmologic examination.
- Educate the patient regarding eye protection.

DISPOSITION

Patients with Bell's palsy should be discharged with close ear, nose, and throat follow-up. Ophthalmology follow-up should be arranged for patients with extensive corneal abrasions or complete facial paralysis. Surgical decompression of the facial nerve in the management of Bell's palsy is somewhat controversial and is not supported by the American Academy of Neurology in its evidence-based review of the literature (18). However, proponents of early surgical intervention recommend that patients with complete facial paralysis who do not respond to medical therapy within 2 weeks of onset should be promptly referred for electroneurography and possible surgical decompression.

The facial distortion and potential social stigma caused by Bell's palsy may be a source of embarrassment for patients, and the impairment of facial expression may affect social interactions. Referral to a facial plastic surgeon may be considered for those with long-standing paralysis. Due to the ocular complications associated with the inability to completely close the eyelid and decreased tear production, patients may benefit from implantation of a gold weight in the upper lid. Facial spasm and synkinesis may be managed by botulinum toxin injections.

Common Pitfalls

- Expensive and unnecessary diagnostic workup for a simple case of Bell's palsy
- Missed corneal abrasion
- Missed comorbidities (e.g., diabetes) that may have predisposed the patient to the disease process
- Prematurely diagnosing Bell's palsy without considering other potential causes of facial paresis

TRIGEMINAL NEURALGIA

Trigeminal neuralgia (*tic douloureux*) is a neuropathic disorder of the trigeminal nerve characterized by recurrent episodes of unilateral facial pain. The trigeminal nerve (cranial nerve V) contains sensory fibers that innervate the face, the mucous membranes of the oral and nasal cavity, and the cornea; its motor fibers innervate the muscles of mastication. Trigeminal neuralgia has an annual incidence of approximately 4.5 per 100,000 persons and typically occurs in those older than 50 years of age, with a female-to-male ratio of 3:2 (19). The right side of the face is slightly more commonly involved. In the rare instances of bilateral involvement, paroxysms of pain never occur simultaneously on both sides of the face (20).

The pathophysiology of trigeminal neuralgia is not completely understood, but it is currently believed to be caused in most cases by an overlying blood vessel compressing the trigeminal nerve near the zone where the root enters into the pons. Episodic pain may result from the spontaneous generation of repetitive action potentials along with cross-excitation of neighboring axons (20–22).

CLINICAL PRESENTATION

The paroxysms of unilateral facial pain in trigeminal neuralgia are acutely intense, lasting from a few seconds to <2 minutes, and patients may experience hundreds of episodes each day. The pain is classically described as excruciating, with a lancinating, stabbing, or electric shock–like quality, and often causes unilateral spasmodic facial contraction or grimacing. The syndrome most commonly affects the maxillary branch (second division; V2), followed by the mandibular branch (third division; V3). Involvement of the ophthalmic branch (first division; V1) is uncommon. Symptoms may be present in the distribution of two contiguous divisions of the trigeminal nerve. Patients often experience *allodynia,* a painful response to non-noxious stimuli. In many cases, episodes may be evoked by trivial stimuli within the trigeminal distribution. Paroxysms may be initiated in such “trigger zones” by lightly

touching a particular region on the face, applying makeup, washing or shaving, chewing, or even by a light breeze.

Trigeminal neuralgia initially presents as a relapsing–remitting disease, with asymptomatic intervals lasting months or years. Over time, however, exacerbations occur with progressively increasing frequency. As pain becomes more sustained, symptoms can become incapacitating. Some patients become fearful of chewing or shaving and may develop an aversion to touching the face.

DIFFERENTIAL DIAGNOSIS

The evaluation of craniofacial pain requires a detailed history and physical examination, and the diagnosis of trigeminal neuralgia should be one of exclusion. Secondary causes of the clinical syndrome of trigeminal neuralgia, including a cerebellopontine angle tumor, aneurysm, or AVM, should be ruled out. In 2% to 4% of cases, trigeminal neuralgia may also be caused by demyelinating diseases such as multiple sclerosis, a diagnosis that should be considered particularly in younger patients (22).

Herpes zoster (shingles), caused by reactivation of dormant varicella zoster virus in sensory ganglia, commonly affects the ophthalmic branch (V1). Patients often present after the typical painful vesicular rash has appeared in a dermatomal distribution, making the diagnosis straightforward. In the prodromal phase prior to onset of the rash, however, patients may complain of a severe unilateral burning or pruritic pain, which is constant; this is distinct from the episodic pain of trigeminal neuralgia. Aggressive treatment within 72 hours of symptom onset with antivirals, such as acyclovir, is generally recommended, but the role of steroids remains controversial. Involvement of the cornea in herpes zoster ophthalmicus requires ophthalmologic consultation.

Postherpetic neuralgia involving the facial nerve, which can occur in 10% of cases of herpes zoster, may cause persistent unilateral facial pain lasting months after the vesicular rash has resolved. The incidence rises with increasing age. This neuropathic pain is typically described as burning and continuous. A history of recent

herpes zoster in the affected dermatomal distribution is key to diagnosis. In addition to opioids, pharmacologic agents commonly utilized for pain management may include tricyclic antidepressants, such as amitriptyline or gabapentin (Neurontin).

Glossopharyngeal neuralgia presents with episodic unilateral pain similar to trigeminal neuralgia, but it is much less common. This syndrome is suspected to result from vascular compression of the glossopharyngeal nerve (cranial nerve IX) (21). Sensory stimulation of trigger zones in the oropharynx typically provokes paroxysms of pain in the ear, throat, or neck, and symptoms may be triggered by swallowing, yawning, or coughing. Nervus intermedius or geniculate neuralgia is extremely uncommon and may cause severe paroxysms of lancinating or stabbing pain deep within the ear.

Temporal arteritis (giant-cell arteritis) characteristically presents with unilateral pain in the temple or forehead and may include symptoms of jaw claudication or episodic unilateral visual loss (*amaurosis fugax*). The pain is typically continuous without the shooting paroxysms seen in trigeminal neuralgia, and there is tenderness upon palpation of the temporal artery.

Other causes of facial or orbital pain such as sinus infection, orbital cellulitis, and glaucoma should be considered. Temporomandibular joint dysfunction may cause facial or otic pain accompanied by a history of jaw popping or clicking, in addition to localized tenderness or limited range of motion of the mandible. Odontogenic pathology including dental caries, dental fractures, or pulpitis should be apparent on physical examination. Oral galvanism, an unusual etiology of facial pain often accompanied by a metallic taste, may be caused by an intraoral electrical current between dissimilar metals in the dental amalgam or crowns of neighboring teeth (23).

ED EVALUATION

The diagnosis of trigeminal neuralgia is made primarily on a clinical basis and requires a thorough history and physical examination. Focused attention should be dedicated to examination of the head

and neck, especially the oropharynx and teeth. Observers may note wincing or facial grimacing in association with paroxysms, which may also be provoked by lightly touching the trigger zones. The neurologic examination should be normal, with no objective abnormalities of the motor or sensory function of the trigeminal nerve. Any sensory deficit should prompt consideration of possible trigeminal nerve compression secondary to a CNS space-occupying lesion, or of multiple sclerosis, and warrants cerebral imaging. Patients with dysfunction of other cranial nerves, signs of increased intracranial pressure, or bilateral or intractable symptoms should initially undergo emergent CT of the head with fine cuts through the skull base. Subsequent diagnostic imaging with MRI and MRA is generally recommended.

KEY TESTING

- Thorough neurologic examination
- CT or MRI of brain if abnormal neurologic examination

ED MANAGEMENT

Patients should be educated regarding the prognosis of the disease, and realistic expectations should be set. In the ED, the severe pain accompanying trigeminal neuralgia may require opioid analgesics. Carbamazepine (Tegretol) is the first-line agent recommended for long-term pharmacologic management and results in good pain control in 70% of patients (20,24). It is commonly initiated at 200 mg daily, and increased by 200 mg/day until symptoms are controlled, up to a maximum dose of 1,200 mg daily. Other anticonvulsants may be required to control symptoms, sometimes in combination, including oxcarbazepine (Trileptal), lamotrigine (Lamictal), phenytoin, valproic acid, and clonazepam, in addition to gabapentin (Neurontin) and baclofen (24). Over time, the response to medications tends to decrease. Some patients, particularly those of older age, may not tolerate the CNS side effects of carbamazepine, which may include drowsiness, dysequilibrium, or confusion. Patients with intractable symptoms may develop

depression and should be directly questioned regarding suicidal ideation.

CRITICAL INTERVENTIONS

- Rule out CNS masses and vascular lesions as the cause of symptoms.
- Rule out odontogenic and other local causes of facial pain.
- Provide adequate pain relief.

DISPOSITION

Once the diagnosis of trigeminal neuralgia has been carefully made on clinical grounds and CNS disease has been ruled out, patients may be discharged home as long as their pain has been adequately controlled. Close follow-up should be arranged to monitor serum carbamazepine levels and response to therapy. Patients may require referral to a neurologist or pain management specialist. Nonemergent surgical intervention may be indicated for those with persistent symptoms that fail to respond to medical therapy. Several options exist, but no procedure is universally effective. Microvascular decompression via suboccipital craniotomy demonstrates a high level of success for immediate and long-term relief from symptoms (25). Less invasive options, performed via percutaneous intervention, include radiofrequency thermal ablation of the trigeminal nerve or Gasserian ganglion, balloon microcompression, and glycerol rhizotomy (24). All of these procedures may result in dysesthesias (22). Stereotactic radiosurgery via gamma knife is a promising alternative, although long-term outcome data are lacking.

Common Pitfall

- Although a patient may have a history and physical examination that suggest a diagnosis of trigeminal neuralgia, this should be a diagnosis of exclusion, given the potentially serious alternatives to be considered.

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CHAPTER 160

Myopathies and Disorders of Neuromuscular Transmission

Erik Nordquist

Although weakness is a common complaint of patients presenting to the emergency department (ED), it is not commonly caused by a primary muscle disorder or a disorder of neuromuscular transmission. Diagnosis and management of these disorders present particular challenges to the emergency physician because these disorders are rare and their clinical presentation is often subtle and variable.

Many neuromuscular disorders can present with rapidly progressive generalized weakness that can potentially cause life-threatening ventilatory compromise. It is important for the emergency physician to have an organized approach that is safe, quick, and thorough.

Commonly recognized conditions fall into the categories of myopathies (diseases of the muscle), disorders of the neuromuscular junction (myasthenia gravis [MG]), or peripheral neuropathies.

MYOPATHY

Myopathy is a muscle disease unrelated to any disorder of innervation or neuromuscular junction. Primary muscle disease presents with muscle weakness as the predominant symptom.

Impaired function while performing activities of daily life and muscle pain may be some of the other symptoms.

CLINICAL PRESENTATION

Weakness is generally progressive, proximal, and symmetric in distribution. Myopathy typically spares the extraocular, facial, and bulbar muscles (distinguishing the myopathies from MG and other disorders of neuromuscular junction). Although myopathic disease has gradual onset with a slow progression of symptoms, rapidly progressive generalized weakness can occur. An overview of the spectrum of myopathic disorders is given in Table 160.1.

TABLE 160.1
Classification of Myopathies

Inflammatory
Collagen vascular diseases (polymyositis, dermatomyositis, SLE, RA)
Idiopathic
Other (granulomatous, eosinophilic)

Infectious
Trichinosis
Cysticercosis (*Taenia solium*)
Toxoplasmosis
HIV
Coxsackie A and B viruses
Influenza
Lyme disease
Staphylococcus aureus

Endocrine/Metabolic
Endocrine
Addison disease
Cushing disease
Hypothyroidism (CK may be mildly elevated)
Hyperthyroidism (CK may be normal)
Hyperparathyroidism
Hyperaldosteronism
Electrolyte abnormality (Na, K, Ca, Mg, P)

Drug-Induced
Myopathy (steroids, AZT, lovastatin, cocaine, colchicine)
Myositis (procainamide)
Rhabdomyolysis (alcohol, opiates, barbiturates, phencyclidine, amphetamines)
Neuroleptic malignant syndrome (neuroleptics)
Malignant hyperthermia (general anesthetics, depolarizing muscle relaxants)

Hereditary
Muscular dystrophies
Periodic paralysis (hyperkalemic, hypokalemic, and normokalemic)
Metabolic

Others
Trauma
Ischemia
Sepsis

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; HIV, human immunodeficiency virus; CK, creatinine phosphokinase; AZT, zidovudine.

Hereditary myopathies include the various forms of muscular dystrophy, the metabolic myopathies, and periodic paralysis. Muscular dystrophies are chronic, progressive, inherited myopathies that present from early childhood to adolescence. The various types are differentiated by mode of inheritance, age at onset, rate of progression, and selectivity of muscle involvement (1). Duchenne dystrophy, observed in boys younger than 5 years, causes the most severe disease. Cardiomyopathy is common in affected children. Weakness and muscle wasting in a child with marked elevation of creatine kinase (CK) (10 to 20 times normal) occurs with Duchenne dystrophy, but other dystrophies (e.g., fascioscapulohumeral, limb-girdle, myotonic) are associated with more modest CK levels. Patients with mild cases may lead fairly normal lives, but progressive weakness and scoliosis impairing pulmonary function often result in recurrent infections and exacerbation of weakness. Diagnosis of muscular dystrophies is made on the basis of family history, clinical features, and the results of CK determination, electromyography, and muscle biopsy.

Metabolic myopathies are disorders of glucose or lipid utilization and energy production in skeletal muscle. They have common abnormalities of muscle energy metabolism that result in skeletal muscle dysfunction. Metabolic myopathies have a wide age range of symptom onset. Most patients present early in life (i.e., infancy, childhood, young adulthood).

Metabolic myopathies present with exercise intolerance, muscle cramps, and myoglobinuria. Cramps and muscle discomfort may occur after brief exercise or after prolonged physical activity. Glycogen is the main source of energy during brief exercise, and free fatty acids are the most important source of fuel during prolonged exercise. Cramps are the hallmark of glycogen-storage diseases (e.g., McArdle disease). In lipid-storage disease (e.g., carnitine palmity transferase [CPT] deficiency), muscle discomfort and exercise intolerance occur only after prolonged exercise and are worse during fasting (2).

Metabolic myopathies presenting with progressive muscle weakness may mimic limb-girdle muscular dystrophy or

polymyositis and are a common manifestation of deficiencies of acid maltase, debrancher enzyme, and carnitine.

Periodic paralyses are a group of diseases that cause patients to present with acute weakness caused by potassium shifts, leading to muscle dysfunction. A genetic defect of the potassium, calcium, or sodium-ion channels in muscle cell membranes is responsible for the paralysis, which may last from hours to days. Acute periodic paralysis may be classified as hypokalemic or hyperkalemic.

Acute hypokalemic periodic paralysis may be primary (i.e., familial) or secondary to excessive renal or gastrointestinal (GI) losses. In these cases, intracellular shift of potassium depolarizes the cell membrane, rendering it inexcitable. No muscle contraction can occur; hence, the patient experiences paralysis. However, paralysis of the respiratory muscles is uncommon.

The diagnosis of hypokalemic periodic paralysis is based on patient history, serum potassium determination (usually 2.5 to 3.5 mEq/L during attacks), and occasionally provocative testing performed in a controlled setting by a neurologist. In Asians and Hispanics, hypokalemic periodic paralysis can occur in association with thyrotoxicosis, so thyroid function tests should also be ordered (3). Familial periodic paralysis usually occurs in Caucasian males, is autosomal dominant, and may last as long as 36 hours. Attacks generally occur at night or in early morning upon awakening and can be precipitated by a diet high in carbohydrates, rest following exercise, or stress (4).

In the hyperkalemic form of periodic paralysis, attacks are more frequent, are of shorter duration (usually <2 hours), and are provoked by cold exposure, rest following exercise, fasting, or the ingesting of potassium (4). During an attack, the serum potassium is in the range of 5 to 7 mEq/L.

Polymyositis, an inflammatory disorder of skeletal muscle, is the most common primary myopathy to affect adults. Muscle damage is caused by T-cell–mediated and compliment-mediated autoimmune attack. Clinically similar to adult polymyositis, dermatomyositis is an idiopathic inflammatory myopathy associated with characteristic

dermatologic manifestations. Dermatomyositis is frequently associated with an underlying malignancy.

Symptoms of adult polymyositis gradually develop over a period of 3 to 6 months. Diagnosis is usually delayed because, unlike in dermatomyositis, no associated rash occurs before onset of muscle disease. Patients usually present with symmetric proximal muscle weakness in the upper and lower extremities. Distal muscle weakness may occur late in the course of the disease. Patients may report muscle pain and tenderness that may be confused with polymyalgia rheumatica. Constitutional symptoms include morning stiffness, fatigue, anorexia, fever, and weight loss. Dysphagia secondary to oropharyngeal and esophageal involvement occurs in about a third of patients and is a poor prognostic sign. Dysphonia is also a poor prognostic sign but is much less common. Ocular muscles are never involved in generalized polymyositis. However, isolated orbital myositis, an inflammatory disorder involving the extraocular muscles, is well described. Facial and bulbar muscle weaknesses are extremely rare manifestations.

The diagnosis of polymyositis is made on the basis of a combination of proximal muscle weakness, elevated muscle enzymes, detection of autoantibodies, characteristic electromyogram, and muscle biopsy (5). The erythrocyte sedimentation rate is often normal or only mildly elevated and is not a reliable indicator of disease severity.

DIFFERENTIAL DIAGNOSIS

Myopathic weakness may be caused by MG, inflammatory polyneuropathy (Guillain–Barré syndrome), neurotoxin exposure (e.g., botulism, tick paralysis, organophosphate poisoning), severe electrolyte abnormalities, drug- and alcohol-induced myopathy, periodic paralysis, and rarely polymyositis.

The differential diagnosis of subacute or chronically progressive weakness includes polymyositis, the muscular dystrophies, MG, polymyalgia rheumatica, and drug-induced myopathy. Proximal muscle weakness can also present because of hypothyroidism,

hyperthyroidism, hyperparathyroidism, Addison disease, Cushing syndrome, hypokalemia, hypophosphatemia, or hypomagnesemia. Chronic alcohol abuse can produce a syndrome of proximal muscle weakness and wasting, often with coexistent evidence of alcoholic peripheral neuropathy.

ED EVALUATION

In the face of profound weakness, immediate attention to the ventilatory status and airway stabilization are indicated before performing a detailed history and physical examination. Patient evaluation should focus on distinguishing neurologic from muscular dysfunction. Key components of the history include onset and time course, symmetry and fluctuation of symptoms, sensory deficits, involvement of proximal or distal muscle groups, association with activity such as climbing stairs, difficulty swallowing, precipitating factors, associated pain or stiffness, and sensory deficits. Complaints that suggest a central nervous system origin include diplopia, dysphagia, ataxia, or hemiparesis. Proximal muscle involvement causes difficulty performing activities such as rising from chairs, getting out of the bathtub, climbing stairs, and combing hair. Distal muscle involvement is suggested by weak grasp and handwriting problems.

Information should also be elicited about family history, underlying medical illnesses, medication use, and exposure to homemade or contaminated food. Steroids (especially fluorinated steroids), lipid-lowering agents, azidothymidine, alcohol, colchicine, pentachlorophenol (PCP), heroin, and cocaine may cause myopathies.

On physical examination, the patient should be tested for the ability to perform simple tasks (e.g., lifting arms above head, ability to make a tight fist, rising on the toes, or rising from the chair). Determine the distribution of muscle involvement including the extraocular, facial, or bulbar musculature. Pathologic muscle fatigue may be elicited by having the patient sustain an upward gaze, count loudly, or hold the arms horizontally. The muscles should be

inspected for size and irritability and palpated for tenderness. The neurologic examination must include an evaluation of pupillary size and reactivity, sensory function, and deep tendon reflexes (DTRs). DTRs and sensory perception should be normal in myopathies. DTRs may be diminished or absent in hypokalemic paralysis. A careful search for an adherent tick is important when appropriate.

Using the history and physical examination, it is generally possible to exclude disorders of neuromuscular transmission such as MG, peripheral neuropathy, and lower and upper motor neuron disease from the diagnosis of myopathy. The diagnosis of MG is suspected on the basis of weakness and fatigability in the typical distribution without loss of reflexes or impairment of sensation or other neurologic function. Peripheral neuropathy is characterized by areflexia, sensory ataxia, varying degree of cutaneous sensory deficit, and variable degrees of motor dysfunction. Lower motor neuron dysfunction and early denervation is characterized by insidiously developing asymmetric weakness, progressive muscle wasting and atrophy, and loss of DTRs. Finally, upper motor neuron disease is characterized by spasticity in the extremities (usually legs more than arms), brisk tendon reflexes, up-going plantar reflexes, and minimal to no sensory deficits.

Essential laboratory studies should include a complete blood count, erythrocyte sedimentation rate, thyroid function test, CK with isoenzymes, electrolytes, calcium, magnesium, phosphorus, myoglobin, serum creatinine and blood urea nitrogen (BUN), urinalysis (looking for myoglobin), chest x-ray (CXR), and ECG. Arterial blood gas (ABG) and bedside spirometry or peak flow should be performed to evaluate for ventilatory compromise.

KEY TESTING

- CBC
- Electrolytes, calcium, magnesium, phosphorus, myoglobin, serum creatinine, and BUN
- Erythrocyte sedimentation rate
- Thyroid function test

- CK with isoenzymes
- Urinalysis for myoglobin
- ABG and bedside spirometry/peak flow to evaluate for ventilatory compromise

ED MANAGEMENT

In patients with neuromuscular disease presenting with severe and rapidly progressing weakness, the crisis is usually precipitated by an intercurrent illness, most commonly a respiratory tract infection. These patients often present with ventilatory compromise, ineffective cough, and difficulty handling secretions. Decompensation to respiratory failure can be rapid. Immediate attention should be directed to oxygenation and ventilatory status. Serial physical examination, ABG determination, and spirometry are essential, and endotracheal intubation should be performed at the earliest sign of difficulty. Normal levels of pCO_2 and pO_2 are often maintained nearly to the point of profound respiratory failure and respiratory arrest.

The need for intubation and mechanical ventilation is best guided by serial measurement of vital capacity. A declining vital capacity or a vital capacity <15 mL/kg is an indication for urgent intubation. Patients with severe weakness should be ventilated, at least initially, in the controlled mode.

Attention to hemodynamic stability is the next priority, with continuous electrocardiographic monitoring and evaluation of fluid needs. CK determination and urinalysis are mandatory to identify acute rhabdomyolysis.

For polymyositis, prednisone is the first-line treatment of choice. Typically, the dose is 1 mg/kg/d, either as a single dose or divided. This high dose is usually continued for 4 to 6 weeks, until the muscle strength improves. Corticosteroid myopathy can occur during the course of treatment and must be distinguished from reactivation of muscle disease. CK level is usually within reference ranges in cases of steroid myopathy. No improvement is observed with higher doses of steroids, and the condition worsens if the dose

is increased. Immunosuppressive agents, such as methotrexate, azathioprine, or mycophenolate mofetil, are often initiated with the steroid therapy or may be reserved for patients who do not respond to initial therapy. Patients with poor prognostic indicators, such as dysphagia or dysphonia, usually require immunosuppressive agents.

Acute attacks of the hyperkalemic form of periodic paralysis often do not require treatment as they are brief. However, in more severe attacks, calcium gluconate (1 to 2 g IV) or glucose and insulin (1 amp $D_{50}W$ with 5 units of regular insulin IV) can be given. To prevent attacks, chronic therapy with a thiazide diuretic or acetazolamide may be given.

Treatment of acute hypokalemic periodic paralysis includes 60 to 120 mEq KCl given incrementally. Potassium administration should proceed slowly, as total body potassium stores are generally normal, to avoid posttreatment hyperkalemia. Acetazolamide prophylaxis and avoidance of high-carbohydrate meals are useful in chronic management (4).

DISORDERS OF NEUROMUSCULAR TRANSMISSION

The neuromuscular junction is the critical link between the central nervous system and the musculoskeletal system. Maintaining integrity of neuromuscular transmission is essential for effective communication between nerve and muscle and is required for maintaining skeletal muscle function, including the mechanism of breathing. Although disease states associated with malfunction of the neuromuscular junction only rarely present in the ED, these conditions are potentially fatal ailments; therefore, they must be considered in all patients who present with isolated or generalized muscle weakness of unknown etiology (Table 160.2). Alternatively, these disorders can be divided according to the site of derangement as seen in Table 160.3.

TABLE 160.2
Disorders of Neuromuscular Transmission

Congenital
Congenital myasthenia gravis
Acetylcholinesterase deficiency

Toxin-Induced
Clostridium botulinum
Snake/scorpion envenomation
Paralytic shellfish poisoning

Autoimmune
Myasthenia gravis
Lambert–Eaton syndrome

Poisoning
Organophosphate poisoning, carbamates

Drugs
Magnesium
D-Penicillamine
Aminoglycosides
Chloroquine
Fluoroquinolones
Phenytoin
β-Blockers
Quinidine
Procainamide
Chlorpromazine
Lidocaine

TABLE 160.3
Division of Disorders of Neuromuscular Transmission by Categories

Presynaptic
Lambert–Eaton syndrome
Botulism
Hypermagnesemia
Scorpion toxin

Synaptic
Organophosphate poisoning
Acetylcholinesterase deficiency

Postsynaptic
Myasthenia gravis
Congenital myasthenia
Snake venom

The hallmark of weakness associated with failure in neuromuscular transmission is fatigability. The patient may present to the ED with complaints of gradual weakness followed by the precipitous onset of muscular exhaustion. Typically, muscle weakness resolves briefly after a short rest and then worsens again. Neuromuscular transmission failure should also be considered in patients who report complaints of more generalized symptoms such

as chronic fatigue and shortness of breath, especially when there is no other obvious explanation for the clinical presentation.

MYASTHENIA GRAVIS

Clinical Presentation

MG, the most common disease of neuromuscular transmission, is an autoimmune disorder in which antibodies are directed against the acetylcholine (ACH) receptor, reducing the number of available receptors and impairing neuromuscular transmission (6). This disease is almost always associated with an abnormality of the thymus gland, either thymoma (15%) or thymic hyperplasia (75%). The thymus appears to be the site where B cells are sensitized to the ACH receptors, initiating the disease process. A reduction in the number of ACH receptors results in a characteristic pattern of progressively reduced muscle strength with repeated use of the muscle and recovery of muscle strength following a period of rest.

The incidence of MG is estimated to be about 15 per million people (6). The disease is most common in women in their mid-twenties, although it can occur at all ages. The peak incidence for men is the sixth to eighth decade of life.

The hallmark of MG is pathologic fatigue, caused by the loss of the generous physiologic reserve that normally supports transmission across the neuromuscular junction. Muscle weakness worsens with sustained activity and improves with rest. Patients commonly report worsening of symptoms as the day progresses.

MG is a disease of insidious onset, developing over a period of weeks to months. The muscle weakness occurs at first in transient attacks, at times precipitated by infection, stress, or pregnancy. The extraocular muscles are most commonly affected, and the most typical presentation is one of recurring episodes of diplopia and ptosis that are often noticed later in the day. There may be weakness of eye closure, weakness of the muscles of facial expression, or difficulty chewing. Transient dysarthria and dysphagia are common. Patients may also have involvement of the

proximal limb, truncal, and respiratory muscles and note difficulty climbing stairs or combing their hair.

The disease is extremely variable in its clinical presentation and may affect diverse muscle groups in an asymmetric, unpredictable manner, fluctuating in intensity over time. Spontaneous remissions and relapses are common, and the ultimate progression of the disease is highly variable. Respiratory crisis requiring mechanical ventilation occurs in up to 20% of patients.

Differential Diagnosis

The differential diagnosis includes drug-induced myasthenia, Lambert–Eaton myasthenic syndrome, neuroasthenia or psychoneurotic fatigue, botulism, inflammatory polyneuropathy (Guillain–Barré syndrome), periodic paralysis, and other causes of oculomotor paralysis (diabetes, multiple sclerosis, aneurysm). History, physical examination, and simple laboratory investigations should enable the emergency physician to readily distinguish between these entities. It is important for the emergency physician to consider the possibility of one of these diagnoses before making a diagnosis of functional or psychiatric illness.

ED Evaluation

The clinical evaluation of the patient presenting with a history of episodic weakness and fatigue involving extraocular, facial, or bulbar musculature should focus on obtaining a careful history, ruling out an underlying precipitating illness, demonstrating pathologic fatigue on physical examination, and considering possible etiologies.

On physical examination, the physician can perform provocative maneuvers, the simplest being extraocular movements. Fatigue with repeated muscle contraction supports the diagnosis. Other maneuvers that may be used to unmask underlying neuromuscular fatigability include having the patient count up to 100 or chew for 30 seconds while observing signs of functional deterioration. It is important to remember that the patient with MG has normal pupils,

DTRs, and sensation. A major focus of evaluation of MG in the ED is ongoing evaluation of the patients' respiratory status and ability to handle secretions. Bedside spirometry is helpful as a baseline as is ABG analysis looking for evidence of CO_2 retention.

The clinical diagnosis of MG is supported by noting a positive response to a bedside test (Tensilon test or ice pack test). IV edrophonium chloride (Tensilon) is a short-acting anticholinesterase inhibitor. Administration produces rapid improvement of ocular symptoms in patients with MG. Edrophonium should be used with caution, especially in cardiac patients, because of its potential for causing bradycardia. When this test is performed, the patient should be placed on a monitor, and atropine should be available at the bedside. Administer 2 mg of edrophonium IV. This dose can be repeated every 60 seconds up to a total dose of 10 mg. Evaluate the patient for improvement of weakness after each dose. Reversal of eyelid ptosis is the most specific sign. A false-positive response to edrophonium chloride has been reported in amyotrophic lateral sclerosis, Lambert–Eaton myasthenic syndrome, Guillain–Barré syndrome, wound botulism, cavernous sinus lesions, poliomyelitis, and alcoholic myositis (7).

The ice pack test will often improve ptosis in patients with MG. In the ice pack test, a bag of ice is applied to the closed eyelid for 2 minutes. The degree of ptosis should be evaluated immediately after removing the bag of ice (7).

A more definitive test is a repetitive nerve stimulation study or single-fiber electromyography. In MG, there is a decrement in the amplitude of the evoked muscle action potential when the motor nerve is repetitively stimulated at 3 cycles/sec.

If the diagnosis of MG is confirmed further testing should include an assay for circulating anti-ACH receptor antibodies. A CXR, thyroid function tests, and serologic testing for associated autoimmune diseases should also be performed.

KEY TESTING

- Tensilon test or ice pack test

- CBC
- Electrolytes, calcium, magnesium, phosphorus, myoglobin, serum creatinine, and BUN

ED Management

The major focus of ED management of all disorders of neuromuscular transmission is ongoing evaluation of the patient's respiratory status. The maintenance of a patent airway may be difficult because of increased oral secretions and inadequate protective reflexes. Evidence of respiratory failure may be noted on ABG, pulmonary function tests, or pulse oximetry. Rapid sequence intubation should be modified because depolarizing paralytic agents (e.g., succinylcholine) have less predictable results in patients with myasthenia. The relative lack of ACH receptors makes these patients relatively resistant to succinylcholine; therefore, higher than usual doses of succinylcholine may be necessary to induce paralysis or one may use a nondepolarizing agent, such as rocuronium.

Once the airway is secured, investigation into the cause of the weakness or exacerbation of myasthenia may be undertaken. There are five major therapeutic options in managing patients with MG: anticholinesterases, immunosuppressives, thymectomy, plasmapheresis, and IV immunoglobulin (8).

Anticholinesterases are considered first-line agents for treatment of MG. Their primary action is to increase the concentration of ACH at the synapse. Pyridostigmine is the most frequently used agent in this class. Although the anticholinesterases provide symptomatic relief, they do not influence the progression of the disease. The initial dose of pyridostigmine is frequently 30 mg every 8 hours.

Immunosuppressive therapy is added to the medication regimen of patients whose symptoms are inadequately controlled by anticholinesterase drugs. Corticosteroids are the initial agent of choice followed by other agents such as azathioprine, cyclosporine, or mycophenolate mofetil, if steroids are contraindicated or ineffective.

Thymectomy is indicated in selected patients younger than 60 years of age who have the generalized form of MG and in those individuals who have thymoma (8). Randomized controlled trials evaluating the efficacy of thymectomy in MG are lacking; however, observational studies have noted patients who undergo thymectomy are twice as likely to show improvement.

Plasmapheresis and IV immunoglobulin (IG) are two short-term therapeutic options that are particularly useful when rapid clearance of antibody is required either to improve symptoms in myasthenic crisis or in patients in whom immunosuppressive treatment has been initiated. The recommended dose for IG is 2 g/kg over 2 to 5 days, and the improvement begins within 4 to 5 days following administration (9,10).

Some medications including anticonvulsants, neuromuscular blockers, some antibiotics, and major analgesics (Table 160.4) should not be administered in patients with MG. Acute intercurrent medical and surgical problems in patients with MG should always be managed in consultation with a neurologist (11).

TABLE 160.4
Common Drugs Capable of Impairing Neuromuscular Transmission or Exacerbating Weakness in Patients with Myasthenia

Antibiotics	**Psychotropics**
Aminoglycosides	Chlorpromazine
Ampicillin	Lithium
Clarithromycin	Phenothiazines
Clindamycin	**Analgesics/Muscle Relaxants**
Fluoroquinolones	Benzodiazepines
Anticonvulsant	Ketamine
Phenytoin	Lidocaine
Gabapentin	Narcotics
Cardiovascular	**Other Drugs**
β-Blockers	Glucocorticoids
Calcium channel blockers	Magnesium sulfate
Quinidine	Iodinated contrast agents
Procainamide	Statins

Myasthenic Crisis Versus Cholinergic Crisis

One of the confusing factors in treating patients with MG is rapid worsening of the disease caused by insufficient medication (i.e., myasthenic crisis) and side effects of excessive medication (i.e., cholinergic crisis) since they both have similar presentations. Cholinergic crisis results from an excess of cholinesterase inhibitors (i.e., neostigmine, pyridostigmine, physostigmine) and resembles organophosphate poisoning. Excessive ACH stimulation of striated muscle at nicotinic junctions produces flaccid muscle paralysis that is clinically indistinguishable from weakness due to MG. As a rule, in cholinergic crisis, worsening muscle weakness should be accompanied by symptoms of cholinergic excess, including salivation, lacrimation, urination, diarrhea, gastric distress (cramps), emesis, miosis, and bradycardia. Edrophonium can be a useful tool. This agent should make myasthenic weakness better and should exacerbate the cholinergic crisis. Unfortunately, edrophonium has limited use in an acutely decompensating patient. Therefore, it is recommended that all anticholinesterase medications be stopped in myasthenic crisis (11).

In practice, the distinction between myasthenic crisis and cholinergic crisis may not be very relevant, because initial

management does not involve the administration of cholinergic agents for the patient with myasthenic crisis.

Myasthenic crisis is a true emergency and usually requires respiratory support. Fifteen percent to 20% of myasthenic patients will experience at least one episode of myasthenic crisis (11). In the majority of patients with myasthenic crisis, an underlying precipitating event can be identified. Infection is the most common risk factor, followed by aspiration pneumonitis and changes in medication (especially initiation or withdrawal of corticosteroid). In 30% to 40% of the patients with myasthenic crisis, no precipitating factor can be identified (11). Management of the patient with myasthenic crisis requires general supportive measures and rapid reduction in anti-ACH receptor antibody load. Plasmapheresis is beneficial in myasthenic crisis, and improvement in the patient's clinical status can be seen within a few days. IV IG should also be considered. In a critically ill patient with a secured airway, high-dose steroid therapy should be initiated immediately. All medications that may impair neuromuscular transmission should be discontinued.

BOTULISM

Botulism is caused by a neurotoxin produced by the anaerobic organism *Clostridium botulinum. C. botulinum* toxin irreversibly binds to the presynaptic membrane and prevents release of ACH. A rapidly progressive descending paralysis follows and is accompanied by prominent, autonomic symptoms and respiratory involvement. Because the disorder is at the neuromuscular junction, there is no sensory deficit and no sense of pain.

Botulism may vary from a mild illness to a fulminant, fatal one. Cranial nerve findings in the presence of GI symptoms should alert the ED physician to the diagnosis of botulism. Prodromal symptoms of nausea, vomiting, diarrhea, and a dry, painful throat develop hours to days after ingestion of contaminated food. Neurologic symptoms are usually noted within 72 hours of ingestion and include anticholinergic effects (dry eyes, dry mouth, dilated pupils,

absent pupillary light reflex, ileus, and urinary retention) and fluctuating but rapidly progressive weakness, with early involvement of the extraocular and bulbar muscles (with ptosis, diplopia, dysphagia, and dysphonia as common early symptoms). The disease then progresses over several days to involve all the muscles of the trunk and extremities. Respiratory compromise can develop rapidly as the symmetric paralysis descends (12).

See Chapter 352, for detailed information on the clinical presentation and management of botulism.

LAMBERT&NDASH;EATON SYNDROME

Lambert–Eaton myasthenic syndrome is a rare autoimmune condition affecting the presynaptic membrane. Failure of neuromuscular transmission in Lambert–Eaton syndrome is caused by the insufficient release of a neurotransmitter at the presynaptic terminal. Antibody-mediated blockade of the voltage-gated calcium channel (VGCC) compromises rapid influx of calcium, which results in deficient neurotransmitter release.

Lambert–Eaton syndrome exists in a primary form but may be a manifestation of a paraneoplastic disorder. Malignancy is a common cause of rapidly evolving symptomatology in patients with Lambert–Eaton syndrome. The majority of patients with Lambert–Eaton syndrome are older than 60 years of age, but it has been described in all age groups.

The weakness in Lambert–Eaton syndrome is severe at the onset, but it improves soon after initiation of activity and then it deteriorates. Muscle weakness in Lambert–Eaton syndrome tends to be symmetrical and is most pronounced in the lower extremities. Altered gait after prolonged walking usually is the initial symptom. This weakness may progress to inability to rise from a chair or walk up stairs. Ocular and bulbar symptoms are not common and are mild in nature when present. Autonomic symptoms are common and occur in more than half of the patients. On physical examination, proximal muscle weakness is the most prominent clinical finding. The peculiar weakness in Lambert–Eaton syndrome patients may be

demonstrated during hand grip. The initial grip may be weak but gets stronger, only to weaken again (13).

The treatment for nonneoplastic cases of Lambert–Eaton myasthenic syndrome includes symptomatic therapies, such as 3,4-diaminopyridine, and immunologic therapies, such as glucocorticoids, azathioprine, IV IG, and plasma exchange. The neoplastic variant may respond to similar treatment; in addition, it requires treatment of the underlying malignancy (14).

TICK PARALYSIS

Tick paralysis is the result of envenomation from the gravid female tick and presents as an ascending flaccid paralysis or as an acute ataxia (15). In the United States, the disease occurs primarily in children during warmer months and is caused by the common dog tick (*Dermacentor variabilis*) or female wood tick (*Dermacentor andersoni*). The primary abnormality is in conduction in the peripheral nerves at the neuromuscular junction. The presentation is similar to Guillain–Barré syndrome. The presenting symptoms are ascending symmetric paralysis over 1 to 2 days, eventually involving the bulbar muscles. Ataxia may be present and may be the earliest finding. Sensory changes are rare, and DTRs are absent or decreased. The physician should perform a careful physical examination noting the presence and subsequent removal of the tick. The ticks are often found in the scalp, especially at the hairline. The removal is followed by prompt recovery. Unrecognized, the patient may progress to respiratory paralysis.

The definitive treatment for tick paralysis involves a careful examination for detection of the tick, and its removal.

DISPOSITION

Patients with severe weakness require admission to an intensive care setting for supportive care, monitoring of cardiorespiratory status, treatment of any underlying illness, and further diagnostic evaluation. Admission is indicated for patients with slowly progressive neuromuscular weakness if there is any concern about

the patient's respiratory reserve, if the degree of pharyngeal muscle weakness suggests a risk of aspiration, if rhabdomyolysis is suggested by CK determination and urinalysis, or if the patient cannot function satisfactorily at home. The decision to manage the problem on an outpatient basis must be made after consultation with the primary care physician, internist, or neurologist and on the condition that follow-up can be reliably arranged.

CRITICAL INTERVENTIONS

- Determine the need for intubation and mechanical ventilation by serial measurement of vital capacity. A declining vital capacity or a vital capacity <15 mL/kg is an indication for urgent intubation.
- Use a rapid-onset nondepolarizing agent (i.e., rocuronium, vecuronium) when paralysis is needed for intubating patients with MG.
- Perform a thorough search for an underlying precipitating illness in a patient with myopathy or MG who presents with an exacerbation.
- Perform a thorough search for a tick in patients presenting with new weakness.
- Obtain electrolytes on patients presenting with weakness.

Common Pitfalls

- Attributing a history of episodic weakness to neuroasthenia (psychogenic weakness) without considering the possibility of a neurologic disorder (e.g., periodic paralysis, MG, or multiple sclerosis).
- Failing to take a careful focused history in a patient presenting with a possible neurologic complaint.
- Failing to perform a thorough search for an underlying precipitating illness in a patient with myopathy or MG who presents with an exacerbation.
- Attempting an edrophonium test or other pharmacologic maneuvers in the acute management of myasthenic patients

presenting in crisis. Acute treatment involves attention to airway and ventilatory status with a low threshold for endotracheal intubation. Management decisions should be made in consultation with a neurologist.

- Prescribing medications that may exacerbate weakness in MG. Emergency physicians must be aware of drugs that can impair neuromuscular function. Treatment decisions should be made in consultation with a neurologist.

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CHAPTER 161 Demyelinating Disease

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The term demyelinating disease is applied to a group of central nervous system (CNS) diseases that affect the myelin sheath but largely spare the axon. The major subgroups of demyelinating disease have been classified as follows: Group 1, demyelinating disease in which a disease process of exogenous origin affects and destroys normally formed myelin sheaths; and Group 2, dysmyelinating disease in which defective formation of myelin exists as a result of an inborn error of metabolism. This error of metabolism is usually a genetically determined enzymatic disturbance.

Multiple sclerosis (MS) is the most common autoimmune inflammatory disease of the CNS, affecting more than two million people worldwide. More than 400,000 people are affected in the United States. The disease occurs with an incidence of about 7 per 100,000 per year and a lifetime risk of 1 in 400. MS is a disease of young people, typically aged 18 to 50 years. MS is uncommon in children <10 years of age and usually presents before the age of 55. The onset tends to be earlier in women than in men. The female to male ratio is approximately 2:1. MS is more frequent in Caucasians of northern European origin and less common in Africans, Asians, and Mediterranean populations.

Although the cause of MS remains unknown, there appears to be an interaction between undefined environmental factors and genetic susceptibility to produce an inflammatory autoimmune response mediated by autoreactive T cells directed against components of myelin. Direct proof of an autoimmune cause is lacking, however,

and no specific autoantibody or autoreactive T cell directed against a self-antigen in the CNS can passively transfer MS to experimental animals.

The name *multiple sclerosis* speaks to the multitude of lesions throughout the CNS that have a sclerotic appearance on pathological specimens. Clinically, the manifestations of MS result from disruption and abnormal transmission of nerve impulses within the CNS by focal areas of demyelination.

MS is most often characterized by exacerbations of acute or subacute onset that last for days to months. Exacerbations are more commonly manifested by the reappearance of previous signs and symptoms than by the development of new ones. Recovery between exacerbations may be complete or incomplete. Relapsing, remitting disease refers to a situation in which the clinical course between exacerbations is stable. In general, a pattern of intermittent exacerbations is more common in the earlier stages of the disease, whereas progressive deterioration, with or without superimposed exacerbations, is more common in the later stages (secondary progressive course). A small percentage of patients experience disease progression from the onset, with or without superimposed exacerbations (primary progressive and progressive relapsing disease, respectively) (1).

CLINICAL PRESENTATION

The classic clinical picture of MS is that of multiple neurologic symptoms disseminated in space and time. The diagnosis of MS cannot definitely be made in the emergency department (ED). When symptoms first appear, they often develop steadily over days. Visual complaints often occur early. Symptoms such as blurring of vision, alteration in visual acuity and diplopia are common. Up to 40% patients with MS have optic neuritis, but up to 40% of patients with optic neuritis do not go on to develop MS. No single clinical feature or diagnostic test is sufficient for a final diagnosis, although some are relatively characteristic.

The diagnosis of MS continues to focus on objective demonstration of dissemination of lesions in time and space. This temporal perspective is generally unavailable to the emergency physician seeing the patient at only one point in time. In addition, diagnostic test results that enhance the confidence of a clinical diagnosis of MS are often not immediately available in the ED. Ultimately, the diagnosis of MS is a life-altering condition that imposes a significant psychological burden and should therefore not be made without a substantial degree of certainty.

The nature of the deficit depends on the anatomical location of the demyelinating lesion and its size and age (acute vs. chronic). The demyelinating process can also result in the generation of ectopic impulses, abnormal transmission of impulses between neighboring nerve fibers, and increased mechanical sensitivity. These phenomena are the basis for the generation of symptoms such as Lhermitte sign (an electric shock-like, tingling, or vibrating sensation in the torso or extremities that is produced by flexion of the neck against resistance), flashes of light on eye movement (phosphenes), and paroxysmal symptoms such as trigeminal neuralgia, ataxia, and dysarthria or painful tetanic posturing of the limbs triggered by touch or movement. Conduction in partially demyelinated axons fails with an increase in temperature, giving rise to characteristic worsening of symptoms with a rise in temperature as may occur with exercise or a warm bath (Uhthoff phenomenon) (1). Demyelination can occur anywhere within the CNS and the possible clinical manifestations of MS are therefore extremely varied. However, MS lesions have a predilection for certain sites, resulting in a relatively limited distribution of typical initial symptoms (2). Although no symptoms or neurologic findings are pathognomonic, some are characteristic and should heighten the clinician's diagnostic suspicions. The majority of patients present with one or more of the following signs and symptoms (see Table 161.1 for the common initial symptoms of MS).

TABLE 161.1
Common Initial Symptoms of Multiple Sclerosis

Visual loss
Paresthesias and numbness
Diplopia and oculomotor dysfunction
Weakness: monoparesis, paraparesis
Lhermitte sign
Incoordination, unsteady gait, abnormal balance
Acute transverse myelopathy
Vertigo
Bladder, bowel dysfunction
Tremor
Trigeminal neuralgia

Decreased visual acuity and symptoms related to oculomotor dysfunction are among the most common initial presenting symptoms of MS. Optic neuritis characteristically presents with subacute monocular loss of vision although simultaneous or sequential loss of vision can occur in both eyes. Visual loss typically progresses over days to 2 weeks and is accompanied by headache or retroorbital or periocular pain in most but not all cases that may be exacerbated by movement of the eye. Maximal loss of visual acuity varies from blurring to absence of light perception in the affected eye. Alteration of color vision and visual field defect may occur. Slit lamp exam is usually normal but occasionally may reveal cells and flare in the anterior chamber. The optic disc appears swollen on initial presentation in 36% to 58% cases. An afferent pupillary defect (Marcus Gunn pupil) consisting of diminished response to a direct light stimulus and a normal consensual response to a light stimulus in the opposite eye may be noted. Approximately 50% to 60% of patients with optic neuritis will have periventricular white-matter abnormalities consistent with demyelination on an initial magnetic resonance imaging (MRI) scan. Optic nerve involvement may remain as an isolated manifestation, but if demyelination is found on MRI as well, 72% of those patients will convert to MS

within 15 years, in contrast to 25% of those with a normal MRI (3,4).

Nystagmus and diplopia occur commonly in patients with MS. The finding of internuclear ophthalmoplegia (INO), especially in a young adult, is very suggestive. This form of dysconjugate gaze, localized to the medial longitudinal fasciculus (MLF) of the brainstem, involves limited adduction of one eye and nystagmus in the abducting eye on lateral gaze. Although there are other potential etiologies for INO, such as ischemia and neoplasm, these are much less common.

Sensory symptoms are among the most common presenting symptoms of MS and include numbness, tingling, pins and needles, tightness and coldness of the limbs or trunk. Radicular pain and itching in a dermatomal distribution can occur. Symptoms are variable in distribution and can be referable anatomically to the spinothalamic, posterior column and dorsal nerve root or can occur distally in the extremities or in a patchy distribution. Motor weakness may occur as paraparesis, hemiparesis, or monoparesis and is generally accompanied by signs of upper motor neuron dysfunction (e.g., hyperreflexia, hypertonia, and positive Babinski sign) (1). Transverse myelitis can be the initial neurologic event. Symptoms include ascending weakness and numbness below the level of the lesion.

The brainstem can be affected by MS plaques. Neuroanatomically, both ascending and descending tracts are found within the brainstem in close proximity. Corticospinal, corticobulbar, spinothalamic, lemniscal, vestibular and cerebellar tracts, and interneural pathway connections can be affected. Likewise, 11 of the 12 cranial nerves have either nuclei in the brainstem or synaptic connections within the brainstem.

Patients with Known Multiple Sclerosis

In most cases, the natural history of MS is characterized by episodes of neurologic dysfunction alternating with periods of stabilization or remission of symptoms. Common signs and symptoms of chronic

disease are listed in Table 161.2. Patients with known MS may present to the ED because of an exacerbation of previous deficits, because of the development of new deficits, or because of medical complications of the disease.

TABLE 161.2
Common Chronic Problems of Multiple Sclerosis

Problem	Drugs Used in Treatment
Weakness: monoparesis, paraparesis, hemiparesis, quadriparesis	Corticosteroids, potassium-channel blockers (i.e., 4-aminopyridine; 3,4-diaminopyridine)
Spasticity	Baclofen (oral or intrathecal), benzodiazepines, dantrolene, tizanidine
Paresthesias	Amitriptyline, carbamazepine, gabapentin, corticosteroids if disabling
Bladder dysfunction	Depends on type of impairment
Optic atrophy, blurred vision, central scotoma	Intravenous methylprednisolone for acute optic neuritis
Internuclear ophthalmoplegia, diplopia	Corticosteroids
Loss of balance, incoordination, ataxia tremor	Clonazepam for tremor, corticosteroids for balance
Cognitive changes	Disease-modifying agents (e.g., interferon beta, glatiramer acetate); assessment for depression
Depression	Antidepressants
Sexual dysfunction	Sildenafil, intracavernosal prostaglandins (for erectile dysfunction)
Fatigue	Amantadine, CNS stimulants
Vertigo	Meclizine, prochlorperazine, diazepam, metoclopramide
Paroxysmal symptoms: itching, burning, twitching, Lhermitte sign	Carbamazepine, phenytoin, tricyclic antidepressants, low-dose antipsychotics, gabapentin
Pseudobulbar palsy	Amitriptyline, levodopa, bromocriptine

Factors that have been cited as having an association with occurrence of MS exacerbations are infection (including minor respiratory infections and gastrointestinal infections), and the

postpartum period. Pregnancy itself has not been associated with an increase in frequency of attacks (1,5).

Common secondary complications in patients with MS are pneumonia, infections of the urinary tract, septicemia, respiratory failure, pulmonary embolism, bladder and renal calculi, and pressure ulcers of the skin (2). Elevated body temperature, occurring as a result of infection or because of exposure to heat, can be associated with a transient increase in neurologic symptoms (Uhthoff phenomenon). Exacerbations that include dysphagia can result in aspiration pneumonia.

Fatigue is a common complaint of patients with MS. It typically increases with exercise, heat exposure, or as the day progresses. Spasticity, a manifestation of upper motor neuron disease, is characterized by increased muscle tone, hyperreflexia, decreased mobility, painful muscle spasms, and weakness. There is conflicting evidence as to whether seizures occur more frequently in MS patients than in the general population. When seizures occur, they should not be attributed to MS until other causes have been ruled out. Similarly, aphasia and dementia should prompt a search for alternate causes.

Major depression has a lifetime occurrence of 50% in patients with MS. A recent critical review did not find adequate evidence to substantiate concerns that newer disease-modifying agents for the treatment of MS might be associated with an increase in the incidence of depression or worsening of depressive illness. Treatment of depression with usually psychotherapy and pharmacotherapy are often effective (6).

DIFFERENTIAL DIAGNOSIS

As previously noted, the diagnosis of MS is generally a clinical diagnosis that is made over a prolonged period of observation and is supported by laboratory and MRI data. There must be a minimum of two separate clinical episodes suspicious for an MS attack separated over a period of time with evidence of two separate CNS lesions. It is imperative that the diagnosis is made only after confirmation of

all data in support of the diagnosis and that all other potential diagnoses are ruled out. There is no single test that provides a definitive diagnosis.

The differential diagnosis of an acute neurologic deficit is broad and includes the intracranial and spinal cord processes listed in Table 161.3. Some of the more common diseases capable of causing multifocal CNS lesions disseminated over time are systemic lupus, Lyme disease, sarcoidosis, and CNS vasculitis. Because MS is a disease that is confined to the CNS, patients generally lack the rheumatologic and constitutional symptoms and laboratory abnormalities that are present in many of these other disease states. Spinal cord compression by mass lesions or hematomas must be considered in the patient who presents with symptoms referable to the spinal cord. The differential diagnosis of transverse myelitis includes both infectious (e.g., herpes simplex) and postinfectious causes. Optic neuritis may be caused by syphilis, demyelination following vaccination or viral infection, sarcoidosis, systemic lupus erythematosus, herpes zoster, and diabetes mellitus.

TABLE 161.3
Differential Diagnosis of Acute Focal Neurologic Deficit

Bleeding (Spontaneous or Traumatic)	**Vascular**
Subdural hematoma	Thrombosis
Intraparenchymal hemorrhage	Embolism
Epidural hematoma	**Metabolic**
Subarachnoid hemorrhage	Hypoglycemia
Infection	Hyperosmolar hyperglycemia
Abscess	Vitamin B_{12} deficiency (spinal cord)
Brain	**Miscellaneous**
Epidural	Postictal
Subdural	Migraine
Meningitis, encephalitis	Bell palsy
Neoplasm	Guillain–Barré syndrome
Primary	Psychogenic (diagnosis of exclusion)
Metastatic	

ED EVALUATION

The diagnosis of MS requires the demonstration of focal neurologic signs and symptoms scattered over time and space. When faced with a patient with one or more focal neurologic deficits in whom MS is suspected, a critical task of the ED provider is the exclusion of other disease entities that may mimic the diagnosis and require specific immediate treatment. The definitive diagnosis of MS is most appropriately left to the neurologist in the non-ED setting.

Just as no neurologic findings are pathognomonic for MS, no laboratory test is universally diagnostic. Diagnostic evaluations used to confirm the diagnosis in situations in which the diagnosis cannot be made definitively on clinical grounds include visualization of anatomic dissemination of lesions in time and space with MRI of the brain and spinal cord; assessment of inflammatory and immunologic dysfunction through cerebrospinal fluid (CSF) examination; and demonstration of alteration of conduction in a pattern consistent with demyelination through the use of evoked potentials (EPs) as outlined by the McDonald criteria for the diagnosis of MS (1,7,8).

MRI is the most sensitive and specific test used to make the diagnosis of MS (9). T2-weighted brain imaging is superior in sensitivity to contrast-enhanced computed tomography (CT). More than 90% of patients with MS have MRI abnormalities, but there are no findings that are entirely pathognomonic for MS. Because myelin has a relatively short T2 and T1 relaxation times due to its lipid content, normal myelin is hypointense to gray matter on T2-weighted images and hyperintense on T1-weighted images. In MS, there is a reduction in myelin content; as a result white matter becomes less hydrophobic and takes on more water. A decrease in myelin and an increase in water content prolong the relaxation times of both T1- and T2-weighted images, resulting in more signal on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, and less signal on T1-weighted images.

Characteristic lesions observed on MRI are plaques typically found in the periventricular region and juxtacortical white matter. MS plaques usually appear as discrete foci, ovoid in shape with well-

defined margins. Most are small and irregular, however some of these lesions can coalesce forming larger-sized lesions. Plaques correspond pathologically to multifocal areas of demyelination and perivascular infiltration of lymphocytes, macrophages, and plasma cells. Typical lesions are ovoid and are arranged like fingers radiating away from the walls of the lateral ventricles. In addition, lesions commonly involve the corpus callosum, white matter abutting the temporal horns, trigones of the lateral ventricles, brainstem, cerebellum and spinal cord. Signal enhancement with gadolinium is characteristic of the disruption of the blood–brain barrier that occurs with active inflammatory lesions. The number, size, and distinctive location of areas of increased signal found on MRI help distinguish MS from other neurologic diseases.

MRI is used to monitor the course of the disease and its response to treatment and is useful in identifying alternate diagnoses such as intracranial neoplasm, vascular abnormalities, and spinal cord lesions. A negative MRI does not, however, have sufficient sensitivity or negative predictive value to rule out the diagnosis (10). Diseases that may produce similar lesions include ischemia, systemic lupus erythematosus, Behçet disease, other vasculitides, human immunodeficiency virus (HIV), and sarcoidosis.

Findings on MRI are common in patients with optic neuritis, even when there is no other clinical evidence of MS. MRI has been demonstrated to have prognostic value in predicting conversion from isolated syndromes, such as optic neuritis, myelitis, and INO to MS (3,4).

CSF examination can help to confirm the diagnosis by demonstration of immune and inflammatory mediators of disease. For the diagnosis of MS, CSF abnormality is defined as the presence of oligoclonal immunoglobulin G (IgG) bands different from bands in the serum or the presence of an elevated IgG index (7,8). Oligoclonal bands may be present even when the total CSF IgG content is normal. Studies have shown very poor correlation between the presence of oligoclonal banding and the degree of MS-induced disability. Changes in CSF IgG patterns have found not to be specific for MS. Patients with infection of the CNS, both acute

and chronic, and brain neoplasms can also demonstrate changes in immunoglobulin levels. Other common CSF findings include elevated total protein and modestly increased mononuclear cell count (<50 cells/μL). In addition, CSF analysis permits the exclusion of infection as the cause of symptoms.

EPs are electrodiagnostic studies that measure the electrical potentials (voltages) that are evoked in response to the application of brief sensory stimuli. Demyelination causes abnormal axonal conduction that can be picked up on EP testing as abnormal potentials. In the past, prior to the development of MRI, visual evoked potentials (VEPs) were utilized in the diagnosis of MS. VEP often demonstrated a delay in conduction of visual responses from retina to occipital (visual) cortex. These studies were positive in 90% patients with clinically obvious MS. Both VEPs and somatosensory evoked potentials (SSEPs) may also detect subclinical sites of demyelination. This modality falls into the domain of the neurologist and is not part of the ED evaluation.

KEY TESTING

- Thorough neurologic examination
- MRI of brain to aid in initial diagnosis of MS
- Search for infection in patient with established MS
  - CBC
  - UA
  - CXR

ED MANAGEMENT

Treatment of acute exacerbations of MS is most appropriately undertaken in consultation with a neurologist. The anti-inflammatory effects of steroids have traditionally been the primary therapy for relapses in patients with known disease. Corticosteroids shorten the duration of relapses and their short-term morbidity but have not been demonstrated to alter the evolution of the disease or to prevent relapses (1,11,12). There are no rigid guidelines for the use of steroids, but protocols generally include high-dose IV

methylprednisolone, 1 to 2 g daily for 3 to 10 days, with or without an oral taper (12). For the rare patients who cannot tolerate corticosteroids or have had a prior poor response, intramuscular adrenocorticotropic hormone (ACTH) is an option. However, there is a significant incidence of weight gain, hypertension, and edema as compared with steroids (11).

A recent Cochrane review comparing different routes of steroid administration (i.e., IV vs. oral) failed to demonstrate a clear advantage of one over the other, giving weight to the notion that oral steroids are an effective alternative to parenteral steroids (13). An exception is in the treatment of optic neuritis. A recent meta-analysis concluded that corticosteroids did not result in an improvement in eventual return to baseline vision, but that IV corticosteroids did result in faster recovery. On the other hand, oral steroids appeared to be associated with more likely recurrences of optic neuritis. Thus, initial treatment with high-dose IV corticosteroids followed by oral formulations is thought to be reasonable (14).

If a relapse is deemed to be corticosteroid-refractory, plasmapheresis can be considered. It has recently been given a Class B recommendation from the American Academy of Neurology (12,15), but is not recommended for the progressive types of MS.

Current research has focused on two areas: (1) preventing disease burden from acute relapses, and (2) stabilizing MS in the long term. Interventions are aimed at suppressing inflammation, limiting demyelination, enhancing remyelination, and improving conduction in demyelinated fibers. As previously noted, some short-term treatments may accelerate recovery from relapses but do not prevent future relapses or eventual disabilities (16). Long-term management typically involves disease-modifying therapies (DMTs). Currently, there are at least eight DMTs approved for MS by the US and European drug-regulating bodies. Interferon-beta and glatiramer acetate are currently the most commonly prescribed agents. The annual relapse rate of patients treated with these drugs is lower than that in those treated with placebo by up to 30% (12,16). Interferon-beta also lowers the progression of disability; glatiramer

acetate has not been proven to do so. For the most part, interferons and glatiramer acetate are first-line MS treatments as they have a good safety profile, reasonable tolerability and efficacy, and low toxicity. Nevertheless, their use may be limited by adverse events (such as flu-like symptoms, depression, injection site necrosis, elevated liver enzymes, leucopenia, and anemia) and cost. As always, risk–benefit ratios have to be determined by both physician and patient. Other approved treatments with more potentially serious adverse effects are being studied, including natalizumab, fingolimod, dimethyl fumarate, and teriflunomide (7,16). Therapies currently under investigation include mitoxantrone, alemtuzumab, laquinimod, rituximab, daclizumab, and cladribine (7,16). Administration of disease-altering drugs generally is the domain of the neurologist.

In the patient with known disease who presents with fever, sources of infection should be sought and treated aggressively. Patients with bladder dysfunction are particularly susceptible to urinary tract infection; decubitus ulcers and pneumonia are other common sources of infection that should be considered. Antipyretics should be administered because of the Uhthoff phenomenon. An elevated temperature that is related to heat exposure should be treated by active cooling measures. Table 161.2 lists some of the more common fixed neurologic symptoms of MS along with their treatments.

CRITICAL INTERVENTIONS

- Do not make the initial diagnosis of MS in the ED.
- Initiate high-dose methylprednisolone in the treatment of optic neuritis.
- Diagnose and treat fever in MS patients because elevated body temperature, occurring as a result of infection or exposure to heat, can be associated with a transient increase in neurologic symptoms.

DISPOSITION

The patient with newly onset clinically suspected MS may warrant hospital admission to complete the diagnostic workup, to exclude other causes of signs and symptoms, and to undergo aggressive treatment of debilitating symptoms. For the patient with known MS, determination of the need for hospitalization depends on the general medical condition as well as the neurologic status. Patients may also require hospitalization for medical complications of MS (e.g., infection), for the administration of aggressive treatment of neurologic symptoms, and for the supportive care necessary because of disability during disease exacerbations.

Common Pitfalls

- Failure to identify and treat other disease entities in the patient with known or suspected MS.
- Failure to consider the possibility of intercurrent medical illnesses, especially those that commonly affect the chronically ill neurologic patient (e.g., urinary tract infection, pneumonia, decubitus ulcers).
- Failure to realize that rheumatologic or constitutional symptoms or abnormal laboratory values should call the diagnosis of MS into question.
- Making a diagnosis of MS in a patient with progressive disease at a single site (e.g., spinal) when other diagnoses have not been adequately excluded.
- Failure to consider MS in the young patient presenting with focal neurologic signs and symptoms. The presenting symptoms of MS can be vague and transient, and can seem bizarre. A psychogenic etiology remains a diagnosis of exclusion.

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CHAPTER 162

Parkinsonism and Other Movement Disorders

Todd A. Taylor

Parkinsonism, or Parkinson syndrome, is a group of progressive degenerative central nervous system disorders characterized by cardinal motor signs of bradykinesia, tremor, rigidity, and postural instability. Idiopathic Parkinson disease (PD) is the most common cause of parkinsonism and accounts for 80% of cases. Secondary parkinsonism, from a host of disparate causes, constitutes the remaining 20% (see Table 162.1).

TABLE 162.1
Causes of Parkinsonism

Parkinson disease (PD)
Neurodegenerative processes
Multiple system atrophy (MSA)
Progressive supranuclear palsy (PSP)
Corticobasal degeneration (CBD)
Drugs—phenothiazines, butyrophenones, anticonvulsants
Toxins—Methylphenyl tetrahydropyridine (MPTP), carbon monoxide, manganese, rotenone
Trauma
Malignancy—lymphoma, glioma
Arteriosclerotic parkinsonism
Infections—epidemic encephalitis, von Economo encephalitis

The incidence and prevalence of parkinsonism and PD are increasing, reflecting the aging population, and are now afflicting 1 million in America (1–3). There does not appear to be a genetic predisposition for PD when the disease begins after age 50 years, although there may be one for early-onset disease (3). PD is more common in men than in women and appears to be more common in whites than in other groups (1). Both PD and secondary parkinsonism have increased morbidity and mortality rates compared with the general population (1,4,5).

Although the precise cause and pathophysiology of PD is not known, recent studies suggest inflammation, oxidative stress, and abnormal protein accumulation leading to cell death in the substantia nigra (6–8). Profound localized depletion of the neurotransmitter dopamine in the substantia nigra is the biochemical marker for the disease (9,10). The mainstay of therapy for PD is neurotransmitter replacement in the form of levodopa or dopamine agonists. Infections (von Economo pandemic of encephalitis lethargica), toxins (the designer drug methylphenyl tetrahydropyridine [MPTP], the pesticide rotenone) (7), and medications (phenothiazines) are known causes of secondary parkinsonism (Table 162.1).

In practice, the diagnosis of parkinsonism and PD is made on clinical grounds, but the ultimate diagnosis still rests with neuropathologic confirmation at autopsy (11). Neuroimaging is typically used to rule out other causes but is unrevealing in cases of PD. PD has distinct cellular degeneration of the substantia nigra with characteristic Lewy bodies (12). The various secondary parkinsonian syndromes show etiology-specific pathologic changes in the extrapyramidal system and the cortex of the brain. Precisely how the neurochemical and pathologic changes in parkinsonism result in dysfunction of the regulation of tone and motor activity is not completely understood (5). Advanced imaging techniques such as functional magnetic resonance imaging (MRI) and positron-emission tomography are contributing to a better understanding of functional anatomy (13).

CLINICAL PRESENTATION

Patients can present to the emergency department (ED) with complaints referable to undiagnosed parkinsonism or with complications of previously diagnosed illness. Emergent interventions are rarely needed for the disease itself. However, it is important to make the diagnosis as soon as possible because effective symptomatic treatment is available, and there is the possibility of slowing disease progression.

The clinical manifestations of parkinsonism develop insidiously and gradually. The four cardinal signs are resting tremor, bradykinesia, rigidity, and gait disturbance (14). Typically some combination of these, together with a good response to levadopa therapy, is used to make the diagnosis (14). Motor deficiencies are usually asymmetric. Rigidity may be present on flexion and extension of the extremities and neck, and "cogwheel" rigidity on passive extension of the elbow or circumduction of the wrist may be noted. There are two types of rigidity in PD. The "lead pipe" rigidity is an increase in resistance to passive movement (15). Cogwheel rigidity is described as a catching sensation throughout passive range of motion (15). Early on, ambulation is generally slow; short or shuffling steps (*marche à petits pas*), instability, and falls occur later. The classic tremor of PD is a 3 to 6 Hz distal resting tremor that increases in periods of anxiety. An essential tremor is often confused for the resting tremor of PD. An essential tremor is an action tremor occurring during intentional motion as opposed to the resting tremor of PD. The resting tremor of PD disappears during voluntary movement (1). Monotonous speech and decreased speech volume are other early features, and there is eventual development of drooling, dysphagia, and masked facies. Sensory findings are generally absent. The presence of early dementia and psychosis (unrelated to medicines), autonomic dysfunction (orthostasis), cerebellar findings, and supranuclear gaze palsy suggest one of the secondary causes of parkinsonism (5,11).

In patients with known PD, complications of therapy or a worsening of symptoms while on therapy is often the reason for

presentation to the ED. The so-called on–off phenomenon, sudden wide fluctuations in motor function, ranging in severity from dyskinesia to freezing, can be particularly troubling to patients. This is thought to correlate with fluctuating drug levels throughout the day. “Wearing off,” or loss of therapeutic effect, should prompt a reassessment of the medication regime and also confirmation that secondary parkinsonism has not been erroneously diagnosed as PD, as one of the ways to rule out PD is the nonresponse to dopamine therapy. Orthostasis, nausea, vomiting, and acute psychosis can be caused by various dopaminergic and anticholinergic agents. Differentiating disease progression from medication inadequacy or excess can be difficult but is an important part of ED management.

Other complications related to general motor disability (e.g., traumatic injuries caused by falls) are significant reasons for ED presentation. In addition, many older patients, the cohort most affected by parkinsonism, have multiple medical conditions that can be more difficult to manage in the setting of progressive parkinsonism.

DIFFERENTIAL DIAGNOSIS

The primary entities in the differential diagnosis of parkinsonism are idiopathic PD and secondary parkinsonism. To help distinguish PD from secondary parkinsonism on a clinical basis, Gelb et al. (11) have suggested specific diagnostic criteria for PD: bradykinesia, rigidity, and the asymmetric onset of resting tremor, all of which must have a substantial and sustained response to levodopa or dopamine-agonist therapy. The presence of postural instability, freezing phenomena, hallucinations, dementia, severe dysautonomia, or supranuclear gaze palsy within the first 3 years of disease presentation suggests a secondary form of parkinsonism (12). PD has a gradually progressive course; rapid progression strongly suggests another form of parkinsonism (12).

ED EVALUATION

The ED evaluation of a patient with clinical symptoms suggestive of parkinsonism consists primarily of a history and physical examination. For patients with new symptoms, clinical assessment is aimed at identifying patients with a clinical picture that is consistent with parkinsonism and parkinsonian syndromes. It should be noted that even neurologists, according to one study, make the correct diagnosis only 82% of the time (16). The focus of the emergency physician should not be to make the diagnosis but rather to recognize patients who have parkinsonism symptomatology and referring them to a neurologist. MRI is useful in the comprehensive evaluation of parkinsonism but rarely is indicated in the ED (17).

For patients previously diagnosed with parkinsonism, evaluation should focus on progression of disease, complications of medical treatment, and concomitant medical conditions.

ED MANAGEMENT

Strategies for the management of parkinsonism in the ED should be coordinated with the physician who will treat the patient for the long term.

For patients who are newly diagnosed with PD, treatment includes agents to alleviate disabling symptoms, as well as agents that are potentially neuroprotective. Table 162.2 outlines treatment options. Levodopa and dopamine agonists are the mainstay of symptomatic treatment. Levodopa, a dopamine precursor, is more commonly used for initial treatment. Carbidopa blocks the peripheral metabolism of levodopa, allowing lower doses of levodopa to be effective centrally. The levodopa–carbidopa combination drug (Sinemet) has thus become a mainstay of treatment. It is desirable to use the minimum amount of levodopa necessary to control symptoms, because the metabolism of levodopa is thought to contribute to an excess of oxyradicals in the substantia nigra, leading to further cell degeneration. For this reason, dopamine agonists are sometimes used instead of levodopa. These medications are not as effective as levodopa but avoid the associated theoretical increase in cell destruction. Moreover,

limiting the dose of levodopa reduces the drug's peripheral side effects (nausea, vomiting, and orthostasis) (10). Agents with neuroprotective effects (dopamine agonists, monomine-oxidase [MAO]-B inhibitors) are other common alternatives (6). The anticholinergic drug benzatropine is prescribed selectively for patients with tremor predominance. For those with severe disease refractory to medical management, deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus has been shown to significantly improve motor symptoms, although this therapy does have inherent risks and limitations as well (18–20).

TABLE 162.2
Management of Parkinson Disease[a]

Medical

Dopamine Precursor

Levodopa is a precursor of the pathologically deficient dopamine, which is able to cross the blood–brain barrier; improves symptoms; and is most often used in combination with carbidopa

Side effects include dyskinesia, anorexia, nausea, vomiting, postural hypotension

Peripheral Dopa-Decarboxylase Inhibitor

Carbidopa is a peripheral dopa-decarboxylase inhibitor and decreases peripheral breakdown of levodopa, allowing lower-dose therapy

Side effects include exacerbation of central dopaminergic side effects when levodopa dose is not reduced sufficiently

Dopamine Agonist

Pramipexole/ropinirole is a nonergot-based dopamine agonist used as adjuvant to levodopa or as early primary therapy

Side effects include nausea, vomiting hypotension, sleepiness, hallucinations, confusion, and compulsive behavior

Bromocriptine is a dopamine agonist used as adjuvant to levodopa; decreases the dopamine requirement, thus allowing lower-dose levodopa therapy[b]; and also appears to decrease dyskinesias and "on–off" side effects

Side effects include hypotension, nausea, vomiting, constipation, fatigue, and hallucinations

Pergolide is a dopamine agonist used as adjuvant to levodopa; and is also used by some as monotherapy, particularly early in young-onset PD

Side effects include hypotension, nausea, vomiting, constipation, confusion, hallucinations, dyskinesias, and dystonias

Monoamine Oxidase-B Inhibitor

Selegiline is a MAO-B inhibitor thought to reduce the peroxide produced as MAO-B metabolizes dopamine[c] and may also have some therapeutic effect

Side effects include sleep disturbances, psychosis, agitation, confusion, and dyskinesias

Anticholinergic Drugs

Benztropine is a striatal muscarinic blocker and is useful in treating the tremor of PD

Side effects include typical anticholinergic symptoms and signs

Surgical

Electrical deep-brain stimulation

Posteroventral pallidotomy

Neural-cell transplantation

PD, Parkinson disease; MAO-B, monomine-oxidase-B.

[a]Dosing regimens are very individualized and should be coordinated with the patients' neurologist or primary physician.

[b]Khandhar SM, Marks WJ. Epidemiology of Parkinson's disease. *Dis Mon*. 2007;53(4):200–205.

[c]Lachenmayer L. Differential diagnosis of parkinsonian syndromes: dynamics of time courses are essential. *J Neurol*. 2003;250(suppl 1):I11–I14.

For patients with known PD, ED management is directed at recognizing the inadequacy or excess of the medication regimen and adjusting dosages accordingly. The “on–off ” phenomenon is thought to be caused by fluctuations in drug concentrations. Changing doses or dosing intervals and adding other antiparkinsonism agents should be done only after consultation with the neurologist. A sustained-release levodopa–carbidopa combination appears to reduce the total levodopa requirement, as well as variations in drug concentration (21). Medication excess may cause acute psychiatric and cognitive side effects, such as psychosis, hallucinations, delusions, agitation, and confusion. This may require a decrease in dopaminergic and anticholinergic medications and the initiation of antipsychotics (10). The peripheral side effects of excessive dopamine (nausea, vomiting, and orthostasis) can also be treated by reducing levodopa doses. There also appears to be a small chance that the discontinuation of dopaminergic therapy may cause neuroleptic malignant syndrome (NMS) (22). The symptoms of NMS closely mimic those of PD (i.e., confusion, rigidity, tremor), so the clinician should ensure that medications are continued on patients being admitted to the hospital. The treatment of NMS in this circumstance consists of administering bromocriptine and restarting the patient’s Parkinson medications. Optimizing the balance of various agents can be difficult and should be coordinated with the patient’s primary physician.

The management of the parkinsonian syndromes other than PD is generally less effective. Parkinsonism caused by prescription medications may improve with cessation of the implicated agent, but parkinsonism associated with prior MPTP use is not reversible. Symptoms of neurodegenerative parkinsonism can be managed with the same agents used for those of PD, but there tends not to be a sustained response to therapy.

For all parkinsonian syndromes, injuries from falls, infections (e.g., aspiration pneumonia), and concomitant medical conditions should be evaluated and managed as with other patients, keeping in

mind the limitations imposed by the patient's chronic level of functioning.

CRITICAL INTERVENTIONS

- Keep NMS on the differential for the decompensated Parkinson patients with medication noncompliance
- Coordinate all management strategies and medication changes of Parkinson patients with the patient's long-term physician

DISPOSITION

Whether the diagnosis of parkinsonism is being considered in the ED or the patient is being seen for complications of therapy or progression of symptoms, the patient's primary care physician or neurologist should be consulted. This assures continuity of care, which is essential to optimize the management of this chronic condition. Rarely is admission to the hospital or transfer to a tertiary care center indicated for parkinsonism itself. Complications such as sepsis or injuries from falls are more likely to be indications for inpatient management.

Common Pitfalls

- The diagnosis of parkinsonism may be missed in patients with vague complaints of dizziness, unsteadiness, or inability to walk, unless the signs are specifically sought on careful neurologic examination.
- The complex medical regimens for PD require precise modifications to maximize clinical benefit while minimizing side effects.

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SECTION XVI
Psychiatric Emergencies

Section Editor: JEFFREY J. SCHAIDER

CHAPTER 163 Medical Clearance

Kerryann B. Broderick

One in eight or nearly 12 million emergency department (ED) visits in the United States, in 2007 were due to mental health and/or substance use disorders (1). Mental health-related ED visits increased 75% between 1992 and 2003 (2).

Before the patient can be transferred to a psychiatric facility or service, the emergency physician (EP) is responsible for identifying any significant medical condition. The term *medical clearance* (many would debate is not an accurate term of what we perform) was developed in the 1970s. Weissberg's 1979 article (3) describes the common scenarios in which EPs apply the concept of medical clearance: (a) the psychiatric patient found to have no physical illness, (b) a psychiatric patient with a known medical condition that is not currently impacting the psychiatric illness, and (c) the psychiatric patient whose acute medical issue has been treated and is now ready for transfer to a psychiatric facility.

There is a lack of standardized nomenclature in this area. The terms *organic disease* and *functional disease* are, perhaps, most frequently used. Organic disease denotes nonpsychiatric causes, and functional disease indicates a psychiatric cause. Defining a mental disorder as "organic," however, implies that a nonorganic or functional mental disorder is unrelated to physical or biologic factors or processes (4,5). In fact, many chemical neurophysiologic and genetic factors have been documented to be related to psychiatric disease. The terms "functional" and "organic" were eliminated from the DSM manuals and it now distinguishes mental

disorders due to medical conditions or secondary mental disorders from primary psychiatric conditions (6).

In fact, the role of EPs is to determine if the patient has a medical condition that is either (a) masquerading as psychiatric illness or (b) the one that needs treatment urgently before the patient can be treated by a psychiatric service/facility. The prevalence of physical illness among psychiatric patients appears to be dependent upon the population studied. One study specifically reviewing ED practice found that 80% of patients in whom medical disease should have been identified in the ED were documented as "medically clear" (7), whereas another study found "medical problems" in only 19% of ED patients (8).

CLINICAL PRESENTATION AND ED EVALUATION

Patients who require medical clearance may be separated into two general categories: those with a known psychiatric illness and those without a prior psychiatric diagnosis but presenting with abnormal behavior and thought. The clinical evaluation of these patients includes focused history and physical exam, directed laboratory and ancillary tests, and consideration of the care available by the receiving psychiatric facility or service. In January 2006, ACEP published a clinical policy guideline on many of the issues outlined in this chapter (9).

Important questions include time frame involved in the onset of symptoms and other events leading up to presentation. Obtaining history from patients and their perception of the current situation and using all other potential sources (emergency medical personnel, caretakers, and caseworkers) will ensure the most comprehensive and accurate history.

Psychiatric patients with substance abuse comorbidity have a significantly higher number of ED visits than those without substance abuse (10). A detailed history on medication use, recent changes, and noncompliance, both prescribed and not prescribed, are important as these frequently cause or contribute to psychiatric complaints, especially in the elderly.

Medical problems must be excluded or identified and treated appropriately. Infections, particularly central nervous system, cardiopulmonary, and urinary, can aggravate a patient's underlying illness. Questions regarding history of fever, weight loss, appetite, recent surgery, and trauma should be included.

When a patient presents with psychiatric symptoms but does not have a known psychiatric disorder, it is critical to differentiate primary psychiatric illness versus secondary psychiatric illness (medical etiology). Factors strongly supporting a medical cause include age older than 40 years with no prior psychiatric history, abnormal vital signs, recent memory loss, and clouded consciousness (5,11). Medical conditions may manifest with significant psychiatric symptoms. The differential diagnosis of medical conditions that can present with psychiatric symptoms is broad. Table 163.1 includes some of these conditions.

TABLE 163.1
Treatable Causes of Acute Mental Disorders Due to a General Medical Condition

Cardiac
- Dysrhythmias
- Congestive heart failure
- Myocardial infarction

Pulmonary
- Chronic obstructive pulmonary disease
- Pulmonary emboli
- Hypoxia

Hepatic
- Cirrhosis
- Hepatitis
- Wilson disease

Renal
- Worsening of mild nephritis by urinary tract infection
- Dehydration with elevation of BUN >50 mg/dL

Vascular
- Subdural hematoma
- Cerebrovascular accident
- Infection
- Vasculitis

Endocrine Disease
- Thyroid disease
- Cushing disease
- Diabetes
- Addison disease
- Hypoglycemia

Electrolyte Imbalance
- Hyponatremia
- Hypernatremia
- Hypercalcemia
- Hypoglycemia

Vitamin Deficiencies
- Thiamine
- Niacin
- Riboflavin
- Folate
- Ascorbic acid
- Vitamin A
- Vitamin B_{12}

Drug-induced
- Alcohol
- Tranquilizers
- Over-the-counter preparations
- Any drug used to treat medical illness (e.g., phenytoin, aminophylline, digitalis, steroids)

Exogenous Toxins
- Carbon monoxide
- Bromide
- Mercury

Lead
- Tumors
- Nonconvulsive status epilepticus
- Normal pressure hydrocephalus
- Depression

Multiple studies have documented that both emergency medicine and psychiatric physicians do a less-than-optimal job at documenting the physical examination (7,12). Psychiatrists surveyed reported completing a physical examination in only 13% of their inpatients, citing that they feel incompetent to do so (12). Therefore, it is very important that the EP perform a thorough search for evidence of medical illness that needs urgent treatment.

Two of the more frequent conditions encountered are delirium and dementia, and distinguishing between these two can be very important. Delirium is most often due to a medical condition and is an acute condition. Dementia is a more chronic condition. A mnemonic useful in rapid differentiation between delirium and dementia is COMA: *c*onsciousness, *o*rientation, *m*emory, and *a*ffect. Patients with dementia should have no significant alterations in these areas. The vital signs and a mini-mental status exam also help to distinguish between these two conditions (see Chapter 152).

Ancillary testing is a matter of great debate in the literature. Some facilities require mandatory testing, whereas others rely on their EP's judgment. Parmar and others studied 598 patients prospectively and found that after cleared by the EP, psychiatry ordered lab or radiographic testing on 44% of patients transferred and only 0.5% had an abnormal result which led to a disposition change. The total reimbursement for this added testing was $37,682 (13). Most would agree that a thorough history and physical will guide most clinicians in indicated ancillary testing. Studies have demonstrated that where history is obtainable, patient self-reporting on medical symptoms has a 94% sensitivity of predicting disease (8).

Although there is no consensus from the literature on laboratory testing, there are some useful guidelines. New-onset psychiatric complaints may signal the need for more extensive testing for a medical etiology (14). Routine testing in patients older than the age of 40, especially in the geriatric population, may have a higher pretest probability for significant positive results that either

demonstrate the etiology of the symptoms to be medical or signal the need for urgent treatment prior to medical clearance (15–17).

Clinicians should order focused testing (Accu-Chek, complete blood count, electrolytes, thyroid studies, urinalysis, toxicologic screen) based on history, physical exam, and vital signs. Alcohol levels and toxicologic screens may be useful in cases wherein the role of these substances in the patient's altered mental status is not clear.

A head computed tomography (CT) is warranted for patients with altered mental status or abnormal findings on neurologic exam. However, the decision to perform a head CT on patients with new psychiatric illness is less clear. In one study, abnormal head CT findings were found in 8% of 100 consecutive alert patients with psychiatric illness, but it was not clear that these findings were contributing to the patients' acute psychiatric illness (14).

DIFFERENTIAL DIAGNOSIS

Medications may be an important source of acute psychiatric symptoms. Anticholinergics, sympathomimetics, and serotonergics may be the etiology of a patient's altered thoughts. Patients taking stimulants such as cocaine, methamphetamines, and PCP may also exhibit psychosis. Common withdrawal syndromes associated with acute psychiatric features include alcohol withdrawal, particularly delirium tremens.

Elderly patients are particularly susceptible to toxic effects of medications owing to polypharmacy, dosing errors, and altered metabolism. If a medication is identified as the precipitant, clear instructions for dosing changes or drug substitution must be communicated with caregivers.

Thyroid diseases may be the etiology of acute psychiatric symptoms. Thyrotoxic patients may appear manic, delusional, or confused. Extremes in glucose can cause profound mental status changes. Those with adrenal disease are also susceptible to profound behavioral changes, which may mimic psychiatric symptoms. See Table 163.1 for additional causes of acute mental disorders.

KEY TESTING

- Focused testing based on history, physical examination, and vital signs
- glucose
- complete blood count
- electrolytes, BUN, creatinine
- thyroid studies
- urinalysis
- toxicologic screen

ED MANAGEMENT

Extreme agitation is often part of the syndrome of delirium or psychiatric disease and can significantly interfere with evaluation. Chemical restraint (CR) is a safe and effective method for controlling agitated or overtly violent patients (18,19). CR is accomplished by administering a standard dose of a high-potency antipsychotic medication, such as haloperidol or droperidol, in 5- to 15-minute intervals. Research indicates that the combination of antipsychotic medication with lorazepam is more effective than either medication alone, though the synergistic effects may cause excessive sedation (18–20) (see Chapter 167).

CRITICAL INTERVENTIONS

- Perform a thorough search for evidence of medical illness that needs urgent treatment.
- Distinguish between delirium and dementia.
- Control agitated or overtly violent patients with rapid tranquilization when indicated.

DISPOSITION

Some psychiatric facilities require toxicology tests, blood alcohol levels, or various ancillary tests to be done before they accept patients in transfer. Although some studies have shown that most patients accurately self-report drug use (21), and although

toxicology results usually do not impact the ED care, psychiatrists may find this information useful in their treatment of the patient (8). Shah et al. recently published a screening tool (22) that was modified from the one Zun previously developed (23). Psychiatry service ordered subsequent testing in 2.5% of those "cleared," of which none of these required any alteration in disposition or urgent treatment (22). The development of guidelines and protocols and a system for assuring that they are routinely reviewed and updated are essential to both patient safety and cost control.

Hospital admission is clearly warranted for patients with identified medical illnesses that are associated with a risk of morbidity or mortality. Hospital admission is also necessary if the patient's behavior jeopardizes further medical evaluation or care. Patients with delirium should be admitted for specific treatment if the cause is known or for further evaluation if the cause is unknown, with psychiatric consultation as needed.

Patient care may be transferred to a psychiatric service if an appropriate medical screening examination has been performed and it has been determined that the patient does not require further evaluation or treatment for an underlying medical condition, or for a medical condition that may be causing or exacerbating psychiatric symptoms.

Common Pitfalls

- Delirious patients who present to the ED are often inappropriately referred to a psychiatrist. This is especially true for those who present with bizarre and agitated behavior.
- Psychiatric patients who behave in a bizarre or disruptive manner may not be approached with the same sense of urgency or seriousness as are patients with cardiovascular disease or trauma. Clinicians often medically clear these patients without conducting a complete and thorough evaluation.
- Like disordered perception, the patient etiology that results in patient violence is often unclear, and these patients are often referred to a psychiatrist. A significant proportion of violence

that occurs in psychiatric settings results from underlying medical illness or drug intoxication (24).

- Clinicians often fail to take seriously the complaints of elderly patients, commonly attributing their symptoms to "old age" (16,25). Premature labeling tends to preclude the exhaustive physical, neurologic, and laboratory evaluation necessary to identify potentially reversible causes of dementia or delirium.

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CHAPTER 164

Depression and Suicidal Ideation

Robert S. Hockberger and Joseph Ravera

Depression is the most common psychological disturbance affecting humankind: data from 2005 estimated a lifetime prevalence of 13% for the US population (1). Similarly, a 2006 Centers for Disease Control survey of over 200,000 US adults found that 9% met the diagnostic criteria for major depressive disorder (2). Suicide, the most notable sequela of depression, is the 11th most commonly reported cause of death in the United States, accounting for approximately 35,000 deaths annually (3). The number of annual suicide deaths is likely underestimated and may actually approach 100,000 (4). A 2003 audit of US workers found that depression costs employers approximately $44 billion per year in lost productivity (5).

Patients frequently seek nonpsychiatric medical care shortly before committing suicide. Up to 45% of those who commit suicide have visited a physician in the months prior to their death (6). It may be difficult for physicians without formal psychiatric training to recognize and evaluate depression and suicide potential, because many patients do not complain of depression or readily admit to suicidal ideation unless specifically questioned (7,8). Emergency physicians (EP) are further hampered by the hectic environment of the emergency department (ED), constantly changing priorities that limit one's ability to spend significant time with individual patients, and difficulty in obtaining after-hours psychiatric consultation. Nevertheless, the EP's ability to make these assessments and to

decide when to seek urgent psychiatric referral or hospitalization for potentially suicidal patients is a vital link in the effective management of a highly disabling and often fatal affliction. A 2001 US Public Health Service report emphasized the vital role of the ED in enhancing suicide-prevention efforts and recommended that guidelines be developed for the assessment of suicide risk among persons receiving care in the ED by 2005 (9). Although several scoring systems and clinical prediction rules are available, there are still no universally accepted guidelines for the determination of suicide risk.

CLINICAL PRESENTATION

Depression and suicidal ideation generally present in one of two ways. Most commonly, patients present overtly with chief complaints of suicidal ideation, request for psychiatric help, or following suicide attempts. Alternatively, depressed patients may present with occult complaints, most commonly multiple vague, ill-defined somatic symptoms such as weakness, malaise, weight loss, headache, and back pain; however, a thorough medical evaluation should be made before attributing such physical complaints to a psychological cause. Depressed individuals frequently have low self-esteem; loss of interest in or lack of enjoyment of previously pleasurable activities; depressed mood; loss of energy; poor appetite and weight loss (weight gain less often); sleep disturbances, including insomnia or hypersomnia; decreased attention span and ability to concentrate; decreased productivity at school, work, or home; episodes of tearfulness or crying; irritability or excessive anger (particularly in adolescents); feelings of hopelessness and worthlessness with a pessimistic attitude toward the future; and recurrent thoughts of death (7).

The potential for suicide should be considered in the following groups of patients:

1. Patients who have made a recent suicide attempt or have experienced recent suicidal ideation. Although most completed suicides involve firearms, drug overdose accounts for 70% to

90% of all suicide attempts (10). Major and minor tranquilizers and antidepressants have replaced barbiturates and other sedatives as the major agents involved in intentional overdose.

2. Patients who state that they are depressed or who complain of symptoms of depression.
3. Patients who present with problems related to chronic alcoholism, drug abuse, or any psychiatric disorder (particularly affective disorders, psychosis, and panic attacks).
4. Patients who present with apparently unintentional overdoses, self-inflicted gunshot wounds, lacerated wrists, falls from heights, or motor vehicle accidents of unclear cause (i.e., one-car, one-victim accidents in clear weather).

In some settings, a triage nurse may provide an initial screening assessment of suicide risk on selected or all patients presenting to the ED. When this occurs, communication of positive results with subsequent providers is critical to assure further evaluation and appropriate care.

DIFFERENTIAL DIAGNOSIS

A number of psychiatric and medical disorders may present with symptoms of depression. Approximately 80% of people suffering bereavement have one or more symptoms of depression for 1 year or more following the death of a loved one (10). Persons suffering from an adjustment disorder may develop similar symptoms within several months of the onset of psychological stresses (e.g., economic loss, physical illness, or troubled interpersonal relationships) with which they are unable to cope. The diagnosis of organic affective syndrome is made when symptoms of depression are found to accompany organic neurologic disease such as organic brain syndrome, stroke, tumor, or trauma. Symptoms of depression may be exacerbated or even caused by medications, including antihypertensive drugs (β-blockers, clonidine, methyldopa, and reserpine), antidepressants, antihistamines, neuroleptic agents, sedative hypnotic drugs, cimetidine, and alcohol (11).

When these diagnostic possibilities have been eliminated in a patient exhibiting symptoms of depression, a final diagnosis of dysthymic disorder (depressive neurosis or minor depression) or major affective syndrome (major depressive disorder) should be considered. This difference is one of degree, with each of these disorders falling somewhere on the disease spectrum of depressive illness, and the final diagnosis is best left to a psychiatrist.

ED EVALUATION AND MANAGEMENT

The clinical assessment of depression and suicide risk is an art as well as a science. Patients feel more at ease speaking about difficult personal issues when health professionals exhibit a friendly, nonjudgmental, supportive attitude and convey their willingness to listen. However, several studies have shown that many health professionals do not display these qualities, particularly ED staff. Reasons cited for this situation include inadequate time and staffing, patient behavior that is perceived as either abusive or manipulative, value conflicts, and staff frustration regarding ineffective disposition and follow-up options (12,13). Expression of a negative or hostile attitude by a respected authority figure, such as a physician or nurse, reinforces a depressed patient's feeling of diminished self-worth and may increase the likelihood of another suicide attempt.

Overtly depressed and suicidal patients are not very diagnostically challenging, but covertly suicidal patients presenting solely with somatic complaints can pose a diagnostic dilemma. Subtle presentations of a psychiatric problem may include midnight visits for minor complaints, multiple nonspecific somatic complaints involving many organ systems, unusual patient requests, indications of difficulties at home (particularly domestic violence), and trauma of unclear etiology. These potentially "silently suicidal" patients should be assessed in a sympathetic but direct manner.

Studies evaluating the utility of questionnaires and scales used to assess patients for depression in the outpatient setting have shown a wide range of sensitivity and specificity and many are cumbersome to use (14). In general, a stepwise approach should be used when

approaching patients who may have occult depression and may be silently suicidal. First, the presenting complaint should be addressed by asking general questions about the patient's home, work, and social situations. These general questions should be followed by specific questions regarding the signs and symptoms of depression. Finally, the physician should ask direct questions regarding suicide, such as these:

"Have you ever felt so bad that you thought about killing yourself?"

"Do you have thoughts of harming yourself now?"

"What plans have you made to do this?"

Physicians should not be reluctant to ask patients directly about suicidal thoughts from fear that doing so might bring to the surface subconscious thoughts of suicide and result in suicidal behavior. There is no evidence to support this concern; to the contrary, most depressed patients are relieved by the opportunity to openly discuss their problems when the clinician demonstrates an interest and a willingness to listen.

The main objective of the ED management of markedly depressed and suicidal patients is protecting them from further self-harm while performing an assessment and arranging for appropriate disposition. Suicidal patients must be kept under constant observation by a staff member and should be accompanied at all times, including restroom visits. Patients must be searched for medications and weapons and placed in a quiet area of the ED that is free of potentially harmful objects. No potentially suicidal patient should be allowed to leave the department before an evaluation is completed. All states have statutes permitting physicians to detain individuals deemed to be dangerous to themselves or others. Mechanical restraints should be used only when necessary to protect the patient or healthcare providers. The reasons for using restraints and the manner of restraint must be documented in the medical record. Restrained patients must be rigorously monitored and evaluated for complications. Chemical restraints such as intramuscular haloperidol or lorazepam may be required for patients who remain

agitated or violent, but these agents can impair psychiatric evaluation and should be avoided when possible.

Following the medical management of a patient's overdose, injury, or associated medical problems, the patient's degree of depression and potential risk for suicide should be assessed. Many studies have attempted to identify patients at high risk for suicide. Although no combination of clinical characteristics has been found that accurately identifies all patients likely to complete suicide, a number of high-risk characteristics have been determined. For example, a young woman who takes a few aspirin as a suicide gesture after fighting with her boyfriend is at less risk for successfully committing suicide than an elderly man who tries to hang himself on the anniversary of his wife's death. Most patients fall somewhere between these two extremes, and estimating a particular individual's risk for suicide is often difficult (11,15,16). Adding to this challenge for EPs is the fact that potentially suicidal patients often present at night and on weekends when psychiatrists are not readily available for consultation.

There is added difficulty in rural settings. Although depression rates are similar in urban and rural areas, studies indicate a higher rate of suicide in the latter, thought to be related to greater social isolation and lethality of method (firearms) in rural populations (17,18).

EPs should follow guidelines and protocols for suicidal risk assessment developed for their particular practice setting. Consultation may be provided by an on-call psychiatrist, by a psychiatric emergency team (PET) staffed by trained psychiatric nurses or social workers, by a patient's private physician or by the on-call primary care provider. EPs should be familiar with their state or county's policy regarding patients who have been placed on emergency psychiatric holds in the prehospital setting. In some areas, these holds mandate a psychiatric evaluation before they can be rescinded.

There are no studies demonstrating that hospitalization of high-risk patients prevents further suicide attempts or completed suicides. This lack of evidence, combined with national trends

toward providing more cost-effective outpatient treatment regimens, may place the busy EP in the position of making disposition decisions with high medicolegal risk.

The vast majority of patients attempting suicide do not go on to successfully complete suicide, which has led numerous investigators to develop and test a large number of clinical rating scales to predict suicide risk (19). Several studies have looked at screening tools to assess depression and suicide risk in ED patients (20–23). The modified SAD PERSONS scale (MSPS) has been used in the ED setting to guide the decision to admit patients based on suicide risk. The SAD PERSONS mnemonic incorporates several high-risk characteristics, which can help the clinician assess potentially suicidal patients (Table 164.1) (24,25). In one study, for nonintoxicated patients whose history can be corroborated by family or friends, the numerical SAD PERSONS score correlated closely with the need for hospitalization as determined by a psychiatrist. In this study, hospitalization was deemed necessary in almost all patients with a high SAD PERSONS score (>8), in approximately half of patients with intermediate scores (6 to 8), and in almost none of the patients with low scores (<6). The authors concluded that patients with an MSPS of <6 can be safely referred for expedited outpatient psychiatric evaluation, but a score of 6 or greater required emergent psychiatric evaluation and often hospitalization (sensitivity of 94% and specificity of 71%) (24). A more recent study prospectively evaluated six clinical rating scales, including the MSPS. The outcome variable was eventual admission based on a psychiatrist's assessment of suicide risk. In this study, all six scales had 100% sensitivity for identifying patients requiring hospitalization. This confirmed the usefulness of the MSPS in the emergency setting. The remaining five scales were just as sensitive but were more complex and less practical for use in the ED (15). Although the MSPS is a rapid and convenient tool to help organize, document, and communicate the assessment of a patient's suicide potential, a low score (<6) should not preclude emergent psychiatric consultation when the physician is uncomfortable with his or her assessment or when the patient requests to see a

psychiatrist. Strict cut-off scores alone should not be used to dictate consultation and admission to the hospital.

TABLE 164.1
SAD PERSONS Score

Factor	Description	Points
S = Sex	Male	1
A = Age	<19 or >45 yrs	1
D = Depression or hopelessness	Admits to depression or decreased concentration, appetite, sleep, libido	2
P = Previous attempts or psychiatric care	Previous attempt or previous inpatient or outpatient psychiatric care	1
E = Excessive alcohol or drug use	Stigmata of chronic addiction or recent frequent use	1
R = Rational thinking loss	Organic brain syndrome or psychosis	2
S = Separated, divorced, or widowed	Recent or on anniversary	1
O = Organized or serious attempt	Well-thought-out plan or life-threatening presentation	2
N = No social supports	No close family, friends, job, or active religious affiliation	1
S = Stated future intent	Determined to repeat attempt or ambivalent	2

SCORE

Score	Risk
<6	Low
6–8	Intermediate
>8	High

CRITICAL INTERVENTIONS

- Assess for depression and suicidal potential in patients with psychiatric disorders including substance abuse, in patients with multiple nonspecific somatic complaints, in victims of domestic violence, in patients with apparently unintentional overdose, and in victims of trauma of unclear etiology.

- Document your assessment in a consistent and standardized method; the modified SAD PERSONS scale is one approach that has been validated in the ED setting.
- Monitor potentially suicidal patients carefully in the ED; whenever possible, use patient sitters and avoid the use of restraints.

DISPOSITION

Potentially suicidal patients generally require hospitalization and admission to an inpatient psychiatric unit. Discharge from the ED should not be considered unless the following conditions have been met:

- The patient's injuries or associated medical problems do not necessitate hospitalization.
- The patient states that he or she is no longer suicidal and is not intoxicated, demented, or psychotic. Patients should be directly asked about the presence of auditory hallucinations and must be specifically assessed for signs of psychosis.
- The acute precipitant of the crisis has been identified, addressed, and resolved.
- The patient has cooperated with an evaluation and is deemed to be at very low risk for suicide. In general, nonpsychotic younger patients whose attempts involve low risk, high likelihood of rescue, and high manipulative intent can be discharged safely.
- Psychiatric consultation has been obtained (at least by telephone), and hospitalization is judged unnecessary.
- Short-term outpatient follow-up (within 1 to 2 days) has been arranged. The reliability of such patients in keeping follow-up appointments is poor. When ED personnel demonstrate a positive, supportive attitude and the patient is given a scheduled outpatient follow-up appointment at the time of discharge, patient compliance with follow-up improves markedly (26,27,28).

- The patient agrees to return to the ED immediately if further self-destructive urges arise.
- A positive, supportive environment with family or friends is available into which the patient can be released. Arrangements should be made to ensure removal of all pills, poisons, and weapons, especially guns, from the home.

A potentially suicidal patient should not be transferred to another facility or to a psychiatrist's office unless accompanied by medical personnel or family members who agree to deliver the patient and maintain close observation of the patient during transport.

Common Pitfalls

- "Accidental" trauma may be a manifestation of suicidal behavior. When the stated mechanism of injury is questionable or inconsistent with the injury seen, a more in-depth evaluation of the patient's emotional state and motives is warranted to screen for depression and suicide risk.
- Information obtained from a potentially suicidal patient must be corroborated with family or friends. Patients who vehemently deny suicide intent, refuse to answer questions, give abrupt answers to questions, or appear anxious to leave the ED may be committed to finishing the act they began.
- Anxiolytics, antidepressants, or any other potentially lethal medication should not be prescribed to patients who are depressed or potentially suicidal. More than half of patients who die by intentional overdose use a single prescription drug (9).

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CHAPTER 165 Anxiety Disorders and Panic Attack

James A. Comes, Douglas A. Rund, and Basheer Lotfi-Fard

Anxiety is a common complaint of patients who present to emergency departments (ED). It is a nonspecific symptom that has diverse causes and clinical manifestations. Anxiety can be the chief complaint of a patient with a primary anxiety disorder, but often it accompanies a comorbid medical disorder. It is important for the emergency medicine physician to recognize an underlying emergent medical disorder in the anxious patient and be able to diagnose those patients in whom anxiety has become a pathologic condition (1).

CLINICAL PRESENTATION

Subjectively, the anxious patient feels a sense of worry, apprehension, and nervousness often accompanied by physical symptoms that reflect sympathetic activity (e.g., palpitations, sweating, dry mouth, dizziness, paresthesia, and faintness). Anxiety is a pathologic condition when the patient's physical and emotional responses surpass the normal response to a perceived threat and interfere with optimal functioning (2).

Clinically significant anxiety that is not associated with general medical illness, substance use, or substance withdrawal may warrant diagnosis of a primary anxiety disorder. Anxiety may be a feature of almost any psychiatric condition and is often prominent in schizophrenia, other psychotic disorders, depression, and bipolar

disorders. The emergency physician should have a general understanding of the clinical characteristics of all major psychiatric disorders, their chronic modes of treatment, and the ED assessment and management of acute presentations.

Panic attacks are extremely distressing experiences that often lead to ED visits. As many as 20% to 44% of patients with chest pain who come to the ED have a panic disorder (3,4). Recent surveys of the adult US population report an annual prevalence rate of 1% to 2% and a morbid risk (lifetime risk) of 2% to 4%. These episodes are abrupt, almost paroxysmal, in onset and progress rapidly to a degree of anxiety grossly disproportionate to any perceived threat or danger. The total duration is usually 10 minutes or less and almost never as long as 30 minutes. Following cessation of the acute episode, patients typically experience considerable residual anxiety centered on concerns about possibly having a life-threatening illness. Some patients describe their first panic attack as the worst experience of their lives.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of panic attacks depends on the specific circumstances in which they occur. Situational or cued panic attacks occur in association with particular experiences or stimuli, which may be internal or external, recognized or unrecognized. Uncued panic attacks are experienced as occurring “out of the blue” and are especially frightening because of the assumption that they are a symptom of life-threatening illness. The only psychiatric condition in which uncued panic attacks occur is panic disorder.

Most medical conditions are associated with some degree of anxiety, but certain conditions can be present with anxiety as a predominant feature. Examples include asthma exacerbation, hypoglycemia, pulmonary embolism, myocardial infarction, mitral valve prolapse, paroxysmal atrial tachycardia, thyrotoxicosis, pheochromocytoma, and carcinoid syndrome (5). In addition, anxiety itself may exacerbate a medical comorbidity because its associated symptomatic responses create demands on previously

impaired organ systems (6). Panic attacks may also be associated with substance use (caffeine or stimulants) and withdrawal (alcohol, barbiturates, or benzodiazepines). After these conditions have been ruled out, psychiatric diagnoses should be considered.

In phobic disorders, panic attacks may occur in connection with the unreasonable degree of fear associated with a particular stimulus or situation that the person makes effort to avoid. In acute and posttraumatic stress disorders, panic attacks may be triggered by environmental reminders, distressing memories, or flashbacks of the traumatic experience. In obsessive-compulsive disorder, panic attacks may be caused by situations in which the person fears being overwhelmed by the obsessional concern (7).

ED EVALUATION

It is critical to exclude a primary or comorbid medical disorder in the initial and ongoing assessment of patients with anxiety (8). Anxiety and depressive disorders are common among patients presenting with chest pain. However, the prevalence of anxiety and depressive disorders may be similar in patients with chest pain of cardiac and noncardiac origin (9).

Because of their inherently short duration, most panic attacks are clinically evaluated only retrospectively. Patients commonly seek emergency medical care following these upsetting experiences, especially if the attack was uncued. By the time they are examined, vital signs usually have returned to baseline. Even during the actual attacks, objective physiologic changes may be far less impressive than the degree of distress suggests. Panic attacks are brain events, and any peripheral changes are secondary manifestations. They are clinically recognized from the description of the person's internal experience, not from externally observable characteristics.

ED MANAGEMENT

Reassurance is the first-line intervention in patients with anxiety disorders. Patients should be assured that they are safe and will

receive help. A firm, direct approach in a quiet, comfortable environment helps the patient feel secure and in better control (10).

If a supportive interview is unsuccessful, pharmacologic intervention may be considered. Benzodiazepines can be used to treat acute anxiety. Collectively, benzodiazepines are similar in their clinical effect, although they differ in pharmacokinetic properties. Short-acting benzodiazepines with a rapid onset (half-life: 5 to 20 hours) include lorazepam (Ativan) and alprazolam (Xanax). For patients with history of substance abuse, hydroxyzine (Atarax, Vistaril) may be considered a useful alternative over benzodiazepines (11).

Once a diagnosis of panic attack is established, the patient should be reassured the panic attack is not imminently life-threatening. There may be serious long-term consequences if left untreated, and treatment options as an outpatient should be discussed (e.g., cognitive behavioral therapy or use of selective serotonin reuptake inhibitors).

CRITICAL INTERVENTIONS

- Assess patients with panic attacks for suicidal ideation, because there is a high rate of depression in these patients (12).
- Administer short-acting benzodiazepines for acute anxiety.

DISPOSITION

Most patients with anxiety disorders can be discharged from the ED with primary care or psychiatric follow-up. Patients who are actively suicidal, violent, or significantly disabled by their anxiety should be admitted to the hospital. Likewise, when the cause of acute anxiety is unclear, short-term admission for further medical and psychiatric evaluation should be considered. If benzodiazepines are prescribed, only a small quantity should be given, and close follow-up and subsequent psychiatric evaluation should be arranged.

Common Pitfalls

- Assuming that an acutely anxious patient, even one known to suffer from an anxiety disorder, has no medical problem. Patients presenting with anxiety must be presumed to have a medical condition as the cause until it is ruled out by an appropriate evaluation.

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CHAPTER 166

Schizophrenia and Bipolar Disorder

James A. Comes, Douglas A. Rund, and Basheer Lotfi-Fard

CLINICAL PRESENTATION

Schizophrenia

Schizophrenia is a devastating mental illness characterized by psychosis, apathy and social withdrawal, and cognitive impairment, which results in impaired functioning in work, school, interpersonal relationships, and leisure time. It is the most common and severe form of psychotic illness with a prevalence estimated at about 1% (1).

Symptoms of schizophrenia usually develop between ages 16 to 30 years and persist through the patient's lifetime. Although the onset of illness is often gradual and insidious, all patients experience periods in which contact with external reality is grossly impaired (*active phase*). After the active phase, most patients continue to show signs of the illness (but at less than psychotic intensity) in a *residual phase*. Many patients show a pattern of progressive deterioration over time, with multiple episodes of active illness followed by accumulating residual symptoms.

Although a patient with schizophrenia may present in any phase of the illness, psychotic symptoms are a common presentation to the emergency department (ED). Worsening of their psychosis may be from a situational stress, an underlying medical condition, or nonadherence to their medication. They may also present with suicidal behavior, violence, or an adverse reaction to their

neuroleptics. As a general rule, any psychiatric symptom may be seen in the active phase of schizophrenia. However, in order for an episode to meet criteria for an active phase of schizophrenia, one of the "positive symptoms" of schizophrenia (delusions, hallucinations, disorganized speech, or disorganized behavior) must be present. Often, different positive symptoms co-occur during the active phase of schizophrenia.

Delusions are false beliefs, based on incorrect inference about external reality, that are firmly sustained despite what constitutes incontrovertible and obvious proof or evidence to the contrary. Common forms of delusions include persecutory, paranoid, grandiose, and somatic. Bizarre delusions involve beliefs that are patently false and totally implausible and nonsensical. Bizarre delusions are very frequent in schizophrenia and have increased diagnostic discrimination in comparison with nonbizarre delusions.

Hallucinations are perceptual experiences that have a compelling sense of reality, like true perceptions, but without external stimulation of the sensory organ. Hallucinations may occur in any sensory modality with auditory hallucinations being the most common. Hallucinations may be fleeting, recurrent, or continuous for years, and content varies from indistinct muttering to elaborate conversations involving several parties. Voices may be familiar or unfamiliar. Commonly the language is coarse, hostile, insulting, belittling, or derogatory, but it may also be comforting, praising, instructing, or neutral.

Grossly disorganized behavior encompasses a wide range of abnormalities such as prolonged childlike silliness, severe agitation, inability to satisfactorily complete normal activities of daily living, displays of affect markedly inappropriate to circumstances, intense verbal or physical aggressiveness that is unpredictable and unprovoked, and serious loss of normal social inhibitions, and other actions that seem so odd or unusual as to suggest that the individual is grossly out of contact with external reality. *Disorganized thoughts* include derailment, blocking, circumstantiality, tangentiality, neologisms, over inclusive, and concrete thinking.

Catatonia is a syndrome of abnormal motor control and responsiveness in patients who are otherwise alert and conscious (in fact, often these patients are hyperalert). Catatonia is often associated with schizophrenia, but it can also be seen in a wide variety of other psychiatric and medical conditions. Common symptoms of catatonia include *catalepsy* or *stupor, posturing, waxy flexibility,* and *mutism.* However, catatonia more rarely can present as *catatonic excitement* (a very dangerous state of extreme and constant agitation, hyperactivity, and purposeless motion) or *malignant catatonia* (an acute onset of fever, excitement, autonomic instability, and delirium).

By contrast, *negative symptoms* are those that suggest a loss or complete cessation of some normal mental function. *Affective flattening* or *blunting* is a marked reduction or absence of external signs of emotion. It includes generalized lack of responsiveness, immobile and unresponsive facial expression, decreased spontaneous movements, paucity of expressive gestures, poor eye contact, and lack of vocal inflection. *Alogia* is a reduction in quantity of thought, reflected in decreased fluency and productivity of speech. It includes *poverty of speech,* and *poverty of content of speech. Avolition* (apathy) is a reduction or loss of ability to initiate and persist in goal-directed activities, such as poor grooming, impersistence at work or school, and physical anergia (2).

Bipolar Disorder

Bipolar disorder (previously known as *manic depressive disorder*) is a mood disorder whose major feature is changes of mood from periods of mania to depression. The prevalence of bipolar disorder is 1% and, unlike unipolar depression, men and women are equally affected.

A manic episode is defined as a distinct period of elevated, expansive, or irritable mood that lasts for at least 1 week and causes marked impairment in functioning. The patient typically has an increased energy level, pressured speech, and a decreased need for sleep. The patient may also have racing thoughts, distractibility, and

flight of ideas. Patients may also get involved in activities with high potential for unpleasant consequences; for example, such as frequently spending money recklessly, becoming involved in high-risk sexual activity, and engaging in risk-taking behavior.

Delusions or hallucinations may be present, making it difficult to distinguish from schizophrenia. Grandiose delusions are frequently seen in mania and include having special powers or being a powerful figure. Manic patients are often impulsive, show poor judgment, and can have a great deal of disruption in their personal life. They can also cause a great deal of stress to their family, who are often the ones who refer the patient for emergency evaluation (3).

DIFFERENTIAL DIAGNOSIS

Patients presenting with psychotic behavior have a broad differential diagnosis. It may be a manifestation of schizophrenia, delirium or dementia, an underlying medical disorder, substance abuse, major depression, mania, or a delusional disorder. Transient hallucinations may occur in nonpsychotic mental disorders (acute bereavement) and are not considered psychopathologic.

The medical conditions that can cause manic or psychotic symptoms include disorders of the central nervous system (seizures, tumors, multiple sclerosis), metabolic (hyperthyroidism, hypoglycemia), infectious (encephalitis, pneumonia, uremia), and systemic (collagen vascular disease, lupus) diseases. Also, the effects of many substances (steroids, cocaine, alcohol) and medications (benzodiazepines), both in intoxication and withdrawal, can mimic these conditions (4).

ED EVALUATION

The role of the ED assessment in patients presenting with psychotic or manic behavior is threefold. First, and most importantly, is to recognize and treat any life-threatening medical conditions that may be causing or exacerbating the psychiatric complaints. Second is to rapidly stabilize the patient’s psychotic behavior and ensure safety

to the patient and providers. And lastly, often in consultation with a mental health professional, is to determine the appropriate disposition. The extent of the medical examination and evaluation depends on the patient's history and circumstances. New-onset psychosis in a previously normally functioning person strongly suggests a medical condition (particularly if the person is elderly). In cases wherein the patient has a long history of mental illness, including numerous hospitalizations and previous or current treatment, the cause of psychotic presentation may well represent worsening or recurrence of symptoms associated with the patient's ongoing psychiatric condition. Yet, psychosis may also be the effect of a new or worsening medical condition superimposed on the underlying mental illness (5).

The initial evaluation includes review of prehospital information gathered by police and emergency medical services (EMS). The physician encounter should consist of clear, simple, direct questions about the patient's chief complaint or reason for being in the ED in a tone that is understanding, calm, and nonjudgmental. The patient's speech and behavior should be observed for signs of disorganization, delusions, or hallucinations. Questioning about the onset of illness, psychiatric hospitalizations and other psychiatric care, and medical history are essential. Although patients may be forthright about the circumstances that led to an ED visit, much information can be gleaned from review of the medical record and collateral information provided by family and/or care providers. The mental status exam should include an assessment of general appearance, level of consciousness, mood, spontaneous speech, and orientation to time and place. All patients should have a complete set of vital signs. Abnormal vital signs should be addressed (particularly fever) and not prematurely be attributed to anxiety or agitation. The physical exam should be driven by the chief complaint, patient's mental status, psychiatric history, concurrent conditions, and age. Lastly, the physician should highlight the plan for subsequent management, for example, telling the patient that a mental health professional will be called in to help with additional

evaluation. Answers to the patient's questions should be clear, concise, and straightforward (6).

ED MANAGEMENT

Managing the undifferentiated agitated or psychotic patient remains complex and challenging especially if the patient is disruptive, argumentative, or refusing care. Not only must the ED physician attempt to deescalate the situation but also quickly ascertain whether the care providers, other patients, and the patient are safe from potential harm.

The initial step in treating an acutely psychotic patient is to make the patient aware of your concern about their behavior, offer assistance to help reduce their agitation, and acknowledge that they are safe. Patients with escalating aggression or agitation or potential for violence may require rapid tranquilization and physical restraint. This should be done rapidly, nonpunitively, and with appropriate well-trained staff (7).

Droperidol (Inapsine) and haloperidol (Haldol) are particularly effective when emergent sedation is needed for the safety of the patient and healthcare providers and are often used in conjunction with short-acting benzodiazepines. However, droperidol and haloperidol are not recommended (FDA Black Box warning) in patients suspected or known to have cardiac dysrhythmias or QT prolongation. Case reports have occurred in patients receiving droperidol at or below recommended doses, with no known risk factors for QT prolongation and some cases have been fatal. In September 2007, the FDA released a warning that torsades de pointes and QT prolongation might occur in patients receiving haloperidol, particularly when the drug is administered intravenously or at doses higher than recommended. These warnings, however, do not preclude their use, yet it is prudent to exercise caution when using them in patients who may have conditions that put them at risk for QT prolongation.

More recently, newer agents known as second-generation antipsychotics—risperidone, quetiapine, paliperidone, ziprasidone,

lurasidone, iloperidone, olanzapine, and aripiprazole—with less motor side effects (dystonia, akathisia or restlessness, parkinsonism, and neuroleptic malignant syndrome) have been introduced for treatment. The list of approved drugs for the treatment of bipolar disorder and schizophrenia continues to grow rapidly. Despite the initial enthusiasm that these agents would not only improve the positive psychotic symptoms, but also the negative and cognitive aspects of the illness, the efficacy toward negative and cognitive symptoms of the illness have not been borne out to date. Additionally, the second-generation antipsychotics, to different degrees, induce a high incidence of metabolic side effects (weight gain, hyperglycemia, diabetes, elevated triglycerides, and cholesterol) (8). However, second-generation antipsychotics offer calming effects with a far lower incidence of the acute dystonia or sedation seen with conventional antipsychotic agents. For patients with known schizophrenia or bipolar disorder presenting with psychotic symptoms in the ED, these agents are often first-line treatment (9). Oral doses should be offered first, and several agents are available in dissolvable forms. However, dissolvable tablets do not have a faster onset of action compared with their conventional oral dosage forms and possess the same side-effect profile. Antipsychotics should be avoided in elderly patients with dementia as much as possible. The FDA has given a Black Box warning for all antipsychotics for the treatment of elderly patients with dementia-related psychosis as these patients have a higher mortality rates as compared with placebo.

Sometimes a patient's behavior is extreme enough that seclusion or physical restraint is necessary to assure the safety of the patient and others. At all times, the least restrictive method should be used, and the patient should be closely monitored and reassessed. Physicians should be familiar with their facilities' current protocols and the laws regarding these measures.

CRITICAL INTERVENTIONS

- Administer chemical restraints with or without physical restraints to the agitated patient before the patient becomes violent.
- Patients requiring physical restraints must also receive anxiolytics and/or antipsychotics.

DISPOSITION

The acutely psychotic or manic patient needs evaluation by a mental health professional and, probably, hospitalization if the potential for violence or self-harm is suspected. The psychotic patient who expresses suicidal or self-harming thoughts or who has attempted suicide is at risk because he or she can exhibit unpredictable behavior in the immediate future.

New psychiatric symptoms (not caused by a medical condition) or worsening symptoms (suggesting some kind of crisis or management failure) should ideally be managed in the ED in consultation with a psychiatrist. Patients unable to care for self due to severe psychosis, chaotic living environment, poor judgment, confusion, or extreme impulsivity require mental health consultation and may need to be transferred to a facility that can accommodate observation and reassessment over a prolonged period of time. Patients with chronic stable psychiatric illness that appears to be under good control can be referred for outpatient management as circumstances dictate, but consultation with a mental health professional or a discussion with the patient's psychiatrist may facilitate evaluation and help ensure adequate follow-up (10).

Common Pitfalls

- Missing a life-threatening medical condition that presents primarily with abnormalities of thought and behavior.
- Neglecting to consider patients' risk of harm to themselves or others, owing to suicidal or homicidal ideation, impulsivity, or poor judgment.
- Attributing physical complaints to somatization without sufficient evaluation to rule out a concurrent emergent medical condition.

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CHAPTER 167 The Agitated or Violent Patient

Katherine Bakes and Vincent J. Markovchick

One of the most common and dramatic patient presentations in the emergency department (ED) is the out-of-control, agitated, and violent patient. Screaming and combative behavior immediately get the attention of staff, patients, and visitors. Violence is a substantial ED problem, with one study reporting 75% of attending physicians experiencing verbal threats, 28% a physical assault, 12% confrontation outside of the ED, and 4% victimization by stalking (1). An Emergency Nurses Association (ENA) survey found 86% of emergency nurses reported having been a victim of job-related violence (2). Nurses are in fact more likely to experience violent events than physicians, with more associated acute stress and commensurate decrease in productivity (3).

Times of ED crowding are particularly high risk for violent events, with one study showing a fourfold odds of experiencing patient care–related violence increased over baseline (4). With two-thirds of US metropolitan EDs experiencing crowding, it is crucial to develop evidence-based institutional protocols to address times of heightened violence risk, particularly at a time when the Affordable Care Act may lead to increased ED volumes. Formal security plans, which include environmental modifications, employee education and training, use of security and law enforcement, surveillance, and the discovery and handling of concealed weapons, have demonstrated decreased employee assault rates.

Treatment of the violent or agitated patient often begins in the field by emergency medical technicians (EMTs) and law enforcement. If possible, advanced notification via communications with field personnel should be provided to the ED so as to mobilize the resources and the beds for management of such patients. This will obviate the situation wherein a patient is held in a public area such as a hallway for a prolonged period of time while the staff scrambles to free up a bed in an appropriate treatment room.

When necessary for patient care or provider safety, chemical sedation or physical restraint can commence in the field, necessitating the appropriate prehospital protocols. EMTs should contact the base station to discuss appropriate treatment of such patients and to give advance notification of patient arrival. In many instances, it is not possible to obtain a coherent history from the patient. Careful questioning of EMTs, family members, bystanders, friends, or anyone else who has observed the evolution of this patient's behavior should be undertaken. Members of appropriate personnel, including security, should be mobilized to safely transport and, when necessary, physically restrain such patients. The situation must be brought under control expeditiously to ensure the safety of staff and the patient, and to prevent secondary effects of severe agitation such as hyperthermia, metabolic acidosis, and rhabdomyolysis.

DIFFERENTIAL DIAGNOSIS

The first role of the emergency physician is to rapidly identify reversible causes of acute organic brain syndromes that, if not treated, may cause morbidity and potential mortality. Examples of these are hypoglycemic reactions, hypoxia, thyroid storm, bath salts abuse, severe amphetamine or cocaine toxicity, hyperthermia, anticholinergic toxicity, and alcohol intoxication or withdrawal. In addition, the ultimate role of the emergency physician is to differentiate organic from functional disorders. (See Chapter 152 for a detailed description of the mental status examination and the differentiation of organic from functional disease state.)

Evaluating for quickly reversible causes of agitation should include a point-of-care blood glucose test (hypoglycemia), oxygen saturation measurement (hypoxia), and a physical examination for the presence of possible toxidromes. Life-threatening sympathomimetic agitated states (i.e., cocaine and methamphetamine intoxication) may be identified by the presence of one or more of the following: significant tachycardia, hypertension, hyperthermia, extreme violent muscular activity, and dilated pupils. Violent postictal states may be identified by a history of a seizure and secondary signs on physical examination of major motor seizures (i.e., tongue lacerations and incontinence). When feasible, a mini-mental status examination should be performed as well as a complete neurologic examination.

If any focal neurologic deficits are identified, the differential diagnosis should be expanded to include central nervous system pathology such as brain tumors, seizures, ischemic stroke, or intracranial hemorrhage. Specific toxidromes should be identified (i.e., hyperthermic, sympathomimetic, anticholinergic, and cholinergic presentations), as each requires a specific therapy. Features of delirium, new violent or psychotic behavior (particularly in patients older than 40 years of age), abnormal autonomic signs, visual hallucinations, or an acute time course should raise a concern that the cause of the patient's agitation may be organic in nature.

Alcohol intoxication is a frequent ED presentation and has been linked to aggression. The association is attributed to cognitive and emotional difficulties: decreased tolerance for frustration, diminished capacity to perceive and process multiple cues at once, increased response to strong situational stimuli, limitations in problem-solving despite an exaggerated sense of power, and a diminished appreciation for consequences with associated increased risk-taking behaviors.

"K2" and "Spice" are examples of a relatively new class of designer cannabinoids. Easily available on the Internet and some convenience stores, these drugs are sometimes referred to as "legal highs" due to their ability to evade standard drug screens (5). Numerous formulations of designer cannabinoids are available, from

powders and liquids, to smoking mixtures, with case reports describing a myriad of effects, from nausea to psychomotor agitation, diaphoresis, and palpitations. Other reports have included sedation, hot flushes, burning eyes, xerostomia, mydriasis, tremors, palpitations, and tachycardia (6).

Excited delirium syndrome (ExDS) was first described in forensic literature as delirium with severe agitation that, if untreated, can lead to death. In a 2009 consensus white paper, the American College of Emergency Physicians (ACEP) recognized ExDS as "a unique syndrome which may be identified by the presence of a distinctive group of clinical and behavioral characteristics that can be recognized in the pre-mortem state" (7). Although an imprecise syndrome, clinical features include tolerance to significant pain, rapid breathing, sweating, severe agitation, elevated temperature, delirium, noncompliance or poor awareness to direction from police or medical personnel, lack of fatiguing, "superhuman" strength, and inappropriate clothing for the current environment. Because ExDS deaths have occurred with minimal restraint, early chemical sedation is recommended.

ED EVALUATION AND MANAGEMENT

Staff safety and expeditious control of the violent or agitated patient should not overshadow the need to consider an organic etiology for violent behavior. Easily diagnosed and reversible etiologies for agitation should be quickly excluded or treated. A thorough physical examination, including a reliable temperature and pulse oximetry, is mandatory and may require chemical sedation to obtain. Fever with agitation or violence, without a clear explanation, necessitates a sepsis workup. If the workup fails to identify an etiology and the patient has an organic brain syndrome, a head computed tomography scan and lumbar puncture should be considered to exclude intracranial pathology. Hypoxia must be quickly excluded as a cause of aggressive behavior and treated appropriately. Likewise, hypoglycemia must be diagnosed rapidly, either at the time of IV placement or with a finger stick after physical restraints

are instituted. A toxidrome-focused examination should be performed, which includes vital signs, pupillary and skin evaluation, lung and bowel sounds, and neurologic assessment including mental status. If the history and physical examination do not lead to a clear cause for agitation, laboratory studies such as a urine toxicology screen and serum electrolytes can be considered.

Although control of the violent patient is paramount in ensuring the safety of the ED staff and patients, the need for chemical sedation or restraints may be avoided by applying some basic principles when evaluating the volatile individual. Once in the ED, some simple preventative protocols for decreasing the risk of violence include having patients change into hospital gowns to allow for further searches and a complete physical evaluation. Providers should utilize preventative communication measures for escalating violent behavior such as maintaining an adequate distance from the agitated patient, calmly explaining intentions and the plan to the patient and ED staff, engaging in nonthreatening verbal and nonverbal communication, acknowledging the agitated patient's concerns, and having an exit strategy that includes how to call for help (8).

Features suggesting an organic etiology include a rapid onset, no prior history of psychiatric disease (especially if >40 years of age), visual–olfactory–tactile hallucinations, abnormal vital signs, cognitive deficits, slurred speech, confusion, evidence of substance abuse, disorientation, and a history or physical evidence of trauma.

One staff educational crisis intervention (SECI) on ED violent behaviors significantly reduced patient violence from 17% to 7%. The SECI program included education for physicians, nurses, and security staff that focused on the following: early recognition of potential violent behaviors, team protocols, and awareness of guidelines; regular staff dialog around violence and restraint; medical presence during all security interventions for restraint; and debriefing after each intervention (9). Although no longer required by the Joint Commission, debriefings are recommended, with many institutions utilizing the Crisis Prevention Institute's (CPI) train the trainer model of crisis management and de-escalation.

Pharmacologic Management

When de-escalation techniques fail, chemical sedation can and should be used to prevent harm to patients and staff members. The most common drugs used for this purpose include the neuroleptics haloperidol and droperidol, as well as the benzodiazepines midazolam, diazepam, and lorazepam. Haloperidol should be dosed 5 to 10 mg intramuscular (IM) every 10 to 30 minutes. Peak serum levels occur approximately 30 minutes after IM and 3 to 6 hours after oral administration. Unlike the phenothiazines such as thioridazine, haloperidol does not cause respiratory depression, has negligible anticholinergic side effects, and rarely causes hypotension. A 2012 Cochrane review on the use of haloperidol for psychosis-induced agitation or aggression found that haloperidol should not be given alone, but rather in combination with the anticholinergic-antihistamine promethazine (up to 50 mg), which enhances haloperidol's tranquilizing effects while minimizing undesirable side effects such as acute dystonia (10). The traditional combination of haloperidol plus a benzodiazepine was never a highly rated alternative (11).

Owing to the high potency of haloperidol, extrapyramidal side effects (dystonia, torticollis, opisthotonos, or oculogyric crises) are common and not dose-related, occurring in 20% of people in the first 24 hours. Akathisia, a feeling of uneasy restlessness, has been reported to occur in up to 75% of people receiving 5 mg of haloperidol. Fortunately, these side effects are easily treated in minutes with diphenhydramine 25 to 50 mg IM or IV or benztropine 2 mg IM or IV. Prophylactic treatment should be considered in patients with a history of or a fear of developing extrapyramidal side effects. Because the onset of side effects can be delayed on the order of hours, the patient can be prescribed oral benztropine 2 mg or diphenhydramine 25 mg at discharge and instructed to take them if symptoms develop. Although more common with the low-potency antipsychotics, haloperidol also has the theoretical potential to lower the seizure threshold and thus should be avoided with

patients who are postictal, prone to seizures, or experiencing amphetamine or cocaine toxicity.

In 2007, the FDA has published a “Black Box” warning for the IV use of haloperidol owing to a dose-dependent IV risk of prolongation to the QT interval. These warnings are often based on rare events through voluntary reporting, which can be biased or incomplete and often lack proof of causality. Ironically, many common ED medications can prolong the QT interval, including antiarrhythmics (e.g., amiodarone, procainamide, adenosine), most antiemetics (e.g., ondansetron), antimicrobials (e.g., erythromycin, azithromycin, moxifloxacin, levofloxacin, fluconazole), antipsychotics (e.g., haloperidol, quetiapine), antihistamines (e.g., diphenhydramine, hydroxyzine, loratadine), antihypertensives (e.g., nicardipine), and tricyclic antidepressants (12).

Based on case reports of potentially fatal cardiac events, the FDA has revised the label for haloperidol, warning that the QT prolongation and risk of torsade de pointes were increased with IV administration, particularly when given to patients on other QT-prolonging medications or at greater than recommended doses; the FDA went on to recommend continuous ECG monitoring with the administration of IV haloperiodol (13). Since the warning, investigators have shown that a total cumulative dose of IV haloperidol of <2 mg can safely be administered without ongoing electrocardiographic monitoring in patients without concomitant risk factors (underlying heart conditions, electrolyte imbalances such as hypokalemia and hypomagnesemia), concomitant proarrhythmic drug use, and mechanical ventilation (13).

Droperidol (2.5 to 5 mg IM or IV), another antipsychotic, has a shorter half-life than haloperidol. Droperidol’s antiemetic effect is advantageous for patients restrained supine and at risk for vomiting and aspiration. As with haloperidol, droperidol has demonstrated a risk of increasing QT intervals, and thus also carries an FDA Black Box warning. Droperidol’s Black Box warning was given after reports of adverse events were submitted through MedWatch from 1997 to 2001 and published in two studies reporting prolongation of the QT intervals (12). In a 2003 review of the literature surrounding

the FDA position as well as local experience of approximately 12,000 patients over a decade, Shale et al. (14) concluded that the evidence does not support discontinuation of droperidol for control of the violent patient. They noted that the evidence for the FDA warning was based on 100 adverse cardiovascular events and either 18 or 25 deaths (depending on conflicting reports) (14).

Unfortunately, all neuroleptics have the potential of causing dose-dependent prolongation of the QT interval and precipitation of torsade de pointes by blockade of cardiac potassium channels. Thioridazine was given an FDA Black Box warning in 2000 owing to multiple reports of sudden unexplained cardiac deaths. Droperidol has also carried an FDA Black Box warning since 2001, owing to an apparent association with QT prolongation, and its use has significantly decreased, presumably because of fear of adverse outcomes (15,16). However, as with all medications, its use should be based on a risk–benefit analysis.

The three benzodiazepines often used for sedation are midazolam, lorazepam, and diazepam. Although diazepam is often preferred owing to its low cost, lorazepam and midazolam have the advantage of superior IM absorption and bioavailability. Lorazepam is preferred in patients with cirrhosis or alcohol dependence, as its metabolism is maintained in the setting of liver disease. The side effects of these medications are mainly sedation and respiratory depression. Large doses of benzodiazepines, as may be necessary for acute amphetamine or cocaine toxicity, may be given only in a closely monitored environment wherein active airway control may be instituted if respiratory depression ensues.

A double-blind randomized clinical study of 180 acutely agitated ED patients compared 5 mg of IV midazolam with droperidol every 5 minutes. Midazolam was found to produce more sedation than droperidol at 5 minutes but equivalent sedation at 10 minutes. The midazolam group had statistically more adverse events related to airway management, with three patients requiring transient assisted ventilation and one requiring endotracheal intubation. Of note, the QT_c at 30 minutes did not differ between the groups, and there were

no adverse events related to QT prolongation (17). The TREC (rapid tranquillization clinical trial) collaborative group conducted a randomized controlled trial of 301 patients with acute agitation and compared midazolam 15 mg IM with haloperidol 5 mg or 10 mg IM plus promethazine 50 mg IM. Midazolam was statistically more effective than haloperidol plus promethazine at producing sedation at 20 and 40 minutes after injection. Twice as many patients in the midazolam group were asleep at 20 minutes as were in the haloperidol group. Two severe adverse events were noted: one patient with epilepsy developed a seizure after haloperidol plus promethazine injection, and one patient in the midazolam group developed respiratory depression and cyanosis requiring reversal with flumazenil (18). Multiple investigators have evaluated the combination of a benzodiazepine with a neuroleptic for the control of acute agitation. However, the recent Cochrane review on haloperidol found no benefit in combining haloperidol with lorazepam for acute control of the agitated patient; evidence does not support regular use of these combinations (10).

The newer atypical antipsychotics are also being investigated for the use in acute behavioral control. These agents, which include risperidone, olanzapine, and ziprasidone, may be more expensive, but often have a more favorable side-effect profile. Experience with these medications in the emergency setting is limited, however (16). These medications also have the propensity to cause QT prolongation, although none currently carry an FDA Black Box warning.

When an organic etiology of agitation is suspected or if there is no clear psychiatric diagnosis, providers should use IM haloperidol or IM benzodiazepine alone. For primary psychiatric disorders such as schizophrenia, psychotic depression, and personality disorders, IM olanzapine or ziprasidone are preferred over IM haloperidol. In cases of mania, risperidone, alone or with a benzodiazepine, is recommended over haloperidol (11).

IM ketamine (5 mg/kg) or IV ketamine (1 mg/kg) has been used for some time outside of the United States for sedation of the agitated patient. A small retrospective study of 11 trauma patients

in the prehospital setting reported its effectiveness, but there are concerns with potential side effects of increased oral secretions, vomiting, laryngospasm, hypertension, and emergence phenomena. However, no drug used in this setting is without risks, and ketamine may prove a useful addition to the armamentarium of the emergency physician who needs immediate control over an aggressive or dangerous patient. A study of 13 patients receiving prehospital ketamine found that 3 patients developed hypoxia (2 requiring intubation) and 10 had emergence reactions which were successfully treated with small doses of benzodiazepines (19).

Although further evidence is needed, ketamine has shown to be successful in small samples of patients with ExDS (20). The ACEP consensus group recommends immediate control of ExDS, endorsing early use of benzodiazepines, ketamine, or intranasal midazolam for speedy chemical control.

Physical Restraints

Unfortunately, many patients prove too agitated for the aforementioned approach, and necessitate physical restraints. ED staff should avoid hogties or hobble restraints, whereby the patient's hands and feet are tied together behind the back. This method of physical restraint has occasioned multiple reports of sudden death, particularly when the patient was kept in the prone position and in the setting of intoxicants. One study found that compared with the supine position, hobble restraints significantly impacted respiratory function and were associated with decreased forced vital capacity, forced expiratory volume, and maximal ventilation.

When necessary, four-point soft leather restraints should be utilized. At least five staff members should restrain the patient, one for each limb and a fifth to stand at the head of the bed to calm and to explain the process to the patient. To avoid undermining a therapeutic relationship with the patient, the physician should not be a member of this team. Restraints should be secured firmly, yet loosely enough to allow a finger to move between the restraint and the extremity. All patients should be assumed to be at risk of

aspiration and therefore should be restrained on their side or with the head of the bed slightly elevated. Restraint of an upper limb in hyperabduction and extension for a prolonged period of time may cause peripheral nerve injury, so it should be repositioned at the patient's side as soon as adequate control of the patient is attained.

The Centers for Medicare and Medicaid Services (CMS), which works with the Joint Commission, has put forth guidelines on the use of seclusion or restraint (see below). Although restraint-related complications are infrequent, to maintain patient rights and avoid the liability associated with placing a patient in restraints, a hospital protocol should be established. It should include documentation of the following: necessity of restraints, alternative measures attempted, and orders for the continuation of restraints and decided end-points for discontinuation of restraints. The Joint Commission requires that a patient be assessed every 15 minutes after placement of restraints for signs of injury associated with the application of restraint or seclusion; nutrition and hydration; circulation and range of motion in the extremities; vital signs; hygiene and elimination; physical and psychological status and comfort; and readiness for discontinuation of restraint or seclusion (21). The use of restraints can be minimized; the most successful institutional protocols for reducing the need for physical restraint include leadership involvement, facility culture change, the learning of concrete de-escalation skills, and the use of data to drive system change (11,22).

Federal directions on the use and standards for seclusion or restraint include the following:

- Physician or other independent licensed practitioner must see and evaluate patient within 1 hour of initiating intervention.
- Use of seclusion or restraint only when clinically justified and after consideration of alternative treatment options.
- Time-limited orders: 4 hours for adults; 2 hours for adolescents; 1 hour for children (<9 years old), with renewal after 24 hours requiring a physician or licensed independent practitioner to see and assess the patient.
- Continuous in-person patient monitoring and periodic re-evaluation with the intent to discontinue intervention at the

earliest possible time; face-to-face re-evaluation before each renewal of initial time-limited orders.

- Notification of clinical leadership (i.e., medical director) after 12 hours of continuous seclusion or restraint and every 24 hours thereafter.
- With patient-informed consent, prompt family notification when seclusion or restraint is initiated.
- Deaths must be reported to the CMS (12).

Unfortunately, often not discussed is the cost to the healthcare provider caring for the traumatized, agitated, or violent patient. Secondary traumatic stress (STS) or compassion fatigue (CF) are common culprits of burnout in emergency medicine. A study of emergency nurses found that 54% reported irritability, 52% avoidance of patients, and 46% intrusive thoughts about patients; in all, 33% met all criteria for STS (23). STS disorders typically go unrecognized by affected personnel, despite chronic and critical incident stressor putting providers at risk for posttraumatic stress reactions and subsequent substance abuse (24). Emergency providers should be monitored for appropriate self-care, cognitive and emotional changes (e.g., difficulties with safety, trust, control, or intimacy), and healthy work–life balances (25). Involvement in stress management activities can prevent or minimize STS symptomatology (23).

CRITICAL INTERVENTIONS

- Diagnose and treat reversible causes of agitation, such as hypoxia and hypoglycemia.
- Approach the volatile patient in a safe environment, utilizing de-escalation techniques.
- Use a documented hospital-based protocol after instituting physical restraints that includes justification for its use and frequent reassessment of the patient's condition.
- Obtain pharmacologic control of the violent medical patient using an atypical antipsychotic, with or without a benzodiazepine.

- Obtain pharmacologic control of the violent psychiatric patient using haloperidol and/or a benzodiazepine.

DISPOSITION

Once the patient is under control and an organic etiology has been excluded, disposition will depend on the patient's course in the department. The patient might require psychiatric evaluation for suicidal or homicidal ideation or for being gravely disabled. Alternatively, the patient may be discharged once the acute violent or agitated behavior subsides. This usually requires a short observation period until an intoxicant is metabolized. Finally, if the patient has been physically violent toward staff, he or she may be arrested and discharged to the appropriate authorities.

Common Pitfalls

- Failure to undress the patient and search for weapons.
- Failure to take steps to minimize the risk of aspiration and peripheral nerve injury in a restrained patient.
- Failure to provide adequate doses of sedative agents.

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CHAPTER 168

Factitious Illness, Malingering, and Conversion Disorder

Jeffrey S. Dubin and Mark Smith

Factitious disorder, malingering, and conversion disorder constitute a spectrum of medical conditions in which the patient's symptoms are false, pretended, or grossly exaggerated. The patient's symptoms may be voluntary (malingering and factitious disorder) or may be an involuntary expression of an underlying psychological conflict (conversion disorder) (1). Distinguishing the physiologic conditions from the functional while addressing the patient's psychologic issues is a test of the emergency physician's diagnostic acumen and therapeutic skill.

FACTITIOUS DISORDER

CLINICAL PRESENTATION

The syndrome of factitious disorder with physical symptoms is better known as Munchausen syndrome, named by Asher (2) after novelist Rudolph Raspe's character, Baron Munchausen, who enjoyed a series of fabricated adventures. Munchausen patients are impostors who invent bizarre and often fantastic stories and accept painful and potentially dangerous procedures (e.g., cardiac catheterization, exploratory laparotomy) to reach their presumed goal: to become a patient and assume the "sick role" (1). There is no

other secondary gain, thus distinguishing the Munchausen patient from the malingerer.

Munchausen patients typically present to the emergency department in a dramatic fashion, with a constellation of physical symptoms, plausibly suggesting the presence of substantial pathologic illness that is not present. Examples of Munchausen practices:

- Applying mydriatics to stimulate anisocoria (3)
- Misusing an insulin pump to induce hypoglycemia (4)
- Creating skin lesions or placing foreign bodies in skin (5)
- Overdosing with caffeine to induce tachyarrythmia (6)
- Feigning respiratory distress that results in intubation (7)

Munchausen patients are typically young or middle-aged men (although the age range spans the pediatric to the geriatric) and often report a medical history of previous hospitalizations and operations, in many cases performed in other cities. They are knowledgeable about hospital routines and may have worked in the medical field but are often vague or inconsistent about their own medical details. Munchausen patients are clever, realistic, and facile in their simulation of clinical reality, but the extent and severity of symptoms are often out of proportion to physical findings and demeanor, and may seem almost too classic. The Internet has not only made it easy for Munchausen patients to find descriptions of disease symptoms to mimic, but has enabled a new outlet for the medical imposter. Munchausen by Internet has been described when persons without disease join Internet support groups and pose as having true illness and disrupt these online communities (8).

Munchausen patients have been characterized as hostile, dependent persons with poor impulse control and a history of self-destructive behavior. They tend to be socially isolated, rarely are accompanied to the emergency department by friends or family and, once admitted to the hospital, usually have no visitors. When confronted, they usually become hostile and querulous, deny the allegation of factitious disorder, and sign out of the hospital against medical advice.

When parents falsify illness in their children, the disorder is termed *factitious disorder by proxy* (FDBP). FDBP describes abuse in which the perpetrator (most often the mother) is motivated by the desire to assume the sick role by proxy or to seek attention from the hospital staff (1). Whenever this diagnosis is considered, it is important to define the specific abuse to the child. FDBP refers to the context of the abuse and the disorder of the parent. FDBP is child abuse and should be treated as such (9). Examples of FDBP are as follows:

- Infant apnea, cyanosis, seizures from smothering (9)
- Severe diarrhea and hypernatremia in infant (10)
- Factitious hypoglycemia in children (11) and elders (12)
- Self-induced premature labor and resultant neonatal injury (13)

DIFFERENTIAL DIAGNOSIS

Munchausen syndrome must be distinguished both from organic disease and malingering and from three conditions in which the production of nonorganically based symptoms is not voluntary: conversion disorder, somatization disorder, and hypochondriasis.

In the absence of explicit evidence to the contrary, the clinician should presume that there is an organic basis for the patient's complaints. When the patient fits the pattern of presentation for Munchausen syndrome, however, evidence should be sought to confirm or disprove that suspicion. In contrast to the Munchausen patient, the *malingerer* has a clearly understandable external incentive and goal other than wanting to be a patient. In the three somatoform disorders (conversion disorder, somatization disorder, and hypochondriasis), the patient's symptoms are involuntary. *Conversion disorder* is discussed in subsequent paragraphs. The patient with *somatization disorder* has a chronic history of multiple symptoms involving different organ systems in a fluctuating and recurrent pattern that is not adequately explained by a physical disorder. The *hypochondriac* patient presents with fear and concern about the presence of disease and, despite reassurance, misinterprets

normal bodily sensations and physical signs as pathologic conditions.

ED MANAGEMENT

Until a diagnosis of factitious disorder is confirmed, the patient should be treated as if an organically based disease is present. The usual diagnostic and therapeutic procedures should be followed. There are a myriad of symptoms and signs that patients with factitious disorder may feign. Kenedi et al. have compiled an extremely useful table of diagnostic tools clinicians should consider when evaluating suspected Munchausen patients (14).

If Munchausen syndrome is suspected but not confirmed, the physician may treat the patient in a modified manner (e.g., consider serial cardiac enzymes, no potentially harmful medications, and discharge home rather than admission for a suspected Munchausen patient with chest pain and normal ECG). When Munchausen syndrome is confirmed, the physician may elect to confront the patient in a supportive and nonthreatening manner, although the establishment of a therapeutic alliance between patient and physician is unlikely. There is no difference in outcomes of a confrontational versus nonconfrontational approach; most Munchausen patients will not participate in psychotherapy (15).

Patients who are labeled with Munchausen syndrome can still become organically ill. Procedures that have been performed because of their imposture may predispose them to real illness (e.g., a small-bowel obstruction may occur as a result of adhesions from a previous exploratory laparotomy for abdominal pain). Other patients may need medical treatment for self-induced physical ailments. The physician must not neglect to care for these patients because of their underlying psychopathologic condition.

An important caveat in the diagnosis of FDBP is that this is a very challenging diagnosis to make. If FDBP is suspected, consultation with a child abuse specialist is recommended prior to contacting child-protective services to help confirm these suspicions or avoid misdiagnosis in cases where no abuse exists (16).

DISPOSITION

If any doubt exists about the diagnosis of Munchausen syndrome and if the purported illness warrants hospitalization, the patient should be placed in observation for further evaluation. If the diagnosis of Munchausen syndrome is certain, however, the patient should be denied admission to the hospital for the presenting complaint. Psychiatric care is of little value and likely to be refused, if offered.

MALINGERING

CLINICAL PRESENTATION

Malingering is the voluntary and conscious presentation of false and exaggerated physical or psychological symptoms in pursuit of a recognizable goal. Such goals typically include avoiding work or other unpleasant obligations, obtaining shelter, obtaining controlled substances, or obtaining financial compensation through litigation. Malingerers may either exaggerate or invent symptoms.

In contrast to factitious disorder, in malingering the goal is clear and understandable, the behavior is conscious and situationally appropriate, and the symptoms abate once the goal is attained.

Malingerers present to the emergency department with a variety of demands or complaints. Some patients who complain of migraine headache or renal colic are seeking narcotic analgesics. Noncontrast helical computed tomography scan or sonography for nephrolithiasis is helpful, as the presence or absence of hydronephrosis is useful in distinguishing whether the possibly chronic stone is responsible for the degree of pain presented by the patient. Other individuals may present to the emergency department after missing several days or even weeks of work and request a retroactive “sick slip” because of a medical problem, the presence of which is difficult to document definitively. Patients who have been in minor motor vehicle accidents may present with exaggerated symptoms of cervical or lumbar strain in an effort to document damages and collect financial compensation.

Patients with underlying psychiatric disorders may feign exacerbations of mood and thought disorders so as to be hospitalized for secondary gain. These patients can be difficult to evaluate. Often they are admitted to the psychiatric service with a comorbid psychiatric diagnosis, with malingering strongly suspected.

DIFFERENTIAL DIAGNOSIS

Malingering is suggested if the patient over-dramatizes complaints, symptoms, or physical signs; overreacts during the physical examination; is uncooperative during the diagnostic evaluation; declines to appear when scheduled for diagnostic testing; or is reluctant to accept a favorable prognosis. The history, physical examination, and laboratory data may not support the severity of the patient's complaints, particularly those that lack objective correlates for diagnosis (e.g., migraine). During their evaluation, some patients may reveal their true objectives (e.g., a prescription for narcotic analgesics or a medical excuse from work).

Patients apparently suffering an acute neuromuscular syndrome may complain of symptoms that do not fit an anatomically consistent pattern or may exhibit weakness during testing that is belied by their ability to carry out other activities when they are not being examined. Patients complaining of low-back strain may demonstrate a disparity between the "straight leg-raise" test performed in a sitting versus supine position and, while in the supine position, the patient may not make an appropriate effort at raising the affected leg (detectable by placing a hand under the contralateral heel and feeling for the expected downward pressure associated with true effort).

If drug-seeking behavior is suspected, a review of past medical records or state narcotic database or other prescription database may be enlightening.

ED MANAGEMENT

Because the malingering patient may become defensive, angry, and hostile when confronted with the suspicion that the symptoms are false or exaggerated, the physician is often tempted to comply with the patient's demands rather than risk a confrontation. Furthermore, the diagnosis of malingering can rarely be made with complete certainty. Because each patient reacts to illness or injury differently, the degree of volition or willfulness that underlies the patient's exaggeration of symptoms is not always clear.

Perhaps a prudent way to deal with a suspected malingerer is to give the patient a minimal amount of gratification and to invoke general rules or established policies that prevent the physician from filling the patient's demands completely. It is worthwhile to record on the patient's chart suspicions or questions about the patient so that the next treating physician is aware of the concerns.

DISPOSITION

The usual criteria for admission to the hospital should apply, depending on the patient's complaint. If the physician is convinced that the patient is malingering, a firm stand should be taken against admission.

CONVERSION DISORDER

CLINICAL PRESENTATION

Patients with conversion disorder present with physical symptoms that are not under voluntary control and cannot be explained as a manifestation of a physical disorder or on the basis of a pathophysiologic mechanism. The physical symptoms are unconscious expressions of underlying psychological conflict. These symptoms are often immediately preceded by an acute psychological stress, and that precipitant should be sought. Conversion disorder was previously called *hysterical neurosis, conversion type.* Conversion symptoms have long been theorized to result from an autohypnosis after a traumatic event. Furthermore, adult victims of severe childhood abuse appear to be more prone to

developing conversion reactions as adults compared with their nonabused peers (17). Patients with conversion disorder often have other somatoform disorders (18).

The most typical conversion symptoms involve loss of neurologic function: blindness, aphonia, psychogenic seizures, paralysis, anesthesia, tunnel vision, gait abnormality, unresponsiveness, and amnesia (19). The conversion disorder symptom usually has a sudden onset. *La belle indifférence,* an attitude of relative unconcern despite the seriousness of the symptom, has historically been cited as a sign of conversion disorder. However, comprehensive review of the literature concluded that seeming unconcern on the part of the patient does not distinguish between conversion disorder and a stoic response to an organic disease (20). The diagnosis of conversion disorder depends on demonstrating that the patient's symptoms are not due to organically based malfunction. With most neurologic presentations of conversion disorder, this is not difficult, because the patient's deficits usually do not make neuroanatomic sense. The physician's knowledge of neuroanatomy is usually better than the patient's; moreover, the patient is not consciously trying to fool the physician. Nevertheless, these cases may sometimes mimic real disease patterns, including classic stroke presentations (21).

Typical "mistakes" made by the conversion disorder patient with neurologic symptoms include the following:

- Acute onset of sensory loss in a sharp stocking-glove pattern (although this may be mimicked by the peripheral neuropathies of diabetes or alcoholism)
- Complete paralysis and sensory loss of one leg, with preservation of deep-tendon reflexes and antigravity muscle activity
- Hemianesthesia without contralateral pain-temperature loss or with nonanatomic midline splits in vibratory sensation
- Complete loss of motor function on one side of the body, with inability to turn the head to the side of paralysis (indicating contralateral sternocleidomastoid muscle dysfunction)
- Psychogenic seizures: Features include presence of fluttering eyelids or closed eyelids, thrashing of extremities, pelvic

thrusts, and evidence of responsiveness to environmental stimuli during an apparent grand mal seizure. Typically absent are tongue biting, incontinence, physical injury, or postictal state (22)

- Inconsistencies in physical signs during unresponsiveness: Will not permit an upraised and suspended arm to strike the face when released but rather allows it to glide harmlessly over the face (note that substantial injury can occur to the nose and mouth if the arm does drop directly onto them). Vigorously resists manual eye opening by the physician (23)
- Inconsistencies in blindness: Ability to avoid injury and misstep when "blind" or with tunnel vision the visual field extending into space may be described as cylindrical rather than cone-shaped

DIFFERENTIAL DIAGNOSIS

Conversion disorder must be distinguished from organic illness, malingering, and Munchausen syndrome as well as from somatization disorder and hypochondriasis.

The tendency should be strongly resisted to diagnose conversion disorder in any patient with vague symptoms. Up to 30% of patients who have been given a diagnosis of conversion disorder at some time are eventually found to have organic disease that could explain these symptoms (24). Illnesses such as systemic lupus erythematosus, multiple sclerosis, and hyperthyroidism may present in the emergency department as subtle perturbations of physical functions; hypoglycemia can present in myriad different guises.

Patients with conversion disorder lack the characteristic features of the Munchausen patient: There is no tendency to submit to multiple procedures, and there is a lack of sophistication with respect to medical terminology. Unlike the malingering patient, there is no conscious fabrication of illness or disability.

ED MANAGEMENT

Patients with conversion disorder must be handled delicately, deftly, and with respect. These patients have usually experienced a recent or remote traumatic experience. It is unacceptable to confront the patient with an assertion or proof that the illness is faked or not real. The patient should be told that, although the symptoms are bothersome, they do not appear to be manifestations of a serious illness. Planting the suggestion that they will improve over the next several hours can sometimes relieve symptoms. Patients with aphonia can be told that they will be able to whisper; patients with paralysis can be told that they will begin to experience movement in their toes. Simultaneously, the physician can probe for underlying psychosocial conflicts that might have led to the appearance of the symptom.

CRITICAL INTERVENTIONS

- Treat patients with suspected but not confirmed Munchausen syndrome as if an organically based disease is present until the diagnosis is confirmed.
- Resist diagnosing conversion disorder in any patient with vague symptoms.
- Treat suspected malingering patients with a minimal amount of gratification and invoke general rules or established policies that prevent the provider from fulfilling the patient's demands completely.

DISPOSITION

The neurologic consultant may assist the physician in differentiating organic from nonorganic illness. If the diagnosis of conversion disorder is secure and the patient's symptoms persist and prevent the patient from carrying out the activities of ordinary living, a psychiatric consultant may assist in the process of symptom resolution in the emergency department.

Many patients with conversion disorder experience resolution of their physical symptoms during their emergency department stay, but some require admission to the hospital. If the diagnosis of

conversion disorder is uncertain and if the presenting symptom could signify dangerous illness, hospital admission is warranted. Even when the diagnosis of conversion disorder is clear, patients whose manifestations persist and who cannot manage on their own (e.g., psychogenic unresponsiveness or paralysis) require inpatient care.

Common Pitfalls

- Failing to appreciate that the patient has an unusual presentation of an organic illness.
- Permitting unpleasant aspects of the patient's personality to result in dismissal of the patient's problem as "psychogenic."
- Inadequately distinguishing among malingering, conversion disorder, and Munchausen syndrome.
- Classifying all patients with symptoms having no discernible anatomic cause as "crocks."
- Losing interest in caring for the patient once it has been determined that the patient's symptoms are not organically based.

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CHAPTER 169 Bereavement and Grief Reactions

Kenneth V. Iserson

Death, especially when it is sudden and unexpected—as often happens in the emergency department (ED)—shocks and devastates patients' family and friends. For them, it is a sentinel, life-changing event, with every nuance burned into their memories. As Thomas Mann wrote, "A man dying is more the survivors' affair than his own" (1). Furthermore, such losses may deeply affect emergency medicine personnel, despite their almost constant exposure to life's disasters. These factors make death notifications and dealing with the survivors both vitally important and extremely difficult. These strong reactions magnify both the importance and the difficulty of death notifications.

INTERACTING WITH SURVIVORS

Even though notifying survivors of a loved one's death is one of the most difficult parts of their job, emergency clinicians rarely are taught the skills necessary to perform this task. Death notifications are emotionally draining: 70% of emergency physicians find notifying survivors to be personally difficult. This is not surprising given the results of one study that found only one-half of them received any type of death-notification education in medical school and only one-third received any such training during residency (2). This educational deficit occurs even though there are roughly 2.5

million deaths in the United States annually, with about one-third of them occurring in EDs (3).

TELEPHONE NOTIFICATIONS

The first interaction after a sudden, unexpected death may occur when emergency medicine personnel contact the survivors (4). This often must be done via telephone. Yet, this can be problematic, not only because the telephone call has to convey shocking and unexpected news, but also because the caller and the recipient are strangers. The person designated to make the call should first identify him- or herself and establish the identity of the person with whom he or she is speaking. Always deliver the news to an adult and try to determine whether someone is present to provide emotional or physical support.

One question consistently arises: Should emergency medicine personnel notify someone of a death by telephone? Most Americans, especially if they live nearby the hospital, prefer to be told that the patient is "critical," and then to be told of the death when they arrive at the hospital. Thus, callers are often advised to say that the patient is in critical condition and that their presence is requested. The caller should slowly recite any necessary contact information and tell the recipient to write it down; then they should have them repeat it back. However, if the recipient demands to know whether the person is dead, the notifier must answer the question truthfully. The majority of those who wish to be told immediately are men.

When calling relatives outside of the local area, tell them of the death. They should never be put in a position of rushing to the side of a "critical" or "dying" relative who is already dead.

If no one is at home, or if no adult is present, the notifier should leave a message. The only information appropriate to leave on a telephone or electronic (i.e., text, email) message system is the message that a specific person, identified by name or position (e.g., the son of George White), should return the call as soon as possible. Leave the name and telephone number of someone who will be available for the next 24 hours and who should have information

about the death. This may require providing a telephone number for the main ED (with instructions to ask for the charge nurse) or for the hospital's chaplain or social worker. Within the hospital or the ED, there should already be a system for each shift to pass on relevant information to the next. Protocols and other materials (English and Spanish) are available to teach and to aid emergency medicine telephone notifiers (4–8).

MEETING SURVIVORS: THE &LDQUO;FAMILY ROOM&RDQUO;

When survivors arrive, a medical staff member, chaplain, social worker, or specially trained volunteer should be available to meet them immediately. Such greeters usually were not involved in the resuscitative effort (9). They should memorize an introductory message to use when meeting survivors. The format will always be the same; only the specific information changes. Here is one example:

Mr. and Mrs. Smith? I'm [greeter's name and position]. The paramedics brought your son to the emergency department after he was involved in a bad car crash. The trauma team that has been working on him tells me that he was found unconscious and has not awakened. I'm not sure about his other injuries. We're going to go to a quieter area and I'll get someone from the team to speak with you (4).

The key points to remember when delivering this message are to identify the survivors, identify the ED representative, give only basic information, and guide the survivors to a quiet place. This quiet or "family" room is a place wherein survivors can wait until someone needs them (e.g., to give them updates on resuscitative efforts or the news about the death) and wherein they can have some privacy to grieve. All EDs should have a dedicated family room equipped with comfortable seating, tissues, and a telephone with long-distance access (4).

VIEWING RESUSCITATIONS

Traditionally, survivors have not been permitted to view resuscitation attempts. That attitude, however, is gradually giving way to a more enlightened view.

The argument against allowing survivor onlookers has been that resuscitations often involve large teams with too many people and unclear communications, and with team leaders who are unwilling or unable to make firm, timely, and rational decisions (10). Having family members present supposedly adds another complication and introduces the possibility of legal consequences stemming from an onlooker fainting, or otherwise becoming another patient. Those objecting to survivor presence during resuscitations have also raised concerns about correctly identifying survivors and about patient privacy, especially in light of HIPPA (the Health Insurance Portability and Accountability Act of 1996). They also are concerned that survivors may misinterpret the team's discussions or actions. Finally, team members may feel that family members will judge their actions (11). Emergency medical systems personnel, however, routinely encounter this during resuscitative attempts.

Despite such concerns, studies in both the United States and Britain have shown that nearly all survivors who witnessed emergency medicine resuscitative efforts found the experience helpful. As John Jesus wrote, "Resuscitation efforts may actually benefit families more than they have the potential to benefit the patients" (11). Many survivors (76%) thought that witnessing the resuscitation facilitated their grieving, and 64% felt that their presence was helpful to their dying family member (12). Psychological tests of survivors who witnessed resuscitation attempts, performed at 3 and 9 months after the event, showed that this group had fewer episodes of "intrusive imagery," such as flashbacks of the events leading to the death, than did those not present at the resuscitation (relatives in the control group). They also had lower levels of anxiety, depression, posttraumatic avoidance behavior, and grief (13).

The American Heart Association now endorses giving family members the opportunity to be present as long as the patient has not previously objected. This position stems from the benefit

families can derive from their presence during resuscitation attempts, the lack of harmful effects on them from viewing these resuscitations, and their quasi-right to be there based on the nature of their relationship to the patient (11,14,15).

Moreover, the presence of these survivors does not hinder the resuscitative efforts and often leads to quieter, more effective team efforts. Concerns about properly identifying survivors is misplaced, since physicians, as well as EMS personnel, can rely on the "reasonable reliance" concept (what a prudent person would believe and act on). In addition, HIPPA permits revealing health information about unconscious patients to family if there is an expectation that the patient would approve. Finally, while physicians may not bear legal responsibility for syncope survivors, having a staff member accompany them and ensuring that they are seated is good practice (11).

Experience has shown that survivors who witness ED resuscitative attempts never question whether the team "tried hard enough," do not ask whether the person is *really* dead, and spend less time in the ED trying to come to terms with the death. Moreover, survivors may actually thank the emergency medicine team for their efforts, a situation that rarely occurs under other circumstances, and the emergency medicine staff never has to "notify" survivors of the death.

The general procedure is as follows:

1. Ask survivors whether they want to view resuscitative efforts.
2. If they do, quickly brief them about what they will see, and assign a knowledgeable staff member (usually a chaplain, social worker, or ED nurse) who can answer their questions to accompany them.
3. Provide a chair so they can sit, particularly if they are elderly, and allow them to leave and re-enter as they wish.
4. Staff should attempt to cover as much of the patient as is compatible with effective resuscitative efforts.
5. Advise team members that family is in the room.
6. Encourage the survivors to talk to and touch the patient.

7. Decisions to pronounce the patient dead, while often discussed with the family, are generally announced by telling them "we must stop now." Never ask family members whether to stop the resuscitative effort; this is purely a medical decision.

Experience shows that the process of having key survivors view resuscitations often works best if EMS personnel notify the receiving hospital in advance of such a request. This allows the emergency medicine team time to decide whether they will permit it (if it is not policy), to advise team members, and to designate someone to escort the relative to the resuscitation room at the appropriate time.

If the family is present when it is clear that resuscitative efforts should cease, explain this to the family before supportive measures are discontinued. This provides them with a chance to "say good-bye" before the death is pronounced. Such procedures are standard in most pediatric EDs, as well as for pediatric resuscitations performed in the majority of general EDs.

NOTIFYING SURVIVORS IN THE ED

When key survivors have not witnessed resuscitation attempts, the most common postresuscitative scenario in EDs is that emergency medicine personnel must inform survivors of the death. But, unlike the relationship found in most in-hospital patient deaths, the emergency medicine personnel usually have had no chance to establish a "bond" with the survivors. Instead, they must quickly establish survivors' confidence in them while at the same time delivering devastating news. Staff should project an image of one "who has the information" rather than acting authoritatively or coercively. Emergency medicine staff should strive to eliminate any perception of racial, social, or cultural differences between them and the survivors, as this may lead to a sense of distrust (16).

One technique medical personnel often use to deliver the news about sudden unexpected death is that of "presaging," or leading up to this news by dribbling out bits and pieces of bad information over a very short period of time. Also called "hanging crepe," this

technique allows survivors to gradually understand that something very bad has occurred.

"How much emotion should I show when delivering the news?" is a frequently asked question. During resuscitative attempts, caregivers must put their emotions "on hold" to perform their duties in the most effective way for the patient. If the resuscitation is unsuccessful, it is okay to express some emotion when delivering the news of the death to survivors, but staff must retain enough control to help and support the family.

BARRIERS TO EFFECTIVE ED NOTIFICATIONS

Emergency medicine personnel are at a distinct disadvantage when dealing with survivors of sudden unexpected deaths. First, the physicians and nurses in emergency medicine are usually aggressive, action-oriented people who want to see an instantaneous return for their expended energies. They often see a patient's death as a personal failure—an assault on their sense of accomplishment and satisfaction—and respond accordingly (17). In addition, except in rare instances, they have never met either the deceased patient or the survivors. Other barriers are listed in Table 169.1.

TABLE 169.1
Barriers to Effective ED Death Notification

No pre-existing relationship with medical staff
Survivor stress: fear, grief, remorse, anxiety, panic
Time: Staff has limited time, needs to treat other patients/crises, and may be interrupted to make other decisions
Strange environment: surroundings, noise, smells, lack of privacy
Survivor status/behavior: anger, inebriation, disbelief, not available
Cultural or language differences
Medical staff stress: must deliver bad news, ask for autopsy (or notify about medical examiner requirements), ask for organ/tissue donation, and allow time in the midst of other patients' emergencies
Medical staff anger: decedent caused other injuries or deaths
Uncertainty: often not clear about the exact cause or manner of death
Sense of failure: "losing" a patient often pervades discussions

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Resuscitative efforts effectively halt most other activity in the majority of EDs. Once resuscitation is terminated, the clinicians may be overwhelmed by the onslaught of other patients whose problems demand their immediate attention. Because of this backlog of sick patients who have been ignored during the resuscitative attempt, survivors are often given too little attention. Compounding this is the fact that emergency physicians' coping mechanism is often to immediately return to normal work activities (18).

SURVIVOR REACTIONS

Intervention strategies to facilitate survivors' grieving processes may help them avoid significant future psychiatric sequelae. Survivors' overall reactions are variously described as grief, mourning, and bereavement. *Grief* denotes the intense emotions and physical symptoms associated with the loss. *Mourning* is a social expression of grief. *Bereavement* is the total normal response to loss.

Grief is a normal process initiated by major personal loss, such as the loss of a spouse, parent, child, or significant other. Grieving is characterized by an intense, in-depth review of the survivor's relationship with the decedent. A grieving person repeatedly reviews memories of the decedent and only gradually confronts each one with the realization that it no longer corresponds to something

real. The grief response may also include physical ailments and guilt, such as feeling responsible for the death or for failing to resolve interpersonal conflicts with the decedent (Table 169.2). This process continues until the grieving person is gradually reconciled to the loss. Grieving serves the psychological purposes of breaking emotional ties with the decedent and reestablishing attachments to living persons. Most survivors' symptoms resolve without the need for specific professional interventions. Some EDs have invited survivors back to answer their questions several months after the death, although whether this is beneficial remains uncertain (19).

TABLE 169.2
Common Grief Reaction Symptoms and Statements

1. **Denial**
   - Loneliness
   - Agonizes over the death
   - Wants to die
   - Feels hopeless
   - I should have died instead
   - Never be happy again
   - Little control over sadness
   - Frequently cries
   - Somnambulism
   - Heaviness in heart
   - Difficulty accepting death's permanence
   - Feels like I am in shock

2. **Panic Behavior**
   - Panic attacks
   - Heart beats faster; dizziness
   - Frequently frightened; startle easily
   - Frequent muscle tension
   - Dyspnea, fatigued, shaky
   - Feels sick more often; headaches; back pain
   - Burning in stomach
   - Worries excessively

3. **Blame and Anger**
   - Frequently feels bitter, resentful
   - Feels revengeful
   - Hostile feelings; gets angry often
   - Blames/wants to harm others

4. **Detachment**
   - Feeling worthless; without confidence
   - Confused about who I am
   - Feels unable to cope
   - Don't know myself
   - Afraid I will lose control
   - Feels detached
   - Avoids tenderness

5. **Disorganization**
   - Forgets new information
   - Forgets easily: names, numbers
   - Difficulty concentrating, remembering, thinking
   - Tasks are insurmountable

Note: "Personal growth" is a subsection of this checklist. Individuals at this stage are unlikely to present to EDs with symptoms related to grief or bereavement.

Adapted from Hogan NS, Greenfield DB, Schmidt LA. Development and validation of the Hogan Grief Reaction Checklist. *Death Stud*. 2001;25:1–32.

Grief expressions are determined by cultural mores (20). Some people express grief histrionically, with loud crying and sobbing, whereas others remain still, with little visible emotion. Although they display no overt signs, survivors may be deeply affected and grieving over the death (21). Several responses can be perplexing and may be misinterpreted by staff. A frequent initial reaction is denial, a psychological defense that closes off perceptions of painful immediate reality. The survivor may question the physician closely for proof of the decedent's identity or may continue to refer to the decedent as if he or she were alive (22). At other times, survivors display antagonistic and angry feelings toward staff members, accusing them of being negligent or of not doing all they could have done. This anger often represents the survivors' own unconscious anger toward the decedent for abandoning them, or it may stem from guilt about unresolved conflicts with the decedent.

Emergency medicine professionals may have difficulty in coping with initial survivor reactions, such as withdrawal (inaccessible, mute, refuses to listen), denial (of fact, feelings, reality), anger (directed at nurse, doctor, self), isolation (feelings of aloneness), bargaining ("I'll pay anything not to have . . ."), inappropriate responses, guilt, and crying. Although emergency medicine personnel often fear physical violence toward the notifier, this rarely occurs. However, violence harmful to a survivor, such as punching a wall, or among survivors is common. Teenage boys and young adult men seem to be the most prone to expressing their grief in these self-destructive manners.

Educate survivors about the symptoms of grief and reassure them that these symptoms are normal. Depressed mood, sleep disturbance, crying, difficulty with concentration, loss of interest, anxiety, and weight loss are the most common symptoms (23). Provide anti-anxiety or hypnotic medications to survivors only if requested and only after a formal evaluation of the individual involved. Limit the supply to that needed for only a few days.

Arrangements should always be made for other family members or friends to stay with a survivor for the next 24 to 48 hours, because suicide is a possibility, especially for a spouse who has been married for many years (24,25). If a survivor appears to be suicidal or homicidal, ask them about this and, if appropriate, obtain a formal psychiatric consult.

Support groups may help some survivors. The ED should have a preprinted list of telephone numbers and addresses of local and national support groups that they can give to survivors.

VIEWING THE BODY

Identifying the patient can be very difficult in some cases. Many patients needing resuscitation arrive in the ED without identification, usually either because they had none available or because the police have it. Care must be taken to corroborate the decedent's identity before any survivors are notified. To do this, emergency medicine personnel or the investigating officers may have to ask survivors about their relative's general characteristics (height, skin, and hair color), identifying marks (scars, tattoos, birthmarks), or deformities (prior amputations).

Making decedent identifications is vital after disasters such as the World Trade Center attacks or 2004 Southeast Asian tsunami, in which many bodies are missing or unidentified. Survivors may feel "emptiness, frustrated or unresolved grief" that can be partially assuaged only by identifying the dead (26–28).

In the ED, offer survivors the opportunity to view the body (4). Viewing the body facilitates the grief reaction. If they are reluctant or unwilling to do so, do not make them feel that their decision is wrong. Many survivors prefer not to view the body (29). Never refer to the decedent as "the body" or "it." Instead, use the person's proper name or a personal pronoun. Warn survivors about the visible effects of trauma and resuscitation, and also of postmortem skin changes such as cyanosis or livor mortis.

Prepare the body for ED viewing. Remove blood and emesis before family members see the body. Describe any medical

equipment that must be left in place until the medical examiner completes the necessary postmortem examination and explain why it is still there (30). Cover the body with a sheet or blanket, but leave the head and hands exposed for the family to touch, and encourage them to do this. Move the body to a private room, if possible. Let them cut off a lock of hair, if requested. Allow family to be alone with the body, unless there are legal reasons (e.g., ongoing police investigation) for not doing so. Staff should remain available nearby, but outside the room, to provide support to the family. Most family members will leave within 15 minutes.

MAKING FINAL ARRANGEMENTS

Part of death notification involves answering survivors' questions in a knowledgeable manner. To do this requires knowing something about body disposition options, medical examiner/coroner laws and procedures, and organ and tissue donation (30–32). These subjects are rarely discussed in medical or nursing curriculums.

After the family has viewed the body, it is then appropriate to have them to sign any necessary documents (4,22). Many survivors are concerned about postmortem paperwork, so having an experienced person guide them through the process is very useful (29). Offer the use of a telephone to call a funeral home. Ask again if there are any questions. Generally, no question should remain unanswered, unless the information is unavailable. Tell them how to reach you if they have questions at a later time.

Explain the roles of medical examiners and the police in cases of sudden, unexpected, or violent deaths and how the decedent's belongings will be handled. If you will be signing the death certificate, tell them the cause(s) of death that you will list. If an autopsy is mandatory, as it is in many ED deaths, explain that the medical examiner will determine the cause of death at a later time. If the cause of death is unclear, autopsy results will be helpful, inform the family of this and ask them for permission for an elective autopsy (30).

The issue of organ and tissue donation should be broached before family members leave the hospital; in fact, most states require that this option be addressed. Two ways to broach the subject are to ask, "Has your family ever discussed organ or tissue donation?" or "Our hospital offers organ and tissue donation. Would you like to discuss this further with someone from the transplant program?" If the family expresses an interest, contact the appropriate agency immediately.

Have lists of clergy and housing accommodations available for out-of-town survivors. Unless personal effects and clothing removed from the body are needed by the medical examiner or for a police investigation, these should be given to survivors. Advise them of the condition of clothing and place it in a paper or plastic belongings bag; never use a trash bag. Tell survivors when they have completed everything they need to do and that they may leave whenever they like. The physician or a designated staff member should accompany the survivors to the door.

DEATH-NOTIFICATION EDUCATION

Although it is rarely done (4,33), educating emergency medicine professionals about sudden-death notification is vital, as doing it poorly can adversely affect both the survivors and the healthcare professionals involved. Such education succeeds when it is combined with direct observation during actual death notifications, subsequent evaluation, feedback and, when necessary, further education (34). Educational resources and materials to help remind ED staff of the steps involved are available (4–8,32,35).

The easiest and most effective way to provide this education is to add a module to the resuscitation courses that emergency medicine personnel must take on a periodic basis (34). Such education can help the staff deal with their own emotions (e.g., feelings of defeat, guilt, impotence, and incompetence) and fear of death, and with survivors' reactions. It can also help avoid the common problem of emergency medicine staff trying to reduce their own stress by delaying the news, thus increasing the family's anxiety, or by

rushing into the room unprepared and presenting the news in an awkward manner.

A staff that is aware of the dynamics of grieving and of survivors' needs can facilitate the grief process, cushion the trauma of loss, and establish a basis for a healthy grief response (4,36).

Common Pitfalls

- Poor communication.
- Remarks such as "Everything will be okay" or "It was God's will," which may prematurely seal off the grief response.
- Failing to use a "D" word (Death, Dead, Died) to clearly indicate that the patient has died.
- Not allowing and encouraging survivors to express their feelings.
- Impeding or impairing survivors' ability to grieve by routinely prescribing medication.
- Failing to address survivors' support systems.
- Not offering family members the option of organ and tissue donation.

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of Galen Press, Ltd., Tucson, Arizona, to the content of this chapter through permission for reproduction of much of the material used in this chapter.

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SECTION XVII
Dermatologic Emergencies

Section Editor: JEFFREY J. SCHAIDER

CHAPTER 170

Life-Threatening Dermatoses

Kenneth J. Neuburger

Cutaneous lesions are often the first clinical sign of serious systemic disease. In this chapter, the focus is on the recognition and acute management of the common life-threatening dermatoses listed in Table 170.1. These disorders can be conveniently grouped into diffuse red rashes, vesiculobullous eruptions, localized or discrete lesions, and purpuric or hemorrhagic lesions (Table 170.2). The following dermatologic findings should alert clinicians to a potentially serious eruption (1):

- Confluent erythema
- Facial edema or central facial involvement
- Skin pain
- Palpable purpura
- Skin necrosis
- Blisters or epidermal detachment
- Positive Nikolsky sign
- Mucous membrane erosions
- Urticaria
- Swelling of tongue

Several entities are not discussed in detail here but deserve brief mention. *Palpable purpura* is a skin manifestation of vasculitis; it is not a manifestation of thrombocytopenia or clotting disorder. Involvement may be limited to the skin or may be systemic. Treatment is for the underlying vasculitic disorder.

TABLE 170.1
Life-Threatening Dermatoses

Diffuse Red Rashes
- Urticaria with anaphylaxis[a]
- Toxic shock syndrome[a]
- Kawasaki disease
- Toxic epidermal necrolysis[a]
- Staphylococcal scalded skin syndrome[a]
- Generalized exfoliative erythroderma[a]
- Pustular psoriasis
- Cutaneous T-cell lymphoma[a]
- Systemic lupus erythematosus

Localized or Discrete Lesions
- Erysipelas and cellulitis[a]
- Gonococcemia[a]
- Ecthyma gangrenosum[a]
- Brown recluse spider bite
- Behçet syndrome
- Malignant melanoma[a]
- Kaposi sarcoma and AIDS[a]
- Basal cell carcinoma[a]
- Squamouus cell carcinoma[a]

Vesicobullous Diseases
- Pemphigus[a]
- Pemphigoid[a]
- Stevens–Johnson syndrome[a]
- Toxic epidermal necrolysis[a]
- Disseminated zoster
- Disseminated herpes simplex

Purpuric or Hemorrhagic
- Meningococcemia[a]
- Gonococcemia[a]
- Disseminated intravascular coagulation
- Palpable purpura[a]
- Brown recluse spider bite
- Rocky Mountain spotted fever[a]
- Miscellaneous hematologic disorders

[a]Discussed in this chapter.
Adapted from Krusinski PA, Flowers FP. Life-threatening dermatoses. In: Flowers FP, Krusinski PA. *Dermatology in Ambulatory and Emergency Medicine, a Clinical Guide with Algorithums.* Chicago, IL: Year Book Medical; 1984.

TABLE 170.2
Identification of Life-Threatening Diseases Associated with Fever and Rash

Disease	History	Characteristics of Rash	Distribution of Rash	Associated Clinical Findings	Diagnostic AIDS
Rocky mountain spotted fever	Tick exposure (75%) May–September in temperate zone states Heaviest endemic area: middle Atlantic states and Southeast	Initial maculopapular petechiae appearing on second to sixth febrile day and usually painless	Begins on wrists, ankles, forearms, spreading within 6–8 hrs to palms, soles, trunk	Prodrome of fever, headache, myalgias Hyponatremia, normal to slightly increased WBC, thrombocytopenia, hypoalbuminemia	Biopsy of involved skin with immunofluorescence and other serologic tests. Serology: Complement fixation more sensitive and more specific than Weil–Felix agglutination
Meningococcemia	Tends to occur in late winter, early spring Outbreaks in military recruits, crowded living conditions	*Acute:* May be maculopapular initially. Small petechiae with irregular borders (smudging), at times with vesicular or grayish ulcer. May coalesce. Painful *Chronic:* Maculopapules, petechial vesicles, or pustules; tender nodules	*Acute:* Extremities and trunk in random fashion *Chronic:* Extremities, particularly over joints	*Acute:* Meningitis, disseminated intravascular coagulation, shock, acidosis *Chronic:* Rash appears with recurrent cycles of fever over 2–3 mos	*Acute:* Aspiration of center of skin lesions for Gram stain, culture (up to 60% positive). Blood cultures Cerebrospinal fluid culture and Gram stain *Chronic:* Blood culture usually positive during febrile episode. Biopsy findings resemble leukocytoclastic angiitis
DGI	Incidence higher in women than in men Young, sexually active Onset often related to menstruation	Pustules on erythematous base most characteristic. Also, macules, papules, pustules, and bullae less commonly	Over extremities, with relative sparing of face and trunk; usually few (5–40) lesions	Migratory polyarthralgia, tenosynovitis, septic arthritis	Gram stain of lesion Blood, joint fluid culture (50%) prove diagnosis Cervical, rectal, throat cultures support diagnosis
Pseudomonas septicemia	Hospitalized patients, especially with neutropenia or burns	*Vesicles:* Isolated or in small clusters rapidly becoming hemorrhagic *Ecthyma gangrenosum:* Round, indurated, ulcerated painless lesion with central gray eschar *Maculopapular lesion:* Small erythematous lesion resembling "rose spots" Gangrenous cellulitis	Random Axillary or anogenital area, thigh Trunk Localized	Generally extremely toxic, with fever; septic picture	Aspiration of lesions for Gram stain culture Cultures of blood, urine, sputum, etc.
Toxic shock syndrome	Young female predominance, especially with menses Rare in men 1–4 d prodrome of fever, myalgias, arthralgias, and diarrhea	*Erythroderma:* Seen at presentation Diffuse, blanching, macular (deep-red "sunburned" appearance) Resolves within 3 d, followed 5–12 d later by desquamation, most commonly of hands and feet *Mucosal hyperemia:* Pharynx, conjunctivae, vagina	Diffuse, hands and feet predominantly	Fever, severe hypotension, multisystem involvement (GI, muscular, renal, hepatic, hematologic, CNS)	Clinical criteria (see Chapter 148) Identification of toxin producing strain of *S. aureus* Negative serology for RMSF, leptospirosis, measles

CNS, central nervous system; RMSF, Rocky mountain spotted fever.
Reproduced with permission from Stein JH, ed. *Internal Medicine*. 5th ed. St Louis, MO: Mosby; 1998:1382.

Generalized exfoliative erythroderma (formerly called exfoliative dermatitis) is a diffuse, widespread dermatitis that covers most of the body surface. This condition not only causes pruritus and pain but may be complicated by hypothermia; fluid, electrolyte, and protein loss; invasion of bacteria and opportunistic organisms through the skin; and high-output congestive heart failure secondary to severe vasodilatation. The causes of exfoliative erythroderma include previously existing skin diseases (e.g., psoriasis, atopic eczema, contact dermatitis) (50%); drug eruptions (10%); lymphoproliferative disorders (e.g., Hodgkin disease, leukemia, Sézary syndrome) (15%); and idiopathic (25% to 40%). Mortality is $<5\%$.

Other potentially life-threatening entities, such as angioedema (see Chapter 176) and disseminated herpetic infection, are discussed in other chapters.

Finally, a brief discussion at the end of the chapter focuses on the recognition of the various types of skin cancer.

DIFFUSE RED RASHES

Staphylococcal scalded skin syndrome (SSSS) (Fig. 170.1) occurs in children and, rarely, adults and is caused by an exotoxin from an

infecting strain of coagulase-positive *Staphylococcus aureus*. The disease may present as a prodrome of fever, irritability, malaise, and exquisite skin tenderness; in other cases, the child presents with the sudden onset of generalized erythema. The skin is red, warm, and very tender. Ill-defined, flaccid bullae then desquamate in large sheets. Gentle lateral stroking of the skin causes the epidermis to separate (Nikolsky sign).

Therapy consists of systemic antibiotics effective against methicillin-resistant *Staphylococcus* (due to its increased incidence). Children older than 1 year and with mild symptoms may be treated as outpatients. Children who appear toxic and infants should be admitted. Despite proper treatment, most of the superficial body surface will desquamate but, because the site of blister cleavage is in the superficial layer of the epidermis, healing occurs rapidly over 7 to 14 days.

Toxic epidermal necrolysis (TEN) (Fig. 170.2) is a disease of adults in which the skin also sloughs in large sheets. Although it is very similar in appearance to SSSS, it is quite different. It has been accepted that erythema multiforme, Stevens–Johnson syndrome (discussed later in the chapter), and TEN are a progression of severity of the same disorder (2). All usually start with a prodrome of fever, malaise, and myalgia. The skin is initially diffusely painful, hot, and red. Within days, blisters and large areas of denuded skin develop; erosive, sloughing lesions of the oral mucosa are common. The Nikolsky sign is positive.

The differences between TEN and SSSS are noteworthy. SSSS almost always occurs in children and is secondary to staphylococcal infection. TEN almost always occurs in adults and is most often precipitated by drugs such as phenytoin, carbamazepine, lamotrigine, phenobarbital, antibiotic sulfonamides, allopurinol, and nonsteroidal anti-inflammatory agents (3). About 62% are probably caused by medications, 23% possible, and the other 15% unlikely to be drug related (3). Mucous membrane involvement in SSSS is rare and limited to the lips but, in TEN, erosive oral lesions are common. Although SSSS sloughs only the superficial layers of epidermis, TEN desquamates the entire thickness of the epidermis, accounting for the

high associated mortality rate. The mortality rate in SSSS is very low, whereas that of TEN can be >50%.

The diagnosis of TEN is made by clinical presentation and confirmed by biopsy. Treatment is removal of the precipitating agent, if possible, and consists of judicious fluid, electrolyte therapy, and prevention of infection (4). Early transfer to a burn center is standard of care (4). There are conflicting studies concerning use of intravenous immunoglobulin (IVIG) in the therapy for TEN (4). IVIG, if used, should be started early in the course at doses of 1 g/kg daily (5) up to 2 to 3 g/kg daily for 4 to 5 days (4,5). Corticosteroid treatment is being reevaluated as it may or may not be useful depending on dosing, and time of use in the disease process. There are case reports of rapid improvement with cyclosporine, administered 3 to 10 mg/kg daily for 8 days to weeks (4,5). Plasmapheresis, antitumor necrosis factor therapy, and *N*-acetylcysteine treatments show some promise, but need further study (4,5).

FIGURE 170.1 Staphylococcal scalded skin syndrome. A 10-day-old Caucasian boy with staphylococcal scalded skin syndrome. He was treated with fluids, oral dicloxacillin, and wound care. His skin healed completely and without scarring within 2 weeks of this photograph being taken. (From Avery GB, Fletcher MA, MacDonald MG. *Neonatology: Pathophysiology and Management of the Newborn.* 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:1199, with permission.)

Toxic shock syndrome (TSS; see Chapter 192) is an acute, febrile illness originally associated with localized infection by strains of *S. aureus* that produce an exotoxin (TSST-1) (6) that results in the clinical signs and symptoms. Currently enterotoxins A, B, C, G, H,

and I have also been implicated in causing TSS (6,7). Characteristic signs and symptoms include an early macular rash, hypotension, abnormalities in multiple organ systems, and acral desquamation occurring 1 to 2 weeks after the onset of the illness (Fig. 170.3). Originally about 90% of the *S. aureus* isolates from patients with TSS produce the exotoxin. Eighty-five percent to 90% of cases were reported in menstruating women (6,8). In fact, the disease was originally described in association with the use of highly absorbent vaginal tampons that could be kept in place for many hours before being discarded (6). Other cases are associated with localized infection in men, children, and nonmenstruating women (9). A new population assessment was done in 2000–2006 with 61 cases (33 menses related and 28 other sites). TSST-1 was found in 80% of isolates and more prevalent in menstruating than nonmenstruating situations (89% vs. 50%). Enterotoxins A, B, and C were found more often in nonmenstrual infections versus menstrual (100% vs. 25%). Methicillin-resistant *S. aureus* (MRSA) was found in four cases (8).

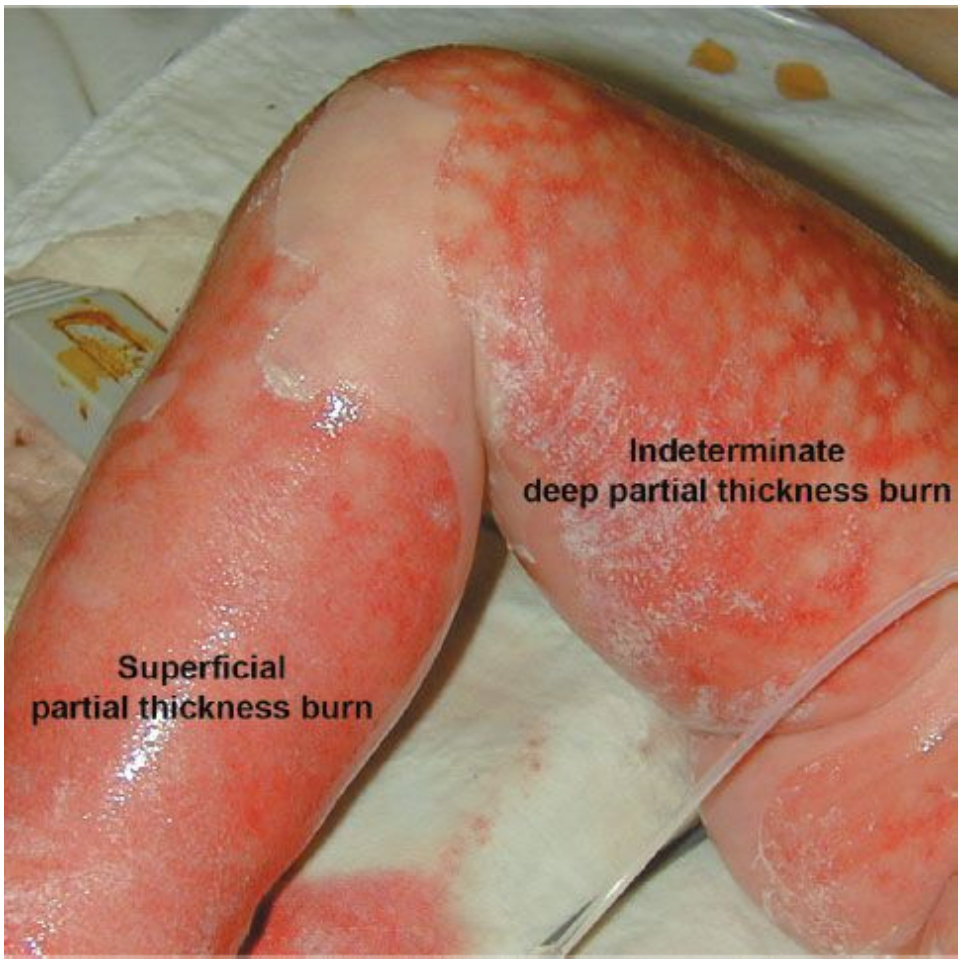

FIGURE 170.2 Toxic epidermal necrolysis that may extend into the reticular dermis (deep partial thickness) or the papillary dermis (superficial partial thickness). The peripheral zone of hyperemia correlates with a superficial or first-degree burn and might be similar to a sunburn. (From Mulholland MW, Lillemoe KD, Doherty GM, et al. *Greenfield's Surgery Scientific Principles and Practice.* 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)

FIGURE 170.3 Toxic shock syndrome. Desquamation of the skin of the palm in a patient with staphylococcal toxic shock syndrome. (From Sweet RL, Gibbs RS. *Atlas of Infectious Diseases of the Female Genital Tract*. Philadelphia, PA: Lippincott Williams & Wilkins; 2005, figures 9–2.)

The early cutaneous rash is scarlatiniform and blanches with pressure; it can be difficult to appreciate because it is often quite pale. Coincident with the rash, there is often erythema of the mucous membranes of the oropharynx, conjunctivae, and vagina. Desquamation of the skin of the distal extremities occurs 1 to 2 weeks after the onset. Hair and nail loss follows 1 to 2 months later.

Strict criteria for the diagnosis of TSS are fever, hypotension or orthostasis, an erythematous macular rash, involvement of at least three organ systems, and the presence of an *S. aureus* infection. Most patients have facial and extremity edema. The illness can proceed rapidly. Hypotension may appear early; most patients present to the hospital with at least orthostasis.

The differential diagnosis of TSS includes Rocky mountain spotted fever (RMSF), scarlet fever, sepsis, Kawasaki disease (rare in those older than 8 years), leptospirosis, Colorado tick fever (in which

photophobia is common), and other viral infections. Supportive treatment for dehydration and hypotension includes fluid replacement and the use of pressors, if necessary. The adult respiratory distress syndrome is common in serious cases.

Although it has not been proven that antibiotics are always necessary for recovery, provided the site of located staphylococcal infection is removed (e.g., removal of tampons or incision of abscesses). While awaiting culture results, treatment should cover MRSA. Vancomycin plus clindamycin, or linezolid alone are appropriate. Clindamycin and linezolid both decrease toxin production while vancomycin does not (9).

IVIG should be considered in those with a poor response to intensive therapy after several hours (less than 6 hours). The dosing is not well defined but should probably be greater than the original study dose of 1 g/kg the first day and 0.5 g/kg on days 2 and 3 (9). Because TSS recurs in a large percentage of women with tampon-associated TSS who continue to use tampons, women with a history of TSS should no longer use tampons. All symptomatic patients suspected of having TSS require admission for vigorous supportive treatment.

The hallmark of streptococcal TSS, first described in the mid-1980, is a relatively early onset of shock and multiorgan failure. The currently proposed criteria for streptococcal TSS are isolation of group A streptococci from a sterile or nonsterile site, hypotension, and at least two of the following: renal impairment, coagulopathy, liver function test abnormalities, adult respiratory distress syndrome, soft-tissue necrosis, and rash (which may be generalized macular or possibly scarlatiniform and may desquamate) (6,10). Treatment is with high-dose penicillin (20 to 24 million units/d); cephalosporins, clindamycin, erythromycin, vancomycin, and penicillinase-resistant penicillins are also effective. Cases with an indeterminate source should be treated as in staphylococcal toxic shock. Aggressive supportive care is mandatory, as is surgical drainage or debridement for abscess, pyonecrosis, or necrotizing fasciitis. Again, IVIG is recommended if an adequate response is not seen within 6 hours. The IVIG dose should be 1 g/kg on day 1 and 0.5 g/kg on days 2 and

3 (9). Even with prompt treatment, mortality ranges between 20% and 30%.

VESICOBULLOUS DISEASES

The spectrum of acute, self-limited immunologic reactions causing vesicles includes bullous erythema multiforme, Stevens–Johnson syndrome, and TEN. These are probably the same disease with increasing severity and more skin and mucous membrane involvement (11). The causes are the same as those listed in the previous discussion of TEN, although erythema multiforme can be related to herpes simplex and mycoplasma, and Stevens–Johnson syndrome is usually related to drugs. The classic lesion of erythema multiforme is the target lesion, a central gray wheal or bulla surrounded by concentric rings of erythema and normal skin. As the name implies, however, many types of lesions may be present simultaneously: macules, papules, urticaria (though non pruritic), and bullae. The extremities are involved more than the trunk; the palms and soles are often affected. The rash appears abruptly and may be accompanied by fever, malaise, and pruritus.

Farther along the spectrum is bullous erythema multiforme, with less than 10% skin involvement and target lesions, followed by Stevens–Johnson syndrome, with 10% to 30% skin involvement (11) accompanied by constitutional symptoms and affecting at least two mucous membranes. A prodrome of fever, malaise, and myalgia is followed by the explosive appearance of blisters on mucous membranes and skin. Symmetric blistering begins on the dorsa of the hands and feet and on extensor surfaces. Erosive lesions begin on oral mucosa, lips, and bulbar conjunctiva and can extend to the pharynx, larynx, esophagus, and genital mucosa (Fig. 170.4). Ocular lesions can result in corneal ulceration, panophthalmitis, and even blindness, requiring early recognition and treatment. The prognosis of Stevens–Johnson syndrome is usually good (7). However, the disorder may progress to an illness clinically indistinguishable from TEN, with large confluent bullae and sloughing of epidermis in sheets.

FIGURE 170.4 Stevens–Johnson syndrome. Erythema multiforme major (Stevens–Johnson Syndrome). Bullae and crusts are noted on the lips, and targetoid lesions are seen on the hand. (From Goodheart HP, MD. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

Milder cases of Stevens–Johnson syndrome can be treated with oral antihistamines and topical corticosteroids; more severe cases require hospital admission. More severe cases can be treated as noted for TEN earlier in the chapter. Corticosteroids, antitumor necrosis factors and *N*-cetylcysteine need to be further evaluated before they can be recommended for treatment (4,7).

PEMPHIGUS VULGARIS

Pemphigus vulgaris, a rare disease, occurs mostly in adults 40 to 60 years old and is distinguished from other blistering diseases by its fulminant course. Early identification and aggressive treatment may avert a poor outcome. Initially, blisters may be localized to small areas of the mucous membranes or skin; lesions may be present for months before the blistering becomes generalized. The lesions are typically painful flaccid bullae that may rupture easily or painful erosions where bullae have ruptured (Fig. 170.5). They have a

predilection for the scalp, face, chest, axillae, and groin. These painful erosions or collapsed bullae can persist despite successful treatment of skin lesions. The Nikolsky sign is positive. Half of patients present initially with oral lesions; 90% have oral lesions at some time during the course of the illness.

FIGURE 170.5 Pemphigus vulgaris. **A:** Bulla. **B:** Erosion. (From Berg D, Worzala K. *Atlas of Adult Physical Diagnosis.* Philadelphia, PA: Lippincott Williams & Wilkins, 2006.)

The diagnosis of pemphigus is made by biopsy of intact skin adjacent to a bulla. Direct immunofluorescent staining for antiepithelial antibodies localized to the epidermal cell membrane is confirmatory. Indirect immunofluorescence of the patient's serum or blister fluid detects a pemphigus antibody that reacts with epithelial cell membranes of most species. Therapy is with corticosteroids, and immunosuppressive agents.

Bullous pemphigoid is an autoimmune blistering disease occurring mostly in the elderly. The bullae of bullous pemphigoid, unlike those of pemphigus vulgaris, are tense rather than flaccid, and oral lesions are less common The Nikolsky sign is negative. Bullous pemphigoid

is characterized by spontaneous remissions and exacerbations and a low mortality rate; most patients experience complete remission. As with pemphigus vulgaris, the diagnosis is made by biopsy of the skin adjacent to a blister. Direct immunofluorescence studies reveal antibodies bound to the basement membrane; these antibodies can often be found in the serum as well. Mild cases are treated with topical corticosteroids or intralesional injections; severe cases require systemic corticosteroids with or without immunosuppressive agents.

LOCALIZED OR DISCRETE LESIONS

Patients with gram-negative sepsis may manifest the skin lesions known as *ecthyma gangrenosum* (Fig. 170.6). Originally described in *Pseudomonas* septicemia, they may also occur with bacteremia due to *Escherichia coli* or *Klebsiella* and have been reported in the absence of disseminated infection (12). Because the lesions of ecthyma gangrenosum are manifestations of life-threatening illness, the diagnosis must be made early. Ecthyma gangrenosum is a true dermatologic emergency; patients with it are critically ill and usually immunocompromised (e.g., with leukemia or lymphoma). Treatment with newer antimicrobial regimens for carbapenemase-producing organisms may be needed in select cases (13).

FIGURE 170.6 Ecthyma gangrenosum. (From Berg D, Worzala K. *Atlas of Adult Physical Diagnosis.* Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)

The appearance of the lesion can vary, depending on the stage of the illness at presentation. Beginning as a painless macule or vesicle, it indurates and assumes the appearance of a pustule or bulla on a blue or red base. The lesion then sloughs, leaving a gangrenous ulcer, usually several centimeters in size. These solitary or multiple lesions usually occur mainly in the perineal region or on the extremities.

Disseminated gonococcal infection (DGI) usually occurs in individuals with asymptomatic infection of the pharynx, rectum, or genitalia. The patient commonly presents with fever, skin lesions, arthritis, periarthritis, tenosynovitis, or any combination of these signs. DGI occurs most commonly in women during menstruation or pregnancy, but it can occur in any patient with gonococcal infection.

The skin lesions are pustules or vesicles on an erythematous base about 5 mm in diameter, but they may also be petechial, bullous, papular, or hemorrhagic. These are usually relatively few (fewer than 10 to as many as 30), and they typically appear on the extremities and resolve rapidly (usually in <1 week). The periarthritis of DGI presents with joint swelling and tenderness, which are often transient and migratory. Septic arthritis occurs most commonly in the larger joints (knees, hands, ankles, and elbows, in descending order of occurrence). Complications such as endocarditis, meningitis, and sepsis are rare.

The diagnosis of gonococcemia (Fig. 170.7) is a clinical one. Any sexually active person with polyarthritis, tenosynovitis, and typical skin lesions can be given a presumptive diagnosis of gonococcemia with little doubt as to its accuracy. Gonococcal cultures or polymerase chain reaction (PCR) testing should be performed on specimens obtained from all mucous membrane surfaces and blood and (when appropriate) joint fluid. The diagnosis can also be made on the basis of a prompt response to empiric antibiotic treatment (see Chapter 184). Antibiotic treatment regimes include ceftriaxone 1 g IV or IM daily plus azithromycin 1 g orally or doxycycline 100 mg

twice daily for 7 days. It is important to follow the most current CDC recommendations closely, as resistance patterns change (14).

FIGURE 170.7 Disseminated gonococcemia. *Neisseria gonorrhoeae* may disseminate from mucosal surfaces via the bloodstream and produce arthritis/arthralgia and a rash. The most characteristic lesion is the hemorrhagic vesicopustule seen in the web space of the teenage girl's hand. There is a pustule on the sole of her foot. (From Fleisher GR, Ludwig W, Baskin MN. *Atlas of Pediatric Emergency Medicine.* Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

The differential diagnosis should include Reiter syndrome (a syndrome of urethritis, conjunctivitis, and arthritis that usually occurs after a diarrheal illness, has dissimilar skin lesions, and does not respond to antibiotics); meningococcemia (which has more numerous petechial lesions); immune complex diseases (which may have joint manifestations but a different type of skin lesion); and rheumatic fever.

Admission is indicated only for patients with severe systemic signs and symptoms or severe joint involvement (especially of weight-

bearing joints) and those who cannot be followed closely as outpatients.

Erysipelas is a superficial cellulitis that progresses rapidly in extent and involves the associated lymphatic channels. The classically described offending organism is the group A streptococcus, but groups B, C, and G streptococci and *S. aureus* have also been isolated (15). The infection is most common in infants and children and in the elderly. The source in most cases is probably an inapparent wound. Erysipelas may range from a self-limited process that resolves spontaneously, even without antibiotics, to a rapidly progressive and severe infection leading to bacteremia. Admission is indicated for patients with extensive facial or neck involvement or for patients with fever and a toxic appearance.

The involved skin is erythematous, warm, and tender to palpation and has an advancing margin that is slightly elevated. Fever is common. The diagnosis is usually clinical, because local aspiration is rarely positive. Punch biopsy may be useful, but it is usually not readily available. The differential diagnosis includes cellulitis, maxillary or frontal sinus infections (if localized to the face), and erysipeloid (if localized to the hands).

Treatment with penicillin is rapidly effective if erysipelas is due to streptococci, but, because it is rarely easy to identify the causative organism, either a first-generation cephalosporin or a penicillinase-resistant penicillin should be used to cover methicillin-sensitive *Staphylococcus.* Clindamycin, vancomycin, or linezolid should be used if MRSA is possible, and may be used in the penicillin-allergic patient. Hospital admission is based on the patient's clinical status. Some affected individuals may be treated as outpatients with close follow-up and admitted if there is no response or any worsening after 1 to 2 days of oral antibiotic therapy.

Cellulitis, an acute, spreading inflammation of the skin and subcutaneous tissue, appears as a warm, tender, erythematous area with indistinct margins. Its differentiation from erysipelas is based on the appearance of the advancing edge of the infection. In cellulitis, the edge is not raised. In practice, the clinical management of patients with erysipelas and with cellulitis is similar. Erysipelas is

more likely, however, to require prompt initiation of antibiotic therapy because it can progress so rapidly.

PURPURIC OR HEMORRHAGIC LESIONS

Neisseria meningitidis colonizes the nasal mucosa in humans (5% to 15%) but may invade the bloodstream and cause disease. Most cases occur in children and adolescents, although any age group may be affected. The mortality of meningococcemia is higher than that of meningococcal meningitis.

Meningococcemia (Fig. 170.8) usually follows an upper respiratory tract infection with flu-like symptoms of headache, myalgias, nausea, and vomiting. The severity of the disease can range from an indolent, slowly evolving infection to a fulminating illness causing prostration within a few hours after the onset of symptoms. The classic skin lesions can be petechial, macular, or maculopapular with pale gray vesicular centers. All are a few millimeters in size but may progress to a confluent hemorrhagic rash. They are most commonly localized to the extremities and trunk but may appear on any part of the body. Meningitis presents with the usual symptoms of meningeal irritation —neck soreness, photophobia, headache—whereas, in meningococcemia, meningeal signs are typically absent (16).

FIGURE 170.8 Meningococcemia. Infection with *Neisseria meningitidis.* (From Fleisher GR, Ludwig W, Baskin MN. *Atlas of Pediatric Emergency Medicine.* Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

Gram stain and culture of scrapings of the skin lesions are positive in only about half of cases. The diagnosis must often rest on clinical findings and is confirmed by positive cultures of blood or cerebrospinal fluid.

One should entertain the diagnosis of meningococcemia in any patient who presents with fever, malaise, and a petechial or maculopapular rash and include it in the differential diagnosis of other bacteremias (e.g., *Haemophilus influenzae, Streptococcus pneumoniae, S. aureus*), subacute bacterial endocarditis, gonococcemia (few distal papular, hemorrhagic lesions), vasculitis (usually distal purpuric lesions), enteroviral exanthems, and RMSF.

The treatment of choice for meningococcemia is high-dose IV antibiotics. Penicillin G (2 million units every 2 hours), ampicillin (2 g every 6 hours), chloramphenicol (4 g/d), and ceftriaxone (up to 4 g/d [100 mg/kg] in children) have all been shown to be effective. Complications such as shock, disseminated intravascular coagulation, adult respiratory distress syndrome, or metabolic acidosis require aggressive supportive care. Prophylaxis is recommended for close school and household contacts. Rifampin, 600 mg (10 mg/kg for children, 5 mg/kg for infants younger than 1 month), is given orally twice daily for 2 days. Single-dose therapy of ciprofloxacin, 500 mg orally, or ceftriaxone, 250 mg IM, are also alternatives for adults.

A related syndrome, chronic meningococcemia, presents as periodic fever, localized rash, myalgia, and arthralgias lasting for several days. The number of skin lesions is small. Episodes may recur over a period of weeks to months. The diagnosis is established by positive cultures (especially of blood) during the febrile episodes. A fair percentage of patients proceed, if untreated, to an acute phase of disease. The differential diagnosis includes subacute bacterial endocarditis, rheumatic fever, gonococcemia, and Henoch–Schönlein purpura.

Treatment is the same as for acute meningococcal disease, except that lower doses of IV antibiotics are generally considered sufficient to eradicate the infection. All patients suspected of having meningococcal disease should be admitted to the hospital for evaluation and treatment, regardless of clinical appearance.

RMSF (see Chapter 186) is an acute infectious disease caused by *Rickettsia rickettsii* and transmitted by the bites of several species of ticks (*Dermacentor andersoni* in the western US, *Dermacentor variabilis* in the eastern US, and *Amblyomma americanum* in some southwestern areas) (Fig. 170.9). RMSF is not limited to the Rocky mountain area; in fact, the areas of highest incidence are in the South Atlantic region and western south-central states. The organisms can be introduced directly into the skin by a tick bite or may enter broken skin with the tick's feces. Once the infection is established, the organisms invade vascular endothelial cells, causing localized thrombosis and necrosis. The disease is manifested clinically by fever, rash, myalgia, and headache. It ranges in severity from a mild, self-limited illness to severe, life-threatening disease (17).

FIGURE 170.9 Rocky mountain spotted fever. (Courtesy of Sidney Sussman, MD.)

RMSF is seen most commonly in the late spring and early summer. The incubation period ranges from 3 to 12 days. There is an abrupt onset of fever, chills, arthralgia, and headache, which is usually severe, with or without nausea, vomiting, and photophobia. The rash appears between the second and sixth days of the illness, beginning peripherally on the wrists, ankles, and forearms as a macular erythematous rash and extending to the palms, soles, and torso. The lesions become maculopapular in a few days in most cases and become petechial shortly thereafter (2 to 4 days after the start of the rash). The rash may be absent in 12% to 17% of cases and may be

difficult to appreciate in dark-skinned individuals (1). Areas of decreased circulation, such as the distal extremities, nose, and ear lobes, may develop areas of infarction; finding such lesions on the scrotum or vaginal area can be an additional clue to the diagnosis.

The differential diagnosis of RMSF includes TSS, meningococcal meningitis, Kawasaki disease, measles, leptospirosis, Colorado tick fever, enteroviral infections, any cause of disseminated intravascular coagulation and vasculitis, mononucleosis, rat-bite fever, atypical measles, and other rickettsial diseases. Among the latter are murine typhus and epidemic typhus, which both have rashes that usually begin on the trunk rather than on the distal extremities.

The treatment of choice for RMSF is doxycycline (100 mg every 12 hours) for 7 to 10 days or tetracycline (25 to 50 mg/kg in divided doses four times daily, not to exceed 2 g/d). Years ago because of concern over dental effects of tetracycline, chloramphenicol (50 to 100 mg/kg/d in four divided doses) was used to treat children, and is currently recommended in pregnancy. Tetracycline usually does not affect enamel formation in the incisors, canines, and bicuspids after age 7 (18,19). Moreover, in children younger than 5 years, it is unlikely to result in any apparent change in tooth color when fewer than five courses of therapy are given in the usual oral dosage (18,19). More recent studies on tooth enamel staining have not shown staining in teeth owing to short courses of doxycycline in children ages 2 to 8 years (18,20) and with an average age of 5 years (18,20). The American Academy of Pediatrics Committee on Infectious Disease revised their recommendations in 1997 and named doxycycline as the antibiotic of choice for treating possible or confirmed RMSF and ehrlichial infections in children, regardless of age. The dose of doxycycline in children weighing <100 lb is 2.2 mg/kg body weight in divided doses twice daily. The adult dose is 100 mg twice daily.

SKIN CANCER

Skin cancers are life-threatening if not diagnosed early. Yet early diagnosis can lead to cure rates in more than 90% of patients in the most common types of skin cancer. Discussion in this chapter focuses

on clinical recognition as described further, illustrated with supplementary photographs. As management is primarily by the dermatologist, definitive diagnostic points and treatment are discussed only briefly.

Basal cell carcinoma (BCC) (Fig. 170.10) is the most common skin cancer. It is usually found in men older than 50 years. Ninety percent are on the sun-exposed head and neck, with the trunk being the next most common site. There are four types. The *noduloulcerative* BCC begins as a small pearly papule that enlarges over the years into a nodule with a waxy edge, a few telangiectatic vessels, and an ulcer on the surface. The *pigmented type* looks the same with the addition of some black or brown pigment. *Sclerosing basal cell cancer,* usually on the face, looks like a whitish scarred patch without any ulceration or telangiectases. *Superficial basal cell cancer* is the most innocuous-looking, resembling a dermatitis. It usually appears on the back and the chest and it looks like a reddish patch with slight scale. The border may have telangiectatic vessels and be slightly raised. The center may be atrophic with superficial ulceration.

FIGURE 170.10 Basal cell carcinoma (BCC). Pearly papule: The tumor exhibits typical rolled pearly borders with telangiectases and central ulceration. (From Elder AD, Elenitsas R, Johnson BL, et al. *Synopsis and Atlas of Lever's Histopathology of the Skin.* Philadelphia,

PA: Lippincott Williams & Wilkins; 1999, p 2, clin. fig. IA1; p 163, clin. fig. IVE3; p 167&#044.)

Squamous cell carcinoma (Fig. 170.11) accounts for 20% of all skin cancer other than melanoma. It occurs most commonly on sun-exposed areas of the face, scalp, lip, ear, and neck and the dorsal hand. Scars from radiation or burns may develop squamous cell carcinoma and are more likely to metastasize. The most common lesion is a quickly growing nodule with an ulcerated center and a firm raised border surrounded by redness. Cure rates are 90%, and metastasis (4% overall) manifests as regional lymphadenopathy.

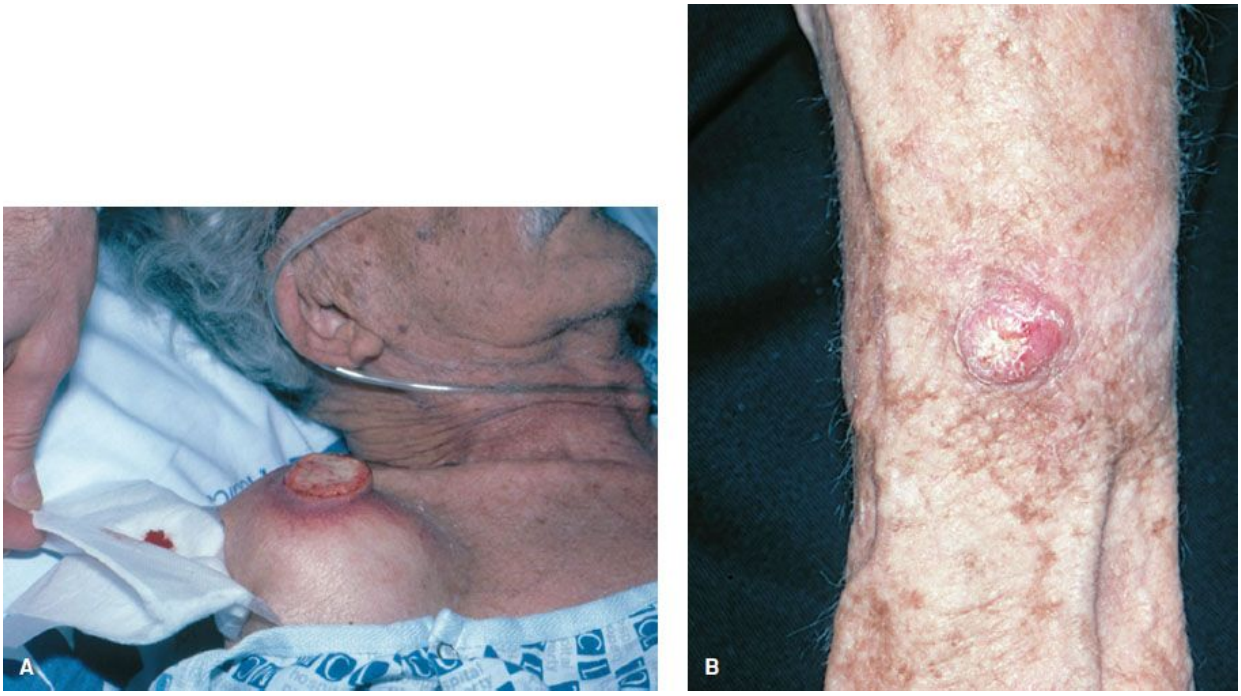

FIGURE 170.11 Squamous cell carcinoma. **A:** This neglected tumor has ulcerated. **B:** This reddish nodule is indistinguishable from BCC. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

Malignant melanoma (Fig. 170.12) is a pigmented skin cancer developing on previous nevi or de novo on sun-exposed areas, such as the face and forearms, or on the back of men and the lower legs of

women. Amelanotic melanomas are rare and challenging to diagnose. Although melanomas make up only 1% of the skin cancers in the US, they account for >60% of the deaths. Yet, the most common type, the superficial spreading melanoma, has 5-year survival rates of almost 98% when thin and removed early. It has five cardinal features (5):

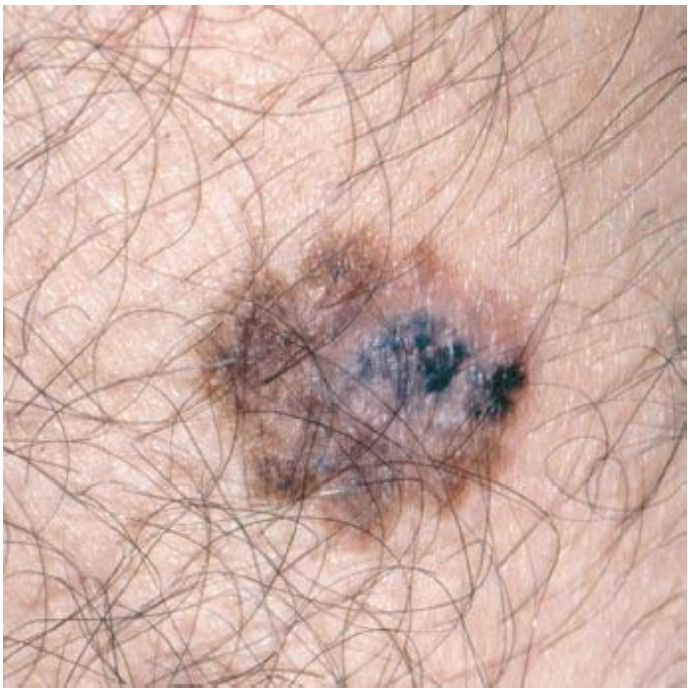

FIGURE 170.12 Malignant melanoma. Note the variegation in color and the irregular, notched border. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

1. **A**symmetry
2. **B**order is irregular
3. **C**olor is mottled, haphazard display of brown, black, gray, and pink (beware of no color in amelanotic melanoma)
4. **D**iameter >6 mm (the size of a pencil eraser)
5. **E**nlargement growth in size; elevation, usually with surface distortion (2)

Changes in a recent or longstanding skin lesion that are suspicious include changes in size, shape, pigmentation, surrounding erythema,

induration, friability, and ulceration (9).

Diagnosis of all the skin cancers relies on early clinical suspicion and referral to a dermatologist for diagnosis by removing the lesion for pathologic diagnosis and staging. Additional chemotherapy or radiotherapy may be indicated for metastasis squamous cell carcinoma or advanced melanoma.

Kaposi sarcoma (Fig. 170.13) is a vascular neoplasm seen in the United States, mostly in patients with AIDS and low CD4 cell counts. With the advent of effective therapy to manage HIV, Kaposi is uncommonly seen now. It can also occur sporadically in elderly men and in Europeans and Africans unrelated to their HIV status.

FIGURE 170.13 Kaposi's sarcoma. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

It appears as red, purple, or brown papules or plaques, solitary or multiple, on skin or mucous membrane. Internal organs may be involved as well, including the gastrointestinal (GI) tract and lungs. Diagnosis is made by clinical appearance in the appropriate individual. Management focuses on controlling the underlying disease.

Cutaneous T-cell lymphoma (mycosis fungoides; Fig. 170.14) is a cancer of CD4 cells. It usually affects people in their forties and fifties, twice as many men as women, twice as many blacks as whites. They report asymptomatic or pruritic patches of abnormal-appearing skin unresponsive to treatment. Occasionally, they may have fever, night sweats, and weight loss. Sezary syndrome is considered to be an erythrodermic, leukemic variant of mycosis fungoides with generalized erythroderma, lymphadenopathy, and atypical T-cells (Sezary cells) in the peripheral blood. Patients with Sézary syndrome have a worse prognosis than those with mycosis fungoides and erythroderma but without lymphadenopathy and atypical T-cells in the blood (6). The diagnosis is made by multiple lesional biopsies over time. Treatment can either be systemic for more advanced disease or related to the skin disease.

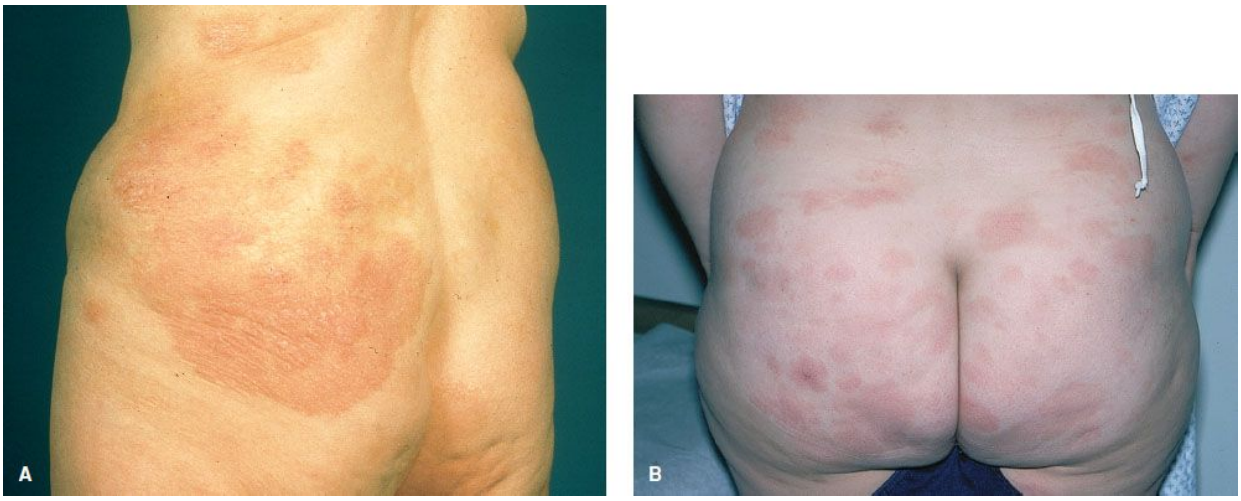

FIGURE 170.14 Mycosis fungoides. **A:** A 66-year-old woman presented with a 30-year history of erythematous scaly patches and plaques with telangiectases, atrophy, and pigmentation. (From Elder AD, Elenitsas R, Johnson BL, et al. *Synopsis and Atlas of Lever's Histopathology of the Skin*. Philadelphia, PA: Lippincott Williams & Wilkins; 1999, p 2, clin. fig. IA1; p 163, clin. fig. IVE3; p 167&#044.) **B:** Lesions have characteristic "smudgy," poorly defined patches and plaques in a typical location. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

CRITICAL INTERVENTIONS

- Search for Nikolsky sign in diffuse red skin rashes.
- Initiate antibiotics for patients with suspected meningococcemia.
- Recognize that most melanomas are pigmented and develop changes in size, shape, and pigmentation.

Common Pitfalls

- TEN can easily be confused with SSSS. TEN requires the removal of any possible precipitating agent, most commonly a drug; SSSS must be treated with appropriate antibiotics. The prognosis of the two diseases is markedly different.
- The rash of TSS may be indistinct. The diagnosis should be considered in any patient with fever and signs of volume depletion, even in the absence of a history of tampon use. The disease can occur in men and children.
- Bullous pemphigoid can easily be confused with pemphigus vulgaris. Early consultation with a dermatologist may be necessary to avoid misdiagnosis and inappropriate treatment.
- In a febrile, seriously ill patient, skin lesions may be a manifestation of sepsis. The lesions should be opened and their contents Gram-stained and cultured.
- Rapid identification and treatment are crucial in ecthyma gangrenosum. The underlying septic process can be fatal if not treated promptly.
- The diagnosis of gonococcemia is often overlooked in persons presenting with tendinitis without any history of injury.
- The early rash of meningococcemia may be macular, maculopapular, or petechial.
- In RMSF, the rash is absent in a significant proportion of cases. An increased index of suspicion is necessary for any patient presenting with a viral-like illness in the late spring or early summer.
- Although BCC is usually waxy and ulcerative, it may also appear to be an innocuous dermatitis.

- Asymptomatic or pruritic patches of abnormal skin which are unresponsive to treatment may represent cutaneous T-cell lymphoma.

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CHAPTER 171

Papulosquamous Eruptions

Mark Spektor and John J. Kelly

Papulosquamous lesions are characterized by papules and scaly desquamation of the skin. The lesions may also be macular and erythematous. Diseases in this group include psoriasis, seborrheic dermatitis, pityriasis rosea (PR), lichen planus, and secondary syphilis. Other diseases that may be part of the differential diagnosis include tinea, discoid lupus erythematosus, mixed connective tissue diseases, and scabies. Papulosquamous eruptions are the most common cutaneous manifestations of human immunodeficiency virus (HIV) infection, and their appearance may be the first clue of HIV infection in an otherwise asymptomatic host (19). In addition, a large number of drugs are known to cause papulosquamous eruptions.

When evaluating a papulosquamous eruption in the emergency department (ED), the physician should look for clues to help differentiate the possible etiologies. Is the rash disseminated or localized? Does it appear on specific areas of the body, such as the elbows, knees, scalp, palms, soles, web spaces, or sun-exposed areas? Is it a well marginated, ring-shaped, or isolated lesion (herald patch)? Are the papules pruritic or purple? Answering these basic questions and using the algorithm in Figure 171.1, most papulosquamous diseases are diagnosed without dermatologic consultation.

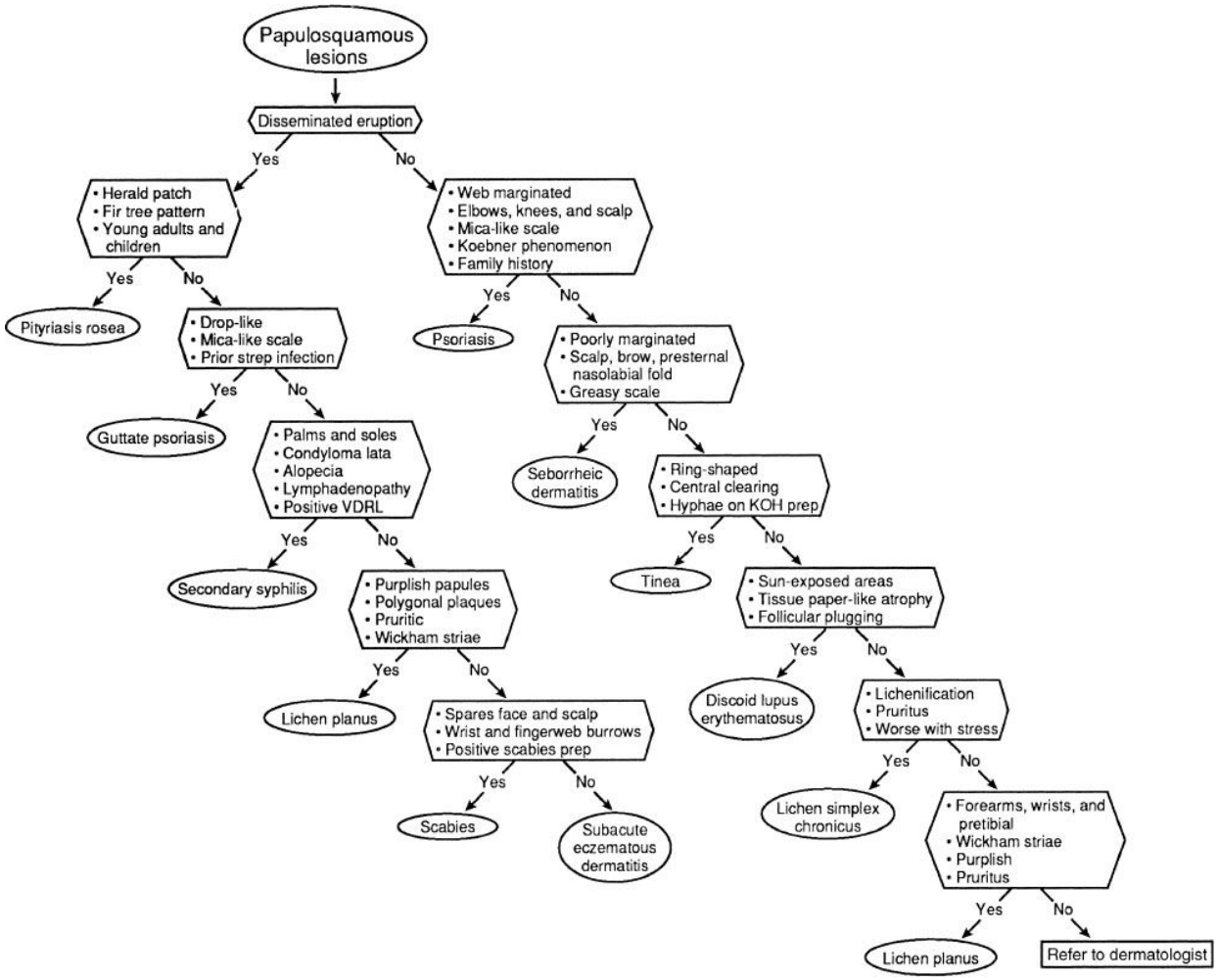

FIGURE 171.1 Algorithm for papulosquamous diseases. (Reproduced with permission from Flowers FP, Krusinski PA. *Dermatology in Ambulatory and Emergency Medicine*. Chicago: Year Book Medical; 1984.)

PSORIASIS

Psoriasis, the most common papulosquamous dermatosis, is found in about 0.6% to 4.8% of the general population (18). The disease is slightly more common in men, and no reliable data exist to support the common assumption that psoriasis is less common in blacks (9,18). Although it is more common during the second and third decades, it may manifest itself at any age and has been reported to be present at birth. The pathogenesis of psoriasis is not completely understood, although there is clearly a genetic component, and

several chromosomal loci have been implicated. T cell-mediated autoimmune mechanisms, such as those involving cytokines, appear to drive development of the plaques, which may begin in response to an environmental factor such as a viral antigen (20). New therapies are focusing on T cell biologic agents.

CLINICAL PRESENTATION

The most common form of psoriasis, plaque psoriasis, occurs in approximately 80% of patients. In this type of disease presentation, lesions are characterized by well-delineated, salmon-colored papules that are soon covered by silvery white scales (Fig. 171.2). They involve both the dermis and epidermis; the depth of involvement depends on their age and location. As the lesions age, the epidermal layer thins, exposing underlying capillary beds. These capillary beds may bleed when the overlying keratotic epidermis is sheared away by mechanical force. This phenomenon, known as the *Auspitz sign,* is diagnostic of psoriasis. Common sites for plaque psoriasis are the scalp, extensor surfaces of the extremities, palms, soles, nails, and the intergluteal cleft. Patients may present with inverse psoriasis in which the lesions affect the flexural sites such as axillae and antecubital and popliteal fossae.

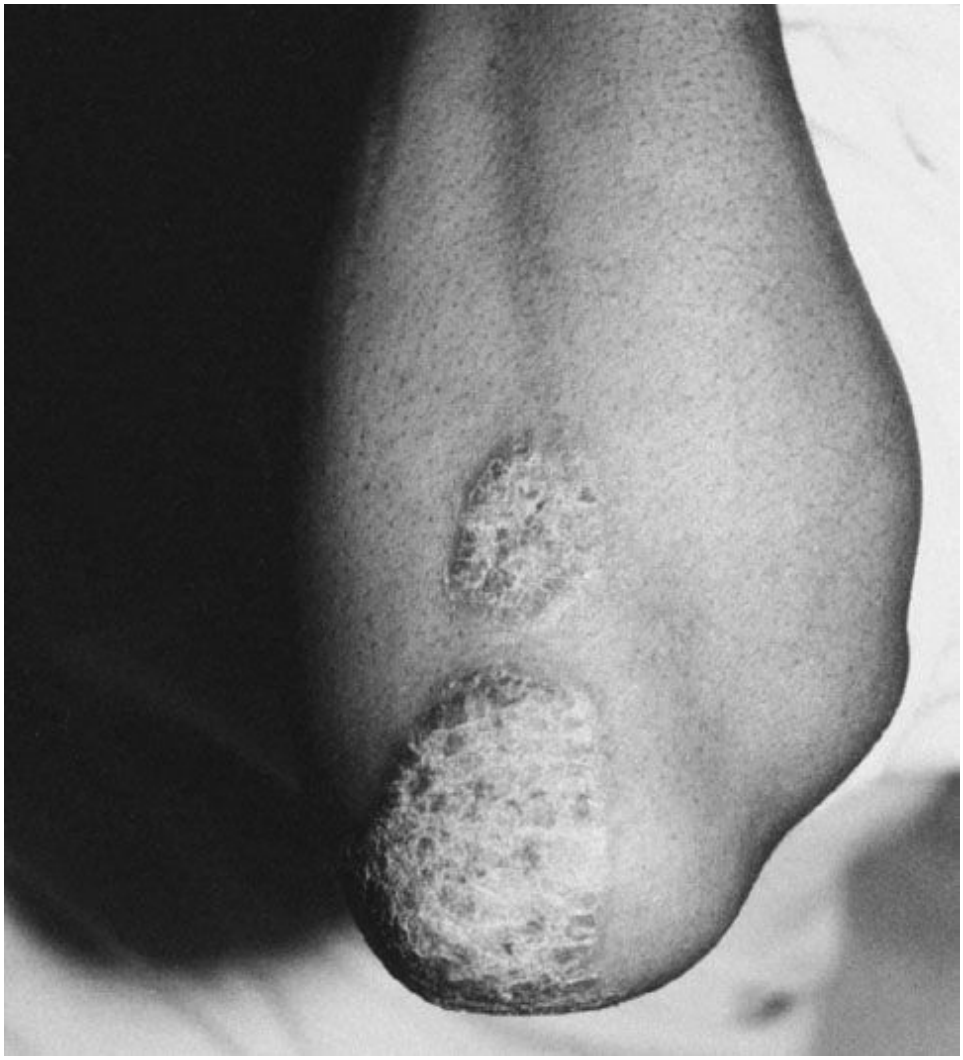

FIGURE 171.2 Well-defined erythematous, scaling plaques on the extensor surface of the arm in a patient with psoriasis.

Between 5% and 42% of patients with psoriasis develop psoriatic arthritis, which is seronegative for rheumatoid factor. The arthritis is typically asymmetric and involves fingers and toes. Cutaneous lesions precede joint disease in 60% to 70% of the cases but may present simultaneously. In 20% of patients, the onset of arthritis is prior to the skin changes (2).

Nail abnormalities are eventually seen in most patients. The nails are commonly pitted and show a brownish or whitish discoloration and an accumulation of scale on the nail bed. Nail changes may precede skin finding in up to 4% of patients (Fig. 171.3) (20).

FIGURE 171.3 Psoriasis of the nails.

Pustular psoriasis is characterized by erythematous areas covered with sterile pustules. It may be localized or general and may affect the hands and feet in addition to the trunk and extremities. In extreme cases, pustules become confluent, forming large lakes of pus. Generalized pustular psoriasis has an acute onset associated with malaise, pyrexia, and leukocytosis, and it is potentially fatal if untreated. Factors known to induce generalized pustular psoriasis include a tapering of the dose of systemic corticosteroids, withdrawal of potent topical steroids, nonsteroidal anti-inflammatory agents, pregnancy, viral upper respiratory tract infections, and beta-hemolytic streptococcal infections (7).

Guttate psoriasis usually follows streptococcal infections. It is characterized by sudden appearance of lesions on the trunk and extremities.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of psoriasis includes tinea cruris, candidiasis, secondary syphilis, PR, cutaneous lupus erythematosus, and seborrheic dermatitis (6), and intertrigo when the eruption

occurs in the intertriginous areas. Seborrheic dermatitis may resemble psoriasis of the scalp but usually has finer and more widespread yellow scaling. A helpful clue in differentiating psoriasis from other conditions is the presence of psoriatic nail changes: pitting of the nails and separation of the nail from the underlying nail bed (6). Guttate psoriasis on the trunk is easily confused with PR.

ED EVALUATION

After a thorough history for chronic recurrent rash, inspect the entire skin, especially the scalp, extensor surfaces of the extremities, palms, soles, nails, and the intergluteal cleft. If the diagnosis is unclear based on history and physical examination, laboratory investigation based on clinical findings, including a rapid plasma reagin (RPR) to exclude syphilis, is appropriate.

ED MANAGEMENT

Mild psoriasis is usually treated with topical preparations and phototherapy. More severe or widespread cases may require systemic treatment. Topical therapy includes emollients, corticosteroids, tars, anthralin, salicylic acid, tazarotene, and vitamin D analogues. The use of tars has been described since 1925 (8) but has fallen out of favor owing to limited effectiveness and staining. Coal tar and salicylic acid shampoos are still widely used in psoriasis of the scalp (21).

Topical corticosteroids are the most prescribed medications for psoriasis treatment. Corticosteroids are highly and rapidly effective; however, side effects such as cutaneous atrophy, striae, and formation of telangiectasia have limited their long-term utility. Vitamin D analogues such as calcipotriol, calcitriol, and tacalcitol have emerged as an alternative to corticosteroids. These agents exert their effect through inhibition of epidermal proliferation, enhancement of cornification, and inhibition of inflammation (21). Although they lack the side effect profile of corticosteroids, vitamin D analogues have a somewhat limited effectiveness (15). Topical retinoids such as tazarotene have been utilized for treatment of

psoriasis. They have been shown to be as effective as mid- and high-potency steroids. Local irritation is a common side effect (13). Topical immunosuppressants such as tacrolimus and pimecrolimus have recently gained acceptance. More severe cases of psoriasis may require systemic treatment or phototherapy. Systemic therapy includes methotrexate, cyclosporin, systemic steroids, systemic retinoids, and most recently the biologics. This class of drugs includes etanercept, infliximab (21), adalimumab, and ustekinumab. Initiation of systemic medication and phototherapy should be made under the direction of a dermatologist.

DISPOSITION

Psoriasis is rarely dangerous or life threatening and is usually best cared for by a dermatologist who can follow up the patient over time. Topical steroids or coal tar may be initiated in the ED, but treatment with ultraviolet A (UVA) or systemic therapy should be performed under the direction of a dermatologist, usually in the hospital. The patient who appears toxic should be admitted for intravenous antibiotics.

Common Pitfalls

- Psoriasis of the trunk and extremities is rarely confused with other diseases, but in the intertriginous areas, it may be confused with tinea cruris, candidiasis, or intertrigo. Close examination with a Wood's light and potassium hydroxide (KOH) preparation should help differentiate these diseases. Some patients may have both diseases.
- If steroids are used to treat psoriasis, systemic steroids should be avoided. They are very effective but can cause long-term side effects, and the disease often rebounds when steroids are stopped.
- New cases of psoriasis, sudden, severe exacerbations, or cases refractory to treatment should alert the clinician to the possibility of HIV infection.

PITYRIASIS ROSEA

PR is an acute, self-limited, inflammatory dermatosis seen most commonly in children and adolescents. PR has been reported in all ages, but approximately 50% of cases occur before the age of 20 years. It affects both genders equally and has an increased incidence in spring and fall (11). The etiology is uncertain, but an association with viral infection such as human herpesvirus 6 and 7 has been suggested, with little data to support the idea (5). In addition, many drugs have been reported to cause PR-like reactions (Table 171.1).

TABLE 171.1
Drugs Associated with Pityriasis Rosea–Like Eruption

Ketotifen
Captopril
Isotretinoin
Metronidazole
D-penicillamine
Levamisole
Gold
Bismuth
Arsenic
Barbiturates
Clonidine

CLINICAL PRESENTATION

PR is characterized by oval, salmon-colored, pruritic, scaling patches on the neck and trunk that follow Langer lines (skin cleavage lines) (Fig. 171.4). On the back, this produces a so called Christmas tree pattern. The rash may be found on the palms and soles, and it may involve the oral mucosa and gingiva. Characteristically, this generalized eruption is preceded by a 2- to 5-cm herald patch, but it is absent in up to 50% of patients. Within 7 to 14 days, other lesions appear, which, in young children, may involve the face, scalp, and distal extremities. Oral lesions may be present in up to 16% of patients (22). An atypical presentation (inverse PR) spares the trunk, affecting only the face and extremities. Papular form of PR has also

been described (1). The rash usually lasts 4 to 7 weeks but may last up to 5 months.

FIGURE 171.4 Circular and ovoid papules and plaques with scaling on the trunk and proximal extremities in a patient with pityriasis rosea.

The most common complaints associated with PR are pruritus and mild constitutional symptoms such as malaise, fever, and lymphadenopathy. It poses no risk to the fetus if it occurs in pregnant women and it does not appear to be contagious.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes tinea corporis when there are a few lesions and secondary lues when there are many (although luetic lesions tend to be less pruritic). The herald patch is commonly misdiagnosed as ringworm. A KOH preparation of scrapings from the lesions is negative, however. Examination of tinea corporis with a Wood's light produces a bright green fluorescence, but no fluorescence is seen with PR. Guttate psoriasis, which is distributed mainly on the trunk, has thicker, more silvery scales than does PR. Lichen planus may have a similar appearance, but the lesions are

purple, not salmon colored. Eruptions resembling PR may also be caused by numerous medications (Table 171.1). Because the skin eruption of secondary syphilis may mimic that of pityriasis, a venereal disease research laboratory (VDRL) or RPR should be drawn.

ED EVALUATION

Conduct a thorough history and skin examination, looking for classic features such as the herald patch and Christmas-tree distribution. Obtain an RPR to exclude syphilis if the diagnosis is unclear.

ED MANAGEMENT AND DISPOSITION

Pityriasis is a benign, self-limited disease that does not require therapy. Symptomatic treatment for pruritus may include emollients, antihistamines, and intermediate-strength topical steroids. Treatment with erythromycin has been shown to be effective (17), but the mechanism of action remains unclear. One current hypothesis suggests that erythromycin may provide an anti-inflammatory and immunomodulatory effect (3). UVA may accelerate resolution of the lesions.

If the diagnosis is made with certainty, consultation with a dermatologist is unnecessary. The patient may be discharged to follow up with the family physician. If the diagnosis is in question, the patient should be referred to a dermatologist. If the rash lasts more than 3 months, the physician should be prompted to reconsider the original diagnosis.

Common Pitfalls

- PR is often misdiagnosed. The herald patch can resemble tinea corporis and may be incorrectly treated with antifungal medication until the generalized rash appears.
- Later, the generalized rash may be mistaken for lichen planus or a drug eruption. A careful history and physical examination decrease the likelihood of these errors.

- The wise clinician draws an RPR test or VDRL test to rule out "the great masquerader."

LICHEN PLANUS

Lichen planus is a relatively uncommon inflammatory dermatitis characterized by violaceous, flat-topped papules. The disease is most common between ages 30 and 60 and is seen with approximately equal frequency in men and women. Viral and bacterial agents and genetic predisposition and immunologic factors have been suggested as causes. In addition, several drugs have been implicated in causing a lichen planus–like eruption (Table 171.2).

TABLE 171.2
Drugs Causing Lichenoid Drug Reactions

Beta blockers	Captopril
Methyldopa	Thiazides
Furosemide	Gold
Antimalarials	Quinidine
Oral hypoglycemic agents	Phenytoin
Carbamazepine	Antituberculous agents
Antihistamines	Phenylbutazone
Antipsychotics	Bismuth
p-Aminosalicylic acid	Lithium

CLINICAL PRESENTATION

The lesions of lichen planus may be described using the six Ps: pruritic, polygonal, planar, purple papules, and plaques. Most appear to be slightly scaly with a fine reticular pattern of white dots and lines on their surface (Fig. 171.5). They are commonly found on the wrist, volar surface of the forearms, and pretibial areas, but may also appear on the scalp, palms, soles, lips, and genital mucosa. On the palms and soles, they are commonly yellowish and nonpruritic. The lesions commonly develop at sites of trauma (Koebner phenomenon). For this reason, they are often found in a linear pattern, presumably owing to scratching. More than one-half of patients with cutaneous

lichen planus have oral mucosal lesions as well. These are whitish plaques with a lacy, whitish, reticular pattern (Wickham striae) (Fig. 171.6). Patients may present with oral lesions alone.

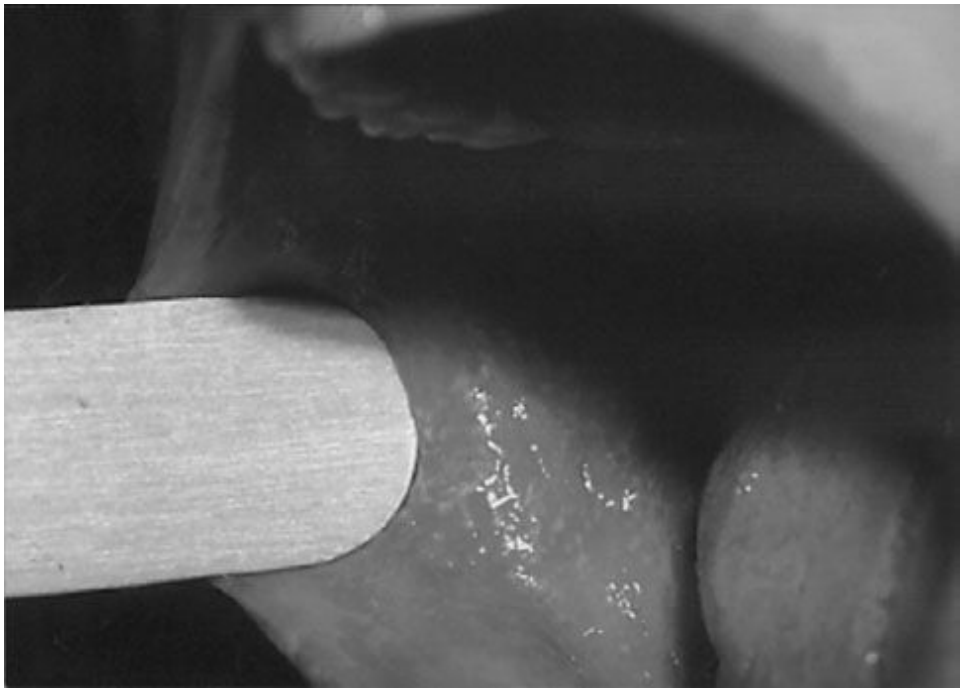

FIGURE 171.6 Oral lesions of lichen planus.

FIGURE 171.5 Gray to violaceous flat-topped papules on the flexural surface of the forearm in a patient with lichen planus.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of lichen planus includes psoriasis, fungal infection, secondary syphilis, PR, and discoid lupus erythematosus. When the mucous membranes are involved, leukoplakia and candidiasis are considerations.

ED EVALUATION

Perform a thorough examination of the skin, palms, soles, and oral mucosa. Order an RPR to exclude syphilis if the diagnosis is uncertain.

ED MANAGEMENT AND DISPOSITION

Lichen planus is a self-limited disease that may last for weeks to years. Most patients experience a spontaneous resolution within a year. Several cases of squamous cell carcinoma have been reported in association with oral lichen planus (12). Therefore, proper follow-up arrangements are required. Treatment includes antihistamines for pruritus and topical steroids for inflammatory lesions. Occasionally, with widespread lesions, systemic steroids may be used. In cases that are resistant to corticosteroids, retinoids such as acitretin may be considered (4). Biologics such as efalizumab have also been shown to be effective (3). Patients with lichen planus should be referred to a dermatologist for long-term follow-up, although treatment with topical agents and antihistamines may be initiated in the ED.

Common Pitfalls

- Lichen planus frequently involves the oral mucosa; in fact, 15% to 25% of patients with oral lichen planus never develop skin lesions. It is also one of the few rashes that may affect the palms and soles. A close physical examination, not only of the obvious lesions on the arms and trunk but of the mouth, palms, and soles, is important in making the correct diagnosis.
- In light of the recently described association between lichen planus and the hepatitis C virus (HCV), patients should be referred for prompt evaluation for HCV infection (16).

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is a chronic, superficial, inflammatory process affecting regions of the body with increased sebaceous gland activity. It is more common in males and occurs in infants younger than 12 months, among adolescents, and in elderly persons. It is more severe in winter. It is particularly common in patients with HIV infection. The etiology is unclear, but it may be caused by dysfunctional sebaceous gland activity owing to hormonal activity (23) or a reaction to the common skin yeasts *Malassezia ovalis* and *Pityrosporum ovale*.

CLINICAL PRESENTATION

The lesions of "oily" seborrheic dermatitis are characterized by poorly defined margins, mild erythema, and greasy yellow scales (Fig. 171.7). "Dry" seborrheic dermatitis exhibits small, dry, powdery scales and little or no erythema. Secondary lesions due to scratching may be seen around the primary lesions. Areas commonly affected include the scalp, face (especially the eyebrows and nasolabial folds), axilla, groin, buttocks, and inframammary folds. In infants, the scalp is frequently affected and is known as *cradle cap*. When the scalp is affected in adults, it is called *dandruff*.

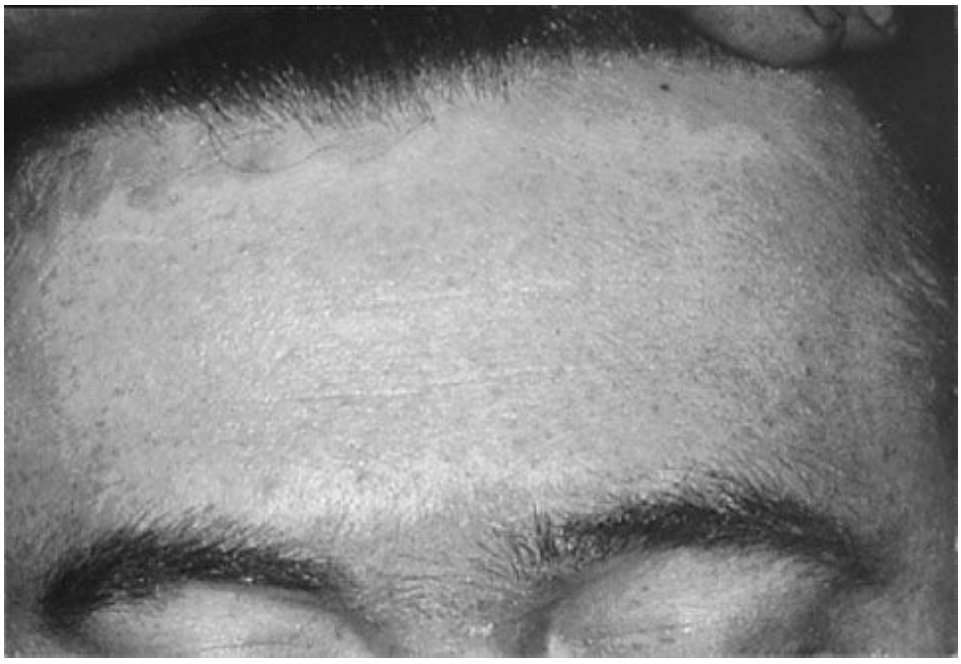

FIGURE 171.7 "Oily" seborrheic dermatitis along scalp hairline and eyebrows.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes psoriasis, tinea, and atopic dermatitis in children. Lesions affecting the scalp, axilla, and groin may be difficult to differentiate from psoriasis. Involvement of the knees, elbows, and nails favors psoriasis. Persistent pruritic lesions that do not respond to therapy may be tinea. In infants, seborrheic dermatitis is commonly seen on the scalp, axilla, and diaper area. Lesions on the forearms and shins favor atopic dermatitis.

ED EVALUATION

Conduct an examination focusing on the scalp, face, axilla, groin, buttocks, and inframammary folds.

Order an RPR if the diagnosis is uncertain.

ED MANAGEMENT AND DISPOSITION

Encouragement of good hygiene is vital in the treatment of seborrhea. Frequent cleansing with soap removes oils from affected areas and therefore decreases the symptoms. Antiseborrheic shampoos containing sulfur, salicylic acid, coal tar, or selenium sulfide provide adequate therapy for most patients. They should be used daily and rubbed into the scalp, with a 5- to 10-minute wait before rinsing. Topical antifungals such as ketoconazole 2% cream and ketoconazole or ciclopirox shampoos have shown good efficacy (10). Topical steroids may be used in areas with dense scale; however, one must be aware of side effects such as atrophy and telangiectasia. Patients with seborrheic dermatitis may be treated on an outpatient basis by the emergency physician and then referred to a dermatologist or the patient's family physician.

Common Pitfalls

- Seborrheic dermatitis is often misdiagnosed. It occurs in infancy as cradle cap and usually does not appear again until puberty. It

is associated with an oily complexion and is often precipitated by fatigue or stress.
- Possibility of HIV infection should be considered.

SECONDARY SYPHILIS

Syphilis (see Chapter 184, "Sexually Transmitted Diseases") is a sexually transmitted infectious disease caused by *Treponema pallidum.* The rash of secondary syphilis appears 9 to 90 days after the onset of the chancre; the average is 3 weeks. Most individuals contract the disease from sexual activity with a person in the early stages of syphilis. The risk of transmission ranges from 9% to 63%, and incidence has been reported at a rate of 3.2 cases per 100,000 persons (18).

CLINICAL PRESENTATION

The rash of secondary syphilis is generalized, painless, and nonpruritic. A primary chancre may be present in as many as one-third of patients with secondary syphilis. As many as 60% of patients do not report recall having a chancre (18). The rash involves the skin and the mucous membranes in 30% to 50% of the cases. On the skin, it tends to follow the lines of cleavage, especially on the trunk. It has a special predilection for the palms and soles (Fig. 171.8). The lesions are scaling, "raw ham," or copper-colored papules and plaques that are discrete and sharply demarcated rather than confluent (Fig. 171.9). Annular plaques on the mouth, nose, and lip areas are virtually diagnostic. The patient's presenting complaint may be an apparently unrelated other symptom, such as headache, sore throat, malaise, and generalized arthralgia.

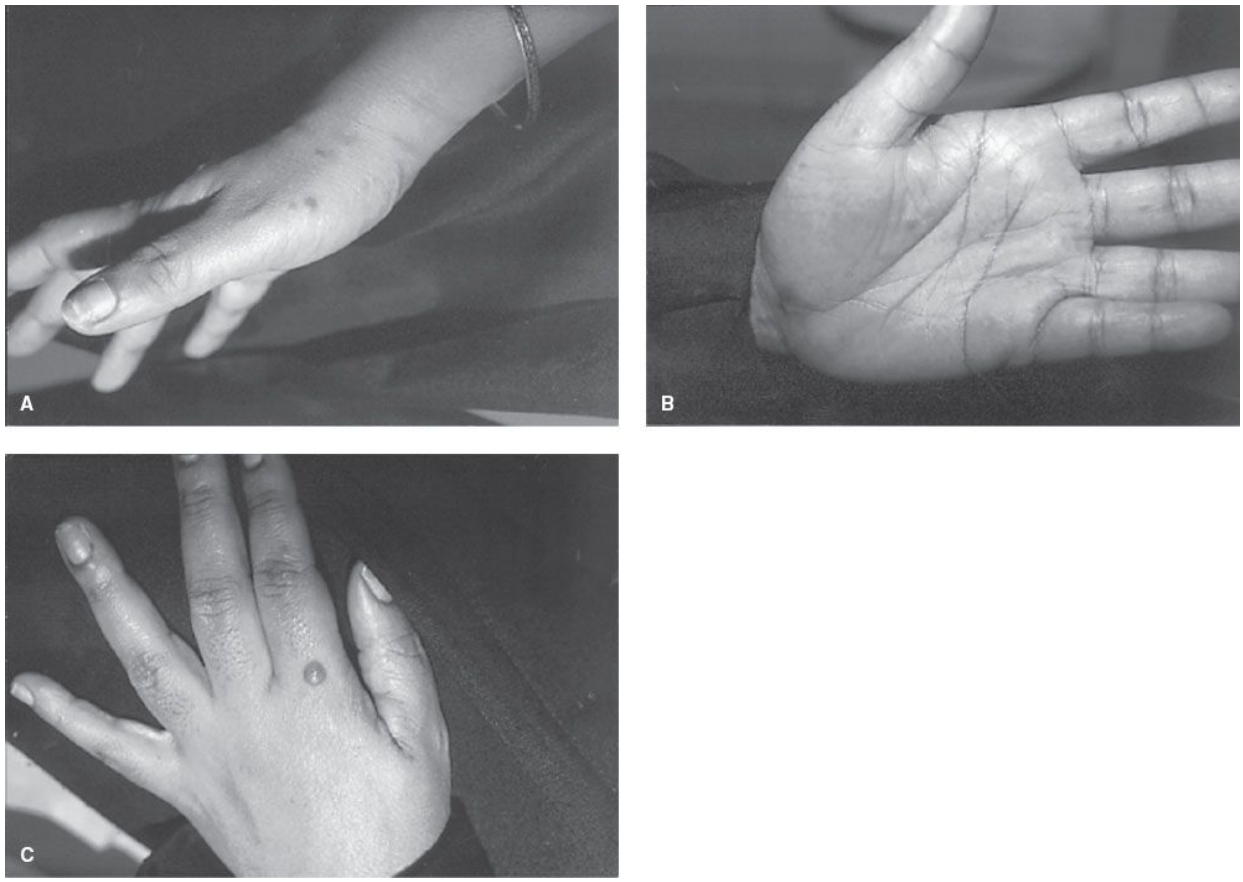

FIGURE 171.8 A–C: Secondary syphilis.

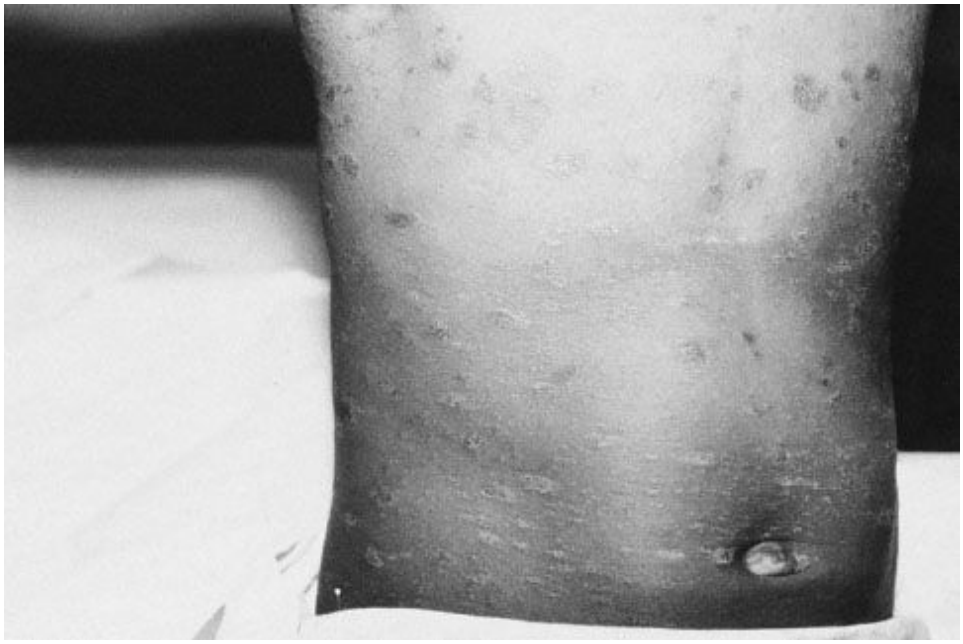

FIGURE 171.9 Diffuse erythematous papules and plaques with scaling in a patient with the rash of secondary syphilis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of secondary syphilis includes PR, Rocky Mountain spotted fever, meningococcemia, drug reaction, and lichen planus. Palmar lesions that mimic secondary syphilis may be secondary to drug eruption.

ED EVALUATION

The examination should include a search for chancre, for mucous membrane lesions, and for annular lesions of the mouth nose or lip. Order an RPR.

ED MANAGEMENT AND DISPOSITION

Diagnostic studies such as VDRL or RPR should be ordered. Dark-field examination of scrapings from lesions may also be performed. If either test is positive, the patient is treated in the ED with either benzathine penicillin G (2.4 million units IM) or aqueous procaine penicillin G (600,000 units IM daily for 8 days). Patients allergic to penicillin may be treated with tetracycline or erythromycin for 10 days.

If the diagnosis of secondary syphilis cannot be made in the ED, the patient should be referred to a private physician or clinic pending the results of VDRL or RPR testing. Hospital admission is unnecessary for secondary syphilis, but the patient should be instructed to abstain from sexual contact until the diagnosis is clear and any necessary treatment has been administered and to refer all sexual partners to testing and treatment, as indicated.

CRITICAL INTERVENTIONS

- Order an RPR in patients with papulosquamous lesions of unclear etiology.

Common Pitfalls

- Failing to elicit a history of a primary lesion preceding the rash. This history and an adequate sexual history are helpful in the initial diagnosis.
- Failing to appreciate the typical erythematous, hyperpigmented, and scaly papules on the palms and soles may lead to an inappropriate diagnosis.
- Because of the strong association of HIV and syphilis, patients newly diagnosed with syphilis should be referred for HIV testing.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of photographs by Howard Goldman, DO, to the content of this chapter.

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CHAPTER 172 Blistering Disorders

Lisa R. Palivos

Vesicular lesions are commonly seen in the emergency department. Like other dermatologic lesions, vesicles can present a challenge in determining their etiology, contagiousness, and proper treatment (1–4).

Vesicles are circumscribed epidermal elevations 1 to 4 mm in diameter that usually contain clear fluid. Several characteristics help distinguish the lesion from other vesicular disorders, including the nature of the contained fluid (seropurulent, serosanguineous), the shape of the lesion's apex (rounded, acuminate, umbilicated), the pattern of the eruption (discrete, irregularly scattered, grouped, linear), and the distribution over the body and associated mucous membrane involvement.

In this discussion, there are two types of vesicular disorders: those appearing in groups and those that are individual or disseminated.

GROUPED LESIONS

Herpes Simplex

Herpes simplex infections are caused by two different DNA virus types: HSV-1 and HSV-2. Both viruses can infect oral or genital mucosa and are spread by direct contact. HSV-1 usually affects the lips and is often referred to as a fever blister or cold sore. HSV-2 is the virus most frequently associated with genital herpes. The hallmark of herpes simplex virus (HSV) infections is the ability to infect epithelial cells and then travel up the peripheral nerve to the

dorsal root ganglia where it may remain latent for years followed by reactivation.

CLINICAL PRESENTATION

Herpes simplex is characterized by recurrent, painful, vesicular lesions of the lips, genitalia, hands, rectum, or eyes. The lesions of herpes simplex are typically tightly clustered vesicles on an erythematous base and evolve into pustules and erosions over 5 to 7 days. Grouped, crusted erosions are the typical presentation. Associated symptoms may include fever, local pain, regional lymphadenopathy, fatigue, and malaise. Urinary retention occasionally occurs with genital lesions and generally requires hospital admission.

Primary lesions are usually more widespread with a bilateral distribution. Recurrent lesions typically are tightly clustered and unilateral and occur in the same location as previous episodes of infection. Recurrences are usually milder, involve fewer lesions, and heal faster. Approximately 50% of patients with recurrent lesions have a 24-hour prodrome of local itching, burning, tingling, and stinging. Precipitating factors for recurrence include stress, fever, infections, sunburn, menstruation, cosmetic facial procedures, dental interventions, or trauma.

Primary lesions usually resolve in 2 to 3 weeks, but the duration may be longer in immunocompromised patients. Typical sites of involvement are the oral, genital, and periorbital areas and the fingertips (herpetic whitlow), but any body area may be involved. Oral infections can cause gingivostomatitis, or pharyngitis. Herpetic whitlow is an infection of the pulp and lateral aspect of the finger. This may occur from autoinoculation with a primary oral or genital infection. With periorbital lesions, fluorescein staining of the cornea is necessary to identify dendritic lesions. Herpetic keratitis is the most common cause of corneal blindness and presents with pain, photophobia, and blurry vision. Patients with herpetic keratitis should be referred to an ophthalmologist. Herpes gladiatorum is contracted by athletes, especially wrestlers. It is transmitted by direct skin-to-skin contact and usually appears in the head and neck region.

With the increasing incidence of the acquired immunodeficiency syndrome and the growing use of bone marrow and solid organ transplantation, more severe manifestations of herpes infections are being seen (5). Neonatal herpes occurs when the virus is transmitted from an infected mother to the neonate, with the highest risk occurring when the mother has primary genital herpes during delivery. Along with the cutaneous lesions, the infected neonate may develop multiorgan involvement with high mortality rate. HSV vaccines are currently in early clinical trials.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of herpes simplex includes aphthous stomatitis; tinea cruris; hand, foot, and mouth disease; herpangina; and primary syphilis. Aphthous stomatitis consists of one or two painful lesions in the mouth, but they are not in a circumscribed area. Although early tinea, which is vesicular, can be difficult to distinguish from herpes, later tinea has central healing. Lesions in hand, foot, and mouth disease are asymptomatic. Herpangina lesions are found in the posterior oropharynx and not outside the mouth. The chancre in primary syphilis is classically painless and the borders are indurated.

ED EVALUATION

Diagnosis of herpes simplex is usually made clinically. Viral cultures of vesicular fluid or direct fluorescent antibody stain of scraped lesions may be helpful for definitive diagnosis. The presence of intranuclear inclusions and multinucleated giant cells on a Tzanck preparation supports a diagnosis of herpes infection but does not distinguish between HSV and varicella zoster virus. Polymerase chain reaction and serology testing are not widely available and are expensive. Point-of-care HSV-2 and HSV-2-LFIA rapid test kits are available. The 10-minute tests only require a few drops of blood from a finger stick to detect the presence of HSV-2 antibodies to confirm genital herpes diagnosis and also identify asymptomatic carriers. They do not detect HSV-1.

ED MANAGEMENT AND DISPOSITION

Acyclovir is the most widely used antiviral agent in clinical use. Treatment with 200 mg of oral acyclovir five times per day or 400 mg three times a day for 10 days is indicated for primary genital herpes. However, the duration of symptoms is decreased only minimally with this therapy and only if started within 24 hours after onset of the rash. Time for crusting decreases from 2.7 to 2.2 days. Other medications that are effective and available for treating herpetic infections are famciclovir and valacyclovir (Table 172.1). All three oral agents have been shown to reduce the frequency of symptomatic recurrences of genital herpes. Over-the-counter tetracaine cream (Viractin) may reduce healing time of recurrent herpes labialis by about 2 days. Topical penciclovir 1% cream (Denavir), which is more effective than acyclovir cream, can reduce average time to healing of recurrent orolabial HSV infections by 0.7 days and the duration of pain by 0.6 days (6).

TABLE 172.1
Treatment of Genital Herpes Simplex

Treatment of Genital Herpes Simplex	Primary Infection	Recurrent Lesions	Suppressive Therapy
Acyclovir	200 mg × 5 d OR 400 mg tid for 10 d	400 mg tid OR 800 mg bid for 5 d	400 mg bid for 12 mos
Famciclovir[a]	250 mg tid for 10 d	125 mg bid for 5 d	250 mg bid for 12 mos
Valacyclovir[a]	1 g bid for 10 d	500 mg bid for 3 d	1 g qd for 6–12 mos

[a]Reduction in dosage is recommended in patients with reduced renal function. Valacyclovir should not be prescribed in patients with HIV or transplant recipients because of the observation of TTP and hemolytic uremic syndrome. Famciclovir is contraindicated with Denavir.

In children with oralfacial or gingivostomatitis, generally, only supportive treatment with hydration and topical anesthetics (viscous lidocaine, diphenhydramine elixir) is needed. Importantly, patients receiving suppressive antiviral medication should be counseled that they may still transmit HSV to their sexual partners. Intravenous therapy (5 mg/kg every 8 hours) should be considered for patients with urinary retention, compromised immunity, or life-threatening disseminated infection.

Common Pitfalls

- Failure to instruct patients about measures to prevent transmission to others.
- Failure to admit patients with genital herpes and urinary retention.
- Failure to admit patients with disseminated infection.
- Failure to recognize herpetic whitlow and making an incision, which may lead to spread of infection.

HERPES ZOSTER

Herpes zoster (HZ) (shingles) results from the reactivation of a dormant varicella zoster virus that entered the dorsal root ganglia during an earlier episode of chicken pox. HZ can occur in patients of any age who have had a previous infection of varicella zoster virus. The incidence of HZ increases with age, peaking in the seventh decade. Reactivation factors include fever, wind, UV light, illness, or stress. An attack of HZ does not confer immunity, and it is not unusual to have two or three episodes in a lifetime.

CLINICAL PRESENTATION

HZ is characterized by unilateral vesicular eruption along one or two adjacent dermatomes that is associated with severe pain. Dermatomes T3–L3 are most frequently involved (Fig. 172.1). Occasionally, the lesions may extend beyond the midline. There is usually a prodrome of pain, itching, burning, and hyperesthesia in the same dermatome 4 to 7 days before the lesions appear. Fever, headache, and malaise along with lymphadenopathy may also precede the eruption. The pain may imitate myocardial infarction, appendicitis, renal colic, or migraine headache and may present a diagnostic dilemma until the characteristic rash develops. The eruption begins as an erythematous maculopapular rash that gives rise to vesicles containing purulent fluid. These pustules either umbilicate or rupture before forming crusts. The crusts fall off in 2 to 3 weeks.

FIGURE 172.1 Herpes zoster. Lesions can involve more than one dermatome. (Courtesy of Scott Sherman, MD.)

When the ophthalmic division of the trigeminal nerve is involved, HZ ophthalmicus results. Lesions can appear on the forehead, eyelid, and nose. Symptoms include headache, fever, malaise, and eye pain. Ocular involvement is common and each individual should have a thorough eye examination. Hutchinson sign (lesion at the tip of the nose) usually heralds ocular involvement. Urgent (next-day) ophthalmology referral is indicated. When the sensory branch of the facial nerve is involved, HZ oticus results. Lesions appear in the ear, mouth, face, neck, or scalp. Patients can complain of severe otalgia, vertigo, hearing loss, or loss of taste in the anterior two-thirds of the tongue. When associated with facial paralysis, the disease is called *Ramsay Hunt syndrome.* Treatment consists of acyclovir, corticosteroids, and diazepam for vertigo. Facial paralysis and hearing loss may be permanent. Patients should be referred to an ear, nose, and throat specialist urgently. Hospitalization should be considered in severe cases.

The severe pain associated with HZ is the principal reason that patients seek medical care. Traditionally, pain that is present while the rash persists or in the first 30 days from onset has been termed *acute pain.* Pain that is present after this period is termed *postherpetic neuralgia* (PHN) and may persist for months to years after lesions have disappeared. As age increases, the risk and duration of PHN also rise. Nearly half of the patients older than 60 years have this complication. Other complications of HZ include secondary bacterial infections, pneumonitis, and meningitis. HZ virus vaccine (Zostavax) is available for the prevention of shingles and PHN in persons 60 years or older.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes chemical burns, Bell's palsy, conjunctivitis, and trigeminal neuralgia. The blisters in poison ivy often occur in a linear "dermatomal," but they are painless.

ED EVALUATION

The diagnosis of HZ is based on history of pain and appearance of the dermatomal rash. Laboratory tests are not necessary. Scraping for a Tzanck smear or viral culture is usually negative, and a biopsy is usually required for definitive diagnosis. HZ ophthalmicus is diagnosed by slit lamp detection of corneal dendritic lesions.

ED MANAGEMENT AND DISPOSITION

A meta-analysis found that acyclovir reduces pain duration and prevalence, especially in patients 50 years of age or older (7). The recommended therapy is acyclovir 800 mg five times a day for 7 days. Famciclovir 500 mg or valacyclovir 1,000 mg tid for 7 days has also been shown to decrease the median duration of PHN (8,9). Treatment should be started within 72 hours to be effective. Symptomatic treatment with oral analgesics and Burow solution–soaked compresses three times a day is often helpful as well.

It is unclear whether adding prednisolone is beneficial (10). Corticosteroids do not change the incidence or duration of PHN, but they may improve the quality of life (time to return to usual activity,

cessation of use of analgesic agents, and time to return to uninterrupted sleep) in patients older than 50 years of age with acute HZ (11,12). A tapering dose of 60 mg/day for 7 days, then 30 mg/day for 7 days, then 15 mg/day for 7 days can be used. Relative contraindications to the use of corticosteroids include hypertension, renal insufficiency, diabetes, osteoporosis, and peptic ulcer disease. The incidence of adverse effects is higher in patients treated with corticosteroids.

The treatment of PHN includes analgesics (oxycodone), lidocaine patches, tricyclic antidepressants, (nortriptyline), and gabapentin. Lidocaine patches are very effective and should be applied to the skin rash along the affected dermatome. A referral to a pain specialist may be necessary.

Ophthalmologic consultation is indicated if the ophthalmic division of the trigeminal nerve is involved. Dissemination beyond the original dermatomes should raise the suspicion of immunodeficiency. Immunocompromised patients with severe disease should receive acyclovir 10 to 12 mg/kg IV infused over 1 hour every 8 hours. If lesions persist or there is concern for acyclovir resistance, consider foscarnet 40 mg/kg IV every 8 hours.

Hospital employees who are exposed to patients with HZ should be tested for antibody to the varicella zoster virus. Isolation for 8 to 21 days after exposure is recommended when antibody is not detected. If antibody is present, isolation is unnecessary (13). Varicella zoster immune globulin (VZIG) is recommended within 72 hours for exposed immunocompromised contacts.

Common Pitfalls

- Failure to instruct patients about measures to prevent transmission. Patients with HZ can transmit the virus as chickenpox to persons who have not already been infected.
- Failure to recognize a central cause of facial paralysis.
- Failure to recognize and treat ocular involvement.
- Failure to recognize or admit immunocompromised individuals.

ALLERGIC CONTACT DERMATITIS

Because allergic contact dermatitis is a result of delayed hypersensitivity, skin lesions may appear hours to days after exposure to the offending antigen, and it is often difficult to identify the antigen. Commonly identified etiologic agents include poison ivy, oak, and sumac; soaps; detergents; and perfumes. Pruritus is the initial symptom, which is quickly followed by erythema and vesiculation. Areas with a thin stratum corneum (such as eyelids and genitalia) may swell severely. Without treatment, symptoms may persist for 2 to 3 weeks.

Mild contact dermatitis may be treated with topical corticosteroids. For severe cases, oral prednisone (40 to 60 mg/day for 7 days) accelerates resolution of symptoms (usually within 24 to 48 hours) and poses minimal risks of adverse effects.

FIXED DRUG ERUPTION

Like HSV, fixed drug eruption causes recurrent episodes of skin lesions in one location. Unlike herpes simplex, however, fixed drug eruption generally leaves persistent slate gray to brown hyperpigmentation after the attack resolves. The most commonly implicated drugs include phenolphthalein (e.g., Ex-Lax, Feen-A-Mint), tetracycline, sulfa, and barbiturates. Symptoms usually arise 1 to 2 days after ingestion. Pruritus generally occurs first, followed by the appearance of clusters of vesicles or bullae in a hyperpigmented macule. The process resolves in 2 to 3 weeks, after discontinuation of the offending agents.

OTHER CAUSES OF VESICULAR ERUPTIONS

Dyshidrotic eczema (pompholyx) usually occurs on the medial and lateral aspects of the fingers and sometimes on the palms and soles. It is intensely pruritic and responds to topical corticosteroids. If severe, oral steroids can be used.

The vesicular eruption of tinea pedis may usually be diagnosed clinically by potassium hydroxide staining of vesicle fluid. Treatment is with a topical antifungal agent such as clotrimazole.

Accompanying involvement of the hands is often an eczematous reaction.

Atopic dermatitis is generally accompanied by a personal or family history of eczema, allergic rhinitis, asthma, or urticaria. Nonetheless, the eruption is usually precipitated by physical irritation (wool gloves, soap, and water) or emotional stress. Treatment with topical steroids is effective.

Dermatitis herpetiformis (unrelated to the herpes viruses) may be confused with scabies or neurotic excoriations. It generally presents with broken, excoriated vesicles on an erythematous base. It usually begins on extensor surfaces and is pruritic. Treatment is with dapsone and oral antihistamines.

INDIVIDUAL OR DISSEMINATED VESICLES

Varicella

Varicella (chickenpox) is primarily a disease of childhood, but it is not uncommon in adults. It is acquired by direct contact with infected lesions or inhalation of airborne droplets. Varicella begins with replication of the virus at the sites of contact and is followed by the development of a primary viremia, which establishes replication in the reticuloendothelial system. A secondary viremia occurs after 1 week, which disseminates the infection to the skin. The virus then establishes latency in the sensory ganglion. Reactivation of the latent infection causes HZ.

CLINICAL PRESENTATION

Varicella presents with a rash, low-grade fever, and malaise. The lesions start as erythematous macules, progress to vesiculation with the classic “dew drop on a rose petal” appearance, become pustules, and finally crust over (Fig. 172.2). The hallmark of varicella rash is the simultaneous presence of lesions in all stages of development. The lesions usually appear on the trunk and face and then spread to other areas of the body, including scalp, mouth, ears, and genitalia. They are intensely pruritic. There may be a history of exposure 10 to 14 days before the rash. Varicella is highly contagious. Second attack

rates for this virus may reach 90% for susceptible household contacts. Patients are considered infectious 2 days before the appearance of the rash until all vesicles have formed crusts, which is usually 5 to 6 days after the first appearance of the eruption. The severity of the illness varies from individual to individual and is inversely related to age. An attack of chickenpox usually confers lifelong immunity, although secondary attacks can happen. Varicella vaccine is now available in the United States and is approved for children and adults.

FIGURE 172.2 Varicella. The lesion starts as a 2- to 4-mm red papule, then develops into an irregular outline (rose petal) as a thin clear vesicle appears on the surface (dewdrop).

Varicella is usually a benign illness in immunocompetent patients. Immunocompromised individuals or those using immunosuppressive drugs, especially systemic corticosteroids, are at a greater risk for complications (14). The most common complication in children is secondary bacterial skin infections after scratching, leading to a cellulitis. Varicella pneumonitis is rare in children but is the most common serious complication in adults. It can present with

tachypnea, cough, fever, and pleuritic chest pain leading to acute respiratory distress syndrome. Other complications include hepatitis, nephritis, orchitis, and encephalitis. Encephalitis in children is usually self-limited and includes cerebellar ataxia, nystagmus, and headache. Adult encephalitis has a mortality rate of 35% (15). Reye syndrome is an encephalopathy with fatty liver and is associated with salicylate use. Twenty to 30% of Reye syndrome cases are preceded by varicella (16).

Varicella during pregnancy poses a risk to both mother and child. The highest risk for fetal varicella syndrome is between 13 to 20 weeks of gestation. It is characterized by small infant size, cicatricial skin lesions, limb hypoplasia, and other anomalies. For newborns, the risk of infection and complications is greatest when the mother develops chickenpox 5 days before to 2 days after delivery. These infants have an increased chance of dissemination as they lack both maternal antibodies and a mature immune system. They should be given VZIG. VZIG is effective in preventing chickenpox in exposed susceptible, especially immunocompromised individuals (Table 172.2).

TABLE 172.2
Varicella Zoster Immune Globulin Indications

Immunocompromised children
Newborns whose mother had varicella 5 d before to 2 d after delivery
Infants exposed in nursery
All premature infants <28 wks
Susceptible pregnant women
Healthy or immunocompromised adolescents and adults who are unvaccinated and susceptible postexposure prophylaxis[a]

[a]Administration may prevent or reduce intensity of disease. It is not indicated once clinical disease has developed. VZIG may be administered within 96 hr after exposure.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes disseminated zoster, disseminated herpes simplex, eczema herpeticum, and folliculitis.

ED EVALUATION

Diagnosis is usually made clinically. Laboratory tests are not necessary. A Tzanck smear and viral culture may aid in making the diagnosis. A chest x-ray should be obtained if respiratory symptoms develop. A lumbar puncture is needed if encephalitis is suspected.

ED MANAGEMENT AND DISPOSITION

Treatment of varicella in healthy children is optional because the disease is self-limited. Symptoms can be managed with supportive care consisting of daily baths and soaks to destroy the virus. Close cropping of the fingernails, calamine lotion, and antihistamines to avoid excessive excoriations can provide relief. Isolate the patient, especially from immunocompromised hosts. Aspirin and Caladryl lotion, which can lead to an anticholinergic response from excessive skin absorption, should be avoided. Acyclovir should be considered in children up to age 12 who are being treated with corticosteroids or long-term salicylate therapy, or those with chronic cutaneous or pulmonary diseases (17). Acyclovir, if started within 24 hours of rash development, has been shown to reduce the number of lesions, the duration of fever, and pruritus. Treatment after the first day of illness is of no value in uncomplicated cases of varicella (18). All immunocompromised individuals with varicella should be hospitalized for intravenous acyclovir (Table 172.3). Hospitalization is also required for skin sepsis, pneumonitis, dense or hemorrhagic rash, and bleeding.

TABLE 172.3
Treatment of Varicella

Acyclovir—adults—800 mg 5×/d for 7 d
13–18-yr-olds—20 mg/kg/dose PO qid for 7 d
Peds—20 mg/kg/suspension PO qid for 5 d (max. 800 mg PO qid)
Immunocompromised—10 mg/kg IV q8hr slowly over 1 hr[a]
Famciclovir—500 mg PO tid for 5–7 d[b]
Valcyclovir—1,000 mg PO tid for 5–7 d[b]

[a]With rapid IV injection, acyclovir crystals may precipitate in the collecting ducts causing renal toxicity, therefore infuse slowly over 1 hr and maintain adequate hydration.
[b]Famciclovir and Valcyclovir have not been evaluated in children.

COXSACKIEVIRUS AND ECHOVIRUS INFECTIONS

Coxsackievirus and echovirus infections may cause papulovesicular lesions that are evenly spread across the face and torso. Associated symptoms may include fatigue, malaise, fever, vomiting, and diarrhea. Resolution occurs spontaneously in 10 to 14 days, and treatment is symptomatic.

Hand, foot, and mouth disease caused by coxsackieviruses presents with tender, flat-topped, whitish vesicles 3 to 4 mm in diameter on the palms and soles and in the mouth. It is commonly associated with mild systemic complaints. The duration is generally 4 to 5 days and no treatment is necessary.

INSECT BITES

Vesiculobullous skin lesions may occur as hypersensitivity reactions to insect bites, commonly those of fleas, bedbugs, and mites. A clue to the diagnosis is a linear or grouped pattern of lesions; some may have central puncta. Treatment is with topical corticosteroids and oral antihistamines, and avoidance of further contact with the insect.

CRITICAL INTERVENTIONS

- Initiate acyclovir within 24 hours of the onset of rash in adult varicella and within 72 hours of onset of HZ.
- Obtain ophthalmology consult for patients with herpetic keratitis due to herpes simplex or with involvement of the ophthalmic division of the trigeminal nerve in HZ.

Common Pitfalls

- Failure to instruct patients about measures to prevent transmission of varicella.
- Failure to admit immunocompromised patients with varicella.

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CHAPTER 173

Purpuric Eruptions

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The term *purpura* (Latin meaning “purple”) refers to any skin or mucous membrane eruption resulting from bleeding into the skin. The defining characteristic of purpuric lesions is the absence of blanching, whereas color persists with compression.

Broadly speaking, purpura may result from abnormalities in primary or secondary hemostasis (thrombocytopenia, abnormal platelet function, clotting factor deficiency, abnormal clotting factor function) or disruptions in vascular integrity (trauma, infection, vasculitis, medications, collagen disorders). Deficiencies in platelet number or function are a far more common cause of purpuric skin lesions than are defects or deficiency of a single procoagulant clotting factor (1).

The etiologies of purpura are extensive and range from the trivial (e.g., actinic purpura in the elderly, “bruises” secondary to minor trauma) to the life-threatening (e.g., meningococcemia, thrombotic thrombocytopenic purpura [TTP]) (Table 173.1). Rapid differentiation of benign from potentially serious causes of purpura is essential, as it allows for the initiation of emergent treatments where indicated while minimizing unnecessary evaluation.

TABLE 173.1
Causes of Purpura by Morphologic Characteristics

Nonpalpable Purpura

Thrombocytopenia

- Decreased platelet production (bone marrow disorders): irradiations, medications (**Table 173.2**), bone marrow failure, neoplasm
- Increased platelet destruction: immune-mediated (ITP, SLE, CLL, HIV, medications), posttransfusion, neonatal, nonimmune (consumptive coagulopathies, DIC, TTP, HUS, purpura fulminans, artificial surfaces)
- Platelet sequestration: hypersplenism, hypothermia

Abnormal platelet function

- Congenital platelet function defects
- Acquired platelet function defects: medications (see Table173.2), renal/hepatic insufficiency

Mechanical purpura

- Local trauma
- Increased hydrostatic pressure: suction, CPR, high altitude, Valsalva, ligature, strangulation

Factitious purpura

- Self-abuse: Munchhausen's disease, religious stigmata, Gardner-Diamond syndrome

Disorders of vascular connective tissue

- Actinic (senile) purpura
- Metabolic purpura: scurvy, corticosteroid use
- Connective tissue syndromes: Ehlers–Danlos syndrome, osteogenesis imperfecta, Marfan syndrome

Pigmented purpuric disease

Nonpalpable or Palpable

Infectious (3,4)

- Bacterial: Neisseria, Haemophilus, Streptococcus, Rickettsia, Bordetella, Capnocytophaga, Brucella (5)
- Viral: enterovirus, coxsackie, respiratory syncytial virus, rubella, measles, ECHO virus, hepatitis A, hepatitis B, parvovirus B19, cytomegalovirus, varicella, viral hemorrhagic fevers
- Fungal: Candida, Trichosporon
- Protozoal: strongyloides, malaria

Palpable

Dysproteinemias

- Waldenström macroglobulinemia
- Cryoglobulinemia, cryofibrinogenemia

Purpura fulminans

- Warfarin-induced skin necrosis
- Protein C or protein S deficiency
- DIC
- Severe infections such as meningococcemia

Vasculitides

- Hypersensitivity vasculitis: Henoch-Schönlein and other allergic purpuras, collagen vascular disorders, infections (e.g., streptococcus, hepatitis B, cytomegalovirus, Epstein–Barr virus), dysgammaglobulinemias, malignant neoplasms, cryoglobulinemia, serum sickness
- Granulomatous vasculitis: Wegener, giant cell

Microvascular occlusion

- Platelet plugs
- Cholesterol embolization
- Embolus from atrial myxoma, septic or marantic endocarditis
- Hemoglobinopathy occlusion

SLE, systemic lupus erythematosus; CLL, chronic lymphocytic leukemia; DIC, disseminated intravascular coagulation; HUS, hemolytic uremic syndrome.

CLINICAL PRESENTATION

Patients with purpura may present to the emergency department due to concern about the rash itself or because of symptoms accompanying the rash. Regardless of the appearance of the rash or associated symptoms and signs, the presence of spontaneous bleeding ("wet" purpura) is a grave sign requiring immediate intervention (2). The cause is usually thrombocytopenia, and the emergent treatment is platelet transfusion. The immediate threat to life is intracranial hemorrhage (2). Severe anemia and shock from blood loss are possible but not common.

Patients without spontaneous bleeding ("dry" purpura) may have extensive petechiae or ecchymoses on the skin but are in less immediate danger. However, spontaneous bleeding may develop at any time, so rapid determination of the cause is still indicated.

Purpuric lesions vary in color, size, consistency, shape, associated erythema, and distribution. These morphologic variations may provide clues to the etiology of the lesions. Purpuric lesions must have a shade of color consistent with hemorrhage. Lesions may be red, blue, purple, yellow-brown, green, or black (1). Lesions are classified by their varying sizes. Lesions <3 mm are termed *petechiae,* whereas lesions >3 mm are termed *purpura* (3). Lesions >1 cm in diameter are termed *ecchymoses* (1). They may be flat and nonpalpable or raised and palpable, with a round or a retiform (branching) shape. Associated erythema may be prominent or absent. The distribution may be localized or generalized. Purpura may appear with a variety of other lesions, depending on the underlying cause and stage of development.

DIFFERENTIAL DIAGNOSIS

The etiologies of purpura are extensive and they encompass hematologic, dermatologic, infectious, traumatic, and rheumatologic entities (see Table 173.1) (1). In addition, purpura may be caused by a variety of drugs, which can cause small-vessel or platelet

disorders by direct toxicity, inhibition of function, or immune-mediated mechanisms (Table 173.2) (6,7).

TABLE 173.2
Drugs Causing Purpura

Analgesics	
	Acetylsalicylic acid, acetaminophen, nonsteroidal anti-inflammatory drugs, codeine
Antibiotics	
	Antituberculous agents, penicillins, sulfonamides, chloramphenicol, nitrofurantoin, tetracyclines, erythromycin, cephalosporins, aminoglycosides, streptomycin
Anticonvulsants	
	Barbiturates, carbamazepine, diphenylhydantoin, primidone, valproate sodium, lamotrigine
Antihypertensives	
	Methyldopa, reserpine
Anticoagulants	
	Coumadin, heparin, GIIB/IIIa inhibitors
Cardiovascular agents	
	Atropine, quinidine, digitalis, nitroglycerin, propranolol, acenocoumarol
Antirheumatics	
	NSAIDs, gold, corticosteroids, sulfasalazine
Diuretics	
	Thiazides, furosemide, spironolactone
Hypoglycemics	
	Tolbutamide, chlorpropamide, metformin
Sedatives–hypnotics	
	Meprobamate, phenobarbital, chlordiazepoxide
Antipsychotics, antidepressants	
	Tricyclic antidepressants, phenothiazines
Miscellaneous	
	Metoclopramide, antimetabolites, chemotherapeutic agents, ethanol, allopurinol, estrogens, oral contraceptive pills, heroin, quinine, hydroxychloroquine, antihistamines, guaifenesin, clofibrate, chlorpheniramine, arsenicals, cimetidine, griseofulvin, iodides, dextroamphetamine, bismuth, organic hair dyes, menthol, insecticides, benzene, metal compounds

The lesions of purpura are characteristic and difficult to mistake for other types of lesions. Other erythematous rashes, such as viral

exanthems and urticaria, can be differentiated from purpura by their light-red color, and in that they blanch with pressure. Similarly, telangiectases and hemangiomata are discrete collections of abnormally dilated blood vessels that appear bright red and usually blanch with pressure. Diascopy, the use of a glass slide to apply pressure over a lesion, is a simple visual method to differentiate lesions due to vascular dilation (which blanch with pressure) from those due to purpura (which do not).

Some lesions are purpuric but do not reflect an underlying illness, and are sometimes classified as mechanical or factitial purpura (3). Purpuric lesions may be created by trauma or increased hydrostatic pressure in normal skin. Examples of mechanisms potentially resulting in purpuric lesions are self-inflicted trauma, forceful or protracted vomiting or sneezing, strangulation, suction, and coining (3,8).

ED EVALUATION

The initial focus of the emergency department evaluation of purpura is to identify and initiate treatment of any life-threatening disorders. Empiric, potentially life-saving treatments (e.g., platelet transfusion or intravenous antibiotics) should be initiated based on the presumptive diagnosis and preliminary laboratory results without awaiting definitive diagnosis. Intracranial hemorrhage should be considered in any patient presenting with purpura associated with neurologic abnormalities, and emergent treatment, usually with platelet transfusion, should be initiated. Meningitis and/or meningococcemia are suggested by purpura associated with fever, altered mental status, headache, neck stiffness, or systemic toxicity, and require emergent resuscitation and treatment with antibiotics. While the initial rash associated with meningococcal infection may be a maculopapular eruption resembling a wide variety of viral exanthems, more than 50% of patients have petechiae or purpura upon presentation (9,10). Active bleeding or wet purpura should likewise be considered a dermatohematologic emergency. Attention should be paid to the presence of bleeding gums, epistaxis,

intraocular hemorrhage, guaiac-positive stool, menorrhagia, or hematuria. Marked thrombocytopenia is almost universally the cause of wet purpura, and platelet transfusion should not be delayed while awaiting laboratory confirmation when bleeding is significant.

In patients presenting with purpura without signs or symptoms of a life-threatening emergency, evaluation should be pursued to elucidate the cause of the purpura. A directed patient history should include recent infections, recent medication or drug ingestion, irradiation or chemical exposure, and systemic symptoms. History of abnormal or spontaneous bleeding (frequent epistaxis, bleeding after dental or other minor procedures, menorrhagia, etc.) should be elicited. Questions relating to hepatic, renal, rheumatologic, or hematologic disease, malignancy, immunosuppression, or human immunodeficiency virus (HIV) infection are also pertinent. A complete list of medications and allergies should be obtained. Except for hereditary coagulation disorders, which rarely present as purpura, and rare hereditary thrombocytopenias, the family history is usually unremarkable. The social history should include questions regarding alcohol and drug use and risk factors for HIV.

Initial physical examination should pay particular attention to markers of serious systemic illness such as fever and other vital sign abnormalities, altered mental status, meningismus, or active bleeding.

Characterization of the purpuric lesions may provide clues to etiology. The distribution of the lesions may suggest specific disease processes. Senile or actinic purpura occurs on sun-exposed areas, usually the forearms, of elderly patients. Vasculitic purpura is usually symmetric and predominates in the lower extremities (e.g., Henoch-Schönlein purpura) (Fig. 173.1). A more generalized distribution of discrete petechiae may be noted when purpura is associated with bacterial illness such as meningococcemia or subacute bacterial endocarditis. Purpuric lesions in thrombocytopenia tend to occur in areas of minor trauma or areas of pressure, such as the belt line or over bony prominences. The purpura of scurvy classically appears as perifollicular petechiae, whereas that of Rocky Mountain spotted fever begins over the distal

joints and spreads centrally. The lesions of purpura fulminans are large, symmetric ecchymoses of the lower extremities and buttocks, often with infarcted areas or bullae.

FIGURE 173.1 Henoch-Schönlein purpura. (Courtesy of Dr. Sate Hazma, dermatopathology fellow, University of Birmingham, and Dr. Amy Theos, Assistant Professor, Department of Dermatology, University of Alabama at Birmingham.)

Lesions may be categorized into groups of likely diagnosis based on size, palpability, morphology, and the associated erythema (1,3). Nonpalpable purpuric lesions result primarily from a decrease in the number of functioning platelets or from mechanical insults to the vascular barrier. Nonpalpable purpuric lesions >1 cm may be caused by major trauma or minor trauma coupled with a procoagulant defect or poor dermal vessel support (1). Palpability results from edema, which most commonly results from inflammation, but also may be seen with microvascular occlusion and ischemia (1). Erythema is usually present with inflammation and absent with microvascular occlusion and ischemia.

When bacterial infections cause purpura, the lesions may have a central purulent papule (e.g., disseminated gonococcemia). Immune-

mediated vasculitides often have lesions of erythema, bullae, or urticaria in association with palpable purpura. Coumadin-associated vasculopathy may result in necrotizing ecchymoses.

The physical examination may further reveal specific abnormalities in certain causes of purpura. In thrombocytopenia, the optic fundi and mucous membranes may show petechiae. Painful joint effusions may accompany various types of immune-mediated purpura, disseminated gonococcemia, and coagulation disorders. Lymphadenopathy or lesions characteristic of Kaposi sarcoma may be indicators of HIV seropositivity, which may present with purpura in up to 9% of cases (11). Lymphadenopathy may also be found in patients with lymphoma, infectious mononucleosis, and leukemia. Splenomegaly (as well as other forms of hypersplenism) may also be noted in these same illnesses but is absent in most other types of thrombocytopenic purpura (e.g., idiopathic thrombocytopenic purpura) and coagulation defects (1).

All but trivial causes of purpura (e.g., actinic, mechanical, factitial) require laboratory studies to elucidate the underlying cause. As thrombocytopenia is the most common cause of clinically significant purpura, a platelet count is a required component of initial testing. Easy bruising may be noted with platelet counts of 30,000 to 50,000/μL, whereas spontaneous ecchymoses or petechiae usually do not appear until the platelet count is less than 30,000/μL. Internal bleeding, including intracranial hemorrhage, rarely occurs with platelet counts $>$10,000/μL (12). For example, in a study of patients with thrombocytopenia secondary to immune thrombocytopenia (ITP), minimal bleeding after trauma was uncommon unless the platelet count was less than 60,000/μL, whereas self-limited bleeding, spontaneous bleeding requiring intervention (e.g., nasal packing for epistaxis), and severe life-threatening bleeding did not occur until platelet counts were $<$40,000, $<$12,000, and $<$6,000/μL, respectively (13).

A complete blood count with differential serves as a screen for anemias, bone marrow disorders, various malignancies and infection. The peripheral blood smear screens for abnormal red blood cell and platelet morphology which may be indicative of

hemolysis and various platelet abnormalities, respectively. Prothrombin time and activated partial thromboplastin time screen for coagulation or mixed platelet and/or coagulation disorders (14,15). Determination of bleeding time may be of limited use in the emergency department in confirming platelet dysfunction or vascular disorders. The fibrinogen level, along with fibrin–fibrinogen degradation products (FDP, D-dimer), may also be useful (14). Because therapy with blood products is sometimes necessary and their use may confound subsequent diagnosis, extra tubes for type and screen and for other platelet and coagulation assays should be obtained before treatment.

On subsequent (usually inpatient) evaluation, the following tests may be indicated, depending on the suspected etiology: bone marrow aspiration, skin biopsy, bleeding time, autoimmune disease screening tests, clotting factor assays, and platelet function tests (15).

KEY TESTING

- CBC
- PT/INR, PTT
- Peripheral blood smear
- Fibrinogen level, fibrin degradation products
- D-dimer

ED MANAGEMENT

First, life-threatening complications of spontaneous bleeding should be stabilized, and efforts should be made to ascertain the cause of purpura. As described, the history, physical examination, and laboratory studies should allow rapid determination of the category of illness causing the purpura and associated symptoms.

When thrombocytopenia is the cause of purpura, platelet transfusion should be considered only when there is evidence of abnormal bleeding. Generally, each unit of platelets may be expected to raise the platelet count by about 5,000 to 10,000/μL (16). Spontaneous mucous membrane or CNS bleeding can usually

be controlled when the platelet count is restored to more than 20,000/μL. Platelet transfusion is relatively contraindicated in disorders caused by intravascular thrombosis such as TTP because platelets may contribute to further thrombosis. In TTP, plasma exchange is the only treatment for which there is firm data on its effectiveness (17). When immune-mediated thrombocytopenia is likely, as in immune thrombocytopenic purpura or posttransfusion purpura, the half-life of transfused platelets is short (hours) compared with that for other disorders (days) (2). In these cases, alternative therapy, such as corticosteroids, immunoglobulins, or splenectomy may eventually be indicated (12,18).

Coagulopathies presenting with spontaneous bleeding may be treated by replacement of specific coagulation factors. In acquired coagulopathies from coumadin or liver disease, vitamin K is indicated. Fresh frozen plasma may be helpful in a variety of coagulopathies and thrombolytic disorders when specific factor replacement is not available or cannot be determined (19).

If purpura is thought to be due to a drug (Table 173.2) regardless of the suspected mechanism, that drug should be discontinued. Anticoagulants or platelet inhibitors (in proper dosages) may be reinstituted, if indicated, when the disorder is controlled.

Specific therapy directed to underlying disorders should be initiated once the etiologic factors have been defined and a diagnosis established.

CRITICAL INTERVENTIONS

- Intervene immediately with the combination of purpura and spontaneous bleeding (wet purpura).
- Intracranial hemorrhage should be considered in patients presenting with purpura and associated neurologic symptoms.
- Meningococcemia and/or meningitis suggested by purpura associated with fever, altered mental status, meningismus, or systemic toxicity represent a life-threatening emergency requiring immediate treatment.

DISPOSITION

Because purpura may reflect hematologic, rheumatologic, traumatic, or infectious disorders, consultation is obtained from appropriate specialists once trivial causes of purpura have been excluded. When the diagnosis is unclear, a dermatology consultation is warranted. Because the underlying disorders that are responsible for purpura often have the potential for progressing to life-threatening emergencies, patients with purpura are often admitted to the hospital for confirmation of the diagnosis and definitive treatment. Patients presenting with spontaneous bleeding or life-threatening complications, such as CNS hemorrhage or septic shock, require immediate hospital admission, usually to an intensive care unit.

Emergency transfer of patients with life-threatening complications of purpuric illness is indicated when the needed blood products, specialty consultation, or level of care are not available. Stabilization with intravenous fluids and emergently indicated blood products (when available) should be accomplished before transfer, after consultation with the accepting physician. Patients whose illness may progress rapidly should be considered for air ambulance transfer when ground transport times would be prolonged.

Common Pitfalls

- Failure to recognize the signs and symptoms of emergent conditions associated with purpura, such as intracranial hemorrhage and serious bacterial infections, may result in devastating delays in treatment.
- Failure to consider the trivial causes of purpura may result in unnecessary time and expense spent in pursuing a diagnostic workup.
- Drugs are a common cause of purpura and, unless an adequate history of drug exposure is obtained, the causal agent may initially be missed.
- Dismissing associated mucous membrane or spontaneous bleeding (wet purpura) may result in delay in therapy (usually

platelet transfusion) and increased risk of life-threatening hemorrhage.
- Premature administration of drugs or blood products may delay laboratory diagnosis, and in some cases, may worsen the disease process responsible for the purpura.

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CHAPTER 174
Urticaria

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Urticaria, or hives, is a commonly occurring vascular reaction of the superficial dermis of the skin resulting in pruritic wheals that form in response to a triggering stimulus. *Acute* urticaria is characterized by symptomatic attacks lasting less than 6 weeks and *chronic* urticaria is characterized by attacks that last 6 weeks or longer, with episodes of the latter tending to be less frequent and less severe than the former. One of the most common skin lesions seen in emergency medicine, urticaria can occur in any age group, but children and young adults are more commonly affected. In a majority of cases, a trigger cannot be determined (1).

The etiologies of urticaria are extensive and complex in nature (2). Generally, they may be broken down into several broad categories based on their underlying pathophysiology (Table 174.1). In most cases, however, the cause of urticaria is primarily mast cell degranulation, which releases histamine as well as a wide array of vasoactive peptides. The released histamine binds to receptors (predominantly H_1) in the microvasculature, especially the postcapillary venules, causing superficial local edema (wheals) and vasodilation (flare). Histamine also binds to H_1 receptors in the histamine-selective (itch-specific) C nerve fibers, making them more irritable and causing pruritus. In many cases, this reaction is allergic in nature and mediated by IgE, following prior sensitization (type I hypersensitivity), but degranulation can also occur by other immunologic and nonimmunologic routes (3,4). Histologically, urticaria involves only the superficial dermis, distinguishing it from

angioedema, which involves the deeper dermis. Perivascular lymphocytic and mast cell infiltration are also features.

TABLE 174.1
Classification of Urticaria

Allergic	Autoimmune
Food	Hormonal
Most drugs	Psychosomatic
Insect bites and stings	Physical
Contact urticaria	Dermographism
Pseudoallergic	Cholinergic
Aspirin and NSAIDs	Solar
Dyes and food additives	Delayed pressure
Irritant	Aquagenic
Plants	Vibratory
Opioids	Cold
Infection	Idiopathic
Viral	
Bacterial	
Parasitic	

NSAID, nonsteroidal anti-inflammatory drug.

It should be noted that type I hypersensitivity occurs in two phases —the immediate reaction, which occurs within the first hour after antigen challenge, and the late phase, which occurs several hours later, usually peaking at 3 to 9 hours. The late phase is not always noticeable, and the delay time, severity, and duration are variable and depend on the allergen dose. This late phase is due to continued synthesis and release of vasoactive substances by mast cells and can produce much more involved and long-lasting edema than the immediate wheals.

High-quality estimates of the prevalence of either acute or chronic urticaria are lacking. A recent survey conducted in Germany showed an 8.8% (95% CI 7.9% to 9.7%) lifetime prevalence for urticaria of any type and a 1.8% (95% CI 0.6% to 1.1%) lifetime prevalence for chronic urticaria (5). Chronic urticaria in this population afflicted women (70.3%) more than men. Chronic urticaria is also notable for

being diagnosed later in life, most often in the third or fourth decade.

CLINICAL PRESENTATION

Urticaria is characterized by slightly raised, sharply defined, erythematous, blanching wheals. They are typically pruritic, though usually nontender. The wheals may appear anywhere on the body and are often localized to the site of irritation but can cover large areas of the body with systemic triggers such as food allergies. The color of the wheals ranges from pink to red and central clearing may be present. The shape can be round, ovoid, or ring like, commonly with serpiginous borders, and multiple wheals may be aggregated into large plaques, giving an irregular appearance. Wheal size can range from a few millimeters to plaques that cover significant regions of the body. One of the hallmarks of urticaria is that the affected region can change size and new areas may become affected over time. Individual wheals typically last less than 8 to 12 hours; a longer persistence suggests urticarial vasculitis or delayed pressure urticaria (see below).

Table 174.2 summarizes the types and triggers of urticaria. Foods and drugs are the most common causes of acute urticaria. They act through both immunologic and nonimmunologic mechanisms (6). Among foods, nuts, berries, shellfish, chocolate, fish, tomatoes, and eggs are frequent causes of acute urticaria. In urticaria of chronic duration, milk, cereals, beef, pork, cheese, garlic, onions, and spices may be responsible. Food additives, both natural and synthetic, are also important etiologic factors. Reaction timing can be anywhere from within minutes of ingestion to many hours later. Worthy of particular mention is scombroid poisoning (7), which is a type of food poisoning that is classically associated with the *scombridae* family of fish such as mackerel and tuna, but can be caused by many other species. These fish contain large quantities of the amino acid histidine in their muscle tissue, which is converted to histamine by bacterial histamine decarboxylase in improperly stored fish.

TABLE 174.2
Agents Known to Cause Urticaria

Medications
Aspirin, NSAIDs
Antibiotics, particularly penicillin and other β-lactams
Iodides
IV contrast dyes
Many other drugs
Foods
Dairy products
Eggs
Wheat
Legumes (including peanuts and soy)
Tree nuts
Seafood (fish, molluscs, crustaceans)
Fruits (particularly berries)
Environment
Dander
Dust
Molds
Contact
Latex
Nickel
Cosmetics and lotions
Household cleansers
Soaps and shampoos

NSAID, nonsteroidal anti-inflammatory drug.

Many medications have the potential to cause an allergic response and should always be considered as a possible cause of urticaria. Antibiotics, particularly the β-lactams, and aspirin/NSAIDs are the most common drugs that cause urticaria, with aspirin and NSAID intolerance having been identified in 20% to 40% of patients with chronic urticaria. Urticaria may occur from 15 minutes to 24 hours (average 1 to 4 hours) after aspirin ingestion. The condition usually resolves within a day or two but may last up to 2 weeks. The pathogenic mechanism of aspirin intolerance is unclear, but a likely hypothesis is that mast cell degranulation is due to rapid PGE_2

depletion by drugs capable of inhibiting COX-1 and is not an allergic reaction. It usually appears in the third decade of life and is often accompanied by wheezing, increased bronchial secretions, rhinorrhea, and flushing (8).

With physical urticaria, wheals and itching develop at sites of a physical stimulus (9). Urticaria factitia or dermatographism is defined as a whealing reaction of the skin within 10 minutes of stroking or scratching the skin. Clinically, dermatographism occurs within seconds after stimulation and fades within 30 minutes. It is often a response to contact with seatbelts or brassieres. In contrast to dermatographism, delayed pressure urticaria is a response to more sustained physical pressure applied to the skin (10). It produces itchy, often painful wheals. These lesions can be delayed up to 12 hours and may last several days. Common causes are tight-fitting garments, prolonged walking (feet), or sitting (buttocks).

Cholinergic urticaria is characterized by pruritic, follicular-bound, 1- to 4-mm wheals surrounded by a red flare and produced within 15 minutes of a stimulus. Exercise, hot baths, spicy food, and emotional stress can precipitate episodes of cholinergic urticaria, which usually begins on the upper thorax and neck before spreading to the entire body, often sparing the palms and soles. The exact pathophysiology is unclear but may involve an autoimmune reaction to a sweat antigen. Clinically, patients can present with varied symptoms, including lacrimation, salivation, diarrhea, abdominal pain, weakness, flushing, and headache. Rarely, severe, life-threatening symptoms (e.g., angioedema, bronchospasm, vascular collapse, and hypotension) can occur.

Solar urticaria presents as a whealing response within 10 minutes in skin exposed to ultraviolet or visible irradiation from any source, though UVA is most commonly implicated. In addition to hives, symptoms may include wheezing, dizziness, and (rarely) hypotension; all resolve within 1 to 3 hours after the light stimulus is removed (11).

Cold urticaria occurs on exposed areas, such as the face and hands, and is commonly induced by swimming. It occurs within minutes of exposure, usually during rewarming, and can be elicited by placing

an ice cube on the skin, holding cold objects in the hand, or drinking cold fluids (leading to lip swelling). It also may be associated with other symptoms, including syncope and shock.

Other physical urticarias include generalized aquagenic urticaria, which is induced by contact with water of any temperature; vibratory urticaria, in which localized swelling occurs within minutes of local vibration (e.g., lawn mowing, power tool use); and adrenergic urticaria, an extremely rare variant of stress-related urticaria, characterized by blanched, vasoconstricted skin surrounding very small erythematous wheals. The inhalation of allergens may also induce hives, but respiratory symptoms typically predominate. Common aeroallergens include household dust, pet dander, pollens, and mold.

Insect bites can cause widespread urticarial lesions that are distinct from the common local erythematous and vesicular reaction. Wasps, hornets, fleas, gnats, mites, mosquitoes, and bedbugs are common offenders.

Urticaria can also occur during a blood transfusion. This reaction is known to be an antibody-mediated response to a donor's plasma proteins and is not a signal of transfusion-related hemolysis. This occurrence is not an indication to stop the transfusion, and treatment with an antihistamine will suffice.

Urticaria can also be caused by an infection, particularly in children. Bacterial, fungal, viral (especially the prodrome of hepatitis A, B, and C), and parasitic agents have all been implicated, some of which are thought to be a likely cause for urticarias of chronic duration. In most cases, urticaria does not appear to be related to hypersensitivity to the infectious agent. The exception is children in whom viral illnesses commonly cause a rash that resembles urticaria. These lesions typically resolve with resolution of the viral infection.

Contact urticaria is whealing of the skin due to exposure to certain substances in susceptible patients. A diverse range of agents have been implicated, including food, metals (nickel, platinum, rhodium), and hair-care products. Of particular concern to health care workers is the emergence of latex allergy, which presents as a local or generalized urticaria but can rapidly progress to angioedema and

anaphylaxis. For this reason, many hospitals are now moving toward a completely latex-free environment.

Pruritic urticarial papules and plaques of pregnancy (PUPPP) is the most common skin condition associated with pregnancy (12). The disorders are often seen in the third trimester or (rarely) in the early postpartum period. These small (1- to 2-mm) lesions appear suddenly on the abdomen and can spread symmetrically to include the trunk and extremities, often coalescing into large plaques. The face, palms, and soles of the feet are usually spared. The etiology is unknown, but may involve connective tissue damage in the striae distensae. They are not associated with increased fetal or maternal mortality or morbidity and usually clear within 1 week of delivery. The wheals and pruritus of PUPPP are not relieved with antihistamines and are instead treated with topical corticosteroids.

Serum sickness is a type III hypersensitivity reaction that can cause urticaria and is of particular concern as more monoclonal antibody therapies have been developed. Symptoms normally appear 7 to 10 days after serum administration. Patients commonly present with fever, chills, rash, and urticaria. Glomerulonephritis is common.

Finally, several underlying systemic diseases may be responsible for unexplained chronic urticaria. Systemic lupus erythematosus, acute febrile neutrophilic dermatosis (Sweet syndrome), bullous pemphigoid, reticular erythematous mucinosis, Schnitzler syndrome, cutaneous mastocytosis (urticaria pigementosum), urticarial vasculitis, and cryopyrin-mediated autoinflammatory disorders are all recognized causes (13).

DIFFERENTIAL DIAGNOSIS

Uncomplicated urticaria can be most easily differentiated from other conditions by the characteristic painless, pruritic, slightly raised wheals. If the history and physical examination reveals findings that are suspicious for an underlying cause (e.g., thyroid disease or infection), additional tests and consultation may be warranted. Although useful for avoiding the trigger in the future, differentiating between the various causes of urticaria is normally not necessary as

the treatment in the emergency department (ED) is identical for all forms of urticaria.

Some differential diagnoses worth mentioning are as follows.

Angioedema involves the deeper dermis and mucous membranes and typically presents as a swelling of the face (especially the lips and eyes), extremities, and/or genitalia. It can occur concurrently with urticaria. It is often associated with abdominal symptoms and is more often life threatening. The two most common causes of angioedema are angiotensin-converting enzyme inhibitors and hereditary angioedema. Chapter 176 of this text covers angioedema.

Urticarial vasculitis causes lesions that may be clinically indistinguishable from urticaria, but the individual wheals last from 24 to 72 hours, are less likely to be pruritic, and may be painful or associated with a burning sensation. Secondary pigmentation and scaling are common, as are systemic symptoms such as fever and arthralgia.

Urticaria pigmentosa is a cutaneous mastocytosis that presents as disseminated tan or brown papules that form wheals within 10 minutes of vigorous rubbing with a blunt instrument (Darier sign).

KEY TESTING

- No routine laboratory testing is recommended for uncomplicated urticaria that responds to antihistamines.
- Additional tests and consultation may be warranted, depending on the findings of the history and physical examination.

ED EVALUATION

Patients must be carefully evaluated and observed closely due to the risk of urticaria escalating to anaphylaxis, with particular attention paid to the patient's airway, breathing, and circulation (ABCs). Once a patient is deemed hemodynamically stable, a more detailed history and physical examination should be performed.

The history of present illness is a key part of diagnosing urticaria. Patients should be queried about the timing and onset of symptoms; any previous episodes of urticaria, asthma, allergies, or any other

atopic conditions; foods eaten; insect stings; and physical or environmental exposures. Urticaria may be delayed after exposure, so the history should cover the past 12 hours before the onset of symptoms. The history should also include a complete inventory of all medications taken by the patient, paying particular attention to antibiotics and aspirin or other NSAIDs. Many patients will not consider OTC medications or supplements (vitamins, botanicals, etc.) to be significant and will neglect to mention them. Since many of these substances can elicit urticaria, it is very important to specifically inquire about them. It is also important to inquire about recent travel, as this may provide clues about potential infections and parasites.

The physical examination should include a thorough skin examination with the patient undressed, noting any other skin conditions. All urticarial lesions should be described in detail as to size, shape, pattern, color, and temperature. The distribution of wheals may provide clues to the etiology of the condition since physical urticaria may be localized to skin sites exposed to vibrations, pressure, latex, cold, sun, or water. Particular importance should also be placed on looking for signs of insect bites or stings. The face and extremities should be inspected for signs of angioedema, which can present concurrently with urticaria. A thorough pulmonary examination should also be performed as respiratory complications such as wheezing, shortness of breath, and airway compromise may occur with urticaria. Particularly, if deep cutaneous edema is noted, the physician must ensure that the airway is patent and uninvolved. A thorough physical examination should also look for signs of infection or other systemic conditions as potential causes.

In a majority of cases, a precise underlying cause of urticaria will not be identified (1). Beyond a good history and physical examination, extensive evaluation in the ED is not indicated. However, simple maneuvers, such as placing an ice cube on the forearm (cold urticaria), immersing a hand in warm water (cholinergic urticaria), or “writing” on the skin (dermatographism),

may be performed in an attempt to elicit symptoms if the clinical history is suggestive.

ED MANAGEMENT

In the emergency room, the primary therapeutic intervention to treat urticaria has been directed at relief of pruritus. The most immediate concern is that all potentially offending agents and exposures should be eliminated to reduce progression of the rash and clinical symptoms. The mainstay of treatment for urticaria (Table 174.3) is antihistamines, though steroids may be considered in severe cases, especially when angioedema is present. Urticaria that progresses to anaphylaxis is treated with epinephrine (see Chapter 175).

TABLE 174.3
Treatment of Urticaria

Class	Medication	Adult Dosing	Pediatric Dosing	Considerations
H_1 blockers				
1st generation	Diphenhydramine (Benadryl)	25–50 mg PO/IM/IV q6h	1 mg/kg PO q6h	Sedating, avoid with concurrent monoamine oxidase inhibitors (MAOIs) pregnancy category B
	Hydroxyzine (Vistaril)	25–100 mg PO/IM qid	0.5–1 mg/kg/dose IM q4–6h 2 mg/kg/d PO divided tid	Sedating, cannot be given IV pregnancy category B
	Cyproheptadine (Periactin)	4 mg PO tid	0.25 mg/kg/d divided tid	Sedating, pregnancy category B
	Chlorpheniramine (Chlortrimeton)	4 mg PO q4h		Sedating, pregnancy category B
2nd generation	Cetirizine (Zyrtec)	5–10 mg PO qd	2–5-yr-old: 2.5 mg PO bid	Less sedating than 1st generation, available in chewable tablets pregnancy category B
	Fexofenadine (Allegra)	60 mg PO bid	6–11-yr-old: 30 mg PO bid	Nonsedating pregnancy category C
	Loratadine (Claritin)	10 mg PO daily	<2–yr-old: not established 2–5-yr-old: 5 mg PO qd	Nonsedating pregnancy category B
Corticosteroids	Prednisone	40–60 mg PO qd for 3–5 d; no taper required	1–2 mg/kg/d divided bid	Caution in diabetics pregnancy category D
	Methylprednisolone (Solu-Medrol)	125 mg IV/IM	0.5–2 mg/kg/d IV/IM/PO (max: 125 mg)	Caution in diabetics pregnancy category D
	Hydrocortisone	15–240 mg IV bid 0.5–2.5% topical qd or bid	1–5 mg/kg/d IV (max: 500 mg)	Caution in diabetics pregnancy category D PUPPP only pregnancy category C

H_1 Receptor Antagonists (Antihistamines)

Antihistamines reduce symptoms by binding to H_1 receptors in the blood vessels and histamine-selective (itch-specific) C nerve fibers, reducing permeability and irritability, respectively. They do not prevent mast cell degranulation. The antihistamines are divided into two generations. First-generation drugs (e.g., diphenhydramine, chlorpheniramine) distribute readily into the CNS and are relatively nonspecific for H_1 receptors, having antimuscarinic, anti-serotonin,

and anti–α-adrenergic activity. This leads to a wide variety of adverse effects, most notably sedation. Second-generation drugs (e.g., loratadine, cetirizine, fexofenadine) are much more highly specific for H_1 receptors and are less lipid soluble, making them less capable of traversing the blood–brain barrier and dramatically reducing sedative and other CNS effects. Note that relief with any antihistamine may be incomplete as many additional vasoactive peptides can be released by mast cells.

Second-generation, nonsedating antihistamines are considered first-line treatment for urticaria (14–16). In controlled studies, these drugs have been shown to be more effective than first-generation antihistamines at reducing wheals and erythema (17), and they have few adverse side effects, making them safer and raising patient compliance. Dosing should begin at the usual therapeutic dose and, if ineffective, can be increased until four times the normal therapeutic dose has been administered. Evidence of the effectiveness of higher doses is mixed, but appears safe and is worth consideration. First-generation drugs can also be used, but have a markedly increased adverse effect profile, including tachycardia, constipation, urinary retention, dizziness, and orthostatic hypotension. The first-generation drug diphenhydramine does have the advantage of potential IV administration for faster relief of symptoms (oral administration of all antihistamines can take 1 to 2 hours to reach peak blood concentration).

Solar urticaria and delayed pressure urticaria have both been shown to be refractory to antihistamine treatment (18). In both cases, antihistamines should be attempted, however. Solar urticaria that is resistant to antihistamines is usually treated with phototherapy and/or plasmapheresis, neither of which are useful in the ED (11). Fortunately, the condition clears in a few hours after removal from the triggering light source. Few effective options exist for delayed pressure urticaria that does not respond to antihistamines, aside from high-dose corticosteroids (10). PUPPP is not relieved with antihistamines and is instead treated with topical corticosteroids.

Steroids

Corticosteroids are not normally used to treat mild, uncomplicated urticaria (14–16), but may be useful in severe cases, especially when angioedema or respiratory complications exist. When used, a short, 3- to 5-day course with no taper is all that is required.

Epinephrine

Epinephrine is the first-line treatment in the setting of urticaria accompanied by anaphylaxis. Epinephrine may be administered intravenously (1 mL of 1:10,000 solution over several minutes, repeated every 5 to 15 minutes as necessary or followed by a drip of 1 to 4 μg/min). Epinephrine can be also given intramuscularly (0.3 to 0.5 mL of 1:1,000 solution every 3 to 5 minutes). After first-line therapy has been started, antihistamines, corticosteroids, and intravenous fluids should be administered. Bronchodilators may also be given as deemed necessary.

Other

Several studies have investigated the use of H_2 receptor antagonists (e.g., famotidine, cimetidine), both as monotherapy and in combination with H_1 receptor antagonists. However, a recent Cochrane review concluded that the evidence was insufficient to make a recommendation as to their use (19). Recent literature also shows little evidence for the effectiveness of leukotriene receptor antagonists (e.g., montelukast) in treating most forms of urticaria (20). Although potentially useful in the management of some forms of chronic urticaria, they have little place in the ED. Many other drugs have been investigated for efficacy in treating urticaria, with mixed results, though there is not enough evidence to recommend their routine use in the ED at this time (14–16).

One final interesting development is that soaps with a higher pH can significantly irritate and weaken the skin, which could either provide an entry route for allergens or exacerbate existing urticaria (21). It may be useful to advise patients with chronic idiopathic urticaria to test the pH of their soap (pH paper can be purchased

online) and to switch brands if it is higher than pH 6.5, which is the normal upper boundary of the skin's pH.

Special Considerations

Solid data are lacking concerning the use of antihistamines in pregnancy, though most are recognized as safe. The majority of antihistamines are listed as pregnancy category B, though a few (e.g., fexofenadine, desloratadine) are category C and should be used with caution or avoided in pregnancy. All antihistamines cross into the placenta and can be found in very small amounts in breast milk (<0.1% of maternal dose). First-generation drugs should be avoided immediately before parturition as this can cause respiratory depression and seizures in the neonate. Systemic corticosteroids are pregnancy category D and should only be used in life-threatening situations. Low-dose topical corticosteroids are pregnancy category C and can be used with caution in PUPPP.

Second-generation antihistamines are recommended for treatment of urticaria in pediatric populations due to their increased safety profile (22). In infants and young children, first-generation antihistamines can additionally cause a paradoxical central nervous system stimulation. Care must also be taken to ensure that pruritus is well controlled so as to prevent excessive scratching and subsequent infection. In addition, it is important to review underlying etiologies and exposure risks that are more specific to young children and infants.

Elderly patients are more vulnerable to adverse effects of first-generation antihistamines such as cognitive decline, delirium, inattention, and altered consciousness due to penetration of the blood–brain barrier. This is particularly problematic in patients with underlying dementia. Special consideration should also be given to elderly diabetic patients who may need to have their insulin dose altered to compensate for the predictable increase in blood glucose during steroid therapy.

CRITICAL INTERVENTIONS

- Administer epinephrine, antihistamines, and steroids for life-threatening urticaria accompanied by cardiovascular collapse, laryngeal edema, or bronchospasm.
- Second-generation antihistamines are the first-line therapy in the treatment of most uncomplicated urticaria without respiratory involvement.

DISPOSITION

Most acute urticaria begins to respond to treatment within 2 hours. Patients should generally be observed for at least this period of time or until definitive improvement is documented. Only patients with anaphylaxis, signs of airway compromise, or hemodynamic instability (hypotension) require admission. Persistent urticaria that fails to improve with antihistamine therapy should prompt further investigation. Urticaria with respiratory complications warrants prescribing injectable epinephrine. All patients should be advised that alcohol, aspirin, and NSAIDs can worsen symptoms. Antihistamines and steroids, if necessary, should be continued on an outpatient basis. Patients should be given instructions to return to the ED if a significant delayed reaction develops. Follow-up with an allergist may be advisable with severe or recurrent symptoms.

Common Pitfalls

- Patients should be carefully monitored. Urticaria may be the first sign of serious angioedema or anaphylaxis.
- First-generation H_1 receptor antagonists can cause side effects that include dry mouth, diplopia, blurred vision, tachycardia, constipation, and urinary retention. Sedation may also be prominent and may hinder performance at school or at work.
- Urticarial skin lesions may be the first manifestation of infection, parasitic infestation, or systemic diseases such as systemic lupus erythematous or urticarial vasculitis.
- Extensive laboratory workups in the ED are usually unnecessary and should be discouraged. A thorough history and physical examination are typically all that is needed.

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SECTION XVIII
Allergic and Immunologic Emergencies

Section Editor: JEFFREY J. SCHAIDER

CHAPTER 175

Anaphylaxis

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Anaphylaxis is an acute, life-threatening condition; immediate recognition and treatment are critical. Manifestations may range from minor symptoms such as rash or lip swelling to sudden death from upper airway obstruction or shock. Even the patient who presents with urticaria alone can subsequently develop hypotension, bronchospasm, or laryngeal edema and should thus be treated with the same urgency as the patient with the full-blown anaphylactic syndrome.

The constellation of anaphylactic symptoms results from massive release of chemical mediators from mast cells and basophils throughout the body. For anaphylaxis to occur there must have been previous sensitization to a foreign substance, against which immunoglobulin E (IgE) was made by antibody-producing B lymphocytes. IgE binds to mast cells and basophils. On re-exposure to the foreign substance, antigen binds to the IgE on mast cells, which triggers massive release of chemical mediators from these cells. Anaphylaxis may also occur by mechanisms independent of IgE (formerly referred to as anaphylactoid reactions), including direct stimulation of mast cells and basophils or via activation of the complement cascade or the coagulation system (1–3).

Mediators released from activated mast cells include histamine, leukotrienes, prostaglandins, platelet-activating factor, tryptase, and cytokines. These mediators lead to an abrupt increase in vascular permeability and vasodilation, thereby resulting in hypotension, urticaria, and angioedema of the skin, upper airway, and gastrointestinal tract. Leukotrienes are potent bronchoconstrictors as

well. In life-threatening anaphylaxis, concomitant activation of complement, coagulation pathways, and the kallikrein–kinin system may contribute as well (2,3).

It is estimated that 1% to 3% of the population are at risk for anaphylaxis during their lifetime and that 1% of these episodes will be fatal, resulting in 1,000 to 1,500 anaphylactic deaths per year in the United States (4). Penicillin is the most feared cause of anaphylaxis, accounting for up to 75% of fatal drug reactions. More than 5% of the population report sensitivity to penicillin, yet more than 90% of these patients are skin-test negative and will not react. Penicillin allergy is generally manifested by urticaria alone or a delayed maculopapular drug eruption, but an estimated 25 of 100,000 patients treated with penicillin experience an anaphylactic reaction, and one will die. There is cross-reactivity among all penicillin derivatives including amoxicillin, dicloxacillin, piperacillin, and ampicillin. First- and second-generation cephalosporins demonstrate cross-reactivity in 2% to 3% of penicillin-allergic patients (documented by a positive penicillin skin test). Patients with reported penicillin allergy who are skin-test negative have less than a 1% cross-reaction rate.

Reactions to third- and fourth-generation cephalosporins appear negligible but these agents should still be used with caution if there is a history of life-threatening anaphylaxis. The cephalosporin-allergic patient will react to other cephalosporins and the penicillins, ampicillin and amoxicillin. Penicillin- and cephalosporin-allergic patients do not react to the monobactam, aztreonam, except for those allergic to ceftazidine. The safety of imipenem in the penicillin-allergic patient parallels the penicillin–cephalosporin risk profile, while the risk with meropenem and ertapenem is negligible (5,6).

Systemic allergic reactions to Hymenoptera stings are estimated to occur in about 1% of children and 3% of adults, and they account for approximately 40 to 100 anaphylactic deaths per year in the United States (7,8). Although 90% of stings are in children, 90% of fatalities to hymenoptera stings occur in adults, as children often manifest urticaria alone, adults present with hypotension or syncope. In emergency department (ED) series of anaphylaxis, hymenoptera

stings comprise 18% to 29% of cases (1,9–11). Yellow jackets, and to a lesser extent hornets, account for the majority of stings in the United States, especially in the late summer during dry spells. Honeybees are also a common culprit, with the Africanized form in the southern United States noteworthy for its aggressive pursuit and swarming behavior. Wasps, fire ants, harvester ants, and bumblebees are other stinging hymenoptera. Depending upon the severity of a systemic reaction, patients have a 15% to 75% risk of future reactions. In contrast, patients with large local reactions (>10 cm) are very low risk for systemic reactions on re-exposure. Secondary infection of hymenoptera stings is unusual, except when fire ant pseudopustules are unroofed. Kissing bugs in the Southwest are the most common nonhymenoptera insect whose bite can cause anaphylaxis. Bites and stings of other insects have been reported rarely to cause anaphylaxis; they include the horsefly, deerfly, blackfly, mosquito, caterpillar, centipede, and bedbug (7,8).

The administration of iodinated contrast media results in minor reactions like a transient rash in up to 2% of patients, but may exceed 4% in atopic or asthmatic patients and 7% in those with a history of prior contrast reactions. Anaphylaxis occurs in about 0.5% of IV iodinated contrast administrations, with 0.01% to 0.04% being life threatening. Contrast media reactions result from non-IgE mechanisms like direct mast cell degranulation or complement activation; thereby prior exposure is not required. Contrary to popular belief, there is no cross-reactivity in patients allergic to fish, shellfish, or topical iodine. There is no cross-reactivity of iodinated contrast with gadolinium, which has a reaction rate of less than 0.1% (12).

Foods are an increasingly recognized cause of fatal or near-fatal anaphylaxis and are the most common cause of anaphylaxis in outpatients, accounting for one-third of cases overall and for more than one-half of episodes in children. Peanuts, tree nuts, shellfish, milk, eggs, and wheat are most commonly implicated, but the latter three are limited to infants and toddlers. Shellfish predominates in adults, whereas nuts are the most common cause in older children. Peanuts and tree nuts account for more than 90% of fatalities (about

150 deaths per year in the United States), with highly allergic individuals reacting to the mere touch or smell of the food. Food-induced anaphylaxis manifests primarily with airway obstruction and rarely with hypotension. Gastrointestinal involvement is much more common in food reactions (40%) compared to other causes of anaphylaxis (4%) (13,14). Noteworthy is the presentation of anaphylaxis and abdominal pain subsequent to the ingestion of sushi, attributed to allergy to the Anisakis worm that may parasitize raw fish. Exercise and medications (NSAIDs) appear to have a facilitating effect in some food reactions (15). Oral allergy syndrome occurs in patients with a history of tree and weed pollen allergy in which there is sudden burning in the mouth and throat after ingestion of fresh fruit, nuts, or vegetables, followed by mild angioedema and sometimes modest systemic allergic symptoms.

NSAIDs are the most common medications causing anaphylaxis in the outpatient setting, often unrecognized due to their frequent use and over-the-counter availability (16). NSAIDs may also precipitate asthma exacerbations in over 5% of asthmatics and in the majority of patients with asthma and nasal polyps. NSAIDs also cause flares in patients with chronic urticaria and may facilitate anaphylaxis to other allergens.. Aspirin and all NSAIDs should be assumed to cross-react unless the patient has a clear history of tolerance to other NSAIDs; more than half of reactions are to a single NSAID. If an NSAID is required, COX-2 inhibitors (celecoxib, meloxicam) and nonacetylated salicylates (salsalate, diflunisal) can be used safely. For analgesia, acetaminophen in doses no more than 650 mg is the safest option (17).

Various parenteral therapeutic agents have been associated with anaphylaxis. After repeated administration, monoclonal antibodies like infliximab, or chemotherapeutic agents like platinum compounds, taxanes, and L-aspariginase, can result in acute allergic reactions (18). About 5% of patients administered alteplase (tPA) for ischemic stroke develop orolingual angioedema without other manifestations of anaphylaxis (19).

Exercise-induced anaphylaxis is usually associated with prior food or drug (NSAID) ingestion, but it can occur independently as well.

Episodes are more common and severe during weather temperature extremes, after alcohol, and during prolonged exertion, yet many patients find that there is no reproducible pattern and most patients have exercised for years before experiencing their first episode. Wheat is the most commonly implicated food, followed by shellfish, fruits, and vegetables (15). Cold exposure itself can precipitate urticaria and sometimes anaphylaxis in patients who have cold urticaria, an inherited disorder. Perioperative anaphylaxis is usually related to paralytic agents or latex and is manifested by circulatory collapse with a paucity of skin findings. Exposure to human proteins such as blood products, insulin, or seminal fluid may rarely result in anaphylaxis. Many agents have a histamine-releasing effect, resulting in diffuse flushing but rarely anaphylaxis; these include opiates, thiamine, vitamin K, and vancomycin (20). Idiopathic anaphylaxis accounts for up to one-third of cases in various series and is notable for rapid-onset and recurrent, unpredictable episodes, often requiring chronic antihistamines and steroids to achieve remission Table 175.1 (21) summarizes etiologic factors in anaphylaxis.

TABLE 175.1
Etiologic Agents in Anaphylaxis

IgE-Mediated Proteins

Venoms: hymenoptera (e.g., yellow jacket, hornet, wasp, honey bee, fire ant), kissing bug, biting flies, rattlesnake, jellyfish (8)

Foods: peanuts, tree nuts, shellfish, grains, milk, eggs, wheat (13,14)

Aeroallergens: allergy extracts, contaminated food

Biologics: infliximab, etanercept, adalimumab

Enzymes: streptokinase, chymopapain

Human proteins: insulin, ACTH, seminal fluid

Equine antisera: botulinum toxin, snake antivenom (rare with Fab fragments)

Vaccines: influenza, MMR, yellow fever (egg), tetanus

Miscellaneous: latex, protamine

IgE-Mediated Haptens

Antibiotics: penicillins, cephalosporins, sulfonamides, fluoroquinolones, tetracyclines (18)

Chemotherapeutic agents: platinums, taxanes, L-aspariginase

Neuromuscular blockers: succinylcholine, rocuronium

Prostaglandin Inhibition

NSAIDs: aspirin (excluding nonacetylated salicylates), indomethacin, ibuprofen, naproxen, etc. (17)

Complement Activation

Blood products: gamma globulin, plasma, whole blood

Dialysis-related

Direct Mast Cell Degranulation

Drugs: opiates, vancomycin, thiopental

Vitamins: thiamine, vitamin K

Polysaccharides: dextrans

Radiocontrast media: ionic >> nonionic

Physical Factors

Exercise-induced anaphylaxis (15)

Food- or NSAID-related anaphylaxis unmasked by exercise

Cold-induced urticaria and anaphylaxis

Idiopathic (21)

Repeated intermittent exposure to a substance or drug increases the risk of sensitization; the more direct the route to the systemic circulation, the greater the likelihood and severity of a reaction. The possible routes of exposure in descending order of severity are

intravenous, intramuscular, subcutaneous, intradermal, inhalational, oral, other mucous membranes, and topical.

Symptoms of anaphylaxis usually begin <30 minutes after exposure and are often immediate. Antigens given orally may have a 2-hour delay before symptoms occur. In general, the more immediate the reaction, the more life-threatening it is. Symptoms may last only a few minutes, even without therapy but, on average, persist for 2 to 4 hours, with the exception of angioedema, which often persists beyond 24 hours. About 5% of patients with anaphylaxis experience a biphasic course, with recurrent anaphylaxis within 8 hours, despite earlier resolution. Delays in or inadequate use of epinephrine and steroids are often implicated in the recrudescence of symptoms (22).

CLINICAL PRESENTATION

Anaphylaxis is often heralded by premonitory symptoms (Table 175.2). Pruritus of the palms and soles, tingling about the mouth and tongue, generalized warmth, tightness in the chest, and a lump in the throat are commonly described. Dizziness or syncope secondary to hypotension may be presenting manifestations of anaphylaxis in the absence of any other signs or symptoms of allergic reaction.

TABLE 175.2
Symptoms and Signs of Anaphylaxis

Reaction	Symptom	Sign
Urticaria	Itching	Raised wheals diffusely, wandering, evanescent
Angioedema	Nonpruritic tingling	Swelling of lips, eyes, hands, uvula, tongue
Laryngeal edema	Hoarseness	Inspiratory stridor
	Dysphagia	Intercostal and clavicular retractions
	Lump in throat	
	Airway obstruction	Cyanosis
	Sudden death	
Bronchospasm	Cough, dyspnea, chest tightness	Wheezing, tachypnea, retractions
Hypotension	Dizziness	Hypotension (mild to severe)
	Syncope	
	Confusion	Tachycardia
	Oliguria	
Rhinitis	Nasal congestion	Mucosal edema
	Itching and fluid	
Conjunctivitis	Tearing	Lid edema, injection, chemosis
	Itching	
Gastroenteritis	Cramping	Normal examination
	Diarrhea	
	Vomiting	
Altered sensorium infants)	Irritability somnolence	Nonfocal neurologic examination
Gynecologic (pregnancy)	Vulvovaginal pruritis, uterine contractions, preterm labor	Mucosal edema & erythema

More than 90% of patients have urticaria or angioedema. Urticaria (edema of the upper dermis) appears as raised erythematous wheals in evanescent pruritic patches. Angioedema represents edema of the deep dermis and appears as puffy, nonpitting areas of skin or mucous membrane. Angioedema is generally painless and nonpruritic; patients note only tingling and swelling in the affected areas. It tends to be most prominent about the face and lips and less so on the hands and arms.

Laryngeal edema resulting in acute upper airway obstruction is the principal cause of death from anaphylaxis. The onset can be dramatic and may be mistaken for a sudden cardiac death or acute upper airway obstruction from a foreign body. Angioedema of the lips, uvula, tongue, and oropharynx is less likely to obstruct the airway but must be treated aggressively because of the likelihood of concomitant edema of the larynx. Uvular edema, in particular, is a

helpful marker for potential laryngeal involvement. Frequently, however, the patient complains of hoarseness and a lump in the throat, and the examination of the oropharynx is completely normal. Indirect laryngoscopy may reveal supraglottic or laryngeal edema, but this examination should not delay the prompt administration of epinephrine in a patient with these complaints.

Bronchospasm is common in the anaphylactic syndrome, but it tends to be mild unless the patient has a pre-existing history of asthma. Pulmonary edema, although reported in anaphylaxis, is generally considered a rare terminal event and not part of the syndrome.

Refractory hypotension is second only to laryngeal edema as a cause of death from anaphylaxis. A drop in blood pressure of 20 to 30 mm Hg is typical, but there is great variability. When sudden in onset, syncope or sudden death may occur.

Although it is usually overshadowed by other symptoms, abdominal cramping can occur in anaphylaxis, most notably in food-related episodes. Angioedema of the gut lining causes this colic as well as vomiting, diarrhea and, rarely, hematochezia. Rhinitis, nasal obstruction, chemosis, and conjunctivitis are other common manifestations of mucous membrane involvement, but they are not life threatening Acute coronary syndrome, takotsubo cardiomyopathy, and ventricular tachycardia have been reported, and nonspecific ST-T wave changes are commonly seen on the electrocardiogram in patients suffering from anaphylaxis. These cardiac manifestations are generally attributed to hypotension, hypoxia, and overzealous epinephrine therapy, although histamine and cytokines may induce coronary vasospasm and cardiac dysrhythmias (20).

Unique manifestations of anaphylaxis may be seen in specific patient subgroups. In pregnancy, vulvar and vaginal itching, low back pain, uterine cramping and preterm labor are described (23). In infants, neurologic presentations may predominate, with irritability, persistent crying, and somnolence (1,24,25).

DIFFERENTIAL DIAGNOSIS

The diagnosis of anaphylaxis is often obvious when antigen exposure is rapidly followed by urticaria, angioedema, bronchospasm, upper airway edema, and hypotension. Confusion in the diagnosis may occur when a delay in the development of symptoms obscures a cause-and-effect relation or when the syndrome is only partially expressed. Differentiating acute, severe urticaria, for example, from anaphylaxis is a moot point. The greatest confusion may arise when anaphylaxis presents as isolated hypotension; it should, therefore, be considered in the differential diagnosis of syncope and vascular collapse.

The acute development of isolated angioedema of the skin and upper airway is a common presentation of anaphylaxis, but it may also be due to hereditary angioedema (HA). This rare, autosomal dominant disease is characterized by the absence of a functional C1 inhibitor, allowing free activation of the complement cascade. HA is characterized by repeated episodes of angioedema of the skin (hands, feet, genitalia), upper airway, and gut. Episodes generally date from adolescence, clustering in the 11- to 45-year age range (26,27).

Attacks of HA may be precipitated by minor trauma, stress, and medications (estrogens, angiotensin-converting enzyme inhibitors [ACEIs]), but most occur without an external trigger. Vomiting and severe colicky abdominal pain is common and can mimic an acute abdomen or progress to small bowel obstruction from mucosal edema. Both urticaria and hypotension are absent in HA. Laryngeal edema can cause acute airway obstruction and death, but usually the progression is gradual, peaking in 8 hours. Typically, the edema will plateau for 24 hours, followed by gradual resolution over the next 2 days A reduction in the C4 level during an attack is diagnostic. Although it is routine to administer epinephrine, antihistamines, and steroids to patients with anaphylactic angioedema, these are generally ineffective in the hereditary disorder. C1 inhibitor concentrate is the most effective treatment in HA patients with airway compromise, providing relief of symptoms within 30 to 60 minutes. Fresh frozen plasma is an effective substitute, and it does not appear to exacerbate symptoms as was once suspected. Icatibant, a bradykinin receptor antagonist, or ecallantide, a kallikrein

inhibitor, administered subcutaneously has shown efficacy as well (26,27).

Rapid development of edema of the upper airway may also result from viral or bacterial infection. However, pain, fever, and findings of erythema and exudate are not present in anaphylaxis. Airway compromise may occur in Stevens–Johnson syndrome and toxic epidermal necrolysis, but mucosal sloughing and bleeding distinguish them from anaphylaxis.

ACEIs produce cough in 10% to 20% of patients and life-threatening tongue and palatal angioedema in 0.1% to 0.7%. African Americans account for 70% to 90% of cases, with smoking, increasing age, and female gender further increasing the risk. Although the appearance is indistinguishable from anaphylactic swelling, the development is more gradual, and other features of anaphylaxis are absent. Patients may have been taking ACEIs for up to 10 years before an initial episode; the mean is 2 years, and about one-fourth of episodes occur within the first month of treatment. Angiotensin receptor blockers may be substituted for ACEIs, but similar angioedema has been described. ACEI-associated angioedema may be resistant to standard therapy but responds to fresh frozen plasma and bradykinin–kallikrein antagonists similar to HA (28,29).

Rarely, patients may experience stridor and obstructive airway symptoms secondary to vocal cord dysfunction or as a manifestation of hysteria; indirect laryngoscopy is the only means to verify these suspicions.

Scombroid fish poisoning may mimic anaphylaxis, presenting with acute urticaria, flushing, peppery taste in the mouth, vomiting, diarrhea, abdominal cramps, headache, and dysphagia. This syndrome occurs shortly after eating fish with a high histidine content (such as tuna or mahi-mahi) for which there has been a breach in the refrigeration process sometime between the catch and consumption, leading to bacterial breakdown of histidine to histamine. A clustering of cases of apparent anaphylaxis is often the clue to this entity (30).

Transient flushing seen in monosodium glutamate reactions may be confused with anaphylaxis, but the prominence of headache and

numbness or tingling distinguishes it from an allergic reaction.

Systemic mastocytosis and the carcinoid syndrome may present with intense flushing and hypotension, mimicking anaphylaxis; prominent gastrointestinal symptoms, hepatomegaly, and provocation by alcohol help distinguish these entities. There has been increased recognition of mastocytosis in patients with idiopathic anaphylaxis. An elevated tryptase level between attacks is suggestive (21).

The systemic capillary leak syndrome is a rare disorder characterized by life-threatening episodes of hypovolemic shock, often accompanied by truncal and extremity swelling. Transient polycythemia and hypoalbuminemia during attacks are pathognomonic; the presence of a monoclonal gammopathy may provide a clue to the diagnosis between attacks.

Laboratory confirmation of anaphylaxis is problematic and rarely required. Plasma histamine rises transiently but normalizes within 60 minutes from onset. Serum tryptase peaks at 60 to 90 minutes from onset and may remain elevated for up to 5 hours, but it is less sensitive.

ED EVALUATION AND MANAGEMENT

Evaluation of the upper airway and careful blood pressure monitoring are the immediate priorities in the care of the patient with possible anaphylaxis. Angioedema of the lips, tongue, uvula, and soft palate, as well as symptoms of hoarseness, stridor, dysphagia, or lump in the throat should alert the physician to progressive airway compromise. Such patients are treated immediately with epinephrine 0.3 to 0.5 mL (1:1,000 dilution) IM (0.01 mL/kg in children to a maximum of 0.3 mL). For both children and adults, the IM route is preferred, as it has been demonstrated to have a faster onset and significantly higher blood levels than the subcutaneous route. The lateral thigh is the preferred injection site, demonstrating superior bioavailability compared to the deltoid region. The dose can be repeated at 5- to 15-minute intervals, to a maximum of 1 mg of epinephrine. β-adrenergic stimulation promotes the synthesis of cyclic AMP in mast cells, which blocks further

release of chemical mediators. Epinephrine also exerts a therapeutic benefit by its α-adrenergic effect, causing vasoconstriction, which results in an improvement in blood pressure and a decrease in swelling of edematous tissues (2,3).

The patient is placed on a cardiac monitor and given oxygen by cannula, and an intravenous line of normal saline is established. If hypotension is present, saline should be infused wide open until the blood pressure responds (typically 1 to 2 L in an adult or 1 or 2 20-mL/kg boluses in a child). If hypotension persists or is profound from the outset, or if airway obstruction appears imminent, intravenous epinephrine may be administered. The most common error made in this situation is to give too much epinephrine too fast, precipitating cardiac dysrhythmias or chest pain. An aggressive approach would include the administration of 1 mL of 1:10,000 epinephrine diluted in 10 mL of normal saline and given as a slow IV push over 3 to 5 minutes (20 to 33 μg/min to 100 μg total). If life-threatening symptoms persist, this bolus can be repeated (31). A more conservative consensus approach recommends the preparation of a drip consisting of 1 mL (1 mg) of a 1:1,000 dilution of epinephrine in 250 mL of D5W infused at 1 to 10 μg/min (0.014 to 0.14 μg/kg/min) If cardiac arrest occurs in anaphylaxis, the epinephrine protocols above are not adequate treatment, and the dose should be escalated to 1 to 3 mg over 3 minutes (2,3).

Massive angioedema may preclude orotracheal intubation, such that cricothyroidotomy may have to be performed. Aerosolized epinephrine (racemic 2.25% solution, 0.5 mL in 3.5 mL saline; or levo-epinephrine 1:1,000, 5 mL) may decrease supraglottic and laryngeal edema, buying time while preparations are made to establish an airway and parenteral epinephrine can be administered. In addition, heliox decreases airflow resistance and improves ventilation in upper airway obstruction, providing a very valuable temporizing measure. If IV access is unavailable, sublingual or intraosseous injection or endotracheal administration of epinephrine is considered. If improvement in blood pressure and airway obstruction are incomplete, epinephrine can be continued 0.3 mL IM at 20-minute intervals or by an epinephrine drip (1 to 10 μg/min).

Hypotension generally responds to one or two IM doses of epinephrine and rapid saline infusion. It is important that the hypotensive patient be kept supine or in Trendelenburg position if the airway is not compromised, as they are exquisitely sensitive to preload, and assumption of an upright posture can lead to a precipitous drop in cardiac output and subsequent arrest, referred to as the empty heart syndrome. If hypotension persists, virtually all patients will respond to IV epinephrine. Patients who are refractory to IV epinephrine may respond to methylene blue, an inhibitor of nitric oxide production, given as an IV bolus of 1.5 to 2 mg/kg (32). Most patients with anaphylaxis do not require such intensive therapy, however. In general, one or two doses of epinephrine subcutaneously at 15- to 20-minute intervals and 1 L of saline IV are adequate. Patients with acute, severe urticaria alone may benefit from a single dose of epinephrine, yet it is usually not necessary because there is no life threat. Bronchospasm in anaphylaxis is responsive to epinephrine alone, but in patients with pre-existing asthma, repeated albuterol nebulizations may be necessary (2,3).

Corticosteroids are recommended in all patients with anaphylaxis. Although there is no immediate benefit to their administration, steroids speed the resolution of angioedema and urticaria and are thought to prevent a biphasic course in anaphylaxis (22). Dosage recommendations are similar to those for status asthmaticus: methylprednisolone (Solu-Medrol), 125-mg intravenous push, followed by 60 mg every 4 to 6 hours in patients whose symptoms persist despite standard therapy. Milder episodes are often treated with oral prednisone 40 to 60 mg initially.

Steroids have an important role in prophylaxis of anaphylaxis in patients allergic to iodinated radiocontrast material requiring IV contrast. The most common regimen is prednisone 40 mg orally at 13, 6, and 1 hour prior to administration of contrast (2,3). Although strong clinical evidence is lacking, consensus opinion suggests that all patients with anaphylaxis should receive an antihistamine such as diphenhydramine (Benadryl), 25 to 50 mg, to a maximum of 100 mg if needed. The route of administration depends on the severity of the reaction. Although less effective for pruritus, H_2 blockers (famotidine

20 mg or ranitidine 50 mg IV push) appear equivalent to H_1 blockers in urticaria and anaphylaxis, and they may offer an advantage if sedation and anticholinergic side-effects are undesirable. The combination of H_1- and H_2 blockers are superior to either agent alone, especially in severe anaphylaxis (33). The addition of fexofenadine (Allegra) or cetirizine (Zyrtec) orally allows more complete histamine blockade without associated sedation or anticholinergic effects and is safe when added to traditional antihistamines. Antihistamines should not be relied upon as the sole treatment in anaphylaxis, except perhaps in the most mild, self-limited of cases.

Preventing further exposure to the antigen is critical; for instance, a tourniquet can be placed above an injection site, the stinger of a honey bee can be removed, offending chemicals can be washed off, and even charcoal can be considered.

Throughout therapy, the vital signs are reassessed frequently, and the airway is checked for edema of the uvula or oropharynx. The patient is asked about symptoms of laryngeal edema or bronchospasm and examined for signs of stridor, retractions, or wheezing. These assessments are made at 1- or 2-minute intervals at first, with the intervals lengthened as the patient stabilizes.

For patients older than age 60 or those with a cardiac history, saline is given cautiously for hypotension while monitoring closely for volume overload. Epinephrine should not be withheld in patients with potential upper airway obstruction or in those with hypotension unresponsive to volume loading. A test dose of epinephrine, 0.15 mL (1:1,000) IM can generally be given safely. If no chest pain or cardiac dysrhythmias develop, another test dose or a full dose is then given. IV epinephrine should be avoided in these patients unless death appears imminent without its use, but limiting the infusion to 1 to 4 μg/min. Pre-existing medications which the patient is taking may aggravate an episode of anaphylaxis or make the patient unresponsive to therapy. Most noteworthy is the patient on a β-adrenergic blocker, which may exacerbate bronchospasm as well as limit the efficacy of epinephrine, leading to a net α-adrenergic effect. In this situation, glucagon, 1 to 2 mg given IV over 5 minutes may be

of great benefit, repeating the dose up to 5 mg total if needed, followed by an infusion of 5 to 15 μg/min titrated to response (18). Terbutaline, 0.25 mg subcutaneously, may also be considered. ACEIs have also been reported to aggravate hypotension and angioedema in anaphylaxis, necessitating more aggressive management Table 175.3 (2,34) summarizes treatment guidelines for anaphylaxis.

TABLE 175.3
Treatment of Anaphylaxis

1. Remove antigen, delay absorption.
2. Maintain an adequate airway and keep supine if airway will allow.
3. Epinephrine
   - 0.3 mL SC 1:1,000; given IM in the lateral thigh, repeat at 5- to 15-min intervals.
   - If severe may increase dose to 0.5 mL.
   - If shock or incipient airway obstruction, give 1 mL of 1:10,000 dilution diluted further in 5–10 mL saline slow IV over 3–5 min, repeating as indicated by clinical response.
   - If protracted severe symptoms, start a drip: 1 mg in 250 mL DSW, 1–10 µg/min.
   - If patient is >60 yr old or has a cardiac history and life-threatening symptoms exist, give a test dose of 0.15 mL IM (1:1,000). If shock resistant to other measures or imminent airway closure, consider a drip as above.
   - If cardiac arrest occurs, give 1 mg IV over 1–3 min. Repeat if no response.
4. Volume expansion with normal saline or lactated ringer
   - Shock: 1 L over 15 min, then repeat 1 or 2 more times if needed
5. Antihistamines
   - Diphenhydramine: 25–50-mg IM or IV push. May repeat within 15 min to a maximum of 100 mg, then smaller doses q2–4h as needed.
   - H2 blocker: Famotidine 20 mg or ranitidine 50 mg IV push repeated at 6-h intervals as needed; given as an adjunct to diphenhydramine if refractory to treatment or if sedation and anticholinergic effects are a problem.
6. Methylprednisolone
   - 125-mg IV push; may repeat 60 mg q4h if persistent symptoms.
7. If resistant hypotension:
   - Continue aggressive fluid resuscitation
   - Trendelenburg position
   - Epinephrine infusion titrated to toxicity
   - Methylene blue 1.5–2-mg/kg IV push (if refractory despite above measures) (32)
8. If imminent airway obstruction (stridor, drooling, hoarseness):
   - IV epinephrine as noted above
   - Nebulized racemic epinephrine (0.5 mL of 2.25% in 3.5-mL normal saline) or epinephrine (5 mL of 1:1,000 dilution)
   - Heliox by mask (70/30 or 80/20 with additional O_2 by nasal canula)
   - Prepare for intubation or cricothyrotomy
9. If resistant bronchospasm (usually pre-existent asthma):
   - Albuterol by nebulization (3–6 mL of 0.083% solution) ± ipratropium; repeat as needed.
10. If β-blocker–accentuated anaphylaxis: (34)
    - Glucagon 1 mg IV push over 4–5 min; repeat as needed up to 5 mg, then 5–15 µg/min drip
    - Terbutaline 0.25 mg subcutaneously every 15 min or isoproterenol drip
11. Outpatient regimen if stable for discharge:
    - Prednisone 40–60 mg/d for 3 d
    - Prescribe one or two antihistamines for 3 to 5 d (only one per class)
      - H_1 blocker (traditional)
        - Diphenhydramine 25–50 mg q6h prn
        - Hydroxyzine 25 mg q6h prn
      - H_1 blocker (nonsedating)
        - Cetirizine 10 mg/d
        - Fexofenadine 180 mg/d
      - H_2 blocker
        - Famotidine 40 mg/d
        - Ranitidine 300 mg/d
    - Prescribe EpiPen 2-Pak or an Auvi-Q autoinjector and refer to allergist if idiopathic or high risk of recurrence (food, bee sting)

Fatalities in anaphylaxis may occur in up to 2% of cases. Foods are generally responsible in children to young adults, while medications and venoms are the etiology in older adults. Risk factors for fatality in anaphylaxis include asthma, delay in administration of epinephrine, cardiopulmonary disease, upright posture maintained during the attack, systemic mastocytosis, and other atopic diseases (4,11).

CRITICAL INTERVENTIONS

- Administer epinephrine intramuscularly immediately for patients presenting with hypotension or acute angioedema of the lips, tongue, uvula, and soft palate.
- Administer epinephrine slow IV push or via infusion pump if there is imminent airway compromise, profound hypotension, or progression of symptoms despite IM epinephrine.
- In addition to IV epinephrine, treat supraglottic and laryngeal edema with aerosolized epinephrine while preparing to establish an airway.
- Hypotension should be treated with aggressive fluid resuscitation as well as maintaining the patient supine or in Tredelenburg position to enhance preload.
- Administer corticosteroids and antihistamines (H_1 and H_2) to all patients with anaphylaxis.

DISPOSITION

If all symptoms of anaphylaxis resolve rapidly and completely with initial therapy, the patient can be observed in the ED without further treatment. If symptoms do not recur in the next 2 to 4 hours, the patient may safely be discharged and should continue on a 3-day course of prednisone (40 mg/d) or a single dose of dexamethasone (10 to 20 mg) and a long acting antihistamine, such as fexofenadine (180 mg/d), cetirizine (10 mg/d), or famotidine (40 mg/d), saving diphenhydramine 25 mg as rescue therapy for pruritis or rash. An epinephrine autoinjector, such as EpiPen or Auvi-Q) should be prescribed for patients with food-related, Hymenoptera, and

idiopathic anaphylaxis. Both the EpiPen 2-Pak and the Auvi-Q contain two doses of epinephrine as well as a training device. Discharge instructions should caution the patient to avoid any suspected inciting cause such as medications, foods, chemicals, or even exercise. The patient should be instructed to return to the ED immediately if hoarseness, dysphagia, wheezing, dyspnea, dizziness, or worsening rash with swelling develops. Follow-up with an allergist should be recommended, particularly if no obvious etiology has been identified in the ED or if desensitization is indicated.

Patients who had a life-threatening manifestation on presentation (shock or upper airway obstruction), even if it resolved with acute therapy, should be admitted. Those who had a slow or incomplete response to therapy or any worsening of symptoms during ED evaluation and treatment also require admission, as do elderly or debilitated patients or those with serious underlying cardiac disease. If hypotension or significant airway compromise persists, admission to an ICU is mandatory. For most of the remaining patients, a 12- to 24-hour observation period is indicated (10).

Because anaphylaxis can progress in such a fulminant manner, transfer to another institution is not recommended unless prolonged observation in the ED has shown the patient to be stable.

Common Pitfalls

- Giving epinephrine undiluted and too rapidly when intravenous administration is required (31).
- Withholding epinephrine therapy in the elderly or cardiac patient with imminent airway obstruction or refractory shock.
- Not recognizing the possibility of recrudescence of symptoms 4 to 8 hours after an initial complete response to therapy (22).
- Not identifying common etiologies of anaphylaxis, including over-the-counter NSAIDs, foods (shellfish, nuts), antibiotics (despite the lack of previous reactions and regardless of duration of therapy), antihypertensive drugs (β-blockers, ACEIs), and exercise.
- Not treating upper airway symptoms such as hoarseness, foreign body sensation, and dysphagia, with prompt administration of IM

epinephrine.
- Not recognizing uvular and pharyngeal angioedema as warning signs of laryngeal involvement.
- Relying solely on epinephrine, antihistamines, and steroids in patients suspected of having HA or ACEI angioedema, and not considering the use of fresh frozen plasma, icatibant, ecallantide, or C1 inhibitor concentrate.
- Failing to recognize that anaphylaxis can present with shock or acute airway obstruction alone, without any other manifestations of the classic anaphylactic syndrome.
- Failing to prescribe EpiPen or Auvi-Q and to provide allergy referral to patients with idiopathic anaphylaxis and those at high risk for recurrent episodes.

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hospitalization in emergency department patients with anaphylaxis. *J Allergy Immunol.* 2013;131:1103–1108.

CHAPTER 176

Angioedema

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Angioedema is transient edema of deep dermal and subcutaneous tissues characteristically localized to the face, lips, intraoral, and throat structures (1,2). The potential for rapid, life-threatening airway compromise from laryngeal edema makes identification and prompt treatment of angioedema of special importance to emergency physicians (1).

Angioedema can be classified according to its most common etiologies:

- Allergic reactions to food, drug, or environmental triggers
- Use of angiotensin-converting enzyme inhibitors (ACEIs)
- Hereditary or acquired angioedema (HAE or AAE)
- Idiopathic causes (2,3).

These etiologies of angioedema can be further classified by their respective pathophysiology, which involve mainly two immunologic mechanisms (Table 176.1). In angioedema associated with allergic reactions, mast cell degranulation with histamine release is responsible (1,2). In cases associated with ACEIs, HAE, and AAE, the angioedema is mediated by the process of bradykinin formation (1,2,4). In addition, a significant number of cases of angioedema occur with no clear cause; numbers as high as 21% to 59% have been reported for idiopathic angioedema (3,5). The end result, regardless of the underlying etiology or mechanism, is an increased permeability of submucosal or subcutaneous capillaries and venules, resulting in fluid extravasation and subsequent edema (1).

TABLE 176.1
Causes of Angioedema

	Mechanism	Treatment Considerations
Allergic	IgE/mast cell/ histamine-mediated	Treatment consists of epinephrine, H_1- and H_2 blockers, and corticosteroids
ACEI-induced/ HAE/AAE	Bradykinin/C1 inhibitor-mediated	Treatment consists of fresh frozen plasma (FFP), C1 inhibitor concentrate, icatibant, or ecallantide. Epinephrine, H_1- and H_2 blockers, and corticosteroids are not effective, but should be trialed first in the emergency setting for angioedema of unclear etiology
Idiopathic	Unknown	Treat as angioedema of unclear etiology

Acute allergic angioedema is mediated by a type 1 hypersensitivity reaction involving allergen binding to IgE receptors on mast cells. The resulting degranulation and histamine release can produce both angioedema as well as more traditional manifestations of allergic reactions such as urticaria, bronchospasm, and even anaphylaxis (1,2). Typical triggers include foods, drugs, contrast dye, latex, environmental allergens, and insect stings (1). This histamine-mediated mechanism is also the common pathway for most drug-related angioedema, including angioedema caused by β-lactams, sulfonamides, opiates, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs), with the notable exception of ACEIs (1).

With approximately 40 million people taking ACEI medications worldwide, ACEI-associated angioedema is becoming an increasingly prevalent disease entity with an incidence approaching 2% according to some studies (2,6). African American patients have a four to five times greater incidence of angioedema; smoking, older age, and female sex are additional risk factors (6). The pathophysiology of ACEI-associated angioedema relates to angiotensin-converting enzyme's dual role in inhibiting both the renin–angiotensin pathway (thereby lowering blood pressure) and the degradation of bradykinin, a powerful vasodilator (2). The initial presentation of ACEI-associated angioedema is highest during

the first month of use, but about a third of cases present more than 6 months after initiation of ACEI therapy, sometimes up to several years (2,6).

Epidemiologic data regarding HAE and AAE are sparse; the incidence of HAE is reported to be between 1:50,000 and 1:100,000 persons, with AAE being even more rare (4). In both HAE and AAE, decreased C1 inhibitor activity results in upregulation of the kinin–kallikrein system, leading to increased bradykinin levels, mast cell degranulation, and vascular permeability (2). The pathophysiology of HAE is due to a genetic defect leading to decreased levels or function of the native C1 inhibitor or in some cases due to a mechanism involving estrogen (1,2,4). Features that suggest HAE include presentation at younger age, often in the first three decades of life, a positive family history, and recurrent attacks of otherwise unexplained angioedema or abdominal pain (2,4). A family history is not always present, however, due to *de novo* gene mutations and varying degrees of gene expression (2). Also, a history of attacks in setting of stress, trauma, or surgery, even minor surgery such as dental procedures, is suggestive of HAE (1,2). The pathophysiology of AAE is less understood, but is likely the result of either increased consumption of C1 inhibitor or an autoantibody binding to C1 inhibitor rendering it nonfunctional (1,2). The latter can occur in B-cell lymphoproliferative disorders including malignancies such as lymphoma and various autoimmune diseases (1,2). An additional feature that suggests AAE is presentation at greater age, often after the fourth decade of life (2,7).

In comparison to angioedema in adults, angioedema in the pediatric population is a rare and much less studied phenomenon (2). The allergic variant is the most common with frequent links to food and other environmental triggers (2). In one small study, angioedema was attributed to food in 40%, insect bites in 30%, upper respiratory infections in 20%, and antibiotic use in 10% of cases (8). Compared to adults, children with angioedema have better prognosis; most respond rapidly to treatment and are less likely to require airway intervention or intensive care unit (ICU) admissions (8).

CLINICAL PRESENTATION

Patients with angioedema characteristically present with complaints of swelling in:

- Face and lips
- Tongue, soft palate, and uvula
- Oropharynx and larynx
- Bowel walls manifesting as abdominal pain, nausea/vomiting, diarrhea, or ascites
- Distal extremities
- Genitals (1)

The typical time course of symptoms is onset within minutes to hours and resolution within one or several days. On physical examination, the edema is nonpitting, nonpruritic, usually does not involve gravitationally dependent areas, and can be painful owing to distension and swelling of the skin (2). Up to 15% of patients with angioedema will develop some degree of airway obstruction (2). Important clinical clues that suggest airway involvement include:

- Dyspnea and respiratory distress
- Voice change
- Hoarseness
- Stridor
- Dysphagia
- Drooling (9,10).

Also, urticaria, bronchospasm, or even anaphylaxis may present if the angioedema is allergic in nature. Abdominal wall involvement leading to abdominal complaints such as pain, nausea or vomiting, diarrhea, and ascites are a less recognized manifestation of angioedema and may be a diagnostic challenge for emergency physicians (2,4,8). They can occur in isolation without the usual facial involvement, and at times the abdominal pain can be so severe that it is mistaken for an acute surgical abdomen (2).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of angioedema is broad (Table 176.2). In the ED, important common alternative diagnoses to consider include dependent edema (for example, due to congestive heart failure), acute abdominal pathology (for example, appendicitis), and infections (for example, cellulitis and abscess) (1,7).

TABLE 176.2
Differential Diagnosis of Angioedema

Infection
Bacterial (cellulitis, erysipelas, Ludwig angina)
Parasitic (trypanosomiasis, trichinosis, filariasis)
Pharyngitis or peritonsillar abscess
Autoimmune disorders
Systemic lupus erythematous
Sjögren syndrome
Polymyositis or dermatomyositis
Scleroderma
Tumors of the head and neck
Superior vena cava obstruction
Trauma
Burns
Congestive heart failure
Acute abdominal pathology
Urticaria
Contact dermatitis
Nephrotic syndrome
Hypothyroidism

ED EVALUATION

The diagnosis of angioedema in the acute setting is established primarily on clinical grounds. Laboratory studies are of limited utility in the ED. Nevertheless at follow-up, a number of diagnostic tests are available, including complement component C4, which is usually low in patients with HAE and AAE, but normal in allergy- and ACEI-induced angioedema, as well as C3, C1q, and C1 inhibitors, which may serve to further differentiate between HAE and AAE and their respective subtypes (1,2,4). Diagnostic imaging

similarly has little to offer in the ED. Nevertheless, for abdominal manifestations of angioedema, ultrasound and computed tomography (CT) scans of the abdomen and pelvis may be helpful to either exclude potentially dangerous alternative diagnoses or support the diagnosis of abdominal angioedema by demonstrating characteristic findings of bowel wall edema and sometimes ascites (2).

As always, initial ED evaluation of suspected angioedema should focus on airway, breathing, and circulation. As deterioration can be rapid, timely evaluation and frequent reassessment of the airway are the first priorities for the emergency physician (9). Symptoms of dyspnea, stridor, hoarseness, and voice change suggest airway compromise and have been shown in retrospective chart reviews to correlate with immediate or eventual airway intervention and ICU care (9,11). The anatomic location of the angioedema also has important prognostic implications, although the literature is limited. Retrospective chart reviews have shown that isolated edema of the face, lips, or soft palate conferred a good prognosis with no patient requiring airway intervention or ICU admission. Evidence of laryngeal edema, on the other hand, universally resulted in either airway intervention or ICU admission, while tongue edema showed no clear tendencies (2,3,11). One chart review addressed the particular use of fiber optic nasopharyngoscopy and showed that the presence or absence of laryngeal edema on fiber optic examination was highly predictive of which patients would or would not require immediate or eventual airway intervention (11). Based on these data, the authors recommend the use of fiber optic nasopharyngoscopy if available whenever there is a clinical suspicion of laryngeal edema, especially if dyspnea, stridor, hoarseness, or voice change is present or if there is significant tongue swelling.

Next, adequate circulation should be ascertained in case of suspected allergic reaction or anaphylaxis with careful blood pressure monitoring. With the airway, breathing, and circulation assessment complete and therapy initiated if needed, a goal-directed history and physical examination should follow, focusing on finding

the etiology of the angioedema, which can in turn guide the eventual medical management.

ED MANAGEMENT

The basic concepts of managing angioedema in the ED are outlined in Figure 176.1. For unstable patients who require immediate definitive airway intervention, orotracheal intubation by direct or video laryngoscopy is recommended. Concomitant preparation for cricothyrotomy is essential should direct laryngoscopy fail. If airway intervention is occurring on a less emergent basis, the safest option is nasotracheal fiber optic intubation, preferably in a controlled environment such as an operating room (2,9). Nasotracheal fiber optic intubation can be especially helpful if there is significant tongue swelling (2). Ultimately, the best choice of intubation technique will incorporate consideration of patient stability, anticipated difficulty of the airway, the provider level of comfort with the array of techniques, and local practice patterns. The risk of increasing laryngeal edema through the trauma of repeated intubation attempts should also be taken into consideration (2). Rescue airway devices such as laryngeal mask airway (LMA) and blind insertion airway devices are not effective for laryngeal edema, but may be considered if the edema is limited to the more proximal airway such as tongue and soft palate (2). Finally, any hypotension due to anaphylaxis should be treated with intramuscular or intravenous epinephrine and intravenous fluids (Fig. 176.1) (2).

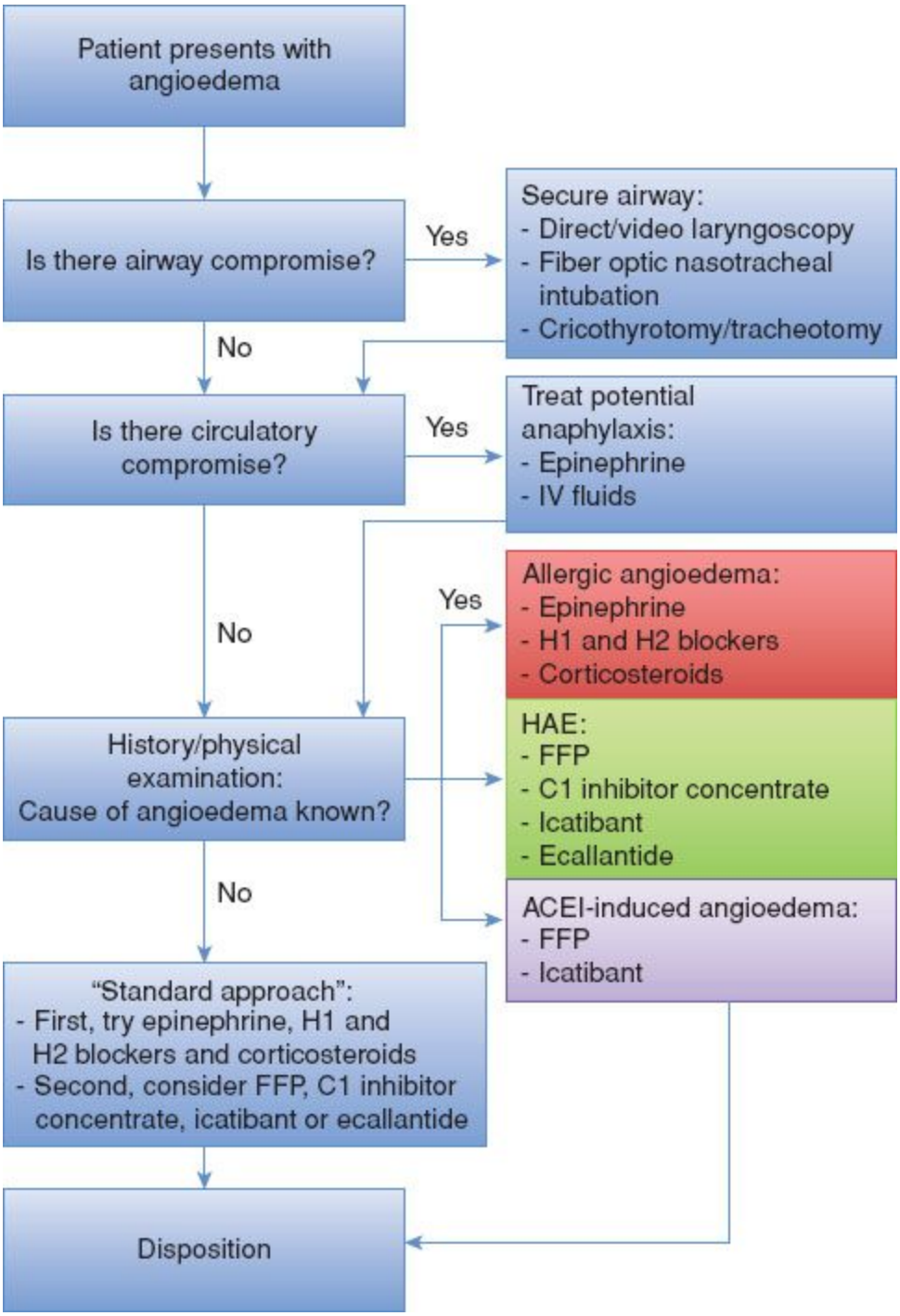

FIGURE 176.1 Clinical approach to angioedema. AAE, acquired angioedema; IV, intravenous; HAE, hereditary angioedema; FFP, fresh frozen plasma; ACEI, angiotensin-converting enzyme inhibitor. (Modified from Wilkerson RG. Angioedema in the emergency department: An evidence-based review. *Emerg Med Pract.* 2012;14(11):1–21.)

Once any airway or circulatory compromise has been addressed, a number of pharmacologic options are available to treat angioedema. It is important for emergency physicians to identify the key features of the various etiologies of angioedema because the best choice in medications depends on the underlying disease mechanism (Fig. 176.1; Table 176.1) (2). If the underlying mechanism is already known, for example, if the patient has a past medical history of HAE or presents after exposure to an obvious allergic trigger, every effort should be made to tailor therapy to these etiologies. Realistically, however, the cause of angioedema is difficult to ascertain in the ED based on history alone or using current diagnostic tools. In these cases of angioedema of unclear etiology, the authors propose a "standard approach."

In this "standard approach", all angioedema is assumed to be allergic in nature at first and treated initially with epinephrine, H_1- and H_2 blockers, and corticosteroids, since these agents are widely available, inexpensive, and generally safe (Fig. 176.1; Tables 176.1 and 176.3) (2). Epinephrine should be administered intramuscularly or in severe cases intravenously. H_1 blockers, (primarily diphenhydramine, but second-generation antihistamines can also be considered), H_2 blockers (such as cimetidine and ranitidine), and corticosteroids can be administered intravenously or orally (Table 176.3) (2). H_1 blockers offer the main antihistamine effect, though the addition of H_2 blockers may potentiate the effect as extrapolated from studies on urticaria (2). A short oral course of corticosteroids may be administered as a prophylactic measure against a rebound reaction (2). While these agents are effective for histamine-mediated allergic angioedema, they are ineffective for bradykinin-mediated ACEI-associated angioedema, HAE, and AAE (2).

TABLE 176.3
Medical Treatment of Adult Angioedema

Medication	Dose	Frequency	Route
Epinephrine 1:1,000	0.2–0.5 mg	q5–15min	IM
	0.1 mg, or 1–4 µg/min	Infusion over 5 min, or drip	IV
H_1 blocker			
Diphenhydramine	25–50 mg	q4–6h	IV/PO
H_2 blocker			
Cimetidine	300 mg	q6h	PO
Ranitidine	50 mg	q6–8h	IV
	150 mg	BID	PO
Corticosteroids			
Methylprednisolone	60–125 mg	Daily	IV
Prednisone	20–60 mg	Daily	PO
Fresh frozen plasma (FFP)	2 units/kg	×1	IV
C1 inhibitor concentrate (Berinert)	20 U/kg IV	×1	IV
Icatibant	30 mg	×1	SC
Ecallantide	10 mg	×3	SC

For angioedema of unclear etiology refractory to these first-line therapies, as well as for known HAE, and to lesser extent, ACEI-induced angioedema or AAE, there are several alternative agents for consideration. These agents include fresh frozen plasma (FFP) and several newly developed therapies: purified C1 inhibitor concentrate, icatibant, and ecallantide (Fig. 176.1; Table 176.1) (2,4). The recommended dosing for these agents is listed in Table 176.3 (2). The first of these therapies, FFP, contains exogenous C1 inhibitor and angiotensin-converting enzyme and has been shown to be effective for HAE and ACEI-induced angioedema in case reports, though not for AAE (2,12). Purified C1 inhibitor concentrate has also been shown in several clinical trials to be both effective and safe for HAE with only mild reactions reported (2,13,14). One formulation, Berinert, was recently approved in the United States for acute presentation of HAE (2). Data are currently unavailable for the effectiveness of C1 inhibitor for ACEI-induced angioedema and AAE. Icatibant and ecallantide are both agents that modify the kinin–kallikrein pathway, icatibant as a bradykinin receptor

inhibitor, and ecallantide as a kallikrein inhibitor (2,4). Like C1 inhibitor concentrate, both agents have been shown in clinical trials to be effective for acute attacks of HAE and recently approved for use in the United States (2,15,16). Both medications have a favorable side effect profile; however, rare hypersensitivity reactions including anaphylaxis have been reported with ecallantide (2,15,16,17). With the exception of case reports suggesting the effectiveness of icatibant for ACEI-induced angioedema, there is little evidence that either icatibant or ecallantide is effective for ACEI-induced angioedema or AAE (2). In summary, while purified C1 inhibitor concentrate, icatibant, and ecallantide offer great potential for the management of HAE, data on their effectiveness for ACEI-induced angioedema and AAE are limited. Moreover, these newer agents are still not available at all hospitals and can be costly, ranging from $4,700 to $9,500 per dose (2). Thus, it is suggested that these therapies be considered as second-line therapy options for angioedema of unclear etiology.

For pediatric patients presenting with acute angioedema, management is similar to that of adults, with initial emphasis on airway, breathing, and circulation (14). Epinephrine, H_1- and H_2 blockers, and corticosteroids are particularly important first-line pharmacologic interventions in pediatric patients since allergic angioedema is more common (Table 176.4) (1). For pediatric cases of HAE, FFP, and Berinert C1 inhibitor concentrate are considered appropriate therapies (Table 176.4) (14). Icatibant and ecallantide are currently not approved for pediatric use (2).

TABLE 176.4
Medical Treatment of Pediatric Angioedema

Medication	Dose	Frequency	Route
Epinephrine 1:1,000 dilution	0.01 mg/kg (max 0.3 mg)	q10–15min	IM
H_1 blocker			
Diphenhydramine	1 mg/kg (max 50 mg)	q4–6h	IV/IM/PO
H_2 blocker			
Cimetidine	Infants 10–20 mg/kg/d	Divided q12h	IV/IM/PO
	Children 20–40 mg/kg/d	Divided q6h	IV/IM/PO
Ranitidine	2–4 mg/kg/d (max 200 mg)	Divided q6–8h	IV/IM
	4–8 mg/kg/d (max 300 mg)	Divided q12h	PO
Corticosteroids			
Dexamethasone	0.6 mg/kg	Daily	IV/IM/PO
Prednisone	2 mg/kg	Daily	PO
Fresh frozen plasma (FFP)	2 units/kg	×1	IV
C1 inhibitor concentrate (Berinert)	10–20 U/kg IV	×1	IV

An often overlooked component of addressing angioedema in the ED is prevention and patient education. Patients with allergic angioedema should avoid any potential triggers including discontinuing any inciting drugs. If allergic angioedema or anaphylaxis is suspected, an epinephrine autoinjector device should be prescribed (1,2). Patients who had angioedema from one kind of ACEI should avoid other drugs within the ACEI class (2,6). Whether angiotensin receptor blockers (ARBs) should be used by patients with previous ACEI-induced angioedema is controversial, and data are limited (2). The incidence of developing angioedema in this group is estimated to be 10% or less (18,19). Nevertheless, the risk of angioedema should be weighed against the indications for ARBs, particularly in cases when ARBs are thought to be more beneficial than other antihypertensive drugs.

CRITICAL INTERVENTIONS

- Perform rapid assessment and management of airway compromise and anaphylaxis.
- Treat all cases of angioedema with epinephrine, H_1- and H_2 blockers, and corticosteroids, before considering FFP, C1 inhibitor concentrate, icatibant, or ecallantide.

- Identify potential precipitating agents, especially allergic triggers and ACEIs.

DISPOSITION

The disposition of patients with angioedema is determined by the severity of initial symptoms, the anatomic location of the angioedema, the disease course, and response to therapy. As general guideline, patients who may warrant ICU admission include those with:

- Airway compromise and laryngeal edema requiring definitive airway
- Symptoms of dyspnea, stridor, hoarseness, or voice change
- Diffuse tongue involvement

In contrast, patients who may be admitted to a floor unit or discharged home include those with:

- Involvement limited to the face, lips, and soft palate
- Localized tongue involvement (9)

The patients who are candidates for discharge should be observed for a period of at least 4 to 6 hours in the ED to ensure no further extension of the edema (2). Outpatient referral for further work-up may be appropriate, especially in cases of recurrent angioedema. Allergy skin testing for allergic angioedema, prophylactic drug regimens for HAE, and work-up for underlying malignancy or autoimmune disease for AEE may all be addressed outpatient (1,2).

Common Pitfalls

- Failure to adequately assess and manage the airway
- Failure to adequately reassess for airway deterioration
- Failure to observe low-risk patients for an adequate period of time before discharge
- Failure to address underlying precipitants and discontinue their use

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Aparajita Sohoni to the contents of this chapter.

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CHAPTER 177

Drug Allergy and Other Drug Reactions

Paul Jhun

An adverse drug reaction (ADR) is defined by the World Health Organization as a "noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment" (1). ADRs occur in 10% to 20% of hospitalized patients and account for 3% to 6% of all hospital admissions (2,3), many of whom present to the emergency department for diagnosis and care.

ADRs are classified as type A or type B reactions. Type A ADRs are predictable reactions that can affect any healthy patient, given sufficient dose and duration, due to the known pharmacologic properties of the drug (drug interactions, overdose/toxicity, side effects). Type B ADRs are unpredictable hypersensitivity reactions that affect a susceptible subset of the population due to unpredictable individual immunologic response. Type B ADRs include true immunologic drug reactions, idiosyncratic drug reactions, and drug intolerance (expected side effects at subtherapeutic doses). Type A reactions constitute 80% to 90% of ADRs, while Type B reactions make up 10% to 20% of ADRs (2,3).

DRUG ALLERGY THEORY

Drug allergy or hypersensitivity accounts for 6% to 10% of ADRs. The multivalency theory proposed by Karl Landsteiner forms the current understanding of the immunologic pathophysiology of drug allergies (4). By definition, a monovalent antigen has only one site

of attachment. Landsteiner proposed that drug antigens must be presented to the immune system in multivalent form in order to: (1) sensitize the immune system, inducing immunoglobulin synthesis; and (2) activate the immune system, eliciting the mast cell and basophil release of vasoactive mediators. Multivalency can be achieved through four main mechanisms: (1) the antigen is already a large macromolecule with multiple repeating epitopes, such as recombinant proteins, antisera, vaccines, or insulin; (2) the antigen is a hapten, a small molecule able to bind with larger macromolecules, that can form a multivalent hapten-carrier complex, such as β-lactam antibiotics, heavy metals, antithyroid medications, or quinidine; (3) the antigen undergoes metabolism, generating intermediate haptens capable of forming multivalent hapten-carrier complexes, such as antimicrobial sulfonamides, phenytoin, procainamide, or acetaminophen; or (4) the antigen directly binds certain T-cell receptors and activates the immune system, such as sulfamethoxazole, carbamazepine, lamotrigine, or lidocaine (5). Of note, a few small molecules have multiple recurrences of a single epitope, creating an inherently multivalent antigen, such as succinylcholine.

Risk factors predisposing a patient to drug hypersensitivity reactions include the genetic predisposition of the patient (history of atopy, history of prior drug reactions, and familial propensity), the characteristics of the drug (inherent reactivity, preparation, dosage, frequency, and duration of therapy), and the disease state (concomitant medications or diseases). Interestingly, specific drug hypersensitivity reactions have been associated with certain disease states, such as when sulfonamides are administered to patients with AIDS or when amoxicillin is administered to patients actively infected with Epstein–Barr virus (6,7).

CLINICAL PRESENTATION

Classification of Reactions

Drug hypersensitivity reactions are conceptually categorized according to the Gell and Coombs four-group classification system:

type I acute IgE-mediated response, type II delayed IgG/IgM-mediated cell destruction, type III delayed immune complex reaction, and type IV delayed T-cell-mediated hypersensitivity.

Type I reactions are mediated by previously sensitized patients who have preformed drug-specific IgE antibodies attached to the surface of their mast cells and basophils. When the patient is re-exposed to the offending drug, the circulating drug antigen binds the drug-specific IgE antibodies activating the mast cells and basophils, leading to immediate vasoactive mediator release and clinical sequelae such as urticaria, flushing, pruritis, angioedema, laryngeal edema, bronchospasm, gastrointestinal distress, and hypotension.

Type II cytotoxic reactions result when an offending drug binds to certain cell types and acts as an antigen. When drug-specific IgG or IgM antibodies bind these complexes, the cells are destroyed. Almost all type II reactions involve formed elements of the blood leading to hemolytic anemia, thrombocytopenia, or neutropenia, and their respective clinical sequelae.

In type III reactions, the drug antigen binds drug-specific IgG, forming immune complexes that precipitate in various tissues, clinically presenting as serum sickness, drug fever, or vasculitis.

Type IV reactions are mediated by sensitized T lymphocytes that recognize a particular drug antigen and recruit other lymphocytes and mononuclear cells to the site of that antigen. Type IV reactions classically have prominent dermatologic findings due to the fact that there are nearly twice as many T cells residing in the skin compared to circulation (8). Clinical manifestations include contact dermatitis, morbilliform or maculopapular eruptions, exfoliative dermatitides, or drug-induced hypersensitivity syndrome. However, type IV reactions may also involve specific organs without cutaneous findings, such as isolated drug-induced hepatitis, interstitial nephritis, or pneumonitis.

The World Allergy Organization proposed a simpler, two-group clinical classification system to help practitioners identify IgE-mediated reactions, based on the timing of symptom onset: immediate and delayed reactions (9). Immediate reactions are those

beginning within 1 hour of first dose administration and are likely IgE-mediated type I reactions. Delayed reactions are those appearing after 1 hour of dose administration and are not likely to be IgE-mediated.

Drug reactions that resemble type I IgE-mediated hypersensitivity reactions, but are not immune-mediated, are termed *idiosyncratic* or *pseudoallergic* reactions. Most pseudoallergic reactions are clinically indistinguishable from true allergic reactions because they often share the final common pathway of mast cell and basophil activation. Of note, the term *anaphylaxis* is reserved for immune-mediated type I hypersensitivity reactions, while the terms *anaphylactoid* and *nonallergic anaphylaxis* are preferred for idiosyncratic reactions. Common medications and their idiosyncratic reactions include radiocontrast media (RCM)-induced urticaria and hypotension, opiate-induced urticaria, aspirin-induced bronchospasm, nonsteroidal anti-inflammatory drug-induced urticaria, and vancomycin "red man syndrome."

DIFFERENTIAL DIAGNOSIS

Given the broad spectrum of clinical presentations of drug adverse reactions, physicians should include ADRs as part of their differential diagnosis.

ED EVALUATION

The diagnosis of drug hypersensitivity reactions in the emergency department is largely dependent on the patient history and presentation. Particularly for the emergency physician, early recognition and diagnosis of anaphylaxis is critical, while recognition of severe exfoliative dermatitides and drug-induced hematopoietic or organ damage is important in determining appropriate management and disposition. Important historical information includes assessing risk factors such as previous exposures to the same or similar drugs, a complete list of medications to determine allergenic potentials, and temporal association of drug administration times to symptom onset to

establish a causal link. Improvement of symptoms after withdrawal of the suspected drug is suggestive information. A suspicion for immune-mediated cell destruction should prompt the physician to obtain a complete blood count with a peripheral smear. An indirect Coombs test, if available, may be helpful in diagnosing immune hemolytic anemia.

While objective testing is available for certain drug allergic reactions, such tests require referral to an allergy–immunology specialist for implementation and interpretation. Skin testing is conducted primarily to evaluate suspected type I hypersensitivity reactions, although limitations include lack of standardization and validation for many drugs. Patch testing can be performed for evaluating contact dermatitis caused by topically applied medications. In vitro tests, such as radioallergosorbent or enzyme-linked immunosorbent assay tests are largely investigational and not standardized or validated, so are of limited value. Drug provocation testing by graded challenges can be performed, but should be done so by appropriate specialists after careful consideration of risks and benefits for a particular individual. The best studied drug allergen testing involves penicillin. Intradermal skin testing is the diagnostic procedure of choice for evaluating suspected IgE-dependent penicillin allergy (5,7).

ED MANAGEMENT

The standard management of drug hypersensitivity reactions includes prompt discontinuation of the medication and provision of supportive care that is specific to the type and severity of manifestations. Mild pruritis, flushing, and urticaria may be treated with antihistamines. Corticosteroids may be indicated for severe systemic or cutaneous reactions, immune complex reactions, or drug-induced hematologic diseases. Early epinephrine is the mainstay of treatment for anaphylactic reactions. Oxygen and airway support, inhaled β-agonists, intravenous fluids, and pressors also may be required.

Although type B ADRs are unpredictable, several steps can be taken to minimize the chance of developing a drug hypersensitivity reaction. Perhaps most importantly, medications should be prescribed only when necessary. A careful history of risk factors for drug reactions, including prior ADRs, should be obtained. If a drug allergy exists, crossreactive drugs should be avoided. The oral route should be used when possible (1,5,7). Preparations that are less sensitizing are preferred when available. Documentation in the medical record of any apparent reaction may help avert a similar or worse reaction in the future. Finally, when potentially immunogenic parenteral agents are given in the emergency department, patients should be observed for at least 1 hour after administration, to ensure an immediate IgE reaction does not occur.

CRITICAL INTERVENTIONS

- Recognize and administer epinephrine promptly for anaphylaxis (adult: epinephrine 0.2 to 0.5 mg [1:1,000 {1 mg/mL} solution] IM, or epinephrine 0.1 mg [1:10,000 {0.1 mg/mL} solution] IV; pediatric: epinephrine 0.01 mg/kg [1:1,000 {1 mg/mL} solution] IM, maximum single dose of 0.3 mg) (10)
- Obtain, document, and be aware of a history of prior drug hypersensitivity reactions
- Identify and withdraw offending drug(s) and provide alternative drug therapy if indicated

DISPOSITION

Disposition decisions for patients with drug reactions hinge on the nature and severity of the reaction. Patients who present with mild reactions, respond well to treatment, and are reliable with good support systems may be considered for expedited discharge to home. In borderline cases, a period of observation of several hours may be helpful. Patients with persistent or recurring airway edema, bronchospasm, hypotension, cardiovascular complications, or altered mental status require admission to the hospital in an intensive care setting. Patients who receive treatment for an initially

severe reaction but who rapidly improve are typically either observed for a period of 6 to 12 hours or admitted to the hospital; in the case of anaphylaxis, this facilitates treatment if a late-phase reaction occurs. Discharged patients should receive instructions including cautions regarding possible delayed or recurrent reactions. Referral to or consultation with an allergy–immunology specialist is indicated in suspected cases of drug hypersensitivity reactions, especially suspected cases of IgE-mediated reactions. Further testing can be performed and patients can be evaluated for induction of drug tolerance or desensitization for offending drugs that are medically necessary.

PENICILLIN ALLERGY AND CROSSREACTIVITY

Penicillin and its derivatives are among the most widely prescribed antibiotics and are the most common cause of drug-induced allergic reactions. Penicillin can be responsible for any of the four types of Gell and Coombs. The overall incidence of reported adverse reactions to penicillins is estimated to be up to 10% of patients (7). Interestingly, up to 90% of these individuals are able to tolerate penicillin after complete evaluation and testing (7). This could be due to inaccurate clinical history of penicillin allergy or more importantly could be due to the gradual loss of penicillin-specific IgE that happens in patients over time. Studies have shown that approximately 50% of patients with IgE-mediated penicillin allergy lose sensitivity 5 years after their last reaction, and approximately 80% lose sensitivity after 10 years (11,12). Life-threatening anaphylaxis secondary to penicillin after parenteral administration appears to be uncommon, with an incidence of 1 to 2 per 10,000 treated patients (7). Patients with a suspected history of IgE-mediated penicillin allergic reaction should be referred to an allergy–immunology specialist to undergo skin testing, which is the most reliable method for evaluating IgE-mediated penicillin allergy. In patients who report a reaction history concerning for anaphylaxis, especially if the reaction was recent, penicillins and

crossreactive drugs should generally be avoided until evaluation by a specialist.

Regarding crossreactivity risks with the use of the other β-lactam antibiotics in a patient with a confirmed penicillin allergy, crossreactivity rate is high with first-generation cephalosporins and these drugs should generally be avoided. Most second- and all third- and fourth-generation cephalosporins appear to have negligible crossreactivity (13). Carbapenems appear to have low crossreactivity rates of about 1% in limited studies (14,15). Monobactams do not appear to immunologically crossreact, likely due to its distinctly different chemical structure (5,7). Overall, recent studies have shown that cephalosporin administration in patients with a reported history of penicillin allergy, unconfirmed by skin testing, resulted in an allergic reaction in 1% of patients, while cephalosporin administration in patients with confirmed penicillin-allergy patients resulted in an allergic reaction in 2% of patients (7,13). A recent consensus allergy and immunology guideline states that patients with a complete, negative penicillin skin testing may receive cephalosporins safely (7). However, if the patient has a reported history of penicillin but has not received skin testing, this guideline states that the practitioner has the option of either (1) obtaining penicillin or cephalosporin skin testing to determine the safety of cephalosporin administration or (2) directly administering the cephalosporin (only in the absence of severe and/or recent penicillin allergy reaction history), with the knowledge that there is a very small but real risk for allergic reaction. In such cases of direct cephalosporin administration in a patient with a reported but unconfirmed history of penicillin allergy, crossreactivity risk can be further mitigated by administering a third- or fourth-generation cephalosporin.

RADIOCONTRAST MEDIA REACTIONS

More than 15 million diagnostic radiographic examinations using RCM are performed in the United States each year. Adverse reactions due to RCM are reported to have an annual incidence of

2% to 12%, with deaths estimated between 1 to 3 per 100,000 administrations (16,17). RCM adverse reactions can be categorized into hypersensitivity reactions and chemotoxic reactions.

RCM-induced hypersensitivity reactions are further divided into immediate and delayed types. Immediate hypersensitivity reactions generally present within 1 hour of administration and are believed to be idiosyncratic, nonimmune-mediated, and independent of dose and infusion rate. These acute reactions share the final common pathway of mast cell activation and vasoactive mediator release, are clinically indistinguishable from type I reactions, and are treated similarly. Delayed RCM hypersensitivity reactions are type IV reactions that can present several days after administration and are generally self-limited (18).

As newer generation RCM products have been developed, the incidence of adverse reactions has also decreased. First-generation RCMs are ionic monomers that are categorized as high-osmolar RCM (>1,400 mOsm/kg), compared with normal serum osmolality. Second-generation agents, such as iohexol, are nonionic monomers that are categorized as low-osmolar RCM (500 to 900 mOsm/kg). The newest agents are nonionic dimers, such as iodixanol, that have the same osmolality of plasma and are categorized as iso-osmolar RCM. Estimated rates of severe, immediate hypersensitivity reactions are 0.1% to 0.3% for the high-osmolar RCM and 0.01% to 0.04% for low-osmolar RCM (1,17). Of note, seafood or shellfish allergy is not an independent risk factor for RCM hypersensitivity reactions and no special precautions need to be taken for such patients (1).

Chemotoxic RCM reactions are related to the RCM chemical properties and are dependent on dose and infusion rate. These reactions include nephrotoxicity, vasovagal reactions, and iodine-induced thyroid dysfunction. Regarding contrast-induced nephropathy (CIN), there is no specific treatment once acute kidney injury develops, so management is aimed at prevention. The mechanism of CIN is thought to be related to renal vasoconstriction and/or direct renal cytotoxic effects of the contrast agent, and the diagnosis is based on the increase in the serum creatinine level

beginning within 24 to 48 hours of RCM administration. Risk factors for CIN include chronic kidney disease, diabetes mellitus, multiple myeloma, and causes of reduced renal perfusion such as advanced heart failure and hypovolemia. A high total dose of RCM as well as first-generation RCM are additional risk factors. The use of low osmolar or iso-osmolar RCM in patients with pre-existing chronic kidney disease is associated with decreased incidence of CIN compared to high osmolar RCM (19,20).

The risk-to-benefit ratio of a contrast study should be considered before it is ordered and performed. If possible, ultrasound or magnetic resonance imaging should be utilized. If RCM must be used and the patient has a history of prior anaphylactoid reaction, the patient can be pretreated with corticosteroids and antihistamines to decrease the likelihood of recurrent anaphylactoid reaction. One common protocol is shown in Table 177.1. To minimize the risk of developing CIN, recommended approaches have included infusion of isotonic sodium chloride or sodium bicarbonate before and after the administration of contrast (e.g., 3 mL/kg/hr for 1 hour before and 1 mL/kg/hr for 6 hours after) (20). Also, while evidence is conflicting, some suggest benefit from adjunctive treatment with N-acetylcysteine, 1,200 mg bid the day before, and the day of the radiocontrast administration (20). Finally, nonsteroidal anti-inflammatory drugs should be avoided as they increase the risk of nephrotoxicity.

TABLE 177.1
Premedication Protocol Prior to Administration of Radiocontrast Media to a Patient with Prior History of Anaphylactoid Reaction

Time Prior to Contrast Administration (hr)	Medication
13	Prednisone 1 mg/kg PO
7	Prednisone 1 mg/kg PO
1	Prednisone 1 mg/kg PO and diphenhydramine 1 mg/kg PO/IM[a]

[a]H2-antihistamine may also be included, if desired.

Common Pitfalls

- Failure to obtain medication list and drug allergy history
- Administration of crossreactive drugs to patients with a known drug hypersensitivity reaction
- Failure to diagnosis and quickly manage anaphylaxis

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CHAPTER 178

Multisystem Autoimmune Disease

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Patients with multisystem autoimmune disorders may present for initial medical evaluation with a bewildering array of symptoms or complaints. Many of the tests needed to diagnose these “rheumatic disorders” cannot be performed during an emergency department (ED) visit. However, the emergency physician must recognize that an autoimmune disorder may be responsible for the patient’s clinical picture and must decide which patients require admission and which can safely undergo an outpatient evaluation. Likewise, when a patient with known multisystem autoimmune disease presents to the ED with new symptoms, the physician must determine whether they represent an exacerbation of known disease, a manifestation of an unrelated disorder, or a complication of therapy.

Evolving therapies and variations in individual response to treatments make rheumatologic consultation appropriate in many cases. Although the ultimate cause of the autoimmune disorders remains a mystery, it is increasingly clear that specific autoantibodies directed against cellular components are markers for, and probable causes of, many of the manifestations. Positive tests for these antibodies not only correlate with current symptoms but are also predictive of the patient’s course. The use of these specific disease markers can improve accuracy in diagnosis and can guide therapy directed at specific pathologic entities.

Despite the fact that definitive therapies for most autoimmune disorders are lacking, there is often much that can be done to

alleviate symptoms and prevent progression of tissue damage. Every pharmacologic treatment has a potential for toxicity that must be balanced against the potential benefit it may provide to the patient.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is the prototypical autoimmune disease. Its prevalence is 1 in 2,000 with a 10:1 predominance of women over men and a predilection for nonwhites. The prevalence is 1 in 750 for black women between the ages of 20 and 64 (1).

The cause of SLE remains unknown; hormonal, metabolic, genetic, environmental, and infectious factors have all been proposed as etiologic agents. The pathophysiology of SLE involves the production of autoantibodies initiated by an unknown stimulus. These antibodies react with cell constituents and initiate an inflammatory response that results in the activation of the complement pathway and the elaboration of chemotactic factors and other inflammatory mediators. Antibody-dependent cytotoxic leukocytes are also activated.

Antinuclear antibodies (ANAs) are almost invariably detected in patients with SLE. Although ANAs are found in low titers in many other autoimmune and nonrheumatologic disorders, high titers are more specific for SLE. High titers of antibodies to double-stranded DNA are seen only in patients with SLE (2). Antibodies to the Smith antigen are also specific for SLE, as well as being associated with more severe symptoms. During active SLE, complement levels are depressed and may be helpful in following the course of disease (1).

CLINICAL PRESENTATION

SLE can affect any tissue or organ and has been said to have replaced syphilis as “the great imitator” of other diseases (1). Patients often make multiple visits to physicians before SLE is initially recognized. Some of the more common manifestations are listed in Table 178.1.

TABLE 178.1
Systemic Lupus Erythematosus: Characteristic Features and Suggestive Signs and Symptoms

System	Presentation
Constitutional	Fever, fatigue, malaise, weight loss
Vascular	Raynaud phenomenon, arterial occlusion, extremity ulcers
Dermatologic	Diffuse alopecia, malar rash, discoid rash, photosensitivity
Hematologic	Hemolytic anemia, leukopenia, thrombocytopenia, thrombosis
Immunologic	False-positive serologic test for syphilis
Gastrointestinal	Nausea, vomiting, oral ulcers
Cardiac	Pericarditis, myocarditis
Pulmonary	Diffuse interstitial pneumonitis, pleuritis, pleural effusion
Musculoskeletal	Nonerosive arthritis
Renal	Glomerulonephritis, nephrotic syndrome
Reproductive	Spontaneous abortion, preeclampsia
Neurologic	Psychosis, depression, mania, seizures, headache, organic brain syndrome, aseptic meningitis, peripheral neuropathy

The most typical initial complaints are fatigue and arthralgias, but fever, anemia, anorexia, and a malar rash are other common presenting symptoms. The arthralgias are commonly fleeting and migratory, typically appearing in the proximal interphalangeal and metacarpophalangeal joints, the wrists, and the knees, but they may also be due to frank synovial inflammation.

The rash of SLE varies from a slight blush to a well-demarcated and somewhat edematous maculopapular erythematous eruption covering both cheeks and the bridge of the nose. It tends to spare the nasolabial folds but can cause scarring and atrophy of skin structures. The rash is characteristically exacerbated by sun exposure and may often cause a patient to seek medical attention before any other symptoms of SLE have developed.

Although the kidneys are commonly affected in SLE, nephrotic syndrome and peripheral edema are rarely seen before other manifestations of disease have led to the diagnosis of SLE (3). Patients with SLE frequently present with acute, potentially life-

threatening problems. Complaints of chest pain, abdominal pain, and neurologic dysfunction can indicate an acute flare of disease or a serious complication of therapy. Patients with acute chest pain, with or without fever, may have pleuritis, pericarditis, or pneumonitis. Abdominal pain may indicate an acute flare of polyserositis.

Neurologic problems of virtually any type may be seen in SLE. Most common are central disorders ranging from mood disorders to frank psychosis. Seizures are also common, especially in younger patients. SLE should be in the differential diagnosis of new-onset seizures, especially in young women.

The lupus anticoagulant, also called the anticardiolipin antibody or antiphospholipid antibody, is an antibody that produces an artifactually prolonged partial thromboplastin time in vitro but a "paradoxical" procoagulant effect in vivo. Although antiphospholipid antibodies are associated with SLE, they may occur as a part of a distinct pathologic entity referred to as the antiphospholipid syndrome (4,5). Both conditions can lead to deep venous thrombi, pulmonary emboli, stroke, chronic ulcers of the extremities, and thrombocytopenia (4,5). Patients with recurrent or unusual thrombosis should be evaluated for antiphospholipid autoantibody and SLE (6). Recent studies have shown that patients with the antiphospholipid syndrome are at increased risk for cardiovascular disease.

Patients with known SLE may present to the ED with either exacerbations of their disease or complications of therapy.

DIFFERENTIAL DIAGNOSIS AND ED EVALUATION

Given the variety of possible presentations, the differential diagnosis of SLE is exceedingly broad. A thorough history and physical examination are required to identify multisystem involvement and recurrent symptoms. The differentiation of SLE from the other autoimmune syndromes may require repeated rheumatologic evaluation and specific autoantibody testing.

Tan et al. (7) have published a list of 11 criteria diagnostic for SLE (Table 178.2). The diagnosis is established if 4 or more of these findings are present serially or simultaneously. A medication history must be elicited to rule out drug-induced lupus. Attention to detail in evaluating the patient with nonspecific symptoms may lead one to suspect the diagnosis of SLE. The diagnosis should be particularly entertained in women of childbearing age who have recurrent or vague symptoms that do not clearly point to a discrete disease entity.

TABLE 178.2
Diagnostic Criteria for Systemic Lupus Erythematosus[a]

1. Malar rash	Fixed erythema, flat or raised, over the malar eminences.
2. Discoid rash	Erythematous raised patches with adherent keratotic plugging. Atrophic scarring may occur.
3. Photosensitivity	
4. Oral ulcers	Incudes oral and nasopharyngeal, observed by physician.
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion.
6. Serositis	Pleuritis or pericarditis documented by electrocardiogram or rub or evidence of pericardial effusion.
7. Renal disorder	Proteinuria >0.5 g/d, or >3+, or cellular casts.
8. Neurologic disorder	Seizures without other cause or psychosis without other cause.
9. Hematologic disorder	Hemolytic anemia or leukopenia (<4,000/μL), or lymphopenia (<1,500/μL), or thrombocytopenia (<100,000/μL) in the absence of offending drugs.
10. Immunologic disorder	Positive lupus erythematosus cell preparation or anti-dsDNA or anti-Sm antibodies or false-positive VDRL.
11. Antinuclear antibodies	An abnormal titer of ANAs by immunofluorescence or an equivalent assay at any point in time in the absence of drugs known to induce ANAs.

ANAs, antinuclear antibodies.
[a]If four of these criteria are present at any time during the course of disease, a diagnosis of SLE can be made with 98% specificity and 97% sensitivity.

Drug-induced SLE is a distinct entity that has been associated with many medications, including procainamide, hydralazine, anticonvulsants, chlorpromazine, isoniazid, methyldopa, penicillamine, quinidine, propylthiouracil, and sulfasalazine. Drug-induced SLE has a milder course than idiopathic SLE and does not cause renal or central nervous system involvement (8). Specialized ANA testing panels reveal only histone-binding ANAs rather than the multiple varieties characteristic of SLE (1).

The evaluation of patients with established SLE should focus on the presenting complaint. However, attention should also be given to signs and symptoms of the potentially life-threatening

complications of SLE, such as thrombotic disease, pleural and pericardial effusions, and infections secondary to immunosuppressive therapy.

Patients presenting with new-onset monoarthritis or oligoarthritis generally require diagnostic arthrocentesis to rule out infection or crystal-induced arthritis. Fluid should be sent for Gram stain, culture, cell count and differential, and examination for crystals. The synovial fluid in autoimmune arthritis is typically inflammatory, with an elevated white cell count (20,000 to 80,000/μ L mixed polymorphonuclear cells and lymphocytes), a negative Gram stain, and no crystals.

The specific organs affected by SLE and the severity of the disease vary widely between individuals and over time in any given individual. Not only does the variability of the disease make diagnosis difficult, but, with the exception of the characteristic rash, each of the manifestations of lupus may occur from other causes. Although a presentation of one of these conditions alone would not prompt consideration for autoimmune disease, recurrent symptoms or the sequential development of multiple conditions associated with lupus warrants referral for ANA testing.

ED MANAGEMENT

The specific presentation dictates the management indicated in the ED. Patients presenting with mild symptoms may require nothing more than screening for renal and hematologic involvement with a urinalysis and complete blood cell count. More severe symptoms are managed as in any other disease. For example, a large pleural effusion should be tapped, and anticoagulation should be started for thromboembolic disease.

ST elevations and PR depressions seen on the electrocardiogram that are associated with a pericardial friction rub indicate pericarditis. If pericarditis is suspected, a careful evaluation should be made for signs of pericardial tamponade including a bedside echocardiogram if available. Elevated neck veins, elevated pulsus paradoxus, or hypotension should prompt a formal urgent

echocardiogram to rule out tamponade. Infectious complications should be considered in patients with established disease who are taking chronic immunosuppressive medications.

Patients with significant pleural or pericardial effusion, or any thrombotic complication, require hospital admission and rheumatologic consultation. Immunosuppressed patients with documented infection require admission for parenteral antibiotics.

Neuropsychiatric complications are frequent in SLE. Cerebritis, aseptic meningitis, seizures, ischemic strokes, peripheral neuropathy, and acute psychosis are all recognized manifestations of SLE. Corticosteroid treatment and other immunosuppressive agents predispose to infectious meningitis and corticosteroid-induced psychosis.

The acute presentation of an SLE patient with a neuropsychiatric complaint is always a challenge. The diagnosis of lupus flare should be made only after infectious etiologies have been ruled out. Patients presenting with severe disease are often treated with "stress" doses of corticosteroids (hydrocortisone, 100 mg intravenously, or methylprednisolone, 125 mg intravenously) and often receive empiric broad-spectrum antibiotic coverage after samples of blood, urine, sputum, and possibly cerebral spinal fluid are obtained for culture.

Patients with established disease who present with a flare of symptoms may require the initiation of corticosteroids or an increase in the dose. When more than 5 to 10 mg of prednisone a day is required, many rheumatologists prescribe combination therapy in an effort to limit adverse effects. Medications commonly used include nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarial agents, cyclophosphamide, and mycophenolate mofetil. More recently B-cell inhibitors, including rituximab and belimumab, have been found useful in treatment of SLE patients resistant to more traditional therapy. Because every therapeutic agent has adverse effects, the risks of medication must be weighed against the morbidity of the clinical presentation. The aggressiveness and urgency of treatment depend on the presence of major organ

involvement. Changes in a patient's usual medication regimen are best carried out in conjunction with the patient's rheumatologist.

DISPOSITION

Patients with suspected or newly diagnosed SLE may be managed as outpatients, if the manifestations are mild and a life-threatening pathologic process is absent. An ANA panel should be ordered. Rheumatologic consultation can be obtained by telephone concerning any further studies, initiation of corticosteroid therapy, and appropriate follow-up. Newly diagnosed patients with SLE should be educated about the importance of adequate sleep and avoidance of ultraviolet light. Ibuprofen and estrogens may exacerbate disease and should be avoided (3). Hypertension should be controlled vigorously because it appears to have a synergistic effect in exacerbating renal disease. In drug-induced lupus, after the medication is discontinued, symptoms usually resolve within days to weeks (8,9).

Common Pitfalls

- Failure to recognize vague, atypical complaints as a presentation of SLE or other autoimmune disease.
- Failure to include SLE in the differential diagnosis of patients with pericarditis, pleuritis, renal dysfunction, neurologic symptoms, or recurrent venous thrombosis.
- Failure to differentiate disease exacerbation from an adverse effect of therapy.
- Failure to suspect infection in an immunosuppressed patient.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by widespread synovial inflammation and, often, progressive destruction of joints. It affects women three times as often as men. The prevalence increases with age and is approximately 1%.

The pathophysiology of RA involves the production of immunoglobulins against native IgG; these immunoglobulins are referred to as rheumatoid factor. Helper T-cells are also activated and produce lymphokines that promote cellular proliferation (10). Recently, researchers have identified autoantibodies to the citrullinated protein filaggrin that seem to be sensitive and specific for RA. Citrullinated proteins are exclusively produced in the synovial tissue. These autoantibodies to citrullinated proteins may be the initial target of the autoimmune response in RA (11). Activation of the inflammatory response leads to the elaboration of vasoactive substances, chemotactic factors, and complement in synovial tissues. Mononuclear cells infiltrate the subsynovial stroma, and polymorphonuclear cells appear in the synovial fluid. A "pannus" of inflamed, thickened, redundant synovium invades and replaces cartilage and periarticular bone and tendon. Polymorphonuclear cells in the synovial fluid release lysozymes that break down hyaluronic acid polymers in the synovial fluid and articular cartilage (1). Although the symptoms and signs are primarily related to the joints, RA is a multisystem autoimmune disease that frequently involves the heart, lungs, and blood.

CLINICAL PRESENTATION

RA typically presents initially as constitutional symptoms such as low-grade fever, weight loss, fatigue, and lymphadenopathy. Joint stiffness in the morning or after periods of inactivity may also be a complaint.

Articular symptoms initially involve any number or size of joints. Either arthralgia (pain) or arthritis (inflammation) may be present in an unpredictable pattern. Later, in established disease, the typical symmetric pattern of arthritis develops.

The most commonly affected joints are the metacarpophalangeal and proximal interphalangeal joints, wrists, knees, and upper spine. Although some cases of RA remain mild or even resolve, the typical course is one of unpredictable exacerbations and remissions with progressive deformity and disability.

As tissue damage progresses, typical ulnar deviation of the carpometacarpal joints and valgus deformity of the knees develop. Baker cysts may develop in the popliteal fossa. Of prime importance for the emergency physician is the development of instability of the atlantoaxial joint, with laxity and even rupture of the transverse ligament. The result is an unstable cervical spine, which may lead to spinal cord compression following even apparently trivial injury (6).

RA is a systemic disease. Over time, subcutaneous nodules over the elbows, occiput, and sacrum, thought to be vasculitic in origin, develop in 20% to 25% of patients. Pericarditis, pleuritis, pulmonary fibrosis, scleritis, Sjögren syndrome, nerve entrapment, and vasculitis may also occur. Felty syndrome, consisting of splenomegaly, anemia, thrombocytopenia, and granulocytopenia, sometimes complicates RA.

DIFFERENTIAL DIAGNOSIS AND ED EVALUATION

RA is rarely misdiagnosed when it reaches the stage of symmetric polyarthritis in characteristic joints. At earlier stages, or with milder involvement, the clinical picture may be suggestive of inflammatory or infectious joint disease or other autoimmune diseases. When joint manifestations become apparent, infectious and crystalline synovitis must be considered.

In practice, most patients presenting to the ED with oligoarthropathy should have joint aspiration to rule out infection or crystal-induced arthritis. Although RA or another autoimmune disorder may be suspected, the definitive diagnosis is made at follow-up, when further data, such as final culture results, rheumatoid factor tests, and response to anti-inflammatory therapy, are available.

In 2010, the American College of Rheumatology and the European League against Rheumatism developed new diagnostic criteria that focus on early diagnosis (Table 178.3) (12). In practice, most such patients presenting to the ED must have other significant disease ruled out (e.g., infectious arthritis, SLE). Although there may

be a suspicion of RA, the definitive diagnosis is usually made on further evaluation at follow-up.

TABLE 178.3
ACR/EULAR Criteria for the Diagnosis of Rheumatoid Arthritis

Target population (who should be tested?): Patients who	
1. have at least one joint with definite clinical synovitis (swelling)	
2. have synovitis not better explained by another disease	
Classification criteria for RA (score-based algorithm: Add score of categories A–D; a score of >6/10 is needed for classification of a patient as having definite RA)	
A. Joint involvement	Score
1 large joint	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least one small joint)	5
B. Serology (at least one test result is needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least one test result is needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
<6 wks	0
>6 wks	1

RF, rheumatoid factor; ACPA, anticitrullinated protein antibodies; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate.

From Aletaha D, Neogi T, Silman AJ, et al. Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League against rheumatism collaborative initiative. *Ann Rheum Dis*. 2010;69:1580–1588.

Patients with known RA who present with an exacerbation of joint inflammation require evaluation for possible secondary infections or crystalline arthropathy. Others may present with new systemic symptoms. Although the problem may be related to RA, this relationship should not be assumed to be the case until other

serious causes have been excluded. Evaluation based on presentation should be pursued as in any patient without RA. Special consideration should be given to complications of therapy; for example, pulmonary interstitial disease may be a result of either RA or treatment.

If a diagnosis of RA is considered, a rheumatoid factor titer should be ordered. If other autoimmune disorders are considered possible, other autoantibody titers, complement levels, and an erythrocyte sedimentation rate (ESR) may be indicated. Monoarticular or oligoarticular arthritis should cause one to consider crystalline and infectious arthritis. Joint aspiration is indicated, as well as oropharyngeal and genital cultures for *Neisseria gonorrhoeae.*

Few laboratory test results are abnormal in RA, and the results tend to be nonspecific. The ESR is elevated and parallels disease activity. There may be a mild normocytic anemia. A test for mixed cryoglobulins, reflecting large amounts of circulating immune complexes, may be positive, but complement levels are usually normal. Arthrocentesis of involved joints typically yields sterile fluid with hallmarks of inflammation such as decreased mucin clot formation and 20,000 to 80,000 white blood cells per microliter, of which 50% to 70% are polymorphonuclear cells (13). The classic laboratory finding of a positive serum rheumatoid factor is found in 80% of patients, but a positive rheumatoid factor can also be found in 1% to 5% of persons without RA (e.g., patients with other rheumatic disorders, leprosy, tuberculosis, liver disease, or bacterial endocarditis).

ED MANAGEMENT AND DISPOSITION

NSAIDs are the mainstay of chronic treatment of RA. Patients experiencing a flare of known disease often require therapy in addition to NSAIDs. These therapies include heat modalities, antimalarial agents, sulfasalazine, methotrexate, and surgical replacement of joints. Recently, several biologic therapies have become available for RA that interfere with the action of tumor necrosis factor, B-cells, T-cells, and interleukin-6. These drugs have

been shown to improve symptoms and slow progression of disease in those patients who have had an inadequate response to traditional therapies (14,15).

Corticosteroids are usually reserved for the treatment of extra-articular manifestations. Each of the therapeutic agents has associated adverse effects. Sulfasalazine may cause leucopenia. The antineoplastic agents can cause myelosuppression and a host of other adverse effects. Biologic therapy has been associated with infections and may be associated with increased incidence of demyelinating disease, lymphoma, and worsening symptoms of congestive heart failure. These antineoplastic and biologic agents should be initiated only after discussion with a rheumatologist who will be observing the patient.

Appropriate disposition depends on the severity of the presenting symptoms. Outpatient treatment is appropriate in individuals who do not appear toxic, including those with a new diagnosis of RA. These patients should be started on a standard dose of an NSAID and have rheumatologic follow-up arranged. Patients who appear ill require hospital admission for more intensive evaluation to rule out infectious disorders and rheumatologic consultation. Hospitalization may be required for social reasons or when disability prevents adequate functioning at home.

Common Pitfalls

- Prescribing corticosteroids as a first-line therapy for RA.
- Failure to recognize nonspecific complaints as a manifestation of autoimmune disease.
- Failure to consider possible C1–C2 instability when intubating an RA patient.

SCLERODERMA

Scleroderma (or systemic sclerosis) is an autoimmune disorder characterized by abnormal collagen production that results in pathologic fibrosis of the skin and internal organs. It occurs equally in all races and geographic areas, but it is four times more common

in women than in men. In most cases, the onset is during the third decade of life (16). The course is typically progressive over decades, but it may be fulminant and fatal. Collagen accumulation and endothelial cell proliferation in the vascular intima lead to severe narrowing of the arterial lumen.

Scleroderma can be classified according to its predominant manifestations. The CREST syndrome consists of subcutaneous calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia and is associated with a specific antibody (17,18). “Diffuse scleroderma” denotes the full systemic disease. A third subset is mixed connective-tissue disease or undifferentiated connective-tissue disorder, which combines features of SLE, scleroderma, and polymyositis. Clinical criteria have been developed for the diagnosis of systemic sclerosis (Table 178.4).

TABLE 178.4
Clinical Criteria for the Diagnosis of Systemic Sclerosis

Major Criterion	
Proximal scleroderma	Typical sclerodermatous skin changes involving areas proximal to the metacarpophalangeal or metatarsophalangeal joints or affecting other parts of the extremities, face, neck, or trunk; usually bilateral, symmetric, and almost always including similar changes in the digits
Minor Criteria	
Sclerodactyly	Sclerodermatous skin changes limited to the digits
Digital pitting, scars, or loss of substance from the finger pad	Depressed areas at the tips of digits or loss of digital pad substance from the finger pad tissue as a result of digital ischemia rather than trauma or exogenous causes
Bibasilar pulmonary fibrosis	Bilateral reticular pattern of linear or lineonodular densities that are most pronounced in basilar portions of the lungs on standard chest roentgenogram; may assume appearance of diffuse mottling or "honeycombing lung" and should not be attributable to primary lung disease

Classification as definite systemic sclerosis requires the presence of the major criterion or two or three of the minor criteria. From D'Cruz DP, Khamashta MA, Hughes GR. Systemic lupus erythematous. *Lancet*. 2007;369:587–596.

CLINICAL PRESENTATION

Patients with scleroderma most commonly present to the ED because of painful fingers due to Raynaud phenomenon, dyspnea due to restrictive lung disease, or dysphagia due to esophageal dysfunction. Malignant hypertension due to scleroderma renal disease is a true emergency.

Raynaud phenomenon is present in virtually all cases of scleroderma and is the initial manifestation in 70% of cases. Skin involvement is usually first manifested as edema of the fingers. As the disease progresses, the skin becomes shiny and taut with loss of the normal skin folds. Joints become immobilized from tight encasement in thickened skin and from contractures of muscles, tendons, and palmar fascia.

DIFFERENTIAL DIAGNOSIS AND ED EVALUATION

Established scleroderma causes a characteristic taut, smooth appearance of the hands and face. This sign should be apparent to the physician, although the patient may not have noticed the gradual changes.

Early disease may be difficult to recognize, however. The most common early symptom is painful fingers caused by Raynaud phenomenon, but this symptom is a nonspecific feature of many autoimmune disorders that may also be caused by occlusive arterial disease, repetitive trauma to the fingers, cryoglobulinemia, neurogenic lesions, or vasospastic drugs. Raynaud phenomenon unassociated with scleroderma is extremely common in women. Specific autoantibody testing may distinguish early cases of scleroderma from other causes of Raynaud phenomenon. Radiography of the hand may also be helpful. Subcutaneous calcinosis and resorption of the tufts of the distal phalanges are pathognomonic findings. More than 90% of patients with scleroderma have a positive ANA test.

An awareness of the systemic manifestations of disease is important in the evaluation of the patient with known scleroderma. Systemic collagen deposition may result in cardiac conduction abnormalities or cardiomyopathy, restrictive lung disease and pulmonary hypertension, gastrointestinal dysmotility and malabsorption, and renal arteriolar necrosis leading to malignant hypertension. Recognition of these manifestations in patients with advanced illness is critical.

ED MANAGEMENT

The majority of patients with Raynaud syndrome do not have symptoms requiring treatment in an ED. Patients with persistent vasospasm may respond to simple interventions, such as warming of the hands or oral administration of nifedipine. Only rarely are more invasive maneuvers, such as interarterial or local phenoxybenzamine or prazosin, required.

Systemic manifestations may require evaluation for dysfunction caused by scarring in many organ systems. Intestinal hypomotility

may be treated with metoclopramide. Esophageal reflux should be treated with antireflux maneuvers and medications as necessary. Patients with increased blood pressure, renal failure, and internal organ involvement are frequently treated with angiotensin-converting enzyme inhibitors.

DISPOSITION

Most patients with scleroderma do not require hospitalization, but admission may be necessary for dehydration due to gastrointestinal dysfunction or for pulmonary compromise. Patients with hypertensive emergency caused by renal crisis should be placed on nitroprusside and admitted to an intensive care unit. Patients with pulmonary artery hypertension can be treated with the endothelin receptor antagonist bosentan, which also has been shown to decrease the incidence of digital ulcerations in scleroderma (19).

Only those women with severe Raynaud phenomenon and those men without a history of trauma to the hands require periodic monitoring for the development of scleroderma. Patients should be instructed in the importance of keeping the hands warm and avoiding nicotine and caffeine. Suppressive pharmacologic therapy may be necessary if attacks are frequent.

Patients with signs and symptoms beyond Raynaud phenomenon should be referred for diagnostic autoantibody testing, occupational therapy, or orthopedics.

Common Pitfalls

- Failure to consider the systemic manifestations of scleroderma.
- Failure to recognize scleroderma as the cause of a hypertensive emergency.

GIANT-CELL ARTERITIS

Giant-cell arteritis is characterized by inflammation of branches of the carotid artery (temporal arteritis) or the aortic arch (Takayasu arteritis) and can present with emergent manifestations.

CLINICAL PRESENTATION

Temporal arteritis usually occurs in women older than 50 years. Symptoms may be nonspecific: Fever, headache, myalgias, and fatigue. Patients may have the syndrome of polymyalgia rheumatica, manifested by chronic stiffness and aching of the neck, shoulder, and hip girdle. There is frequent vestibular dysfunction and hearing loss at presentation (20). Chronic or subacute headache is often the presenting complaint.

The temporal artery may be tender and nodular (21), and there may be jaw claudication. The chief complication of temporal arteritis is monocular visual loss caused by ischemic optic neuritis. Visual loss or impairment generally occurs 3 or 4 months after the onset of initial symptoms (22).

Takayasu arteritis has a predilection for involvement of branches of the aortic arch. It is a rare disease. Patients are usually young women who present with nonspecific symptoms of fever, night sweats, fatigue, myalgias, and weakness. Signs of large vessel occlusion with decreased peripheral pulses, cerebrovascular accidents, or myocardial ischemia occur only months to years after initial presentation (23).

DIFFERENTIAL DIAGNOSIS AND ED EVALUATION

The differential diagnosis of patients with temporal arteritis is wide because of the nonspecific symptoms. Mild anemia is typical. A markedly elevated ESR in a patient older than 50 with headache and nonspecific symptoms, particularly polymyalgia rheumatica, should prompt further evaluation.

Takayasu arteritis, although rare, should be considered in any young female with signs of large vessel ischemia (e.g., cerebrovascular accident, upper extremity ischemia, cardiac ischemia).

ED MANAGEMENT AND DISPOSITION

Patients with suspected temporal arteritis rarely need admission to the hospital. Prompt diagnosis and treatment are essential to

prevent visual impairment. In the ED, patients should be started on 40 to 60 mg of prednisone daily. Arrangements should be made for definite follow-up and semi-urgent temporal artery biopsy. Response to corticosteroid treatment is usually dramatic, with relief of systemic symptoms and headaches within days. Treatment is generally continued for 1 to 2 years.

The diagnosis of Takayasu arteritis is not usually made in the ED. The diagnosis should be entertained in young women who need admission for large vessel occlusive disease. Angiography of the affected vessels shows narrowing or occlusion of large vessels with well-developed collateral circulation (24). Recent advances in computed tomography (CT) and magnetic resonance angiography (MRA) make these modalities important in evaluating the great vessels in patients (25). No treatment has been proven effective, but corticosteroids, cyclophosphamide and Tocilizumab an interleukin-6 inhibitor have been used.

Common Pitfalls

- Failure to consider temporal arteritis in an elderly patient who presents with headache or shoulder and neck stiffness.
- Failure to consider Takayasu arteritis in a young woman with signs of large vessel occlusion.

CRITICAL INTERVENTIONS

- Perform a diagnostic arthrocentesis to rule out infection or crystal-induced arthritis in patients presenting with new-onset monoarthritis or oligoarthritis.
- Treat cervical spine trauma in the RA patient carefully because of the development of instability of the atlantoaxial joint.
- Initiate corticosteroid therapy in the ED in the patient suspected of having temporal arteritis.

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SECTION XIX
Infectious Disease Emergencies

Section Editor: JEFFREY J. SCHAIDER

CHAPTER 179

Bacteremia, Sepsis, and Septic Shock

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Bacteremia is defined as the presence of viable bacteria in the blood. Bacteremia can be transient, which is commonly seen after injury to mucosal surfaces (e.g., from tooth brushing, urethral catheterization, sigmoidoscopy, etc.). In these cases, the intact host defenses neutralize the bacteria and their harmful products, preventing clinically significant manifestations of infection. In other situations, bacteremia triggers an activation of the inflammatory cascade, causing a condition known as sepsis. Sepsis is characterized by a host response to an infectious stimulus via endogenous mediators of systemic inflammation. In sepsis, the host response is as important as the source of infection in terms of pathophysiology and disease severity. Historically, definitions of sepsis have been diverse.

To promote uniformity of inclusion criteria in sepsis clinical trials, consensus conference definitions of sepsis were published by the American College of Chest Physicians and the Society of Critical Care Medicine in 1992 (Table 179.1) (1). The consensus conference definitions introduced the term *systemic inflammatory response syndrome* (SIRS). Indicators of systemic inflammation (SIRS criteria) are defined as the presence of two or more of the following conditions: (a) temperature $>38^{\circ}C$ or $<36^{\circ}C$, (b) heart rate >90 beats per minute, (c) respiratory rate >20 breaths per minute (or a $PaCO_2$ <32 mm Hg), or (d) white blood cell count $>12{,}000/mm^3$ or $<4{,}000/mm^3$ (or $>10\%$ band forms). The consensus conference also defined the terms *sepsis, severe sepsis,* and *septic shock*. *Sepsis* is

defined as two or more SIRS criteria in the presence of a known or presumed infection. *Severe sepsis* is defined as sepsis plus acute organ dysfunction attributable to sepsis. *Septic shock* is defined as profound sepsis-induced hypotension (systolic blood pressure [SBP] <90 mm Hg or a drop >40 mm Hg) accompanied by hypoperfusion abnormalities such as oliguria, acidosis, or alteration of mental status that is refractory to intravascular volume expansion (1). Although the SIRS classification is important from a research and epidemiologic perspective, the SIRS criteria are often overly sensitive and nonspecific in the emergency department (ED) setting and convey no incremental mortality risk. An increasing number of dysfunctional organs and septic shock are associated with increased mortality (2).

TABLE 179.1
Definitions

Systemic Inflammatory Response Syndrome (SIRS)

The physiologic response to a variety of severe clinical insults manifested by two or more of the following:

A. Temperature >38°C or <36°C

B. Heart rate >90 beats/min

C. Respiratory rate >20 breaths/min or a $PaCO_2$ <32 mm Hg

D. White cell count >12,000 cells/L, <4,000 cells/L, or >10% immature (band) forms.

Sepsis

The systemic response to infection manifested by the presence of SIRS.

Severe Sepsis

Sepsis associated with organ dysfunction or hypoperfusion. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

Septic Shock

Sepsis with hypotension (systolic blood pressure <90 mm Hg) despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

Multiple Organ Dysfunction Syndrome (MODS)

Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

Adapted from American College of Chest Physicians, Society of Critical Care Medicine, Consensus Conference. Definitions of sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med*. 1992;20:864–874.

Angus et al. (3) utilized international classification of diseases (ICD-9) codes for infection and acute organ dysfunction to estimate that 751,000 severe sepsis cases occur in the United States every year. An ED-based epidemiologic study estimated 571,000 cases of severe sepsis present to the ED annually. The incidence of sepsis cases is projected to increase sharply in the future because of age-based shifts in the demographics of patient populations.

In large clinical trials of septic shock, control arm mortality rates have ranged from 24% to 60% (4–6). Although septic shock mortality reportedly decreased from the 1960s to the 1990s, an increase in mortality (1.5% per year) has been observed since 1995 (7). This increase has been attributed to the emergence of multidrug resistant organisms, increasing numbers of immunosuppressed

patients, and an age-based shift in the demographics of sepsis patients. With advances in cardiovascular and respiratory support of high-severity patients, the major threat to survival is not a sudden decompensation or a specific complication but a process of progressive failure of multiple organs. This process has been termed *multiple organ dysfunction syndrome* and is the major cause of death in patients with severe sepsis and septic shock.

CLINICAL PRESENTATION

Bacteremia is usually found in association with an acute illness and symptoms of fever, chills, and general illness forming the so called toxic state. Bacteremia and sepsis are dynamic processes in which the observed clinical manifestations depend on the point in the disease course the patient presents and the degree that the body's immune system and inflammatory cascade have been activated. Patients who progress to sepsis typically present with signs of systemic inflammation including fever, tachycardia, tachypnea, or elevated white blood cell count. Not all patients have a classic presentation or dramatic inflammatory response such as the elderly and the immunocompromised. The ED presentation of sepsis is not always clinically apparent in the initial stages. Because sepsis can be devastating, the ED physician must maintain heightened awareness and index of suspicion when evaluating patients with suspected bacteremia or sepsis.

Patients who progress to severe sepsis (sepsis plus organ failure) develop one or more organ dysfunctions including neurologic, respiratory, renal, hepatic, metabolic (acid–base), hematologic, or cardiovascular dysfunction. Central nervous system dysfunction typically presents as lethargy or acute alteration of mental status. Respiratory system dysfunction may include acute hypoxemic respiratory failure from acute lung injury/acute respiratory distress syndrome (ALI/ARDS). Acute renal insufficiency is common and may progress to oliguric renal failure. Cholestasis is the most common sign of hepatic dysfunction. Metabolic derangements include hyperglycemia and severe metabolic acidosis (usually from elevated lactate levels). Hematologic manifestations include a consumptive

coagulopathy, which is typically subclinical (8) but may present initially with thrombocytopenia and progress to disseminated intravascular coagulation (DIC).

The cardiovascular manifestations of sepsis are numerous, for septic shock is the most complex of all shock profiles. In septic shock, three different components of shock etiology may be occurring at the same time, especially during acute phase ED management (9). Septic shock may have features of cardiogenic shock (secondary to cytokine-induced myocardial depression), hypovolemic shock (secondary to profound capillary leak), or distributive shock (secondary to vasodilation). Because the proinflammatory response in sepsis causes diffuse microvascular injury with capillary leak, the septic shock patient often has a markedly decreased cardiac preload, especially in the initial phases of ED resuscitation. Although septic shock is typically considered a high–cardiac output vasodilatory shock (“warm shock”), the combination of myocardial depression and markedly decreased preload in the early hours of disease presentation cause the early stages of sepsis to sometimes manifest a low cardiac output (“cold shock”).

Fluid resuscitation administered in the acute phase of therapy actually modulates the hemodynamic profile of septic shock (9). Only after achieving restoration of cardiac-filling pressures with aggressive intravascular volume expansion will a septic shock patient be able to generate a high cardiac output. Despite cytokine-induced depression of the cardiac ejection fraction, a high cardiac output can be generated (after restoration of cardiac-filling pressures) because of tachycardia and ventricular dilation. Hypoperfusion abnormalities in septic shock may persist despite a normal or high cardiac output caused by marked peripheral vasodilation and alterations in blood flow distribution to the tissues (distributive shock) (10). The hallmark of septic shock is vasodilation (low systemic vascular resistance), causing arterial hypotension that requires vasopressor support. At the microcirculatory level, tissue perfusion abnormalities may exist in the absence of arterial hypotension and may manifest as lactic acidosis in normotensive sepsis (11).

DIFFERENTIAL DIAGNOSIS

The clinical signs of bacteremia and sepsis may be subtle and difficult to detect. In other instances, infection and systemic inflammation may be obvious, but the source of the infection may be difficult to identify. Although an inflammatory response is often caused by a bacterial infection, other possible etiologies must be considered. Acute infections caused by viruses, rickettsiae, mycobacteria, and parasites may present as acute "sepsis," but severe infection caused by these organisms is less common than that caused by bacteria. Early diagnosis of sepsis requires an awareness of specific predisposing host factors.

In addition to identifying the presence of a bacterial infection, one needs to localize the source of infection (i.e., pulmonary, intra-abdominal, skin, urogenital, or cerebrospinal fluid) and determine the most likely organism(s). This knowledge will help guide therapy, including source control and antibiotic selection. Consideration must be given to a wide variety of host factors that may alter the spectrum of probable organisms such as recent hospitalization or an immunocompromised state (HIV, chemotherapy, elderly, diabetes, etc.).

Diagnoses such as pancreatitis, congestive heart failure, adrenal dysfunction, hypothalamic injury, overdose, diabetic ketoacidosis, anaphylaxis, heat exhaustion, and neuroleptic malignant syndrome may mimic the inflammatory response seen with sepsis.

Although an elevated temperature often represents infection, at times it may be misleading. Hyperthermia and heat stroke may mimic many of the cardiopulmonary and neurologic manifestations of sepsis. Chills are not expected with heat stroke. Identification and confirmation of a source of infection through history, physical examination, laboratory testing, and radiologic studies can help narrow the differential.

The recognition of the shock state is essential in the approach to the septic patient. Patients with an SBP <90 mm Hg with accompanying evidence of tissue hypoperfusion (e.g., encephalopathy, acidosis, oliguria/renal insufficiency, poor skin perfusion, etc.) after an initial fluid challenge are considered to be in

shock. In septic shock, although initially a low–cardiac output "cold shock" state may be observed, the patients are classically (post resuscitation) in a hyperdynamic state with warm extremities and tachycardia. Cardiogenic shock patients tend to have cool extremities as a result of a compromised cardiac output and may show signs of cardiac ischemia through complaints of chest pain, shortness of breath, or an acute injury pattern on electrocardiogram. Hemorrhagic shock patients will typically have evidence of low hemoglobin concentrations, a source of blood loss, and cold and clammy extremities accompanied by flattened neck veins, tachycardia, and the absence of infectious symptoms. Patients with anaphylactic shock can typically be identified by an urticarial rash, pruritus, bronchospasm, throat tightness, and a history of exposure to a known allergen. Patients with neurogenic shock caused by spinal cord injury should be easy to identify by evidence of paralysis. Assessing the etiology of the patient's shock state is critical for guiding clinical management.

One must consider a broad differential in determining the presence of an infection, whether it is bacterial, viral, parasitic, or otherwise. In assessing the response to infection to determine whether it is sepsis, many other diagnoses need to be entertained. Once a shock state is reached, assessing the presence or absence of characteristic findings of the various shock profiles may help to determine the etiology of the shock.

ED EVALUATION

Because sepsis may progress rapidly, the ED evaluation must be expeditious. Appropriate stabilization measures are often carried out simultaneously with assessment. Vital signs must be reviewed. Unexplained tachycardia or tachypnea may be early clues to infection. Oral temperatures do not always accurately reflect core temperature. Rectal temperature measurement is recommended in any patient with suspected hypothermia or fever.

The physical examination should concentrate on potential sources for sepsis including lungs, abdomen, urinary system, central nervous system, and skin as the most common locations. Violation of a

mucosal or cutaneous barrier carries the risk of sepsis. All indwelling catheters and lines are possible sources of infection.

A wide variety of laboratory and ancillary tests are potentially useful in assessing the septic patient, but the following basic tests usually yield the most information: chest radiograph; serum electrolytes, glucose, blood urea nitrogen, and creatinine determinations; complete blood cell count, including white blood cell count and differential; urinalysis; blood cultures; and cultures of overt foci of infection. A serum lactate level helps to assess severity of illness and to predict risk (12).

Many of the patients who present to the ED with fever and possible sepsis have localizing signs or symptoms, which identify a focal infection. More difficult to assess are those patients without localizing signs or symptoms. One study found temperature >101°F, indwelling vascular catheter, clinical suspicion of endocarditis, age >65 years, chills, vomiting, hypotension, neutrophils >80%, white blood count >18,000 cells/mm^3, bands >5%, platelets <150,000 cells/mm^3, and creatinine >2 mg/dL to be associated with an increased prevalence of bacteremia (Table 179.2) (13). Applying the rule was shown to be 98% sensitive and 29% specific in a derivation set and 97% sensitive and 29% specific in a validation set.

TABLE 179.2
Presence of Bacteremia in Adults Presenting to the Emergency Department with Suspected Infection

Major Criteria:		Minor Criteria: (1 Point Each)
Suspect endocarditis	(3 points)	Temp 101–102.9°F (38.3–39.3°C)
Temp >103°F (39.4 °C)	(3 points)	Age >65 yr
Indwelling vascular catheter	(2 points)	Chills
		Vomiting
		Hypotension (systolic blood pressure <90 mm Hg)
		Neutrophils >80%
		White blood cells >18,000 cells/mm^3
		Bands >5%
		Platelets <150,000 cells/mm^3
		Creatinine >2 mg/dL

Decision rule: Either 1 major criterion or 2 or more minor criteria is an indication to obtain a blood culture. If these criteria are not present, a blood culture is not indicated by the rule.

Assessing patients for severity of illness and risk of mortality is always difficult, especially in the ED. A number of scoring systems have been created for this purpose in the intensive care unit (ICU) patients, including the APACHE-II, SOFA, MODS, and MPM-II scores. There is one scoring system specifically derived and validated in the ED setting for patients with suspected infection, the mortality in emergency department sepsis (MEDS) score. The MEDS score was created to identify patients at increased risk of death among ED patients presenting with possible infection. The components of the rule and scoring system are shown in Table 179.3. The different risk factors are "red flags" that should be sought to identify ED patients who are at increased risk of death during their hospital admission (14).

TABLE 179.3
Mortality in Emergency Department Sepsis Rule

Variable	Odds Ratio	95% CI	Points
Terminal illness (<30 d predicted mortality due to underlying illness—e.g., end stage CA, AIDS)	6.1	(3.6–10.2)	6
Tachypnea (RR >20 breaths/min) or hypoxia (pox <90%)	2.7	(1.6–4.3)	3
Septic shock (SBP <90 mm Hg after fluid challenge)	2.7	(1.2–5.7)	3
Platelets <150,000/mm^3	2.5	(1.5–4.3)	3
Bands >5%	2.3	(1.5–3.5)	3
Age >65 yr	2.2	(1.3–3.6)	3
Lower respiratory infection	1.9	(1.2–3)	2
Nursing home resident	1.9	(1.2–3)	2
Altered mental status	1.6	(1–2.6)	2
Mortality Estimates:			
Mortality Risk	**Points**		**Mortality**
Very low	0–4		0.9%
Low	5–7		2%
Moderate	8–12		7.9%
High	13–15		20%
Very high	>15		50%

MEDS score used to identify ED patients with suspected infection at increased risk of death. Mortality estimates are determined using a point system derived from the clinical variables.
RR, respiratory rate; SBP, systolic blood pressure.

ED MANAGEMENT

Stabilization often begins before assessment is complete. Careful attention to the basic principles of the ABCs of emergency medicine resuscitation is essential (airway, breathing, and circulation). One should have a low threshold for intubation. Wheeler and Bernard reported that 85% of patients with severe sepsis are ultimately intubated. Early intubation not only protects the airway but also reduces work of breathing and improves oxygen delivery (15). Adequate intravenous (IV) access should be ensured, cardiac monitoring should be instituted, and fluid resuscitation should begin. Early and aggressive resuscitation to reduce tissue hypoxia and organ dysfunction, coupled with appropriate antibiotics or surgical intervention, is warranted to reduce subsequent morbidity and mortality.

KEY TESTING

Laboratory testing:

- Complete blood count with differential (assess for leukopenia or leukocytosis, low hematocrit and adequate platelets, bandemia for immature cells)
- Basic chemistry
- Serum lactic acid level (for risk stratification)
- Consider liver function tests to assess for organ dysfunction or a gall bladder source of infection
- Urinalysis and culture as indicated
- Cerebrospinal fluid analysis as indicated

Radiology (guided by presentation)

- Chest x-ray
- Ultrasound or CT, based on potential focus of infection
- Cardiac echo as indicated

Fluids

Almost all patients with sepsis require IV volume expansion. The amount and rate of IV fluid infusion are guided by assessment of the patient's volume and cardiovascular status. Because of peripheral vasodilation and capillary leakage that are seen with sepsis, large quantities of fluid may be required to support the circulation. Volume administration may be best guided by observing the response of the central venous pressure (CVP) or pulmonary artery wedge pressure to aliquots of fluid given over a short period of time. In the absence of CVP monitoring, if there is a concern of causing pulmonary edema with aggressive intravascular volume expansion, fluid administration should be titrated using continuous pulse oximetry. Fluid administration is continued and slowed down when the supplemental oxygen requirement begins to increase.

It is important to maintain an aggressive fluid resuscitation in the elderly or those with a history of congestive heart failure. These patients require careful monitoring as the fluids are administered. Colloids (albumin, hetastarch) have no proven benefit over crystalloids (normal saline or Ringer lactate) in resuscitation (16).

Rivers et al. demonstrated the benefits of aggressive and goal-directed resuscitation of the septic patient in a randomized, double blind, placebo controlled trial (see Chapter 4, Shock). They used a combination of CVP monitoring, arterial blood pressure monitoring, and continuous measurement of mixed venous saturation from the superior vena cava ($ScvO_2$) to guide an aggressive ED resuscitation protocol for patients with septic shock or normotensive patients with a serum lactate level >4 mmol/dL. By continuously optimizing preload, perfusion, and oxygen delivery in the first 6 hours of a patient's care, mortality was reduced by 16% (absolute risk reduction).

The goal-directed protocol brings ICU level care into the ED and mandates an early resuscitation targeted to meet specific end points. Figure 179.1 summarizes the protocol. It normalizes preload by mandating a CVP of 8 to 12 mm Hg and corrects preload with fluid boluses if the CVP is low. Perfusion pressure is corrected with vasopressors and afterload reduction to obtain a mean arterial pressure between 65 and 90 mm Hg. Once preload and perfusion are normalized, the $ScvO_2$ is checked as a marker of tissue hypoxia. If preload and perfusion are normalized, and the $ScvO_2$ <70%, the patient is considered to be in a state of tissue hypoxia. This problem is addressed by first assuring that the patient has adequate oxygen carrying capacity (hematocrit >30%). If the hematocrit is low, the early goal directed therapy (EGDT) protocol calls for the patient to be transfused packed red blood cells. If the patient has adequate oxygen carrying capacity, and the $ScvO_2$ <70%, the EGDT protocol calls for dobutamine to improve cardiac output. Once all goals are met (ideally within the first 6 hours), the patient parameters are continuously monitored to ensure they stay in the normal range. A more recent randomized trial by Jones et al. demonstrated that the use of lactate clearance >10% was noninferior to $ScvO_2$ <70% as an endpoint of resuscitation. This supports the use of lactate clearance as an alternative endpoint (17). Treatment beyond the airway control and fluid resuscitation has four components: (a) parenteral

antibiotics, (b) removal or drainage of infected foci, (c) vasopressors, and (d) adjunctive therapies (e.g. steroids).

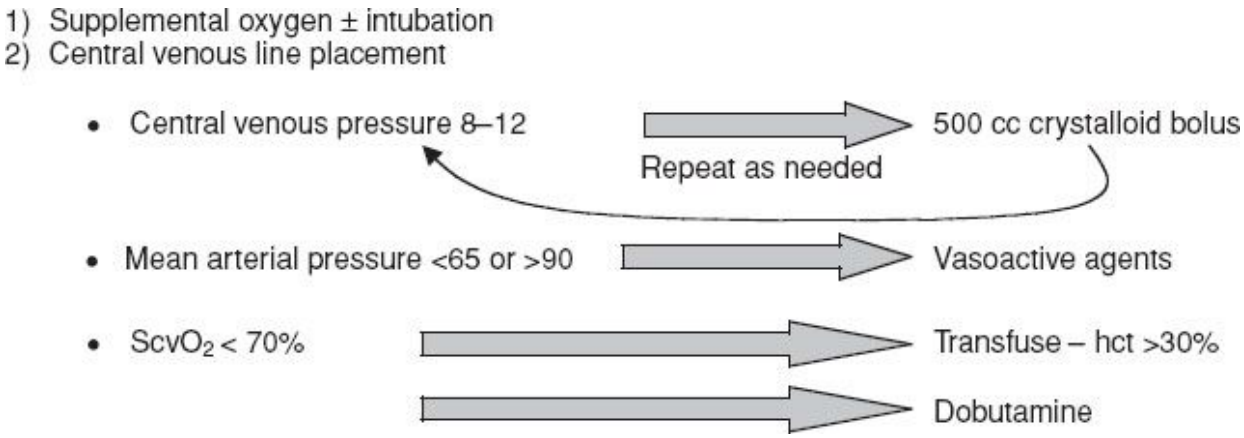

FIGURE 179.1 Summary of goal-directed therapy protocol.

Antibiotics

Initial parenteral antibiotics should be administered early in the ED course. Selection of particular agents is empiric, based on assessment of the patient's underlying host defenses, potential sources of infection, and probable responsible organisms. Antibiotics must be "broad-spectrum," covering both gram-positive and gram-negative bacteria, because both classes of organisms produce an identical clinical picture (Table 179.4).

TABLE 179.4
Antibiotic Regimens in Patients with Sepsis

	Modifying Factors	Antibiotic
Sepsis unknown source	Immunocompetent	Ceftriaxone (2 mg q12h IV) or Pipercillin (3 g q4h IV) or Imipenem (0.5 g q6h IV) or Meropenem (1 g q8h IV)
	For better *Pseudomonas* sp coverage	*plus* Gentamicin (2 mg/kg load then 1.7 mg/kg q8h IV)
	Immunocompromised (includes neutropenia and burns)	Pipercillin (3 g q4h IV) *plus* Gentamicin (2.0 mg/kg load then 1.7 mg/kg q8 h IV) or Ceftazidime (2 g q8h IV) *plus* Vancomycin (1 g q12h IV)
	Recent hospitalization or institutionalized	Add Vancomycin (1 g q12h IV) to the above regimen
Abdominal infection	Immunocompetent	Ampicillin (30 mg/kg q4h IV), *plus* Gentamicin (2 mg/kg load then 1.7 mg/kg q8h IV), *plus* Metronidazole (1.0 g q12h IV)
IV catheter infection (remove catheter)	Outpatient acquired MRSA suspected	Ceftriaxone (2 mg q12h IV) *plus* Vancomycin (1.0 g q12 h IV)
IV drug abuse	MRSA not suspected	Nafcillin (2 g q4h IV) *plus* Gentamicin (2 mg/kg load then 1.7 mg/kg q8h IV)
	MRSA suspected	Vancomycin (1 g q12h IV) *plus* Gentamicin (2 mg/kg load then 1.7 mg/kg q8h IV)

IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

For immunocompetent patients with an unknown source of sepsis, administer a single antibiotic with broad spectrum coverage such as ceftriaxone, piperacillin, imipenen, or meropenem. Immunocompetent patients with a suspected abdominal source of sepsis should receive ampicillin, gentamicin, and metronidazole or equivalent coverage from alternative antibiotics. A single broad-spectrum antibiotic is possible for immunocompromised septic patients, but most clinicians administer two broad-spectrum antibiotics with overlapping coverage (piperacillin plus gentamicin, or ceftazidime plus vancomycin). Septic patients who have had a recent hospitalization or are coming from a medical facility should receive vancomycin in addition to the other antibiotic coverage.

Patients with a history of IV drug abuse or those with indwelling catheters must also have appropriate antistaphylococcal coverage. Antipseudomonal coverage is critical in patients with neutropenia or burn sepsis.

Within these general guidelines, no one combination of antibiotics is clearly superior to another. The early and appropriate use of antibiotics has been shown to improve mortality (17). Failure to include adequate antibiotic coverage for the causative organism has been associated with an increased mortality risk.

Vasoactive Agents

If the patient's blood pressure does not respond to several liters of isotonic crystalloid (usually 4 L or more), despite an adequate preload being achieved (i.e., CVP 8 to 12 mm Hg), vasopressors are necessary. Several different agents (including norepinephrine, dopamine, phenylephrine, and vasopressin) are used to effectively achieve the blood pressure targets in septic shock (Table 179.5).

TABLE 179.5
Vasoactive Drugs Commonly Used in Septic Shock

Vasoactive Agent	Typical Dose	Vasoconstriction	Inotropy	Chronotropy
Norepinephrine	2–30 µg/min	++	+	+
Dopamine	6–20 µg/kg/min	+ (low dose) ++ (high dose)	++	++
Phenylephrine	20–200 µg/min	++	0	0
Vasopressin	0.01–0.04 U/min	++	0	0
Dobutamine	2.5–10 µg/kg/min	0 (mild vasodilation)	++	++

The two drugs most commonly used for initial management of septic shock are dopamine and norepinephrine. A relatively recent randomized trial demonstrated that the two drugs yielded equivalent outcomes overall; however, dopamine tended to be discontinued due to tachycardia (18). Only the subset of patients placed on vasopressors due to cardiogenic shock showed an outcome benefit with norepinephrine, while the septic shock subgroup showed no outcome benefit. Given the rate of undesired tachycardia with

dopamine, the evidence supports norepinephrine as the first vasopressor of choice in sepsis. Dopamine would be an acceptable second choice. Alternatively, the use of a pure α-agonist agent (vasoconstrictor) such as phenylephrine will not cause or exacerbate tachycardia and will probably also achieve blood pressure targets. The increase in afterload on the heart without any augmentation of cardiac contractility may decrease cardiac output in a patient who already has myocardial depression (either sepsis-induced or pre-existing).

Vasopressin is an agent that is gaining a larger role in management of septic shock (19). Via vascular smooth muscle receptors, vasopressin is a potent vasoconstrictor. In septic shock, a relative deficiency of endogenous vasopressin may develop, and this deficiency is thought to contribute to the pathophysiology of vasodilatory shock in sepsis. Low-dose vasopressin infusion can produce a dramatic restoration of blood pressure in septic shock. Consensus recommendations regarding the use of vasopressin in sepsis advocate that the agent be administered to patients with septic shock refractory to other vasoactive drugs (i.e., when other agents fail to achieve blood pressure targets) (20). The agent should only be administered in low doses (0.01 to 0.04 U/min) to replace a relative deficiency of endogenous vasopressin.

Because of potent vasoconstriction, vasopressin should be avoided in patients with known atherosclerotic heart disease and should not be administered in high doses. The vasoconstriction can increase afterload on the heart, which may impair cardiac output, especially if the patient has poor cardiac contractility. There are multiple trials currently under way to investigate whether or not vasopressin administration in septic shock improves outcome.

Inotropic support may be required for the patient with septic shock. If septic myocardial depression is identified either by echocardiography or by low-mixed venous oxygen saturation, an inotropic agent may be necessary. Although dobutamine is the most commonly used inotropic agent, it may cause mild vasodilation that could decrease blood pressure slightly. Administration of dobutamine may require some support from another vasoactive drug to safely

maintain blood pressure. As with dopamine, dobutamine may induce or exacerbate tachycardia to such an extent that diastolic-filling time and stroke volume decrease. Extreme tachycardia should be avoided if possible.

Adjunctive Therapy

The concept of corticosteroids as potent mediators of inflammation has been well explored in sepsis. There is theoretical and experimental support for the use of corticosteroids in severe sepsis and septic shock. Initially, a number of randomized human studies found that large doses of corticosteroids failed to prevent the development of shock, reverse the shock state, or improve the 14-day mortality. In a subsequent study Annane et al. were able to demonstrate a benefit of steroid supplementation in patients with adrenal suppression. However, a subsequent multinational, multicenter study of corticosteroids for severe sepsis patients (with an overall lower severity compared to the Annane trial) failed to show a mortality benefit. Steroids were more effective in reversing hypotension from presumptive adrenal suppression; however, there was an increase in secondary infection. While the data are still unclear, it is reasonable to consider steroid supplementation therapy in septic patients with hypotension refractory to vasopressors.

CRITICAL INTERVENTIONS

- Provide early airway management.
- Initiate aggressive fluid resuscitation.
- Identify the source of infection.
- Administer appropriate broad-spectrum antibiotics.
- Initiate aggressive resuscitation targeted to physiologic endpoints
- Fluid resuscitate to a CVP of 8 to 12 mm Hg.
- Start vasopressors for MAP <65 mm Hg after adequate initial fluid resuscitation.
- Transfuse to hematocrit $>30\%$ and initiate dobutamine if $ScvO_2$ $<70\%$.

DISPOSITION

The disposition of patients with a fever and no localizing signs of infection presents a dilemma. Otherwise healthy individuals who appear well and at low risk for occult bacterial infection can be discharged with instructions for fever control and a warning to return if symptoms persist or worsen. Patients who are elderly, have underlying immunodeficiency, or have disorders that predispose them to bacterial infection and other sepsis syndromes require a low admission threshold.

Given the 30% to 50% mortality for patients with septic shock and the benefit of intensive therapy, all patients with septic shock should be admitted to an ICU. Patients who are perceived to have high risk of developing septic shock, including normotensive patients with lactic acidosis, should be admitted to an ICU.

Common Pitfalls

- Failure to consider serious bacterial infection as a possibility in the evaluation of subtle signs and symptoms.
- Restriction of fluid resuscitation for fear of inducing pulmonary edema. Large quantities of fluid may be required in patients with sepsis.

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CHAPTER 180 Skin and Soft Tissue Infections

Clifford Rice

FOLLICULITIS AND CUTANEOUS ABSCESS

CLINICAL PRESENTATION

Folliculitis is an inflammation of hair follicles due to infection, overhydration, chemical irritation, or physical injury of the skin (1). The most common sites of involvement are the apocrine areas of the upper back, chest, buttocks, hips, and axillae. However, folliculitis can occur in any hair-bearing region of the body. The most common infecting organism is *Staphylococcus aureus,* but streptococci and gram-negative organisms are implicated in many cases. Since the mid-1990s, community-acquired methicillin-resistant *S. aureus* (CA-MRSA) has become an increasingly common and important cause of skin infections and folliculitis (2). Other bacterial causes include *Pseudomonas aeruginosa,* which has been reported after exposure to hot tubs and ordinary baths and showers (2). The individual lesion of folliculitis is a 2- to 5-mm dome-shaped pustule with a central hair shaft surrounded by a rim of erythema. Superficial folliculitis is often primarily pruritic rather than painful and heals without scarring. If inflammation progresses deeper into the follicle, pain and tenderness develop, and scar formation is more likely to occur with healing.

Pseudofolliculitis is a foreign body reaction caused by close shaving in persons of African descent. It is a noninfectious, inflammatory condition that can affect both men and women. The hair shaft becomes trapped below the follicle exit and, because of its propensity

for tight curling, grows into the follicular wall. Sycosis barbae is a deep infectious progression of pseudofolliculitis that, if untreated, can lead to significant facial scarring.

An untreated follicular infection, or one that does not resolve on its own, can evolve into a *furuncle, abscess,* or *carbuncle.* A furuncle is an infection of the hair follicle that extends into the subcutaneous tissue where it forms a small abscess. The bacteriology is the same as that of folliculitis, including CA-MRSA. A carbuncle is formed by multiple interconnecting furuncles that drain through several skin openings. Common locations of carbuncles include the chin, back of the neck, and scalp.

Cutaneous *abscesses* can also originate in any part of the body through local breaks in the skin. While skin abscesses can develop in healthy individuals, patients with diabetes, immunologic disorders, and inflammatory bowels disease, as well as intravenous (IV) drug abusers are at greater risk compared to the general population. Pure *S. aureus* is cultured in common abscesses; streptococci, gram-negative organisms, and anaerobes are recovered in other cases, often as polymicrobial cultures (3,4). CA-MRSA has recently been reported to be responsible from 21% to 80% of skin infections and abscesses (2). Among prisoners in San Francisco, the occurrence of CA-MRSA has increased from 29% of cases in 1997 to 74% in 2002 (2).

Prevalence of CA-MRSA in emergency department (ED) patients has been found to be as high as 56% in purulent skin and soft tissue infections, almost all of which are the same type, USA-300 (5). These soft tissue infections can be found in healthy children and young adults and can be severe and even life threatening. Although some can be traced back to hospital MRSA (H-MRSA), most infections are arising in the community de novo. Unexpectedly, CA-MRSA is genotypically and phenotypically unrelated to hospital-acquired MRSA (4). Fortunately, few strains are multiply resistant to antibiotics. There are no clear clinical characteristics that help differentiate between CA-MRSA and H-MRSA infections. CA-MRSA infections tend to occur in clusters; therefore, cultures are important to obtain in a suspected outbreak. Also, multiple risk factors for CA-

MRSA have been cited in the literature, including incarceration, men who have sex with men, patients with multiple abscesses at the same time, and IV drug abuse, among others (5).

A cutaneous abscess presents as a red, painful, usually fluctuant mass. The patient typically experiences discomfort and swelling for several days before presentation for care. Systemic symptoms (fever, chills, tachycardia, and malaise) are unusual, but can occur if the abscess is extensive, is surrounded by significant cellulitis, or extends along a mucous membrane such as the rectum or oral cavity.

Cutaneous abscesses are frequently associated with other conditions. Hidradenitis suppurativa is a recurrent, suppurative, and scarring disease of the apocrine glands, most commonly involving the axillae and pubic regions of persons of African descent. Their greater concentration of apocrine glands leaves these persons more susceptible to infection from chemicals (deodorants, depilatories), trauma (shaving), or poor hygiene. Hidradenitis can be divided into acute and chronic phases. In the acute phase, when burning and itching predominate, single abscesses can develop. In the chronic phase, sinus formation and honeycombed scarring can be seen. Multiple and recurring abscesses are not uncommon.

Abscesses of the buttock and perineum can arise from multiple sources (3). An abscess in the proximal buttock crease is often associated with pilonidal disease. This condition generally afflicts hirsute young males, but its origins are unclear (1). Ingrown hair or, possibly, congenital remnants of hair follicles and squamous epithelium at the sacrococcygeal junction predispose to abscess formation.

When an abscess arises close to the anus, careful differentiation has to be made between a true perianal and a simple buttock lesion. Perianal abscesses originate from anal crypts, are very painful on rectal examination, and are often associated with systemic symptoms such as fever, malaise, and anorexia (4,6). If left untreated, they can dissect proximally into the ischiorectal space and become perirectal abscesses. Recurrent or persistent buttock and perianal abscesses can originate from fistulous tracts created by inflammatory bowel disease.

Bartholin gland abscess is a common problem that can arise from duct obstruction and infection with vaginal flora. The Bartholin glands are located within the vaginal vestibule at the 4 o'clock and 8 o'clock positions. A cyst or infection manifests as a mass medial to and often including the labia minor. The predominant organisms are anaerobic, including *Bacteroides fragilis* and peptostreptococci, and are associated with a variety of gram-negative enteric organisms in mixed culture (6). Of the identified aerobic organisms, *Neisseria gonorrhoeae* is the most important because treatment of these abscesses should include antibiotics for sexually transmitted diseases.

DIFFERENTIAL DIAGNOSIS

When considering folliculitis, the differential diagnosis includes acne vulgaris, impetigo, cutaneous fungal infections, skin infestations (scabies), insect bites, HIV-associated eosinophilic folliculitis, and viral disorders (herpesvirus). The lesions of a systemic bacterial infection (*P. aeruginosa* and *N. gonorrhoeae*) can appear like scattered follicular disease. Abscesses have to be differentiated from other nodular lesions, such as uninfected cutaneous cysts, malignant tumors, nodular fungal lesions, and foreign body granulomas.

ED EVALUATION

When assessing a patient for folliculitis, furuncles, or a cutaneous abscess, the most important differentiation is between those lesions that contain pus and those that do not. Whenever there is doubt, bedside ultrasound or needle aspiration can be used to differentiate between superficial induration and the presence of a localized subcutaneous fluid collection suggesting abscess (Fig. 180.1) (7). If pus is discovered, incision and drainage should follow. There is controversy as to whether at-risk patients and patients in communities with high CA-MRSA prevalence should routinely have wound cultures done or routinely receive antibiotics. Generally, these are not recommended unless there is surrounding cellulitis, systemic toxicity, or recurrent abscesses (8).

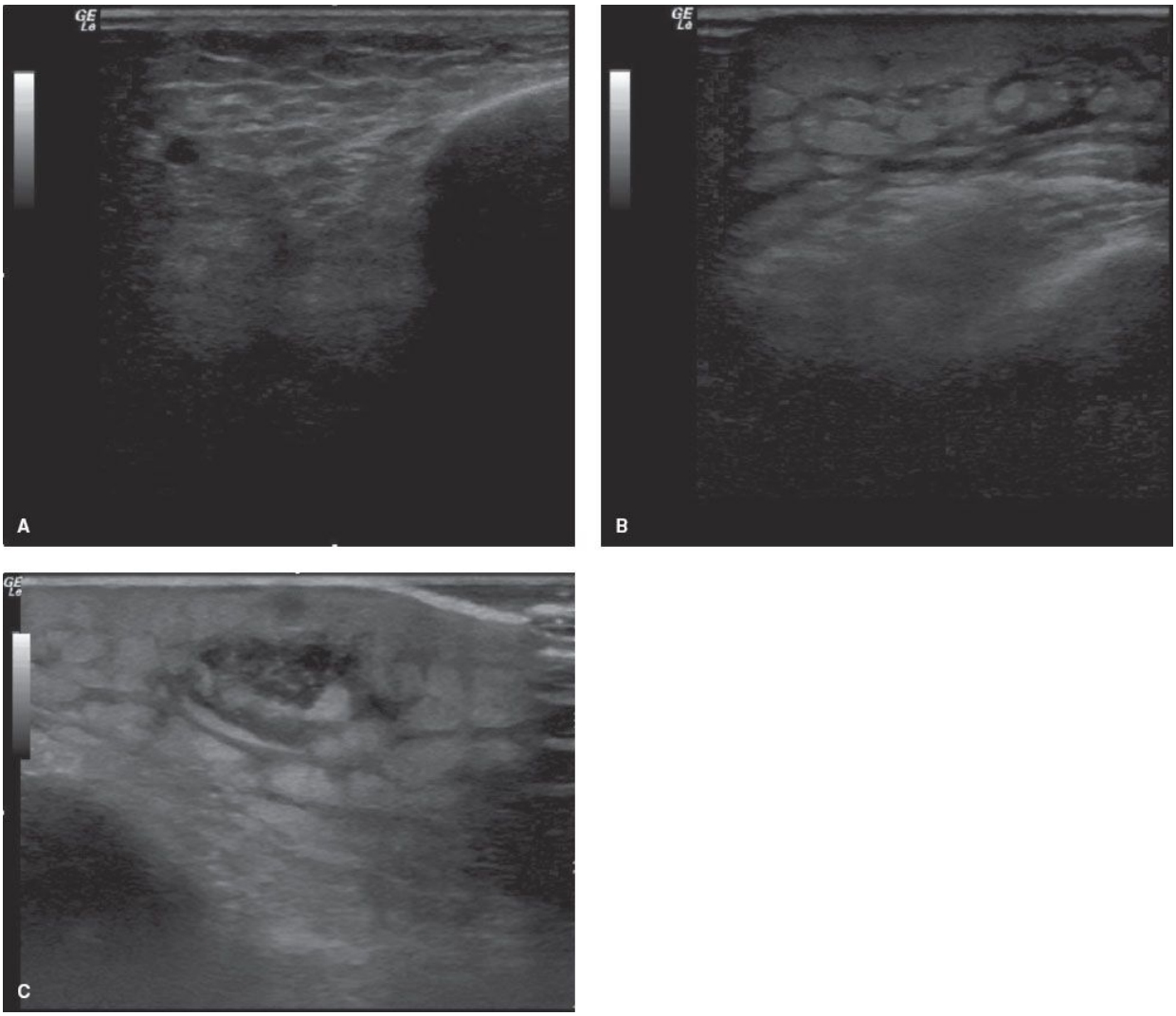

FIGURE 180.1 Ultrasound can be used in the arena of soft tissue infection to detect the presence or absence of localized fluid collections suggesting abscess. **A:** Ultrasound of normal superficial soft tissue. **B:** Ultrasound of cellulitis demonstrating the cobblestone appearance of the soft tissue when induration if present. **C:** Ultrasound demonstrating a well circumscribed fluid collection with surrounding cobblestoning seen in a patient with cellulitis with underlying abscess.

An assessment of underlying conditions is necessary to determine the overall risk to the patient. Patients with diabetes, immunosuppression, blood dyscrasia, altered white blood cell function, or valvular heart disease are at greater risk from cutaneous

infections. The presence of systemic signs such as malaise, fever, and tachycardia indicates a more widespread involvement of the cutaneous infection and requires a somewhat more extensive ED evaluation.

KEY TESTING

- Labs
  - Wound cultures in the presence of surrounding cellulitis, systemic toxicity, or recurrent abscesses
- Imaging
  - Bedside ultrasound to assess for subcutaneous fluid collection and help guide management

ED MANAGEMENT AND DISPOSITION

Treatment for folliculitis depends on the extent and depth of follicular involvement. For uncomplicated common folliculitis and hot tub folliculitis, removing the offending agent and a gentle regimen of once- or twice-daily skin cleansing with mild hand soap often suffices. This regimen can be supplemented by topical applications of antibiotics such as bacitracin and polymyxin B (Polysporin) or mupirocin (Bactroban). Pseudofolliculitis is managed by allowing the involved hair areas, usually on the face, to grow at least 2 to 3 mm above the surface. Special commercially available razors (PFB foil-guarded Remington and Norelco electric razors) are designed for people with this condition.

If the folliculitis is painful or more extensive and involves the deep portions of the follicle, a 5- to 7-day course of oral antibiotics is added to the aforementioned measures (Table 180.1). The risk of CA-MRSA has to be considered as well in the choice of antibiotics. Patients with recurrent folliculitis should seek follow-up for consideration of prophylactic measures, such as the prolonged administration of an oral clindamycin or intranasal mupirocin to eliminate an *S. aureus* carrier state (9).

TABLE 180.1
Oral Antibiotic Regimens for Adults with Uncomplicated Cutaneous Infections

Condition	Antibiotic	Dose	Interval
Erysipelas	Penicillin	500 mg	q6h
	Amoxicillin	500 mg	q8h
	Erythromycin	250 mg	q6h
MRSA	Clindamycin	300–450 mg	q6–8h
Furuncles, carbuncles, skin abscess, and purulent cellulitis (cellulitis with purulent drainage, with exudate, and without underlying abscess)	TMP-SMX	2 DS tabs	q12h
	Doxycycline	100 mg	q12h
	Linezolid	600 gm	q12h
Non-MRSA	Dicloxacillin	500 mg	q6h
Nonpurulent cellulitis	Cephalexin	500 mg	q6h
(Cellulitis without purulent drainage, without exudate, and without underlying abscess)	Clindamycin	300–450 mg	q6–8h
Empiric treatment for MRSA and β-hemolytic streptococci	Clindamycin	300–450 mg	q6h
Furuncles, carbuncles, skin abscess, and cellulitis	Amoxicillin *PLUS*	500 mg	q8h
	TMP-SMX	1 DS tab	q12h
	Amoxicillin *PLUS*	500 mg	q8h
	Doxycycline	100 mg	q12h
	Linezolid	600 mg	q12h
Hot tub folliculitis	Ciproflaxacin	250–500 mg	q12h
Impetigo	Mupirocin Ointment	Apply to affected area	q8h
Bartholin abscess	Ceftriaxone *PLUS*	250 mg IM	once
	Doxycycline	100 mg	bid

Untreated folliculitis can progress to a furuncle. If the furuncle has yet to suppurate, as demonstrated by the inability to obtain pus on needle aspiration, a regimen of warm soaks and antibiotics is recommended (Table 180.1). For the buttock and perineal area, warm soaks or sitz baths are recommended at least twice a day. Patients should be seen within 48 to 72 hours for follow-up, at which time surgical drainage can be performed if the furuncle has suppurated. Carbuncles are more likely to present as obvious suppuration that will require surgical drainage.

Incision and drainage are indicated for most cutaneous abscesses. Appropriate analgesia, sedation, and anesthesia should be provided. For most small superficial abscesses (<5 cm), local anesthesia of the

skin over the abscess usually suffices. For very small abscesses, ethyl chloride spray can be followed by immediate incision. Local anesthesia can be supplemented by administering a parenteral opioid before intervention. For large or deep abscesses or those located in particularly sensitive areas, such as the perineal region, consideration can be given to IV administration of short-acting sedative and analgesic agents with appropriate monitoring.

Before incision, the abscess is cleansed with povidone-iodine or a similar skin cleanser. The incision is made with a number 11 surgical blade attached to a knife handle. To provide for maximum drainage and access, the length of the incision should be at least two-thirds the diameter of the actual cavity to allow for digital or gentle instrument probing and disruption of loculations and pockets in the irregularly shaped cavity. Probing is followed by saline irrigation with a soft-tipped catheter attached to a syringe. Probing and irrigation are terminated when the effluent is pus-free and blood-tinged.

The cavity is lightly packed with gauze tape (one-fourth or one-half inch wide) to encourage further drainage. Excessive packing can result in obstruction of drainage. A bulky dressing is usually necessary to absorb continuing secretions. The packing can most often be removed at follow-up in 48 to 72 hours. This is followed by a regimen of warm soaks or sitz baths at least two times a day until drainage ceases. An abscess cavity takes 10 to 14 days to heal. Large abscesses take longer to heal and may need to be repacked once or twice at 48-hour intervals.

Special considerations apply to the management of Bartholin abscess. The incision is made on the medial portion of the abscess, close to the vaginal introitus, to avoid excessive bleeding. Instead of gauze packing, a small balloon-tipped (Word) catheter is recommended for drainage (10). This is followed by once- or twice-daily sitz baths. The catheter is left in place for 4 to 6 weeks to produce epithelialization of the incision and drainage site and to reduce the risk of abscess recurrence.

Early consultation should be considered for patients with facial, perianal, pilonidal, and Bartholin abscesses and infection secondary

to parenteral drug abuse. For cosmetic reasons, the approach to drainage of facial abscesses (e.g., needle aspiration, mucosal approach) should be discussed with a consultant. Perianal abscesses often require general anesthesia in an operative setting. Patients with pilonidal and Bartholin disease require appropriate follow-up because of the potential for recurrence. Soft tissue infections in parenteral drug users can be deceptively extensive and involve the deep soft tissue; affected patients are also at risk for systemic and cardiac valvular disease. They often require hospital admission for evaluation and treatment.

Ordinarily, simple, uncomplicated, cutaneous abscesses need not be treated with systemic antibiotics (11,12). Antibiotics are indicated for abscesses associated with fever, abscesses surrounded by a wide area of cellulitis, abscesses in which previous incision and drainage (I and D) has failed, and in high-risk patients (i.e., diabetics, immunocompromised patients).

If oral antibiotics are appropriate, treatment should cover both β-hemolytic streptococci as well as MRSA. Oral antibiotic options are clindamycin, trimethoprim-sulfamethoxazole plus a β-lactam, a tetracycline plus a β-lactam, or linezolid alone. If the infection is known to be CA-MRSA, the antibiotic options are: clindamycin, trimethoprim-sulfamethoxazole, a tetracycline, or linezolid (13) (Table 180.1).

If IV treatment is deemed necessary, wound cultures should be obtained, and antibiotic therapy should empirically cover CA-MRSA awaiting culture results. Parenteral antibiotic options include vancomycin, linezolid, daptomycin, telavancin, and clindamycin (15) (Table 180.2). Knowledge of local drug sensitivities is important because of wide variability across the country (2).

TABLE 180.2
Intravenous Antibiotic Regimens for Adults with Serious or Complicated Cutaneous Infections

Condition	Antibiotic	Dose	Interval
MRSA	Vancomyin	15–20 mg/kg	q8–12h
Furuncles, carbuncles, skin abscess, purulent cellulitis (cellulitis with purulent drainage, with exudate, and without underlying abscess), and necrotizing soft tissue infections	Daptomycin	4 mg/kg	q24h
	Linezolid	600 mg	q12h
	Telavancin	10 mg/kg	q24h
	Clindamycin	600–900 mg	q8h
Non-MRSA	Cefazolin	1–2 g	q8h
Furuncles, carbuncles, skin abscess, and nonpurulent cellulitis	Oxacillin	2 g	q4h
	Nafcillin	2 g	q4h
(Cellulitis without purulent drainage, without exudate, and without underlying abscess)	Clindamycin	600–900 mg	q8h
Necrotizing soft tissue infections	Piperacillin–tazobactam	3.375 or 4.5 g	q6h
secondary to gram-negative and anaerobic pathogens	Ticarcillin-clavulanate	3.1 g	q4h
(If MRSA a possibility add vancomycin)	Ceftriaxone *PLUS*	1 g	q24h
	Metronidazole	500 mg	q8h
	Ciprofloxacin *PLUS*	400 mg	q12h
	Metronidazole	500 mg	q8h

Manipulation of an abscess can cause bacteremia in 30% of cases but is most relevant in patients with pre-existing cardiac valve disease. These patients must be given adequate antibiotic prophylaxis, as recommended by the American Heart Association guidelines, before intervention (14,15). Antibiotic prophylaxis is reasonable for procedures involving infected skin, skin structures, or musculoskeletal tissue only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from infective endocarditis (IE) (15). Cardiac conditions associated with the highest risk of adverse outcome from IE include prosthetic cardiac valve or prosthetic material used for cardiac valve repair, previous IE, unrepaired cyanotic congenital heart disease (CHD), including palliative shunts and conduits, completely repaired congenital heart defect with prosthetic material or device (whether placed by surgery or by catheter intervention, during the first 6 months after the procedure), repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization) and cardiac transplantation recipients who develop cardiac valvulopathy. The antibiotic administered should be administered 30 to 60 minutes prior to the procedure and have activity against staphylococci and β-hemolytic

streptococci. Suitable choices include an antistaphylococcal penicillin or a cephalosporin (cephalexin 2 g PO). Vancomycin (1 g IV) or clindamycin (600 mg PO/IM/IV) may be administered to patients unable to tolerate a β-lactam or who are known or suspected to have an infection caused by a methicillin-resistant strain of staphylococcus (24).

Common Pitfalls

- Failing to perform needle aspiration or ultrasonography because an abscess is mistaken for a small area of cellulitis or a furuncle
- Making an abscess incision that is too small to permit adequate drainage
- Mistaking a perianal abscess for a buttock abscess
- Prematurely removing the Word catheter from a Bartholin abscess
- Failure to consider the possibility of cardiac conditions associated with the highest risk of adverse outcome from IE when performing a procedure on an infected skin structure and then providing antibiotic prophylaxis.
- Failing to consider CA-MRSA as the cause of cellulitis or abscess

CUTANEOUS CELLULITIS

CLINICAL PRESENTATION

Cellulitis is an acute, spreading infection of the deep dermis and subcutaneous fat characterized by pain, warmth, swelling, and erythema. It is most often caused by group A *Streptococcus* and *S. aureus* (9). CA-MRSA has also been shown to cause cellulitis (12). The first sign of common cellulitis is local skin discomfort, which is rapidly followed by frank tenderness, erythema, and swelling (16). Within 24 hours, there is noticeable expansion of the process, even though the margins themselves are indistinct. In spite of the progression, fever and chills occur in $<10\%$ of cases (16). Lymphangitic "streaking" that extends from the primary site proximally is a very specific and reliable diagnostic sign. In the

preantibiotic era, this progression was known as “blood poisoning” and not uncommonly led to death.

Erysipelas is an infection of the upper dermis and superficial lymphatics caused almost exclusively by group A streptococci, although occasional cases are due to *S. aureus*. Erysipelas is most common in infants and young children, but it occurs in adults as well (3). It can begin as a result of minor skin trauma, surgical intervention, or a pre-existing skin condition. In adults, it is likely to occur in the setting of venostasis, lymphedema, diabetes, or alcohol abuse. In contrast to common cellulitis, the lesion of erysipelas is sharply demarcated, indurated, and easily palpable. Characteristically, it is also shiny red. It is usually associated with fever and an elevated white blood cell count. Untreated lesions can form bullae that break down and leave raw, weeping surfaces.

A serious form of cellulitis formerly seen in children, and occasionally in adults, is caused by *Haemophilus influenzae* type B (HiB). Although most commonly involving the face and the periorbital tissues, HiB cellulitis can also involve the arms and legs. In adults, it may originate as a respiratory infection and then involve the neck and chest. In children, the cellulitis often takes on a blue-red to purple-red appearance. In both adults and children, HiB cellulitis is associated with systemic toxicity and a significant risk of sepsis and secondary site involvement. With the widespread vaccination of children against HiB, the rates of infection caused by this organism have fallen.

Aeromonas hydrophila and *Vibrio vulnificus* are two water-related organisms that can cause uncommon forms of cellulitis (17,18). The skin infection of *A. hydrophila* follows local trauma and exposure to fresh water; early infections are indistinguishable from streptococcal cellulitis but often progress to bullae, abscess formation, and foul-smelling exudate. *V. vulnificus* cellulitis occurs after trauma and exposure to salt water. The infection can range from mild cellulitis to an aggressive infection associated with vesicles, bullae, and myositis that can mimic gas gangrene.

DIFFERENTIAL DIAGNOSIS

Cellulitis can be difficult to distinguish from other cutaneous conditions. The most serious condition to be considered is thrombophlebitis, particularly when the lower extremity is involved. Cellulitis can be differentiated by the presence of fever, lymphangitic streaking, an advancing margin, and an elevated white blood cell count, although these findings are not consistently present.

Viral and drug-related exanthems can be localized but usually are associated with recognizable precipitants and specific syndromes.

Dermatitis can appear red and somewhat warm but is usually associated with considerable itching and scaling. Secondary infection of dermatitic lesions, however, is not uncommon.

Insect stings, particularly those due to *Hymenoptera,* can cause significant local reactions that can be confused with cellulitis, and these reactions can persist up to 7 days (19). As compared with cellulitis, insect stings produce more pain than tenderness, cause more edema and less erythema, and are pruritic.

Fungal infections of the skin, particularly with *Candida,* appear in characteristic locations (often intertriginous), have a distinctive appearance (moist, bright red), and can be identified by potassium hydroxide staining.

ED EVALUATION

Cellulitis and erysipelas localized to a small area in an otherwise healthy patient, needs no invasive or laboratory testing. With more extensive cellulitis, a white blood cell count is performed to check for signs of systemic involvement and to gauge the severity of infection. Because of the low bacterial count in the lesions of cellulitis, aspiration of the advancing margin for gram stain and culture is of little value. In any event, these tests do not aid in immediate treatment decisions.

In compromised hosts and in patients in whom *H. influenzae* infection is suspected, a more extensive workup is indicated. The incidence of bacteremia ranges from 5% in toxic streptococcal cellulitis to 90% in *H. influenzae* cellulitis. Gram stain and culture, though of low yield, can be performed in an attempt to identify the causative organism. Older patients and those with underlying

conditions such as diabetes or immunocompromised states should be evaluated for metabolic derangements and any evidence of other sites of involvement. Outlining the margins of the cellulitis with a marker can aid in the monitoring and follow-up of patients with cellulitis by indicating lesion progression or regression. In symptomatic patients, imaging including x-ray, CT, MRI, and ultrasound of the affected area can be useful in assessing for deeper infections and abscesses.

KEY TESTING

- Labs
  - CBC
  - Blood cultures in patients presenting with systemic toxicity
- Imaging
  - X-ray, CT, MRI, and bedside ultrasound can be used to help assess patients presenting with concern for deep space infections and abscesses

ED MANAGEMENT AND DISPOSITION

Localized cellulitis and mild, uncomplicated erysipelas in patients without risk factors can be treated as outpatients. Oral penicillin, amoxicillin, or erythromycin can be used to treat erysipelas. The selection of antibiotic therapy for cellulitis, according to the 2011 Infectious Disease Society of America guidelines, is steered by presence or absence of purulence (13). A purulent cellulitis is defined as a cellulitis with the presence of purulent drainage or exudate without an underlying abscess. A nonpurulent cellulitis is defined as a cellulitis without purulent drainage, exudate, or underlying abscess.

Patients with purulent cellulitis should be treated empirically for infection due to MRSA. Oral antibiotic choices include clindamycin, trimethoprim-sulfamethoxazole, a tetracycline, or linezolid (13).

Patients with nonpurulent cellulitis should be treated empirically for infection due to β-hemolytic streptococci and methicillin-susceptible *S. aureus* (MSSA) with a β-lactam. Patients not

responding to treatment with a β-lactam alone should have their antibiotic regimen change to include coverage for CA-MRSA (13). See Table 180.1.

Oral antibiotics are begun, and close (48- to 72-hour) follow-up is arranged. Duration of treatment ranges from 7 to 14 days. As a rule, antibiotics are continued for 3 days after the resolution of clinical findings. Resolution of cellulitis of the lower extremities can be slow because of dependency and associated edema (20). For this reason, strict elevation for several days is mandatory. If significant resolution has not occurred within 2 or 3 days, a brief hospitalization might be necessary.

Other indications for hospital admission and infectious disease consultation are the presence of signs of systemic toxicity; underlying illnesses such as diabetes; specific involvement of areas such as the face, orbit, hand, perineum, or extensive lower extremity (particularly with pre-existing edema); presumed *H. influenzae* infection; or suspected gram-negative organisms or mixed infections. Patients who require admission should be treated with broad spectrum IV antibiotics. Parenteral antibiotic options include vancomycin, linezolid, daptomycin, telavancin, and clindamycin (Table 180.2).

Common Pitfalls

- Failing to instruct patients about elevation and care of the involved area
- Misdiagnosing deep vein thrombosis as lower extremity cellulitis
- Failing to arrange follow-up in 48 to 72 hours for patients with cellulitis
- Unnecessarily treating insect stings with antibiotics
- Failing to appreciate deeper infection or underlying abscess

DEEP CUTANEOUS AND NECROTIZING SOFT TISSUE INFECTIONS

Deep cutaneous and necrotizing soft tissue infections are a group of disorders with many predisposing factors and a wide spectrum of

bacteria (21). Though early recognition and aggressive treatment are important ways of reducing an already high mortality, these infections can be deceptively benign in appearance (21). This benign presentation is no better illustrated than in group A streptococcal infections caused by streptococci, sometimes called “super strep,” that elaborate highly toxic super antigens (22). Patients with soft tissue involvement can complain of severe, disabling pain without skin or soft tissue changes. Early recognition of these infections before they evolve to full blown streptococcal toxic shock syndrome is important to reducing morbidity and mortality (see Chapter 192, “Toxic Shock Syndromes”).

CLINICAL PRESENTATION

Early in the clinical course, attempting to separate the various types of deep infections into discrete syndromes is made difficult by the fact that they share many characteristics. However, it is recognition of these characteristics that alerts the clinician to a potentially emergent condition.

1. These infections occur in settings that include trauma, foreign body penetration, contamination with soil, surgical intervention, ischemia, or diabetes.
2. Tissue involvement is extensive, but classic signs of common cellulitis (heat, redness, induration) are often not present.
3. As the infection progresses, blebs, maceration, and exudate appear.
4. The hallmark of these infections, though not always present, is crepitance secondary to gas formation.

Specific deep cutaneous infections are summarized in Table 180.3.

TABLE 180.3
Deep Cutaneous and Necrotizing Soft Tissue Infections

Characteristics	Crepitant Cellulitis	Synergistic Necrotizing Cellulitis	Necrotizing Fasciitis	Clostridial Cellulitis	Clostridial Myonecrosis
Predisposing conditions	Wounds, decubiti, peripheral vascular disease, diabetes	Diabetes, obesity, advanced age	Postoperative wounds, perianal infection, chronic cutaneous ulcers, intravenous drug use	Contaminated wound	Devitalized tissue, focal contamination
Onset	Gradual	Subacute, over several days	Variable, indolent to fulminant	Gradual, 4–5 d	Acute, 1–3 d
Pain	Mild	Severe	Minimal, sometimes hypesthesia	Mild	Severe, early
Systemic toxicity	Mild to moderate	Moderate to severe	Marked	Mild to moderate	Marked, early
Overlying skin	Minimal, discoloration brown to gray	Blue-gray, necrosis	Initially spared, then pale followed by gangrene	Minimal change, occasional blebs	Initially normal, then pale bronze discoloration followed by necrosis
Exudate	Minimal, dark	Thin, reddish brown ("dishwater pus")	Rare, serous	Thin, dark	Serosanguineous
Odor	Foul	Foul	Foul	Rarely foul	"Mousy," slightly sweet
Gas formation	Abundant	Mild, up to 25%	Little	Abundant	Initially minimal, eventually moderate
Muscle involvement	No	Prominent feature, moderate spread	Rare, late	No	Prominent
Common pathogens	Anaerobes, Enterobacteriaceae	*Bacteroides fragilis*, streptococci, Enterobacteriaceae	Enterobacteriaceae, streptococci, *Bacteroides*, peptostreptococci	*C. perfringens*, *C. septicum*, *C. novyi*	*C. perfringens*, *C. septicum*, *C. novyi*

From Brillman JC, Quinzer RW, eds. *Infectious Disease in Emergency Medicine*. Boston, MA: Little, Brown and Company; 1992:822–823.

Crepitant cellulitis occurs most commonly in the setting of pre-existing, lower extremity, peripheral arterial disease; decubitus ulcer; or a moderately severe traumatic wound. Also known as nonclostridial anaerobic cellulitis, this is a gas-forming infection that results from the synergistic interaction of anaerobic bacteria (*Bacteroides* species and peptostreptococci) and of gram-negative bacteria of enteric origin. In spite of its seriousness, it is usually gradual in onset, with mild local tenderness, and is not likely to cause serious systemic toxicity. In the area of involvement, the skin is minimally discolored and may appear grayish to brown, depending on local vascularity. The exudate, if present, is dark and foul smelling. The hallmark of this infection is crepitance and abundant gas formation, as seen on radiographs. The infection remains localized to the skin and subcutaneous tissues without extending to the muscle.

Synergistic necrotizing cellulitis has also been called nonclostridial gangrene and nonclostridial anaerobic myonecrosis. Fournier gangrene of the male genitalia and perineum is a variant of this condition. Synergistic necrotizing cellulitis occurs most often in older patients with serious underlying disease such as diabetes, congestive heart failure, or renal failure, and in the setting of obesity and perirectal infections. Gram-positive streptococci (both aerobic and anaerobic), gram-negative enteric bacilli, and anaerobes (*B. fragilis*),

interacting synergistically, have been implicated in this infection (1). The onset can be acute or subacute, but the infection rapidly progresses to severe local and systemic toxicity with high fever. There is often severe pain at the site of infection, and the skin is blue-gray. Necrosis of the fascia and muscle occurs. Twenty-five percent of cases have clinical crepitance and gas evident on radiographs. The exudate is thin and foul-smelling and has the appearance of dish water. Bacteremia occurs in 50% of cases and mortality has been reported to be as high as 75% (12).

Necrotizing fasciitis is predominantly a disease of the subcutaneous tissue and fascia, with early sparing of the skin and very late involvement of the muscle. This condition can occur after trauma or abdominal surgery or with perirectal infections, cutaneous ulcers, IV drug abuse, and infections of the head and neck. A wide range of organisms, including gram-negative enteric bacilli, gram-positive streptococci (aerobic and anaerobic), and other anaerobes, has been implicated. Although the infection is usually mixed, it can also be caused by single organisms, such as group A *Streptococcus* (23). The onset is acute and the patient develops severe systemic toxicity. In the early stages, the skin appears erythematous and is minimally painful. Later, as the subcutaneous tissue becomes involved, there is mottling, discoloration, marked edema, and bleb formation as a result of interruption of the blood supply to the skin. The exudate is foul-smelling and seropurulent but not abundant. Although gas can be seen on radiographs, clinical crepitance is unusual.

Clostridial cellulitis, also known as *clostridial anaerobic cellulitis,* is most commonly a result of traumatic wounds. The presence of foreign debris, soil, and necrotic tissue allows rapid growth of clostridial organisms, including *Clostridium perfringens, Clostridium septicum,* and *Clostridium novyi.* It is distinguished from clostridial myonecrosis (gas gangrene) by the lack of muscle involvement. Unlike gas gangrene, the onset is gradual, and systemic toxicity is only mild to moderate. Skin changes are minimal, but there is a thin, dark, occasionally foul-smelling exudate at the site of the wound. The most prominent features of the wound site are crepitance and gas formation that often extend well beyond the actual area of

cellulitis. The gas tends to appear on a radiograph as aggregates of bubbles in the subcutaneous tissues.

Clostridial myonecrosis, or gas gangrene, almost always results from a deep injury to skeletal muscle that causes ischemia and tissue necrosis. The same organisms that cause clostridial cellulitis are responsible for this disorder. The incubation period can range from 7 hours to 6 weeks, but once symptoms begin, severe deterioration can occur within 6 hours. Muscle swelling and severe pain are prominent features. Systemic toxicity, as a result of the many toxins elaborated by the clostridial organisms, is profound and leads to tachycardia and an altered sensorium, although fever is not a prominent feature. The involved skin has a yellow or bronze appearance, and the skin involvement progresses to bulla formation and green or black patches of necrosis. A serosanguineous discharge can develop with a characteristic "mousy" odor. Gas formation is minimal at the onset but extends throughout the muscle in a feathery pattern as it dissects through muscle fibers and bundles. Intravascular hemolysis, with thrombocytopenia, is often present. *Affected patients can die within hours.*

DIFFERENTIAL DIAGNOSIS

There is little difficulty in recognizing the picture of full-blown deep cutaneous and necrotizing soft tissue infections. Occasionally, they can be confused with such conditions as dry ischemic vascular gangrene, pressure necrosis of a limb, acute deep venous thrombosis, and pre-existing changes of venous insufficiency. Air can be introduced into the skin by traumatic lacerations and occasionally can cause some diagnostic concern.

It is important to emphasize, however, that these infections can be missed when they are not full blown. This is where difficulty can arise for the patient presenting to the ED in the early stages of infection.

ED EVALUATION

The presence of a suspected deep cutaneous infection mandates an extensive and aggressive evaluation with early surgical consultation.

This must be initiated promptly and carried out while any resuscitative or stabilizing interventions are in progress. Standard hematologic, biochemical, and clotting profiles are obtained as are arterial blood gas studies, a chest radiograph, and an electrocardiogram. A type and crossmatch may be indicated to correct blood loss or anemia. Imaging of the affected area with x-ray, CT, MRI, and/or ultrasound can be helpful in heightening suspicion for a deep space infection; however, it does not rule in or out the diagnosis. Obtaining imaging should not delay surgical consultation or definitive treatment.

A wound culture is taken and a gram stain performed immediately, particularly if a clostridial etiology is suspected. The presence on gram stain of gram-positive rods with few white blood cells indicates a clostridial infection. A finding of many white blood cells on the smear is more suggestive of a synergistic or mixed bacterial infection. Radiographs of anatomic areas of concern are obtained to look for soft tissue gas. Because the infection can advance up to 10 cm an hour, the area of involvement should be outlined with a marker and checked at frequent intervals.

KEY TESTING

- Laboratories
  - CBC
  - Blood glucose, electrolytes, BUN, Cr
  - Blood cultures, wound cultures
  - Lactate
  - CK
  - CRP
  - PT/ PTT/INR
- Imaging
  - X-ray, CT, MRI to assess for the presence of gas in tissue
  - Ultrasound to assess for the presence of fluid tracking along facial planes

ED MANAGEMENT AND DISPOSITION

Because it can progress so rapidly, clostridial myonecrosis is a true emergency. Concurrent with ED evaluation, planning and execution of intervention is carried out in consultation with a surgeon. A combination of hyperbaric oxygen (HBO), surgery, and antibiotics provides optimal treatment (24). HBO can arrest the advance of the hemolytic, necrotizing, and potentially lethal tissue toxins. HBO produces a tissue level of 300 mm Hg, which is 50 mm Hg in excess of that required to cause bacteriostasis and halt production of tissue toxins. HBO significantly reduces the need for extensive debridement and amputation and assists the surgeon in demarcating clearly necrotic from viable tissue. If necessary, however, a fasciotomy can be performed before HBO is done to relieve compartmental swelling and pressure.

In clear cases of clostridial myonecrosis or cellulitis, high-dose penicillin is still the antibiotic of first choice. Clindamycin can be used in β-lactam–sensitive patients. If the diagnosis is uncertain, the antibiotics listed in Table 180.2 are also appropriate choices. Antitoxin therapy has never proven efficacious.

The primary treatment for other deep cutaneous infections consists of antibiotics and surgical intervention (21). Patients with an immunocompromised state or rapidly spreading infection can benefit significantly from adjunctive HBO; this intervention should be considered for all patients with these infections, especially Fournier gangrene (24). Broad-spectrum antibiotics are usually initiated empirically in the ED (Table 180.2).

CRITICAL INTERVENTIONS

- When draining an abscess, be sure the incision extends across at least two-thirds the diameter of the actual cavity to allow for gentle probing and disruption of loculations.
- Initiate therapy for *N. gonorrhoeae* and *Chlamydia trachomatis* when treating Bartholin abscesses.
- Treat *clostridial myonecrosis* with a combination of HBO, surgery, and antibiotics.

Common Pitfalls

- Failing to recognize a deep cutaneous infection because of a lack of the classic skin changes of cellulitis
- Failing to perform a Gram stain in the ED
- Failing to take radiographs and thus missing subcutaneous gas
- Initiating only limited-spectrum antibiotics
- Delaying surgical consultation

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CHAPTER 181

Tetanus

Daniel T. Wu

Tetanus ("lockjaw") is a severe and often fatal disease caused by the gram-positive anaerobic organism *Clostridium tetani.* The infection has been described in the medical literature as far back as the 5th century BC, and the organism can be found almost ubiquitously in nature, especially in soil and feces (1). The success of an aggressive vaccination program started in the 1940s, combined with improved sterilization procedures, has made tetanus a rare disease in the United States. There were an average of 31 cases per year in the United States from 2000 to 2007, dropping to an all-time low of 18 cases in 2009 (1). Despite the availability of an effective vaccine, tetanus still remains prevalent in many Third World countries with an estimated incidence of 500,000 to 1 million cases per year and a mortality rate as high as 20% to 30% (2–4).

The *C. tetani* bacterium is heat sensitive and cannot survive in the presence of oxygen, but it produces spores that are heat resistant and can survive indefinitely until they germinate. This germination can occur weeks after entry into a wound and accounts for many of the infections that occur after a wound has fully healed. Under anaerobic conditions, the spores germinate into mature organisms and release two neurotoxins, tetanolysin and tetanospasmin. Tetanolysin is known to cause tissue damage but is not thought to be a major contributor to the clinical manifestations of tetanus. Tetanospasmin is a very potent neurotoxin, which enters peripheral nerves and travels retrograde to the central nervous system (CNS) where it disrupts the release of inhibitory neurotransmitters such as γ-aminobutyric acid (GABA). This disruption leads to uncontrolled

motor nerve activity and the clinical manifestations of muscle spasms and autonomic instability that characterize tetanus infections. The incubation period is approximately 1 week but can be as short as 2 to 3 days or as long as several weeks (1,5,6). A shorter incubation period is generally associated with more severe disease and an increased risk of death.

CLINICAL PRESENTATION

There are four different types of tetanus infections: generalized, localized, neonatal, and cephalic.

Generalized tetanus is the most common type and represents approximately 80% of all tetanus infections in the United States and developed countries. Symptoms usually start with muscle stiffness and pain, most often occurring in the facial and jaw muscles causing trismus, and frequently resulting in the characteristic facial appearance known as *risus sardonicus*. The symptoms spread to the neck, torso, and extremities. Tetanic spasms of the back muscles produce opisthotonos, where only the back of the head and the heels rest on the bed. Spasms may involve the muscles of respiration, producing a fixed chest wall and eventual asphyxia.

Systemic symptoms in mild cases are often minimal, but in severe cases marked autonomic disturbances are seen with tachycardia, wide swings in blood pressure, hyperpyrexia, and cardiac dysrhythmias. These manifestations appear to be due to excessive catecholamine release and are the most common cause of death from tetanus. Trivial stimuli may trigger not only severe spasms but also wide swings in vital signs.

Localized tetanus is a less common form of the disease and accounted for 17% of cases in the United States from 1998 to 2000 (5). This form of the disease manifests as localized spasms around the area of initial infection and may last for weeks before fully resolving. The prognosis of localized infections is very good with a mortality rate of approximately 1% (2,5). It is important to note that what may appear to be a localized infection could be the early stages of a generalized infection.

Neonatal tetanus is a generalized form of tetanus that occurs in neonates during the first few weeks of life and is often caused by infection of the umbilical stump. The initial symptoms are spasms, rigidity, and poor feeding. Neonatal tetanus has become a rare disease in the United States since the introduction of the tetanus vaccine and modern sterilization techniques. It remains a serious problem in many developing countries where babies are born without passive immunity because their mothers have not been vaccinated. Worldwide, the neonatal form of tetanus accounts for more than half of all tetanus deaths (7).

Cephalic tetanus is a very rare variant of the disease that often occurs after head injury or otitis media. Trismus and cranial nerve involvement are characteristic. The seventh and sixth cranial nerves are most commonly involved. Cephalic tetanus can initially be misdiagnosed as Bell palsy.

DIFFERENTIAL DIAGNOSIS

The only entity that an established case of tetanus may be confused with is strychnine poisoning. Muscle spasms associated with strychnine poisoning may resemble those of tetanus, but there are several important differences. The muscles of the jaw are not involved early in the course of strychnine poisoning or may be spared completely. In tetanus, the jaw muscles are involved early in the course, and trismus is almost always present. In a patient with strychnine poisoning, muscle rigidity disappears completely between spasms.

The early stages of tetanus may be confused with psychoneurotic complaints and with dystonic reactions from such agents as phenothiazines. Dystonic reactions can be rapidly and safely treated and ruled out by the administration of benztropine or diphenhydramine. Dental infections may produce trismus, but there is no progression, and signs of local infection are almost always present.

ED EVALUATION

The diagnosis of tetanus remains a clinical one, and laboratory testing offers little or no benefit. Wound cultures and serum antitoxin antibody levels can be obtained, but neither is available quickly enough to make the diagnosis during the initial presentation of the disease (8). Wound cultures for tetanus are positive only about 30% of the time. Laboratory studies, although not diagnostic for tetanus infections, should be sent to rule out other etiologies and to assess oxygenation status in severe infections.

The source of the infection should be investigated. Wounds secondary to acute trauma account for the majority of cases in the United States, but an acute skin wound is not necessary to contract a tetanus infection, and the incubation period can be quite long. Of the confirmed tetanus cases from 2001 to 2008, only 72% reported a wound from acute trauma, with almost 10% of cases reporting no wounds or infections (1).

The majority of cases in the United States have occurred in patients who were inadequately vaccinated or who had an unknown vaccination history. Several groups appear to be at risk for developing tetanus. These groups include the elderly, diabetics, and injection-drug users (IDUs) (1,5,9). The elderly are at a greater risk because of declining immunity over time (9,10). Protection, as defined by adequate serum antibody levels, decreases with age, and it was found that only $>30\%$ of people older than 70 years of age had protective levels of antibodies (9).

ED MANAGEMENT

The management of tetanus has three goals: stabilizing the patient, neutralizing the toxin, and removing any remaining organisms.

In the initial stages, management is largely supportive with emphasis on airway control. Patients with severe infections may require ventilatory support to prevent asphyxiation from severe muscle spasms. Airway management may be difficult because of trismus and may require the use of paralytic agents. Succinylcholine can be used in early tetanus but should be used with caution, if at all, in the later stages of the disease because of the risk of

hyperkalemia secondary to the up-regulation of acetylcholine receptors. Prophylactic intubation should be considered in the early stages of cases in which the airway may be threatened. Severe muscle spasms and rigidity can be treated with benzodiazepines but often require large doses.

The toxin should be neutralized by the administration of tetanus immune globulin (TIG). The dose is 3,000 to 6,000 units intramuscularly (IM) for both adults and children (1,11). Some authorities have recommended part of the dose be locally infiltrated around the wound, although this practice may cause local irritation and has not been proven to be beneficial. TIG does not affect toxin already bound to nerve endings, but it can help to remove unbound toxin.

Removal of any remaining tetanus organism is important in limiting the severity of infection. If a wound is identified, it should be cleaned well and debrided to remove any necrotic tissue. Metronidazole is effective in eliminating *C. tetani* and has become the antibiotic of choice, with penicillin as an alternative treatment (11,12).

Autonomic instability, which manifests as hypertension and tachycardia, usually occurs days to weeks after the onset of symptoms and is also a major cause of death. Fatality rates are as high as 28% (2). There is no universally accepted treatment protocol, but labetalol has been used frequently for its β- and α-blocking effects. Other agents that have been used with varying effectiveness include opiates, clonidine, and magnesium.

Clinical infection does not confer immunity, so all patients who recover from tetanus must be actively immunized.

CRITICAL INTERVENTIONS

- Administer tetanus toxoid and TIG for tetanus-prone wounds, if a patient has not previously completed a full vaccination series.
- Administer tetanus toxoid if the patient has not received tetanus toxoid within 5 years for tetanus-prone wounds or within 10 years for nontetanus-prone wounds.

DISPOSITION

All patients with clinical tetanus must be admitted to an intensive care setting for observation and management. Because it is difficult to predict the severity and progression of the disease when it is in its early stages, patients should be monitored to ensure maintenance of an airway and to identify and treat autonomic instability and cardiac arrhythmia.

PREVENTION

With the introduction of an effective vaccine in the 1940s and improved sterilization techniques, tetanus has become an almost entirely preventable disease. There has been a steady decline in both the incidence of the disease and mortality rates. Because almost all recent cases of tetanus in the United States have occurred in persons who have never been vaccinated or have not had a recent booster, it is the responsibility of emergency physicians to inquire about the immunization status of all patients and administer the toxoid and/or immune globulin as indicated.

For clean, minor wounds, tetanus toxoid is indicated if the patient has received fewer than three doses of the vaccine in the past, if the vaccination history is unknown, or if it has been more than 10 years since the last Td booster. For tetanus-prone wounds (those contaminated with feces, dirt, or saliva, as well as burns, crush injuries, and puncture wounds), tetanus toxoid should be administered if the patient has not received it within the last 5 years. TIG should also be administered if the patient has not previously completed a full vaccination series (Table 181.1).

TABLE 181.1
Tetanus Prophylaxis for Wound Management

Vaccination history (prior Td doses)	*Clean, Minor Wounds*		*All Other Wounds*	
	Tetanus toxoid	TIG	Tetanus toxoid	TIG
Unknown or <3 doses	Yes	No	Yes	Yes
3 or more doses	No[a]	No	No[b]	No

[a]Tetanus toxoid should be given if more than 10 yrs since last booster.
[b]Tetanus toxoid should be given if more than 5 yrs since last booster.
Note: Tetanus Toxoid can be given as Td, Tdap, DT, or DTaP.
From Center for Disease Control. *Epidemiology and Prevention of Vaccine-Preventable Diseases* (The Pink Book), 10th ed., and Pickering L, ed. *2006 Red Book: Report of the Committee on Infectious Diseases*, 27th ed. American Academy of Pediatrics; 2000.
TIG, tetanus immune globulin.

The primary vaccination series should be completed by the age of 18 months. Children should receive a booster at ages 4, 11, and every 10 years thereafter.

The tetanus toxoid is available combined with the diphtheria toxoid (DT, Td) or combined with the pertussis vaccine (DTaP, Tdap). The recommended preparation is dependent on the patient's age and prior immunization status. Children younger than 7 years of age should receive the pediatric formulations (DT, DTaP) unless contraindicated. In 2005, Advisory Committee on Immunization Practices (ACIP) recommended that Tdap be given to all patients aged 11 to 64 years for booster immunization instead of Td (if they have not previously received a dose of Tdap). If Tdap is not available, Td can still be used (13). In children between 7 and 10 years of age, both Td and Tdap (if under immunized for pertussis) can be used (11). Updated recommendations in 2010 have extended the use of one dose of Tdap to patients aged 65 years or older, if they have close contact to an infant 12 months of age, or have not previously received Tdap.

Common Pitfalls

- Clinical tetanus infection does not confer immunity, and active immunization should be given to all patients who have infections.
- The elderly are at particular risk for contracting infections because of their declining immunity.

- An acute laceration is not required to develop tetanus. Infections can originate from lacerations that have already started healing or from other sources such as abscesses, ulcers, or injection sites in drug users.

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CHAPTER 182

Meningitis and Encephalitis

Richard M. Kaplan

The annual incidence of bacterial meningitis ranges from 1.3 to 6 cases per 100,000 adults in the United States (US) to 500 cases per 100,000 in the "meningitis belt" of Africa. Recent publications report 4,100 cases of bacterial meningitis a year in the US with a median age of 41 and an overall mortality of 15%. The major causes of bacterial meningitis are *Streptococcus pneumoniae* (58%), group B streptococcus (GBS) (18.1%), *Neisseria meningitidis* (13.9%), *Haemophilus influenzae* (6.7%), and *Listeria monocytogenes* (3.4%) (1–8).

Bacterial meningitis has decreased markedly due to the vaccines for *H. influenzae* type B (Hib), *S. pneumoniae,* and *N. meningitidis.* The vaccines are listed in **Tables 182.1** and **182.2**. The meningococcal vaccines have been recommended for children with terminal complement deficiencies, functional or anatomic asplenia, and other high-risk groups. The quadrivalent meningococcal vaccine (A, C, Y, W-135) is recommended for outbreaks and military personnel.

TABLE 182.1
Pneumococcal and H. influenzae Vaccines

Age	Vaccine
2, 4, 6, 12–15 mos	Pneumococcal conjugate and *H. influenzae* serotype B
>2 yrs	Pneumococcal polysaccharide

TABLE 182.2
Meningococcal Vaccines

Age	Vaccine
6 wks–18 mos	MenHibrix (Hib, MenCY-TT) (conjugate)
9–23 mos	MenACWY-D (conjugate)
2–55 yrs	MenACWY-D, MenACWY-CRM (conjugate)
11–12 yrs	MenACWY with booster at 16 yrs of age (conjugate)
>=56 yrs	MPSV4 (polysaccharide)

For children under the age of 2 months, GBS accounted for 86% of cases of bacterial meningitis. GBS screening during pregnancy has decreased the incidence of these infections. *L. monocytogenes* is generally found in children younger than 3 months, but it is also an important cause of meningitis in elderly and immunocompromised patients.

Nosocomial meningitis may result from invasive neurosurgical procedures (craniotomy, ventricular catheters, lumbar puncture (LP), intrathecal infusions, spinal anesthesia), head trauma, bacteremia, or immunocompromised conditions (3,9,10). Staphylococcal species and gram-negative bacilli are more commonly found in nosocomial meningitis. *S. pneumoniae* has been identified following basilar skull fractures or ENT surgeries. Coagulase-negative staphylococci or *Propionibacterium* acnes have been identified in patients with ventricular drains.

The incidence of meningitis following moderate or severe head trauma has been estimated at 1.4%. The rate of meningitis may increase to 2% to 11% following open compound cranial fractures. Following basilar skull fractures, the median onset for meningitis is 11 days, and infection rates may reach 25% (10).

Fungal meningitis should be suspected in immunocompromised patients. Fungal meningitis was recently reported following epidural

injections with contaminated methylprednisolone products. An index case was reported for *Aspergillus fumigatus* (11), while a follow-up study documented fungal meningitis due to *Exserohilum rostratum* (12).

Risk Factors

Risk factors associated with bacterial meningitis include age (the very old and the very young), ear-nose-throat conditions (otitis, mastoiditis, sinusitis), neurosurgical procedures, chronic disease, diabetes mellitus, immunosuppression, HIV, men who have sex with men (MSM), alcohol abuse, and tobacco exposure. Overcrowded living conditions (e.g., college dormitories, military barracks) and poverty increase the risk of contracting meningococcal meningitis (13,14). Risk factors for *Listeria* meningitis include an immunocompromised status and the ingestion of *Listeria*-contaminated foods such as uncooked meats, vegetables, soft cheeses, cold cuts, and unpasteurized milk.

Aseptic Meningitis

Aseptic meningitis is primarily of viral etiology and is generally a self-limited symptom complex of fever, headache, and nuchal rigidity with cerebrospinal fluid (CSF) findings of lymphocytosis, variable protein elevation, and normal glucose. Enterovirus is the most common cause of aseptic meningitis (15).

Encephalitis

Acute encephalitis is a viral-related illness in which the brain is injured either as a direct result of viral invasion or as a hypersensitivity reaction to a systemic viral illness. Encephalitis may occur shortly after vaccination for measles, rubella, chickenpox, or rabies. The diagnosis of encephalitis should be considered in patients who present with fever, headache, nuchal rigidity, altered mental status, seizures, or focal neurologic signs. In the United States, the most common causes of acute encephalitis include herpes

simplex virus (HSV), enteroviruses, arboviruses, and HIV. The arboviruses include West Nile virus (WNV), St. Louis, California, Western, and Eastern equine. In 2002, a WNV outbreak of arboviral meningoencephalitis resulted in a 9% mortality (16), whereas mortality due to HSV encephalitis ranges from 30% to 60% (17).

CLINICAL PRESENTATION

Fever, headache, altered mental status, and nuchal rigidity should prompt serious consideration of the diagnosis of meningitis. Fever was reported in 85% to 97%, neck stiffness in 70% to 88%, and altered mental status in 66% to 78%. The triad of these findings has been documented in 21% to 67% of patients with meningitis (3,6,7,9). Infections from CSF shunts may cause only low-grade fever or malaise; meningeal irritation may be seen in less than 50% of these patients.

Several clinical signs should be assessed in the physical examination, but they are not pathognomonic of meningeal irritation. Nuchal rigidity is characterized by neck stiffness and the inability to passively flex and extend the head in a normal manner. The Brudzinski sign occurs when flexion of the neck results in flexion of the knees and hips. The Kernig sign is elicited by extending the knee with the hip flexed; stretching of the lumbar roots causes pain in the hamstring and paraspinal muscles. A prospective study (18) of 297 patients with suspected meningitis observed that neither Kernig sign, Brudzinski sign, nor nuchal rigidity accurately diagnosed meningitis. For nuchal rigidity, the sensitivity was 30% whereas the sensitivities for Kernig and Brudzinski signs were 5%. The jolt accentuation test, horizontal movement of the head at a frequency of 2 to 3 rotations/sec, has also been recommended to assess for the possibility of meningitis. A positive test is a worsening of the baseline headache.

Most patients with meningitis do not present with a rash. Durand (3) reported a rash in 11% (30 of 279), whereas Van de Beek et al. (6,7) reported a rash in 26% (176 of 683), of which *N. meningitidis* was the bacteria in 162 episodes. Petechiae, purpura, and

morbilliform rash are commonly noted in association with meningococcal meningitis (19). In one study, 80% of the patients with *N. meningitidis* had a purpuric or petechial rash, whereas similar findings were noted in 7% of patients with *S. pneumoniae.* Rashes may also be seen with *Staphylococcus, H. influenzae,* or viral meningitis.

Mental status or behavioral changes are commonly noted with encephalitis. Any of the encephalitides may demonstrate hypersomnia as an acute symptom. Following a WNV outbreak in New York City, neurologic abnormalities included abnormal cranial nerve function (22%), diffuse flaccid paralysis (10%), and seizures (3%) (16).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of meningitis and encephalitis includes infectious, neurologic, toxicologic, metabolic, environmental, and behavioral disorders. Migraine and seizures may present with symptoms common to both encephalitis and meningitis. Behavioral alterations (e.g., psychosis, mania) should never be considered to be purely of psychological origin without an evaluation for the possibility of underlying organic causes such as meningitis and encephalitis.

ED EVALUATION

The majority of patients with meningitis or encephalitis who present to the emergency department (ED) display the classic complaints of severe headache and fever. Patients may not present with the "classic" findings, and one must have a low threshold for performing an LP. Increased surveillance is warranted in HIV patients. If meningitis is suspected, appropriate laboratory studies and cultures are drawn, and antibiotics are promptly administered.

Identification of risk factors may aid in the early diagnosis of meningitis. Most risk factors can be identified with a few questions guided by the six I's as follows:

- Infection (upper or lower respiratory tract infection, sinusitis, otitis)
- Immunosuppression (splenectomy, sickle cell disease, corticosteroids, Hodgkin disease, myeloma, organ transplant, HIV)
- Injury (head trauma, neurologic or ENT procedures)
- Indwelling (catheters, shunts, ventricular reservoirs)
- Imbiber (alcoholic)
- Identification (close contacts)

Many of the more common viruses causing outbreaks of encephalitis demonstrate characteristic seasonal and geographic distributions. Arbovirus and enterovirus infections tend to occur in summer and early fall. Eastern equine encephalitis occurs in the eastern United States, and Venezuelan equine encephalitis is generally found in Florida and the southwestern United States, whereas herpes simplex encephalitis demonstrates no characteristic geographic pattern. WNV has spread from the East coast to the Pacific coast with about 85% of human infections occurring in August and September (16). Some important data to be elicited in suspected cases of encephalitis can be summarized through the use of the six V's as follows:

- Vacation/travel (to endemic areas, foreign, or domestic)
- Veterinary or other animal contact (rabies)
- Vectors (recent mosquito or tick bites)
- Viral infections (recent or concurrent)
- Vaccinations (recent for measles, varicella, rubella, rabies)
- Vital statistics (contact health agencies regarding outbreaks)

The physical examination should focus on possible sources of infection including the oropharynx, ears, sinuses, chest, abdomen, and skin. The entire body should be scrutinized for the presence of any rashes.

Computed Tomography Scan

If a patient has a suspected cerebral mass, focal neurologic findings, a prolonged or deteriorating course, or papilledema, a computed tomography (CT) of the head should be performed. Hasbun et al.

(20) reported that an age of 60 years or older, immunocompromised status, history of CNS disease, seizure within the last week, abnormal language, inability to correctly answer two consecutive questions, and abnormal level of consciousness were among the findings associated with an abnormal head CT. The CT scan should be assessed for the presence of a space-occupying lesion, edema, or evidence of brain shift (4).

Lumbar Puncture

Lumbar puncture is the key to confirming the diagnosis of meningitis and encephalitis. Contraindications to LP include infection at the site of the puncture and evidence of obstructive (noncommunicating) hydrocephalus. CSF evaluation includes a cell count and differential, Gram stain, culture, protein, and glucose. CSF tests may also include bacterial antigens, polymerase chain reaction (PCR), lactate, or antibody titers.

Cerebrospinal Fluid Parameters

Gram Stain, India Ink, Acid-Fast

Gram stains of CSF have sensitivities ranging from 50% to 90% (3,6,7). A negative Gram stain does not rule out the possibility of bacterial meningitis. If the Gram stain is negative and one has a high suspicion for meningitis, the patient should be treated with appropriate antibiotics and admitted to the hospital.

There are limited studies evaluating the effects of antibiotics on CSF parameters. It is unlikely that antibiotic administration will alter CSF parameters within 1 to 2 hours (21,22). A retrospective pediatric bacterial meningitis study noted that 44 to 68 hours of antibiotics did not alter the CSF cytology and biochemistry in 65 of 68 children (23).

India ink preparations for the detection of fungal elements in CSF are positive in as few as one-half of cases. Acid-fast smears of CSF for diagnosing tuberculous meningitis are not consistently sensitive.

Antigen, Polymerase Chain Reaction, and Antibody Detection

CSF antigen studies are available for *H. influenzae* type B, *N. meningitidis* A, B, C, Y, W-135, *Streptococcus agalactiae* (group B), *S. pneumoniae,* and *Escherichia coli.* These antigen studies may identify an organism when the Gram stain is equivocal or "negative." After antibiotic therapy, bacterial antigens may persist in the CSF for several days (22).

PCR tests may identify serogroup-specific *N. meningitidis* DNA (14), enterovirus (15), or specific viruses (24). One study used PCR to detect gram-positive bacteria in 86 specimens; 42 were positive with PCR and had negative cultures. There were no positive culture results in patients with a negative PCR (10,25). Antibody detection may also be used for detecting CNS infections. IgM antibodies in the CSF may be detected within 8 days of symptoms in patients with WNV meningoencephalitis (16).

Glucose

The normal ratio of CSF to serum glucose concentration is 0.6. A CSF glucose level of <50 mg/dL or a CSF/serum glucose ratio of <0.5 is noted in more than 50% of cases of bacterial, fungal, and tuberculous meningitis. Normal CSF glucose levels are generally noted in most viral meningitides and encephalitides.

Protein

Normal protein levels in the CSF range from 15 to 45 mg/dL. Subarachnoid space infection results in increased protein permeability of the choroid plexus, ependyma, and pia mater. Marked protein elevations are observed in bacterial, fungal, and tuberculous meningitis. Normal or moderately elevated levels of protein are found in viral meningitides or encephalitides (26). The CSF protein level has been reported to increase 1 mg/dL for every 1,000 red blood cells (RBCs) in the CSF.

Lactic Acid

CSF lactic acid levels are usually normal in viral meningitis and have been reported to be elevated in bacterial, fungal, and tuberculous meningitis (26).

Cell Count and Differential

CSF findings in bacterial meningitis, aseptic meningitis, and encephalitis may not clearly establish a diagnosis. Normal CSF has a white blood cell (WBC) count of <5 cells/mm^3 with only mononuclear cells. After centrifugation, the finding of a single CSF granulocytic cell may be considered normal if the total CSF WBC count is <5 cells/mm.

For bacterial meningitis, CSF cell counts usually range from 100 to 10,000 cells/mm^3 with predominately polymorphonuclear white cells. As many as 10% of patients with bacterial meningitis initially demonstrate a CSF lymphocytosis (27). Not all the parameters are necessarily abnormal with bacterial meningitis. WBC count <100 cells/mm^3, negative Gram stain, or normal CSF glucose and protein levels (6,7,9) may be present in patients with bacterial meningitis.

CSF lymphocytosis with cell counts of 10 to 1,000 cells/mm^3 is usually seen with viral meningitis. In viral meningitis, there is usually a predominance of mononuclear cells, a normal glucose concentration, and a slightly-to-moderately increased protein level. Occasionally, in early cases of viral meningitis, the CSF WBC count will exceed 1,000 cells/mm^3 and the neutrophils will predominate.

In the acute stages of viral encephalitis, a mild-to-moderate rise in mononuclear lymphocytes (e.g., 10 to 250 cells) is noted, with higher cell counts suggestive of concomitant meningeal involvement. In WNV meningoencephalitis, CSF findings include an elevated protein count and pleocytosis with a predominance of lymphocytes.

Mononuclear cells usually predominate in cases of tuberculous, fungal, or aseptic meningitis. Tuberculous and fungal meningitis may also present with CSF findings of neutrophilia, a normal-to-decreased glucose, and an elevated protein.

A traumatic LP may lead to an increase of one WBC for 700 to 1,000 RBCs. The hemorrhagic lesion of herpes encephalitis may lead to an elevated RBC count in the CSF or xanthochromia.

Cultures

The CSF should be cultured in all cases of suspected meningitis. A negative CSF culture has been reported in 11% to 30% of patients

with bacterial meningitis (3,6). The diagnosis of meningitis is made only from the culture in about 20% of cases (28). A retrospective pediatric meningitis study (29) of 16 treated patients with meningococcal or pneumococcal meningitis documented sterile CSF for all nine meningococcal CSF cultures (2 hours), and sterile CSF for only one of seven *S. pneumoniae* cultures (4.3 hours). Overall, negative CSF cultures were seen in 8% of patients who were not pretreated with antibiotics and in 44% who had been pretreated with antibiotics. Sigurdardottir et al. (30) reported negative blood and CSF cultures in 11% of patients with meningitis. Talan et al. (22) noted that only about 50% of patients with bacterial meningitis had positive blood cultures.

ED MANAGEMENT

The patient who presents to the ED with fever, nuchal rigidity, altered mental status, and headache should be considered to have meningitis until proven otherwise. One should also look for atypical presentations of meningitis and be aware that patients may present with only one or two of the findings of the meningitis triad. If meningitis is suspected, antibiotic therapy should be promptly administered. Empiric antibiotic therapy for bacterial meningitis should treat *S. pneumoniae, N. meningitidis,* and *H. influenzae* (Table 182.3). Patients should be promptly treated with a third-generation cephalosporin (cefotaxime or ceftriaxone) and vancomycin (21). Dexamethasone (10 mg) has been suggested to improve outcomes, particularly in patients with penicillin-susceptible pneumococcal meningitis (31).

TABLE 182.3
Empiric Parenteral Antibiotic Therapy for Meningitis in Adults

Ceftriaxone (2 g IV q12h) or cefotaxime (2 g IV q4–6h) and vancomycin (15 mg/kg q8–12h)

If penicillin/cephalosporin allergy and unable to administer third-generation cephalosporin, consider ID consult. Options may include:

Vancomycin (15 mg/kg IV q8–12h) and chloramphenicol (25 mg/kg; max 1 g q6h) or vancomycin (15 mg/kg IV q8–12h) with[a] ciprofloxacin (400 mg IV q8–12h) or other appropriate quinolone

Dexamethasone 10 mg (IV q6h) for suspected pneumococcal meningitis

If suspicion of listeria (adults >50 yrs old):

Ampicillin (2 g IV q4h) or

Trimethoprim/sulfamethoxazole (15–20 mg/kg/d based on trimethoprim component, divided q6h)

[b]Gentamicin (5 mg/kg/d divided q8h); other aminoglycosides have also been recommended

If suspicion of group B streptococcus:

Ampicillin (2 g IV q4h)

Nosocomial Meningitis

Postneurosurgical infection, ventricular or lumbar catheter, penetrating trauma:

Vancomycin (15 mg/kg IV q8–12h) and

cefepime (2 g IV q8h), ceftazidime (2 g IV q8h), or meropenem (2 g IV q8h)

Basilar skull fracture

Vancomycin (15 mg/kg IV q8–12h) and

ceftriaxone (2 g IV q12h) or cefotaxime (2 g IV q4–6h)

If severe allergy to penicillin or cephalosporins:

Aztreonam (2 g IV q8h) or ciprofloxacin (400 mg IV q8–12h) for gram-negative bacilli

If resistant gram-negative rods, such as pseudomonas:

Consider the addition of ceftazidime (2 g IV q8h) and

gentamicin (5 mg/kg/day divided q8h)

If brain abscess:

Ceftriaxone (2 g IV q12h) and metronidazole (500 mg IV q8h)

or

Vancomycin (15 mg/kg IV q8–12h) and cefepime (2 g IV q8h)

If suspicion of cryptococcal infection in the HIV patient, options may include:

Amphotericin B deoxycholate (0.7–1 mg/kg/d) and flucytosine (100 mg/kg/d divided q6h)

Other medications used have included:

Lipid formulations of amphotericin B:

Lipid complex: 5 mg/kg IV q24h

Liposomal: 3–4 mg/kg IV q24h

[a]Quinolones are not promoted for use in bacterial meningitis.

[b]Other aminoglycosides may include tobramycin (5 mg/kg/d divided q8h) or amikacin (15 mg/kg/d divided q8–12h).

There are limited options available to the emergency medicine physician when a third-generation cephalosporin cannot be administered. Chloramphenicol has been recommended, but it may not be available on the hospital formulary. Vancomycin does not by itself provide ideal coverage for empiric treatment of bacterial meningitis. Quinolones have been used for treating bacterial meningitis in patients with a documented penicillin or cephalosporin allergy (32,33).

Highly lipid-soluble antibiotics such as chloramphenicol, rifampin, and trimethoprim achieve high penetration into the CSF (21). Rifampin has a synergistic action with ceftriaxone against β-lactam–resistant *S. pneumoniae* (10,21). Trimethoprim/sulfamethoxazole may be used to treat *L. monocytogenes* if there is an ampicillin allergy. Aminoglycosides have been used for treating CNS infections, but they have poor CNS penetration (32). Ceftazidime (Fortaz) has been recommended for treating bacterial meningitis due to gram-negative rods.

For HIV-associated cryptococcal meningoencephalitis, intravenous amphotericin B deoxycholate and flucytosine are recommended as primary induction and consolidation therapy. If there is concern for nephrotoxicity, lipid formulations of amphotericin B may be considered.

For herpes encephalitis, intravenous acyclovir (10 mg/kg) is administered over 1 hour. The identification of nonviral agents of encephalitis (e.g., syphilis, toxoplasmosis, tuberculosis) will guide specific therapy.

For patients with suspected viral meningitis who are admitted to hospital, the decision to institute antibiotic coverage in the ED should be made by the emergency medicine physician on the basis of the patient's clinical picture and associated risk factors.

Chemoprophylaxis

Chemoprophylaxis regimens for meningococcal disease are listed in Table 182.4. Close contacts (e.g., families, roommates, daycare

contacts) of patients with meningococcal meningitis have an increased risk (400- to 800-fold) of contracting the disease (14). Prehospital and hospital personnel along with other close contacts of patients with meningococcal or *H. influenzae* meningitis should receive chemoprophylaxis. Five percent to 10% of adults are asymptomatic nasopharyngeal carriers of *N. meningitidis,* and most are not pathogenic. There is no indication to treat individuals who are asymptomatic nasopharyngeal carriers. Oropharyngeal or nasopharyngeal cultures are not helpful in determining the need for chemoprophylaxis (14).

TABLE 182.4
Chemoprophylaxis for Meningococcal Disease

Drug	Age	Dosage	Duration and Route[a]
Rifampin	>=1 mo	10 mg/kg BID	2 d oral
Rifampin	Adults	600 mg BID	2 d oral
Ciprofloxacin	Adults	500 mg	Single dose oral
Ceftriaxone	<15 yrs	125 mg	Single IM dose
Ceftriaxone	Adults	250 mg	Single IM dose
Azithromycin	Adults	500 mg	Single oral dose

[a]IM, intramuscular.

Antibiotics that eliminate nasopharyngeal carriage of *N. meningitidis* include rifampin, ciprofloxacin, and ceftriaxone. Azithromycin (500 mg) has also been shown to eradicate nasopharyngeal carriage of *N. meningitidis.* Chemoprophylaxis for *H. influenzae* includes rifampin (20 mg/kg once a day for 4 days; maximum of 600 mg/d). Individuals at risk for pneumococcal meningitis (e.g., postsplenectomy) should receive oral penicillin (500 mg every 6 hours for 7 days).

CRITICAL INTERVENTIONS

- If meningitis is suspected, promptly administer antibiotics. Do not wait for the CT scan and the LP.

- Perform a head CT for suspected cerebral mass, focal neurologic findings, papilledema, immunocompromised state, history of CNS disease, new-onset seizure, or altered mental status.
- Provide prophylaxis to individuals who have had close contact with patients diagnosed with meningococcal or *H. influenzae* meningitis.

DISPOSITION

All patients with bacterial meningitis require IV antibiotics and hospital admission. Patients with uncomplicated viral meningitis may be treated with antipyretics and supportive care and may be discharged from the hospital. For patients with suspected viral meningitis who are admitted to hospital, the decision to institute antibiotic coverage in the ED should be made by the emergency medicine physician on the basis of the patient's clinical picture and associated risk factors.

Common Pitfalls

- Failure to make the diagnosis of meningitis in patients with an atypical presentation.
- Failure to suspect meningitis in patients with a negative gram stain and/or a low CSF WBC count.
- Delay in starting antibiotic therapy when there is a reasonable suspicion of meningitis.

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CHAPTER 183

Brain Abscess and Other Suppurative CNS Infections

David C. Snow

Central nervous system (CNS) infections are uncommon, yet they can produce serious morbidity and mortality if their diagnosis is delayed. CNS suppurative infections include brain abscess, cranial subdural empyema, cranial epidural abscess, and spinal epidural abscess (SEA). These disease entities must be considered when evaluating patients who present with headache, fever, alteration of consciousness, back pain, or new neurologic deficits. Early identification with the administration of appropriate antibiotics and immediate neurosurgical consultation results in an improved outcome (1).

BRAIN ABSCESS

Brain abscess is a focal infection of the brain parenchyma, accounting for approximately 1 in 10,000 hospital admissions (2). It begins with a localized region of cerebritis, and evolves into a collection of pus surrounded by a capsule (3). Due to improvements in the treatment of ear, sinus, and dental infections the overall incidence of this disease process is decreasing, with only 1,500 to 2,500 cases each year in the United States (4). However, an increase in incidence may be seen as a result of enhanced use of neurosurgical procedures, improved imaging techniques, and increased population of immunocompromised patients (5). It remains the most common

intracranial focal suppurative process and occurs about 2% as often as brain tumors.

There is a 2:1 male-to-female predominance. The age distribution relates to the predisposing condition or risk factor. Brain abscesses from an otic origin usually occur in patients younger than 20 years old or older than 40 years old. Most patients with a paranasal sinus focus are 10 to 30 years of age. Approximately 25% of cases occur in children younger than 15 years old. These cases are most commonly caused by cyanotic congenital heart disease or otic sources. An abscess rarely occurs in children younger than 2 years of age, sometimes occurring secondary to gram-negative bacterial meningitis (2,5).

Brain abscesses can arise from bacterial, mycobacterial, fungal or parasitic infections. They result from either direct spread from a contiguous focus of infection or through hematogenous seeding in the setting of bacteremia (6).

Bacterial brain abscesses are typically the result of contiguous spread from the oropharynx, middle ear, and paranasal sinuses (7). These infections can lead to abscess formation by two mechanisms: by direct extension through infected bone or by retrograde thrombophlebitis from emissary and diploic veins (7). Otitis media (chronic) and mastoiditis classically spread to the temporal lobe (50% to 75% of cases) and the cerebellum (one-third of cases). Approximately 85% to 99% of cerebellar abscesses are from an otic source. Frontal and ethmoidal sinusitis spread to the frontal lobe. Dental sources also tend to affect the frontal lobe (2,5). Penetrating trauma and postneurosurgical procedure abscesses account for between 1% and 12% depending on the case series (8–10).

About 25% of cases arise from hematogenous spread from a cardiac or pulmonary source, including lung abscess, bronchiectasis, cyanotic congenital heart disease (tetralogy of Fallot), and bacterial endocarditis. Most of these sources of hematogenous spread occur from areas of relatively low oxygen tension, leading to a strong predominance of anaerobic organisms. Hematogenously spread abscesses tend to be multiple and lie in the distribution of the middle cerebral artery at the gray-white junction where microcirculatory

flow is the poorest. Other causes include hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease), dental extractions, abdominal or pelvic infections, and following esophageal stricture dilation and endoscopic sclerosis of esophageal varices (2,5). There is no clearly identifiable cause in the remaining 10% to 15% of cases (2).

The blood–brain barrier (BBB) is quite resistant to penetration of these microorganisms from the blood into the brain, which is why this condition is so rare despite the frequency of bacteremia. Improved microbiologic culture techniques have yielded a better understanding of the microbiology of brain abscesses. The most commonly isolated microorganisms are gram-positive cocci and anaerobes (9,10). Aerobic and microaerophilic streptococci (*Streptococcus milleri, Streptococcus viridans*) are the most common gram-positive bacteria isolated, being found in up to 70% of abscesses (5). The most commonly isolated anaerobes are *Bacteroides* sp. (from ear or sinus infection) and anaerobic streptococci (from dental and chronic pulmonary infections). *Staphylococcus aureus* and *Staphylococcus epidermis* are frequently isolated from posttraumatic or postsurgical abscesses (10). Gram-negative bacilli, found in 23% to 33% of cases, are associated with chronic otitis, postoperative infections, and abdominopelvic infection (2,5).

Granulocytopenia, cellular dysfunction, and humoral-mediated immune dysfunction are predisposing factors to the development of CNS infections in immunocompromised patients. Acquired immunodeficiency syndrome (AIDS) and the increasing use of immunosuppressive drug therapy have lead to more atypical, fungal, and protozoal brain abscesses such as *Nocardia* sp., *Listeria* sp., *Cryptococcus* sp., *Mycobacterium* sp., *Aspergillus* sp., and *Candida* sp. Fungi in the order *Mucorales* (*Mucor, Rhizomucor*) can cause abscesses in the setting of chronic sinusitis, most commonly in patients with diabetes mellitus (6). *Toxoplasmosis gondii* is the most common cause of brain abscess in patients with AIDS, and is most commonly seen in those with CD4 counts of less than 100 cells/mm^3 (5,10).

Another important subgroup of patients with a compromised immune system is transplant patients. Brain abscesses occur in approximately 1% of transplant recipients. Fungi, particularly *Aspergillus* sp., are the most frequent etiologic agent (6).

CLINICAL PRESENTATION

The classic triad of fever, headache, and focal neurologic deficit is present in less than half of the patients with a brain abscess (4,5). There are no pathognomonic signs for a brain abscess; therefore, history and a high clinical suspicion are important features for proper diagnosis.

Headache, the earliest presenting symptom, is present in 70% to 80% of patients. The headache is usually insidious, occurring over days to weeks. Abrupt onset of the headache is a poor prognostic indicator. Fever is absent in more than 50% of patients. Alterations in consciousness, ranging from drowsiness to coma, occur in 50% of cases, as do nausea and vomiting. A focal neurologic deficit is seen in 50% to 75% of patients and can include aphasia, hemiparesis, visual field deficits, nystagmus, or ataxia. Cerebellar abscesses are usually associated with ataxia and dizziness. Cranial nerve findings are suggestive of a brainstem abscess. Focal or generalized seizures occur in approximately 30% of cases (1,4,9).

DIFFERENTIAL DIAGNOSIS

Primary or metastatic brain tumor can mimic cerebral abscess on a computed tomography (CT) scan. History and CT appearance easily differentiate other infectious diseases such as viral encephalitis, subdural empyema, epidural abscess, and meningitis.

Immunocompromised patients account for a large proportion of patients presenting to the emergency department (ED) with intracranial mass lesions. Because of the wide variety of pathologic processes involving the CNS of immunocompromised patients, brain biopsy is often needed for definitive diagnosis and treatment. Other considerations in this patient population include *Cryptococcus* sp., *Candida* sp., lymphoma, Kaposi sarcoma, and progressive multifocal leukoencephalopathy.

ED EVALUATION

The history and physical examination should focus on sites of potential infection and the possibility of life-threatening complications. Routine laboratory evaluation is rarely helpful. Leukocytosis may be present, but approximately 50% of patients will have a normal white blood cell count (9). An elevated erythrocyte sedimentation rate is seen in only 40% of cases; however, the C-reactive protein may help to distinguish abscess from tumor. Blood cultures are positive in about 10% of cases but should be obtained even if the patient is afebrile. Chest films may reveal a pulmonic source of infection; sinus or mastoid CT scans may identify infection in these areas.

Lumbar puncture for cerebrospinal fluid (CSF) analysis has a relative contraindication when evaluating for brain abscess. The risk of brainstem herniation is significant and the CSF analysis results typically do not aid in the diagnosis (7,9).

When it comes to neuroimaging, it is important to note that the imaging features of the abscess depend on its stage at the time of the imaging procedure. During the “early cerebritis” stage (first 3 days), a CT scan reveals an irregular area of low density representing focal inflammation and edema. This area does not enhance with contrast and represents the necrotic center of the abscess. In the late cerebritis stage (days 4 to 9), patchy enhancement is present, and the necrotic center develops. As the abscess evolves into the early capsule stage (days 10 to 14), a homogenous central area of low density is seen, and a thick, diffuse, ring-like vascular capsule is present. This enhancement correlates with formation of the collagen capsule. During the late capsule stage (after day 14), the ring becomes thinner as the capsular development progresses, and it is narrower on the ventricular surface of the abscess (3). Features that help to identify the mass as an abscess include gas within the center of the mass, a thinner rim (<5 mm), and ependymal enhancement. Patients given corticosteroids may have diminished enhancement of the abscess ring (5).

Magnetic resonance imaging (MRI) and CT scan are the studies of choice when evaluating a patient for a brain abscess. CT is the

imaging study of choice for the initial evaluation of a patient with a suspected brain abscess, with a reported sensitivity of 95% to 99% (5). MRI has better sensitivity and specificity than contrast CT. MRI is better at detecting mass effect, edema, petechial hemorrhage, smaller lesions, and multifocal involvement (11). Thus, if clinical suspicion is high and a CT scan is negative, an MRI should be performed.

KEY TESTING

- CT (initial imaging) and MRI (higher sensitivity and specificity than CT) are the studies of choice.

ED MANAGEMENT

Initial management of the patient with a suspected brain abscess includes airway control and maintenance of adequate ventilation and circulation. If signs of elevated intracranial pressure and/or impending herniation are present, one must act rapidly to reduce the pressure. These treatments are only temporizing measures and include intubating and hyperventilating the patient, elevating the head of the bed 30 degrees, and instituting pharmacologic therapy with mannitol or hypertonic saline. Corticosteroids remain a controversial topic, but for patients with life-threatening cerebral edema or impending herniation, high-dose corticosteroids may be appropriate (12). Immediate neurosurgical consultation is required, but know that an abscess of less than 2.5 cm in size should do well with medical management alone (10).

Definitive management includes antibiotic therapy and neurosurgical evaluation. The recommended treatment for most abscesses is CT-guided stereotactic or free-hand needle aspiration, with cultures sent to ensure appropriate antibiotic therapy (12). These culture results will not be available during the initial ED evaluation, so antibiotics based on the most likely pathogens should be initiated. Table 183.1 outlines the choices of empiric antibiotics based on the suspected source of the abscess and organisms involved. Pending culture and sensitivity results, one standard regimen

includes a third-generation cephalosporin plus metronidazole. In postsurgical abscesses, vancomycin or an antistaphylococcal penicillin should be used to cover methicillin-resistant *S. aureus* (MRSA) (2,5,10,12).

TABLE 183.1
Choices of Empiric Antibiotics Based on the Suspected Source of the Abscess and Pathogens Involved

Source	Anatomic Location	Causative Agent	Treatment[a]
Penetrating trauma	Depends on site	*S. aureus* *Clostridium* sp. Enterobacteriaceae	Cefotaxime + metronidazole
Postoperative	Variable	*S. epidermis* and *S. aureus* Enterobacteriaceae *Pseudomonas* sp.	Vancomycin + ceftazidime
Paranasal sinuses	Frontal lobe	Aerobic & anaerobic *Streptococcus* sp. *Hemophilus* sp. Anaerobes (*Bacteroides* sp., *Fusobacterium* sp.)	Penicillin G + cefotaxime + metronidazole
Otogenic	Temporal lobe Cerebellum	*Streptococcus* sp. Enterobacteriaceae *Pseudomonas aeruginosa* *Bacteroides* sp.	Penicillin G + cefotaxime + metronidazole
Hematogenous	Multiple lesions, often in the MCA territory	Depends on source Endocarditis Intra-abdominal Lung abscess	Nafcillin + metronidazole + cefotaxime

MCA, middle cerebral artery.
[a]The intravenous dosages for adults of these antibiotics are as follows:
Cefotaxime: 1–2 g q4–8h (max 12 g/d)
Ceftazidime: 1–2 g q4–8h (max 12 g/d)
Metronidazole: 500 mg q6h
Nafcillin: 2 g q4h
Penicillin G: 2–4 million units q4h
Vancomycin: 1 g q12h

DISPOSITION

All patients diagnosed with a brain abscess in the ED require admission to the hospital and immediate neurosurgical consultation. If a neurosurgeon is not available, arrangements should be made for transfer to a neurosurgical center after stabilization. Young persons, patients without underlying disease, and patients without neurologic deterioration or mental status changes have a better prognosis. With early diagnosis, advanced neuroradiologic imaging, and rapid treatment, mortality is $<30\%$, but patients presenting with signs of herniation have mortality $>50\%$ (2,5). Persistent neurologic deficits, including seizure, intellectual or behavioral impairment, and motor deficits, are seen in 30% to 55% of patients (5).

CRANIAL EPIDURAL AND SUBDURAL SPACE INFECTIONS

Intracranial subdural empyema and cranial epidural abscess are rare but life-threatening intracranial suppurative infections. Subdural empyema accounts for 15% to 25% of focal intracranial infections, and cranial epidural abscess is much less common. Subdural empyema is a disease of teenagers and young adults, with 70% of cases occurring in the second and third decades of life (13). Epidural abscess rarely occurs in young children and has been reported in patients from ages 12 to 68 years. Both conditions exhibit a 3:1 male-to-female predominance (5,13).

Subdural empyema forms between the dura mater and arachnoid mater, and cranial epidural abscess forms outside the dura mater. Both entities share a similar pathogenesis and etiology, and the two infections can coexist. Subdural empyema is typically a complication of sinusitis, and less frequently of otitis media or mastoiditis. Less frequent is the spread of organisms through Haversian canals in bone as a complication of osteomyelitis (12,13). Other causes include cranial osteomyelitis, mastoiditis, otitis media, head trauma, cranial surgery, ventriculoperitoneal shunt, halo traction pins, orbital infections, and chronic subdural hematoma (5,14). In children, bacterial meningitis is the most common predisposing condition (2).

Multiple pathogens are typically responsible for these infections and are dependent on the initial site of infection. Aerobic, microaerophilic, and anaerobic streptococci, including *S. milleri* and *Streptococcus anginosus,* are common organisms with an otorhinogenic origin. *S. aureus* and coagulase-negative staphylococci are found in sinus, otic, postoperative, and posttraumatic cases, with as many as 46% of postsurgical subdural empyemas caused by *S. aureus* (15). Gram-negative bacilli can usually be seen in otic and posttraumatic sources. Polymicrobial infections are common and a sterile culture may be found in 20% to 30% of cases. In children, the most common causative agents are those responsible for the underlying meningitis (2,5,12,13,15).

CLINICAL PRESENTATION

The clinical presentation of subdural empyema is fever, headache, and nuchal rigidity. The nonspecific symptoms of a sinus or ear infection, fever, and malaise rapidly progress to severe headache and meningismus (13). The headache, present in 90% of cases, is focal, but becomes more generalized. Nausea and vomiting are common. Varying degrees of encephalopathy can be seen, ranging from mild confusion to coma. Third and sixth cranial nerve palsies are seen rarely. Seizures, however, have been reported in 50% of patients (13,14). Postoperative and posttraumatic subdural empyemas have a very indolent course caused by slow accumulation of fluid. Headache is often absent and the disease course is more benign (5).

The presentation of epidural abscess is more insidious. Symptoms can take weeks to months to develop. Patients often present with a long history of nonspecific symptoms without focal signs or mental status changes. Once the fluid mass reaches critical size, nausea, vomiting, headache, drowsiness, and lethargy occur. Focal neurologic signs, seizure, and coma do not occur unless the infection spreads to the subdural space, or cerebral herniation occurs. A patient with an epidural abscess involving the petrous bone may present with pain in the distribution of the fifth cranial nerve, and a sixth cranial nerve motor palsy (Gradenigo syndrome) (16).

DIFFERENTIAL DIAGNOSIS

The initial presentation of subdural empyema and epidural abscess is similar to other intracranial processes. Meningitis, brain abscess, subdural hematoma, subarachnoid hemorrhage, herpes encephalitis, venous sinus thrombosis, and tumor should be considered.

ED EVALUATION

History and physical examination should focus on finding potential sources of infection. A detailed neurologic examination should be performed. Routine laboratory evaluation is of limited value. The white blood cell count may be only mildly elevated and is often normal. The sedimentation rate may be elevated if osteomyelitis is present. Cerebral spinal fluid analysis is usually not helpful and is relatively contraindicated because of the risk of herniation (13).

CT scanning with IV contrast remains the mainstay of ED diagnosis for both subdural empyema and cranial epidural abscess, yet the diagnostic procedure of choice is MRI with gadolinium (13). Subdural empyema reveals a crescent-shaped, hypodense fluid collection in the subdural space with displacement of the arachnoid. A mass effect is common and an enhancing rim may be seen. Epidural abscess appears as a poorly defined, lentiform, extra-axial area of low or intermediate density. These entities can be easily missed by CT, given the proximity of the cranial vault, so MRI should be used when CT scanning is negative in the face of high clinical suspicion (13,17).

KEY TESTING

- Routine laboratory evaluation is of low yield.
- MRI and CT scanning are the studies of choice, with MRI considered the diagnostic test of choice for both disease processes.

ED MANAGEMENT

Once the diagnosis is made, immediate neurosurgical consultation is required. If signs of impending herniation are present, temporizing measures must be employed.

Antibiotic coverage should begin in the ED. The choice of antibiotic should be tailored to the suspected source until culture results are available. A scheme for antibiotic selection is outlined in Table 183.1.

DISPOSITION

All patients require admission. If neurosurgical services are not available, the patient, once stabilized, should be transferred to an appropriate center with available neurosurgical services. Patients with an isolated cranial epidural abscess have an excellent prognosis. Most recover with good neurologic outcome. The mortality for subdural empyema ranges from 9% to 48% (18). Of those patients who survive, 15% to 44% have a persistent neurologic deficit

(seizure disorder, hemiparesis, aphasia). Outcome is directly related to advanced patient age, degree of encephalopathy present, and delay to appropriate therapy (18).

SPINAL EPIDURAL ABSCESS

SEA, although still a rare entity, has doubled in incidence in the past 20 years, with 1.2 to 3 cases per 10,000 patients. This increase is likely due to an aging population, increased use of spinal instrumentation, and the increase in intravascular drug use (19,20). The most important risk factors are diabetes, trauma (e.g., spinal instrumentation), intravenous drug use, alcoholism, advanced age, and an immunocompromised state. Diabetes remains the single most important risk factor, and presents in 15% to 33% of cases (19). Bacteria gain access by hematogenous dissemination in 50% of cases, by contiguous spread in 33% of cases, and in the remaining percentage the source is not identified (20). The most frequently isolated organism is *S. aureus,* with up to 40% being the methicillin-resistant strain. *Streptococcus* sp.*, Escherichia coli, Pseudomonas* sp.*, Klebsiella* sp.*, Acinetobacter* sp., and *Mycobacterium tuberculosis* have also been found (19–21).

CLINICAL PRESENTATION

Back pain (75% of patients), fever (50%), and neurologic deficit (33%) are the classic triad of this disease process, but is only present in a minority of patients, 8% in one case report (20,21). There is a staging system detailing the progression of symptoms and physical findings: in stage 1 there is back pain at the level of the affected spine only; in stage 2 there is nerve-root pain radiating from the involved spinal area; in stage 3 there is motor weakness, sensory deficit, and bladder and bowel dysfunction; and stage 4, paralysis (20).

Irreversible paralysis remains the most feared complication of SEA, with delayed diagnosis one of the main culprits. About half of the cases are initially misdiagnosed (20), so considering this disease in your differential is of the upmost importance.

DIFFERENTIAL DIAGNOSIS

The presentation of an SEA is similar to many types of back pain. Other diagnoses to keep in mind when evaluating a patient with back pain include intervertebral disc herniation, metastatic epidural spinal cord compression, spinal epidural hematoma, and simple back strain. Separating these diagnoses requires a thorough history and physical examination. MRI and CT scan provide further information as to the cause of the back pain.

ED EVALUATION

The diagnosis of SEA is suspected on the basis of clinical findings and supported by laboratory data and imaging studies. Leukocytosis is present in two-thirds of patients, and inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) are almost always elevated, with 100% sensitivity for ESR noted in one study (22). Bacteremia is noted in 60% of patients, so blood cultures should also be utilized (20). CSF analysis should be entertained with caution, as there is a risk of spread of infection if the needle traverses the abscess.

Contrast CT of the spine is better than noncontrast imaging for identifying an abscess, but is still inferior to MRI. MRI is the most useful study for demonstrating an abscess with sensitivity reported to be between 90% and 100% (19–21,23). MR images also demonstrate discitis and osteomyelitis when present, which coexist with up to 80% of patients (20).

KEY TESTING

- Inflammatory markers (ESR and CRP) help with the diagnosis of SEA (22).
- MRI and CT scanning remain the studies of choice for this disease processes, with MRI (preferably with gadolinium) considered the diagnostic test of choice if available (19–21,23).

ED MANAGEMENT

Surgery and antibiotics are the mainstays of therapy. Antibiotics should be started as soon as the diagnosis is established. Appropriate antibiotic choices should provide coverage against staphylococci (typically with vancomycin for MRSA coverage), and gram-negative bacilli with a third- or fourth-generation cephalosporin (e.g., ceftazidime or cefepime). Antibiotics are usually continued for 6 weeks (19,20).

CRITICAL INTERVENTIONS

- Suspect CNS abscess or other suppurative infection in high-risk patients with headache, neck pain, or back pain and order CT or MRI.
- Administer antibiotics in the ED.
- Obtain neurosurgical consultation (or orthopedic spine consultation as appropriate).

DISPOSITION

All patients with an SEA require admission to a neurosurgical or spinal orthopedic surgery service. If these are not available, the patient should be stabilized, should have antibiotics started, and should be transferred to an appropriate center. Neurologic deficits for greater than 48 hours, immunocompromised patients, involvement of the thoracic spinal cord, and MRSA as the causative organism all worsen the prognosis for a complete recovery.

Common Pitfalls

- Failure to suspect a suppurative CNS infection in patients presenting with headache, neck pain, or back pain
- Inappropriate antibiotic selection because the probable origin of the infection was not considered
- Delay in initiating treatment for increased intracranial pressure and obtaining neurosurgical consultation

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CHAPTER 184 Sexually Transmitted Diseases

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Sexually transmitted diseases (STDs) are commonly encountered in the emergency department and primary care settings. The United States has one of the highest rates of STDs in the industrialized world, estimated to be 50 to 100 times higher than other nations, with approximately 110 million total infections and nearly 20 million new cases per year, costing the US healthcare system 16 billion dollars a year in direct medical costs (1–3). The true prevalence and incidence is likely higher, as it is estimated that reported cases of STDs represent only 50% to 80% of reportable STD infections in the United States (4). Diagnosis and treatment is important to prevent future complications of untreated disease, such as infertility, and to prevent the further spread of infection.

The history and physical examination are paramount in diagnosing STDs. Important aspects of the history include symptoms and their duration, history of previous STDs, timing and types of sexual contacts, use of contraceptive agents or devices and, in women, menstrual history. A thorough examination of the genital area is important, with emphasis on observation for lesions and for the presence of discharge. In addition, examination for lymphadenopathy (local and systemic), a joint examination (if the patient is symptomatic), and examination of the skin for rashes and lesions are critical.

Most STDs can be divided into ulcerative diseases (those presenting with ulcers and/or inguinal adenopathy) and

nonulcerative diseases (those presenting with urethral, cervical, or vaginal discharge). **Tables 184.1** and **184.2** list the differential diagnoses of both ulcerative and nonulcerative genital complaints.

TABLE 184.1
Differential Diagnosis of Ulcerative Sexually Transmitted Diseases

Herpes	Scabies
Syphilis (primary)	Pyoderma
Chancroid	Trauma
Lymphogranuloma venereum (LGV)	Excoriations
Granuloma inguinale (Donovanosis)	Behçet disease
Molluscum contagiosum	Drug reaction
Genital warts	Yeast infection
Pediculosis	

TABLE 184.2
Differential Diagnosis of Nonulcerative Sexually Transmitted Diseases

Gonorrhea
Chlamydia
Nongonococcal urethritis
Secondary/tertiary syphilis
Candidal vaginitis
Trichomonas
Bacterial vaginosis

ULCERATIVE SEXUALLY TRANSMITTED DISEASES

Patients may present with complaints of an ulcer or sore on or adjacent to the genitalia. Although there are nonsexual causes of genital ulcers, patients presenting with these lesions should be considered to have a sexually transmitted infection until proven otherwise. Infections presenting with genital lesions may be difficult to distinguish from one another based on examination alone, so history is of particular importance in determining the cause of the

lesion. Key points in the history include the characteristics of the lesion(s) such as the type of initial lesion (vesicle or papule), whether the lesion is single or multiple, is painful or nontender, has regular or irregular borders, or is indurated or soft. If adenopathy is part of the presentation, determine whether it is or is not painful, whether it is unilateral or bilateral, and whether it is fluctuant (Table 184.3).

TABLE 184.3
Characteristics of Ulcerative Sexually Transmitted Diseases

Disease	Nature of Genital Ulcer	Incubation Period	Painful	Inguinal Adenopathy	Diagnostic Tests
Syphilis	Indurated, sharply demarcated, with red, smooth base; heals spontaneously	9–90 d; average 2–3 wks	No	Firm rubbery nodes; nontender	Dark-field examination; serologic
Herpes simplex	Multiple, small grouped vesicles on a red base, which form shallow ulcers; may coalesce; resolve spontaneously but recurrence common	2–7 d	Yes	Bilateral, firm, tender	PCR, culture, serology: nontreponemal (VRDL, RPR) & treponemal (FTA-ABS, TP-PA)
Chancroid	Irregular, sharply demarcated borders with undermined edges, shallow, often multiple	3–6 d	Yes	Unilateral, most common; overlying erythema, fixed and tender, suppuration possible	Culture
Lympho-granuloma venereum	Usually single lesion, papule or ulcer, transient, frequently not noticed	5–21 d	No	Unilateral, most common; firm, tender, matted fixed May suppurate or form fistulas	Culture, direct immunofluorescence, nucleic acid testing of tissue (swab/aspirate); LGV complement fixation (serology)

Treatment is often necessary before test results are available; treatment decisions should be based on the most likely diagnosis. The most common ulcerative diseases in the United States are, in order of incidence, herpes, syphilis, and, in rare outbreaks, chancroid (5). Any patient with an ulcerative lesion should have herpes simplex virus (HSV) testing and syphilis serology sent and, as ulcerative diseases increase the risk of HIV infection, all patients should also be offered HIV testing.

HERPES GENITALIS

Genital herpes is an STD caused by the HSV type 2 (HSV-2) and, less commonly, type 1 (HSV-1). Herpes lesions are by far the most common cause of genital ulceration owing to infection in developed countries, with an estimated 775,000 new cases annually and more than 50 million persons infected in the United States (2,6). Although herpes infection usually does not often produce serious sequelae in nonpregnant patients, genital herpes infection plays a major role in

the spread of HIV as persons infected with genital herpes are more susceptible to HIV infection, and herpes infection can make HIV positive persons more infectious.

CLINICAL PRESENTATION

In immunocompetent individuals, the severity of presentation of symptomatic genital herpes depends on whether it is the patient's first infection with a herpes virus or whether the patient has had prior herpes infection (genital or labial). Primary herpes infection is the initial infection in a patient without circulating antibodies to either HSV-1 or HSV-2. Clinical presentations can be highly variable. After an incubation period of 2 to 7 days, patients often develop systemic symptoms, including low-grade fever, malaise, headache, and myalgias. Grouped, multiple small vesicles on an erythematous base appear on the genitalia and develop into painful, shallow ulcers. The severity of local symptoms reaches its peak between 8 to 10 days, gradually receding over the second week of illness. The lesions of the primary episode are generally present for 2 to 4 weeks until complete healing occurs. Patients may also develop adenopathy, most often during the second or third week. The nodes are usually bilateral, slightly enlarged, nonfluctuant, and mildly tender. Severe external dysuria, another common symptom, is more often seen in women and may lead to urinary retention. Urinary retention can also occur as a consequence of sacral radiculomyelopathy, which may also cause constipation and sensation changes in the lumbosacral distribution. Other uncommon complications of primary herpes infection include aseptic meningitis and transverse myelitis.

Patients with circulating antibodies to HSV-1 who acquire genital HSV-2 infection tend to have a less dramatic course, and their infection resembles that of a recurrence in a patient with known genital herpes.

Herpes is a lifelong infection; the virus remains latent and recurs in 60% to 90% of patients. The symptoms of recurrence are distinctly milder than during the primary infection. Systemic symptoms are rare, and patients typically have fewer lesions with a shorter time to complete healing. Prodromal symptoms occur in more than half of

the patients who experience recurrence, including localized paresthesias, itching, burning, or hypersensitive skin at the site of subsequent lesions. Virus is shed from both primary and recurrent lesions for several days after ulcerations or erosions first appear. It is also important to note that intermittent asymptomatic viral shedding can occur and lead to the transmission of the disease even in the absence of genital lesions.

ED EVALUATION

It is tempting to make the diagnosis of genital herpes based on clinical suspicion, but clinical diagnosis is neither sensitive nor specific, and confirmatory testing is recommended, especially in women of childbearing age. The preferred tests for genital herpes are cell culture or polymerase chain reaction (PCR). The sensitivity of viral culture is low and declines rapidly as lesions begin to heal. False-negative results are common owing to improper collection or transport, and results are reported in 2 to 7 days. PCR assay for HSV DNA is more sensitive than culture and is considered the test of choice for detecting HSV central nervous system infection. Cytologic detection of herpes virus (Tzanck prep or PAP smear) is insensitive and nonspecific and should not be used. Serologic, type-specific testing based on HSV glycoproteins can provide results with sensitivities of 80% to 90% and specificities of more than 96%. These tests may give false-negative results, especially at early stages of infection.

KEY TESTING

- PCR assay for HSV DNA
- HIV
- Serologic test for syphilis (VDRL/RPR)

ED MANAGEMENT

Genital herpes is a lifelong infection without a definitive cure, but skin lesions are self-limited and heal spontaneously unless secondarily infected. Systemic antiviral drugs (acyclovir,

valacyclovir, and famciclovir) are the mainstay of therapy (7), as they partially control the symptoms and signs of herpes, shorten the duration of symptoms, decrease the duration of shedding, and can abort recurrence episodes. Table 184.4 outlines the different treatment regimens for genital herpes. Unfortunately, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued. Suppressive therapy can reduce the frequency of genital herpes recurrences by 70% to 80%, and studies show up to 6 years of acyclovir use and 1 year of continuous use of the other agents is safe (7). Topical antivirals offer minimal clinical benefit and their use is discouraged (7). Other goals of treatment are symptomatic treatment and include pain control and genital hygiene.

TABLE 184.4
Treatment Guidelines

Disease	Recommended Treatment Regimen	Alternative(s)
Chlamydia	Azithromycin 1 g PO in a single dose or doxycycline 100 mg PO BID × 7 d	Erythromycin base 500 mg PO QID × 7 d or Ofloxacin 300 mg PO BID × 7 d or Levofloxacin 500 mg PO QD × 7 d or Erythromycin ethylsuccinate 800 mg PO QID × 7 d
Gonorrhea, urethral, cervical, or rectal	Ceftriaxone 250 mg IM × 1 plus either azithromycin 1 g orally once OR doxycycline 100 mg orally twice a day for 7 d	
Gonorrhea, conjunctival	Ceftriaxone 1 g IM once	
Gonorrhea, disseminated	Ceftriaxone 1 g IM or IV once daily	
Herpes simplex, first episode	Acyclovir 400 mg PO TID × 7–10 d or Acyclovir 200 mg PO 5 times daily × 7–10 d or Famciclovir 250 mg PO TID × 7–10 d or Valacyclovir 1 g PO BID × 7–10 d	
Herpes simplex, recurrent	Acyclovir 400 mg PO TID × 5 d or Acyclovir 800 mg PO TID/d × 2 d or Acyclovir 800 mg PO BID × 5 d or Famciclovir 125 mg PO BID × 5 d or Famciclovir 500 mg PO × 1, then 250 mg PO BID × 2 d Famciclovir 1,000 mg PO BID × 1 d Valacyclovir 500 mg PO BID × 3–5 d Valacyclovir 1 g PO daily × 5 d	
Herpes simplex, suppressive	Acyclovir 400 mg PO BID or Famciclovir 250 mg PO BID or Valacyclovir 500 mg PO QD or Valacyclovir 1 g PO QD	
Syphilis, primary, and secondary	Benzathine penicillin G 2.4 million units IM × 1	Doxycycline 100 mg PO BID × 14 d Tetracycline 500 mg PO QID × 14 d
Syphilis, latent	Benzathine penicillin G 2.4 million units q wk × 3	
Syphilis, tertiary (absence of signs of neurosyphilis)	Benzathine penicillin G 2.4 million units q week × 3	Procaine penicillin 2.4 million units IM daily + Probenecid 500 mg PO 4 times daily × 10–14 d (use only if compliance can be ensured)
Syphilis, tertiary (presence of neurosyphilis)	Aqueous crystalline penicillin G 18–24 million units/d IV administered as 3–4 million units IV q4h or continuous infusion × 10–14 d	
Chancroid	Azithromycin 1 go PO × 1 or ceftriaxone 250 mg IM × 1 or ciprofloxacin 500 mg PO BID × 3 d or erythromycin base 500 mg PO TID × 7 d	
Lymphogranuloma venereum	Doxycycline 100 mg PO BID × 21 d	Erythromycin base 500 mg PO QID × 21 d

All patients should be counseled to refer partners for evaluation and that the disease is transmissible even when asymptomatic. Women of childbearing age must inform their doctor of their history of genital herpes when becoming pregnant. Women who acquire herpes during pregnancy have a significantly increased risk of fatal neonatal herpes infections, and high rates of neonatal morbidity have been reported in association with both symptomatic and asymptomatic primary infections acquired late in pregnancy. Consultation with the patient's primary care doctor is recommended before starting any treatment regimen in pregnant patients, as the safety of systemic acyclovir, valacyclovir, and famciclovir therapy in pregnant women has not been established.

SYPHILIS

Syphilis is a disease caused by the spirochete *Treponema pallidum* and is capable of involving any organ of the body. Transmission occurs primarily during sexual contact, and exposure to moist skin or mucous membranes is necessary for the infection to occur. Since the year 2000, the incidence of this infection has been increasing, with an estimated 55,000 new cases annually (5).

CLINICAL PRESENTATION

The natural history of untreated syphilis infection is described in four stages.

1. Primary. The incubation period varies from 9 to 90 days, with an average of 2 to 4 weeks. The primary lesion is a chancre, which occurs at the point of inoculation. Patients may note that before ulcerating, the lesion may have started as a papule. The chancre is characteristically painless, usually single, and has a smooth, slightly raised edge with sharply defined borders and an indurated base. A few days after appearance of the chancre, if the primary lesion is on the genitals, patients may develop unilateral or bilateral inguinal lymphadenopathy, which is usually painless and is not a prominent feature of the infection. The chancre is indolent and, if not treated, usually persists 2 to 6 weeks before spontaneously healing, and the infection progresses to the secondary stage.
2. Secondary. The average interval between the appearance of the primary chancre and secondary lesions is 5 to 8 weeks. Constitutional flu-like symptoms are common, including low-grade fever, malaise, headache, sore throat, arthralgias, and generalized lymphadenopathy. Patients typically develop a macular rash, which starts on the trunk and spreads to the abdomen, shoulders, and limbs, evolving into a symmetric papulosquamous rash that may resemble pityriasis rosea. The rash often involves the palms and soles with maculopapular lesions. Patients may also develop condyloma lata: hypertrophic, broad-based papules with flat moist tops, most common on the labia, around the anus, and between the buttocks. Lesions may be seen on the tongue and are called mucous patches. When

adenopathy is present, it may be anywhere on the body, and the nodes are discrete, nontender, and rubbery. If untreated, this stage also resolves spontaneously.

3. Latent. This stage begins when secondary symptoms disappear. Patients are asymptomatic during the latent phase, and disease is detected solely by serologic testing. Latent syphilis acquired within the preceding year is referred to as early latent syphilis; all other cases of latent syphilis are either late latent syphilis or latent syphilis of unknown duration.
4. Tertiary. Cardiovascular and central nervous system symptoms predominate in this stage. The symptoms occur 3 to 4 years or later after the primary stage but may be seen earlier in immunocompromised patients such as those with HIV infection. Specific manifestations include meningitis, peripheral neuropathy (tabes dorsalis), thoracic aortic aneurysms, and gummatous lesions of the mucous membranes.

ED EVALUATION

Dark field examination and direct fluorescent antibody tests of lesion exudates or tissue are the definitive methods for diagnosing early (primary) syphilis. However, the sensitivity is only approximately 80%, and lack of availability of dark field microscopy and trained personnel limit the use of this technique (8).

Currently, serologic testing is the mainstay of diagnosis for secondary, latent, and tertiary syphilis. Serologic tests are divided into nontreponemal and treponemal tests, and both are required for definitive diagnosis. Nontreponemal tests measure nonspecific antibodies found in the serum of patients with syphilis. These tests include the venereal disease research laboratory (VRDL) and rapid plasma reagin (RPR) tests, and they vary in their sensitivity based on the stage of syphilis. Nontreponemal tests are positive about 2 weeks after the appearance of the primary lesion. As the results are quantitative, the titers can be followed to determine the response to treatment. However, care must be taken to use the same test and preferably the same laboratory. The antibodies reach their highest levels during secondary syphilis, during which time the sensitivity of

nontreponemal tests approaches 100%. These tests are not specific for *T. pallidum,* however, so false-positive tests do occur. Syphilis is confirmed with the treponemal tests, fluorescent treponemal antibody-absorption (FTA-ABS) or microhemagglutination assay T. pallidum (MHA-TP), which measure specific antibodies formed by the host in response to infection with *T. pallidum.* Treponemal test antibody titers should not be used to assess treatment response (7). Patients suspected of having neurosyphilis typically have CSF-VDRL performed, which is highly specific, but not sensitive.

KEY TESTING

- Serologic test for syphilis (VDRL or RPR)
- HIV

ED MANAGEMENT

For primary and secondary syphilis, benzathine penicillin G 2.4 million units IM × 1 is the treatment of choice (7); see Table 184.4 for alternative treatment regimens and for treatment of latent and tertiary syphilis. Sexual partners within the last 90 days should be tested but treated presumptively; partners after more than 90 days should be evaluated and treated if indicated. If serologic results are not available or follow-up is uncertain, these patients should also be treated presumptively. All patients should be referred for HIV testing. Patients should be referred for re-examination clinically and serologically 6 months and 12 months after treatment, as RPR and VDRL should become nonreactive after successful treatment. A fourfold or greater decrease in titers after 6 months correlates with decreasing antibody levels and successful treatment. Parenteral penicillin G is the only therapy with documented efficacy for syphilis during pregnancy. Because congenital syphilis can be devastating, pregnant women with syphilis in any stage who report penicillin allergy should be desensitized and treated with penicillin (7).

CHANCROID

The gram-negative bacterium *Haemophilus ducreyi* is the causative agent of chancroid. The infection is characterized by painful genital ulcerations and frequent bubo formation. These fluctuant nodes can spontaneously rupture, leading to the formation of inguinal ulceration and excavation. Though common in developing countries (9), the disease is rare in the United States, with usually <100 total reported to the Centers for Disease Control (CDC) annually (5). Infections can occur in small outbreaks in susceptible populations. In addition, as *H. ducreyi* is difficult to culture, the condition may be substantially under-diagnosed.

CLINICAL PRESENTATION

The incubation period is 3 to 6 days, after which a small, tender red papule or pustule appears at the site of inoculation. The papule rapidly progresses to an ulcer, characterized by sharply demarcated edges and sloughing bases, often with necrotic exudates. Multiple lesions are common and lesions may coalesce. About 1 week after the ulcers develop, about half of patients will develop lymphadenitis, which is typically unilateral, painful, and fluctuant. The overlying skin is often thinned and erythematous, and suppuration and spontaneous rupture is common.

ED EVALUATION

Diagnosis is often based on clinical presentation and is often a diagnosis of exclusion, after ruling out other diseases such as herpes and syphilis. Presence of a fluctuant inguinal node in a patient with genital ulcers strongly suggests the diagnosis. Confirming the diagnosis of chancroid requires identifying the organism *H. ducreyi.* This organism is difficult to grow and requires a special medium that is frequently not available. A probable diagnosis can be made if all of the following criteria are met: (a) the patient has one or more painful genital ulcers, (b) the patient has no evidence of *T. pallidum* infection by dark-field examination or serologic testing, (c) the clinical presentation, appearance of genital ulcers, and regional lymphadenopathy are typical for chancroid, and (d) a test for HSV performed on the ulcer exudates is negative (7).

KEY TESTING

- PCR assay for HSV DNA
- HIV
- Serologic test for syphilis (VDRL or RPR)

ED MANAGEMENT

Treatment is curative. The CDC has four recommended regimens (7); see Table 184.4 for more treatment options. All patients should be referred for HIV and other STD testing. About 10% of patients who have chancroid acquired in the United States are coinfected with *T. pallidum* or HSV, and chancroid is a risk factor for HIV transmission. Sex partners during the 10 days preceding the patient's onset of symptoms should be examined. Patients should be referred for re-examination 3 to 7 days after initiation of therapy to confirm response to treatment. The length of time required for complete healing varies by the size of ulcer; advanced disease can lead to scarring despite treatment.

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum (LGV) is characterized by a transient genital lesion followed by lymphatic involvement in the genitalia, pelvic area, and rectum that can lead to chronic complications such as elephantiasis. It is caused by specific serotypes of *Chlamydia trachomatis*. This disease is prevalent in many tropical countries but is rare in the United States, usually occurring in small isolated outbreaks.

CLINICAL PRESENTATION

The incubation period is 3 days to 3 weeks. The primary lesion is a small, painless ulcer that is transient and may go unnoticed. The disease usually presents in the secondary stage, when regional lymphadenitis appears, usually 7 to 30 days after the disappearance of the primary lesion. The enlarged nodes are painful with overlying erythema. Inguinal lymphadenopathy, usually unilateral, may present with the "groove sign," enlargement of the glands above and

below the Poupart ligament. Patients may develop multiple draining sinuses or form a hard inguinal mass. Rectal exposure can lead to proctocolitis and if not treated early can result in colorectal fistulas and strictures. Elephantiasis may develop as a late complication owing to blockage of lymphatic channels.

ED EVALUATION AND MANAGEMENT

Diagnosis is often based on the clinical picture. Serologic testing for the specific serotype of chlamydia that causes LGV is available but is often a "send-out" test with results taking days to weeks to return. Tissue specimens (swab of ulcer or bubo aspirate) can also be tested for *C. trachomatis* by various methods. Other causes of inguinal lymphadenopathy and genital ulcers must be ruled out. Treatment cures the infection and prevents ongoing damage and potential complications. Doxycycline, 100 mg PO bid × 21 days is the preferred treatment. Erythromycin 500 mg PO qid × 21 days is an alternative regimen (7). All patients need referral for HIV testing, and sexual partners should be evaluated and treated.

KEY TESTING

- Culture, direct immunofluorescence, nucleic acid testing of tissue (swab or aspirate)
- HIV
- Serologic test for syphilis (VDRL or RPR)

NONULCERATIVE SEXUALLY TRANSMITTED DISEASES

Nonulcerative sexually transmitted diseases and infections are characterized by urethral or cervical discharge. The two most common nonulcerative STDs are chlamydia and gonorrhea; other causes include nongonococcal urethritis, candidiasis, bacterial vaginosis, and trichomoniasis. Clinical manifestations of infection with chlamydia and gonorrhea closely resemble each other, and the two commonly occur together. Therefore, it is usually not possible to distinguish the two diseases from one another clinically, and patients

are usually treated for both infections. Table 184.2 lists the differential diagnosis for nonulcerative STDs.

CHLAMYDIA

In the United States, chlamydia is one of the most commonly reported STDs, with nearly three million cases estimated annually (5). It is caused by *C. trachomatis* and can cause urethritis, proctitis, epididymitis, prostatitis, cervicitis, perihepatitis (Fitz-Hugh and Curtis syndrome) and pelvic inflammatory disease (PID) (see Chapter 130, "Pelvic Inflammatory Disease").

CLINICAL PRESENTATION

The incubation period is 1 to 3 weeks. Males usually present with symptoms of urethritis or epididymitis. Females, when symptomatic, may complain of symptoms ranging from dysuria to peritonitis. Frequently, women may have only vague, nonspecific complaints, including vaginal discharge or bleeding or abdominal or pelvic pain. Asymptomatic infection is common among both men and women; it is estimated that 75% of infected women and 50% of infected men have no symptoms (10,11). Sexually active adolescent females have a particularly high rate of infection, and chlamydial infection has been found in up to 10% of asymptomatic young women in family planning clinics (11,12). Infection in women can lead to PID, ectopic pregnancy, and infertility. It is estimated that 40% of women with untreated chlamydial infections will develop PID.

ED EVALUATION

Historically, the gold standard for diagnosis was cell culture. However, newer tests have better sensitivity and specificity than culture and are becoming the new gold standard. Nucleic acid amplification tests (NAATs) amplify nucleic acid sequences that are specific for the organism being tested and do not require the presence of viable organisms. NAATs have sensitivities that exceed that of culture (>90% vs. 60% to 80%, respectively), with specificities >99%. NAATs also are more sensitive than other nonculture tests (DNA probe testing, latex agglutination testing)

(13,14). These tests can be performed on both swabs (endocervical or urethral) and urine, although it is recommended to use endocervical swabs in women because the sensitivity is lower when performed on urine (13). Urine screening NAATs are adequate for males, especially when they are symptomatic; urethral swabs are generally not necessary (14). Culture is still preferred when an isolate is needed (e.g., in sexual abuse cases) and should be done in addition to NAATs in these cases (7).

KEY TESTING

- NAAT (Chlamydia and gonococcal) collected from endocervix, urethra, or urine.
- HIV
- Serologic test for syphilis (VDRL or RPR)

ED MANAGEMENT

Treatment consists of azithromycin 1 g PO × 1 dose or doxycycline 100 mg PO bid × 7 days (see Table 184.3 for alternative regimens) (7). Unless coinfection with gonococcal infection is definitively ruled out, the patient should be treated for both infections. Sexual partners need testing and treatment, and the patient should refrain from sexual intercourse until 1 week after completing treatment and after sex partners are treated.

GONORRHEA

Gonorrhea is an STD caused by the gram-negative diplococcus *Neisseria gonorrhoeae.* More than 800,000 new *N. gonorrhoeae* infections occur in the United States each year (5). Patients may present with infection of the urethra, rectum, cervical canal, pharynx, upper female genital tract, or conjunctival sac owing to the organism's predilection for infecting columnar or transitional epithelium.

CLINICAL PRESENTATION

The clinical presentation of localized disease varies depending on the gender of the patient and the site of infection. In men, acute urethritis is the most common presentation. Symptoms include dysuria and a penile discharge, starting within 1 to 14 days of exposure. Purulent urethral discharge and meatal erythema are found on physical examination in symptomatic males. Patients may also complain of testicular pain and swelling, with evidence of epididymitis, although this is an uncommon presentation.

Primary gonococcal infection in women is often asymptomatic; patients may have only vague complaints until complications such as PID have occurred. Symptoms, when they occur, are usually mild or nonspecific and can include vaginal discharge, abnormal vaginal bleeding, abdominal or pelvic pain, or urinary symptoms such as dysuria and frequency. Up to 20% of women with untreated gonorrhea develop PID, with symptoms including abnormal uterine bleeding, abdominal pain, and dyspareunia. Both symptomatic and asymptomatic cases of PID can result in tubal scarring that may lead to infertility or ectopic pregnancy (see Chapter 130 "Pelvic Inflammatory Disease"). Other presenting complaints may include Bartholin abscess or right upper quadrant pain secondary to perihepatitis (Fitz-Hugh and Curtis syndrome).

Other sites of primary infection include the oropharynx, anorectal area, and conjunctiva. Oropharyngeal gonococcal infection is often asymptomatic. Patients may have pharyngitis symptoms such as sore throat and exudative tonsillitis, but even without treatment, most cases are self-limited. Anorectal involvement is more common in homosexual men and heterosexual women. Like pharyngitis, anorectal infection is often asymptomatic. If patients develop symptoms, they may complain of rectal discomfort, anorectal pain, tenesmus, constipation, pruritus ani, and purulent or mucoid anal discharge or bleeding. On anoscopy, the mucosa appears friable, and a mucopurulent exudate may be present. Patients with conjunctival infection present with marked conjunctival erythema and purulent drainage (sometimes copious) and may have chemosis. If untreated, patients may develop vision-threatening complications such as corneal ulceration, endophthalmitis, and globe perforation.

Disseminated gonococcal infection, more common in women than men, results from gonococcal bacteremia. Patients present with systemic symptoms (fever, chills), joint complaints (arthralgias or arthritis, or tenosynovitis) and skin complaints (pustular rash, usually found on the peripheral extremities). The skin lesions are characteristically small tender papules that become pustular (described as necrotic pustules on an erythematous base), and most likely represent septic emboli to small blood vessels. If disseminated gonorrhea involves the joints, the arthritis usually presents with an acute monoarticular arthritis. Although the knee is most commonly involved, symptoms may also include elbows, ankles, wrists, and small bones of the hands and feet. The involved joint is erythematous and warm, may have an effusion, and is painful on passive and active range of motion. Other manifestations include hepatitis, myocarditis, endocarditis, and rarely, meningitis.

The definitive diagnosis of disseminated gonococcal arthritis is made by isolating gonococci from the blood or from an area reached hematogenously: synovial fluid, skin, or cerebrospinal fluid. Presumptive diagnosis is based on the appropriate clinical presentation combined with isolation of gonococci from a source site (urethra, cervix, pharynx, rectum).

ED EVALUATION

In symptomatic males or patients with gonococcal conjunctivitis, Gram stain of the discharge may have a sensitivity and specificity approaching 100% (10,15). The Gram stain is a quick means of diagnosing these cases, with results returned during the ED visit, and sensitivity and specificity of Gram stain are comparable to culture. In females and asymptomatic males, however, the Gram stain is less useful, with significantly decreased sensitivity.

The advantages to culture are that it is relatively inexpensive compared to NAATs, can assess antibiotic susceptabilities, and can be used on samples from any site. Culture is also the test of choice when the results will be used as evidence in legal investigations. On the other hand, accurate results may be limited by improper collection and handling of specimens. To maintain the viability of gonococcal

organisms, specimens should be inoculated directly onto the appropriate medium. Specimens from a sterile site, such as cerebrospinal fluid or synovial fluid, should be plated on nonselective medium such as chocolate agar. Specimens from areas high in normal bacterial flora (such as the cervix, urethra, rectum, or oropharynx) should be inoculated on selective media such as Martin Lewis agar. Immediately after plating, specimens should be incubated at 35°C to 36.5°C and transported to the laboratory in a carbon dioxide–enriched atmosphere (10).

As with chlamydia, NAATs have been shown to have good sensitivity and excellent specificity for detection of gonorrhea from endocervical, urethral, and urine samples. The sensitivity of NAATs is superior to that of culture (7) and endocervical swabs are more sensitive than urine specimens in women, so they are preferred (10,15).

KEY TESTING

- NAAT (Chlamydia and gonococcal) collected from endocervix, urethra, or urine
- HIV
- Serologic test for syphilis (VDRL of RPR)

ED MANAGEMENT

Due to changes in antibiotic resistance, the recommendations for treating gonorrhea were updated in 2012. Oral cephalosporins are no longer recommended. The current recommendation is to treat with a single IM dose of 250 mg of ceftriaxone plus either a 1-g oral dose of azithromycin or a 7-day course of doxycycline, 100 mg orally twice a day. Using the second agent was previously recommended to treat possible concurrent chlamydial infection, but now it is recommended for use in all cases of suspected gonorrhea as this second antimicrobial agent improves efficacy in treating gonorrhea. (see Table 184.4 for other alternatives) (7). Treatment with quinolones is no longer recommended in the United States because of recent increases in quinolone resistance (7). Patients should be instructed

that their partners need referral for evaluation, testing, and treatment. Patients should be instructed to avoid sexual intercourse until therapy is completed and until they and their sex partners are treated and no longer symptomatic. Patients should also be referred for HIV testing.

KEY TESTING

Disease	Diagnostic Tests
Ulcerative STD	
Chancroid	Culture
Herpes simplex	PCR, culture, serology: nontreponemal (VRDL, RPR) and treponemal (FTA-ABS, TP-PA)
Lymphogranuloma venereum	Culture, direct immunofluorescence, nucleic acid testing of tissue (swab or aspirate); LGV complement fixation (serology)
Syphilis	Dark field examination; serologic
Nonulcerative STDs	
Chlamydia	Culture, NAATs
Gonorrhea	Gram stain, culture, NAATs

NONGONOCOCCAL URETHRITIS

Nongonococcal urethritis (NGU) can occur in both men and women. Patients with NGU present with urethral discharge and dysuria or urethral pruritus. The etiology in many cases is unknown, although *C. trachomatis* is implicated as the most common cause; other organisms include *Ureaplasma* and *Mycoplasma.* Diagnosis is made by gram stain (>5 WBC per high-power field and no gram-negative diplococci), positive leukocyte esterase test on urinalysis, or more than 10 WBC per high-power field on urinalysis. All patients with urethritis should be evaluated for both gonorrhea and chlamydia. Treatment consists of azithromycin 1 g orally in a single dose or doxycycline 100 mg PO bid for 7 days (7). In women, other causes of vaginal discharge must be ruled out, including chlamydia, trichomoniasis, bacterial vaginosis, and candidiasis.

CRITICAL INTERVENTIONS

- Obtain syphilis serology on patients with ulcerative lesions.
- Refer all patients with STDs for HIV testing.
- Emphasize the importance of examination and treatment of sexual partners.
- Treat patients with nonulcerative STDs for both chlamydia and gonorrhea.

Common Pitfalls

- A significant number of patients with one STD are also infected with another.
- Treat patients with the expectation that they may not get follow-up. Observed single-dose therapy is the best guarantee of compliance with treatment.
- Syphilis, gonorrhea, chlamydia, and AIDS are reportable diseases in every state. HIV infection and chancroid are reportable in many states. Clinicians should be familiar with local reporting requirements and, if they are unsure, should seek advice from local health departments.

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CHAPTER 185
Lyme Disease

Veronica Vasquez and Sean O. Henderson

Lyme disease (LD) is the most common vector-borne illness in North America. Also known as Lyme borreliosis, it is caused by the spirochete *Borrelia burgdorferi* and is primarily transmitted to humans by *Ixodes* ticks. Transmission of *B. burgdorferi* occurs through injection of tick saliva during feeding. In the United States, LD is endemic in the northeastern and mid-Atlantic regions, as well as in the north-central states (1) (Fig. 185.1). Most human infections with *B. burgdorferi* occur during the months of May through August, when both human outdoor activity and *Ixodes* nymphal activity are at their peaks. Humans primarily acquire *B. burgdorferi* from infected nymphs which, because of their small size, generally go unnoticed. Ticks must usually be attached for at least 36 hours for the transmission of the spirochete to occur, during which time engorgement of the tick is discernible (Fig. 185.2). Early diagnosis and prompt treatment are imperative in preventing morbidity related to the later stages of LD (2).

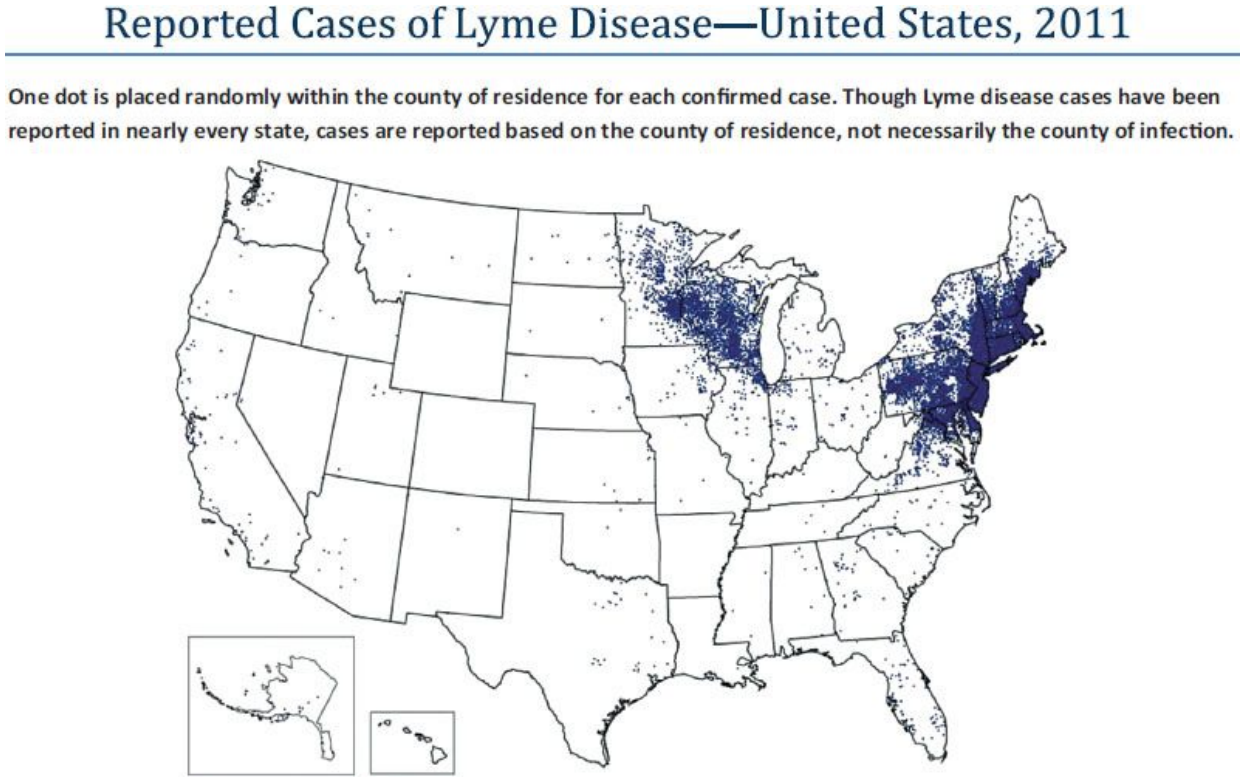

FIGURE 185.1 Reports of cases of Lyme disease to the Centers for Disease Control and Prevention (CDC), United States, 2011 (National Center for Emerging and Zoonotic Infectious Diseases, Division of Vector Borne Diseases, Bacterial Diseases Branch, Centers for Disease Control and Prevention, United States.) One dot is placed randomly within county of residence for each confirmed case. Although Lyme disease cases have been reported in nearly every state, cases are reported from the infected person's county of residence, not the place where they were infected. (Courtesy of Centers for Disease Control and Prevention.)

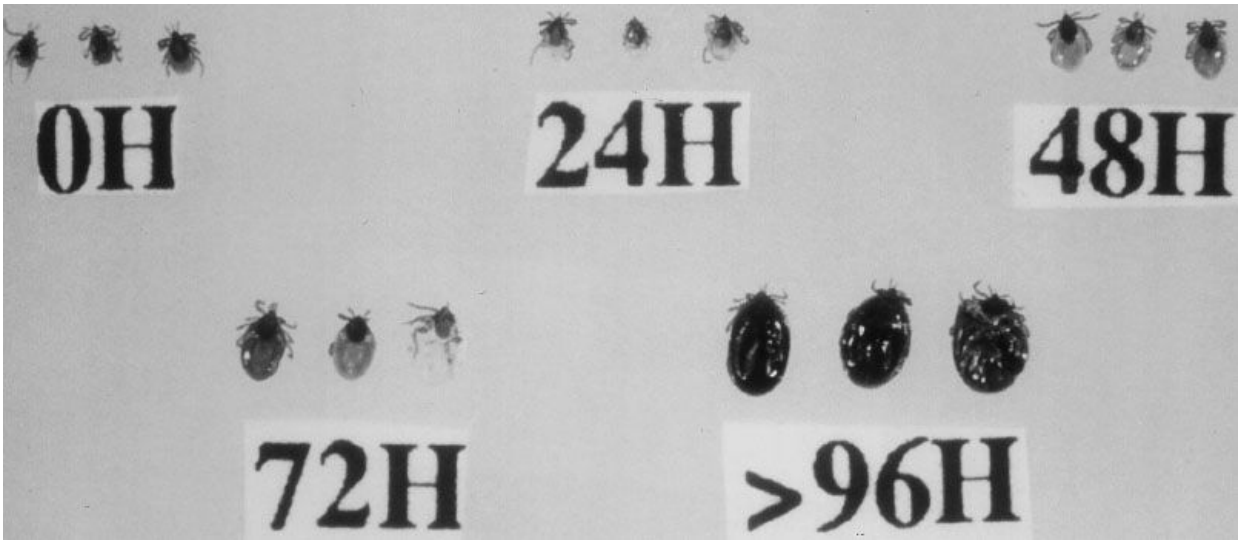

FIGURE 185.2 Nymphal *Ixodes scapularis* ticks demonstrating changes in blood engorgement after various durations of attachment to an animal host. (Photograph is a generous gift from Dr. Richard Falco.)

CLINICAL PRESENTATION

LD is comprised of a broad spectrum of clinical manifestations. The multisystem disorder presents in three clinical stages: (i) early localized infection, (ii) early disseminated infection, and (iii) late disseminated infection (Table 185.1). These stages may overlap, and certain clinical features may appear in isolation or recur at any time. To further complicate the clinical picture, later stages of the disease may present without any preceding signs or symptoms.

TABLE 185.1
Clinical Stages of Lyme Disease

Stage	Time	Manifestations
Early localized infection	7–14 d (range, 3–30 d)	Erythema migrans (EM) with or without nonspecific constitutional symptoms (fever, malaise, fatigue, headache, myalgia, and arthralgia)
		Asymptomatic
Early disseminated infection	Days to weeks	Multiple or secondary EM lesions
		Nervous system
		Musculoskeletal system
		Heart
Late disseminated disease	Weeks to months	Arthritis
		Chronic neurologic manifestations

As with other spirochetal diseases, the portal of entry for LD is the skin or mucous membrane. Similarly, this is followed by widespread dissemination, a subsequent period of latency, and eventual multisystem involvement. LD typically begins with the hallmark cutaneous lesion, *erythema migrans* (EM). This rash is often accompanied by nonspecific constitutional symptoms. In the days to weeks following inoculation, and as the spirochete spreads throughout the body, neurologic and cardiac manifestations may begin to appear. Within months, arthralgias and other neurologic symptoms may also begin to occur (3).

Early Localized Infection

LD symptoms typically begin about 1 to 2 weeks after a tick bite, but can range anywhere from 3 to 32 days (4). EM is the most common clinical characteristic of early LD and is thought to occur in almost 90% of cases (5). The rash often radiates from the actual site of the tick bite but may also begin at a distant location. EM lesions classically appear as a red expanding rash, and vary in appearance (Fig. 185.3). Lesions are usually annular and often have a characteristically target-like appearance, with centrifugal clearing. The average diameter of an EM lesion is 5 to 6 in, but may range anywhere from 2 in to 2 ft (6). Most rashes expand gradually over time but rapid expansion is known to occur. The rash itself may or may not be warm to touch and is generally not painful or pruritic.

Lesions are usually smooth and rarely have some element of central induration, crusting, or necrosis (7). Common locations for tick attachment, and subsequent rash, include the axilla, groin, popliteal fossa, and base of the neck. With antibiotic therapy, the EM rash resolves within several days. Without treatment, primary and secondary lesions may persist for almost 4 weeks and with the likelihood of recurrent lesions.

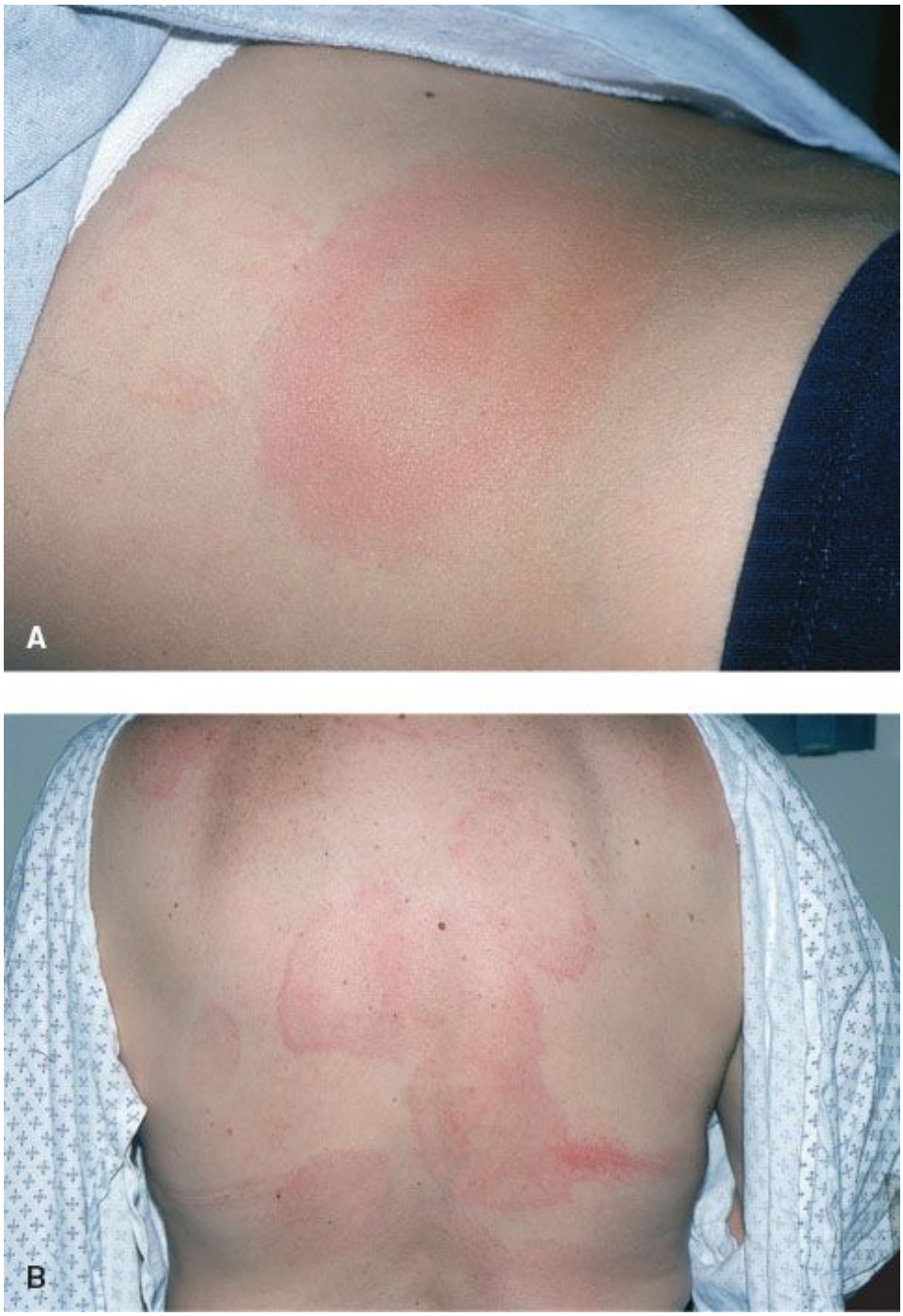

FIGURE 185.3 Erythema migrans rash of Lyme disease. **A:** Erythema migrans lesion on the torso. Note the target-like concentric rings with no scale. **B:** Erythema migrans lesions on the back. The rash may expand rapidly and cover a large area. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders,* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

Early constitutional symptoms in LD vary widely and often resemble a viral syndrome (8). Generalized fatigue and malaise affect the majority of patients. Other common symptoms include headache, low-grade fever, and anorexia. Headache may be accompanied by photophobia, nausea, and stiff neck, but neurologic and cerebral spinal fluid findings at this time are normal. Regional lymphadenopathy near the site of the tick bite often occurs. Musculoskeletal symptoms include arthralgias and myalgias and are frequently migratory and asymmetric. Upper respiratory and gastrointestinal signs and symptoms are uncommon in LD and their presence should suggest an alternate diagnosis (9). Given the nonspecific nature of these signs and symptoms, early LD can be easily misdiagnosed in the absence of the characteristic rash or history of a tick bite.

Early Disseminated Infection

Early disseminated disease occurs after a variable latent period, typically weeks to months after infection. It primarily involves the skin, nervous system, heart, and eyes. Patients may not have had any symptoms of early localized LD prior to the onset of disseminated signs and symptoms. The secondary cutaneous lesions of EM are characterized by multiple, smaller annular lesions (8). These typically spare the palms, soles, and mucosa. Neurologic and/or cardiac manifestations may occur without the presence of cutaneous involvement.

If LD is left untreated, nervous system involvement may affect up to 15% of patients. Neurologic manifestations include lymphocytic meningitis, cranial nerve palsies, peripheral neuropathies, and radiculoneuropathies (10). Lyme meningitis is usually associated with headache, nausea, lethargy, and irritability. Computed tomography will be normal in these patients, and upon cerebrospinal fluid (CSF) analysis, a distinguishing feature of Lyme meningitis is a predominant lymphocytic pleocytosis. Cranial nerve palsies may be unilateral or bilateral, with LD being one of the few causes of bilateral cranial nerve palsies. The facial nerve is the most commonly

affected cranial nerve. Peripheral neuropathies may include motor or sensory radiculopathies as well as mononeuritis.

Lyme carditis occurs in 4% to 10% of untreated LD patients and is usually transient (11). The average time of onset is approximately 5 weeks after the initial infection. Lyme bacterium can infect all aspects of the heart, including the conduction system, inner and outer membranes, muscle, and rarely, the valves. Symptoms of Lyme carditis are nonspecific and include light-headedness, syncope, shortness of breath, palpitations, and chest pain. Cardiac contractility may be transiently decreased due myopericarditis. The most common clinical feature is atrioventricular conduction block cause by impaired electrical signaling, occurring in almost 90% of patients (12). Heart block is often high grade or complete and usually resolves within 6 weeks. Heart block is rarely complete and permanent, requiring insertion of a pacemaker.

Ocular manifestations of LD include conjunctivitis, keratitis, choroiditis, retinal detachment, optic neuritis, and blindness. Papilledema is associated with Lyme encephalitis.

Late Disseminated Infection

Late LD usually occurs months to years after the initial infection. The chronic phase is typically associated with arthritis and less commonly, neurologic symptoms. The arthritic manifestations may be intermittent or persistent, and characteristically involve large joints, especially the knee. Joint effusions may be present but are relatively asymptomatic. Other joints less commonly affected include the shoulder, elbow, hip, and ankle. Prior to antibiotic therapy, almost half of all untreated patients developed attacks of joint swelling and pain. These episodes are usually brief, lasting weeks to months, with variable periods of exacerbations and remissions in between (8). In general, episodes become less frequent and less severe over time. Up to 10% of untreated patients develop chronic synovitis.

Neurologic manifestations of chronic disease vary widely and are often difficult to differentiate from other diseases, especially in the absence of any antecedent symptoms. Severe fatigue is commonly

reported in late disease. LD encephalopathy may manifest as subtle disturbances in cognition, mood, memory, or sleep. Central and peripheral nerve involvement is also a typical feature of late LD. As with early disease, it can involve the cranial nerves, spinal roots, and peripheral plexuses. Patients may experience radicular pain or numbness, including tingling in the hands and feet.

Acrodermatitis chronica atrophicans is a late cutaneous finding seen primarily in Europe. It typically occurs on the extensor surfaces of the body and is more common in older women. Lesions are initially characterized by a slight bluish-red discoloration with edematous infiltration. Over time, the rash may enlarge and eventually atrophies, resembling localized scleroderma (13).

DIFFERENTIAL DIAGNOSIS

Given the wide variety of clinical manifestations of LD, there is an extensive list of differential diagnoses. It is useful to consider common presentations of LD by stage and by system, and by the clinical features that help distinguish them.

In early LD, the range of constitutional symptoms may appear as “flu-like” symptoms. Diarrhea is not a feature of LD and if present, should help distinguish between LD and an enteroviral illness. Fatigue, sore throat, and adenopathy may suggest mononucleosis. Abdominal pain, nausea, and anorexia may be confused with appendicitis or hepatitis. The presence of arthralgias and myalgias may appear consistent with a connective tissue disease or other immune-mediated arthropathy. However, the musculoskeletal pain of LD is typically migratory, monoarticular, and occurs in brief attacks. Chronic fatigue syndrome and fibromyalgia are frequently misdiagnosed as LD (14).

The characteristic skin lesion of LD may be mistaken for the target lesions of erythema multiforme. However, EM does not involve the mucus membranes or palms and soles, as does erythema multiforme. In addition, the lesions of erythema multiforme are usually smaller and do not expand. EM may also be mistaken for erythema nodosum. The lesions of erythema nodosum are typically indurated and painful, whereas EM is not. EM may also appear similar to erythema

marginatum of rheumatic fever, but EM lesions are generally smaller, fewer, and slower in their migration. Other mimickers include hypersensitivity reactions and insect bites, but these typically appear hours, not days, after exposure. Given the gradually expanding area of erythema, EM may also be mistaken for bacterial cellulitis. However, the significant pain and possible toxicity associated with cellulitis is usually sufficient to make the distinction.

The cardiac sequelae of LD may suggest viral myocarditis, acute rheumatic fever (ARF), or acute coronary syndrome. In distinguishing Lyme carditis from ARF, EM usually precedes the cardiac manifestations in LD. In contrast, the cutaneous lesions of ARF typically coincide with the onset of arthralagias. Also, in ARF, there is usually evidence of a preceding streptococcal infection (in the form of an elevated antistreptolysin-O titer.) Valvular involvement is generally not a feature of Lyme carditis as it is in ARF.

The neurologic manifestations of LD give rise to a vast differential including viral or aseptic meningitis, encephalitis, multiple sclerosis, Bell palsy, dementia, and primary psychosis. In Lyme encephalopathy, CSF analysis usually reveals lymphocytosis, elevated protein and the presence of antibodies to *B. burgdorferi*.

The arthropathy of LD may be confused with that of autoimmune musculoskeletal disease, including rheumatoid, psoriatic, and reactive arthritis. Plain radiographs in these conditions may reveal an erosive process that is rare in LD (15). Numerous and symmetric joint involvement would also favor the diagnosis of rheumatoid or psoriatic arthritis over LD. Patients with Lyme arthritis do not have the typical morning stiffness or subcutaneous nodules seen in rheumatoid arthritis and often lack a positive rheumatoid factor.

ED EVALUATION

Prior to the recent advancement of reliable laboratory testing, the diagnosis of LD was essentially clinical (16). The presence of EM, in the context of recent exposure in an endemic area, is still virtually pathognomonic for LD. However, other nonspecific features occurring throughout the early and late stages of LD may make the

diagnosis difficult. Further diagnostic testing may be warranted under such circumstances to assist with the diagnosis of LD.

The initial evaluation of patients with suspected LD should include a detailed travel and exposure history, as well as a thorough skin examination. When the characteristic EM lesion is present in patients who reside or recently traveled to an endemic area, the diagnosis of LD can be made on clinical basis alone. Further testing is neither required nor recommended (17). In patients presenting with signs and/or symptoms of early disseminated or late LD, further serologic testing may be useful. Routine laboratory studies are not clinically useful at any stage of the disease.

Serologic testing should be considered an adjunct to the clinical diagnosis of LD, as it does not exclusively establish nor exclude the diagnosis. The Infectious Diseases Society of America (IDSA) has instituted guidelines for the indications for serologic testing (7). According to the IDSA, serologic testing should be performed in patients who meet **all** of the following criteria:

1. A recent history of having resided in or traveled to a LD endemic area **and**
2. A risk factor for tick exposure **and**
3. Symptoms consistent with early disseminated or late LD

Serologic testing should not be performed in patients with EM, for screening of asymptomatic patients living in endemic areas, or for patients with nonspecific symptoms alone.

Two-tier serologic testing is recommended to support the diagnosis of LD. The most commonly used initial test is enzyme-linked immunosorbent assay (ELISA). ELISA tests can detect both early (IgM) and late (IgG) immunoglobin antibodies. IgM antibodies typically appear 3 to 6 weeks after infection and as such, assays may be negative during the first several weeks. Furthermore, IgM returns to nondiagnostic levels 4 to 6 weeks after their peak. IgG antibodies may be detectable 2 months after initial exposure and typically peak at 12 months. If the ELISA test is positive or equivocal for IgM or IgG, then a Western blot should be performed. If the ELISA is negative, no further testing is recommended (18). False-positive ELISA testing for LD occurs in at least 5% of the general population

and is commonly attributed to other spirochetal diseases (most notably, *Treponema pallidum*), bacterial infections, viral illnesses, and autoimmune disorders. Seropositivity by two-tier testing simply indicates the presence of antibodies to the bacteria causing LD. It alone does not confirm the diagnosis of active LD. In addition, antibodies may be present for years after LD treatment and cure.

Other tests including immunofluorescent staining, lymphocyte transformation tests, and polymerase chain reaction (PCR) should be used with caution, as their accuracy has yet to be established (17). In cases of suspected neurologic involvement, routine CSF analysis should be performed for the evaluation of meningitis. CSF PCR used to detect the presence of *B. burgdorferi* DNA is limited by low sensitivity. Therefore, a negative PCR does not exclude LD. PCR of the urine is of no proven value and should not be used.

KEY TESTING

- No testing is necessary in patients with the characteristic skin lesion and a history of tick bite or those with a rash consistent with EM who live in endemic areas.
- Order serologic testing (ELISA) in selected patients to confirm exposure. Note, however, that false-positive ELISA testing occurs in approximately 5% of the population.
- Do not perform serologic testing for screening in asymptomatic patients or for patients with nonspecific symptoms only.

ED MANAGEMENT

The emergent management of patients with suspected LD should focus on recognizing the many forms of the illness, obtaining appropriate diagnostic studies, and initiating therapy as necessary. Most, if not all, other management may be performed in the appropriate outpatient setting.

Active *B. burgdorferi* infection is usually amenable to antibiotic therapy, and treatment can be started in the emergency department (ED). The decision as to whom to treat can be difficult. This assessment should be based on a combination of clinical presentation

and when appropriate, serologic testing. Fortunately, most decisions regarding antibiotic therapy are essentially nonurgent and can be made in consultation with the patient's primary physician. Treatment is undoubtedly indicated for the patient with the characteristic skin lesion and history of a tick bite in an endemic area. Prompt treatment of early disease shortens the duration of symptoms and usually prevents progression to later stages.

Treatment regimens for LD vary by disease stage and clinical manifestation. Table 185.2 is a summary of recommended antibiotic regimens. Oral therapy with doxycycline or amoxicillin is recommended for treatment of early localized or early disseminated LD. Amoxicillin is preferred for pregnant or lactating women and for children younger than 8 years old (7). Macrolide antibiotics should be reserved for patients who are unable to take doxycycline, amoxicillin, or cefuroxime, and should otherwise not be used as first-line treatment. The overall duration of antibiotic therapy should be tailored to the severity of illness and clinical response time. It should be noted that Jarisch–Herxheimer-like reactions (fever, chills, myalgias, headache, tachycardia, and tachypnea) may occur in the first 24 hours of treatment.

TABLE 185.2
Recommended Antibiotic Regimens

	Drug	Adult Dosage	Pediatric Dosage[a]
Early Lyme Disease			
Alternative	Doxycycline[b]	100 mg PO bid for 14–21 d	Age <8 yrs: Not recommended Age ≥8 yrs: 1–2 mg/kg bid (maximum 100 mg/dose)
	or		
	Amoxicillin	500 mg PO tid for 14–21 d	50 mg/kg/d divided tid (maximum 500 mg/dose)
	Cefuroxime axetil	500 mg PO bid for 14–21 d	30 mg/kg/d divided two doses (maximum 500 mg/dose)
	or		
	Macrolides *(less effective than doxycycline or amoxicillin and not recommended as first-line therapy)*		
	Azithromycin	500 mg PO daily for 7–10 d	10 mg/kg/d (maximum 500 mg/d)
	Erythromycin	500 mg PO qid for 14–21 d	7.5 mg/kg bid (maximum 500 mg/dose
	Clarithromycin	500 mg PO bid for 14–21 d	12.5 mg/kg qid (maximum 500 mg/dose)
Neurologic Disease			
Facial nerve paralysis	As an isolated finding, oral regimens for early disease, used for at least 30 d, may suffice. As a finding associated with other neurologic manifestations, intravenous therapy is recommended.		
Lyme Meningitis[c]	Ceftriaxone	2 g IV daily for 14–28 d	75–100 mg/kg/d IV
Alternative	Doxycycline	200–400 mg/d in two divided doses orally for 10–28 d	
	Penicillin G	18–24 million units IV/d, divided into doses given q4h	200,000–400,000 units/kg/d, divided into doses given q4h
	Cefotaxime	2 g IV tid	150–200 mg/kg/d IV, divided into 3 or 4 doses
Cardiac Disease			
Mild[d]	Doxycycline[b]	100 mg PO bid × 21 d	
	or		
	Amoxicillin	250–500 mg PO tid × 21 d	50 mg/kg/d divided tid
More severe	Ceftriaxone	2 g IV daily by single dose for 14–21 d	75–100 mg/kg/d IV
	or		
	Penicillin G	18–24 million units daily in divided doses for 14–21 d	200,000–400,000 units/kg/d, divided into doses given q4h
Arthritis			
Oral	Doxycycline[b]	100 mg PO bid for 28 d	
	or		
	Amoxicillin	500 mg PO tid for 28 d	50 mg/kg/d divided tid
Parenteral	Ceftriaxone	2 g IV by single dose for 14–28 d	75–100 mg/kg/d IV
	or		
	Penicillin G	20 million units IV daily in divided doses for 14–28 d	300,000 units/kg/d IV

[a]Pediatric dosage should not exceed adult dosage.
[b]Tetracycline, 250–500 mg PO qid, may be substituted for doxycycline. Neither doxycycline nor any other tetracycline should be used for children younger than 8 years old or for pregnant or lactating women.
[c]Regimens for radiculoneuropathy, peripheral neuropathy, and encephalitis are the same as those for meningitis.
[d]Oral regimens are reserved for mild cardiac involvement (see text).
Adapted from Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2006;43(9):1089–1134.

Neurologic Disease

The management of patients with facial nerve palsies attributed to *B. burgdorferi* remains somewhat controversial. Lumbar puncture is not required in all patients, but is recommended in patients with a high clinical suspicion of CNS involvement. Patients with normal CSF may be treated with the same oral regimens used for patients with EM. In patients with evidence of CNS involvement, or other more serious complications (i.e., meningitis, encephalitis, cognitive deficits, or

other cranial neuropathies) treatment with parenteral antibiotic therapy is indicated (Table 185.2).

Cardiac Disease

Antibiotic treatment recommendations for patients with cardiac involvement vary by severity of heart block present (see Table 185.2). Patients with first-degree atrioventricular block or a PR interval <0.30 seconds may be treated orally, whereas those with high-degree atrioventricular block often require parenteral antibiotics. Temporary cardiac pacing may be necessary in severe cases. In most cases, heart block resolves completely with antibiotic therapy.

Arthritis

The diagnosis of Lyme arthritis should be confirmed by serologic testing of synovial fluid whenever possible. Treatment with a month long course of oral doxycycline or amoxicillin is usually effective, but response may be delayed for several weeks to months (see Table 185.2). Anti-inflammatory agents may be helpful in alleviating discomfort caused by an immune-mediated response.

Prophylaxis

Several recent studies have investigated the efficacy of prophylactic antibiotic therapy following a tick bite to prevent LD (19,20). There exists concern that treating only individuals who exhibit signs of illness will render some untreated for subclinical disease. Conversely, treatment may be unwarranted, ineffective and unnecessarily expose patients to medication side effects. A single dose of doxycycline has been shown to be effective in a subset of patients. The IDSA has established specific guidelines for the recommendation of antibiotic prophylaxis for the prevention of LD (Table 185.3) (7). According to these guidelines, patients must meet all of the following criteria: (a) The attached tick is identified as an adult or nymphal *Ixodes scapularis* tick (b) the tick is estimated to have been attached for ≤ 36 hours (by degree of engorgement or time of exposure) (c)

prophylaxis is begun within 72 hours of tick removal (d) the local rate of infection of ticks with *B. burgdorferi* is ≤20% and (e) doxycycline is not contraindicated (i.e., the patient is not <8 years of age, pregnant, or lactating). In patients meeting all of these criteria, the recommended dose of oral doxycycline is 200 mg for adults and 4 mg/kg, up to a maximum of 200 mg, in children ≤8 years of age. (Of note, this regimen has never been tested in children.) As the majority of patients infected with *B. burgdorferi* develop EM, and the typically excellent outcomes with early therapy, an alternative for these patients may be observation of the tick bite site and subsequent treatment if an EM rash develops.

TABLE 185.3
Guidelines for Prophylactic Treatment of Tick Bites

Attached tick is identified as an adult or nymphal *I. scapularis* tick and is estimated to have been attached for ≥36 hrs by degree of engorgement or time of exposure
Prophylaxis is initiated within 72 hrs of tick removal
Local rate of infection of ticks with *B. burgdorferi* is ≥20%
Doxycycline is not contraindicated in the patient being treated

Adapted from Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: Clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2006;43(9):1089–1134.

CRITICAL INTERVENTIONS

- Initiate treatment for patients with a characteristic skin lesion and a history of tick bite or those with an EM rash who live in endemic areas.
- Order the ELISA test to confirm exposure but do not wait for positive assay before beginning therapy.
- Base treatment recommendations on the disease stage and clinical manifestations.

DISPOSITION

The decision regarding disposition of a patient with suspected LD is based on the stage of the disease and the severity of clinical symptoms. Nearly all patients with early LD can be discharged from the ED and appropriately managed as outpatients. Follow-up care should be arranged with a primary care physician, rheumatologist, or infectious disease specialist. Patients with more serious manifestations, including Lyme carditis with high-degree atrioventricular block or with significant neurologic involvement, often require hospital admission for monitoring, supportive care, and intravenous antibiotic therapy.

Common Pitfalls

- Symptoms of late LD may occur without any preceding early symptoms. The initial tick bite may have gone unnoticed or the transient appearance of a rash forgotten, and as such, LD may not be considered in the differential diagnosis.
- Many disorders share nonspecific symptoms often seen with Lyme borreliosis and are commonly misdiagnosed as LD. This frequently results in inappropriate treatment with antibiotics.
- If an attached tick is removed quickly, no other treatment is usually necessary. However, if the tick is engorged, LD prophylaxis may be considered.
- Serologic testing should only be performed in a selected subset of patients. Indiscriminate testing of patients results in a high rate of false-positive tests.

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CHAPTER 186

Rocky Mountain Spotted Fever

Paul I. Musey Jr and Michael A. Gibbs

Rocky Mountain spotted fever (RMSF) is the most common tick-borne illness in the United States and one of the most serious systemic infections seen in clinical practice. Emergency physicians must maintain a high index of suspicion for RMSF and consider early empiric therapy in the patient at risk. In 2010 epidemiologists changed the name of RMSF to Spotted Fever Rickettsiosis to reflect crossreactivity between spotted fever rickettsial pathogens. We will, however, continue to refer to RMSF for the purpose of this chapter.

Education, awareness, and a high index of suspicion have helped to decrease the case fatality rate of RMSF, which had been hovering between 5% and 10%, down to around 0.5% (1). However, the disease continues to confound physicians because of its sporadic occurrence and nonspecific clinical presentation. Difficulties in making the diagnosis are especially relevant because the prognosis is directly related to the timeliness of appropriate treatment. The greatest challenge to physicians is diagnosing RMSF early in its clinical course, when antibiotic therapy is most effective.

In one study, 90% of patients were seen by a physician within 5 days of the onset of symptoms, yet less than half received treatment before day 6. Patients who received antirickettsial therapy within 5 days were significantly less likely to die than were those who received treatment later (6.5% vs. 22.9%). Three independent predictors of a failure to initiate therapy on first presentation to a

physician were absence of a rash, presentation between August 1 and April 30, and presentation within the first 3 days of illness.

In 2004, the Centers for Disease Control (CDC)'s Viral and Rickettsial Zoonoses Branch developed guidelines for the diagnosis and management of RMSF and the other major tick-borne illnesses. This report emphasized that health professionals must (a) recognize epidemiologic features and clinical manifestations of the disease, (b) develop a differential diagnosis that includes tick-borne illness, (c) understand that doxycycline is the treatment of choice for both adults and children, (d) understand that early empiric antibiotic therapy can prevent serious morbidity and mortality, and (e) report suspected and confirmed cases of RMSF to local public health authorities (2). Emergency physicians on the front line will be expected to play a significant role in achieving these outcomes.

Epidemiology

RMSF is caused by *Rickettsia rickettsii,* an obligate intracellular bacterium. It is transmitted by several species of ticks that also serve as the reservoir or natural host. In the eastern states, the American dog tick, *Dermacentor variabilis,* is the major vector; the Rocky Mountain wood tick, *Dermacentor andersoni,* is the predominant vector in western states. More than 95% of cases occur between April 1 and September 1, corresponding to the seasonal life cycle of the tick.

RMSF is prevalent throughout the continental United States, with cases reported from each of the contiguous 48 states except Vermont and Maine. Although first described in Idaho and Montana, RMSF is now infrequent in the western states. There has been a coincident steady increase in the number of cases in the southeastern United States. Between 2003 and 2010, more than half (>60% in 2010) of the reported cases of RMSF came from only five states: North Carolina, South Carolina, Tennessee, Oklahoma, and Arkansas (1,3).

Although previous studies have indicated that the highest incidence of RMSF is in children less than 10 years of age, CDC surveillance data between 2003 and 2010 demonstrate the highest

age-specific incidence among persons aged 40 to 64 years (1–3). The case fatality rate is highest in those aged 40 or older (8.2%, compared to 2.3% for those younger than 40). The case fatality rate is also higher for individuals whose treatment is begun more than 3 days after the onset of symptoms (6.2%, compared with 1.3% for those treated within the first 3 days). RMSF is more common in men than in women, reflecting a greater potential exposure to the tick vector. Despite the fact that RMSF is more common in whites than in African Americans, the case fatality rate is significantly higher in the latter group (16% vs. 3%), a fact most likely related to the difficulty of detecting the characteristic rash on dark skin.

CLINICAL PRESENTATION

RMSF is a systemic vasculitis that may affect any organ system. For this reason, signs and symptoms are varied and often nonspecific. The majority of patients first seek medical attention during the first 2 to 4 days of illness, after an incubation period of approximately 5 to 10 days. A history of a tick bite or the presence of a tick is elicited in just more than half of patients. The onset of illness is usually acute, with fever, chills, headache, and myalgias. Headache tends to be the predominant complaint in adults and can be severe. Nausea, vomiting, abdominal pain, and anorexia are also common early in the course of illness. The clinical findings and their prevalence are summarized in Table 186.1.

TABLE 186.1
Clinical Manifestations of Rocky Mountain Spotted Fever

Signs or Symptoms	Any Time (%)	First 3 Days (%)
Fever (100–102°F)	99	73
Fever (>102°F)	90	63
Fever + rash + tick bite	67	3
Dermatologic		
Any rash	88	49
Rash, maculopapular	82	46
Rash, petechial, or hemorrhagic	49	13
Rash on palms and soles	74	28
Edema	18	3
Conjunctivitis	30	13
Neurologic		
Headache, mild/moderate	91	71
Headache, severe	57	40
Altered mental status	26	6
Meningeal irritation	18	5
Decreased hearing	7	1
Seizures	8	2
Cardiopulmonary		
Pneumonitis	12	2
Dysrhythmias	7	1
Myocarditis	5	0
Gastrointestinal		
Abdominal pain	52	30
Nausea/vomiting	60	38
Diarrhea	19	9
Jaundice	9	2
Musculoskeletal		
Myalgias, mild/moderate	83	57
Myalgias, severe	47	25

From Helmick CG, Bernard KW, D'Angelo LJ. Rocky Mountain spotted fever: Clinical, laboratory, and epidemiological features of 262 cases. *J Infect Dis*. 1984;150:480–488.

A *rash* of one type or another is seen in the majority of patients with RMSF, but "Rocky Mountain spotless fever" has been reported in 5% to 15% of cases (4). The rash may be absent at the onset of symptoms and may not be appreciated in patients with dark skin. The rash usually appears on the third day of illness and is first seen

on the palms, soles, wrists, and ankles and progresses centripetally, but the rash may begin on the trunk (approximately 10%) or have a diffuse onset (approximately 10%). Lesions are initially macular and later evolve to become petechial and maculopapular in 50% of cases. See Figures 186.1 and 186.2. Application of a tourniquet or blood pressure cuff may cause the appearance of additional lesions distally (Rumpel–Leede sign). In severe cases, there may be extensive purpura, skin sloughing, ulceration, and gangrene. Rarely, an eschar may be seen at the site of the tick bite (5).

FIGURE 186.1 RMSF: Petechial rash on forearm. (Courtesy of Steven Manders, MD.)

FIGURE 186.2 RMSF: Maculopapular rash on palms, wrists, and forearms. (Courtesy of Sidney Sussman, MD.)

The *central nervous system* is perhaps the most crucial target "organ" of RMSF. Varying degrees of meningeal inflammation and cerebral vasculitis cause a wide range of neurologic signs and symptoms. Rickettsial encephalitis (severe headache, confusion, stupor, coma, and seizures) carries a particularly grave prognosis (6). Focal neurologic deficits, deafness, sensory neuropathy, tardive dyskinesia, and Guillain–Barré syndrome have all been described in patients with RMSF (5,7).

Neuroimaging with computed tomography (CT) or magnetic resonance imaging (MRI) may reveal a variety of subtle nonspecific abnormalities including infarcts, cerebral edema, meningeal

enhancement, and increased signal of the perivascular spaces. There is some evidence that the presence of these radiographic findings may be associated with a less favorable outcome (8). In patients with central nervous system involvement, the cerebrospinal fluid is almost always abnormal.

The *cardiovascular* effects of RMSF are the result of myocarditis and myocardial vasculitis (9). Clinical manifestations include varying degrees of atrioventricular (AV) block, dysrhythmias (atrial and ventricular tachycardia, atrial fibrillation), and left ventricular dysfunction. It has been hypothesized that cardiac involvement may play an important role in the cases of fatal RMSF.

Rickettsial *pneumonitis* results from microvascular injury and leakage of fluid into the interstitial tissues and alveolar airspaces. This potentially life-threatening complication occurs in 2% to 17% of patients. Signs and symptoms include cough, dyspnea, pleuritic chest pain, and hypoxemia. Chest radiography typically reveals diffuse patchy infiltrates (10).

Up to 80% of patients with RMSF have prominent *gastrointestinal* complaints early in the course of disease, including abdominal pain, nausea, vomiting, and diarrhea. This symptom complex may lead the clinician to incorrectly diagnose acute gastroenteritis or even an acute surgical abdomen. Not surprisingly, patients with RMSF have undergone exploratory laparotomy for suspected appendicitis, cholecystitis, and perforated diverticulitis.

DIFFERENTIAL DIAGNOSIS

When patients present early, the accurate diagnosis of RMSF depends on clinical suspicion and an understanding of local epidemiology. It would not be difficult to imagine attributing fever, malaise, headache, and myalgias in a well-appearing patient to a nonspecific viral syndrome. As the disease progresses, the individual patient with RMSF may be misdiagnosed as having a number of specific viral illnesses (e.g., measles, infectious mononucleosis), meningococcemia, gastroenteritis, acute surgical abdomen, pneumonia, toxic shock syndrome, ehrlichiosis, or encephalitis.

RMSF may also mimic noninfectious entities including idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, drug reaction, and immune-complex vasculitis.

As with RMSF, diagnosis of meningococcemia must be made quickly and accurately. Both diseases may present with headache, fever, nausea, vomiting, and upper respiratory symptoms. However, meningococcemia is typically more abrupt in onset and its rash (petechial without characteristic pattern) appears within 24 hours of symptom onset. Gram stain of cerebrospinal fluid is diagnostic, and the causative organism can also be detected using latex agglutination and counterimmunoelectrophoresis. If either diagnosis is in question, immediate therapy for both RMSF and meningococcemia is mandatory.

Distinguishing RMSF from an enteroviral infection can also be quite difficult. Fever, headache, aseptic meningitis, and a maculopapular rash are common to both presentations. The rash of enteroviral infections usually starts centrally but may also involve the palms and soles. Petechial lesions are not uncommon.

ED EVALUATION

As with most conditions in medicine, the evaluation of a patient suspected of having RMSF begins with a careful history and physical examination. Close attention should be paid to high-risk historical features (recent outdoor activities, i.e., camping, presentation between April and September, presentation in an endemic area, etc.). A viral syndrome with an associated rash should trigger RMSF to be on the differential and prompt further investigation.

Laboratory studies typically available in the emergency department (ED) offer little help in the diagnosis of RMSF. Although routine studies may provide subtle clues, these are inconsistent and nonspecific. *It must be emphasized that treatment must be based on clinical findings alone and should never be withheld while waiting for specific serologic confirmation of the disease.*

Hematologic findings seen in RMSF include a normal or decreased white blood cell count, anemia, thrombocytopenia, and a high

peripheral band count. Anemia and thrombocytopenia are seen in 30% and in 30% to 50% of patients, respectively (11). Hyponatremia is seen in roughly one-fourth of cases. Elevation of serum transaminases and bilirubin may be noted in patients with hepatic involvement (10).

A lumbar puncture is mandatory in all patients with significant headache and fever or signs of meningeal irritation. Elevated cerebrospinal fluid protein and pleocytosis are the typical findings in RMSF. Differential cell counts may reveal either lymphocytic or polymorphonuclear cell predominance. Of note, a cerebrospinal fluid white blood cell count >100 cells/μL is uncommon, occurring in only 11% of cases. Because the distinction between RMSF and meningococcemia can be difficult, a "positive tap" in a patient with high-risk signs and symptoms should prompt immediate therapy for both.

Serologic testing is of value in the retrospective confirmation of RMSF, but is not helpful in the acute setting. Immunofluorescence antibody (IFA) assay is considered the gold standard serologic assay for rickettsial diseases, but enzyme-linked immunosorbent assay (ELISA) is becoming more frequently used. Both tests rely on the presence of antibodies to *R. rickettsii* antigens in sera, and as such, sensitivity is dependent on the timing of collection of the sample. The IFA is estimated to be 94% to 100% sensitive after 14 days, and that sensitivity is increased if paired samples are tested (12). These serologic tests may not be routinely available in all hospital settings but can usually be obtained through state health department laboratories. Because the serologic diagnosis of RMSF can be complex, consultation with local and regional experts will help the emergency physician make the right choice when the diagnosis is in question.

Identification of *R. rickettsii* in skin biopsy specimens can be a helpful diagnostic test for RMSF in the acute setting. This technique can be used only when the rash is present. A punch biopsy should be obtained at the center of a well-defined lesion. Immunofluorescent staining of frozen section samples demonstrates the organism in about 70% of cases.

KEY TESTING

- There is no specific laboratory study to confirm RMSF in the ED. To avoid the increased morbidity and mortality associated with delays in therapy, treatment should be initiated on clinical grounds when the diagnosis is suspected.
- In patients with signs and symptoms of central nervous system involvement lumbar puncture should be performed to rule out alternative diagnoses (e.g., meningococcemia) as well as to aid in the diagnosis of RMSF.

ED MANAGEMENT

It is not only appropriate but essential for the clinician practicing in an endemic area to initiate antibiotic therapy in the patient with clinical findings suggestive of, but not necessarily diagnostic of, RMSF without the aid of serologic testing.

Doxycycline is considered the drug of choice for the treatment of RMSF in both adults and children. The recommended dose is 100 mg administered twice daily (orally or intravenously) for adults, or 2.2 mg/kg body weight per dose for children $<$45.4 kg (100 lb). Intravenous therapy is indicated for patients who are severely ill (not appropriate for outpatient management) or who are not able to tolerate oral medications (2).

The use of doxycycline to treat children with RMSF is no longer a subject of controversy. Historical concerns over dental staining were based on studies that involved children who had received prolonged courses of the drug. Limited use of doxycycline in young children does not result in significant discoloration of permanent teeth, and the clinician should never withhold appropriate therapy in this setting (13).

Chloramphenicol is the treatment of choice for RMSF during pregnancy. Tetracyclines are contraindicated in pregnancy because of the risk of malformation of teeth and bones in the fetus and hepatotoxicity and pancreatitis in the mother. The recommended dose is 50 to 100 mg/kg/d. Side effects associated with chloramphenicol include bone marrow depression, hemolytic

anemia in patients with the Mediterranean form of glucose 6-phosphate dehydrogenase deficiency, “gray baby” syndrome in premature infants and neonates, and (rarely) aplastic anemia. Because chloramphenicol is metabolized by the liver, drug interactions may occur in patients taking either inhibitors or inducers of hepatic enzymes (2).

Regardless of the agent selected, patients should be treated for at least 7 to 10 days, and therapy should be continued as necessary until the patient is afebrile and clinically improved for 24 to 48 hours (11).

Successful treatment of the critically ill patient with RMSF requires meticulous attention to fluid and electrolyte balance. Widespread systemic vasculitis and resultant fluid shifts may cause hypotension, oliguric renal failure, disseminated intravascular coagulation, adult respiratory distress syndrome, and shock. In the treatment of these complications, the clinician must maintain a delicate balance between adequate restoration of intravascular volume and overresuscitation with precipitation of pulmonary edema. Isotonic saline should be given in small serial boluses. Vasopressors may be required in patients with impaired tissue perfusion that is unresponsive to fluid therapy. Hemodynamic monitoring with a pulmonary artery catheter may provide the treating physician with an extra margin of safety and is recommended in the unstable patient.

Prevention

Emergency physicians play an important role in educating the public about disease prevention. People who reside or work in tick-infested areas should be informed about tick-borne diseases and their prevention. The optimal method for preventing RMSF is the avoidance of tick-infested areas. People entering these areas should wear protective clothing and use tick repellents. Exposed areas of the body should be examined for attached ticks. Ticks should be removed by grasping them with fine tweezers at the point of attachment and pulling slowly and steadily.

CRITICAL INTERVENTIONS

- Suspect RMSF in patients presenting with clinical manifestations and a history of possible tick exposure.
- Initiate antibiotic therapy in the patient with clinical findings suggestive of, but not necessarily diagnostic of, RMSF without the aid of serologic testing.

DISPOSITION

When an otherwise healthy, clinically stable patient presents with one or several clinical findings suggestive of RMSF, it is appropriate to initiate empiric therapy without confirmatory diagnostic testing and to discharge the patient with close follow-up. In endemic areas, patients presenting with a flu-like illness during the spring or summer months are frequently discharged home on doxycycline. In this situation, contact with a primary care provider or a return visit to the ED in 24 to 72 hours is a sensible part of the discharge plan.

Patients presenting with more severe disease should be admitted to the hospital. This group includes those with significantly abnormal vital signs, dehydration, or end-organ dysfunction (e.g., cerebritis, pneumonitis, myocarditis). Prompt administration of antibiotics and early consultation with an intensivist and an infectious disease specialist are also appropriate.

Common Pitfalls

- Failure to consider the diagnosis of RMSF in the patient with fever and a "viral syndrome" during the peak season (April 1 to September 1) in an endemic area
- Failure to recognize that roughly 15% patients with RMSF present without a rash ("Rocky Mountain spotless fever"). Among ultimately fatal cases, a rash is absent at the time of first presentation to a physician in more than 80%.
- Failure to appreciate the often prominent gastrointestinal features of RMSF, resulting in an incorrect diagnosis of gastroenteritis

- Failure to initiate appropriate antirickettsial therapy in a timely fashion
- Overreliance on laboratory testing, which offers little in the acute phase of RMSF, or withholding of indicated therapy while waiting for definitive serologic confirmation of the disease

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CHAPTER 187
Other Tick-Borne Diseases

Ann P. Nguyen

The most prevalent North American tick-borne diseases are: Lyme disease, Rocky Mountain spotted fever, anaplasmosis, ehrlichiosis, tularemia, babesiosis, tick-borne relapsing fever, Colorado tick fever (CTF), and tick paralysis. These diseases peak in incidence from April to September when the feeding activity of ticks coincides most with the outdoor activity of humans (1,2). Lyme disease, Rocky Mountain spotted fever, and tick paralysis are discussed in other chapters. The remaining diseases are discussed here (Table 187.1).

TABLE 187.1
Common North American Tick-Borne Diseases

Disease	Causative Agent	Tick Vector	Geographic Distribution	Clinical Features	Treatment
• Human monocytic ehrlichiosis (HME)	*Ehrlichia chaffeensis* *Ehrlichia ewingii* (Rickettsia)	*Amblyomma* *Dermacentor* *Ixodes*	Southeast South central	• Nonspecific febrile syndrome	Doxycycline or rifampin
• Human ewingii ehrlichiosis (HEE)				• Rash in 10–40% • Elderly and immunosuppressed patients at risk	
• Human granulocytic anaplasmosis (HGA)	*Anaplasma phagocytophilum* (Rickettsia)	*Ixodes*	Northeast Midwest California	• ARDS, thrombocytopenia, DIC, opportunistic infections	Doxycycline or rifampin
• Tularemia	*Francisella tularensis* (Bacteria)	*Amblyomma*	Southeast South central	• Nonspecific febrile syndrome	Streptomycin or gentamicin
		Dermacentor	All regions	• Ulceroglandular, glandular, typhoidal, pneumonic, oropharyngeal, and oculoglandular forms	
• Babesiosis	*Babesia microti* (Protozoan)	*Ixodes*	Northeast	• Fever, sweats, hemolysis • Splenectomized and other immunosuppressed patients at risk	Quinine + clindamycin or Atovaquone + azithromycin
• Tick-borne relapsing fever	*Borrelia* species: *B. hermsii* *B. parkeri* *B. turicatae* *B. dugesi*	*Ornithodoros*	Rocky Mountains Texas, Mexico	• Multiple remissions and relapses • Neonates and pregnant women at risk • Jarisch–Herxheimer reaction when treated	Doxycycline or Tetracycline or Erythromycin
• Colorado tick fever (CTF)	CTF virus (*Coltivirus*)	*Dermacentor*	Rocky Mountains	• Biphasic fever pattern • Prolonged convalescence	Supportive

Ehrlichiosis and Anaplasmosis

Caused by gram-negative intracellular coccobacilli, ehrlichiosis and anaplasmosis are clinically similar, identically managed diseases. Human monocytic ehrlichiosis (HME) is caused by *Ehrlichia chaffeensis* and human ewingii ehrlichiosis (HEE) is caused by *Ehrlichia ewingii.* Lone Star ticks (*Amblyomma americanum*) are the main vector, although *Dermacentor* and *Ixodes* species have also been implicated (3,4). Human granulocytic anaplasmosis (HGA) is caused by *Anaplasma phagocytophilum.* HGA is transmitted by deer ticks (*Ixodes scapularis*) in the Eastern United States and by western blacklegged ticks (*Ixodes pacificus)* in the Western United States (2,5). Transmission via blood transfusion, blood exposure, and transplacental routes have also been documented (3,6).

HME and HEE occur in the Southeastern and South Central United States whereas HGA is distributed in the Northeastern and Midwestern states and California (3,4,5). Since 2000, the Centers for Disease Control (CDC) consider HME and HGA to be reportable diseases. From 2000 to 2010, up to 961 HME and 1,163 HGA cases per year have been identified (7,8). HEE was declared nationally reportable in 2008. This disease has been found only in immunosuppressed patients and is much more rare with 28 reported cases between 2008 and 2010 (7).

CLINICAL PRESENTATION

HME, HEE, and HGA present after a 5- to 14-day incubation period with fevers, headache, myalgias, nausea, vomiting, and occasionally diarrhea. Respiratory symptoms are rare. Up to 20% of ehrlichiosis patients show evidence of central nervous system infection such as meningitis, encephalitis, seizures and coma, whereas in anaplasmosis, peripheral nerve palsies predominate (1,3,4,5). A nonpruritic, erythematous maculopapular or petechial rash appears on the trunks and extremities of most ehrlichiosis patients and 10% of anaplasmosis patients after 5 to 7 days of illness (1,3,4,5). While typically displaying milder disease than adults, children more often experience rash, abdominal pain, and altered mental status (1,6).

Most patients recover spontaneously within 2 weeks, although up to one-third of anaplasmosis patients and half of ehrlichiosis patients require hospitalization (2,3,5). Poor outcome is linked to age over 60, HIV infection, immunodeficient states, diabetes mellitus, malignancy, connective tissue disease, and delayed administration of appropriate antibiotics (1,6,9). Complications occur in 10% to 20% of patients and include septic shock, acute respiratory distress syndrome (ARDS), thrombocytopenia with life-threatening hemorrhage, disseminated intravascular coagulation (DIC), acute renal failure, myocarditis, rhabdomyolysis, meningoencephalitis, and seizures. Even after appropriate antibiotics, ehrlichiosis carries a 1% to 3% mortality rate and anaplasmosis, 0.5% (3,7,8).

ED EVALUATION AND MANAGEMENT

Aside from the previously described rash, physical examination is generally unrevealing. Some patients have hepatomegaly or splenomegaly. Altered sensorium or meningismus suggest ehrlichiosis while peripheral neuropathies suggest anaplasmosis. Laboratory testing may show leukopenia, thrombocytopenia, anemia, hyponatremia, and mild-to-moderate elevation of aspartate amino transferase (AST) and alanine aminotransferase (ALT).

Polymerase chain reaction (PCR) is the test of choice in the ED (1,3). Diagnosis can also be made by visualizing intracellular bacteria on peripheral blood smear, but these are seen less than 20% of the time in ehrlichiosis and less than 80% of the time in anaplasmosis (2,3). Serologic testing is not helpful in the ED due to its insensitivity during the first 2 weeks of illness (3). Blood cultures may be sent, but are typically unsuccessful in isolating *Ehrlichia* or *Anaplasma* (4).

Test all patients with suspected HME, HEE, or HGA for Lyme disease, as these diseases share the same tick vectors. Coinfection with Lyme disease, which occurs 10% to 30% of the time, is associated with greater disease severity (3,4,5).

If any of the complications listed here occur, initiate resuscitative therapy. Most patients will not be critically ill and will need supportive care only. Initiate empiric antibiotics to high-risk patients,

as confirmatory tests may take days to complete and therapy delay is associated with poor outcome (1,6,9). The drug of choice is doxycycline, 100 mg PO or IV q12h (children: 2.2 mg/kg q12h) for 7 to 10 days (1,2,3,5). An alternative is tetracycline, 500 mg PO q6h (children: 6.25 to 12.5 mg/kg q6h) for 7 to 10 days. Use rifampin, 300 mg PO q12h (children: 10 mg/kg q12h) for 7 to 10 days, in patients allergic to tetracycline antibiotics (5). Pediatric age or pregnancy are no longer considered contraindications to doxycycline (1,3,4,5). If coinfection with Lyme disease is suspected, extend the antibiotic course for a full 14 to 21 days (2,5). Failure to improve after 24 to 48 hours of doxycycline or rifampin indicates a diagnosis other than HME, HEE, or HGA.

DISPOSITION

Admit all patients with complications and those belonging to high-risk groups for 24 to 48 hours of observation. Discharge nontoxic patients on oral antibiotics, with arrangements for re-evaluation in 48 hours and for follow-up of serologic testing.

Tularemia

Tularemia is caused by a gram-negative coccobacillus, *Francisella tularensis*. Half of all tularemic disease is transmitted by tick vectors: the Lone Star tick (*A. americanum*) in the southeastern and south central states, the Rocky Mountain wood tick (*Dermacentor andersoni*) in the western states, and the dog tick (*Dermacentor variabilis*) throughout North America (1). Arkansas, Massachusetts, Missouri, Oklahoma, and South Dakota accounted for 50% of tick-borne tularemia from 2001 to 2010 (10). The remainder of cases are transmitted by insect vectors, handling infected animals (primarily rabbits and rodents), ingesting contaminated meat or water, inhaling aerosolized bacteria, or autoinoculating mucous membranes (1).

From 2001 to 2010, an average of 120 cases per year were recorded in the United States (10). Tularemia occurrences are nationally reportable. The highest incidence and disease severity occurs in children 5 to 9 years old and in elderly persons greater than 75 years old (2,11,12).

CLINICAL PRESENTATION

Two main syndromes are currently recognized: ulceroglandular tularemia and typhoidal (systemic) tularemia (2,11,12). All syndromes begin with an incubation period ranging from 2 to 21 days (3 to 6 days on average) and may last 1 to 4 weeks. Patients display abrupt onset of fever, chills, headache, and myalgias. Cough, vomiting, diarrhea, and diffuse arthralgias often occur. Erythema multiforme, erythema nodosum, or other nonspecific, pruritic maculopapular or papulovesicular rash appears on the extremities of 25% of patients 2 weeks after symptom onset (1,2,11).

Ulceroglandular tularemia is the most common tularemic syndrome, comprising 80% of cases and carrying a 2% mortality rate (2,11,12). It is characterized by a solitary skin ulcer at the tick bite site, developing 2 weeks after constitutional symptoms begin. The ulcer is 0.5 to 3 cm in diameter with sharply undermined borders and a flat black or red base. It can evolve into an abscess or necrotic eschar. Fifteen percent of the time, an ulcer does not appear at all; this variant presentation is referred to as glandular tularemia and is twice as likely to occur in children as in adults (1,2). Regional lymphadenopathy always occurs, with possible suppuration or necrosis of the lymph nodes (2,11).

Typhoidal or systemic tularemia constitutes 20% of cases but accounts for 50% of fatalities (11). Patients display the nonspecific febrile syndrome described above, but appear toxic and may progress to overwhelming sepsis. Eighty percent of patients with typhoidal tularemia will develop tularemic pneumonia, which presents with a dry cough, pleuritic chest pain, and dyspnea. Thirty percent of patients with ulceroglandular tularemia develop this condition (12). It is caused by hematogenous spread or direct inhalation of aerosolized bacilli and affects adults 10 times more often than children (12,13).

Complications are usually due to the pneumonic or typhoidal forms and include ARDS, meningitis, pericarditis, endocarditis, hepatic failure, renal failure, rhabdomyolysis, peritonitis, osteomyelitis, DIC, and septic shock (11,12). Infection during

pregnancy can result in premature birth, intrauterine fetal demise, or spontaneous abortion (14).

ED EVALUATION AND MANAGEMENT

Examine the patient thoroughly for the pathognomonic ulcer and regional lymphadenopathy. These findings are present in 60% to 86% of adults, but only 45% of children (1,2,13). Lesions are usually found on the lower extremities in cases of tick bite, with corresponding femoral and inguinal lymphadenopathy, and on the upper extremities in cases of animal handling, with epitrochlear and axillary lymph node involvement. Also check the patient's scalp to avoid missing lesions, especially in children. Oropharyngeal involvement may be seen as a yellow-white oropharyngeal pseudomembrane, and ocular involvement may produce corneal nodules, ulcers, and conjunctivitis (1,2). A pulse-temperature dissociation—bradycardia relative to the height of fever—is pathognomonic for typhoidal tularemia (1,11).

Routine laboratory testing is usually unremarkable although there may be mildly elevated transaminase levels, mild hyponatremia, normal to mild leukocytosis, and thrombocytopenia (1,2,13). Chest x-ray may show the "classic tularemic triad" of ovoid opacities, pleural effusions, and hilar adenopathy or may show a variety of unilobar, multilobar, miliary, or cavitary infiltrates (12,13).

Diagnosis is made by serology or PCR. Culture is insensitive and available only in specially equipped laboratories (11,12).

Start antibiotics while awaiting confirmatory testing, as delaying therapy increases morbidity and mortality (12). Streptomycin, 1 g IM q12h (children 15 mg/kg q12h) for 10 days is bacteriocidal and is the drug of choice (1,2,12,13). Also bacteriocidal, gentamicin is a more widely available alternative at 5 mg/kg/d IM or IV qd (children 2.5 mg/kg q8h) for 10 days (1,2,12,13). These drugs may be used during pregnancy (14). A less effective bacteriostatic regimen is doxycycline, 100 to 200 mg IV or PO q12h (children: 2.2 mg/kg q12h) for 14 to 21 days (1,2). Ciprofloxacin, 400 mg IV or 500 mg PO q12h, for 7 to 14 days; or levofloxacin, 500 mg IV or PO qd, for 7 to 14 days are bacteriocidal, but are not FDA approved for

tularemia and cannot be used in pregnant or pediatric populations (14). Abscesses and infected lymph nodes may need incision and drainage. To avoid corneal perforation, an emergent ophthalmology consult is indicated in cases of ocular tularemia.

DISPOSITION

Admit all patients for parenteral antibiotics. Patients may be switched to oral antibiotics after a few days and discharged if clinically well (1,2,3,12).

Babesiosis

Babesiosis is caused by *Babesia microti,* an intraerythrocytic protozoan. Like the plasmodial agent of malaria, *B. microti* causes red blood cell hemolysis. It is transmitted by deer ticks (*I. scapularis*) in the Eastern and Midwestern United States and by western blacklegged ticks (*I. pacificus*) in the Western United States (2,5). Transmission also occurs via blood transfusion and transplacental infection in neonates (3,5,15). National babesiosis surveillance began in 2011; 1,124 cases were reported across the United States that year (16).

CLINICAL PRESENTATION

The disease spectrum ranges from asymptomatic to mild flu-like illness to severe malaria-like disease to fulminant sepsis. Up to 66% of babesiosis patients are also infected with Lyme disease and these patients are believed to experience more severe symptoms (2,17). Symptom onset follows the tick bite by 1 to 6 weeks and consists of high fever, drenching sweats, fatigue, myalgias, and headache. Rash is uncommon and suggests Lyme coinfection if present. Jaundice and hemoglobinuria may result from parasite-induced intravascular hemolysis (2,16).

All immunosuppressed states, particularly asplenia, are risk factors for severe babesial infection (17). Neonates, the elderly, persons taking immunosuppressive drugs, and persons with cancer, HIV infection, hemoglobinopathies, or chronic cardiopulmonary disease are also at increased risk. The chief complications are ARDS (21%),

DIC (18%), congestive heart failure (12%), and renal failure (6%) (2,16,17). Mortality is 6% to 9% in immunocompetent patients and up to 21% in immunocompromised patients (2,17).

ED EVALUATION AND MANAGEMENT

High fever may be the only physical finding, although 11% to 14% of patients have hepatomegaly or splenomegaly, and 4% have jaundice (2,16,17). Routine blood tests may show leukopenia, thrombocytopenia, or markers of intravascular hemolysis (2,16,17).

Diagnosis is traditionally made by serology or direct microscopy of peripheral blood smears, although greater sensitivity and specificity in acute disease makes PCR the ED assay of choice (1,3,5,17). Babesiosis shares the same tick vector and geographic distribution as HGA and Lyme disease, so coinfection with two or more of these pathogens can occur. Test for all three diseases if babesiosis is suspected (1,2,17).

The most evidence-supported regimen is quinine, 650 mg PO q6h to q8h (children: 8 mg/kg q8h), plus clindamycin, 600 mg PO or IV q8h (children: 7 to 10 mg/kg IV q8h), for 7 to 10 days (1,2,5,17). However, because of the frequency of adverse reactions to these drugs, many experts advocate as first-line therapy atovaquone, 750 mg PO q12h (children: 20 mg/kg q12h), plus azithromycin, 500 to 1,000 mg PO on the first day (children: 10 mg/kg), then 250 mg PO qd thereafter (children: 5 mg/kg), for 7 to 10 days (1,2,5,17). Immunosuppressed patients require 6 weeks of antibiotics to prevent persistent parasitemia and relapse (17).

Patients who do not improve within 48 hours of treatment, who have >10% parasitemia (>1% in high-risk individuals), or who have organ failure or massive hemolysis are candidates for exchange transfusion of 8 to 10 units of packed red blood cells (2,5,17).

DISPOSITION

Admit patients with any of the foregoing complications and those belonging to high-risk groups to observe their response to treatment. Discharge well-appearing patients on oral medication and arrange for close outpatient follow-up.

Tick-Borne Relapsing Fever

Tick-borne relapsing fever (TBRF) is caused by spirochetes of the genus *Borrelia,* transmitted by soft ticks (genus *Ornithodoros*), lice, blood transfusion, exposure to infected blood, and transplacental infection of neonates (2,18,19). Patients are bitten by *Ornithodoros* ticks while sleeping in rodent-infested mountain cabins or in the limestone caves of central Texas. TBRF is a notifiable disease only in states abutting the Rocky Mountains, California, and Texas. Together, these states report approximately 25 cases per year (18,19).

CLINICAL PRESENTATION

A 4- to 18-day incubation period (mean, 1 week) is followed by fever, headache, meningismus, myalgias, arthralgias, vomiting, diarrhea, cranial nerve palsies, and a nonspecific maculopapular rash. Symptoms resolve after an average of 3 days, then recur 1 week later. Patients experience an average of two symptomatic and two asymptomatic episodes (2,18,19).

TBRF carries a 15% to 48% perinatal mortality; in utero infection results in severe neonatal sepsis (18,19). No adult deaths have been reported. Other complications include thrombocytopenia, liver failure, renal failure, splenic rupture, myocarditis, pneumonitis, ARDS, encephalitis, meningitis, and visual loss from iritis or endophthalmitis (18,19).

ED EVALUATION AND MANAGEMENT

One-third of patients demonstrate thrombocytopenia and/or hematuria (2,18). Liver enzymes may be elevated. TBRF is diagnosed by microscopic visualization of spirochetes in peripheral blood smears. This is an insensitive method (<70%) as is serology, therefore ED clinicians should obtain blood for PCR (2,18,19).

Doxycycline, 100 mg PO or IV q12h (children: 2.2 mg/kg q12h), for 10 days; erythromycin, 500 mg PO or IV q6h (children: 10 mg/kg q6h), for 10 days; or tetracycline, 500 mg PO or 250 mg IV q6h (contraindicated in children) for 10 days eliminates most relapses

(2,18). A Jarisch–Herxheimer reaction occurs in 50% of patients within 4 to 12 hours of starting antibiotics (18,19). This condition may cause fatal cardiovascular collapse; place affected patients in a critical care unit for hemodynamic monitoring, intravenous fluid resuscitation, and meptazinol therapy.

DISPOSITION

Observe all patients for 4 to 12 hours after initiating antibiotics and discharge the well appearing only afterwards. Admit patients with a Jarisch–Herxheimer reaction to a critical care unit and admit pregnant women and neonates to observe for septic deterioration. Consider admitting infants and very young children.

Colorado Tick Fever

CTF is caused by CTF virus, a coltivirus of the genus *Reoviridae.* Its vector is the Rocky Mountain wood tick *(D. andersonii)* whose habitat extends throughout western North America (2). Blood transfusion-related infections have also been reported (20). CTF is not a CDC-notifiable disease, and only 200 to 400 cases are reported annually in the United States (20,21).

CLINICAL PRESENTATION

CTF is also called *saddleback fever,* for the pathognomonic biphasic fever pattern that occurs in 50% of cases. After a 3- to 14-day incubation period (mean, 5 days), patients present with sudden high fevers, myalgias, and headache. Fevers persist for 2 to 3 days, remit for 2 to 3 days, recur for 2 to 3 days, and then finally resolve. Abdominal pain, nausea, vomiting, diarrhea, meningismus, photophobia, conjunctivitis, pharyngitis, and a nonspecific rash may also occur (1,2,22). Fatalities are rare (1). Complications primarily occur in children and include meningitis and encephalitis (5% to 10%), pneumonitis, myocarditis, hepatitis, epididymo-orchitis, DIC, and gastrointestinal hemorrhage (1,21,22).

ED EVALUATION AND MANAGEMENT

Complete blood count (CBC) may reveal neutropenia and thrombocytopenia (20,21). Diagnosis is made by serology or PCR (1,2,20,21,22). Most patients will not be critically ill, and treatment is purely supportive.

DISPOSITION

The majority of patients will be nontoxic and safe for discharge. Admit patients with complications of CTF.

Differential Diagnosis

The initial presentation of tick-borne illness is nonspecific; this creates a broad differential diagnosis. Each tick-borne illness can suggest one of the other tick-borne illnesses, various viral syndromes, various bacterial sepsis syndromes, bacterial endocarditis, disseminated gonococcemia, typhus, Q fever, tuberculosis, pasteurellosis, or toxoplasmosis. The nonspecific rash resembles that of other tick-borne diseases, various viral syndromes, scarlet fever, Kawasaki disease, toxic shock syndrome, Stevens–Johnson syndrome, or secondary syphilis. Tularemic ulcers and lymphadenopathy suggest bubonic plague, anthrax, sporotrichosis, cat scratch disease, lymphogranuloma venereum, streptococcal or staphylococcal cellulitis, or lymphoma. Lung findings can recall severe acute respiratory syndrome (SARS), hantavirus pulmonary syndrome (HPS), psittacosis, anthrax, or other atypical bacterial, fungal, or viral pneumonia. Neurologic involvement suggests meningococcemia or viral encephalitis. Episodic fever suggests malaria, louse-borne relapsing fever, yellow fever, rat bite fever, brucellosis, or leptospirosis. ED bloodwork may seem consistent with hepatitis, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), various viral hemorrhagic fevers, or dengue.

KEY TESTING

- Examine patients thoroughly for evidence of ticks, tick bites, and/or tularemic ulcers.

- Order a CBC, serum sodium and liver function tests to help make the diagnosis.
- Order disease-specific PCR or serologic assays to confirm the diagnosis. Test patients simultaneously for HGA, babesiosis, and Lyme disease as they share the same tick vector, and coinfection is common.

Common Pitfalls

- Failure to consider tick-borne disease in patients with nonspecific febrile syndromes, rash, jaundice, and/or neurologic complaints
- Failure to obtain an environmental exposure and blood transfusion history in patients with febrile syndromes
- Failure to obtain a history of symptom patterns in patients with febrile syndromes
- Delaying antibiotic therapy until definitive diagnostic tests (culture, PCR, serology, or peripheral blood smear) are resulted

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CHAPTER 188

Tuberculosis

Gregory J. Moran and David A. Talan

Tuberculosis (TB) causes more deaths worldwide than any other single infectious disease. Approximately one-third of all humans are infected with *Mycobacterium tuberculosis*. Approximately 9 million new cases of active disease develop annually, resulting in about 1.4 million deaths worldwide (1).

The incidence of TB in the United States has greatly decreased since the 1950s owing to the introduction of better public health measures and effective anti-TB drugs. Compared to about one third of the world population, only about 3.2% of the United States population is infected with *M. tuberculosis* (2). TB in the United States disproportionately affects immigrants, ethnic minorities, the poor, and homeless populations. Multidrug-resistant strains of *M. tuberculosis* (MDR-TB) have emerged, especially among immigrants and patients with acquired immunodeficiency syndrome (AIDS), and extensively drug-resistant TB (XDR-TB) strains have also been seen (3).

M. tuberculosis is a slow-growing bacterium transmitted between persons by droplet nuclei produced from coughing and sneezing. The small size of the droplets allows them to remain suspended in the air for long periods. Infection can occur if contaminated droplets are inhaled and reach the alveoli. The risk of infection is a function of the level of contamination of the air and the length of time the air is breathed. Small, enclosed areas with poor ventilation are more likely to promote the spread of TB.

M. tuberculosis infection usually begins in the alveoli, where bacilli are able to multiply. Infection spreads through the lymphatics

to regional lymph nodes and subsequently to the bloodstream. In most persons, cell-mediated immunity will develop over 2 to 10 weeks and contains the infection. When this immunity has developed, it is possible to identify *M. tuberculosis* infection with a TB skin test or interferon gamma release assay (IGRA). In this situation, in which the immune system prevents further spread, the person is said to have latent *M. tuberculosis* infection without disease. These people have no clinical symptoms of TB and cannot infect others. Symptomatic disease is referred to as TB.

M. tuberculosis survives within macrophages as a facultative intracellular parasite and thus can remain dormant in the body for many years. Active TB develops within 2 years in about 5% of patients, and another 5% will develop reactivation disease at some later point in life. Reactivation is more likely to occur in people with impaired cell-mediated immunity, such as those with diabetes, renal failure, malnutrition, or immunosuppression. Patients taking tumor necrosis factor (TNF)-antagonists (e.g., infliximab, etanercept, and adalimumab) are at much higher risk for developing active TB.

AIDS patients lack the ability to mount an effective cell-mediated immune response and are thus much more likely to progress to active disease. The risk of latent *M. tuberculosis* infection progressing to active TB in persons infected with human immunodeficiency virus (HIV) is estimated to be 5% to 8% per year, compared with the 5% to 10% lifetime risk for people not infected with HIV (4).

MDR-TB is defined as that due to an organism with in vitro resistance to at least isoniazid (INH) and rifampin, regarded as the two most powerful TB drugs. XDR-TB is defined as TB resistant to at least INH and rifampin, plus resistant to any of the fluoroquinolones (such as ofloxacin or moxifloxacin) and to at least one of three injectable second-line drugs (amikacin, capreomycin, or kanamycin) (3). Factors associated with the presence of MDR-TB include previous treatment (especially patients who were given an inadequate regimen or were not fully compliant), exposure to a known case of MDR-TB, birth or residence in an area of high MDR-TB incidence (Asia and Africa being highest risk), and living in environments such as homeless shelters and prisons, where there

may be a high risk of MDR-TB transmission. HIV-infected patients who are exposed to MDR-TB are at especially high risk of developing the disease.

Several factors contribute to the development and spread of MDR-TB and XDR-TB. One of the most important is incomplete compliance with medications. Failure to take medication as prescribed promotes drug-resistant organisms to develop. The prescribed regimen must contain at least two drugs to which the organism is susceptible. Because susceptibility testing takes several weeks to complete, some patients receive inadequate treatment regimens while susceptibility results are pending. With ineffective therapy, the patient remains infectious to others.

Because patients on inadequate therapy are infectious for longer periods compared to those on adequate treatment, MDR-TB and XDR-TB may have a selective advantage over susceptible strains, which may lead to an increasing incidence of persons with drug-resistant infections. Until more effective therapies or vaccines are available, the best weapon against TB is an aggressive infection control program focusing on early diagnosis, isolation, and directly observed therapy for TB patients.

CLINICAL PRESENTATION

The symptoms of TB vary dramatically, depending on the site and stage of infection and the overall health and immune status of the host. Some patients have mild symptoms that go unnoticed; some can be truly asymptomatic. Such patients can be identified only through exposure history, an abnormal chest radiograph, a positive TB skin or blood test, a positive smear for acid-fast bacilli (AFB), or a positive TB culture.

Early pulmonary TB often causes minimal symptoms. As the disease progresses, patients develop insidious constitutional symptoms such as fatigue, anorexia, weight loss, fevers, and night sweats. Cough progresses slowly over weeks to months, becoming productive of mucopurulent sputum. TB should be considered in any patient at risk who has a cough of more than 2 to 3 weeks' duration.

Hemoptysis due to endobronchial erosion may be present, usually indicating more advanced disease. Some patients present with a more acute onset of fever, chills, cough, and myalgias, similar to an episode of acute bronchitis or pneumonia. Chest findings of rales or consolidation may be present. Patients can have a dull ache or tightness in the chest, or they can have pleuritic pain related to TB pleuritis. Signs of pleural effusion may indicate a tuberculous empyema.

Most cases of disseminated TB have a subacute presentation with systemic symptoms. However, some patients with hematogenous dissemination of TB may present with an acute illness of fever, dyspnea, and cyanosis, mimicking bacterial sepsis. Physical findings can include hepatosplenomegaly, lymphadenopathy, erythema nodosum, and tuberculous lesions visible on examination of the optic fundi. Elderly patients are particularly prone to presenting with unexplained fever and hematologic abnormalities such as pancytopenia or leukemoid reaction.

TB may involve virtually any structure in the body and produce symptoms and signs related to the affected organs and systemic symptoms. In about 15% of TB cases, major involvement is seen at an extrapulmonary site. Granulomatous lymphadenitis is usually caused by *M. tuberculosis* in adults, but nontuberculous mycobacteria are a more common cause in children. The cervical and supraclavicular nodes are the most common sites of infection, but any nodes can be involved. Genitourinary TB can present as recurrent urinary tract infections without the growth of the usual bacterial pathogens (i.e., pyuria without bacteriuria) or simply recurrent fever. Skeletal TB is most common in the spine (Pott disease) and weight-bearing joints and usually presents as fever and localized pain.

Tuberculous meningitis is more common in small children as a complication of initial infection, but it can occur in any age group. TB meningitis typically has a subacute onset and presents as headache, altered mental status, or seizures. Cranial nerve signs attributable to involvement of the basilar meninges can be present. Some patients may have new psychiatric symptoms. The

cerebrospinal fluid characteristically shows a moderate lymphocytic pleocytosis (usually 100 to 500 cells/mm^2), elevated protein, and low glucose. AFB smears and cultures of cerebrospinal fluid are usually negative with TB meningitis, and it is often treated empirically in patients at risk for TB who have an otherwise unexplained meningitis.

HIV-infected patients are especially prone to having atypical presentations of TB. TB usually causes disease at an earlier stage of HIV infection than opportunistic pathogens such as pneumocystis, presumably because TB is more virulent than these other pathogens. Extrapulmonary involvement is much more common in HIV-infected patients with TB, occurring in 40% to 75% of cases, usually with concomitant pulmonary disease. In patients with advanced AIDS, cavitary lung disease and localized extrapulmonary disease are relatively less common, with more typically a diffuse pneumonia mimicking that due to *Pneumocystis jiroveci;* disseminated TB with chronic febrile illness and multiorgan involvement is also more often present (3).

DIFFERENTIAL DIAGNOSIS

Pulmonary TB can potentially mimic many other diseases, including pneumoconiosis, bacterial pneumonia, bronchiectasis, sarcoidosis, lung abscess, neoplasm, and fungal infections such as coccidioidomycosis, histoplasmosis, or pneumocystis. Factors helpful in identifying TB as a cause of illness include history of exposure to TB; characteristic radiographic findings, such as cavitations or apical infiltrates; presence of AFB on sputum smear; and results of skin or blood tests. The diagnosis of TB is ultimately confirmed by the culture of *M. tuberculosis,* but culture may take several weeks.

The possibility of TB should be considered when selecting empirical antibiotics for patients with community-acquired pneumonia. If TB is a possibility, it is advised not to use fluoroquinolones (which are used as second-line TB agents) to avoid the risk of selecting out fluoroquinolone-resistant TB. A regimen

such as ceftriaxone plus azithromycin would be a better choice in this situation.

It may be difficult to distinguish disease due to *M. tuberculosis* from disease due to other mycobacterial species. A number of mycobacterial species other than *M. tuberculosis* have been identified. Many are ubiquitous in the environment and are usually contaminants when isolated, but some have been found to be human pathogens (5). *Mycobacterium avium* complex (MAC) (also known as *Mycobacterium avium-intracellulare*), *Mycobacterium kansasii,* and other mycobacteria are rare causes of pulmonary disease; most other mycobacterial species are associated with skin, soft tissue, and lymph node infections. AFB identified in sputum smears may represent colonization by nonpathogenic mycobacteria, but until they can be definitively identified as such by culture, they should be considered to represent *M. tuberculosis* in a patient with a clinical picture consistent with TB.

MAC is the most common mycobacterial species isolated from persons with AIDS in the United States. Infection typically occurs as a systemic febrile illness in end-stage AIDS patients, rather than as a pulmonary infection in earlier-stage AIDS patients, as with *M. tuberculosis.* A chest radiograph usually does not suggest mycobacterial disease, and pleuritis is uncommon. Acid-fast smears of stool and mycobacterial blood cultures are commonly positive, but acid-fast smears of sputum are often negative, suggesting that the gastrointestinal tract, rather than the lungs, is the portal of entry.

MAC infections in AIDS patients are often difficult to treat effectively, but they may respond to regimens containing clarithromycin or azithromycin, ethambutol, rifabutin, clofazimine, or ciprofloxacin. HIV-infected patients with suspected pulmonary mycobacterial disease should generally be given empiric therapy against *M. tuberculosis* initially. Clarithromycin can be added to the TB regimen for enhanced activity against MAC. Therapy can be adjusted later if MAC or other nontuberculous mycobacteria are cultured.

ED EVALUATION

The most important test in the initial evaluation of patients with suspected pulmonary TB is the chest radiograph. Findings strongly suggestive of pulmonary TB include nodular densities, with or without cavities, which are commonly seen in the apical and posterior segments of the upper lobes or in the superior segments of the lower lobes (Fig. 188.1). Children often have pronounced hilar or mediastinal adenopathy (6).

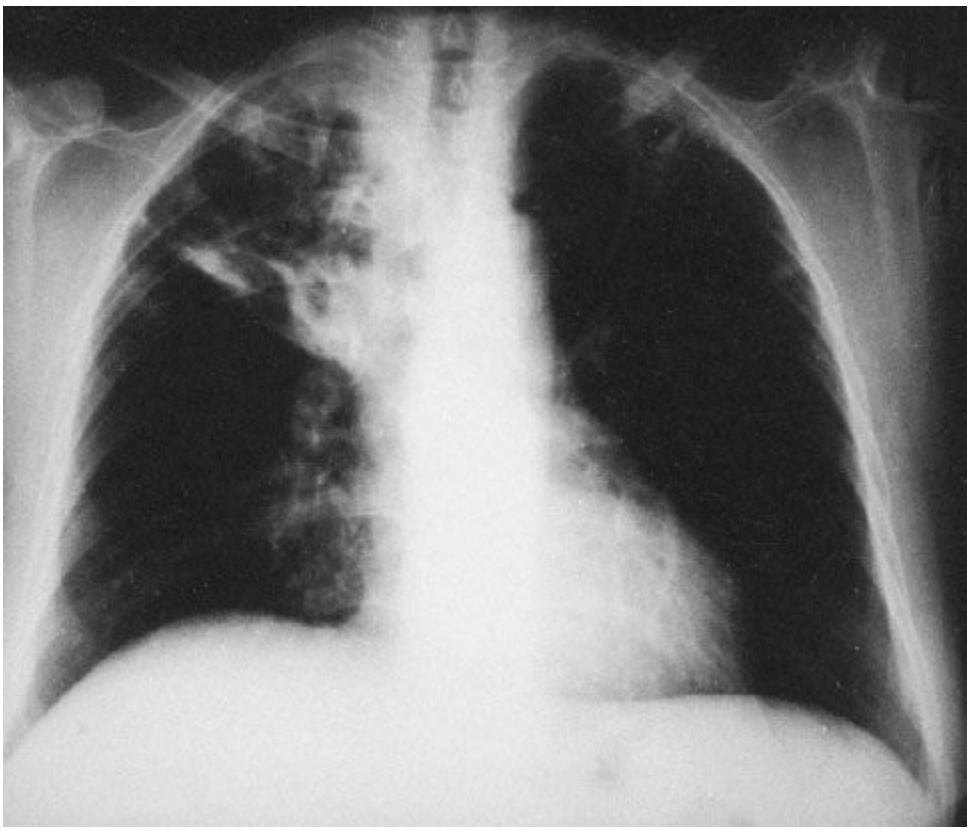

FIGURE 188.1 Chest radiograph demonstrating apical infiltrate with cavitation, typical of pulmonary tuberculosis.

In disseminated TB, the chest radiograph often reveals a miliary pattern, but it can be normal in the early stages. TB has many different radiographic appearances, ranging from normal to lobar consolidation to a diffuse interstitial pattern. Patients with AIDS are especially likely to have TB without the typical radiographic pattern, and they are more likely to have lymphadenopathy on a

chest x-ray. A diffuse interstitial pattern that is easily misdiagnosed as pneumocystis pneumonia may be seen in patients with AIDS (Fig. 188.2).

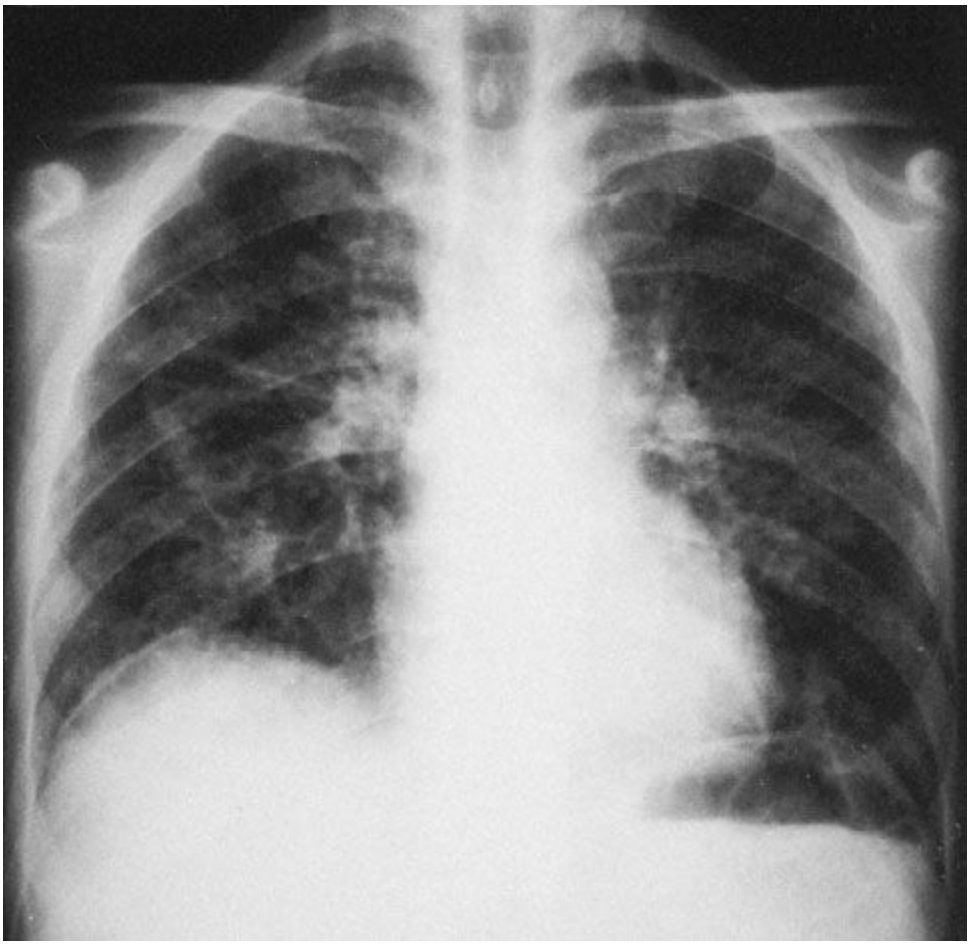

FIGURE 188.2 Chest radiograph of HIV-infected patient with tuberculosis demonstrating hilar adenopathy and scattered interstitial infiltrates. This patient was initially misdiagnosed with pneumocystis pneumonia.

If pulmonary TB is suspected, sputum samples should be obtained for AFB smear and culture. Sputum collection can put health care workers and other patients at risk for exposure to TB and should be performed only in an isolation room adequately equipped with outside ventilation and filters or ultraviolet light. Emergency departments (EDs) may consider having the patient step outside to provide a specimen if these facilities are not available. Ideally, three

successive early-morning sputum samples should be obtained. In certain cases, they can be obtained on an outpatient basis.

A positive AFB smear supports a presumptive diagnosis of TB. A positive smear does not necessarily indicate infection with *M. tuberculosis,* however, because other mycobacteria (e.g., MAC) are also acid-fast. Patients with positive smears are potentially the most infectious because they are usually coughing up large number of organisms. Because culture is more sensitive than AFB smear for the diagnosis of TB, the sample should be sent for culture even if the smear is negative.

AFB smear results are usually not available within the time frame of an ED visit. If there is a high likelihood of TB, the patient can be started on empiric therapy, with further AFB specimens obtained over the next couple of days. Empiric therapy will not significantly affect the diagnostic yield of specimens obtained over the next 1 to 2 days. Delays in diagnosis are a problem with standard techniques because culture usually takes 3 to 6 weeks and susceptibility tests may take 8 weeks. Nucleic acid amplification tests, such as polymerase chain reaction, can rapidly verify *M. tuberculosis* by directly detecting TB-specific DNA sequences. The Centers for Disease Control and Prevention (CDC) now recommends that nucleic acid amplification-based testing should be performed on at least one specimen from patients suspected of TB (7). Advantages of nucleic acid amplification-based testing over traditional AFB smear and culture include greater sensitivity than AFB smear, ability to distinguish TB from nontuberculous mycobacteria in smear-positive specimens, and results in 1 to 2 days rather than weeks required for cultures. A newer molecular diagnostic test can detect TB directly from untreated sputum in less than 2 hours (8).

There are two methods to identify persons infected with *M. tuberculosis:* intradermal tuberculin skin testing (TST) and IGRA. Testing should be targeted at those persons who are at increased risk of recent latent TB infection or with conditions that increase the risk of developing active TB (2,9). Persons for whom testing for latent TB is recommended are listed in Table 188.1, and

interpretation of the TST is summarized in Table 188.2. TSTs or IGRAs cannot distinguish active TB disease from latent TB.

TABLE 188.1
People for Whom Testing for Latent TB Infection is Indicated

People with signs, symptoms, or chest x-ray suggestive of active TB
Recent contacts of people known to have, or suspected of having, active TB
People with HIV infection
People with an abnormal chest x-ray compatible with past TB
People with other medical conditions that increase the risk of TB (e.g., intravenous drug use, diabetes, immunosuppressive therapy, renal failure, rapid weight loss)
Groups at high risk of recent infection with TB, such as immigrants from Asia, Africa, Latin America, and Oceania; medically underserved populations (e.g., homeless); personnel and residents in long-term care facilities and correctional institutions

TABLE 188.2
Criteria for Interpretation of Purified Protein Derivative Skin Tests as Positive

Induration ≥5 mm
Recent contact with someone with active TB
Fibrotic changes on chest radiograph consistent with prior TB
HIV infection
Patients with organ transplants or other immunosuppression
Induration ≥10 mm
Recent immigrants (<5 yrs) from an area with high TB prevalence
Intravenous drug users
Residents or employees of high-risk congregate settings (e.g., prison, nursing home, hospital, homeless shelter)
Mycobacteriology laboratory personnel
Persons with underlying disease that puts them at high risk for reactivation TB (e.g., diabetes, renal failure, malignancy, gastrectomy)
All children <4 yrs, as well as children and adolescents exposed to adults at high risk for TB
Induration ≥15 mm
Persons with no risk factors for TB

Table adapted from Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):1–51.

The Mantoux skin test is performed by injecting 5 units (0.1 mL) of purified protein derivative (PPD) intradermally. The arm is then examined 48 to 72 hours later for induration at the site. A negative TST does not rule out TB; 60% of AIDS patients and up to 30% of those without HIV infection have a reaction of <5 mm even when they are infected. False-positive reactions may be caused by crossreaction with other mycobacteria, such as MAC. A history of bacille Calmette-Guérin (BCG) vaccination generally does not alter the guidelines for interpretation of the TST, but can make the test less specific for TB infection. BCG vaccination usually does not cause a reaction of >10 mm, and the extent of the reaction decreases with time. Because the vaccine is generally given only in areas with a high incidence of TB, a reaction ≥ 10 mm should still be considered positive in these patients (9).

A newer alternative to the traditional TST are blood tests to detect an immune response to *M. tuberculosis*. In patients with prior or current TB infection, the white blood cells release interferon-gamma (IFN-γ) when exposed to synthetic peptides that simulate antigens

present in *M. tuberculosis*. IGRAs detect IFN-γ release to identify patients with TB infection. When compared to TSTs, IGRAs are more specific for diagnosing TB infection, especially in patients who have previously been vaccinated with BCG. IGRAs do not require a second visit for reading, and are less susceptible to variable results from the reader's interpretation (e.g., erythema vs. induration). TSTs are less expensive so are still used as the first-line diagnostic tool at many institutions. TSTs are generally preferred in children <5 years due to lack of data on IGRA (10).

The CDC recommends that facilities serving persons at high risk for HIV infection, TB infection, or both should provide screening for TB and encourage HIV testing. It is also recommended that TB case finding be part of the regular health care provided to all homeless people. Many persons at risk for TB and HIV come into contact with the health care system only for episodic care in EDs.

ED-based screening for TB could potentially identify many patients who would benefit from treatment. However, the cost and time commitment necessary for an effective TB screening program may preclude the development of such a program in many EDs. If a TB screening program cannot be established in the ED, patients at risk for TB should at least be referred to local public health clinics for testing. It is essential that all persons with suspected infectious TB be reported to local public health authorities (11).

KEY TESTING

- Chest radiograph
- Sputum for AFB smear and culture (collected using adequate respiratory precautions)

ED MANAGEMENT

Preventing the Spread of Tuberculosis

The most important issue in the ED is the rapid recognition of infectious TB patients to prevent exposure of ED staff and other patients. The basic principles for preventing the transmission of TB include early identification of persons with active TB, early

initiation of AFB isolation precautions, and initiation of effective therapy to render the patient noninfectious. Lapses in infection control measures have led to nosocomial transmission of MDR-TB between patients and from patients to health care workers.

The ED is potentially a high-risk area for the transmission of TB because patients may be undiagnosed with TB when they present initially and sometimes are crowded together for long periods, especially in busy inner-city EDs that are likely to have a larger number of TB patients. There may be long delays in recognition and initiation of infection control measures for infectious TB patients in the ED, and HIV-infected patients appear to be even more likely to have delays in recognition because they often have atypical presentations (12).

EDs should consider triage protocols to identify possible TB patients early (13). Those with possible TB should have a mask placed before an expedited chest radiograph.

Once a patient is suspected of having active TB, infection control measures should be initiated (11,13,14). These measures are aimed at isolating the source from other patients and reducing the microbial contamination of indoor air. Recommendations include the use of a private room for the source patient with negative pressure in relation to surrounding areas and a minimum of six air exchanges per hour. Air from the room should be exhausted directly to the outside. Use of ultraviolet lamps and/or high-efficiency particulate air filters to supplement ventilation may be considered.

Many EDs do not have the facilities to comply with these recommendations, and the costs associated with fitting a department with such facilities are substantial. If facilities that meet these standards are not available, it is important to at least designate an area for persons with possible TB that will keep them isolated from other patients and will minimize air exchange with other patient areas. Placing an ordinary surgical mask on the patient may help reduce the amount of airborne droplets produced with coughing, but they are not completely effective for preventing the transmission of TB when worn either by TB patients or by those at risk for exposure. Masks used in the conventional manner are not designed

to filter out particulates in the 1- to 5-μ range and can leak large amounts of air around the edges. The CDC recommends that health care workers use masks capable of filtering out at least 95% of particles in the 1-μ range (commonly designated as N-95) for protection against TB.

Respiratory isolation for possible TB should be considered for higher-risk pneumonia patients admitted to the hospital, but most facilities do not have enough isolation rooms for all pneumonia cases. A prospectively validated ED decision instrument was found to have 99.7% negative predictive value for TB in pneumonia patients with no TB history, no previous positive TB skin test, nonimmigrant, not homeless, not recently incarcerated, no recent weight loss, and no apical infiltrate or cavitary lesion on plain chest radiograph (15). AIDS patients with pneumonia of any radiographic appearance are at such increased risk of TB (and delayed recognition) that routine respiratory isolation is recommended. AIDS patients with compatible respiratory and constitutional symptoms and negative X-ray should be considered for chest computed tomography to exclude pulmonary TB.

Treatment of Active Tuberculosis

Initiation of an effective drug regimen is important to prevent the spread of TB, but it is usually not critical to begin treatment immediately in the ED. Presumptive therapy can begin in the ED on the basis of clinical grounds alone if the patient is at risk for TB and has signs, symptoms, and radiographic findings strongly suggestive of TB. Specimens should still be sent for AFB smear, culture, and sensitivity for subsequent management. If cultures are negative or yield only nontuberculous mycobacteria, treatment can be stopped or adjusted accordingly.

Active TB should always be treated with at least two drugs to which the organism is susceptible. Administration of a single drug can lead to the development of a bacterial population resistant to that drug. When two or more drugs are used simultaneously, each helps to prevent the emergence of TB resistant to the other. Because

of concern about MDR-TB, recommended initial therapy for TB includes four drugs. The preferred initial regimen consists of daily rifampin, INH, pyrazinamide (PZA), and ethambutol (often abbreviated as RIPE) (1,3,16). Doses of these drugs can be found in Table 188.3. If four drugs are used in the initial regimen, it is very likely that the organism will be sensitive to at least two of them. The initial regimen is continued for 2 months, at which time the number of drugs and frequency of dosing can be reduced, depending in part on the results of susceptibility testing.

TABLE 188.3
Daily Dosage Recommendation for the Initial Treatment of Tuberculosis

Drug	Children <12 yrs	Adults
Isoniazid	10–15 mg/kg Max 300 mg	5 mg/kg Max 300 mg
Rifampin	10–20 mg/kg Max 600 mg	10 mg/kg Max 600 mg
Rifabutin	Unknown	5 mg/kg Max 300 mg
Pyrazinamide	15–30 mg/kg Max 2 g	15–30 mg/kg Max 2 g
Ethambutol	15–20 mg/kg Max 1 g	15–20 mg/kg Max 1,600 mg

Adapted from Centers for Disease Control and Prevention. Treatment of tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America. *MMWR* 2003;52(No. RR-11):1–77.

Immunocompetent patients usually cease to be infectious within 2 to 4 weeks of starting therapy, assuming the infecting organism is susceptible to the drugs being used and the patient is compliant. Treatment should be continued for at least 6 months in immunocompetent persons. Expert advice should be sought if a patient is suspected of having MDR-TB. Alternative regimens using > four drugs may be recommended for these patients, including drugs such as cycloserine, ethionamide, amikacin, linezolid, and

quinolones. Those who are at especially high risk for MDR-TB include anyone with HIV infection, those with known exposure to MDR-TB, and persons from a geographic area or demographic group with a high incidence of MDR-TB.

Expert consultation should be sought before initiating TB treatment for HIV-infected individuals taking antiretroviral drugs due to the potential for drug interactions (especially with rifampin). Patients coinfected with TB and HIV who have low CD4 counts are at high risk of developing immune reconstitution inflammatory syndrome (IRIS) with initiation of antiretroviral therapy. For that reason, antiretroviral drugs are often held until after TB treatment has been started. IRIS due to known or undiagnosed TB coinfection should be considered in patients who present with worsening symptoms within weeks after starting antiretroviral treatment.

Recommendations for treatment of extrapulmonary TB are generally the same as for pulmonary TB. However, longer courses of 9 to 12 months are usually recommended for TB meningitis, bone or joint TB, or children with miliary TB (1,16). Corticosteroids may be a useful adjunct for tuberculous meningitis or pericarditis.

Common side effects of these medications include hepatitis (INH, rifampin), peripheral neuropathy (INH), optic neuritis (ethambutol), and rarely, purpura (rifampin). Adults should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine or blood urea nitrogen, complete blood count, and platelet count. Serum uric acid should be measured if PZA is used, and a baseline examination of visual acuity should be obtained for patients to be treated with ethambutol.

Patients should be instructed to report any symptoms suggestive of hepatitis or thrombocytopenia. Pyridoxine (10 to 50 mg/d) can be given with INH to persons with conditions in which neuropathy is common, such as diabetes, alcoholism, or malnutrition. The rate of adverse reactions to antituberculous agents increases with age and also appears to be higher in HIV-infected patients. Treatment interruption is generally recommended for patients who develop elevation of alanine aminotransferase (ALT) more than three times

the upper limit of normal in the presence of hepatitis symptoms, or more than five times elevated in the absence of symptoms (17).

Management of Tuberculosis Exposure

Management of persons (including health care workers) exposed to others with active TB involves consideration of the likelihood of the following: (a) the exposed person has been newly infected with *M. tuberculosis,* (b) the infecting strain is drug resistant, and (c) the newly infected contact will develop active TB. Contacts who do not have a history of a positive TST or IGRA should receive one of these tests and, if indicated by symptoms, a chest radiograph and sputum examination. Exposed persons who have a positive IGRA or a TST reaction equal to 5 mm should be considered newly infected and should be considered for preventive therapy once active TB has been ruled out.

Persons with a high-risk exposure and a negative TST or IGRA should have a follow-up test 12 weeks after the exposure has ended; if the test is still negative at that time, no further evaluation is necessary. Because the risk of developing TB is higher for young children, preventive therapy may be considered for all children younger than 5 years of age who are close contacts of TB cases until repeat testing is done at 12 weeks after exposure.

Persons who are known to be HIV-infected or otherwise immunosuppressed and who are close contacts of patients with infectious TB should be carefully evaluated for evidence of TB. If there are no findings suggestive of active TB, preventive therapy with INH may be recommended, even if TST is negative (9).

Management of Positive Tuberculosis Skin Tests

Persons with a positive TST or IGRA should be evaluated for the presence of active TB with a chest radiograph. If the chest radiograph is abnormal or if symptoms suggest TB, an examination of sputum for AFB smear and culture is indicated. Those with no evidence of clinical disease should be referred for consideration of preventive therapy for TB. It is not necessary to initiate therapy

urgently in this situation, but it is important that patients understand the importance of follow-up to obtain preventive therapy. It has been shown in numerous studies that preventive therapy substantially reduces the risk of latent infection progressing to clinical disease. Immunocompetent persons who are not at risk for MDR-TB are generally treated with INH for 6 to 9 months (2). Routine laboratory monitoring is not necessary for most patients receiving INH but should be considered for those with HIV, pregnancy, liver disease, or regular alcohol use.

The effectiveness of preventive therapy for people exposed to MDR or XDR-TB strains has not been prospectively studied, and guidelines for management of such patients are less clear. Consultation with local infectious disease experts familiar with local patterns of resistance and current treatments is recommended. Because the efficacy of drugs other than INH and rifampin for preventive therapy is unknown, persons on alternative therapies should have regular follow-up.

Recommendations for TB therapy are likely to continue to change because of shifting patterns of infection and drug resistance. The most current recommendations can be found in *Morbidity and Mortality Weekly Report* and the publications of the American Thoracic Society.

CRITICAL INTERVENTIONS

- Initiate infection control measure for patients suspected of TB.
- Treat active TB with at least two drugs to which the organism is susceptible. Initial treatment usually consists of four drugs (INH, rifampin, PZA, and ethambutol) pending susceptibilities.

DISPOSITION

Considerations for hospital admission include severity of illness, diagnostic uncertainty, and ability of the patient to avoid transmitting infection to others and to comply with outpatient treatment. Criteria for admission of patients with TB are similar to those for patients with other types of pneumonia. Patients who are

not seriously ill and are not immunocompromised can safely be sent home with close follow-up, but precautions must be taken to avoid the spread of TB to others. Any patient who is discharged home with possible TB must be reported to local public health authorities. It can be assumed that household contacts have already been exposed and will need to be tested.

Patients should be instructed to avoid crowded, enclosed, public areas and to wear a mask for at least the first 2 weeks of therapy to reduce the amount of airborne droplets produced by coughing. Other factors, such as homelessness, degree of compliance with medications, follow-up, and compliance with infection control measures should be considered when making decisions regarding admission. In the United States, laws vary among the states in regard to forced treatment and quarantine of patients who will not cooperate with therapy and are believed to be a public health hazard (18).

Common Pitfalls

- Failure to consider the possibility of TB in a patient presenting with nonspecific systemic complaints
- Failure to rapidly initiate infection control measures for patients suspected of TB
- Risking the spread of TB in the ED by performing high-risk procedures such as sputum induction in infectious TB patients without proper isolation procedures
- Failure to isolate AIDS patients with TB because of misdiagnosis as *P. jiroveci* (pneumocystis) or other infections
- Failure to refer patients at risk of latent TB for TST or IGRA
- Failure to recognize and follow up patients whose cultures may become positive several weeks after an ED visit
- Failure to report persons with suspected TB to local public health authorities

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CHAPTER 189

Infectious Mononucleosis

David A. Jerrard

Infectious mononucleosi is clinically defined by the triad of fever, lymphadenopathy, and pharyngitis, combined with the development of heterophil antibodies and atypical lymphocytosis. It is caused by the Epstein–Barr virus (EBV), which is also strongly implicated in the etiology of nasopharyngeal cancer and Burkitt lymphoma. The causative organism for this disease remained unidentified until the 1960s. The virus is a member of the herpes virus family. It is a DNA virus that has the ability to become latent after an active infection. The most characteristic feature of the disease is its predilection for the young adult population, especially the 15- to 30-year age group (1). A vaccine against EBV infection is in clinical trials (2).

Epidemiologic studies have shown the presence of antibody to EBV (indicating exposure) correlates strongly with immunity, and its absence is highly indicative of susceptibility (1). The age at which individuals develop the infection depends on socioeconomic factors as well as hygiene. Most children in developing countries have been exposed by the age of 3 years, but only 50% of those in economically advanced countries have antibodies by adolescence. Primary EBV infection during childhood is usually subclinical (1). In many college populations, 30% to 75% remain seronegative (2). By adulthood, most individuals are seropositive.

Epidemiologic and laboratory evidence indicates that transmission occurs through the oropharyngeal route, via saliva (3). EBV may be found in throat washings many months after clinical symptoms have abated and may even be cultured from 10% to 20% of completely asymptomatic individuals. Most transmissions occur from

asymptomatic individuals to previously uninfected members of the population. There have been reports of EBV being found in genital secretions, suggesting a possible role of sexual transmission in adults (4).

When EBV is transmitted by saliva, the initial site of replication is in the oropharynx. Both B lymphocytes and oropharyngeal epithelial cells have specific surface receptors for EBV, and replication takes place within these cells. Both humoral and cellular components are important in the immune response to EBV infection. The cellular response, consisting of the elaboration of T lymphocytes having very similar characteristics to suppressor-cytotoxic T lymphocytes, is responsible for controlling B-cell proliferation (5).

CLINICAL PRESENTATION

The incubation period is 4 to 8 weeks (1). Humans are the only known reservoirs. Nonspecific symptoms such as malaise, anorexia, fatigue, and chills often herald the illness and are followed by the development of fever, pharyngitis, and lymphadenopathy. Most patients seek medical care because of sore throat, but headache and myalgia are often complaints as well. Abdominal pain is rare in the absence of splenic rupture.

Pharyngeal exudate is present about one-third of the time, and palatal petechiae may be observed. Anterior or posterior cervical lymphadenopathy is reported in about 90% of patients and tends to be particularly impressive in these areas. Generalized adenopathy is often present. The nodes may be moderately tender or painless (6). Most clinical and laboratory findings will resolve after 30 days. Cervical adenopathy and fatigue may persist (6).

Splenomegaly is noted in about 50% of patients, mostly in the second or third week of illness, and is usually not associated with pain. The spleen becomes infiltrated with large amounts of lymphoid cells with resultant thinning of the splenic capsule and trabeculae. The presence of pain should alert the clinician to the possibility of impending or actual splenic rupture, an uncommon but well-documented complication of the disease that may be life

threatening if not identified and treated promptly (1). The risk of splenic rupture is highest during the second and third weeks of illness, as the increase in size of the spleen is at its peak. The risk is low 4 or more weeks after the infection (7). Though uncommon, rupture is the most prevalent reason for fatalities (8). Though there have been reported cases in which arteriography in combination with embolization has been used, splenectomy remains the most common choice for management (9).

Tonsillitis may occur during any stage of the illness, although it is usually most pronounced during the first 2 weeks of the postprodromal period. Tonsils hypertrophied to the point of "kissing" in the midline are not unusual and do not mandate hospital admission. The distinction between severe pharyngitis and airway compromise is necessary, but tonsillar hypertrophy rarely causes airway compromise (10).

Complications of infectious mononucleosis are rare, but the clinician must be alert to recognize them. Autoimmune hemolytic anemia may appear within 1 to 2 months of initial symptoms. Mild thrombocytopenia develops in approximately half of all cases. The anemia and thrombocytopenia appear to be antibody-mediated and are usually self-limited, lasting approximately 6 weeks (1). Glucocorticoids have been recommended for the treatment of the thrombocytopenia and the hemolytic anemia, but there is little evidence to support their use (1).

A number of neurologic complications of infectious mononucleosis have been described. Cranial nerve palsies (especially Bell palsy) and various forms of encephalitis are the most common. Cerebellar dysfunction and episodes of Guillain–Barré syndrome have been associated with infectious mononucleosis. Yet, typically, less than 5% of patients develop neurologic symptoms (1).

About 90% of patients with infectious mononucleosis have transient elevation of hepatic enzymes, although significant hepatic dysfunction is exceedingly unusual. Observations have been made that correlate between lactate dehydrogenase (LDH) levels and splenic size (11). Roughly half of these patients have mild hepatic tenderness, but hepatomegaly is infrequent. Clinical jaundice may

develop early in the illness, but resolution usually occurs within a few weeks. Subclinical illness that mimics mild viral hepatitis may be caused by infectious mononucleosis.

Although rare, airway obstruction secondary to extreme lymphoid hyperplasia of the tonsils is a potential complication. Airway compromise, as evidenced, for example, by stridor, requires active airway management.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of sore throat is lengthy (Table 189.1). Because several of the entities (e.g., foreign body, retropharyngeal abscess and hematoma, and, rarely, adult epiglottitis) may be associated with airway compromise, it is vital to rule them out as possibilities. Compared with other causes of sore throat, infectious mononucleosis features more prominent systemic complaints.

TABLE 189.1
Differential Diagnosis of Sore Throat

Retropharyngeal abscess
Epiglottitis
Esophageal candidiasis
Peritonsillar abscess
Foreign body
Uvulitis
Pharyngitis (bacterial or viral)[a]
Laryngitis
Cervical adenopathy

[a]Includes infectious mononucleosis.

Generalized lymphadenopathy prompts consideration of other viral illness, AIDS, leukemia, lymphoma, or tuberculosis.

The differential diagnosis of splenomegaly is broad as well. Infectious endocarditis, abscess, and disseminated tuberculosis are all possible infectious etiologies of splenic enlargement. Infiltrative processes such as lymphoma and leukemia must also be included for consideration.

ED EVALUATION

If there is suspicion of adult epiglottitis or retropharyngeal abscess or hematoma, a soft-tissue lateral radiograph of the neck should be performed. In any patient presenting with the complaint of sore throat, indications of airway compromise should be sought.

The diagnosis of infectious mononucleosis is based on clinical, hematologic, and serologic criteria. In a patient strongly suspected of having infectious mononucleosis, certain laboratory features may aid in making a firm diagnosis.

Common laboratory findings include marked lymphocytosis (greater than 50%) (1). The lymphocytosis is characterized by the presence of cells, roughly 10% of the total with atypical morphology. They are larger than mature lymphocytes, have large lobulated or indented nuclei, and have vacuolated or bluish cytoplasm. The finding of at least 10% atypical lymphocytes on a peripheral blood smear has a sensitivity of 75% and a specificity of 92%, respectively, for the diagnosis of infectious mononucleosis (1). Lymphocytosis usually peaks in the second or third week of illness.

Atypical lymphocytosis may be seen in other infections, such as toxoplasmosis, rubella, mumps, and hepatitis (1). Complicating matters further, mononucleosis-like syndromes may be associated with cytomegalovirus infection, toxoplasmosis, and hepatitis A and B. Sometimes these syndromes cannot be distinguished clinically from infectious mononucleosis due to EBV.

Because so many of the symptoms of infectious mononucleosis are nonspecific, serologic evidence may be required to make the diagnosis. Heterophil antibodies (antibodies that react with antigens not responsible for their production) are characteristically produced in infectious mononucleosis (1). The Monospot test is based on this tube dilution principle.

Because many individuals are heterophil antibody negative during the first week of illness, it seems reasonable to omit this test in patients with an illness of recent onset, unless the physical examination raises a high suspicion for mononucleosis. Patients

should be instructed to return for testing if symptoms persist beyond 7 days.

Individuals with infectious mononucleosis produce specific antibodies directed against EBV antigens. Even though the development of detectable heterophil antibodies may be delayed, EBV antibody tests are rarely necessary, because 90% of cases are heterophil positive, and false-positive heterophil results are rare. Illness is usually mild and self-limited) (1). It should be noted, as with heterophil antibodies, antibodies specific to EBV may sometimes not be detectable until several weeks after the onset of illness. Assays specific for antibodies to EBV are the most expensive modality for diagnosing infectious mononucleosis (12).

KEY TESTING

- CBC—marked lymphocytosis often present
- Monospot test

ED MANAGEMENT

The treatment of infectious mononucleosis usually consists of supportive care. There is no specific antiviral therapy. Fever and pharyngeal pain may be ameliorated by acetaminophen. Aspirin should be avoided because of the risk of increasing bleeding tendency due to thrombocytopenia. Adequate rest should be advised, although rest does not seem to expedite recovery. Ampicillin, via an unknown mechanism, causes a rash in roughly 90% of those with infectious mononucleosis. When treating presumed streptococcal tonsillitis in patients with infectious mononucleosis, erythromycin, or penicillin should be prescribed instead of ampicillin. Splenic rupture is rare after 3 weeks of symptom onset. A recent review suggests a return to contact sports after this period of time, once fever and symptoms have abated (13). Patients should be advised that feelings of malaise may linger, sometimes for months.

Severe pharyngitis may be treated with corticosteroids (prednisone, 40 to 60 mg/d, and tapered over 7 to 10 days).

Impending airway obstruction or an inability to take oral medications may necessitate the use of dexamethasone. Symptoms of dysphagia and difficulty breathing are usually improved within 1 to 2 hours of administration of parenteral corticosteroids. Active airway management is rarely necessary. Although corticosteroids do not decrease spleen size or reduce the likelihood of splenic rupture, some benefit may be obtained in decreasing neurologic, hematologic, and cardiac complications. Corticosteroid therapy is not generally recommended for uncomplicated infectious mononucleosis (14).

In patients presenting with abdominal pain, a computed tomography (CT) scan should be performed. Infectious mononucleosis may be the most common reason for splenic rupture (12). Splenic rupture is unlikely to occur in the first 2 weeks of the illness because the capsular and trabecular changes that permit rupture to occur do not develop for 2 to 4 weeks.

CRITICAL INTERVENTIONS

- Perform a soft-tissue lateral radiograph of the neck for suspicion of adult epiglottitis, retropharyngeal abscess, or hematoma.
- Advise avoidance of contact sports for 2 to 6 months after the onset of illness or until there is absence of splenomegaly on follow-up imaging studies (CT and ultrasound) because of risk of splenic rupture.
- Treat severe pharyngitis with corticosteroids.

DISPOSITION

Most patients with infectious mononucleosis do well without any intervention and can be discharged from the emergency department with instructions to return should abdominal pain develop and breathing or swallowing become difficult.

Consultation with appropriate specialists is indicated for neurologic or hematologic complications.

Patients who are unable to maintain oral intake because of difficulty in swallowing or patients who may have possible airway

compromise should be admitted and should begin parenteral corticosteroids.

In the unlikely event of splenic rupture, a surgical consult is imperative. If either CT scanning or surgical backup is not available, the patient should be immediately transferred to a center that has these resources.

Common Pitfalls

- The differential diagnosis of sore throat includes more than simple viral or bacterial pharyngitis. Other infections localized to the throat can have disastrous consequences if they go undetected. These infections include retropharyngeal abscess and epiglottitis.
- Errors in management are usually the result of a failure to examine the patient thoroughly. This error may result, for example, in a failure to diagnose splenic rupture (spontaneous is more common than posttraumatic), an uncommon but potentially dangerous complication.
- Patients should be advised to seek medical attention promptly if they develop difficulty breathing or abdominal pain.
- Ampicillin should be avoided because of the high likelihood that a rash will develop. The rash is morbilliform and develops 5 to 9 days after the antibiotic is started.

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CHAPTER 190

Influenza

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More people died in the 1918 influenza pandemic than in all of World War I. Today, influenza remains a major killer and causes more morbidity and mortality than the acquired immunodeficiency syndrome (AIDS). In nonpandemic years, 20,000 to 40,000 persons die of influenza-related illness in the United States alone (1); in pandemic years, deaths can exceed 100,000. Influenza infections account for tremendous health care expenditures each year. The Centers for Disease Control and Prevention (CDC) estimates that there are between 114,000 and 146,000 hospitalizations per year, with the highest rates of both hospitalization and death being among the elderly and in children younger than 2 years old (2,3).

Influenza is caused by large RNA viruses belonging to the myxovirus groups. Of the three immunologically distinct groups (A, B, and C), influenza A and B are encountered most frequently. Group A is responsible for the majority of the mortality and significant morbidity. It appears to cause more severe disease than type B, making secondary bacterial infection more likely, and is more common in older populations. The disease is spread by large-particle respiratory droplet transmission through coughing or sneezing. The typical incubation period is 1 to 4 days. Adults can be infectious from the day before symptoms begin through 5 days after illness onset. Children can be infectious for more than 10 days after symptom onset.

CLINICAL PRESENTATION

Influenza is an extremely common respiratory illness, characterized by the abrupt onset of fever, sore throat, headache, myalgias, and nonproductive cough. The malaise is often much more extreme than that seen with most other common respiratory illnesses. During an influenza outbreak, influenza can be diagnosed by clinical criteria with a high degree of certainty, with exceptions being in the elderly and in very young children. Young children can present more atypically, often with otitis media, nausea, vomiting, and less prominent respiratory symptoms. In addition, they can present with febrile seizures and symptoms mimicking bacterial sepsis. Symptoms last from a few days to a week in most patients. More severe illness can result if there is pulmonary involvement due to primary viral or secondary bacterial pneumonia, which is the most common cause of death. The vast majority of severe disease occurs in the elderly, the immunosuppressed, patients with chronic cardiovascular or pulmonary disease, and in young children. In addition, pregnancy can increase the risk for serious complications from influenza.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of influenza includes the myriad respiratory and infectious diseases seen in the emergency department (ED). The clinician's major task should be to recognize serious illness that requires specific antibiotic treatment or other aggressive interventions.

Prominent severe headache, meningeal signs, or changes in mental status make it mandatory to rule out meningitis. Sore throat, often seen with influenza, may be due to peritonsillar abscess, epiglottitis, or streptococcal pharyngitis. Myalgia may be due to bacteremia or sepsis, particularly in the elderly. A finding of hypotension or marked orthostasis mandates evaluation for sepsis or toxic shock syndrome, particularly if there is evidence of multiple organ system involvement. Cough or difficulty breathing may be due to bacterial or viral pneumonia, acute bronchospasm, or cardiac processes such as congestive heart failure or myocardial ischemia.

Unfortunately, the differentiation of viral from bacterial pneumonia in the patient with influenza is difficult. Antibiotics should be instituted early if there is any suspicion of a bacterial process.

In the spring of April 2009, an outbreak of H1N1 influenza A virus was observed in many countries, including the United States. In June 2009, the World Health Organization raised its pandemic alert to the highest level, indicating widespread transmission of the disease. The pandemic was not declared to be over until August 2010. In the past few years another major public health concern is the possibility of avian influenza turning into a pandemic. Avian flu is an influenza A virus found chiefly in birds, but isolated human cases have been found in Asia, parts of Europe, the Middle East, and Africa, usually after direct contact with infected poultry. In late March and April 2013, human cases of novel avian influenza A H7N9 infection in China were reported to the World Health Organization. The reported case fatality rates have been alarmingly high, exceeding 50%. Current seasonal influenza vaccines provide no protection against human infection with avian influenza A viruses (4).

ED EVALUATION

The initial evaluation of influenza and influenza-like illness should focus on assessment of the airway, breathing, and circulation. Pulse oximetry is a simple noninvasive test that may provide a quick indication of respiratory compromise. Physical examination should focus on the heart and lungs. A thorough examination of the skin should include a search for any cutaneous manifestations of infectious disease, such as purpura or petechiae.

Patients with significant cough, respiratory symptoms, or abnormalities on lung examination should have a chest radiograph. Lumbar puncture and urinalysis may be indicated if suggested by appropriate symptoms. A complete blood cell count, though nonspecific, may lend support to a diagnosis of superimposed bacterial infection. Tests to determine levels of electrolytes, blood

urea nitrogen, creatinine, and blood glucose should be ordered in those patients with severe derangements of fluid balance or in those who have chronic medical problems or take medications, such as diuretics, that can affect electrolyte balance. Arterial blood gas analysis and serum lactate may be appropriate when hypoxia or sepsis is suspected. Blood cultures should also be obtained if sepsis is a possibility.

Rapid ED influenza tests are readily available. They are immunoassays that can identify influenza A and B viral nucleoprotein antigens in respiratory specimens. Unfortunately, their poor sensitivity limits their usefulness, particularly in high-risk individuals (5). In a meta-analysis of 159 studies that evaluated rapid antigen tests, the pooled sensitivity was 62.3% and the pooled specificity was 98.2% (6). The sensitivity was lower in adults than children and higher for influenza A than influenza B. Thus, a negative result should be interpreted with caution and treatment should not be delayed in high-risk individuals if influenza is suspected. Small studies have shown that awareness of a positive rapid influenza test result in pediatric ED patients can reduce the number of laboratory tests and radiographs, decrease antibiotic use, and increase the use of antiviral drugs (7,8).

Reverse transcriptase polymerase chain reaction (RT-PCR) is the most sensitive and specific test for a relatively rapid identification of influenza. Its use in the ED is still limited because results may not be available for 4 to 6 hours or even longer.

In the past, viral culture has been considered the gold standard for laboratory diagnosis, but results often take 4 to 12 hours and limit any benefit for initial clinical management.

KEY TESTING

- CXR if significant respiratory symptoms
- CBC for suspected superimposed bacterial infection
- Electrolytes, BUN, creatinine, glucose if dehydrated
- Influenza diagnostic testing (rapid or PCR) to confirm diagnosis

ED MANAGEMENT

The initial treatment for patients with suspected influenza is directed at ensuring adequate oxygenation and hemodynamic stability. Patients with viral or bacterial pneumonia, particularly the elderly or those with chronic obstructive pulmonary disease, can present in extremis with an immediate need for endotracheal intubation and mechanical ventilation. Supplemental oxygen should be given to patients with significant respiratory symptoms or low pulse oximeter readings. Although it is not viewed as standard of care, one study showed that referral to a center where extracorporeal membrane oxygenation was available reduced mortality among patients with severe 2009 influenza H1N1 infection (9).

Patients who are tachycardic, hypotensive, or orthostatic should have a large-bore intravenous line placed and receive initial fluid resuscitation with normal saline. Care should be taken to avoid overhydration, particularly in the elderly or in those with a history of congestive heart failure. Standard bronchodilator therapy is indicated for any accompanying reactive airway disease.

If the patient has a coexisting pneumonia, antibiotics should be instituted in the ED, because it is, as a rule, difficult to differentiate viral pneumonia from bacterial pneumonia. Antibiotics should provide adequate coverage against *Haemophilus influenzae* and group B *Streptococcus,* as well as *Staphylococcus aureus,* which is a relatively common bacterial pathogen associated with influenza outbreaks.

The antiviral agents rimantadine and amantadine previously were found to be effective in reducing the severity and duration of illness in high-risk individuals who had not been vaccinated. However, neither is currently recommended by the CDC for influenza treatment or prophylaxis because of high rates of resistance and side effects.

The Food and Drug Administration has approved a new class of antiviral drugs, neuraminidase inhibitors. Neuraminidase permits the virus to penetrate the surfaces of cells and is necessary for

optimal release of virus from infected cells. Inhibitors now available are oseltamivir, given orally, and zanamivir, inhaled through the mouth at a high flow rate. These agents are approved for the treatment of influenza in patients who have been symptomatic for less than 2 days. Initial studies showed only a 1- to 1.5-day decrease in the duration of symptoms, but subsequent research has supported further benefits and indications for these drugs. Both drugs have been shown to be effective in significantly reducing time to alleviation of symptoms, in prophylaxis for close contacts, and in reducing complications in high-risk individuals especially when the drugs are administered within 48 hours of onset of symptoms (10,11). Zanamivir was associated temporally with the termination of a nursing home outbreak that amantadine had failed to control (12). A 2011 meta-analysis concluded that oseltamivir reduced respiratory complications by 28% (13). Other meta-analyses have provided contradictory results regarding reduction in influenza-related respiratory tract complications in healthy adults (14).

The adult dose of oseltamivir for treatment of influenza is 75 mg twice daily for 5 days. Oseltamivir is approved for treatment and prophylaxis in those 1 year of age and older. The pediatric dose of oseltamivir is 30 mg twice daily for $\geq$15 kg, 45 mg twice daily for 15 to 23 kg, 60 mg twice daily for 23 to 40 kg, and 75 mg twice daily for $>$40 kg. Treatment should begin within 2 days of onset of symptoms of influenza. The recommended oral dose of oseltamivir for prophylaxis of influenza in adults and adolescents 13 years and older after close contact with an infected individual is 75 mg once daily for at least 7 days. Therapy should begin within 2 days of exposure. Oseltamivir causes nausea and vomiting in about 10% of treated persons, although most continue taking the drug. When taken with food, the incidence of gastrointestinal side effects is reduced. Transient neuropsychiatric events including self-harm and delirium have been reported after oseltamivir use.

Zanamivir is approved for the treatment of those 7 years of age and older and the prophylaxis of those 5 years of age or older. The dose of zanamivir for treatment of influenza in adult and pediatric patients aged 7 years and older is two inhalations (one 5-mg blister

per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart) for 5 days. Prophylaxis is two inhalations once daily. Zanamivir should be used cautiously in patients with chronic respiratory disease because it can cause bronchospasm and reduction in airflow. A small percentage of patients have difficulty using the inhaler. Understanding proper use should be ensured. The intravenous formulation of zanamivir is being evaluated in clinical trials and is available for compassionate use from its manufacturer.

Treatment with the neuraminidase inhibitors is recommended for the following:

- All patients with high-risk factors (elderly, immunosuppressed, diabetics, adults, and children with other chronic diseases)
- Patients with severe influenza including lower respiratory tract infection
- Pregnant women and women up to 2 weeks postpartum
- Adults 65 years of age and older
- Residents of nursing homes and other care facilities
- Consider for other patients

Prophylaxis recommendations for the neuraminidase inhibitors are as follows:

- Give to high-risk patients who have not been vaccinated.
- Consider for immunosuppressed patients who have been vaccinated.
- Give to high-risk vaccinated patients who received vaccine in poor-match years.
- Give once daily × 6 weeks in season.
- Give × 14 days or until 7 days after onset of last case in nursing home outbreaks.

CRITICAL INTERVENTIONS

- Ensure adequate oxygenation.
- Provide for staphylococcal coverage when treating pneumonia.
- Initiate neuraminidase inhibitors for high-risk patients with influenza.

- Administer influenza vaccine from late September through December to patients at risk for influenza complication and groups capable for influenza transmission.

DISPOSITION

The majority of patients with influenza can be treated as outpatients. Close follow-up should be ensured and the patient should be given specific instructions to return immediately if symptoms progress.

There should be a low threshold for admission for elderly patients, pregnant patients, the immunocompromised, those with chronic pulmonary or cardiac disease, and young children. These patients should be admitted if there is any evidence of pneumonia, which can often progress rapidly. Admission to an intensive care unit should be considered for patients who are hypoxic or show any signs of significant respiratory difficulty.

PREVENTION AND VACCINATION

Influenza vaccines have been shown in numerous studies to be effective in preventing clinical disease (4,15) and extremely cost-effective, especially in persons older than age 65 (16). Each year, a different vaccine preparation is developed, using virus strains believed likely to appear in North America the following winter. The CDC estimated that the effectiveness of the 2012 to 2013 seasonal influenza vaccine in preventing medically attributed infections in all age groups was 56% (4), but as many as 90% of influenza cases can be prevented when there is a good match between vaccine and epidemic strains of the virus (17). Influenza vaccine has also been extremely effective in reducing morbidity and mortality (by up to 80%) in vaccinated individuals who nevertheless develop clinical disease, particularly the elderly and the immunocompromised (18). A number of studies have shown that vaccination reduces influenza-related hospitalizations and deaths in nursing home populations during epidemics (19,20). Also, vaccination clearly lowers cardiovascular mortality and all other case mortality in patients

with cardiovascular disease and other high-risk medical conditions (21). A large 2012 cohort study of community dwelling elderly individuals showed vaccination was associated with a reduction in hospitalizations and death during influenza season (15). The World Health Organization says influenza vaccination may limit the number of false alarms for SARS. Adverse effects of the vaccine itself have been minimal and should not deter its use in the high-risk patient.

Despite the overwhelming evidence supporting the benefits and efficacy of influenza vaccines, many high-risk individuals go unvaccinated. Studies have shown poor vaccination rates in both the elderly and younger persons with high-risk medical conditions such as asthma. Vaccination of health care providers has clearly been shown to decrease mortality in patients (22), but unfortunately the rate of vaccination remains unacceptably low.

Emergency physicians can play a major role in educating patients and the general public about the need for vaccinations in high-risk groups. This should occur before the peak influenza season begins. Target groups for vaccination programs are listed in Table 190.1. Of note, the Advisory Committee on Immunizing Practices of the CDC supports the vaccination of all children older than 6 months and clearly recommends vaccination of children 6 months to 4 years old (23). Vaccinations should be offered between late September and early November, depending on when regional influenza activity is expected to begin. Many EDs offer the vaccine on-site. This approach has been shown to be both needed and feasible (24), even for patients presenting with acute asthma attacks requiring prednisone treatment (25). Emergency physicians are also often in a position to recognize the outbreak of influenza in closed environments such as nursing homes.

TABLE 190.1
Influenza Vaccination Target Groups

Groups at Risk for Influenza Complications

Adults and children with chronic respiratory or cardiovascular disorders
Healthy persons 50 yrs of age or older
All children age 6 mos to 4 yrs
Immunocompromised persons
Pregnant and postpartum patients
People who are morbidly obese

Groups Capable of Influenza Transmission

Residents of nursing homes and chronic care facilities
Physicians
Nurses
Hospital personnel who have close contact with high-risk patients
Home health care or nursing home care providers

Stopping, slowing, or otherwise limiting the spread of an avian flu pandemic has recently become a major focus in the United States and globally. Present efforts are directed at poultry containment, rapid identification of human disease, and limitation of exposure to infected individuals. In addition, there has recently been a heightened focus on vaccine development, improvement in surge capacity, and stock piling of neuraminidase inhibitors, which are felt to be of potential benefit in treating avian flu.

Common Pitfalls

- Failure to recognize that the elderly, the very young, the immunosuppressed, pregnant and postpartum patients, and those with chronic cardiac or pulmonary disease are at high risk for complications from influenza or acute worsening of their baseline chronic disease
- Failure to appreciate that young children can present atypically
- Failure to appreciate the role of *S. aureus* as a pneumonia pathogen during influenza outbreaks
- Failure to start treatment in a high-risk individual because of a negative rapid influenza test
- Failure to be on the alert for nursing home patients with influenza and to notify appropriate officials about potential

outbreaks
- Failure of health care workers to be vaccinated themselves

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CHAPTER 191

Human Immunodeficiency Virus Infection and Related Disorders

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The earliest recognition of a new immunodeficiency syndrome, later identified as being caused by the human immunodeficiency virus (HIV), occurred in 1981, with cases of Kaposi sarcoma (KS) and *Pneumocystis carinii* pneumonia (PCP) occurring in previously healthy homosexual males. The complications of infection, known as the acquired immunodeficiency syndrome (AIDS), continue to cause significant morbidity and mortality both in the United States and worldwide. HIV-related therapeutics made dramatic advances in the mid-1990s, with early use of highly active antiretroviral therapy (ART) and prophylactic agents for opportunistic infections. However, the medical, social, and economic impact of this disease continues to grow.

As of 2010, the United States Centers for Disease Control and Prevention (CDC) estimated the total number of people living with HIV in the United States at 1.1 million, with 636,000 Americans having died of the disease (1). Despite widespread efforts to curtail the spread of the virus, approximately 50,000 new infections occur each year, a number that has not changed appreciably in the past 10 years (1).

EPIDEMIOLOGY

The majority of HIV and AIDS cases in the United States have occurred in men, although the proportion of women infected has risen from 8% in 1985 to 25% in 2010 (2). Minority groups are disproportionately affected. As of December 2010, African Americans and Hispanics represented 58% of males and 79% of females living with HIV. AIDS represents the fifth leading cause of death in African American men aged 25 to 44 (3).

Risk factors associated with an increased likelihood of acquiring HIV infection include men who have sex with men, people who exchange sex for money or drugs, intravenous (IV) drug use, and heterosexual exposure to a high-risk partner. Blood transfusion before 1985 and maternal-to-neonatal transmission represent a small minority of cases. The pattern of incident HIV infections is changing. Worldwide, heterosexual contact is the most common route of HIV transmission. In the United States, new infections among men who have sex with men currently represent 63% of new diagnoses. After several years of decline in the early and mid 2000s, this number has begun to increase, related mainly to infections among younger individuals. In addition, heterosexual contact continues to increase as a mode of transmission while IV drug use has been decreasing for the past decade (2). During the past several years, the greatest increase in reported AIDS cases has occurred among women and minority populations. Recently, African Americans and Hispanics represented 65% of incident cases among males and 80% of incident cases among females (2). Because many of the populations at highest risk for disease are underinsured and have limited or no access to primary care, emergency departments (EDs) are caring for increasing numbers of patients with HIV and AIDS.

PATHOPHYSIOLOGY AND TRANSMISSION

HIV is a cytopathic retrovirus that kills infected cells. In humans, HIV appears to selectively attack CD4 T-lymphocytes, a characteristic that accounts for much of the resulting immunodeficiency. The virus attaches to a host cell via specialized receptors on the cell surface. The viral genome, encoded by a single-stranded ribonucleic acid (RNA) molecule, is reverse transcribed into DNA using the enzyme

reverse transcriptase. Viral DNA is then permanently integrated into the host's genome via an integrase enzyme. Once integrated, viral DNA may lie dormant or may be actively transcribed and translated to produce protein precursors. HIV protease then cleaves these precursor molecules to produce functional enzymes that can be encapsulated into new HIV virions.

ART is directed at reducing levels of HIV RNA by interfering with the enzymes integrase (integrase inhibitors), reverse transcriptase (nucleoside and nonnucleoside reverse transcriptase inhibitors [NNRTIs]), and HIV protease (protease inhibitors [PIs]). However, the emergence of mutant drug-resistant strains, the dormancy of the virus in some cells, and the occurrence of drug toxicity limit the ability to permanently stop viral replication.

Proven mechanisms of HIV transmission include exposure to semen, vaginal secretions, blood products, transplacental (in utero), and breast milk. There have been no documented cases of transmission by casual contact, although reports of possible salivary transmission exist (4). The HIV virion is extremely labile and can be easily neutralized by 50% ethanol, 0.3% hydrogen peroxide, or a 1:10 solution of household bleach.

CLINICAL PRESENTATION, ED EVALUATION, AND MANAGEMENT

Acute HIV Infection and Disease Progression

Forty percent to 90% of patients infected with HIV will develop acute retroviral syndrome 2 to 4 weeks after exposure (5). This syndrome is characterized by a range of nonspecific, "flu-like" symptoms, but, significantly, may include mucocutaneous ulcers, generalized lymphadenopathy, hepatosplenomegaly, or a rash (usually macular or maculopapular). The differential diagnosis for acute HIV infection includes Epstein–Barr virus (EBV), cytomegalovirus (CMV), viral hepatitis, syphilis, rubella, disseminated gonococcal infection, and other viral infections. However, the presence of flu-like symptoms in combination with HIV

risk factors or the more specific signs described earlier should increase suspicion for acute HIV infection.

During this acute phase of infection, standard HIV testing (ELISA antibody testing) is usually negative, although newer fourth generation HIV testing technologies narrow the window allowing for detection of acute HIV infections by including antigen detection as part of the testing algorithm (see below). Time from exposure to HIV antibody detection can vary from 2 to 11 months. If standard ELISA HIV antibody testing is negative and there is a high suspicion for acute HIV infection, RNA viral load testing should be performed. A concurrent antibody test for HIV should be performed to establish that an infection is acute and not chronic. Identification of acute HIV infection in the ED, although relatively uncommon, is important because the risk for viral transmission is much greater during this time due to higher viral loads (6). Therefore, patients with diagnosed or suspected acute infection should be counseled to mitigate behaviors that may spread the virus (6). Furthermore, there is some evidence that initiating ART during acute HIV infection may reduce transmission risk, reduce symptoms of acute infection, and reduce disease progression (7). Consequently, a patient with confirmed acute infection should be seen urgently by an HIV specialist.

HIV results in a broad spectrum of conditions, ranging from an asymptomatic infection to severe immunocompromise. Variables that are most predictive of the stage of disease are CD4 cell counts, viral load, and history of opportunistic infections. Clinical findings that are predictive of significant immunodeficiency include thrush, oral hairy leukoplakia, dermatomal varicella, alopecia, wasting, dermatitis, and generalized lymphadenopathy. The diagnosis of AIDS is made by laboratory evidence of HIV infection and either the presence of an “indicator” condition or laboratory evidence of severe immunosuppression (CD4 <200 cells/mm^3) (7). The most recent CDC definition of AIDS published in 2008 is summarized in Table 191.1 (8).

TABLE 191.1
Case Definition of AIDS and Indicator Conditions

1) Laboratory evidence of HIV infection and presence of an AIDS-defining illness
2) Laboratory evidence of HIV infection and CD4 cell count <200/mm^3

AIDS-defining Illnesses:

- Candidiasis, esophageal or pulmonary
- Cervical cancer
- Coccidiomycosis, extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis (with diarrhea for >1 mo)
- Cytomegalovirus infection (of any organ system other than liver, spleen, or lymph nodes)
- Herpes simplex virus (mucocutaneous ulcer for >1 mo, pneumonitis or esophagitis)
- Histoplasmosis, extrapulmonary
- Isosporiasis (with diarrhea for >1 mo)
- Kaposi sarcoma
- Lymphoma, Burkitt/immunoblastic/primary CNS
- Mycobacterium avium complex or other mycobacterial infection (extrapulmonary)
- Mycobacterium tuberculosis (pulmonary or disseminated)
- *Pneumocystis jiroveci* pneumonia
- Progressive multifocal leukoencephalopathy
- Bacterial pneumonia (recurrent)
- Salmonella bacteremia (nontyphoid)
- CNS toxoplasmosis
- HIV-associated wasting syndrome

Note: The case definition of AIDS is satisfied by either 1 or 2 above. For a more comprehensive list of indicator conditions, refer to the 2008 CDC Case Definition (8).

The average incubation time from initial infection to clinical AIDS is 8 years (7). In the era of modern ART, the burden of chronic disease is increasing in HIV-infected individuals. Reports indicate that mortality in this population from non-AIDS–defining illness may be surpassing mortality from AIDS-defining conditions. Specifically, progressive immunosuppression increases the risk of dementia, cardiovascular disease, cirrhosis (due to alcohol and viral hepatitis), chronic kidney disease, and non-AIDS–defining malignancy (7). In HIV-infected patients admitted to the ICU, *Pneumocystis jiroveci* pneumonia and bacterial pneumonia continue to be significant causes of respiratory failure (9), and septic shock may be associated

with unusual organisms, such as salmonella or *Cryptococcus neoformans,* and a higher risk of adrenal insufficiency (7). Massive gastrointestinal (GI) bleeding can occur secondary to CMV colitis or complications of liver disease, and critical neurologic illness is frequently related to central nervous system (CNS) toxoplasmosis (9).

Median survival time in *untreated* AIDS patients is 3.7 years for patients with CD4 cell counts <200 cells/mm^3, and 1.3 years for patients with a first AIDS-defining illness. Immune reconstitution with ART has been shown to significantly delay progression of opportunistic infections and AIDS-related death.

Diagnosis of HIV Infection

The standard diagnostic test for HIV infection is viral antibody detection with the ELISA. HIV-positive ELISA tests are then confirmed by Western blot (WB), which directly detects viral antigens. Sensitivity and specificity of the current tests are $>99.9\%$. False-negative ELISA tests occur primarily during acute disease before seroconversion. Rates of false-negatives vary according to the prevalence of disease in the population, ranging from $<0.0001\%$ in low-prevalence populations to 0.3% in high-prevalence populations. False-positive tests are less common ($<0.004\%$) and occur among patients who have received transfusions containing HIV antibody or those with other crossreactive antigens or antibodies (e.g., antihepatitis A IgM, antihepatitis B core IgM, and antinuclear antibodies). In children younger than 6 months, a positive test may be due to transplacentally acquired maternal antibodies and does not necessarily imply presence of the disease. False-positive results are most frequent in populations with a low seroprevalence for HIV.

There are a number of rapid HIV tests that are FDA approved, which are simple and easy to use, and which can be implemented at the point of care. These tests use an ELISA-based assay for HIV testing using saliva, fingerstick, or whole blood specimens, and require (as do the traditional ELISA) WB for confirmation. Tests can be performed at the bedside with delivery of results in as little as 10 to 20 minutes. Sensitivity and specificity of these assay is high (e.g., for the saliva OraQuick Rapid HIV-1 Antibody Test [OraSure

Technologies, Inc.], sensitivity and specificity are 99%). Negative tests can be reported as negative.

A new generation of HIV assays has recently been developed. These tests, coined Fourth-Generation (or Combo) HIV assays, test for both HIV antigen and antibody simultaneously, with reflex RNA testing if discrepancies exist between antibody and antigen results. Such platforms shorten the window period for HIV detection by several weeks, permitting diagnosis of very early (acute) infections. The CDC has issued draft recommendations for use of this algorithm in clinical practice, and many hospitals and several EDs have already shown that it can lead to detection of significant numbers of acute HIV infections. Both whole blood and point-of-care versions of the assay exist and have been FDA approved. It is important to recognize that even with these Fourth-Generation assays, there is still a brief window, approximately a 2-week period, where the patient is first infected where antigen may not yet appear in the blood. Viral RNA testing can be done in such instances, but is rarely indicated in the ED.

Emergency physicians should be familiar with the quantitative plasma HIV RNA assay, as it is used routinely for HIV staging and monitoring response to therapy. Test results are reported as copies per milliliter, with survival time directly correlated to viral burden. CD4 lymphocyte count is used to evaluate immunologic status. When this test is unavailable, total lymphocyte count (TLC) count can be used to approximate CD4 count. A TLC $<1{,}000$ cells/μL is highly correlated with a CD4 count of <200 cells/μL.

HIV Testing in the ED

According to the latest 2007 CDC guidelines, HIV testing should be offered at all routine clinical encounters, including the ED. These new guidelines place particular emphasis on the ED as multiple studies have shown the ED to be the most common site within the health care setting for patients with unrecognized HIV. This is felt by many in the public health community to represent a missed opportunity for testing and linkage to care. Proponents of routine testing point to the proven benefits of earlier disease recognition

including slowing the progression of disease, decreasing rates of opportunistic infections, and reduction in the likelihood of disease transmission in the community. Additional direct patient care benefits for HIV testing in the ED are that clinicians' awareness of patients' HIV status can help narrow differential diagnosis (e.g., influenza pneumonia vs. Pneumocystis pneumonia), and improve treatment and disposition decisions.

Fever

All HIV-infected patients who present to the ED with fever need to be thoroughly evaluated. The diagnostic workup for a patient with HIV and a fever is guided by the history, physical examination, and the patient's CD4 count. A person with AIDS is more likely to be infected with atypical organisms than a person with an intact immune system. While this chapter focuses on pathogens that occur almost exclusively in immunocompromised hosts, simultaneous evaluation and treatment for more common organisms is imperative. The initial evaluation of fever in the patient with AIDS should routinely include blood cultures (aerobic, anaerobic, mycobacterial, and fungal), complete blood count, complete metabolic profile, and chest radiograph. Additional testing to consider is summarized in Table 191.2.

TABLE 191.2
Diagnostic Considerations in HIV-Infected Individuals Presenting with Fever

Infectious Symptoms	CD4 Count (cells/mm^3)	Emergency Department Diagnostic Considerations (in Addition to Those for Immunocompetent Patients)
CNS	>250	Serum: RPR or VDRL
		CSF: VDRL and FTA-ABS, culture for bacteria, PCR for HSV/JC, AFB stain, culture for mycobacteria, PCR for *M. tuberculosis*
	<200	Place PPD or obtain interferon gamma release assay
		CSF: culture for fungus, PCR for EBV/VZV, *C. immitis* complement fixation test, *H. capsulatum* Ag
		Serum: C. *immitis* complement fixation test, H. *capsulatum* Ag
		Urine: *H. capsulatum* Ag
	<100	Serum: CMV PCR, *T. gondii* IgG, *C. neoformans* Ag
		CSF: opening pressure, CMV PCR, *C. neoformans* Ag, PCR *T. gondii*, *T. gondii* IgG, India ink stain for *C. neoformans*
Pulmonary	>250	Place PPD or obtain interferon gamma release assay
		Sputum: AFB staining and culture, fungal culture, bacterial culture
		Serum: *H. capsulatum* Ag, *C. immitis* complement fixation test
		Urine: *H. capsulatum* Ag
	<200	Serum: LDH, cryptococcal Ag
		Sputum: induced sputum sent for *P. jiroveci* testing[a]
	<100	Serum: CMV PCR, *C. neoformans* Ag, assay for galactomannan
GI	>250	Serum: Blood cultures (salmonella)
	<200	Stool: assay for *Cryptosporidium parvum*[b], I. *belli*[b], Microsporidia[b]
	<100	Serum: CMV PCR, mycobacterial blood culture for MAC
Generalized	>250	Place PPD or obtain interferon gamma release assay
		Serum: RPR or VDRL
		Urine: urinalysis, bacterial culture
	<200	Serum: *H. capsulatum* Ag, *C. immitis* complement fixation test
		Urine: *H. capsulatum* Ag
	<100	Serum: *C. neoformans* Ag, CMV PCR, mycobacterial blood culture for MAC and TB

Note: For each indication, possible testing is found in the row corresponding to the patient's CD4 cell count *and* all testing for higher CD4 cell counts.

[a]*P. jiroveci* testing of induced sputum depends on the laboratory. Tests can include stains for cysts and trophozoites, such as cresyl violet, Giemsa, Wright, Gram-Weigart or stains for cyst walls, such as Gomori-Methenamine Silver, Gram-Weigart, or toluidine blue. Some laboratories also use immunofluorescent stains (7).

[b]Assays for cryptosporidiosis include acid fast stain, IFA, PCR, EIA, and should be performed only on watery stool. Acid-fast stain of the stool to look for oocysts is the diagnostic test of choice for isosporiasis. Microsporidia are detected using light microscopy with calcofluor-white, Chromotrope 2R, or Uvitex 2B to detect spores (7).

Pulmonary Infections

Pulmonary presentations are among the most frequent reasons for ED visits among patients with known HIV infection (7,10). More than 80% of AIDS patients develop pulmonary disease; *infectious pneumonia,* COPD, tuberculosis (TB), pulmonary hypertension, pulmonary fibrosis, and malignancy involving the lungs are all

increased in patients with HIV (7). The differential diagnosis of infectious pneumonia includes viral, bacterial, mycobacterial, and fungal pneumonias. The more common etiologies are shown in Table 191.3. Although differentiation of these entities in the ED may be difficult, appreciation of the epidemiology and the common findings associated with various pathogens can assist the emergency physician in arriving at a working diagnosis and instituting appropriate treatment and disposition decisions.

TABLE 191.3
Common Causes of Pulmonary Involvement in AIDS

Infection	
Viral	**Protozoa**
Cytomegalovirus	*Pneumocystis carinii*
Herpes simplex virus	*Toxoplasma gondii*
Adenovirus	**Bacteria**
Mycobacteria	*Streptococcus pneumonia*
Mycobacterium tuberculosis	*Haemophilus influenza*
Mycobacterium avium	*Mycoplasma pneumonia*
Mycobacterium kansasii	*Legionella pneumonia*
Fungi	*Staphylococcus aureus*
Histoplasma capsulatum	*Pseudomonas aeruginosa*
Cryptococcus neoformans	*Nocardia*
Coccidioides	*Malignancy*
Candida	**Lymphoma**
Aspergillus fumigatus	*Kaposi sarcoma*
Blastomyces dermatitidis	*Pneumonitis*
	Lymphoid interstitial pneumonitis

The physical examination itself is not likely to aid in establishing a specific diagnosis, but CD4 counts are useful for generating a differential. Patients with CD4 counts >500 cells/mm^3 are most commonly infected with encapsulated bacteria or TB; for those with lower CD4 counts, PCP, fungi, atypical mycobacteria, KS, CMV, and lymphoma are seen with increasing frequency. Patients with fever and productive cough are likely to have a bacterial pneumonia, whereas a nonproductive cough is more likely to accompany PCP,

CMV pneumonia, fungal infection, or neoplasm. Patients with PCP pneumonia often admit to several weeks of symptoms prior to presentation (7). Hemoptysis is most often associated with pneumococcal pneumonia and TB. Fulminant respiratory failure is most likely to be caused by PCP, CMV, or a bacterial etiology.

Evaluation of HIV-infected patients who present with pulmonary complaints should generally include pulse oximetry, chest radiograph, complete blood cell count, arterial blood gas analysis (in the setting of hypoxemia on pulse oximetry), urine Legionella and pneumococcal antigens, sputum culture, and Gram stain. Please refer to Table 191.2 for additional diagnostic considerations. Blood cultures should be obtained in all patients being hospitalized due to the increased risk of bacteremia associated with HIV infection.

KEY TESTING

Pulmonary

- Pulse oximetry
- CXR
- CBC
- ABG if hypoxemia on pulse oximetry
- Blood cultures for hospitalized patients

Radiographic patterns are suggestive of certain disorders but are usually not diagnostic. A focal infiltrate often suggests bacterial pneumonia, whereas a diffuse interstitial or perihilar reticular or ground glass appearance is associated with PCP or CMV. Cysts, blebs, nodules, and pneumothoraces are common with PCP (usually with CD4 <100 cells/mm^3), but negative CXRs have been reported in up to 20% of patients (7) as well. A pneumothorax in an AIDS patient should be presumed to be PCP until proven otherwise. Pleural effusions are commonly seen in AIDS patients. Most effusions are due to bacterial infections, but they can also be seen with PCP, fungal, and parasitic infections. Hilar adenopathy with diffuse pulmonary infiltrates can suggest cryptococcosis, histoplasmosis, mycobacterial infection, or neoplasm. KS can present with cough, fever, and dyspnea and may mimic PCP on chest radiograph, or may present

with effusions. In contrast to KS, lymphoma can present with well-defined large and peripheral nodules. Computed tomography (CT) scan is highly sensitive for a variety of entities (7), and bronchoscopy should also be considered.

Bacterial Agents

In HIV-infected patients, the most common bacterial pulmonary infections are with *Streptococcus pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa,* and *Staphylococus aureus.* Infections with *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and Legionella are relatively less common. Pneumococcal vaccination is an indicated prophylactic intervention for all HIV patients because the risk of pneumococcal bacteremia increases 150- to 300-fold in the setting of HIV infection (7). *P. aeruginosa* is more commonly seen in the setting of AIDS. Treatment of pneumonia should follow standard recommendations (11). Uncomplicated patients can be treated with a macrolide or doxycycline alone, while significant immunocompromise or a plan to hospitalize indicates treatment with a β-lactam or ertapenem plus a macrolide. Patients requiring ICU admission should receive therapy with antipseudomonal activity and potentially be treated with vancomycin or linezolid as well. If PCP is a possibility, trimethoprim/sulfamethoxazole (TMP/SMX) should be *added* to conventional therapy, as described below. In patients with risk factors for TB, treatment with fluoroquinolones should be avoided because it may lead to inadvertent partial treatment of a TB infection and consequent delays in appropriate therapy (11).

Fungal Pneumonias

P. jiroveci (PCP) is one of the most common opportunistic infections and a leading cause of mortality in AIDS. PCP infections typically occur in adults with CD4 counts <200 cells/mm^3. The typical complaint is an insidious, nonproductive cough, dyspnea with exertion, unexplained fever, chest pain, and fatigue developing over days to weeks. Chest CT has a much higher sensitivity for detecting PCP than CXR and will typically show a ground glass appearance;

however, a negative CT does not rule out the disease (7). Arterial blood gas analysis for an increased alveolar–arterial (A–a) oxygen gradient is indicated if there is a suspicion for hypoxemia. LDH is elevated in 90% of PCP pneumonia patients. However, the specificity of LDH is relatively low (4) and it should not be used for diagnosis.

In the ED, a presumptive diagnosis of PCP is made if there is unexplained hypoxia. PCP cannot be grown in the laboratory, and diagnosis is made by indirect immunofluorescent staining using monoclonal antibodies, or a variety of stains. Expectorated sputum is not helpful, but induced sputum has a sensitivity of 56%. Bronchoscopy with bronchoalveolar lavage (BAL), brush biopsy, or transbronchial biopsy is often required, as it has a sensitivity of 95%.

When PCP is suspected in the ED, treatment should be initiated without waiting to obtain a definitive diagnosis. Patients able to take PO therapy can be given two Bactrim DS every 8 hours. IV therapy is TMP/SMX 20/100 mg/kg/d in three divided doses. The duration of TMP/SMX should be 21 days. Systemic corticosteroid treatment, administered as prednisone 40 mg PO bid or methylprednisolone 30 mg IV bid, results in a 50% reduction in mortality for patients with a PaO_2 <70 mm Hg or an A–a oxygen gradient of >35 mm Hg (12). Prednisone should be tapered over 3 weeks. All patients requiring steroids should be admitted to the hospital. Patients being discharged who may have PCP pneumonia require reliable follow-up, as mortality for untreated PCP is 100%. Prophylactic therapy for PCP is recommended with one Bactrim DS PO daily to prevent reinfection and in all patients with CD4 cell counts <200 cells/mm^3.

The mortality for PCP in the setting of respiratory failure is close to 60%. Patients requiring ventilatory support should be maintained on low tidal volumes and plateau pressures with a high index of suspicion for developing pneumothorax. Asymptomatic patients with a small pneumothorax ($<20\%$) may be safely treated with observation or insertion of a Heimlich valve (13).

Histoplasma capsulatum is a fungal infection that can cause respiratory disease in immunocompetent patients and disseminated disease in patients with a CD4 <150 cells/mm^3. It is endemic to the central and southeastern United States, and clinical disease occurs in

5% to 27% of at-risk AIDS patients. The organism grows in soil and is found in bat and bird droppings. Infection with *H. capsulatum* can also affect the bone marrow, GI tract, and CNS and can present with symptoms of malaise, fever, weight loss, meningitis, diarrhea, or cough. It can be detected by culture and by staining of affected tissue or peripheral blood; however, antigen detection in urine, blood, or BAL fluid is also useful. In disseminated disease, urine and serum antigen have sensitivities of 95% and 85% respectively (7). Treatment is liposomal amphotericin B 4 mg/kg IV qd in severe disease or itraconazole 200 mg PO tid for 3 days followed by bid treatment for 1 year in less severe disease (7).

Blastomyces dermatitidis is endemic to the South Central and Midwestern United States. Clinical infection is rare but has a high mortality rate in AIDS patients. Most patients present with fevers, weight loss, and cough and have an abnormal CXR. Diagnosis is by staining and culture of sputum, tissue biopsy, BAL, or CSF culture. Treatment is with amphotericin B.

Aspergillus infection can present as either pulmonary or disseminated disease in AIDS patients. The pulmonary form is characterized by cough, fever, hemoptysis, and dyspnea. A cavitary upper lobe lesion or alveolar or bilateral infiltrates may be seen on chest radiography. It may also cause tracheobronchitis with stridor and wheezing. The disseminated form can present with osteomyelitis, meningoencephalitis, sinusitis, or skin and soft tissue infection. Diagnosis is by tissue biopsy, BAL stain, or culture. Voriconazole is the preferred treatment, but due to interaction with NNRTIs and PIs, amphotericin B 4 mg/kg/d IV is an acceptable alternative (7).

C. neoformans, a ubiquitous fungal pathogen, can cause pulmonary disease in AIDS patients resulting in cough, dyspnea, pleuritic chest pain, fever, and malaise potentially progressing to acute respiratory distress syndrome. Radiograph findings are nonspecific and include consolidation and reticulonodular infiltrates. Serum cryptococcal antigen is the diagnostic test of choice. Treatment is discussed later in this chapter.

Coccidioides immitis is endemic in the southwestern United States. It causes pneumonia in immunocompetent patients, but dissemination occurs in those with a CD4 count $<250/mm^3$ and can include skin, CNS, and GI manifestations. CXR findings are usually abnormal but nonspecific. Diagnosis is made by culture, serology, or histopathology. Fluconazole 400 mg PO qd is used for focal pneumonia, and amphotericin B 5 mg/kg/d IV is used for diffuse pneumonia and nonmeningeal disseminated disease. Fluconazole 1000 mg IV qd is used for meningitis (7).

Tuberculosis

Mycobacterium tuberculosis is one of the leading causes of death in AIDS patients worldwide. The incidence of TB in the AIDS population is estimated to be 50 to 200 times that of the general population (14) due to increased reactivation of latent infections, high attack rates, and rapid progression to clinically significant disease. Pulmonary TB is usually the initial finding in HIV-infected patients with CD4 counts of 200 to 500 cells/mm^3.

Classic presenting symptoms of TB include cough (with hemoptysis), fever, night sweats, and weight loss. However, in patients with advanced immunosuppression clinical manifestations are atypical, and extrapulmonary findings are more common. Frequent sites and manifestations of disseminated disease include peripheral lymph nodes, pleuritis, pericarditis, meningitis, bone marrow, and the GI and genitourinary systems. Classic radiographic findings in immunocompetent individuals include upper lobe lesions with cavitation, pleural effusions, mediastinal adenopathy and alveolar opacities. In patients with CD4 counts <50 cells/mm^3, atypical radiographic features are seen with increased frequency.

ED physicians should maintain a high index of suspicion for TB among HIV-infected patients with pulmonary symptoms. All patients in whom TB is being considered need to be admitted to the hospital in respiratory isolation until the disease is ruled out. The diagnosis of TB by AFB staining and culture of the sputum is difficult as the sensitivity of the AFB smear is only about 50% and not improved with induced sputum or bronchoscopy. Nucleic acid amplification is

more sensitive than an AFB smear and can be done if there is a positive AFB smear or a negative smear and a high clinical suspicion. In miliary TB, blood cultures are positive about 50% to 60% of the time, whereas the sputum culture is positive in only 25% of cases. About one-fourth of HIV-infected patients with active TB will have a false-negative result with PPD testing and interferon gamma release assays (7).

HIV patients with TB should receive four-drug initial therapy with isoniazid, rifampin, pyrazinamide, and ethambutol (11). All HIV-infected patients with a positive PPD (> 5 mm of induration) or interferon gamma release assay or chest x-ray consistent with TB (regardless of screening test results) should be asked about a history of treatment. If they have not been adequately treated, they should receive prophylaxis (chest x-ray abnormalities require exclusion of active TB) with isoniazid 300 mg plus pyridoxine 50 mg PO qd for 9 months (11).

Neurologic Involvement

CNS disease occurs in about 90% of patients with AIDS. A wide variety of neurologic symptoms are seen in patients with HIV, including altered mental status, coma, seizures, headache, and focal neurologic symptoms. Common infectious complications in patients with access to effective ART include progressive multifocal leukoencephalopathy (PML), cerebral toxoplasmosis, and cryptococcal meningitis. CMV ventriculoencephalitis and primary CNS lymphoma are less common. Occasionally, neurosyphilis and tuberculous meningitis are seen as well. Noninfectious complications can include HIV-associated neurocognitive deficits, peripheral neuropathies, metabolic encephalopathy, lymphoma (primary and secondary), and KS. In addition, secondary complications of neurologic disease can cause a presentation with embolic or ischemic stroke, subarachnoid hemorrhage, obstructive hydrocephalus, and Immune reconstitution inflammatory syndrome (IRIS).

Evaluation of HIV-positive patients with altered mental status or headache should proceed as in the non-HIV–infected population. Signs of impending herniation should prompt emergent treatment,

neuroimaging, and neurosurgical consultation. Otherwise, neuroimaging and lumbar puncture (LP) should be obtained in cases of altered mental status or headache in which another cause is not clearly identified or with a clear other indication for workup (i.e., worst headache of life, focal neurologic deficit) (15). For patients with CD4 cell counts <200 cells/mm^3 and/or focal deficits or new seizures, neuroimaging should always proceed LP (16). For patients with CD4 cell counts >200 cells/mm^3 who present with fever and meningismus (in the absence of focal neurologic deficits), immediate LP may be performed. A proposed algorithm for the diagnosis and empiric treatment of HIV patients with suspected CNS disease is presented in Figure 191.1 (17).

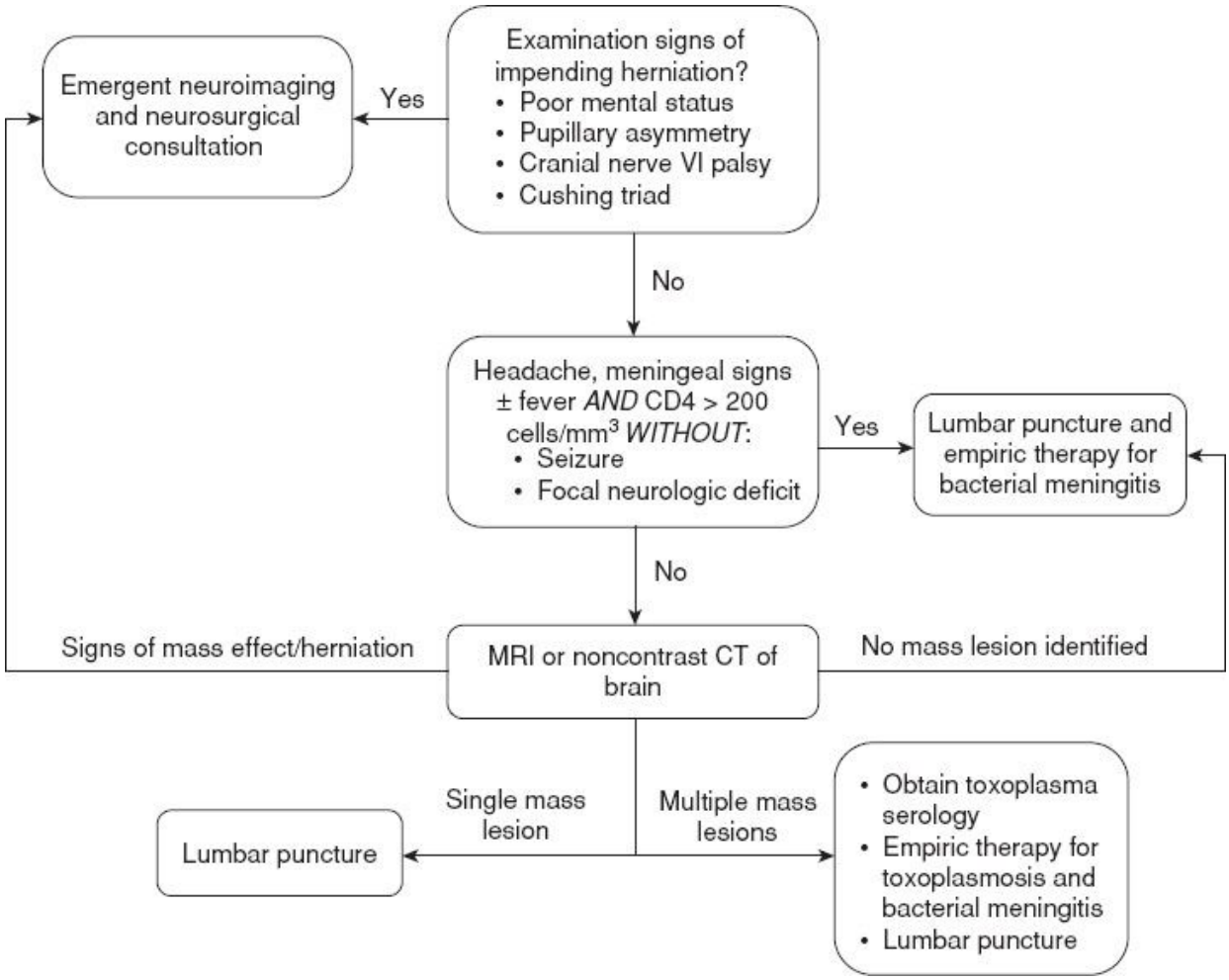

FIGURE 191.1 Algorithm for initial work-up and empiric treatment for patients with HIV and altered mental status. Note that lumbar

puncture should not be performed if there is evidence of mass effect on imaging. (Adapted from Tan IL, Smith BR, von Geldern G, et al. HIV-associated opportunistic infections of the CNS. *Lancet Neurol.* 2012;11:605–617.)

KEY TESTING

Neurologic

- Neuroimaging (CT or MRI)
- LP

Specific CSF studies should include measurement of opening pressure, cell count, glucose, protein, Gram stain, bacterial, fungal, and mycobacterial cultures. Additional testing to consider is detailed in Table 191.2; however, asking the laboratory to retain excess CSF is always prudent. Additional diagnostic considerations include serum *Toxoplasma gondii* IgG levels, chest imaging, and interferon gamma release assay looking for evidence of TB (17).

If the entire ED workup is unrevealing and the patient has significant signs or symptoms, more advanced diagnostic evaluation should be pursued immediately, preferably in the inpatient setting. In addition, all patients with new or changing CNS lesions should be considered for hospital admission.

T. gondii is the most common cause of focal intracranial mass lesions in patients with HIV infection (2% to 4%). Affected patients have CD4 counts of <100 cell/mm^3 and present with fever, headache, and confusion evolving over 1 to 2 weeks. Seizures can occur, and 80% will have focal neurologic deficits. Serum antibiodies to *T. gondii* are highly sensitive for CNS toxoplasmosis in the setting of focal lesions of the brain parenchyma (17). In this way, presumptive diagnosis can be made by the presence of multiple subcortical lesions that show ring enhancement on CT or magnetic resonance imaging (MRI). However, radiographic and clinical features are similar to a wide variety of other CNS disorders (lymphoma, cerebral TB, cryptococcosis, bacterial abscess, and rarely, PML), and definitive diagnosis may require biopsy. Patients

with suspected toxoplasmosis should be admitted and treated empirically with pyrimethamine 200 mg PO × 1, then 50 mg (<60 kg) to 75 mg (>60 kg) PO daily plus sulfadiazine 1,000 mg (<60 kg) to 1,500 mg (>60 kg) PO q6h plus leucovorin 25 mg PO qd (7). Dexamethasone, 4 mg IV, may be used in cases with mass effect causing clinical deterioration. Seizure prophylaxis is not recommended. Bactrim is indicated for chronic suppressive therapy after initial treatment and for prophylaxis for those with a positive serology and a CD4 cell count <100 cells/mm^3.

C. neoformans is a fungus that occurs in up to 10% of AIDS patients, usually with CD4 cell count <100 cells/mm^3. CNS involvement presents with subacute onset of headache, fever, and malaise. Characteristically, meningismus may be absent, and focal neurologic deficits are less common. CSF cryptococcal antigen tests are nearly 100% sensitive and specific, while India ink staining is 60% to 80% sensitive. *C. neoformans* can also cause disseminated disease, and all patients with a positive serum cryptococcal antigen test should undergo an LP regardless of neurologic symptoms (7). Communicating hydrocephalus is responsible for 90% of deaths associated with CNS cryptococcosis. In patients with symptoms suggestive of elevated ICP or opening pressure >25 cm H_2O, CSF should be drained until the pressure falls by 50% or to <20 cm H_2O (17). Cryptococcosis is treated with amphotericin B 0.7 mg/kg/d IV plus flucytosine 25 mg/kg PO qid for 2 weeks and then fluconazole for 8 weeks (7). Suppressive therapy is often continued after successful treatment.

JC virus is present and asymptomatic in most healthy people. In patients with HIV who are immunocompromised, JC virus infection of the brain parenchyma results in PML. Although most cases occur with CD4 cell count <100 cells/mm^3, it may occur at higher CD4 counts. PML commonly presents with multifocal neurologic deficits resulting from demyelinating white matter lesions, and it usually develops over a period of weeks to months. Patients are typically afebrile and do not necessarily complain of pain. Acute presentation causing seizures or mimicking stroke is occasionally seen. CT or MRI shows lesions of subcortical white matter, and the diagnosis is

generally made with PCR (80% sensitivity, 90% to 99% specificity) or brain biopsy. Mean survival is 6 to 9 months, which can be prolonged only through effective immune reconstitution with ART.

CMV occurs in patients with CD4 <50 cells/mm^3 and can cause ventriculoencephalitis, ascending polyradiculomyelopathy, and retinitis. CMV encephalitis will present with headache, fever, and delirium. Ataxia, cranial neuropathy, and nystagmus can be prominent features. PCR or culture of CSF or blood can be used for diagnosis. Patients will frequently have concurrent retinitis, and an ophthalmology evaluation to consider intravitreal ganciclovir is indicated for patients with CMV encephalitis. Treatment for CMV encephalitis is ganciclovir 5 mg/kg IV bid plus foscarnet 90 mg/kg IV bid (7).

CNS lymphoma is usually seen in patients with CD4 <50 cells/mm^3. Patients complain of headache, focal neurologic deficits, or neuropsychiatric symptoms, and lack of fever is characteristic. Seizures frequently occur, and patients can present with symptoms of increased ICP. Imaging more commonly shows a single periventricular or periependymal lesion, and CSF PCR for EBV is 50% to 80% sensitive and >90% specific. Nonetheless, patients are often treated empirically for toxoplasmosis, and definitive diagnosis may require biopsy. The prognosis is poor with median survival of <1 month. Whole-brain irradiation, steroids, and chemotherapy may extend life expectancy to several months.

Treponema pallidum causes neurosyphilis and should be considered in the differential of any HIV-positive patient with meningeal signs, dementia, memory loss, iritis, uveitis, optic neuritis, or new focal neurologic findings. CSF usually shows a mononuclear pleocytosis (>10 WBC/mL). FTA-ABS testing of the CSF is sensitive for neurosyphilis, and can be used as a screen for neurologic involvement (7). VDRL and RPR in the CSF are specific but not sensitive, thus both CSF-VDRL and FTA-ABS should be performed. Patients with neurosyphilis should be treated with aqueous penicillin G 4 million IU IV q4h for 14 days.

HIV-associated neurocognitive deficits are a spectrum of cognitive abnormalities present to some extent in 50% of HIV-positive patients.

Abnormalities can include memory impairment, apathy, cognitive slowing, difficulties with attention and concentration, depression, social withdrawal, incoordination, and ataxia. Physical findings include clonus, frontal release signs, hyperactive deep-tendon reflexes, and (often) hallmarks of advanced AIDS. It is important to recognize that AIDS dementia is a diagnosis of exclusion and is usually confirmed on the basis of neuropsychological testing after brain MRI and LP. The appearance of new signs or symptoms should prompt a workup for treatable CNS processes. HIV-associated neurocognitive decline is slowed by ART.

Peripheral Nervous System

HIV is associated with increased risk for a variety of *inflammatory demyelinating polyneuropathies*. Early in HIV infection, acute demyelinating neuropathies are seen (acute inflammatory demyelinating polyneuropathy [AIDP], Guillain–Barré syndrome); later on, chronic relapsing motor weaknesses are more common (chronic inflammatory demyelinating polyneuropathy [CIDP]). Presentation is typically an ascending paralysis with mild sensory complaints. CSF studies reveal elevated protein levels and a mononuclear pleocytosis. AIDP is treated with plasmapheresis and IVIG, whereas CIDP is treated with prednisone, plasmapheresis, or IVIG.

HIV-associated neuromuscular weakness syndrome is thought to be caused by a reaction to nucleoside analog reverse transcriptase inhibitors (NRTIs). Typical presentation includes acute or subacute new-onset limb weakness, areflexia, ascending paresis, and possible sensory involvement in association with an elevated CPK and lactate. Other conditions such as Guillain–Barré, myasthenia gravis, hypokalemia, stroke, or myelopathy should be ruled out. Stopping the offending medication is usually effective.

Other diseases that can cause peripheral neuropathies include antiretroviral toxic neuropathy, distal sensory neuropathy, tarsal tunnel syndrome, polyradiculitis, vacuolar myelopathy, diabetes, B_{12} deficiency, neurotoxic drugs, alcoholism, and mononeuritis.

Symptoms can be treated with pain-modifying agents such as gabapentin, tricyclic antidepressants, or phenytoin. Ibuprofen is also a reasonable first-line agent with referral to an HIV specialist or neurologist for nerve conduction testing and possible biopsy.

Gastrointestinal Involvement

AIDS-related complications can involve the entire length of the GI tract. Causes of abdominal pain in HIV patients can include intestinal perforation (from CMV, KS, or lymphoma), obstruction or intussusception (from lymphoma or infection), peritonitis and ascites (from histoplasmosis, TB, mycobacterium avium complex (MAC), toxoplasmosis, cryptococcus, or lymphoma), gastritis, and biliary disease. Treatment in the ED should focus on ruling out life threats, supportive care, and obtaining appropriate studies for further investigation.

KEY TESTING

Gastrointesintal

- CBC
- Electrolytes/BUN/creatinine
- Liver function tests
- Stool culture and parasites for diarrhea

Oropharynx

Oral candidiasis is the most common oral manifestation of HIV infection and affects more than 80% of AIDS patients. *Candida albicans* typically involves the tongue and buccal mucosa. It can be distinguished from hairy leukoplakia by its characteristic whitish, lacy plaques, which are easily scraped away from an erythematous base. Microscopic examination of the material by potassium hydroxide smear can confirm the diagnosis in the ED. Fluconazole 100 mg po qd × 14 days is one of the most effective treatments, and posaconazole is used for refractory cases. For all candidal infections in HIV patients, immune reconstitution is an important part of treatment.

Hairy leukoplakia, thought to be caused by the EBV, results in a benign epithelial thickening and typically involves the lateral borders of the tongue causing it to have hair-like projections. In contradistinction to candidal plaques, hairy leukoplakia cannot be easily scraped off. Painful oral and perioral ulcerations may be caused by *herpes simplex virus* (HSV) and can be diagnosed in the ED by the identification of multinucleated giant cells in scrapings of the lesions. Oral HSV should be treated with acyclovir 400 mg PO TID for 10 days. *Aphthous ulcers* are small crateriform ulcers with white to yellow membranes surrounded by an erythematous ulcer. The etiology of aphthous ulcers is unclear. ED treatment of oral ulcers can include lidocaine solution or topical steroids mixed with a topic anesthetic such as Orabase. Patients with oral lesions should be referred to their HIV specialist for potential biopsy, as they are at higher risk for oropharyngeal squamous cell carcinoma and oral involvement with KS.

Esophagus

Esophagitis can present with odynophagia, dysphagia, or chest pain. A CD4 count >200 cells/mm^3 suggests non-HIV–related causes of esophagitis. In patients with CD4 <200 cells/mm^3, candida is responsible for esophagitis in 50% to 70% of cases. Other common causes are HSV, CMV, and aphthous ulcers. The most cost-effective approach to managing patients with esophageal complaints is to initiate empiric therapy for presumptive candidiasis with fluconazole 400 mg PO daily for 3 weeks, which is often curative (11). Refractory cases will then require endoscopy, biopsy, and cultures. Consider admission and empiric IV antifungal agents for those who are refractory or have poor tolerance of liquids and oral medications.

Liver and Biliary Tract

Hepatobiliary complaints can be caused by a wide range of conditions. Hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfection in HIV patients is a complex topic. In addition to traditional concerns with hepatitis viruses, emergency physicians

may encounter acute liver disease from hepatitis B flares related to changes in ART. Hepatic steatosis is also prevalent in HIV patients due to coinfection with HCV, antiretroviral therapies, or more traditional risk factors. Opportunistic organisms associated with hepatitis include CMV, MAC, *M. tuberculosis,* and *H. capsulatum.* In addition, AIDS patients can get cholangiopathy that is commonly caused by cryptosporidium. Patients typically present with right upper quadrant pain with elevated liver enzymes, alkaline phosphatase, and total bilirubin. The initial diagnostic test should be a right upper quadrant ultrasound, and ERCP is often necessary for diagnosis of cholangiopathy. In addition, alcoholism, drug-related liver injury or hypersensitivity (see "ART"), and liver involvement with IRIS are other causes of hepatitis in HIV patients.

Anorectal Disease

Proctitis is characterized by painful defecation, rectal discharge, and tenesmus and can be caused by *Neisseria gonorrhoeae, Chlamydia trachomatis,* syphilis, lymphogranuloma venereum, and HSV. Proctocolitis presents with the same symptoms as proctitis but is accompanied by diarrhea. Typical causative organisms include those just listed plus bacterial agents such as *Shigella, Salmonella, Campylobacter,* and *Entamoeba histolytica.* Diagnostic evaluation in the ED should include anoscopy with evaluation of stool for blood, leukocytes, ova and parasites, bacterial cultures, *N. gonorrhoeae,* and *C. trachomatis;* HSV culture or Tzanck prep; and RPR.

Diarrhea

Diarrhea is a problem in 50% to 90% of AIDS patients, may be chronic or acute, and may vary in severity from multiple loose stools per day to massive fluid loss with prostration, fever, chills, and weight loss. ED evaluation should be directed toward stabilization, hydration, and obtaining appropriate diagnostic studies. Table 191.2 presents diagnostic considerations based on CD4 cell count. In one large study, the most common bacterial causes of acute diarrhea were *Clostridium difficile* followed by Shigella, *Campylobacter jejuni,*

Salmonella, *S. aureus,* and MAC (18). For HIV patients who present with acute diarrhea, the ED physician should consider ordering blood cultures due to the much higher concern for bacteremia (particularly with Salmonella). Most patients with a CD4 cell count >200 cells/mm^3 will improve with conservative therapy, and therefore these patients can be managed similar to non-HIV–infected patients with acute diarrhea. As the CD4 cell count drops below 200 cells/mm^3, Cryptosporidia, Microsporidia, Isospora, and bacteria cause more persistent infection and may require diagnosis and treatment. In patients with CD4 cell count <50 cells/mm^3 CMV may cause colitis, and disseminated MAC may cause severe disease—stool examination for CMV and mycobacteria is not necessary and can be misleading. For those with severe symptoms, CT scanning should be considered to look for pseudomembranous colitis, CMV colitis, lymphoma, and mechanical complications. Noninfectious causes to consider include irritable bowel syndrome, medication side effects (particularly nelfinavir and ritonavir), dietary change, lactic acidosis, and inflammatory bowel disease. Even after workup, about 25% to 40% of HIV patients with acute diarrhea will not have an identifiable cause.

The differential diagnosis of chronic diarrhea in an HIV-infected patient includes antiretroviral medication-associated diarrhea, HIV enteropathy, HIV-associated autonomic neuropathy, chronic pancreatitis-associated malabsorption, chronic infections with organisms mentioned earlier in this section, and malignancies such as KS and lymphoma. *E. histolytica, Giardia lamblia, Isospora belli,* Microsporidia, and MAC are more commonly seen in AIDS patients with chronic diarrhea. ED testing is the same as for acute diarrhea. Ultimately, endoscopy may be necessary to diagnose CMV colitis, mycobacterial or parasitic enteritis, or malignancy-associated diarrhea. 25% of AIDS patients with chronic diarrhea will have no pathogen detected after extensive evaluation.

Table 191.4 presents treatment options for diarrhea in HIV-positive patients. Potential indications for admission of the HIV-infected patient with diarrhea include concern for salmonella bacteremia, CD4 count <200 cells/mm^3, severe symptoms with

dehydration/electrolyte imbalance and acidosis, and chronic diarrhea with advanced malnutrition. In general, patients who can tolerate oral intake and are hemodynamically stable can be discharged from the ED with outpatient follow-up. Patients with nonbloody diarrhea without systemic symptoms can be treated with antimotility agents (loperamide, diphenoxylate, tincture of opium, octreotide, etc.) if needed. If bacterial infection is strongly suspected, the patient can be treated with ciprofloxacin 500 mg PO bid × 5 days, and metronidazole 750 mg PO tid can be given for 7 days if parasitic infection is suspected. As with most HIV-related conditions, immune reconstitution is necessary to control persistent diarrhea.

TABLE 191.4
Selected Pathogens that Cause Diarrhea in HIV-Positive Patients

Pathogen	Clinical Features	Treatment	Comment
C. difficile	Watery diarrhea Fecal leukocytes Recent antibiotic use	Flagyl 500 mg PO TID for 10–14 d	Imodium and lomotil are contraindicated
CMV colitis	Fever Abdominal pain, diarrhea Weight loss CD4 count <50 cells/mm^3	Antivirals: valganciclovir, ganciclovir, or foscarnet	Diagnosis via endoscopy and biopsy Major complications: perforation and hemorrhage
Cryptosporidium parvum	Fever Nausea Vomiting Abdominal Cramps	*ART for immune reconstitution* (only reliably effective therapy) Nitazoxanide 1 g po bid × 60 d	Diagnosis via acid-fast staining of stool specimens, monoclonal antibody, or ELISA
Entamoeba histolytica	Dysentery Liver abscesses	Flagyl 500 mg PO TID for 7–10 d	Parasite transmitted via the fecal–oral route Diagnosis via ova and parasite (O & P) examination of the stool
Isospora belli	Watery nonbloody diarrhea Abdominal pain Fever Vomiting Weight loss	Immune reconstitution with ART TMP-SMX DS 1 tab Q12 for 10 days	Parasite transmitted via the fecal–oral route Diagnosis via ova and parasite (O & P) examination of the stool
Mycobacterium avium complex (MAC)	Diarrhea Fever Night sweats Cough Weight loss	Clarithromycin 500 mg q12h plus ethambutol 15 mg/kg/d PO Prophylaxis when CD4 <50 cells/mm^3: Azithromycin 1,200 mg PO weekly	Disseminated disease occurs with CD4 counts <100/mm^3 ELISA, ART

Malignancies

HIV patients with low CD4 counts are at increased risk for several malignancies including KS, non-Hodgkin lymphoma, lung cancer, lymphoblastic lymphoma, CNS lymphoma, and cervical and anal cancer associated with human papillomavirus (HPV). Patients with suspected anal cancer should be referred for biopsy.

Most HIV-associated lymphomas are B-cell lymphomas, and their incidence increases with lower CD4 cell levels. Non-Hodgkin lymphoma is caused by EBV and is seen most frequently in those with CD4 count <100 cells/mm^3. Patients with lymphoma usually present to the ED with fevers and lymphadenopathy and, depending on the state of disease, a variety of other findings including liver dysfunction, abnormal blood cells, and pulmonary, GI, or CNS complaints. CT scan and biopsy will often suggest the diagnosis.

Dermatologic Involvement

Cutaneous manifestations of AIDS likely to be seen in the ED include neoplasms, drug rashes, dermatitis, HSV, herpes zoster, and molluscum contagiosum. In addition, HIV patients are at an increased risk of bacterial skin infections and bacteremia.

KS is one of the most common HIV-associated malignancies. It occurs mostly in men who have sex with men and is caused by human herpes virus-8 (HHV-8). Lesions are typically firm, purple to black in color, and can be macules, patches, nodules, or papules. Frequent locations are the trunk, face, legs, oral cavity, or genitalia. Complications include lymphedema and visceral involvement. Patients with suspected KS need prompt referral for biopsy. The disease is not curable, and treatment goals are palliative.

HSV is common in AIDS patients and can present as either a localized infection or systemic disease. Localized infections respond well to standard therapy with oral valacyclovir 1 gm PO bid for 14 days. IV therapy with acyclovir 5 mg/kg q8h is required in cases of severe or disseminated infection. Suppressive therapy with valacyclovir 500 mg PO bid is effective in decreasing rates of recurrence (7).

Reactivation of varicella zoster virus is 17 times more likely in patients with HIV than the general population. The clinical course is prolonged, and multidermatomal involvement is common. Outpatient treatment is acceptable for those with single dermatomal involvement who are not significantly immunosuppressed. Regimens include valacyclovir 1 gm PO tid for 10 days in single dermatomal cases and acyclovir 15 mg/kg IV q8h with severe visceral or

cutaneous disease. Admission to an isolation bed is indicated for those with severe multidermatomal zoster, disseminated disease, or ophthalmic zoster (19).

S. aureus, increasingly MRSA, is the most common cause of skin and soft tissue infection in those with HIV. Cutaneous abscesses should be lanced and drained in the ED. Owing to the high risk of bacteremia in HIV-positive patients with skin and soft tissue infections, clinicians should consider lowering their threshold for brief observation or admission for IV antibiotics, particularly in those with low CD4 cell counts, severe cellulitis, and/or fever.

Bacillary angiomatosis is a vascular skin infection most commonly caused by the gram-negative rods *Bartonella henselae* (associated with cats and fleas) and *Bartonella quintana* (associated with the human body louse) in those with CD4 counts <50 cells/mm^3. Lesions range from few to hundreds and are usually red to purple and papular, pedunculated, nodular, or verrucous. Differential includes KS, hemangioma, pyogenic granuloma, dermatofibroma, and cherry angioma. Referral for biopsy is critical, as the infection can disseminate to nearly any organ system. Diagnosis can be made by serology, PCR, or silver staining of tissue specimens. First-line therapy is erythromycin, and relapses are common.

Disseminated C. *neoformans* disease can present with dermal involvement manifesting as nodular, follicular, papular, or ulcerative skin lesions that may resemble molluscum contagiosum. If suspicion for cryptococcus exists, a serum cryptococcus antigen test should be performed, and an LP should be obtained following any positive serum test. Referral for biopsy and culture of the rash is also indicated. Treatment for cutaneous cryptococcus (with a negative LP) is fluconazole, 400 mg/d for 8 weeks, then 200 mg/d.

Other cutaneous manifestations seen frequently in HIV patients include drug eruptions, scabies, papular pruritic eruption (darkened papules on extremities), prurigo nodularis (symmetric lesions on arms and trunk involving lichenification and treated with antipruritic agents and steroids), *N. gonorrhea,* and syphilis.

Ophthalmologic Manifestations

Although a wide range of ophthalmic diseases can occur in patients with AIDS, recognition of two processes is critical for the emergency physician.

CMV retinitis is the most serious ocular opportunistic infection and the leading cause of blindness in patients with AIDS. With advances in ART, the prevalence of CMV retinitis is declining, but patients who discontinue ART may experience symptoms (20). Presenting complaints are variable and may include blurred vision, changes in visual acuity, floaters, flashes of light, photophobia, eye redness, or pain. Diagnosis is based on fundoscopic examination, which usually shows fluffy yellow-white perivascular lesions with areas of hemorrhage. These findings may be easily confused with retinal cotton wool spots, a benign lesion with no prognostic significance. Because of the risk of blindness associated with CMV retinitis, suspicion for the disease requires *immediate* ophthalmologic consultation. Treatment regimen can consist of intraocular ganciclovir implants with oral valganciclovir for vision-threatening lesions or oral valganciclovir alone for lesions on the periphery of the retina. Intravitreous injection of ganciclovir may be given at the time of diagnosis if there is a delay of implant insertion.

Herpes zoster ophthalmicus is another common cause of ocular damage in patients with HIV. The typical presentation is pain or paresthesia in the distribution of cranial nerve V_1, followed by the emergence of the vesicular zoster skin rash. Complications may include conjunctivitis, episcleritis, iritis, and more concerningly, keratitis, secondary glaucoma, and retinitis. All patients with suspected zoster ophthalmicus require immediate ophthalmology consultation. Treatment involves acyclovir 30 mg/kg/d IV for 14 days followed by ganciclovir 1 g PO tid for acute retinal necrosis, or IV ganciclovir 5 mg/kg twice daily, foscarnet 90 mg/kg twice daily, and intravitreal ganciclovir for progressive outer retinal necrosis.

Other ophthalmic complications that occur with low CD4 count include microangiopathy (intraretinal hemorrhages and cotton wool spots; no treatment required), PCP choroidopathy (orange or yellow lesions at posterior pole of retina; treated as with pulmonary PCP), toxoplasmosis retinitis (multiple whitish retinal lesions without

hemorrhage; treated as with CNS toxoplasmosis), and syphilis (uveitis, optic neuritis, chorioretinitis; treated with penicillin G 4 million units IV q4h for 14 days) (7).

Hematology

Chronic anemia in AIDS is characterized by a normocytic, normochromic anemia with a low reticulocyte count and low erythropoietin (EPO) level. ART usually results in improvement. HIV-related infections or malignancies can also be associated with sudden worsening of anemia. Nutritional deficiencies including B_{12} and folate can result in megaloblastic anemia, low reticulocyte count, low serum B_{12}, and low serum folate. HIV medications causing anemia include AZT, TMP-SMX, phenytoin, ribavirin, pyrimethamine, and ganciclovir. Other drugs such as dapsone, primaquine, and ribavirin can cause a hemolytic anemia. HIV-infected patients are also at risk for idiopathic thrombocytopenia, neutropenia, and thrombotic thrombocytopenia purpura (7).

Antiretroviral Therapy

In 1996, with advancing dissemination of ART, the CDC reported a decline in the number of AIDS-related deaths for the first time. Although not commonly instituted in the ED, ART is an important aspect of management in HIV-infected patients, and emergency physicians should have a basic understanding of the classes of drugs available, adverse drug reactions likely to be seen, and the current guidelines for initiating treatment.

There are several classes of antiretroviral drugs including the NRTIs, NNRTIs, PIs, an entry inhibitor, a fusion inhibitor, and an integrase inhibitor. Each group of drugs independently interrupts the normal life cycle of HIV.

The first drug demonstrated to have antiretroviral activity, Zidovudine or AZT, belongs to the NRTIs, which are competitive inhibitors of the viral enzyme reverse transcriptase. Side effects of NRTIs that are relevant to emergency physicians include distal sensory peripheral neuropathy with didanosine (ddI), stavudine

(d4T), and zalcitabine (ddC); pancreatitis with ddI; acute hepatitis (sometimes resulting in fatal hepatic necrosis) caused by hypersensitivity to abacavir (ABC); and hepatitis B flares resulting from institution (due to IRIS) or discontinuation of an NRTI.

NRTI-related mitochondrial toxicity can cause life-threatening lactic acidosis, usually due to ddI, d4 T, or AZT. It can present as myopathy (proximal muscle weakness, tenderness, myalgias, and elevated CPK), lipoatrophy, peripheral neuropathy, and hyperlactatemia. A serum lactate should be checked in any HIV patient taking an NRTI and presenting with nausea, vomiting, abdominal pain, weight loss, or anorexia. Patients with symptomatic lactic acidosis need hospital admission and cessation of antiretrovirals, as they have a high risk of death (21).

The NNRTIs are noncompetitive inhibitors of reverse transcriptase and block RNA-dependent and DNA-dependent DNA polymerase activity. Rash is the most frequent side effect associated with the NNRTIs, with a small minority of patients ($<5\%$) developing Stevens–Johnson syndrome. Symptomatic hepatitis, including fatal hepatic necrosis, has been reported with use of nevirapine. In contrast, most NNRTIs may cause asymptomatic hepatic transaminase elevations, which are relatively benign.

PIs prevent viral replication by blocking activation of viral protein precursors. PIs are associated with a high frequency of side effects. Short-term effects are principally GI (including nausea, diarrhea, and bloating). Long-term effects are metabolic, including insulin resistance, hyperlipidemia, and fat redistribution. PI therapy is associated with an increased risk of coronary atherosclerosis. Other significant side effects of PIs include fulminant hepatitis associated with tipranavir, interaction with some statins to increase the risk of rhabdomyolysis, and an increased risk of bleeding in hemophiliacs (7).

Additional newer classes of drugs include entry/fusion inhibitors and integrase inhibitors. Entry/fusion inhibitors prevent HIV entry into cells by targeting specific viral surface proteins or their corresponding receptors. Enfuvirtide and maraviroc are two entry/fusion inhibitors currently approved for use in combination

with other antiviral agents only in treatment-experienced patients. Major side effects include local injection site reactions and increased rate of bacterial pneumonia (enfuvirtide). Raltegravir is the only integrase inhibitor currently approved for use in patients who have limited or no treatment options. Common side effects include diarrhea, nausea, headache, and fever.

The goal of ART is to reduce viremia, boost the CD4 cell count, halt disease progression, prevent development of resistant variants, and improve the quality of life. The current United States consensus recommendations for initiation of ART are detailed in Table 191.5. The current United States Department of Health and Human Services (DHHS)-recommended first-line ART regimens typically combine two NRTIs with either an NNRTI, a ritonavir-boosted PI, or an integrase inhibitor. Treatment strategies are tailored to the individual patient with special consideration to tolerability, comorbidities, adverse effect profile, drug-to-drug interactions, convenience, and likelihood of adherence. Decisions regarding initiation or change in antiretroviral medications should be made in consultation with the patient's primary care provider or an infectious disease consultant.

TABLE 191.5
Currently Accepted Indications for Initiation of ART in HIV Infection (7)

- CD4 <500 cells/mm^3

OR

- History of an AIDS-defining illness (see Table 191.1)

Any of the following independent of CD4 cell count:

- Symptomatic HIV infection
- Pregnancy
- HIV-associated nephropathy
- Hepatitis B (HBV) or C (HCV) coinfection
- CD4 cell count decreasing by >100 cells/mm^3/yr
- Viral load >100,000 cells/ml
- High cardiovascular disease risk
- High risk of transmission to an uninfected person
- >60 yrs old

Immune reconstitution syndrome can develop weeks to months after AIDS patients begin ART. It is associated with an atypical immune response to latent and subclinical infections presenting with a paradoxical worsening of pre-existing infectious processes as immune function improves. It is a diagnosis of exclusion and should be considered in any HIV patient who recently started or restarted ART. After other serious infections are ruled out, consultation with an infectious disease specialist is warranted. In addition to treating any underlying infections, therapy may include nonsteroidal anti-inflammatory drugs and/or steroids.

Chemoprophylaxis

Chemoprophylaxis is directed toward preventing initial and subsequent episodes of certain opportunistic infections and includes antibiotic therapy as well as vaccinations. Knowledge of the HIV-infected patient's prophylactic regimen can aid the emergency physician in diagnostic and treatment decisions as well as follow-up recommendations. CD4 cell count is the best predictor of the risk for opportunistic infections and is consequently used to make decisions about antimicrobial prophylaxis. Bactrim DS 1 tab daily is the preferred prophylactic regimen for PCP and toxoplasmosis, given to individuals with CD4 <200 cells/mm^3 and CD4 <100 cells/mm^3, respectively. Individuals with CD4 <50 cells/mm^3 should receive azithromycin 1,200 mg once weekly as prophylaxis against MAC. Other prophylactic regimens include valacyclovir prophylaxis against HSV recurrence, antifungal agents to prevent histoplasmosis and coccidiomycosis, and vaccinations against pneumococcus, varicella zoster, hepatitis A virus (HAV), HBV, HPV, and influenza.

CRITICAL INTERVENTIONS

- Make the presumptive diagnosis of PCP in patients with cough, dyspnea, fatigue, and hypoxia without any other explanation.
- Isolate HIV-infected patients with pulmonary symptoms until TB is excluded.

- Perform a CT and LP to evaluate patients with CD4 cell counts <200 cell/mm^3 who have an altered mental status or headache in which another cause is not clearly identified.
- Admit patients with disseminated varicella zoster disease or ophthalmic zoster to isolation beds for IV acyclovir therapy.

DISPOSITION

Disposition decisions for HIV-infected patients are based, as for any patient, on clinical condition, the availability of outpatient resources, and the ability to arrange adequate follow-up.

Patients who are known to be seropositive for HIV but who are not admitted to the hospital should be referred for follow-up or for medical consultation if they do not have an established source of care. Patients who have symptoms or signs suggestive of HIV infection (e.g., weight loss, generalized adenopathy, chronic diarrhea, oral thrush), but who do not require admission should be tested for HIV and receive similar referral.

Circumstances in which admission may be appropriate are similar to other chronically ill and immunocompromised patients. In addition, fever without a source, suspected PCP, new CNS symptoms, intractable diarrhea, and potential retinal infections are especially significant in AIDS patients. When there is doubt about diagnostic or management options, consultation with an infectious disease specialist, neurologist, or AIDS specialist is appropriate.

PREVENTION AND PRECAUTIONS

Numerous studies have shown that a substantial proportion of patients in the ED have unsuspected HIV infection and that HIV seroreactivity cannot be accurately predicted. Because there is no cure for HIV, frequent hand washing, gloves, gown, mask, and eye protection are a necessity when exposure to blood or body fluids is possible. It should be noted, however, that the risk of acquiring HIV through occupational exposure appears to be very low. Transmission risk is estimated at 0.3% for percutaneous exposures and 0.09% for mucocutaneous exposures (7).

The US DHHS provides specific guidelines for emergency physicians caring for health care workers after an occupational exposure to HIV. The policies were most recently updated in 2013 (22), and include significant changes to the 2005 recommendations. For complicated cases, the National HIV/AIDS clinicians' consultation center provides a Postexposure Prophylaxis hotline. The hotline is available 24 hours a day at 888–448–4911. See Chapter 194 in this text for specific recommendations.

Common Pitfalls

- Failure to recognize undiagnosed infection. Because patients often may not volunteer information regarding HIV risk factors, this information must be actively sought whenever a patient with possible opportunistic infection or other symptoms suggestive of HIV infection (e.g., weight loss, fever) is being treated.
- Failure to fully evaluate nonspecific respiratory complaints in those with HIV—particularly later stage disease. Shortness of breath may be the only complaint in patients with PCP. CT should be considered in those with a negative chest x-ray and dyspnea on exertion.
- Failure to fully evaluate complaints of fever in HIV-positive patients who appear well. Fever may indicate systemic infection; blood cultures should be obtained, even in patients who appear nontoxic.
- Chronic low-grade headache or headache different from a patient's usual pattern of headache may be suggestive of CNS infection or malignancy; a head CT and LP are indicated in such patients.

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CHAPTER 192
Toxic Shock Syndromes

Emily Rose

Staphylococcal Toxic Shock Syndrome

Toxic shock syndrome (TSS) associated with *Staphylococcus aureus* is a toxin-mediated, multisystem illness that occurs in primarily healthy people of any age group. It was originally described in 1978. The peak reported incidence, in 1980, was linked to the use of highly absorbent tampons containing polyacrylate rayon. Owing to federal regulations for tampons and public awareness, the incidence of TSS has declined. The incidence of TSS and probable TSS (including menstrual and nonmenstrual categories) is 1 to 3 per 100,000 with a case : fatality rate of 3% to 10% (1,2). The majority of reported cases of TSS have been due to methicillin- susceptible *S. aureus* (MSSA), but cases due to methicillin-resistant *S. aureus* (MRSA) have emerged in association with increased rates of community-acquired MRSA infections (3). Staphylococcal TSS cases are now occasionally associated with necrotizing fasciitis and myositis (1).

Nonmenstrual staphylococcal TSS currently accounts for approximately half of all cases and may occur with any type of *S. aureus* infection. Clinical scenarios associated with nonmenstural TSS include surgical and postpartum wound infections, mastitis, septorhinoplasty, sinusitis, osteomyelitis, arthritis, burns, skin lesions (including varicella zoster), respiratory infections (e.g., influenza, tracheitis, pharyngitis), HIV infection, and enterocolitis. Occasionally, no source is found (3,4). Influenza associated with TSS has a mortality as high as 90% (5). Patients with AIDS may develop

recalcitrant erythematous desquamating disorder, a prolonged clinical course with severe and persistent desquamation (6).

TSS is a superantigen-mediated disease mediated by *S. aureus exotoxins*. Superantigens may activate up to 20% of T cells at one time, resulting in massive cytokine production (1,3). These cytokines are responsible for capillary leak syndrome and account for many of the clinical signs of TSS. Toxic shock syndrome toxin-1 (TSST-1) was the initial exotoxin isolated from *S. aureus* isolates associated with TSS in 1981 (1,7). It is the cause of nearly all menstrual cases of TSS because of its superior ability over other superantigens to penetrate mucosal surfaces (1). Oxygen is required for TSST-1 production. Tampons introduce oxygen into the typically anaerobic human vagina which allows TSST-1 proliferation and mucosal penetration. TSST-1 also causes approximately 50% of nonmenstrual TSS.

Numerous other superantigens, most commonly staphylococcal enterotoxins B and C, contribute to nonmenstrual TSS. Host antibody responses to the *S. aureus* exotoxins play an important role in the pathogenesis of TSS. Up to 40% of humans may be colonized with *S. aureus* and those with damaged skin such as atopic dermatitis are almost always colonized on skin surfaces (1). Approximately 70% to 80% of those in late teenage years and 90% to 95% of individuals in the fourth decade have developed antibodies to TSST-1. Passive immunity is conferred to babies at birth but wanes with time (3). Patients with clinical TSS lack antibody to TSST-1 and often fail to develop appropriate antibodies in their serum secondary to toxin-mediated excessive inflammatory response, cytokine production, and inhibition of antibody production (1). Only 50% of patients develop antibodies after TSS (4,6). Lack of protective antibodies places patients at risk for recurrent TSS and up to one-third of patients will have recurrence (6).

CLINICAL PRESENTATION AND ED EVALUATION

The most common features of TSS include fever, hypotension, and rash. Patients often present with an abrupt onset of flu-like symptoms including fever, malaise, myalgias, chills, headache, sore throat, vomiting, diarrhea, abdominal pain, or dizziness. Severe hypotension can be relatively unresponsive to fluids, last for days, and lead to tissue ischemia, encephalopathy, and organ failure.

A major feature of TSS is the erythematous rash, resembling sunburn, which may be diffuse or patchy in distribution and involves the palms and soles. The rash may be subtle and fleeting, complicating diagnosis. There may also be hyperemia of the conjunctiva, pharynx, tongue, and vaginal mucosa. Desquamation of the skin occurs in 7 to 14 days at the sites of the previous rash. A delayed pruritic maculopapular rash may also occur with desquamation weeks after the disease (3).

Criteria for the diagnosis of staphylococcal TSS defined by the Center for Disease Control (CDC) are provided in Table 192.1. However, TSS can involve every organ system and can produce a wide constellation of symptoms. The diagnosis should be considered if even all criteria are not met.

TABLE 192.1
Criteria for Staphylococcal Toxic Shock Syndrome

1. Fever ≥102°F (38.9°C)
2. Presence of diffuse macular erythroderma ("sunburn" appearance)
3. Desquamation 1 to 2 wks after onset of illness, particularly of the palms and soles
4. Hypotension, defined as a systolic blood pressure of 90 mm Hg for adults and less than the fifth percentile for children younger than 16 years; an orthostatic decrease in diastolic blood pressure of 15 mm Hg with a position change from lying to sitting; orthostatic syncope; or orthostatic dizziness
5. Involvement of three or more of the following organ systems:

   Gastrointestinal: history of vomiting or diarrhea at the onset of illness

   Muscular: elevated creatine phosphokinase level greater than two times the upper limit; or severe myalgia

   Mucous membrane: nonpurulent conjunctivitis, oropharyngeal hyperemia, or vaginal hyperemia or discharge

   Renal: BUN or creatinine greater than two times the upper limit or pyuria (>5 WBC/hpf)

   Hepatic: elevated serum transaminase and bilirubin levels

   Hematologic: thrombocytopenia (<100,000/μL)

   Central nervous system: disorientation or alteration in consciousness without focal neurologic signs and in the absence of hypotension or fever

   In addition, normal results of the following tests, if performed:

   Blood, throat, cerebrospinal fluid cultures (blood culture may be positive for *Staphylcoccus aureus*); antibody tests for Rocky Mountain spotted fever, ehrlichiosis, leptospirosis, and rubella

Toxic shock syndrome is "probable" when at least four of the five criteria are fulfilled.

Modified from American Academy of Pediatrics. Staphylococcal infections. In: Pickering LK, ed. *Red Book: 2012 Report of the Committee on Infectious Diseases.* 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012:653–668.

The clinical presentations of menstrual and nonmenstrual TSS are similar. Super antigen toxins (such as TSST-1) have the ability to inhibit the migration of polymorphic neutrophils (PMNs) to infection and often there is a lack of inflammation around the site of infection. Surgical wound sites and cutaneous infections that harbor toxin-producing *S. aureus* are frequently benign appearing and without with obvious purulence (5).

The diagnosis of TSS is often made on clinical grounds and must be considered in a hypotensive febrile patient with a rash (on examination or by history). The disorder is toxin mediated; therefore, blood cultures are rarely positive (5%) (3). Isolation of *S.*

aureus is not required for the diagnosis of staphylococcal TSS, though 80% to 90% of patients with TSS have *S. aureus* isolated from the mucosa or wound sites. Laboratory examination may demonstrate signs of multiorgan involvement including thrombocytopenia (platelets $<100{,}000$), elevated blood urea nitrogen (BUN) and creatinine, and elevated liver function tests.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of TSS includes *streptococcal* TSS (discussion to follow), Kawasaki disease, staphylococcal scalded-skin syndrome, scarlet fever, Stevens–Johnson syndrome, Rocky Mountain spotted fever, ehrlichiosis, leptospirosis, meningococcemia, typhoid fever, dengue hemorrhagic fever, atypical measles, viral illness, anaphylaxis, heat stroke, gram-negative sepsis, and drug reactions.

ED MANAGEMENT AND DISPOSITION

Initial treatment consists of intravenous fluid replacement. Large volumes (10 to 20 L) of crystalloid are often required to maintain normal perfusion. Hemodynamic monitoring and vasopressors are sometimes necessary. Tampons, nasal packs, or other foreign bodies must be removed. Surgical wounds or areas of infection need to be irrigated; abscesses must be incised and drained. Cultures of the vaginal canal or of the infectious focus or surgical wound should be submitted for culture and susceptibility testing, as TSS is caused by both MSSA and MRSA.

Antibiotics may not affect the clinical course but may be beneficial if the patient is bacteremic or if there is a site of ongoing infection. Antibiotic therapy reduces the likelihood of recurrent TSS in those that previously failed to develop an appropriate antibody response to staphylococcal toxins (1,3,8). Clindamycin (600 to 900 mg IV every 8 hours) suppresses protein synthesis and toxin production. Vancomycin (10 to 20 mg/kg/dose) is added to cover MRSA. If culture and susceptibility results are available and indicate MSSA, clindamycin plus oxacillin or nafcillin are recommended.

Commercially available intravenous immune globulin (IVIG) has anti–TSST-1 antibodies present in varying amounts which may neutralize the toxin in TSS. Many experts recommend its use in severe cases. However, there are no data from controlled clinical trials demonstrating a reduction in morbidity or mortality with the use of IVIG. Risk versus benefit should be considered prior to its use. The role of steroids is unclear and not currently recommended.

Patients with suspected TSS should be admitted to the hospital. Unstable patients should be admitted to the intensive care unit.

Common Pitfalls

- Failure to recognize TSS in young healthy patients with fever and an erythematous rash
- Failure to administer adequate fluid volumes to maintain tissue perfusion
- Failure to seek an occult source of staphylococcal colonization or infection
- Failure to debride or irrigate benign-appearing wounds
- Failure to remove foreign bodies

Streptococcal Toxic Shock Syndrome

In the late 1980 s, a disease similar to staphylococcal TSS, but caused by a strain of group A streptococci (GAS), was recognized (9). This illness, characterized by hypotension and multiorgan failure, was termed *streptococcal toxic shock syndrome* (STSS). The Centers for Disease Control and Prevention case definition of this syndrome is shown in Table 192.2.

TABLE 192.2
Case Definition for the Streptococcal Toxic Shock Syndrome

1. Isolation of group A streptococci
   A. From a normally sterile site (e.g., blood, cerebrospinal fluid, peritoneal fluid, tissue biopsy, surgical wound)
   B. From a nonsterile site (e.g., throat, superficial skin lesion)
2. Clinical signs of severity
   A. Hypotension: systolic blood pressure 90 mm Hg in adults or less than fifth percentile for age in children, and
   B. Two or more of the following signs:
      Renal impairment: creatinine 2 mg/dL for adults or at least twice the upper limit of normal for age
      Coagulopathy: platelets <100,000/μL or disseminated intravascular coagulopathy
      Liver involvement: serum alanine aminotransferase, aspartate aminotransferase, or total bilirubin concentrations at least twice the upper limit or normal for age
      Adult respiratory distress syndrome
      A generalized erythematous macular rash that may desquamate
      Soft tissue necrosis, including necrotizing fasciitis or myositis, or gangrene

An illness fulfilling criteria 1 A and 2 (A and B) can be defined as a definite case.

An illness fulfilling criteria 1B and 2 (A and B) can be defined as a probable case if no other etiology for the illness is identified.

Modified from American Academy of Pediatrics. Group a streptococcal infections. In: Pickering LK, ed. *Red Book: 2012 Report of the Committee on Infectious Diseases.* 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012:668–680.

Group A streptococcal TSS, like staphylococcal TSS, is mediated by toxins that act as superantigens and cause significant release of inflammatory cytokines. Initial infection most commonly occurs through the skin, vagina, or pharynx. Cases of STSS are often associated with minor nonpenetrating trauma or soft tissue infection (10–12). Viral infections, such as varicella and influenza, are thought to provide a portal of entry in other cases, but in many patients, no source of the organism can be identified. Bacterial toxins produced by GAS, particularly streptococcal pyrogenic exotoxins (SPEs), as well as host factors, are thought to play an important role in determining disease severity (13). In contrast to staphylococcal TSS, blood cultures are generally positive (60%). Streptococcal TSS often occurs in the presence of necrotizing fasciitis and myositis. Young children, the elderly, and the

immunosuppressed are at greatest risk, but a large proportion of patients with STSS are young, healthy adults. Risk factors for GAS infection include minor trauma, soft tissue injuries (hematoma, bruising or muscle strain), surgical procedures, viral infections (especially influenza and varicella), and use of nonsteroidal anti-inflammatory drugs (NSAIDs) (13). It is unclear if the association of STSS with NSAIDs is causal, but NSAID use may mask presenting symptoms and contribute to a delay in diagnosis. Invasive GAS infections are increasing in frequency with an estimated 3.5 cases per 100,000 and a case : fatality rate of 36% to 43% for STSS (13).

CLINICAL PRESENTATION AND ED EVALUATION

Streptococcal TSS is typically an acute illness with fever, rapid-onset hypotension, and signs of multiorgan involvement including rapidly progressive renal failure. Flu-like symptoms such as malaise, myalgias, nausea, vomiting, and diarrhea often occur. In distinction to staphylococcal TSS, the diffuse scarlatina-like rash is uncommon in STSS (<10%). Patients often have signs of soft tissue infection such as localized swelling and erythema. The extremities are most commonly affected, but the chest, abdomen, or pelvis may be involved. Pain out of proportion to physical findings, rapid escalation of pain and the presence of vesicles or bullae on the skin are concerning signs of progression to necrotizing fasciitis. About 20% of STSS occur without soft tissue findings. Invasive infections such as pneumonia, pleural empyema, osteomyelitis, pyarthrosis, endophthalmitis, peritonitis, myocarditis, endocarditis, postpartum infections, or overwhelming sepsis may occur in association with STSS (13). Streptococcal TSS nearly always occurs in association with bacteremia (1). Complications include acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and renal failure (often requiring dialysis).

ED MANAGEMENT AND DISPOSITION

Essential management of STSS includes hemodynamic support, early antibiotic therapy, and, when indicated, surgical therapy.

Massive quantities of intravenous fluids (up to 20 L/d) may be necessary to maintain perfusion secondary to intractable hypotension and diffuse capillary leak. Vasopressors may also be required.

Early treatment with antibiotics is critical. Broad-spectrum coverage should be used. Clindamycin is first-line therapy as it suppresses the synthesis of bacterial toxins and has been associated with better outcomes than β-lactam antibiotics alone in patients with STSS (14). In addition to clindamycin (900-mg IV every 8 hours), a carbapenem (imipenem 500 mg every 6 hours or meropenem 1 g every 8 hours) or a combination of drug containing penicillin plus a β-lactamase inhibitor (ticarcillin–clavulanate 3.1 g every 4 hours or piperacillin–tazobactam 4.5 g every 6 hours) should be used (14).

Significant pain to the soft tissue must trigger suspicion for serious infection such as myositis or necrotizing fasciitis regardless of lack of erythema or history of seemingly insignificant trauma. These serious infections require prompt and aggressive surgical debridement. Early surgical consultant is of paramount importance to reduce morbidity and mortality.

IVIG is also recommended by several experts in STSS but the supporting data are limited (14). Anecdotal reports of hyperbaric oxygen have been used in a handful of patients (14).

Patients with suspected TSS should be admitted to the hospital. Unstable patients should be admitted to the intensive care unit.

KEY TESTING

Toxic Shock Syndromes

- CBC
- Electrolytes, BUN, creatinine, glucose
- Liver function tests/liver enzymes
- PT/PTT/INR
- Lactate
- Urinalysis
- Blood cultures

- Wound culture if wound present
- Throat culture if pharyngitis
- CSF if suspected meningitis
- CXR

CRITICAL INTERVENTIONS

- Toxic Shock Syndromes
- Administer aggressive intravenous fluid replacement to maintain perfusion.
- Remove tampons, nasal packs, surgical dressings, or other foreign bodies.
- Incise and drain abscesses, irrigate surgical wounds, and debride areas of infection.

Common Pitfalls

- Failure to consider the diagnosis of STSS early and to institute antibiotics promptly
- Failure to debride soft tissue infections aggressively
- Failure to recognize pain out of proportion to examination even without physical findings could be a sign of STSS

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CHAPTER 193

Parasitic Disease

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Parasitic infestations are much more widespread than many people realize. Parasites affect not only impoverished people in remote countries but can also cause important health problems for the rich and poor throughout the world, including the United States. Parasites are considered by many physicians to be the most undiagnosed infectious disease challenge in the United States today. Diagnosing parasitic infections in the emergency department (ED) can be challenging because there is a large and varied group of organisms that cause parasitic infections with a wide range of clinical symptoms. Parasitic disease, however, can usually be diagnosed through methods available to most emergency physicians, and effective treatments are available that are generally minimally toxic to the human host (1,2). A history of foreign travel or habitation in an endemic area, including certain regions of the United States, should alert the clinician to the possibility of parasitic infection. As with many disease processes, the key is considering parasitic infestation in the differential diagnosis.

Symptoms may not manifest themselves until well after the traveler has returned home. In addition, over the past two decades, the proportion of the US population born abroad has increased steadily, with newer immigrants typically coming from Latin America and Asia (3). The proper treatment of immigrants in the United States requires a familiarity with diseases common in the developing world, such as malaria, amebiasis, and neurocysticercosis. Given the constant change in the globalization of infectious disease, the clinician should always consult current

references, including the Centers for Disease Control (CDC) website (http://www.cdc.gov/travel). Parasitic infestation is a global problem. Here in the United States, the CDC cites food as the catalyst behind 80% of the pathogenic outbreaks.

Four major groups of organisms infest humans. *Protozoans* cause malaria, amebiasis, giardiasis, and many other diseases. Helminths, or worms, including *nematodes* (roundworms), *cestodes* (tapeworms), and *trematodes* (flukes), are also responsible for a wide variety of human illnesses. A comprehensive review of parasitic diseases would encompass infections due to literally scores of organisms, so this chapter is limited to the parasitic diseases most common in EDs in the United States (trichomoniasis is excluded). This chapter is divided into three discussions: systemic illnesses (malaria), predominantly gastrointestinal (GI) disease, and predominantly central nervous system (CNS) disease (cysticercosis).

Malaria

CLINICAL PRESENTATION

Awareness about malaria and measures that travelers can take to avoid infective mosquito bites are more important than ever. Cases of malaria continue to rise in the United States. Thus, fever in a patient with a history of recent travel or habitation in the tropics should suggest the diagnosis of malaria. Caused by four species of the protozoan *Plasmodium* (*P. vivax, P. ovale, P. falciparum,* and *P. malariae*), malaria is the most common parasitic disease in the world. According to the CDC (www.cdc.gov/malaria), malaria currently infects an estimated 350 to 500 million people worldwide and on average, 1,500 cases are reported in the United States annually. Malaria causes <1 million deaths annually (most commonly children in sub-Saharan Africa). Although malaria is no longer considered endemic in the United States, increased immigration from and travel to countries where the disease is common has made malaria more frequent as a presenting complaint in ED in this country (4). The number of cases of malaria acquired by international travel is growing as a result of the increased risk of malaria transmission

where malaria control has faded and also because of the spread of drug-resistant strains of malaria (5). Patients with malaria are frequently misdiagnosed on their initial presentation to the ED, thus increasing their risk for serious morbidity and mortality.

Classic symptoms of malaria:

- Fever, chills, and rigors lasting 4 to 10 hours, culminating in an episode of profuse diaphoresis followed by defervescence.
- This pattern may recur at 2- or 3-day intervals, depending on the species of *Plasmodium* involved.
- General malaise, headache, and, occasionally, hypotension.
- Splenomegaly and jaundice may be seen in established infections. (Physical examination is generally not helpful.)
- Laboratory abnormalities include a mild anemia, neutropenia, thrombocytopenia, and increased prothrombin time. Clinical evidence of impaired hemostasis is rare.

The periodicity of the disease can be explained by examining the life cycle of the infecting organism. In the human, the life cycle of the parasite consists of two stages. The initial stage is known as the liver or exoerythrocytic stage. This is where the parasites multiply in hepatocytes and cause them to rupture. The second stage is known as the blood or erythrocytic stage and occurs when parasites are released into the bloodstream and invade the erythrocytes. This is the cause of clinical illness. *Plasmodium* species may be injected into the human circulation following the bite of the *Anopheles* mosquito, after sharing needles or receiving a blood transfusion, and by congenital transmission. Immature sporozoites migrate to the liver, beginning the exoerythrocytic phase, the duration of which is species-dependent. Ultimately, mature parasites (merozoites) are released into the circulation and invade red blood cells, beginning the erythrocytic phase. Replication within red cells is followed 48 to 72 hours later by red cell lysis and release of further merozoites into the circulation, which again invade erythrocytes and repeat the cycle. The fever corresponds to episodes of red cell lysis.

The classic pattern of periodic fever is not always seen, however, particularly early in the course of the illness. The variability of the clinical course also depends on the infecting species and the host's

immune status. People living in endemic areas often have partial "immunity" that results in much less severe manifestations and symptoms. It is presumed to be an acquired immunity caused by frequent exposure to the infecting organism. Months after leaving an endemic area, these persons may experience relapses that resemble the acute form of the disease, probably caused by a loss of immunity and the release of exoerythrocytic parasites from the liver. *P. vivax* and *P. ovale* can persist for long periods in the exoerythrocytic state. Even patients who have received adequate antimalarial therapy may experience relapses associated with the release of exoerythrocytic organisms. Cases have been reported 2 months to 4.5 years after a traveler's return (5).

P. falciparum causes the most severe type of malaria and is responsible for most complications and deaths related to malaria (4). Falciparum malaria has two important features that account for differences in its presentation and in the severity of the disease it produces. First, this species causes widespread capillary obstruction, resulting in end-organ hypoxia and dysfunction, with severe complications that can include CNS dysfunction, hemolytic anemia, hypoglycemia, pulmonary edema, septicemia, renal failure, or splenic rupture. A second distinguishing feature of *P. falciparum* is that, unlike other malarial species that infect only the most mature red cells, it infects red cells of all ages, resulting in a greater degree of hemolysis and anemia and the potential for acute tubular necrosis. Finally, unlike *P. ovale* and *P. vivax,* cases of *P. falciparum* malaria in patients with late presentations are caused by blood-stage parasites that were drug resistant or had survived incomplete prophylaxis.

ED EVALUATION

The diagnosis of malaria is a difficult one to make because of the disease's nonspecific clinical features—fever, chills, headache, and malaise. Because approximately 90% of travelers who contract malaria do not become ill until returning home, the diagnosis should be entertained for anyone presenting to the ED with a febrile illness and a history of travel or habitation in an endemic area. Kain et al. (6) estimated that approximately 30,000 travelers from

industrialized countries contract malaria each year. A high degree of suspicion is necessary for diagnosis by physicians who rarely encounter this disease. The most common incorrect diagnosis is a viral syndrome, but a history of recurrent fever generally distinguishes malaria from these disorders. Other disorders that cause fever and are endemic in foreign countries, such as viral hepatitis, dengue fever, typhoid fever, and amebiasis, should also be considered. Recent data suggest that a significant number of those presenting with malaria do so later than previously thought. More than 35% of malaria-infested travelers in one study developed malaria more than 2 months after their return. This suggests that we may need to modify treatment to more aggressively treat the liver phase of the disease for effective prevention (5).

The standard way to make the diagnosis of malaria is through demonstration of intracellular forms of the parasite on a thin Giemsa-stained peripheral blood smear. If malaria is strongly suspected, negative blood films should be repeated every 12 to 24 hours for total of three sets. Three negative sets make the diagnosis very unlikely. Sometimes, it is necessary to use the thick-smear technique, which usually requires the expertise of a trained technician. New rapid testing by PCR, and even real-time PCR assays for chloroquine-resistant strains of *P. falciparum* malaria, as well as other methods, are being developed and should aid in the rapid diagnosis of malarial infections (7).

Although admittedly rare in the United States, congenital malaria should be considered when the emergency physician is presented with the febrile infant of an immigrant mother. It has been estimated that about 15% to 20% of all cases of malaria brought back to Western countries from recent travelers are in children (8).

ED MANAGEMENT

Management of malaria in the ED is guided by the severity of the infection. Assessment of airway patency and respiratory, circulatory, and neurologic status should be performed in a timely fashion. The emergency physician should be prepared to treat potential complications such as anemia, coagulopathies, pulmonary edema,

azotemia, hypoglycemia, metabolic acidosis, and hypotensive shock (9).

Volume should be restored and fever controlled. Hypotension usually responds well to crystalloid infusion. Fever usually responds to standard cooling measures; for temperatures <104°F, oral antipyretics are likely to be effective. Acetaminophen is recommended rather than aspirin because of the common occurrence of thrombocytopenia. For patients with high-density parasitemia (>10% parasitemia), altered mental status, nonvolume overload pulmonary edema, or renal failure, exchange transfusion may be helpful (10).

Pharmacologic therapy of malaria is outlined in Table 193.1. Antimalaria pharmacotherapy and prophylaxis continue to pose difficult problems. Most antimalarial agents act on the parasites at blood stage and therefore do not prevent late onset illness (5). Chloroquine remains the oral drug of choice (with hydroxychloroquine being second-line treatment) for acute treatment of all infections except those due to chloroquine-resistant *P. falciparum* or *P. vivax* acquired in Papua New Guinea or Indonesia. For chloroquine-resistant *P. falciparum* infection or for severely ill patients with an unidentified malarial infection, the recommended agents include either oral quinine plus doxycycline (tetracycline or clindamycin may be substituted for doxycycline), atovaquone–proguanil, or artemether–lumefantrine. Mefloquine may be used if the other drugs are not available. Patients with *P. vivax* acquired within Papua New Guinea or Indonesia should use atovaquone–proguanil plus mefloquine as first-line therapy and consider quinine plus doxycycline or tetracycline as alternative treatments. Patients with severe malaria (regardless of species or geographic location where contracted) or those who are unable to tolerate oral medications, should be treated with intravenous (IV) quinidine plus tetracycline, doxycycline, or clindamycin.

TABLE 193.1
Treatment of Malaria

Drug	Adult Dosage	Pediatric Dosage
	Nonresistant Malaria	
Oral Drug of Choice:		
Chloroquine phosphate	600 mg base (1 g), then 300 mg base (500 mg) 6 hrs later, then 300 mg base (500 mg)/d × at 24 and 48 hrs	10 mg base/kg (max 600 mg base), then 5 mg base/kg 6 hrs later, then 5 mg base/kg/d × 2 d
Alternative:		
Hydroxychloroquine	800 mg PO followed by 400 mg PO at 6 hrs, 24 hrs, and 48 hrs	10 mg/kg PO then 5 mg/kg PO at 6 hrs, 24 hrs, and 48 hrs
	Chloroquine-Resistant P. Falciparum Malaria	
Oral Drugs of Choice:		
1. Atovaquone–proguanil	4 adult tablets per day for 3 d 1 adult tablet = 250 mg atovaquone/100 mg proguanil	5–8 kg: 2 peds tabs/d × 3 d 9–10 kg: 3 peds tabs/d × 3 d 11–20 kg: 1 adult tab/d × 3 d 21–30 kg: 2 adult tabs/d × 3 d 31–40 kg: 3 adult tabs/d × 3 d >40 kg: 4 adult tabs/d × 3 d Peds tablet = 62.5 mg atovaquone/25 mg proguanil
2. Aretemether–lumefantrine	4 tablets per dose (3-d treatment schedule: initial dose, followed by second dose 8 hrs later, then 1 dose bid for following 2 d)	5–14 kg: 1 tablet per dose 15–25 kg: 2 tablets per dose 25–34 kg: 3 tablets per dose >35 kg: same as adult dose
3. Quinine sulfate plus either:	650 mg q8h × 3 d–7 d (3-d infections acquired outside SE Asia, 7-d infections acquired in SE Asia)	10 mg/kg PO q8h × 3 d–7 d (3-d infections acquired outside SE Asia, 7-d infections acquired in SE Asia)
a. Clindamycin (PO or IV)	PO: 20 mg/kg/d PO divided 3 times daily × 7 d IV: 10 mg/kg loading dose then 5 mg/kg every 8 hrs; switch to oral meds ASAP; total treatment course of 7 d	Same as adult
b. Doxycycline (PO or IV)	PO: 100 mg PO bid × 7 d IV: 100 mg IV bid; switch to oral meds ASAP; treatment course 7 d	PO: 2.2 mg/kg PO bid × 7 d IV: Children <45 kg receive 2.2 mg/kg IV bid then switch to PO ASAP Children >45 kg is same as adults Treatment course is 7 d
c. Tetracycline	PO: 250 mg PO qid × 7 d IV: Dosage is the same as for PO	PO: 25 mg/kg/d PO divided qid × 7 d IV: Same as for PO
Alternative:		
3. Mefloquine	750 mg PO followed in 6–12 hrs by 500 mg	15 mg/kg PO followed in 6–12 hrs by 10 mg/kg
	Chloroquine-Resistant P. Vivax Malaria	
Drug of Choice:		
Atovaquone–proguanil plus mefloquine	As above	As above
Alternative:		
1. Quinine sulfate plus		
a. doxycycline	As above	As above
b. Clindamycin	As above	As above
c. Tetracycline	As above	As above
	Prevention of Relapses (P. Vivax and P. Ovale only)	
Primaquine phosphate	30 mg PO daily × 14 d	0.5 mg base/kg/d × 14 d
	Severe Malaria or Patient Unable to Take PO MEDS	
Parenteral Drug of Choice:		
Quinidine gluconate	10 mg/kg loading dose (max 600 mg) in normal saline slowly over 1–2 hrs, followed by continuous infusion of 0.02 mg/kg/min until oral therapy can be started	Same as adult dose
Alternative:		
1. Quinidine gluconate plus	24 mg/kg loading dose infused over 4 hrs followed by 12 mg/kg infused over 4 hrs every 8 hrs after the loading dose	Same as adult dose
a. Doxycycline	As above	As above
b. Clindamycin	As above	As above
c. Tetracycline	As above	As above

Adapted from Griffith KS, Lewis LS, Mali S, et al. Treatment of malaria in the United States: A systematic review. *JAMA*. 2007;297(20):2264–2277.

Critically ill patients should have access to continuous cardiac and blood pressure monitoring, while having frequent blood glucose, hemoglobin, parasitemia levels, and electrolyte levels checked. As

stated previously, exchange transfusion may be indicated in patients who meet clinical criteria (10). Finally, newer artemisinin-derived drugs similar to artemether–lumefantrine, such as dihydroartemisinin–piperaquine and artesunate–mefloquine are being tested against multidrug-resistant strains of *P. falciparum* (11–13).

In addition to acute therapy, patients infected with *P. vivax* or *P. ovale* require more prolonged treatment to prevent reactivation of exoerythrocyte forms. These patients should be treated with primaquine phosphate, 30 mg base/d for 14 days for adults and 0.5 mg base/kg/d for 14 days for children. Patients should be screened for G-6-PD deficiency before beginning primaquine therapy, and the drug is contraindicated during pregnancy. Patients who are G-6-PD deficient and for whom primaquine is thus contraindicated should be counseled about the possibility of recurrence (10).

To prevent fatal outcomes in cases of falciparum malaria, the following are required: improved health information and preventive measures for the 30 million travelers who visit regions where malaria is endemic, improved recognition of infection by physicians, and prompt initiation of effective therapy (6).

DISPOSITION

Hospital admission is indicated for patients with severe dehydration, significant underlying medical illness, inability to tolerate oral medications, or evidence of end-organ involvement such as stroke, renal failure, or pulmonary edema. Those whose ability to comply with an outpatient regimen is questionable should also be admitted. Suspected *P. falciparum* infection is commonly considered to require hospitalization because of the increasing prevalence of drug resistance and the potential for life-threatening complications. Severely ill patients or those with significant parasitemia ($>3\%$ of red cells containing parasites) should be treated in an intensive care unit with IV medications.

Prophylaxis is the most important aspect of malaria control in the United States, given the frequency of foreign travel. Before going to an endemic area, travelers should consult an expert to determine

whether chemical prophylaxis is indicated and whether chloroquine resistance has been reported in the area. Decisions about prophylaxis are increasingly complicated as a result of malaria drug resistance. Chloroquine is usually recommended for persons traveling to endemic areas but may not be necessary in all cases, particularly for a short trip to an urban area. When traveling to a chloroquine-resistant area, another drug should be chosen. The particular medication chosen must depend on the pattern of resistance in the area. Malarone (atovaquone/proguanil) is the prophylactic drug of choice for adults traveling to most chloroquine-resistant areas. Other options include mefloquine (Lariam), doxycycline, and hydroxychloroquine sulfate (Plaquenil). Primaquine is also an option for prophylaxis specifically against *P. vivax* for trips of short duration only. See Table 193.2 for prophylactic drug dosages.

TABLE 193.2
Malaria Prophylaxis Drug Regimes

Medication	Adult Dose	Pediatric Dose	Initiation/Termination
Chloroquine	500 mg (300 mg base) per week	5 mg/kg base (8.3 mg/kg) per week	Begin 1–2 wks before and continue 4 wks after travel completed
Malarone • Adult tablet = atovaquone 250 mg/ proguanil 100 mg • Pediatric tablet = atovaquone 62.5 mg/proguanil 25 mg	One adult tablet per day	5–8 kg = ½ peds tab/d 9–10 kg = ¾ peds tab/d 11–20 kg = 1 peds tab/d 21–30 kg = 2 peds tab/d 31–40 kg = 3 peds tab/d >40 kg = 1 adult tab/d	Begin 1–2 d before and continue 1 wk after travel completed
Mefloquine (Lariam)	250 mg (228 mg base) tablet per week	5–10 kg = ⅛ tab/wk 11–20 kg = ¼ tab/wk 21–30 kg = ½ tab/wk 31–45 kg = ¾ tab/wk >45 kg = 1 tab/wk	Begin 1–2 wks before and continue 4 wks after travel completed
Doxycycline	100 mg/d	2 mg/kg/d in children older than 8 yrs up to adult dose	Begin 1–2 d before and continue 4 wks after travel completed
Hydroxychloroquine sulfate (plaquenil)	400 mg (310 mg base) per week	5 mg of base/kg up to adult dose	Begin 2 wks before and continue 4 wks after travel completed
Primaquine	52.6 mg (30 mg base) daily	0.8 mg/kg (0.5 mg/kg base) up to adult dose daily	Begin 1–2 d before and continue 1 wk after travel completed. Only use for prophylaxis for short duration travel in areas with *P. vivax*.

Contraindications to the use of mefloquine include serious psychiatric illness, seizures, or serious cardiac arrhythmias (14). Because no drug regimen guarantees protection against malaria, if fever develops within the first year after travel to a malarious area, travelers should be encouraged to seek medical attention (10).

Consultation of current guidelines for areas of travel can be obtained from the CDC or WHO websites.

Gastrointestinal Disease

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

The GI tract is commonly affected by parasites. This is because exposure occurs readily through fecal contamination of food and water. Protozoans and helminths are common causes of GI symptoms such as abdominal pain, malabsorption, obstruction, diarrhea, rectal prolapse, and pruritus ani. The protozoans that cause GI diseases include *Giardia lamblia, Entamoeba histolytica,* and *Cryptosporidium.*

G. lamblia, a flagellated protozoan, affects the small intestine. It is the most commonly identified intestinal parasite in the United States. This infection may be transmitted through the ingestion of contaminated food or water, by person-to-person contact, or through fecal–oral transmission (15). Patients may experience explosive, watery, foul-smelling diarrhea or may express a more insidious onset of symptoms. Cramping epigastric pain is common; bloody diarrhea is unusual. Physical examination of the abdomen often reveals diffuse upper quadrant tenderness without evidence of peritoneal irritation. Malabsorption may be responsible for the substantial weight loss that is associated with *Giardia* infestations in more than 50% of patients (15). Microscopic stool examination may demonstrate active trophozoites, but cysts are more commonly found. At least three stools taken at 2-day intervals should be examined for ova and parasites. Commercially available tests to detect *Giardia* antigen in the stool exist. The “string test” may be used in an outpatient setting to help diagnose *Giardia* infestation. This test involves the patient swallowing a gelatin capsule attached to a string. The string slowly works its way into the duodenum over 4 to 6 hours, at which time it is pulled up and any blood or other material from the digestive tract still attached to the string is looked at under a microscope. Parts of the parasites or eggs may be observed in a positive test. Because *Giardia* is most often transmitted

by contaminated water or by the fecal–oral route, efforts at prevention should focus on these routes of transmission.

E. histolytica, upon invasion of the colonic mucosa, can cause amebic dysentery with abdominal pain, tenesmus, and bloody stools (16). It may result in severe dehydration. The large bowel is typically most affected. Transmission of amebiasis is linked directly to hygiene and sanitation; risk factors for amebiasis include recent travel and institutionalization. The spectrum of clinical disease ranges from mild diarrhea to fulminant rectocolitis. Massive GI bleeding may occur when amebic trophozoites invade large areas of colonic mucosa and cause ulceration; toxic megacolon, perforation, and peritonitis are other severe complications of amebic dysentery. Extraintestinal infection, most commonly amebic liver abscess (3), may occur with invasion of the trophozoites through the colonic mucosa. The diagnosis of amebic dysentery is made by stool examination for cysts and trophozoites or in biopsy specimens obtained by sigmoidoscopy or colonoscopy (16). More recently, PCR assay techniques have shown greater sensitivities and specificities for both *E. histolytica* and *Entamoeba dispar* species than stool microscopy or culture (17).

Cryptosporidium may affect any part of the GI tract. Immunocompetent patients frequently experience a clinical syndrome similar to that of giardiasis, whereas immunodeficient patients typically develop more serious disease and may die of dehydration and electrolyte abnormalities. In addition to water sources, such as drinking water, pools, lakes, and water parks, there have been several food-borne outbreaks of cryptosporidiosis in North America, including the severe outbreak in Milwaukee (18). Diagnosis is based on the microscopic identification of fecal oocysts, although newer more sensitive techniques, including molecular methods such as PCR, are being used in reference laboratories to identify *Cryptosporidium* at the species level. The disease is typically self-limited. Paromomycin has been used to treat cryptosporidiosis in several cases. Treatment with nitazoxanide, 500 mg twice daily (either in tablet or suspension form) for 3 days, has shown some

promise in treating enteritis and diarrhea caused by *Cryptosporidium* (19).

Infection with the helminths *Ascaris lumbricoides* and *Strongyloides stercoralis* and the hookworms *Necator americanus* and *Ancylostoma duodenale* causes cramping upper abdominal pain when associated with large worm burdens. Patients presenting from tropical climates, particularly Central America, South America, and Southeast Asia, may be infested with more than one of these GI parasites. Hookworms are also endemic in the southeastern United States.

Infection with *A. lumbricoides* and *S. stercoralis* may present with nonspecific abdominal pain and diarrhea. *Ascaris,* a roundworm, can migrate into the biliary system through the ampulla of Vater and induce inflammation and fibrosis of the biliary ducts through chemical irritation. They may also cause partial or intermittent obstruction of the bile ducts (20). Midepigastric and right upper quadrant pain may also mimic peptic ulcer disease. *Ascaris* has also been reported to cause bowel obstruction, especially in children (21). Upper respiratory symptoms can develop due to pulmonary migration of larvae (Loeffler syndrome). *S. stercoralis* larvae may mature within the GI tract, as the gravid adult female releases rhabditiform larvae that rapidly evolve into the invasive filariform larval form. The filariform larvae can penetrate the GI tract or perianal skin, causing the hyperinfection syndrome characteristic of strongyloidiasis (2); this is particularly likely to appear in the immunocompromised patient. Both *Necator* and *Ancylostoma* penetrate the mucosa of the small bowel in heavy acute infestations and cause cramping epigastric pain. In addition, GI blood loss at worm attachment sites may result in a profound hypochromic microcytic anemia.

The physical examination of patients with worm infestation is often unremarkable. Minimal diffuse upper abdominal tenderness may be present, but peritoneal signs are unusual when the worms are intraluminal. Presentation as an acute abdomen does occur, however, when there is complete biliary obstruction or small bowel obstruction secondary to a massive worm burden, as may be the case with acute *Ascaris* infestation. A “whirlpool” pattern of intraluminal

worms may be seen with plain abdominal x-rays (21). In ascariasis and hookworm disease, microscopic examination of the stool often reveals typical ova. Rhabditiform and filariform larvae of strongyloidiasis may be seen in stool samples and Papanicolaou-stained gastric aspirate or sputum smears. The larval forms of *S. stercoralis* are more likely than ova to be visible in the stool samples from these patients. Eosinophilia is common with all helminthic infections and should alert the clinician to this possibility.

Trichuris trichiura and *Enterobius vermicularis* often present as an annoyance rather than the cause of serious illness. Rectal prolapse may occur with massive infestation by *T. trichiura,* the whipworm, particularly in children (1). Large worm burdens with *T. trichiura* may cause a clinical pancolitis and a mild chronic illness (22), which is referred to as "trichuris dysentery syndrome": chronic diarrhea, anemia, and growth retardation (22). In patients with rectal prolapse from trichuriasis, the adult worms are normally visible on the exposed rectal mucosa. Microscopic examination of stool samples demonstrates the typical barrel-shaped ova of *T. trichiura.*

Infestation with the pinworm *E. vermicularis* is the most common helminthic infection of humans, with the prevalence highest among children ages 5 to 10 (9). Pinworm infection causes severe perianal pruritus, especially at night, when female worms crawl out onto the perianal skin to lay eggs (2). This is typically the live worm seen by patients in the perianal region. Examination of the perineum may reveal secondary bacterial infection of perianal excoriated skin. On occasion, dead parasites or eggs deposited in ectopic sites may lead to the formation of granulomas or abscesses (23). For diagnosis, clear cellulose tape may be placed against the perianal skin, lifted off, and then applied, adhesive side down, to a glass slide and viewed under a microscope to identify the characteristic eggs. Family members and other close contacts should be examined and, if necessary, treated.

ED MANAGEMENT

Pharmacologic therapy of GI parasitic disease is outlined in Table 193.3.

TABLE 193.3
Treatment of Gastrointestinal Parasitic Infections

Drug	Adult Dosage	Pediatric Dosage
	Amebiasis (Entamoeba Histolytical): Asymptomatic	
Drugs of Choice:		
1. Iodoquinol	650 mg PO tid × 20 d	30–40 mg/kg/d (max 2 g) PO in 3 doses × 20 d
2. Paromomycin	25–35 mg/kg/d PO in 3 doses × 7 d	25–35 mg/kg/d PO in 3 doses × 7 d
3. Diloxanide furoate	500 mg PO tid × 10 d	20 mg/kg/d PO in 3 doses × 10 d
	Amebiasis (Entamoeba Histolytical): Mild to Moderate Intestinal Disease	
Drugs of Choice:		
1. Metronidazole	500–750 mg PO tid × 7–10 d	35–50 mg/kg/d PO in 3 doses × 7–10 d
2. Tinidazole	2 g PO daily × 3 d	> or equal to 3 yrs: 50 mg/kg/d (max 2 g) PO × 3 d
Either followed by:		
a. Iodoquinol	650 mg PO tid × 20 d	30–40 mg/kg/d (max 2 g) PO in 3 doses × 20 d
b. Paromomycin	25–35 mg/kg/d PO in 3 doses × 7 d	35–50 mg/kg/d PO in 3 doses × 7 d
	Amebiasis (Entamoeba Histolytical): Severe Intestinal Disease and Extraintestinal Disease	
Drugs of Choice:		
1. Metronidazole	750 mg PO tid × 7–10 d	35–50 mg/kg/d PO in 3 doses × 7–10 d
2. Tinidazole	2 g PO daily × 3 d	> or equal to 3 yrs: 50 mg/kg/d (max 2 g) PO × 3 d
Either followed by:		
a. Iodoquinol	650 mg PO tid × 20 d	30–40 mg/kg/d (max 2 g) PO in 3 doses × 20 d
b. Paromomycin	25–35 mg/kg/d PO in 3 doses × 7 d	25–35 mg/kg/d PO in 3 doses × 7 d
	Ascariasis (Ascaris Lumbricoides, Roundworm)	
Drugs of Choice:		
1. Albendazole	400 mg PO × 1 dose	400 mg PO × 1 dose
2. Mebendazole	100 mg PO bid × 3 d or 500 mg PO × 1 dose	100 mg PO bid × 3 d or 500 mg PO × 1 dose
3. Ivermectin	150–200 µg/kg PO × 1 dose	150–200 µg/kg PO × 1 dose
	Enterobius Vermicularis (Pinworm)	
Drug of Choice:		
1. Pyrantel pamoate	11 mg/kg PO × 1 dose (max 1 g); repeat in 2 wks	11 mg/kg PO × 1 dose (max 1 g); repeat in 2 wks
2. Mebendazole	100 mg PO once; repeat in 2 wks	100 mg PO once; repeat in 2 wks
3. Albendazole	400 mg PO once; repeat in 2 wks	400 mg PO once; repeat in 2 wks
	Giardiasis (Giardia Lamblia)	
Drug of Choice:		
Metronidazole	250 mg PO tid × 5–7 d	15 mg/kg/d PO in 3 doses × 5–7 d
Alternatives:		
1. Tinidazole	2 g PO × 1 dose	50 mg/kg PO × 1 dose (max 2 g)
2. Nitazoxanide	500 mg PO bid × 3 d	1–3 yrs: 100 mg PO bid × 3 d 4–11 yrs: 200 mg PO bid × 3 d >12 yrs: 500 mg PO bid × 3 d
	Hookworm Infection (Ancylostoma Doudenale, Necator Americanus)	
Drugs of Choice:		
1. Albendazole	400 mg PO × 1 dose	400 mg PO × 1 dose
2. Mebendazole	100 mg PO bid × 3 d or 500 mg PO × 1 dose	100 mg PO bid × 3 d or 500 mg PO × 1 dose
3. Pyrantel pamoate	11 mg/kg (max 1 g) PO × 3 d	11 mg/kg (max 1 g) PO × 3 d
	Strongyloidiasis (Strongyloides Stercoralis)	
Drug of Choice:		
Ivermectin	200 µg/kg/d PO × 2 d	200 µg/kg/d PO × 2 d
Alternative:		
Albendazole	400 mg PO bid × 7 d	400 mg PO bid × 7 d
	Trichuriasis (Trichuris Trichiura, Whipworm)	
Drug of Choice:		
Mebendazole	100 mg PO bid × 3 d or 500 mg × 1 dose	100 mg PO bid × 3 d or 500 mg × 1 dose
Alternatives:		
1. Albendazole	400 mg PO daily × 3 d	400 mg PO daily × 3 d
2. Ivermectin	200 µg/kg PO daily × 3 d	200 µg/kg/d PO × 3 d

Adapted from Drugs for parasitic infections. *Med Lett Drugs Ther.* 2007;5(suppl).

DISPOSITION

Many GI parasitic illnesses can be treated with the appropriate antiparasitic agents on an outpatient basis. However, there may be specific indications for inpatient treatment, depending on the causative organism, extent of disease, concomitant medical conditions (immunocompromised patients, etc.), and the reliability of compliance with treatment and adequate follow-up.

Indications for inpatient treatment and potential complications:

- Giardia infection: abnormal electrolytes secondary to excessive diarrhea may require hospitalization.
- *E. histolytica* infection: fulminant rectocolitis, massive GI bleeding, perforation, peritonitis, toxic megacolon, and amebic liver abscess are potential complications.
- *Cryptosporidium* infection: severe diarrhea, especially in immunocompromised patients.
- *A. lumbricoides* infection: intestinal obstruction that requires surgery, especially in the pediatric population.
- *S. stercoralis* infection: hyperinfection syndrome may be fatal in the immunocompromised patient.
- *Necator* and *Ancylostoma* infections: severe hypochromic microcytic anemia in patients with heavy worm burdens.
- *T. trichiura* infection: severe anemia or rectal prolapse.
- *E. vermicularis:* rarely if ever requires inpatient care.

Cysticercosis

Parasitic disease may present with CNS pathology and requires the emergency physician to have a basic understanding of the life cycle of the organisms involved to diagnose and treat the infection.

Protozoal infestations such as malaria may present with neurologic manifestations. Falciparum malaria can cause sludging of parasitized red cells in brain capillaries, resulting in severe CNS dysfunction, which can progress to coma and death. Early recognition and treatment are essential to prevent this outcome.

Helminthic CNS disease is caused primarily by two tapeworms: *Taenia solium* (pork tapeworm) and *Echinococcus granulosus. T. solium,* an intestinal parasite in humans, can invade other tissues in

its larval form, causing cysticercosis. Although 60% of reported cases of cysticercosis involve the brain, it is believed that muscular and subcutaneous encystment is more common (24). Humans may acquire the infestation by eating cured or undercooked pork meat that has been infected with the larvae of *T. solium* (24). In addition, infection may be acquired through the fecal–oral route by consuming contaminated food, such as raw vegetables, or water (25). Cysts formed in the brain (i.e., neurocysticercosis) can cause seizures or produce symptoms through mass effect (2). Worldwide and in the United States, cysticercosis is the most common parasitic disease of the CNS (25). Immigrants from endemic areas, such as Mexico and Central America, account for the vast majority of cases in the United States. Cysticercosis is most prevalent in communities where there is close contact between humans and pigs, and where hygiene is poor (25). *E. granulosus* also forms cysts in the CNS that can mimic neoplastic disease by causing compression effects or seizures.

CLINICAL PRESENTATION

Although *T. solium* is the most common parasitosis of the human CNS, it is symptomatic in only 50% of patients (24). Patients with cysticercosis of the brain may present with focal neurologic findings or impaired sensorium. The clinical features depend primarily on the location of the cyst. The cyst may be located in the meninges, brain parenchyma, or ventricles. The common presenting features include:

- seizures (most prevalent)
- adult-onset seizures in the Third World are most often caused by neurocysticercosis (26)
- focal neurologic deficits
- increased intracranial pressure
- obstructive hydrocephalus
- stroke
- status epilepticus and mechanical hydrocephalus (most frequent causes of death)

ED EVALUATION AND MANAGEMENT

The information obtained from laboratory examination is often limited. A mild peripheral leukocytosis and eosinophilia may be seen. Cerebrospinal fluid (CSF) findings suggestive of cysticercal arachnoiditis include an elevated protein level, eosinophilia, and a predominantly lymphocytic pleocytosis. Several immunologic tests of the serum and CSF have been developed to aid in the diagnosis of cysticercosis (25). Microscopic examination of stool preparations may reveal typical eggs, proglottids (gravid uterus segments), or scolices, which are the heads of the worm. Although the patient with neurocysticercosis may no longer have a tapeworm at the time the diagnosis is made, stools of both the patient and family members should be examined for several days (25). Serologic diagnosis is necessary to confirm *E. granulosus* infection.

Laboratory personnel should be consulted to determine the most appropriate procedures for collecting and handling specimens. The laboratory should be informed of the patient's clinical diagnosis to assist in sample analysis. Consultation with an infectious disease expert may be helpful if the clinician is unfamiliar with the potential manifestations of a particular disease.

Computed tomography (CT) scanning of the head may show both calcified and noncalcified cysts (20,25). Contrast-enhanced CT scanning may demonstrate ring-enhancing lesions in both cysticercosis and echinococcal cyst disease. Magnetic resonance imaging (MRI) has been shown to be more sensitive than CT scan for the detection of active neurocysticercosis, because of the superior ability of MRI to image cysts in the brainstem, subarachnoid space, and ventricles. CT, however, is a better modality for imaging inactive, calcified cysts (20).

Treatment of parasitic CNS disease may involve medical or surgical interventions and depends on the clinical signs and symptoms, the presence of active noncalcified or inactive calcified cysts, and the occurrence of complications. In addition to symptomatic treatment, options for the treatment of neurocysticercosis include anticysticercal drugs, corticosteroids, CSF shunting, and surgical cyst removal (25). Most parasitic infections in the active phase with viable cysts are readily treated with safe and

effective agents. Patients can commonly be treated as outpatients, with appropriate follow-up.

If active neurocysticercosis is suspected, praziquantel (50 mg/kg/d in three divided doses for 15 days) or albendazole (400 mg two times a day for 8 to 30 days) should be initiated (10). Albendazole has shown to be superior to praziquantel in reducing the number of live cysts and in clinically relevant outcomes (27). Corticosteroids should be given for 2 to 3 days before and during drug therapy to suppress the inflammatory response induced by destruction and death of the live cysts (10). Albendazole (400 mg two times a day for 28 days) has been used to treat echinococcal cysts. Surgical removal of cysts remains the most effective treatment, especially when obstructive hydrocephalus is a complicating factor (14). Patients who present with inactive disease (e.g., seizures secondary to parasitic calcifications) are not candidates for treatment with antihelminthic agents. Seizures are treated no differently than seizures from other causes. Neurologic or neurosurgical consultation is appropriate for these patients.

DISPOSITION

Most patients with cysticercosis will either remain asymptomatic without treatment or will be able to receive antihelminthic treatment as an outpatient. However, the clinician should be aware of the need for inpatient treatment in patients who present with signs of severe neurocysticercosis infection; patients with status epilepticus, mechanical hydrocephalus, or stroke require inpatient care and definitive neurosurgery.

CRITICAL INTERVENTIONS

- Diagnose malaria using a thin Giemsa-stained peripheral blood smear to demonstrate intracellular forms of the parasite. Repeat negative blood films every 12 to 24 hours to obtain three negative sets if diagnosis is strongly suspected.
- Diagnose infestation with the pinworm E. vermicularis using clear cellulose tape placed against the perianal skin, lifted off, and then

applied (adhesive side down) to a glass slide and viewed under a microscope to identify the characteristic eggs.
- Diagnose cysticercosis with CT and/or brain MRI in addition to serologic testing.

Common Pitfalls

- Failure to consider parasitic disease as a potential etiology for a variety of systemic, GI, CNS, and skin complaints. Parasitic disease should be considered in any patient presenting from an endemic area or with a travel history to an endemic area.
- Failure to consider parasitic infestation in travelers months after their return.
- Failure to consult reference textbooks and current therapeutic guidelines concerning the appropriate diagnosis and treatment for these diseases.

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CHAPTER 194

Blood and Body Fluid Exposures in the Healthcare Worker

Samuel O. Clarke and Peter E. Sokolove

Despite the introduction of a safe and effective vaccine in 1982, hepatitis B (HBV) remains a potential occupational hazard among healthcare workers. Between 804,000 and 1.4 million Americans are infected with HBV, the majority of whom are unaware of their infection status (1). As of 2011, the majority of healthcare providers in the United States have received vaccination against Hepatitis B, and between 93% to 95% are thought to be protected based on vaccination efficacy data (2). Though the incidence of hepatitis B infection in 2007 has declined by 82% since 1990, unvaccinated healthcare workers remain at significant risk (1,3). HBV vaccination plays the central role in prevention of disease among healthcare workers and has reduced the number of HBV cases, hospitalizations, and deaths by about 80% since prevaccine levels (4).

Although the acquired immunodeficiency syndrome (AIDS) accounts for a much smaller number of cases than does hepatitis B, it often causes more concern among healthcare workers. It is estimated that over 380,000 needle stick exposures to blood occur annually among US healthcare workers, equating to roughly 1 in 10 healthcare workers having a significant exposure each year (5). A recent study of patients with penetrating trauma presenting to an urban emergency department (ED) found an incidence of seropositivity for HIV, HBV, or HCV of more than 9%, and the

majority of cases were in patients who were unaware of their seropositive status (6). Despite these risks, as of December 2010, there were only 57 confirmed and 143 possible occupational human immunodeficiency virus (HIV) infections among healthcare workers in the United States (7). Emergency physicians must be well versed in the management of HIV exposures, as both healthcare workers and non-healthcare workers visit the ED for exposure management.

Previously known as non-A non-B hepatitis, hepatitis C virus (HCV) is now the most common chronic blood-borne infection in the United States. Between 3.2 and 5.4 million Americans are chronically infected with this virus, with about 20,000 new infections each year (8,9). Though the overall prevalence of HCV in healthcare workers is similar to that of the general population (1% to 2%), ED personnel are at high risk of exposure. In a recent study from a Midwestern ED, the prevalence of HCV infection among patients was 4% (10). In 2005, about 8% of persons with new HCV infections in the United States reported occupational exposure to blood (8).

CLINICAL PRESENTATION

Healthcare workers frequently present to the ED after exposure to material potentially infected with HBV, HCV, or HIV. First, the exposure must be assessed. Although blood is the single most important source of infection, other fluids may also transmit disease. Semen or vaginal secretions; cerebrospinal, synovial, pleural, peritoneal, pericardial, or amniotic fluid; and tissue are capable of transmitting HIV, HBV, and probably HCV. Unless blood is visible in them, feces, nasal secretions, sputum, sweat, and tears have not been identified as vehicles of transmission for HBV, HCV, or HIV infection. Transmission occurs most effectively through direct percutaneous exposure (e.g., needlestick); although far less likely, exposure through mucous membranes or open skin lesions can also result in HBV, HCV, and HIV transmission. Casual contact, airborne, and fecal–oral transmission have not been documented (8). The factors associated with the greatest risk of HIV transmission after percutaneous exposure are: deeply penetrating injury, presence of visible blood on the injuring object, prior placement of the object in

a patient's vein or artery, and end-stage AIDS in the source patient (11).

ED EVALUATION

An initial evaluation should be made to assess the risk of disease transmission. Information about the injury should be gathered, including the infectious material, instrument procedure performed, depth of penetration, and volume of blood transferred. The source person should be evaluated for HIV and hepatitis risk factors, clinical signs of disease, previous HIV therapy, and viral load or CD4 count, if known.

The healthcare worker should be evaluated for his or her medical history and immunization status for hepatitis B and tetanus. The source blood should be tested for hepatitis B surface antigen (HBsAg), HCV, and HIV antibodies. If the source is found to be positive for HBsAg, the source should also then be tested for hepatitis B e antigen (HBeAg) and direct measurement of viral DNA, as some patients do no exhibit e antigen despite high viral burden (2).

The exposed healthcare worker should be tested for hepatitis B surface antibody (HBsAb), HCV, and HIV. Baseline complete blood count, basic metabolic profile, and liver function tests should be obtained along with urine pregnancy screening, as appropriate (12,13).

The circumstance of testing source patients who are unable or unwilling to consent to testing deserves special mention. There is considerable heterogeneity in state laws regarding unconsented testing, with some states (e.g., Arizona, Maine, New Mexico, Oregon) requiring a court order for any unconsented test, and others (e.g., California, South Carolina, Rhode Island) allowing unconsented testing even in patients with full capacity who refuse voluntary testing (14). Emergency physicians should be familiar with and adhere to laws governing unconsented testing for the state in which they practice. Every attempt should be made to explain the risks and benefits of testing to source patients, as well as the possibility of unconsented testing in certain circumstances.

KEY TESTING

- Source patient: Hepatitis B surface antigen (HBsAg), HCV antibody, HIV antibody, HBeAg, and Hepatitis B viral DNA if source patient is found to be positive for HBsAg
- Exposed worker: Hepatitis B surface antibody (HBsAb)*, HCV antibody, HIV antibody, complete blood count, basic metabolic profile, liver function tests, urine pregnancy

*Unless worker known to be immune against Hepatitis B

ED MANAGEMENT

Hepatitis B Virus Exposure

Two types of products are available for the management of the exposed healthcare worker. Hepatitis B immune globulin (HBIG), derived from plasma containing high titers of antibody to HBsAg, confers passive immunity. Side effects are minimal, and there is no evidence of HBV or HIV transmission with this product. For postexposure prophylaxis, the dose is 0.06 mL/kg intramuscularly. It should be administered within 72 hours of exposure (preferably within 24 hours) and is probably not useful beyond 7 days. The wholesale cost of HBIG in 2010 ranged from $640 to $804 (15).

Hepatitis B vaccine is available for active immunization. It is a recombinant vaccine that is very safe, even in pregnancy. For postexposure prophylaxis of nonvaccinated individuals, 1 mL of vaccine is administered intramuscularly in the deltoid within 7 days of exposure and repeated at 1 month and 6 months. Because about 10% of adults will not initially achieve the recommended antibody titer after this series, antibody levels should be checked 4 to 6 weeks after the series is completed. Nonresponders should be given a second three-dose series of vaccine and retested for antibody levels (16). For healthcare workers who achieve a level of at least 10 mIU/mL, the vaccine is essentially 100% effective in preventing subsequent HBV infection. The wholesale price in 2013 for HBV vaccine ranges from $52.50 to $61.22 per dose (17).

Whether to administer HBIG, HBV vaccine, both, or neither is based on the HBsAg status of the source person and the vaccination status of the exposed healthcare worker (Fig. 194.1) (16). A source person can transmit HBV if HBsAg is present, but the degree of infectivity is best correlated with HBeAg positivity. The risk of seroconversion after a percutaneous injury ranges from 23% to 62% in unvaccinated persons and depends on the HBeAg status of the source (18). Overall, about 25% of those infected with HBV develop acute hepatitis, and 6% to 10% develop chronic infection. These patients are at increased risk of cirrhosis and hepatocellular carcinoma.

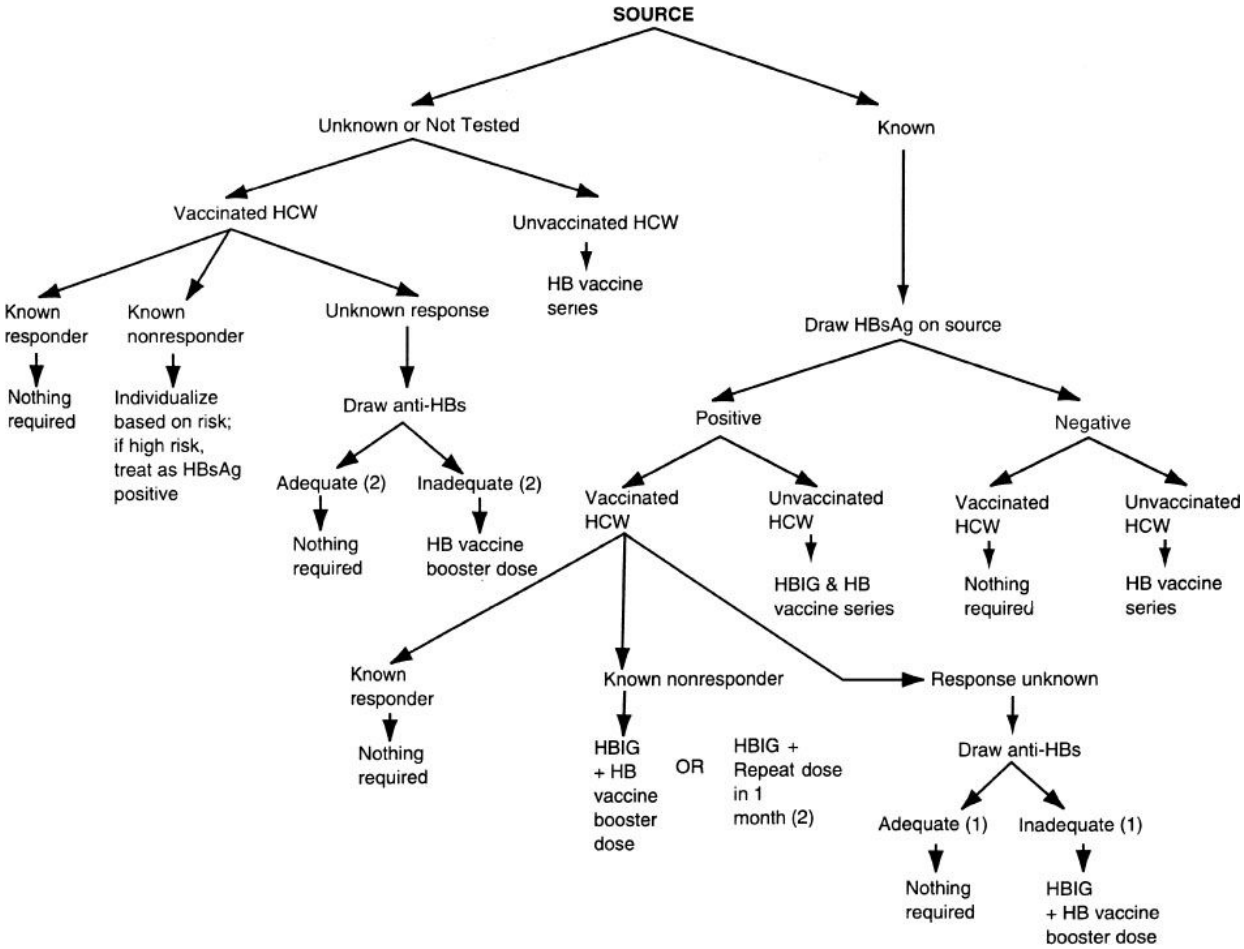

FIGURE 194.1 Hepatitis B exposure algorithm. **1:** Adequate antibody ≥10 mIU/mL. **2:** Preferred for those who have failed to respond to a second three-dose series of vaccine. (Adapted from CDC. Updated U.S. Public Health Service guidelines for the management of

occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. *MMWR Morb Mortal Wkly Rep.* 2001;50(RR-11):22.)

Hepatitis C Virus Exposure

There are currently no agents available for managing exposure of the healthcare worker to HCV (16). Immune globulin is not useful for postexposure prophylaxis of HCV for a number of reasons. In contrast to HBsAb, HCV antibody is only a marker antibody, not a neutralizing antibody. Even if a neutralizing antibody did exist among the donor population, immune globulin is derived from plasma donors that are excluded from donation if they test positive for HCV. Finally, HCV mutates rapidly, and new variants may be unaffected by neutralizing antibodies.

There is currently no vaccine against HCV, as this virus demonstrates great genetic heterogeneity and a high mutation rate. The combination of pegylated interferon and ribavirin is commonly used successfully to treat patients with chronic hepatitis due to HCV (19). Unfortunately, there is currently no postexposure prophylaxis available for HCV, though recently marketed HCV protease inhibitors may play a future role (2). Thus, the use of standard precautions and medical devices with safety features is crucial for preventing HCV exposures (18).

The average risk of acquiring HCV infection after percutaneous exposure is 1.8% and ranges from 0% to 7% (16,18). This risk is similar to the risk of HBV transmission after percutaneous exposure to HBsAg-negative blood. Of those who acquire HCV infection, 55% to 85% will remain infected. The risk of developing cirrhosis ranges between 5% to 25% over periods of 25 to 30 years, and the risk of developing hepatocellular carcinoma is between 1% and 3% per year (19).

Human Immunodeficiency Virus Exposure

ED management of potential exposure to HIV materials consists of serologic testing of the exposed healthcare worker and exposure

source, counseling the healthcare worker on the risk for infection, and consideration of postexposure prophylaxis. Though the use of antiviral agents to prevent HIV seroconversion in exposed healthcare workers was once considered highly controversial, an accumulation of evidence supports the use of certain drugs in many cases. The theoretical basis for postexposure prophylaxis is that antiretroviral agents may prevent or limit the replication of HIV in dendritic cells or regional lymph nodes, which appear to be the initial targets and route of spread of HIV (16). Animal studies as well as studies of prophylactic administration of antiretroviral medications to HIV-infected mothers have demonstrated a significant protective effect from initiation of prophylactic antiretroviral treatment (16). Though transmission during pregnancy is different from percutaneous exposure, these data clearly demonstrate that antiviral agents can be used to prevent blood-borne infection in an HIV-negative individual. The most compelling evidence of postexposure prophylaxis efficacy, however, was a multinational case-control study, performed by the CDC (11). In this study of healthcare workers who had HIV exposures, mostly as a result of hollow-bore needlesticks, the risk for HIV infection was reduced by 81% if AZT was given after exposure. These data prompted the Public Health Service in 1998 to first recommend postexposure prophylaxis for healthcare workers exposed to HIV (16). These recommendations were updated and reaffirmed in 2001 and 2005, and a new revision of the CDC guidelines is currently underway (16,20).

Though AZT is the only drug with clinical data supporting its use for HIV postexposure prophylaxis in humans, multidrug regimens are now employed because of concerns about AZT-resistant strains of HIV and a demonstrated synergistic effect of certain antiviral agents in the treatment of patients for AIDS.

There are now six classes of medications that can be used for HIV postexposure prophylaxis. Most commonly used are the nucleoside reverse transcriptase inhibitors and protease inhibitors. Other choices include nonnucleoside reverse transcriptase inhibitors, *nucleotide* reverse transcriptase inhibitors, integrase inhibitors, and fusion inhibitors (2). Each of these medications has associated risks,

including various side effects, drug interactions, and oncogenic or teratogenic potential. The drug regimen chosen depends upon the exposure severity, the suspicion for antiviral resistance in the source, and the exposed patient's medical history. Expert consultation should be sought to assist with drug selection whenever source resistance is suspected (20). All of the regimens recommend a 28-day course of treatment for a known HIV-positive source or high-risk exposure (2).

When determining whether to initiate postexposure prophylaxis and which agents to choose, the physician must consider a number of factors. The route and severity of exposure help determine the risk of seroconversion and thus the potential benefit of postexposure prophylaxis. If the skin integrity is compromised or if mucous membranes are exposed, transmission is unlikely but can occur. The risk of transmission after a mucous membrane exposure to blood is about 0.1% (1 in 1,000). The risk of transmission can be higher if a large volume of blood is involved or if prolonged contact occurs. The average risk for HIV transmission after percutaneous blood exposure is about 0.3% (1 in 300) but depends on the severity of the exposure (16). Table 194.1 lists the risk factors for HIV transmission after percutaneous blood exposure, as reported in the previously described CDC case-control study (11).

TABLE 194.1
Risk Factors for HIV Transmission after Percutaneous Blood Exposure

Risk Factor	Odds Ratio	95% CI
Deep injury	15	6–41
Blood visible on device	6.2	2.2–21
Procedure with needle placed directly into artery or vein	4.3	1.7–12
Terminal AIDS in source patient	5.6	2–16
Postexposure zidovudine	0.19	0.06–0.52

Adapted from Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. *N Engl J Med.* 1997;337:1487.

The HIV status of the source person is also important when assessing the risk of transmission and choice of antiviral agents. If the source person is currently HIV-negative and has not had a recent retroviral-like illness (symptoms similar to those of acute mononucleosis), postexposure prophylaxis is not indicated. For HIV-positive source persons, the degree of infectivity is related to the patient's viral load. HIV-positive source patients can be categorized as either lower risk (class 1) or higher risk (class 2). Class 1 patients include those with asymptomatic HIV infection and a viral load of $<$1,500 RNA copies/mL. Class 2 patients include those with either symptomatic HIV, AIDS, acute seroconversion, or a viral load above 1,500 RNA copies/mL (20).

Based upon the severity of an exposure and the source HIV status (class 1 or 2), either a basic (two-drug) or an expanded ($\geq$three-drug) regimen is recommended by the CDC (20). The most commonly used *basic regimen* combines AZT and lamivudine (3TC). Other recommended basic regimens are AZT plus emtricitabine (FTC); tenofovir (TDF) plus 3TC; and TDF plus FTC. Alternative basic regimens, to be considered in special circumstances, include 3TC plus stavudine (d4 T); FTC plus d4 T. The preferred *expanded regimen,* used for higher-risk exposures, is made by adding lopinavir/ritonavir (a combination of two protease inhibitors) to the basic regimen. Alternative expanded regimens, to be considered in special circumstances, can be made by substituting other medications in place of lopinavir/ritonavir. The choices include atazanavir (ATV) $\pm$ ritonavir (RTV); fosamprenavir (FOSAPV) $\pm$ RTV; indinavir (IDV) $\pm$ RTV; saquinavir (SQV) $\pm$ RTV, or efavirenz (EFV). Antiviral agents that are generally *not* recommended for postexposure prophylaxis include nevirapine (NVP), delavirdine (DLV), abacavir (ABC), and zalcitabine (ddC). Finally, the HIV fusion inhibitor enfuvirtide can be considered for postexposure prophylaxis but only with expert consultation (2,20).

For skin and mucous membrane exposures, the postexposure prophylaxis regimen chosen falls into three general categories (Table 194.3). For small volume exposures (few drops of blood) from an HIV class 1 source, a basic regimen (two drugs) should be *considered.*

If either the exposure is of large volume (major blood splash) or the source is HIV class 2, a basic regimen should be *recommended.* In cases where there is both a large volume exposure and an HIV class 2 source, an expanded regimen (at least three drugs) should be recommended (20).

At times, emergency physicians need to make postexposure prophylaxis recommendations to patients who have sustained an exposure from either an unknown source (e.g., needle left on an open counter) or, more commonly, from a known source with unknown HIV status. In such circumstances, the need for HIV postexposure prophylaxis should be decided on a case-by-case basis. In cases of an unknown source, postexposure prophylaxis is generally not recommended, but a two-drug regimen should be considered for exposures occurring in an HIV-likely setting (e.g., exposure to a discarded needle on an AIDS ward). For a source of unknown HIV status, rapid HIV testing can be used to quickly determine the need for postexposure prophylaxis (16). Postexposure prophylaxis can be withheld pending HIV test results but only if a 1-hour rapid HIV test is available. Although this test is now used in more than half of academic EDs, it is not available in all practice settings (21). In such circumstances, the decision to start postexposure prophylaxis should be made via discussion of risks and benefits with the exposed person, based upon the source person's likelihood of HIV infection. Postexposure prophylaxis can always be initiated and then stopped or modified once the source person's HIV status has been determined (20).

Animal studies have demonstrated that the efficacy of postexposure prophylaxis is related to the time from exposure to initiation of treatment. Potential HIV exposures should be treated as true emergencies, and postexposure prophylaxis should be initiated within 2 hours of exposure if possible (22). It is unclear how long after exposure treatment can be initiated and still be effective, but animal data suggest that some benefits may persist up to 36 hours (22).

Once HIV postexposure prophylaxis has been initiated, medications are optimally administered for a 4-week course. This can

be challenging, because adverse symptoms are very common, causing about one-third of healthcare workers to discontinue therapy. Thus, patients should be prescribed medications (e.g., antiemetics, antidiarrheal agents) to mitigate the side effects of the selected treatment regimen. Alternative basic regimens are becoming increasingly popular due to the belief that their more favorable side effect profiles result in better rates of compliance (22,23). The New York State Department of Health AIDS institute currently recommends a three-drug regimen of tenofovir, emtricitabine, and raltegravir for initial postexposure prophylaxis (22). All patients sustaining an HIV exposure should be referred for follow-up and re-evaluation, even if postexposure prophylaxis was not initiated, to allow for counseling, postexposure testing, and medical evaluation. When initiating postexposure prophylaxis, follow-up should probably occur within 72 hours. Prompt follow-up is most important if new information about the source becomes available (e.g., viral load, medication resistance), as this may warrant a change in medication regimen (20).

Summary of Acute Management

Acute management includes thorough washing of the exposed area with soap and warm water or flushing of mucous membranes. As with all wounds, the need for tetanus toxoid administration should be considered. HBIG or hepatitis B vaccine or both should be administered as indicated (Fig. 194.1). HIV postexposure prophylaxis should be recommended based on the exposure type and the source HIV status (see Tables 194.2 and 194.3). The healthcare worker should be counseled regarding the risks of HBV, HCV, and HIV infection and modifications of behavior (e.g., abstinence or condom use) to prevent secondary infection of others.

TABLE 194.2
Recommended HIV Postexposure Prophylaxis for Percutaneous Injuries

Infection Status of Source		
Exposure Type	HIV-positive Class 1[a]	HIV-positive Class 2[a]
Less severe[b]	Recommend basic 2-drug PEP	Recommend expanded ≥3-drug PEP
More severe[c]	Recommend expanded 3-drug PEP	Recommend expanded ≥3-drug PEP

[a]HIV-positive, Class 1—asymptomatic HIV infection or known low viral load (e.g., <1,500 RNA copies/mL). HIV-positive, Class 2—symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of postexposure prophylaxis should not be delayed pending expert consultation and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.
[b]Less severe (e.g., solid needle or superficial injury).
[c]More severe (e.g., large-bore hollow needle, deep puncture, visible blood on device, or needle used in patient's artery or vein).
Adapted from CDC. Updated U.S. Public Health Service Guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. *MMWR Morb Mortal Wkly Rep.* 2005;54(RR-9):3.

TABLE 194.3
Recommended HIV Postexposure Prophylaxis for Mucous Membrane Exposures and Non-Intact Skin Exposures[a]

Infection Status of Source		
Exposure Type	HIV-positive Class 1[b]	HIV-positive Class 2[b]
Small volume[c]	Consider basic 2-drug PEP[d]	Recommend basic 2-drug PEP
Large volume[e]	Recommend basic 2-drug PEP	Recommend expanded ≥3-drug PEP

[a]For skin exposures, follow-up is indicated only if there is evidence of compromised skin integrity (e.g., dermatitis, abrasion, or open wound).
[b]HIV-positive, Class 1—asymptomatic HIV infection or known low viral load (e.g., <1,500 RNA copies/mL). HIV-positive, Class 2—symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of postexposure prophylaxis should not be delayed pending expert consultation and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.
[c]Small volume (i.e., a few drops).
[d]The designation, "consider PEP" indicates that postexposure prophylaxis (PEP) is optional and should be based on an individualized decision between the exposed person and the treating clinician.
[e]Large volume (i.e., major blood splash).
Adapted from CDC. Updated U.S. Public Health Service Guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. *MMWR Morb Mortal Wkly Rep.* 2005;54(RR-9):3.

CRITICAL INTERVENTIONS

- Initiate therapy for post-HIV exposure within 2 hours.
- Administer postexposure prophylaxis HBIG within 72 hours of exposure (preferably within 24 hours) and hepatitis B vaccine within 7 days of exposure and repeated at 1 month and 6 months to unvaccinated healthcare workers who are exposed to an HbsAg-positive source.

Common Pitfalls

- A common error in the management of healthcare worker exposures is to provide either unnecessary or inadequate treatment. Unnecessary treatment usually results from an overestimation of the infectious potential of an exposure, such as providing three-drug antiretroviral therapy for a blood splash onto intact skin. Undertreatment can occur if the treating physician is unaware of the benefit of postexposure prophylaxis or if treatment for HIV exposure is delayed. These pitfalls can be avoided by applying a standardized protocol, such as the algorithms presented here. In uncertain or complex cases, consultation with an employee health service or an infectious disease specialist is advised.

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CHAPTER 195

Food Poisoning

Marc C. Restuccia

The Centers for Disease Control (CDC) estimates that roughly 1 in 6 Americans (48 million) become ill, 128,000 are hospitalized and 3,000 die of foodborne illnesses each year (1). This number is an improvement over previous estimates published by CDC of 76 million made ill, 323,000 hospitalized and 5,000 annual deaths (2). Despite these improvements, foodborne illness remains a serious public health problem. Even as advances have been made in decreasing the incidence of certain foodborne illnesses, the incidence of others has either remained the same or worsened somewhat (3). In 1996, the CDC established the Foodborne Diseases Active Surveillance Network, known as FoodNet. This easily accessible resource tracks foodborne illnesses as well as monitors efforts to enhance food safety.

Food can be contaminated during all stages of production. “Modern” industrial sized farms and centralized; worldwide distribution systems create opportunities for amplification of any breakdown in food safety systems. Food can be contaminated with bacteria, viruses, parasites, toxins, and the relatively newly described prions.

For most people suffering from foodborne illness, it is a self-limited process with nausea, vomiting, abdominal pain, and diarrhea. In other patients, however, it can present with neurologic symptoms, hepatic failure, or renal failure. As in many disease processes, the young, the old, and the immunocompromised are at greater risk for significant sequelae. The clinician must also be wary of other, often more serious illnesses, which can be mistaken for food poisoning.

Individual cases of foodborne illness are virtually impossible to diagnose with any certainty, overlapping with nonfoodborne gastrointestinal infections. The diagnosis is most typically entertained and confirmed when multiple persons become ill and the etiology can be traced to a specific event and/or food.

CLINICAL PRESENTATION

Alteration of normal gastrointestinal tract function is the most typical presentation for a patient with a foodborne illness. Nausea, vomiting, diarrhea, abdominal pain, and fever are the most common complaints. However exceptions exist; botulism, caused by the botulinum toxin, classically seen in infants consuming raw honey (4), presents with a progressive paralysis. Other manifestations of foodborne illness can include neurologic symptoms (seen with Scombroid and Ciguatera fish poisoning as well as mushrooms) as well as systemic illness including fever, weakness, jaundice, and arthritis (seen with Salmonella, Toxoplasma, and Trichinella poisoning) (5). Abdominal pain is a frequent complaint in patients with a foodborne illness and it can be difficult to differentiate the cause from other conditions such as appendicitis.

Diarrhea can be watery or bloody. This may be helpful in narrowing down the diagnostic possibilities. Although the presence of watery diarrhea is fairly nonspecific, bloody diarrhea implies an enteroinvasive diarrhea, with the most common cause being *Escherichia coli* 0157-H7 and Salmonella. Campylobacter less commonly causes bloody diarrhea (6).

With progression of the illness, dehydration may develop. Thirst, dry mucous membranes and eventually tachycardia with hypotension can be seen, especially in acutely ill children or the elderly. Altered mental status more commonly affects in the young and elderly. Table 195.1 lists the major manifestations associated with the more common pathogenic organisms.

TABLE 195.1
Bacterial Causes of Food Poisoning

Agent	Incubation	Duration	Common Food Sources	Manifestations	Treatment
Bacillus anthracis[a]	2 d to weeks	Weeks	Insufficiently cooked and contaminated meat	Nausea, vomiting, malaise, bloody diarrhea Acute abdominal pain	Cipro, PCN, or Doxycycline
Bacillus cereus Vomiting	3 hrs	12 hrs	Spices and grains such as rice, especially	Fried rice ingestion	Supportive
Diarrhea (Toxin)	10 hrs	36 hrs	If inadequate refrigeration	(–) fecal leukocytes	
Campylobacter jejuni	3 d	4 d	Unpasteurized milk, dairy products	abdominal pain, fever, diarrhea, biphasic illness (+) fecal leukocytes	FQ, AG, macrolides
Clostridium botulinum (toxin)	30 hrs	Variable	Improper home canning, unpasteurized honey	Flu-like symptoms, descending weakness or paralysis, ptosis paralysis, may have no GI symptoms	Supportive (horse serum antitoxin)
Clostridium perfringens	12 hrs	24 hrs	Meat, meat by-products, poultry (cooked but inadequately refrigerated)	Nonbloody diarrhea (–) fecal leukocytes	Supportive
Cryptosporidium	6 d	6 d	Hand-pressed cider, municipal water supplies, public pools	Vomiting, diarrhea, worse if immunocompromised	Supportive
Escherichia coli 0157:H7 (toxin)	48 hrs	1 wks	Raw or undercooked beef fast food restaurants	Copious bloody diarrhea, (+) fecal leukocytes, rarely HUS, renal failure	Supportive
Traveler's diarrhea enterotoxigenic (toxin)	12–72 hrs	24–72 hrs	Raw vegetables, seafood, improperly cooked food from street vendors, hot pepper sauce, tap water	Watery diarrhea, low-grade fever, (–) fecal leukocytes	FQ, Macrolides, may consider anti-motility agents with antibiotics
Enteroinvasive (invasive)	12–72 hrs	24–72 hrs	Similar to above	Severe cramps, malaise initially watery, then bloody diarrhea, (+) fecal leukocytes	Macrolides, TMS
Listeria monocytogenes	1–70 d	Variable	Beef, pork, poultry, cheese (soft, "Mexican style," Swiss), milk, contaminated after pasteurization fruits and vegetables, other dairy products	More severe in pregnancy immunocompromised, usually (+) fever, may have limited GI symptoms	Ampicillin, PCN, AG
Salmonella (invasive)	24 hrs	5 d	Dairy products, poultry, eggs, chocolate, coconut, dried foods	Watery, bloody diarrhea, (+/–) fecal leukocytes, possible, possible bacteremia	Immunocomp. pts. septic pts., Rx with ceftriaxone FQ, chloramphenicol
Shigella (invasive)	1–3 d	5 d	Any food contaminated with fecal material during processing, ice in developing countries	Copious bloody diarrhea, fever, cramps, rarely; DIC, HUS, sepsis, children may have seizures, usually (+) fecal leukocytes	Macrolides, TMS
Staphylococcus aureus (toxin)	4 hrs	20 hrs	Milk and dairy products, ham, potato salad, custards, pastry	Vomiting, cramps, diarrhea, usually no fever	Supportive
Vibrio b Cholerae	24–72 hrs	3–7 d	Profuse, watery diarrhea and vomiting, can lead to death from severe dehydration	Contaminated water, fish, shellfish, street vended food typically Latin America or Asia	Supportive care, rehydr., TCN, DCN, adults, Macrolides, FQ
Parahemolyticus	2–48 hrs	2–5 d	Watery diarrhea, abdominal cramps, nausea, vomiting	Undercooked or raw seafood, such as fish, shellfish	Supportive care, in severe cases, TCN, DCN, ceftriaxone, or cefotaxime
Vulnificus	1–7 d	2–8 d	Vomiting, diarrhea, abdominal pain, bacteremia, wound infections, more common if immunocompromised	Undercooked or raw shellfish, especially oysters, other seafood, open wounds	Supportive care, TCN, DCN, ceftriaxone, or cefotaxime
Yersinia enterocolitica	15–24 hrs	2 wks	Foods contaminated with fecal material during handling (e.g., tofu, bean sprouts, milk, milk products, water supply)	Diarrhea, fever, abdominal pain, vomiting, bloody stools, may be protracted, can lead to appendicitis operations (+) or (–) fecal leukocytes	Antibiotics of value FQ, TMS, AG

[a]FQ, fluoroquinolones; AG, aminoglycosides; HUS, hemolytic uremic syndrome; TMS, trimethoprim-sulfamethoxazole; DIC, disseminated intravascular coagulation; TCN, tetracycline; DCN, doxycycline; PCN, penicillin.

From Diagnosis and management of foodborne illness: A primer from physicians and other health care professionals. *MMWR*, 2004.

DIFFERENTIAL DIAGNOSIS

The diagnosis of foodborne illness is typically made on clinical grounds. The Physical examination, although important in assessing the volume status of the patient, typically does not distinguish the cause of nausea, vomiting, abdominal pain, fever, and/or diarrhea. As is noted in Table 195.1, the incubation period for many of these illnesses is measured in hours, if not days. A history of recent meals,

especially meals where other individuals may have shared foods and time of ingestion may be helpful to determine the source.

Toxin-producing pathogens such as enterotoxigenic *E. coli, Staphylococcus aureus,* and *Vibrio cholerae* often cause profuse watery diarrhea. Symptoms begin within hours of ingesting contaminated foods. By way of contrast, organisms such as *Cryptosporidium cyclospora* and *Giardia* also lead to a watery diarrhea, typically days to weeks after ingestion. Hikers and campers who drink unfiltered or untreated back-country water are at risk of developing painful abdominal cramping, profuse watery diarrhea, and flatulence from *Giardia* infection.

Invasive organisms such as nonenterotoxigenic *E. coli, Campylobacter, Shigella, Yersinia,* and *Vibrio* infect the cells lining the intestinal tract and cause a bloody diarrhea that typically begins within 24 hours of ingestion. The stools of such patients will typically have both occult blood and fecal leukocytes (8). The parasite, *Entamoeba histolytica* can also cause bloody diarrhea. *Clostridium difficile,* which colonizes the human gastrointestinal tract after the normal flora has been suppressed by wide-spectrum antibiotics, releases toxins which lead to a profuse bloody diarrhea. Although not a foodborne illness, with increased use of wide-spectrum antibiotics, it is an increasingly and difficult to treat condition causing diarrhea, abdominal pain, vomiting, and fever.

Viral infections are the leading cause of nausea, vomiting, and diarrhea. Rotavirus is an illness of young children during the winter months. Norovirus, Hepatitis A, and Parvovirus show no seasonal predilection. Typically vomiting is more prominent in viral gastroenteritis and toxin-related foodborne illness than in other types of gastroenteritis resulting from bacterial or parasitic infections. Characteristics of the history that are consistent with a viral etiology include an incubation period of 20 to 60 hours, a duration of 12 to 60 hours and a high frequency of vomiting (9).

Contamination of food with pesticides or other chemicals during growth, harvesting, or processing can also lead to foodborne illnesses (10,11).

Other conditions that must be considered in the differential diagnosis of anyone presenting to the emergency department (ED) with nausea, vomiting, fever, and abdominal pain include biliary tract disease, peptic ulcer disease, coronary artery disease, appendicitis, intussusception, volvulus, diverticulitis, inflammatory bowel disease as well as poisoning by heavy metals, mushrooms, and seafood toxicity.

ED EVALUATION

The history should focus on recent meals, within 24 to 48 hours prior to presentation. Key questions include what was consumed, how it was prepared, how was it stored after preparation, and whether or not anyone else is ill who consumed the same food. The time of onset, nature, and progression of the illness, particularly the character of the diarrhea should be noted. Patients should be asked about travel, especially to regions with a high incidence of foodborne illness such as Mexico. Any recent use of antibiotics should be ascertained. For patients who are hikers or campers, questions about drinking unfiltered or untreated water in the recent past should be sought. Underlying medical conditions, especially those that may lead to immunodeficiency such as diabetes, or malignancies should be determined. Other significant medical conditions such as coronary artery disease should be identified and noted.

The physical examination should focus on the hydration status of the patient and a general physical examination, with particular attention to the abdomen. Serial examinations including vital signs, allow the treating clinician to rapidly identify and deterioration of the patient's condition. Laboratory testing may rarely assist in identifying the cause of a foodborne illness. Routine blood tests are usually not indicated. The CDC does recommend blood testing for patients with bloody diarrhea, weight loss, dehydration, fever, prolonged diarrhea (three or more unformed stools per day for several days), neurologic involvement (such as paresthesias, other weakness or cranial nerve palsies), sudden onset of symptoms, or severe abdominal pain (5). Laboratory testing is also recommended for the young and old and in those patients with comorbid conditions

or immunosuppression. In these cases, a complete blood count, basic metabolic panel (electrolytes, BUN, creatinine, glucose), and a urinalysis are reasonable. Blood cultures have long been recommended for patients suspected of bacteremia, however recent literature calls this into question (12). Patients with significant abdominal pain, suspicious for a surgical etiology should have either a screening upright CXR bedside ultrasound or abdominal CT as indicated on the basis of their presentation. A screening ECG is indicated if any concern is raised about the potential for an acute myocardial infarct presenting with GI symptoms. This is especially true for women and the elderly.

Patients with severe abdominal pain and bloody diarrhea should have their stool checked for fecal leukocytes. *C. difficile* stool toxin assays should be ordered on patients with a history of recent antibiotic use.

Stool cultures are indicated for immunocompromised or febrile patients with bloody diarrhea, presence of fecal leukocytes or severe, protracted illness. Laboratory protocols and procedures can differ between facilities. Many laboratories are limited to testing for *Salmonella, Shigella, and Campylobacter* species. If *Vibrio, Yersinia,* or *E. coli* O157:H7 are suspected, special collection and handling are usually necessary. Consultation with the hospital's microbiology laboratory is important to ensure proper collection and handling of specimens. Stool should be examined for parasites if the patient has a suggestive travel history, is immunocompromised or has persistent diarrhea.

KEY TESTING

- Routine (most patients): Electrolytes, HCG
- Bloody diarrhea: Fecal leukocytes/occult blood
- CBC, consider blood cultures
- Titer for *C. difficile*
- Immunocompromised: CBC, blood cultures
- Surgical abdomen: Upright chest x-ray
- Bedside ultrasound
- Abdominal/pelvic CT scan

- Preoperative laboratories
- Travel: Stool for ova and parasites
- Concern for an MI: ECG
- Bloody stools/Immunocompromised: Stool culture

ED MANAGEMENT

The first priority for any patient presenting to the ED with nausea, vomiting, diarrhea, abdominal pain, and fever is adequate volume resuscitation. In many patients this can be accomplished with oral rehydration. Some patients however will not be able to tolerate oral hydration and will have to be resuscitated intravenously. Fluid boluses if needed to establish an age normal mean blood pressure, followed by maintenance infusions should be initiated. Antiemetics such as ondansetron or metoclopramide may be helpful, especially if oral hydration is being attempted. Anti-diarrheal medications are now accepted as routine therapy for patients with traveler's diarrhea, typically caused by strains of *E. coli.* However, such medications should not be given to patients with bloody diarrhea as it is thought that their use can prolong symptoms or lead to more serious complications.

Antibiotics are indicated in only a small number of foodborne illnesses. Diarrhea due to viruses and most bacteria does not improve more rapidly with antibiotics and can actually worsen. However, antibiotics may be appropriate in patients who are septic, immunosuppressed, the elderly, or have serious comorbid conditions. Table 195.1 contains recommendations for when antibiotics are appropriate therapy.

The CDC requires notification of state and/or local public health departments for certain foodborne illnesses. Prompt notification of the appropriate local department of public health enables authorities to determine the best course of action to limit the outbreak. Having a centralized repository for such information allows for earlier recognition of a widespread outbreak of a foodborne illness. Such syndromic surveillance is vital in today's environment where not only "natural" but terrorist threats to the food supply cannot be discounted. When more than a few cases of presumed foodborne

illness are identified, rapid identification of the type and source of the foodborne disease will limit the effects on a population.

CRITICAL INTERVENTIONS

- Rapidly provide adequate resuscitation to patients in hypovolemic shock from dehydration.
- Avoid early diagnostic closure; keep the possibility of more serious sequelae/disease processes in mind.
- Notify appropriate public health officials of potential foodborne illnesses, especially if multiple patients are identified.

DISPOSITION

Most patients can be safely discharged home after being rehydrated and demonstrating their ability to keep oral intake down. Discharge instructions should include maintaining a generous intake of fluid and beginning frequent small meals of solid food as soon as tolerated. Patients should be educated on signs and symptoms of dehydration, such as monitoring their urinary output. They should further be advised to return to the ED if symptoms recur, if they are unable to tolerate oral intake, or if they develop a fever or abdominal pain.

Patients with suspected bacteremia or who do not improve with standard therapy should be admitted to the hospital. Nonbacteremic patients may be suitable for observation status. Patients at the extremes of age, underlying comorbid conditions will usually need to be admitted. If the diagnosis is unclear and symptoms continue, admission will be necessary for further evaluation.

Common Pitfalls

- Failure to consider foodborne illness in all patients with nausea, vomiting, diarrhea, abdominal pain, and/or fever.
- Failure to obtain a history of antecedent antibiotic use, travel, camping or hiking, and diet specifics.
- Failure to consider other diagnoses such as appendicitis, aortic aneurysm, pyelonephritis, cholecystitis, pneumonia, pregnancy,

or myocardial infarction.
- Failure to consider the effects of comorbid diseases in the management of patient with foodborne illness.
- Discharging patients who cannot take oral fluids, especially if they have not been adequately resuscitated.
- Failure to notify public health authorities when treating a patient with suspected or confirmed foodborne illness.

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SECTION XX
Hematologic/Oncologic Emergencies

Section Editor: JEFFREY J. SCHAIDER

CHAPTER 196 Bleeding Disorders

Emily Rose

Emergency physicians encounter bleeding on a daily basis. Lacerations, epistaxis, bruising, hematuria, gastrointestinal (GI) bleeding, and blunt and penetrating trauma are common complaints in the emergency department (ED). Most of these patients have normal clotting function and are bleeding because of a local lesion. This bleeding can be controlled by pressure, packing, suturing, or other local therapy aimed at the specific lesion, and bleeding does not recur if the lesion is properly treated.

In contrast, a patient with a bleeding disorder may bleed spontaneously as well as after trauma, and treatment of the local lesion often may not control the bleeding or prevent its recurrence. The disorder may be congenital or acquired and may involve one or more components of the body's complex coagulation system.

PATHOPHYSIOLOGY

Hemostasis is a complex and tightly regulated physiologic process that involves formation of a blood clot at a site of vessel injury while maintaining normal blood flow elsewhere in the body. There are three phases: (1) primary hemostasis, (2) secondary hemostasis, and (3) fibrinolysis (1).

Primary hemostasis involves the formation of a platelet plug and requires healthy blood vessels, von Willebrand factor (VWF), and a sufficient number of normal functioning platelets. Platelets do not adhere to surfaces or aggregate in healthy blood vessels with normal flow. Vessel injury exposes platelets to subendothelial matrix and triggers platelet adhesion to damaged endothelium or exposed

subendothelial components (2). VWF mediates initial platelet adhesion to sites of vascular injury, facilitates platelet aggregation, and acts as a carrier of FVIII (thus protecting it from cleavage and prolonging the factor's half-life in circulation). Following adhesion, agonists such as collagen and thrombin and some agents produced by the platelet itself trigger platelet activation. Platelets change from a disc shape to a spherical shape and increase contact with other platelets. Platelets are then triggered to secrete several substances that enhance further platelet plug formation, which continues through this positive feedback mechanism (3,4).

Secondary hemostasis involves the formation of fibrin strands by activation of the coagulation cascade. This fibrin mesh is incorporated into and around the initial platelet plug, strengthening and further stabilizing the clot (2).

The coagulation cascade has traditionally been separated into three pathways: the intrinsic, extrinsic, and the common pathways. The classical description of the extrinsic and intrinsic pathways has largely been disregarded as it does not correlate well with the in vivo process (3). It is presented in Figure 196.1 for demonstration of the action of anticoagulants and rationale of clotting studies. In the current understanding of coagulation, tissue factor (TF) is exposed, with endothelial injury which initiates coagulation (see Fig. 196.2). TF combines with activated factor VII (FVII), and this complex activates factor X (FX) and factor IX (FIX). Activated FX catalyzes the conversion of factor II (prothrombin) into thrombin (FIIa). In the amplification phase, thrombin activates platelets which results in assembly of coagulation factors on the platelet membrane and release of granule contents. Thrombin also activates factors V, VIII, and FXI. Factor XIII is activated by thrombin and is responsible for creating stable fibrin clot which prevents early removal of the clot by the fibrinolytic system. Endogenous anticoagulants such as antithrombin III, protein C, and protein S and TF pathway inhibitor act to degrade activated coagulation factors and thereby limit further coagulation (1).

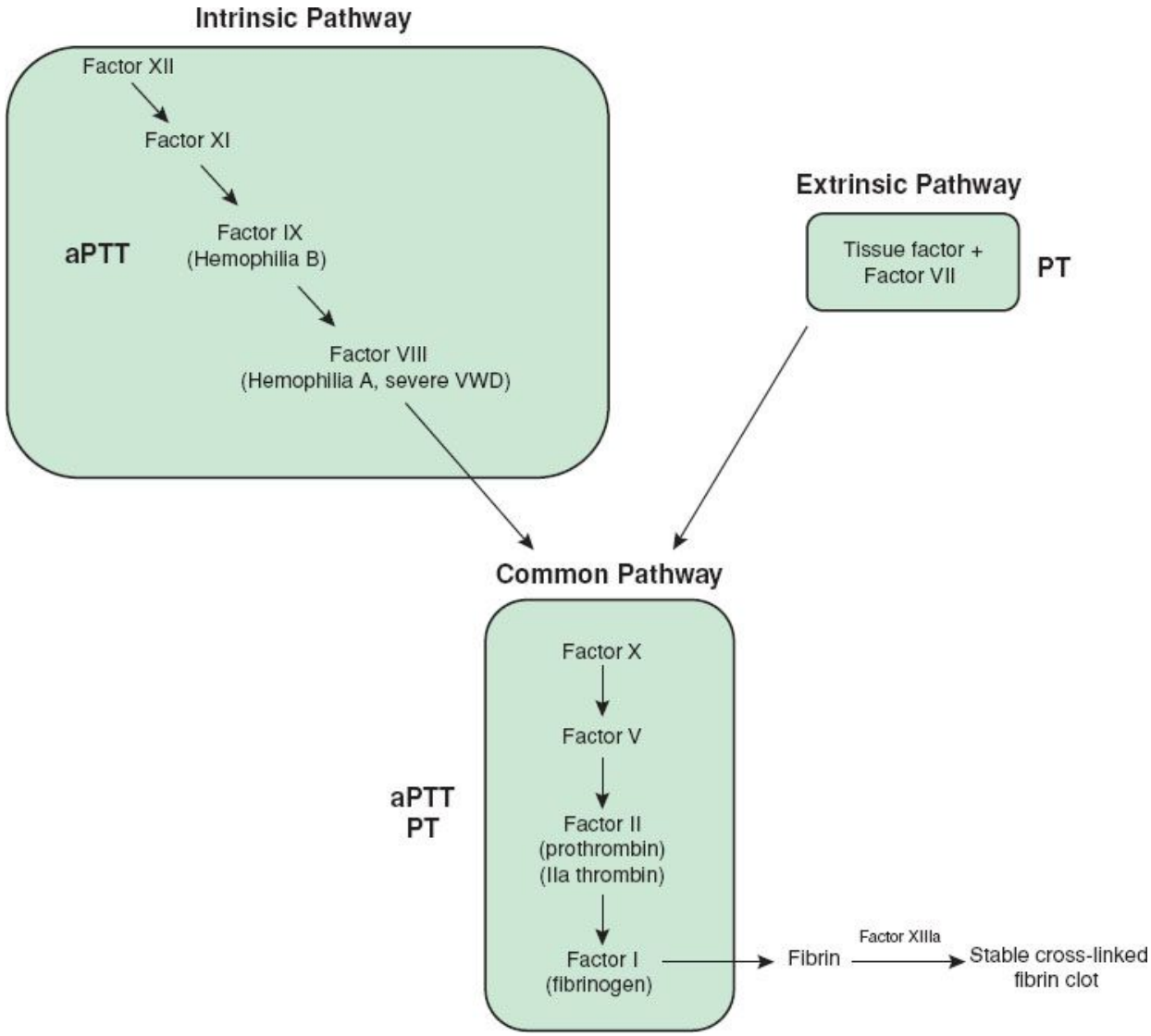

FIGURE 196.1 Simplified Coagulation Cascade. Factors VIII, IX, XI, and XII make up the intrinsic pathway. Deficiency of factors of the intrinsic pathway is measured by the activated partial thromboplastin time (aPTT). Extrinsic pathway factor VII is measured by the prothrombin time (PT). Both pathways join to form the common pathway which involves factors I, II, V, and X. Deficiencies in these factors may prolong both the aPTT and PT.

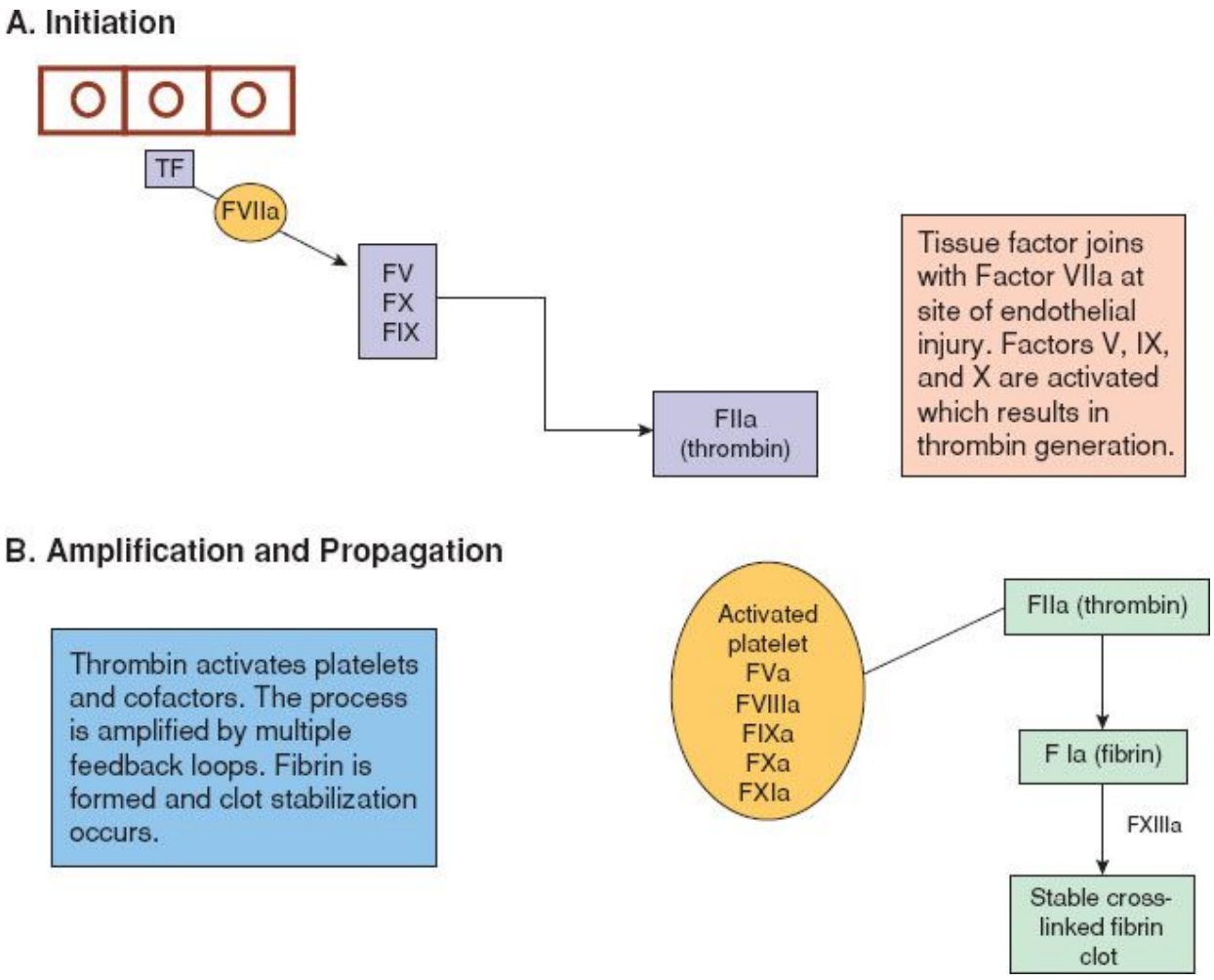

FIGURE 196.2 Simplified in vivo Coagulation Model. **A:** Initiation phase: Tissue factor (TF) joins with factor VIIa (FVIIa) at the site of endothelial injury. Factors V, IX, and X are subsequently activated and a small amount of thrombin is generated. **B:** Amplification and propagation: Thrombin then activates platelets and cofactors, many of which assemble on the surface of the platelet. Multiple feedback loops occur to amplify the process. Prothrombin is converted to thrombin which converts fibrinogen to fibrin and a stable cross-linked fibrin clot is formed.

Fibrinolysis is the process in which the fibrin clot is broken down into degradation products. The fibrinolytic system is activated by many of the same substances that activate the clotting cascade. Active plasmin cleaves fibrin to lyse the clot. Activation of

plasminogen by substances found in the clot localizes fibrinolysis to the clot (5).

When all systems operate in a normal, balanced fashion, there is neither unchecked hemorrhage nor thrombosis in the vascular tree. However, when an inherited or acquired disorder produces an abnormality in one or more components of the system, bleeding may occur. The abnormality may be in the structure of the vascular tree; in the number of platelets; in the platelets' functional ability; in the activity of clotting factors; or in the activity of the fibrinolytic system. The emergency physician must use information from the clinical and laboratory evaluation to identify the abnormal component and treat the patient properly.

CLINICAL PRESENTATION

Bleeding disorders may be congenital or acquired. Disorders may affect primary hemostasis, secondary hemostasis, or both.

Disorders of Primary Hemostasis

Disorders of primary hemostasis include the rare inherited disorders of platelet function, some types of von Willebrand disease (VWD), vascular anomalies (e.g., hereditary hemorrhagic telangiectasia, and Ehlers–Danlos) and acquired conditions such as immune thrombocytopenic purpura (ITP), systemic illness (e.g., renal and liver disease), and medication-induced effects (e.g., aspirin). Typical bleeding symptoms of these conditions include easy bruising, epistaxis, menorrhagia, mucocutaneous bleeding, and postoperative hemorrhage. Bleeding is typically immediate (in contrast to delayed bleeding that occurs in disorders of secondary hemostasis).

Von Willebrand Disease

VWD is the most common inherited bleeding disorder and may affect as much as 1% of the population. There are six different subtypes of VWD and the majority are inherited via autosomal dominant transmission. The clinical presentation and disease severity vary depending on the subtype. Mild-to-moderate mucocutaneous

bleeding predominates and patients present with bruising (often in absence of trauma), epistaxis, prolonged bleeding after dental extraction, menorrhagia, and prolonged/excessive bleeding after childbirth or operative intervention (4). More severe subtypes of VWD present similarly to hemophilia A because there is a functional deficiency of FVIII (6).

Platelet Disorders

Most platelet function disorders are acquired and may be secondary to medication or underlying disease. Inherited platelet function disorders such as Glanzmann thrombasthenia, Bernard–Soulier syndrome, and Wiskott–Aldrich syndrome are rare and present similarly to other disorders of primary hemostasis. Common medications that disrupt normal platelet function include nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, valproic acid, β-lactam antibiotics, and selective serotonin reuptake inhibitors (4). Systemic diseases such as renal failure, liver disease, and malignancy may also induce platelet dysfunction (7).

Immune Thrombocytopenic Purpura

The most common cause of thrombocytopenia secondary to platelet destruction is immune ITP. ITP is seen both in children and adults who were previously healthy. Increased platelet destruction occurs in the spleen along with inhibition of platelet production via autoantibodies. It is immune-mediated and may have no underlying cause (idiopathic/primary) or be associated with an underlying disorder (secondary) (8). Most children with ITP are 2 to 6 years old and many have had a recent viral illness. Otherwise, the history and physical examination are lacking symptoms and signs such as fever, weight loss, anorexia, bone pain, adenopathy, masses, or hepatosplenomegaly that would suggest a more serious condition such as leukemia. Typically, the only examination abnormalities are signs of platelet-type bleeding such as petechiae, bruises, subconjunctival hemorrhage, and signs of mucosal bleeding such as epistaxis. Adult ITP is most common in patients between the ages of

18 and 40 years. The examination in both groups should emphasize detection of life-threatening bleeding, for example, in the central nervous system (CNS), and of signs of other thrombocytopenic conditions such as disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), or leukemia (8).

Disorders of Secondary Hemostasis

Disorders of secondary hemostasis (i.e., coagulation factor deficiencies) typically present with bleeding into soft tissues, muscles, and joints. Bleeding may not start until hours after trauma and may recur at a later time. Platelets function normally to form an initial plug but a stable, fibrin clot is not properly formed. Normal fibrinolysis then results in delayed bleeding (1).

Hemophilia

Hemophilia A and B are the most common inherited factor deficiencies. They are both sex-linked recessive disorders that result in deficiencies of clotting factor VIII (hemophilia A) and IX (hemophilia B). There are approximately 12,000 affected individuals in the United States with hemophilia A and about 30,000 with hemophilia B. Both factors VIII and IX play an important role in the formation of a fibrin clot. Disease severity typically correlates with the degree of factor deficiency. Patients with severe hemophilia have a clotting-factor level of $<1\%$, moderate hemophiliacs have a level between 1% and 5%, and mild hemophilia has a factor level between 6% and 40%. Rarely, a patient with hemophilia will have a concomitant procoagulant deficiency (e.g., Protein C/S or factor V Leiden) and have a less severe clinical presentation than measured factor levels would indicate (1,6,9).

The classic bleeding episode of the severe hemophiliac is spontaneous, painful hemarthrosis of joints (most commonly knees, elbows, and ankles). Patients with moderate hemophilia do not typically develop hemarthrosis but may experience severe muscular and soft tissue bleeding after trauma. Patients with mild disease may only have bleeding episodes associated with trauma and surgical

procedures (6). Recurrent joint bleeds lead to irreversible joint damage (hemophilia arthropathy). To maintain quality of life, severe hemophiliacs are on prophylactic clotting-factor treatment to prevent bleeding episodes.

Other factor deficiencies are rare. Most are also inherited in an autosomal recessive pattern.

Malabsorption may lead to impaired vitamin K absorption. Severe liver disease and/or DIC cause impaired production or concentration of almost all coagulation factors.

Disorders of Both Primary and Secondary Hemostases

Some bleeding disorders combine features of both platelet and clotting-factor deficiencies. Examples include DIC, liver disease, and severe VWD. VWD results from a deficiency in the complex of two proteins, factor VIII and VWF, that circulate together in plasma. Most patients with VWD have bleeding typical of a platelet disorder, but those with severe disease display both mucosal and deep bleeding.

Palpable hematomas, large bruises or ecchymosis in unusual places (such as thorax or back) may suggest both primary and secondary bleeding disorders (4).

Other Bleeding Disorders

Patients with acquired bleeding disorders are more likely to have an underlying illness that affects platelet number or function or clotting-factor levels (e.g., hepatic or renal disorder, disseminated intravascular coagulation [DIC], cancer, or an immunologic process) (see Table 196.1). The development of acquired inhibitors to individual clotting factors is rare in nonhemophiliac patients but is associated with severe, often fatal, bleeding. Factor VIII inhibitors are, by far, the most common. Patients are usually previously healthy individuals, who are often older, and who are often with a history of recent minor injury or surgery. Most do not have a history of major bleeding or a family history of inhibitors. Eighteen percent have an autoimmune disease; 5% note recent penicillin, sulfa, or other drug use. Some postpartum cases have been reported (10,11).

TABLE 196.1
Acquired Hemostatic Defects Associated with Selected Underlying Clinical Conditions

Underlying Clinical Condition	Type of Hemostatic Defect	Cause
Liver disease	Factor deficiency	Decreased synthesis
	Fibrinolysis	Decreased clearance of activators
	Hypercoagulable state	Antithrombin III and protein C deficiency, decreased clearance of activated clotting factors
	Thrombocytopenia	Splenic sequestration
Renal disease	Thrombocytopenia	Decreased marrow production
	Platelet defect	Retained metabolites in the blood
Malabsorption	Multiple factor deficiency	Vitamin K malabsorption
Acute leukemia (especially promyelocytic)	Thrombocytopenia	Decreased megakaryocytopoiesis
	Disseminated intravascular coagulopathy	Increased cellular procoagulant activity
Myeloproliferative disease	Platelet defect	Abnormal thrombopoiesis
	Thrombocythemia/thrombocytopenia	Hyperplastic or replaced (fibrotic) marrow, splenic sequestration
Lymphoma/chronic lymphocytic leukemia	Decreased von Willebrand factor	Adsorption onto tumor, autoantibody
	Low factor VIII	Autoantibody
	Thrombocytopenia	Marrow replacement, splenic sequestration
Dysproteinemia	Thrombocytopenia	Decreased marrow production
	Prolonged thrombin time	Inhibition of fibrin monomer polymerization
Amyloidosis	Factor X deficiency	Adsorption by amyloid
	Capillary fragility	Amyloid vascular infiltration
Systemic lupus	Lupus inhibitor[a]	Antibody to acidic phospholipids
	Factor deficiency	Autoantibodies to coagulation proteins
	Thrombocytopenia/thrombocytopathia	Autoantibodies to platelet glycoproteins

[a]Although the lupus inhibitor produces prolongation of clotting assay results and may exist coincidentally in patients with thrombocytopenia or clotting-factor deficiency that predisposes to bleeding, the lupus inhibitor itself is characterized by a thrombotic rather than a hemorrhagic tendency.

Adapted from White GC, Marder VJ, Colman RW, et al. Acquired disorders of hemostasis. In: Colman RW, Hirsh J, Marder VJ, et al., eds. *Hemostasis and Thrombosis, Basic Principles and Clinical Practice*. 3rd ed. Philadelphia, PA: JB Lippincott Co.; 1994.

Acquired bleeding disorders are often linked to the use of medications that interfere with normal coagulation (e.g., warfarin [Coumadin], heparin, aspirin, NSAIDs, glycoprotein IIb/IIIa inhibitors, direct factor Xa inhibitors, and direct thrombin inhibitors) (see Chapter 198). The effects of aspirin on platelet function are irreversible, lasting the 7- to 10-day lifespan of the platelet; those of NSAIDs last about three to five drug half-lives, after which platelets again participate normally in clot formation. More than 100 drugs are associated with the development of thrombocytopenia (see Table 196.2).

TABLE 196.2
Acquired Disorders of Hemostasis Associated with Drugs

Platelet Function Defects	Thrombocytopenia
Aspirin	Immune Destruction
Nonsteroidal anti-inflammatory drugs	Heparin
Heparin	Quinidine
Dipyridamole	Quinine
Theophylline	Gold
Penicillins	H_2 antagonists
Cephalosporins	Phenytoin
Tricyclic antidepressants	Antibiotics
Phenothiazines	Methyldopa
Clofibrate	Decreased Production
Antihistamines	Ethanol
Ethanol	Thiazides
Dextrans	Chemotherapeutic agents
Selective Serotonin Reuptake Inhibitors	**Coagulation Factor Deficiencies**
	Warfarin
	Penicillins
	Cephalosporins

Hemorrhagic disease of the newborn caused by inadequate vitamin K intake or absorption presents in the first days to weeks of life. Most cases can be prevented by prophylactic vitamin K administration in the newborn period.

The physical examination is directed toward identifying all bleeding sites and recognizing signs of underlying illness. Jaundice, organomegaly, adenopathy, and abnormal masses are sought.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of an acutely bleeding patient can be broken down into congenital (chronic history) versus acquired conditions (occurring over days to weeks) and disorders of primary hemostasis, secondary hemostasis, or both (discussed above). Family history may give important information such as sex-linked inheritance of hemophilia and autosomal dominant inheritance of VWD. However, 30% to 40% of hemophilia occurs from a new, spontaneous mutation and these cases will not have a positive family history (12). Severe congenital coagulation disorders typically

present early in life whereas mild disorders may not present until well into adulthood. It is imperative, particularly in a non-mobile child with bruising, that the emergency physician *always* consider the possibility of non-accidental trauma.

ED EVALUATION

ED evaluation of coagulopathy includes the activated partial thromboplastin time (aPTT), the prothrombin time (PT), and a complete blood count (CBC) with platelet count. The aPTT detects abnormalities of the intrinsic and common pathways and is prolonged by deficiencies of high–molecular-weight kininogen; prekallikrein; factors XII, XI, IX, VIII, X, V, and II; and fibrinogen. The aPTT is also prolonged in the presence of antiphospholipid antibody (formerly termed the *lupus anticoagulant*) and by heparin, warfarin, and fibrin-degradation products. The PT reflects the activity of the factors of the extrinsic and common pathways. It is prolonged by deficiencies of factors VII, X, V, and II and fibrinogen; by warfarin; and by heparin in high concentrations. The PT is more affected by reduced levels of factors VII, V, and X than by decreases in factor II and fibrinogen (see Fig. 196.3) (13).

Normal PT Normal aPTT	↑ PT Normal aPTT
CONGENITAL: FXIII, α_2-antiplasmin, plasminogen activator inhibitor I deficiency **ACQUIRED:** Vitamin C deficiency	**CONGENITAL:** FVII deficiency **ACQUIRED:** Mild vitamin K deficiency, vitamin K antagonists
Normal PT **↑ aPTT**	**↑ PT** **↑ aPTT**
CONGENITAL: FVIII, FIX, FXI, FXIII, PK, HMWK deficiency, VWD **ACQUIRED:** Heparin, factor inhibitors, lupus anticoagulans	**CONGENITAL:** FX, FV, FII deficiency, fibrinogen disorder, combined FV/FVIII deficiency **ACQUIRED:** Severe vitamin K deficiency, liver disease, excess vitamin K antagonist, heparin, DIC

FIGURE 196.3 Effect of various inherited and acquired bleeding disorders on the laboratory tests PT and aPTT. (Modified from Van Herrewegen F, Meijers JCM, Peters M, et al. The bleeding child. Part II: Disorders of secondary hemostasis and fibrinolysis. *Eur J Pediatr*. 2012;171:207–214.)

Patients with factor VIII and IX deficiencies (hemophilia A, B, and some forms of VWD) have a prolonged aPTT and a normal PT. Patients with a normal aPTT and a prolonged PT have a factor VII deficiency, because that is the only factor of the extrinsic pathway not involved in the common pathway. Isolated factor VII deficiency occurs as a rare congenital abnormality and is seen in the acquired form in mild liver disease and in the initial stages of oral anticoagulation or vitamin K deficiency. Although the aPTT, as well as the PT, are prolonged in the fully warfarinized patient, the PT is used for monitoring because of its simplicity. Both the PT and the aPTT are prolonged in moderate-to-severe liver disease, vitamin K deficiency, heparin and warfarin use, afibrinogenemia, and consumptive coagulopathies such as DIC (5).

Specific factor assays can be done to confirm the diagnosis suspected from the history or from abnormalities of the screening PT and aPTT and to provide exact activity levels. However, these assays are rarely available on an emergency basis, and emergency treatment must be initiated without the benefit of such tests.

The CBC is used to assess the degree of anemia produced by the bleeding. The CBC also reveals abnormalities of the white blood cell count, which might suggest leukemia as the etiology of the more clinically obvious thrombocytopenia. Examination of the peripheral blood smear will detect platelet clumping that causes a falsely low platelet count as well as abnormalities of red- and white blood cell number and morphology.

The platelet count is the first step in the evaluation of possible platelet disorders such as ITP or TTP. Patients with counts $<100{,}000/\mu L$ are considered thrombocytopenic; if platelet function is normal, the bleeding time increases in direct proportion to the decrease of the count below 100,000/μL. Platelet counts $>50{,}000$ to

60,000/μL are usually sufficient to control bleeding caused by trauma or local pathology. Patients with platelet counts <5,000 to 10,000/μL are at risk for spontaneous bleeding. However, the platelet count should never be the only criterion considered when assessing a patient's risk of hemorrhage. The underlying condition leading to thrombocytopenia must be sought, and platelet function must also be considered.

No tests are available on an emergency basis that specifically screen for platelet function, as opposed to platelet number. A thorough history and physical examination may suggest that the patient is at risk for a functional platelet disorder (e.g., alcohol or aspirin use). Platelet function has traditionally been measured by the bleeding time. However, bleeding time is invasive, not sensitive or specific, time-consuming, difficult to perform and no has standardized normal for children. It has largely been replaced by the PFA-100 (platelet function analyzer). The PFA-100 is sensitive for platelet defects and severe VWD but may not pick up mild disorders (van Ommen). A few bleeding disorders produce no abnormalities in the available screening tests. Patients with vascular disorders, simple and senile purpura, factor XIII deficiency, and mild forms of other factor deficiencies (factor levels >20% to 25% of normal) have normal aPTTs, PTs, and platelet counts (5).

Whole blood viscoelastic assays such as thrombelastography and rotational thromboelastometry have been shown to be superior in prediction the need for and directing blood transfusion in patients with severe bleeding in nonhemophiliac patients (14–17). These assays may be useful to monitor hemostasis in inhibitor-expressing patients with hemophilia (16).

ED MANAGEMENT

Initial management of the bleeding patient includes airway control, if necessary, adequate ventilation, and oxygenation. If bleeding has led to hypovolemia, crystalloid resuscitation and packed red blood cells should be administered. Local measures should be used to control bleeding (e.g., pressure, packing, suturing, immobilization). See Table 196.3 for treatment options in acute bleeding episodes.

TABLE 196.3
Treatment Options in Acute Bleeding Episodes

Medication	Dose	Indication	Notes
Fresh-frozen plasma (FFP)	10–15 mL/kg IV	Hemophilia B, coagulopathy secondary to factor deficiencies	Use only when FIX concentrates are not available
Cryoprecipitate	1 bag per 6–10 kg every 8–12 hrs	Hemophilia A, VWD, uremia	Use only when FVIII concentrates not available
Platelets	Adults: 1 RDP Children: 5–10 mL/kg	Acute bleeding secondary to platelet deficiency	Restricted to severe, life-threatening bleeding in TTP-HUS, HIT, and DIC
Aminocaproic acid (Amicar)	50–100 mg/kg orally or IV, then 50 mg/kg every 6 hrs	Mucosal bleeding	Prevents dissolution of a hemostatic plug. Avoid in hemophiliacs with hematuria
Factor VIII	20–100 IU/kg every 12–24 hrs	Hemophilia A	See Table 196.5 for % correction recommendations
Factor IX	20–100 IU/kg every 24 hrs	Hemophilia B	See Table 196.5 for % correction recommendations
Factor VIIa	90–120 µg/kg, repeat every 2 hrs	Hemophilia with inhibitors	Off label use for other acute bleeding episodes
VWF Concentrate	20–30 IU/kg (mild bleeding) 50–60 IU/kg (severe bleeding)	VWD, hemophilia A	See Table 196.5
DDAVP	See Table 196.4 for IN, IV, SQ dosing	VWD, hemophilia A, uremia, platelet dysfunction	See Table 196.4
APCC	50–100 IU/kg/dose IV (max 200 IU/kg/d)	Hemophilia with inhibitors	Laboratory tests do not correlate with clinical efficacy
Fibrin sealants, topical thrombin, microfibrillar collagen	Apply to bleeding surface	Local bleeding	Many commercially available; foam, granules, bandages; fibrin sealants often applied with two syringes or Y-connector and tubing

Modified from Rose EAC. Inherited bleeding disorders in infants. In: Sharieff GQ, McCollough M, eds. *Neonatal and Infant Emergencies*. 1st ed. Philadelphia, PA: Cambridge Press; 2009:242–254.

Platelet Disorders and Disorders of Primary Hemostasis

Platelet transfusion should be initiated if there is active bleeding unresponsive to local measures and typical of that caused by a platelet disorder (see Table 196.3) and the platelet count is <50,000/µL. Active bleeding with a platelet count >50,000/µL should prompt a search for another cause of bleeding, such as a functional platelet disorder, a coagulation factor deficiency, or an untreated primary bleeding site (18).

Platelets play an essential role in the maintenance of vascular endothelial integrity and that a minimum number are required to fulfill that function. Below this threshold, thinning and fenestration of the endothelium may lead to spontaneous bleeding. Studies suggest that 5,000 to 10,000 platelets/µL can maintain vascular integrity and that prophylactic transfusion should be given for values below that to prevent intracranial hemorrhage and other significant bleeding. Mucosal bleeding and epistaxis are more predictive of serious bleeding than merely the presence of petechiae and ecchymosis (4). A platelet count of 40,000 to 50,000/µL is sufficient for most procedures including lumbar puncture in the absence of functional platelet defects. A platelet count of 20,000/µL is sufficient

for central venous catheter placement and lumbar puncture in patients with hematologic malignancies (18).

The standard dose of platelets is one random donor platelet (RDP) unit per kg of body weight (4 to 6 units of pooled platelets or one apheresis unit). One RDP unit raises the platelet count by 7,000 to 10,000/μL in healthy adults. Pediatric dosing is 5 to 10 mL/kg. A smaller rise in platelet count may occur in ill, bleeding patients and those with platelet destructive or platelet consumptive disorders and these patients may require repeat transfusion (18). Patients with life-threatening bleeding should be transfused regardless of the etiology of thrombocytopenia. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS), heparin-induced thrombocytopenia (HIT), and DIC are all associated with platelet consumption and they can cause thrombosis as well as bleeding. Because of the thrombotic risk, platelet transfusion is generally considered to be relatively contraindicated in these conditions, and guidance should be sought through hematology consultation (18).

Immune Thrombocytopenic Purpura

Life-threatening bleeding in ITP is treated initially with platelet transfusion, high-dose intravenous steroids and IVIG (1 g/kg/d) for 2 to 3 days (19). The treatment of ITP without acute bleeding depends on the age of the patient. Many children do not receive treatment because 70% to 80% have complete disease remission within 6 months (19). Treatment of ITP in children has not been proven to decrease incidence of intracranial hemorrhage, the most feared complication of ITP (19). Spontaneous remission of ITP occurs in $<$10% adults and so most adults are treated when the platelet count is $<$30,000/μL. First-line therapy includes oral or intravenous glucocorticoids which support the platelet count until spontaneous remission can occur. Prednisone (1 to 2 mg/kg for children and 1 mg/kg for adults per day) is most commonly used. Duration of treatment depends on platelet response. High-dose methylprednisolone (30 mg/kg initially) is used in children and adults resistant to oral prednisone. Length of steroid therapy is determined by platelet response. Other first-line therapies include

IVIG (1 g/kg/d for 1 to 2 days) or IV anti-D globulin (50 to 75 μg/kg/d, given once). Anti-D globulin is only effective in Rh-positive patients with an intact spleen. Both IVIG and anti-Rh(D) increase platelet counts in most patients within several days and the effect may last several weeks. They may cause mild alloimmune hemolysis and intravascular hemolysis may rarely occur with anti-D therapy. It should not be given in patients with an Hbg <8 g/dL. Splenectomy is an effective treatment in persistent cases of ITP and considered as a second-line therapy. Agents such as rituximab and immunosuppressants may be used in resistant cases. Bone marrow evaluation is recommended if there are abnormalities of other cell lines in addition to platelets or with systemic symptoms such as bone pain or splenomegaly (4,8,19). Hemostatic defects in uremia are multifactorial but are primarily related to defects in platelet function. Significant coagulation factor deficiencies occur only in the severely nephrotic patient. Platelet counts are decreased but rarely $<100{,}000/\mu L$. The functional platelet defect is due to toxic retained metabolites, which can quickly reduce the effectiveness of newly transfused platelets. Dialysis at least partially reverses this toxic effect but may not be immediately available for the bleeding patient. Desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]) and conjugated estrogens may be used along with platelets in management of the acutely bleeding uremic patient (see Table 196.4 for DDAVP dosage and administration). Maintaining a hemoglobin ≤ 10 g/dL also appears to decrease bleeding time in uremia (20).

TABLE 196.4
Desmopressin (DDAVP) Dose and Administration

Intranasal	<50 kg: 150 μg IN (one spray into one nostril)
	≥50 kg: 300 μg IN (one spray into each nostril)
Intravenous	0.3 μg/kg diluted into normal saline (15–30 mL for children and 50–100 mL for adults). Administered over 15–30 min
Subcutaneous	0.3 μg/kg

Modified from Ozgonenel B, Rajpurkar M, Lusher JM. How do you treat bleeding disorders with desmopressin? *Postgrad Med J.* 2007;83:159–163.

Von Willebrand Disease

Bleeding patients with VWD need increased plasma levels of VWF and FVIII. In patients with mild VWD, DDAVP is the treatment of choice. DDAVP stimulates the release of VWF and effectively raises plasma concentration of both VWF and FVIII. It may be administered through intravenous, subcutaneous, and intranasal routes (see Table 196.4). Side effects include mild tachycardia, flushing, and headache. DDAVP is a potent antidiuretic agent and hyponatremia potentially resulting in a seizure may occur if the sodium decreases significantly. Water restriction and avoidance of hypotonic intravenous fluids are recommended. DDAVP will not work in patients with nephrogenic diabetes insipidus. Rarely, arterial thrombotic events may occur such as stroke and myocardial infarction. DDAVP will not be effective in type 3 VWD and severe hemophilia A (4,6,7).

More severe forms of VWD require FVIII/VWF concentrates (see Table 196.5). High-purity FVIII concentrates contain no VWF. Minor bleeds require 30 to 50 IU/kg of FVIII/VWF product and major bleeds 40 to 60 IU/kg (6). Antifibrinolytic therapies such as epsilon-aminocaproic acid or tranexamic acid are helpful adjuncts for bleeding. Topical adjunctive hemostatic preparations may be applied to exposed sites of bleeding as well.

TABLE 196.5
Factor Replacement Guidelines in Hemophilia A, Hemophilia B, and von Willebrand Disease

Bleeding Type	%Correction	Hemophilia A (Factor VIII)	Hemophilia B (Factor IX)	VWD (VWF:RCo)
MINOR (e.g., hemarthrosis, hematoma, minor laceration, fracture)	40–50	20–50 IU/kg every 12–24 hrs for 1–3 doses	20–60 IU/kg every 24 hrs for 1–3 doses	Local measures, DDAVP. Rarely, VWF:RCo 15–25 IU/kg is required
MAJOR (ICH, preoperative, significant trauma severe joint/muscle bleed, compartment syndrome)	80–100	50–100 IU/kg every 8–12 hrs; Continuous infusion of 2–5 IU/kg/hrs may be given after initial bolus in severe cases	50–100 IU/kg every 12–24 hrs; Continuous infusion of 5–10 IU/kg/hrs after initial bolus in severe cases	40–80 IU/kg Load and 40–60 IU/kg every 8–12 hrs

IU, International units, RCo, Ristocetin cofactor.

Modified from Coppola A, Di Capua M, Dario MN, et al. Treatment of hemophilia: A review of current advances and ongoing issues. *J Blood Med*. 2010;1:183–195; Rose EAC. Inherited bleeding disorders in infants. In: Sharieff GQ, McCollough M, eds. *Neonatal and Infant Emergencies*. 1sted.. Philadelphia, PA: Cambridge Press; 2009:242–254; and Singleton T, Kruse-Jarres R, Leissinger C. Emergency Department care for patients with hemophilia and von Willebrand Disease. *J Emerg Med*. 2010;39(2):158–165.

Coagulation Disorders and Disorders of Secondary Hemostasis

If the clinical evaluation suggests a congenital single-factor deficiency (e.g., hemophilia A or B), the location of the bleeding determines the therapeutic approach (see Table 196.5). Bleeding into the CNS, neck, sublingual, retroperitoneal spaces, and GI tract is immediately life-threatening. All hemophiliacs with suspected bleeding in these high-risk sites should receive immediate factor replacement therapy to achieve a factor level of 100% of normal. One U of factor VIII per kg of body weight will raise the patient's level by 2%, so 50 U/kg should be given. The ideal body weight rather than actual body weight should be used (21). One U of factor IX per kg raises the level by only 1%, so patients with hemophilia B require 100 U/kg in life-threatening situations (see Table 196.5) (6). This therapy should be initiated without waiting for the results of the aPTT, factor levels, head CT, or other scans. The half-life of factor VIII is 8 to 12 hours, so maintenance therapy should be infused two to three times per day or given as a continuous infusion. Factor IX maintenance therapy is given every 18 to 24 hours. Factor administration should be continued for 14 days if bleeding is located in the CNS, neck, or retroperitoneum (6). A low threshold for admission for observation should be maintained for patients with injury or suspected bleeding in the high-risk sites.

Patients with bleeding disorders are at a higher risk for life-threatening intracranial hemorrhage that may occur spontaneously or after minor head injury. In a large, prospective multicenter study of children with minor blunt head trauma, children with bleeding disorders were twice as likely to be imaged as those without. However, only approximately 1% of patients with both acquired and congenital bleeding disorders sustained an intracranial hemorrhage (22). Vigilance should be maintained about the possibility of intracranial hemorrhage with a low threshold to obtain imaging. However, the risk versus benefit of irradiation from a CT scan must always be assessed, particularly in a young patient at risk for cumulative radiation exposures.

Minor bleeding into the soft tissues, muscles, oral cavity, urinary tract, and limited hemarthrosis can be treated with 20 to 40 U/kg (1,6). Patients with massive hemarthrosis and bleeding into large joints such as the hip and shoulder should receive at least three doses of 50 U/kg. The presence of limb hematomas should prompt a thorough search for signs of compartment syndrome. If this condition is suspected, 50 U/kg of the appropriate factor should be administered and surgical consultation should be obtained. However, most patients are observed 6 to 8 hours after the infusion for spontaneous resolution (10). Rest, ice, and compression, as well as crutches and limited weight bearing, should be prescribed after joint and limb bleeds, followed by physical therapy. The addition of antifibrinolytic therapy (tranexamic acid mouthwash and oral epsilon-aminocaproic acid) to combat the effects of saliva in cases of bleeding from oral mucosa, gums, anterior tongue, and dental extraction sites may hasten effective coagulation when used with factor infusion.

The safety of plasma-derived factors has improved with better screening of blood products and viral irradiation techniques. No HIV, hepatitis B, or hepatitis C seroconversion has been reported in previously unexposed hemophiliacs since 1987. However, recombinant factors VIII and IX are most commonly used in young hemophiliacs secondary to fear of transmission of new and/or unknown pathogens. The choice of the appropriate factor VIII product for each hemophilic patient is one that should be made in concert with the patient's hematologist, if possible. All currently marketed factor VIII products are considered safe from the standpoint of HIV, hepatitis B, and hepatitis C transmission. High-purity products are those from which nonfactor VIII protein contaminants have been removed. These products should be used in HIV-positive hemophiliacs to protect against the development of anergy and lowering of CD4 counts that can occur with less pure products. Intermediate-purity products contain plasma protein, but not viral contaminants. Recombinant factor products cost two to three times more than plasma-derived products and are sometimes in short supply because of limited manufacturing capacity.

Recombinant factor products are prescribed most often for newly diagnosed hemophiliacs and for those in whom no blood-borne infections have developed.

Because recurrent joint bleeds are so debilitating, many severe hemophiliacs are on prophylactic treatment with factor concentrates. Prophylactic treatments have successfully prevented significant bleeding in severe hemophiliacs and allowed many with severe hemophilia to lead a near-normal lifestyle (23).

Noncritical bleeding in patients with mild hemophilia A (with baseline FVIII levels >10%) may be responsive to DDAVP (see Table 196.4 for DDAVP dosage and administration). A three- to fivefold increase in factor VIII and VWF may occur with peak effects 30 to 60 minutes after the dose (7).

Treatment advances have allowed hemophiliacs to have a longer life expectancy than ever before. This has brought new management challenges as older hemophiliacs are developing conditions such as cardiovascular disease and cancer. Treatment of hemophiliacs with these complex conditions are currently managed by expert consensus and evidence-based management has not yet been formulated (23,24). An example of recommendation for surgery is normalizing the coagulopathic condition with continuous factor infusion and then treating the patient as if they were not coagulopathic with prophylactic doses of low–molecular-weight heparin (24).

The future may hold the definitive cure of hemophilia with gene transfer therapy. Another goal in hemophilia management is wider treatment availability to the third world.

The most challenging aspect of hemophilia management is the development of inhibitory alloantibodies against FVIII or FIX. Inhibitors render treatment with factor replacement concentrates ineffective in achieving hemostasis. They occur in approximately 20% to 30% of severe hemophilia A and 3% to 5% of those with hemophilia B (6,23). The mechanism of inhibitor production is not completely understood. Those treated with recombinant FVIII have a higher incidence of inhibitors than those treated with plasma-derived products. Inhibitors to VWF are extremely rare (6).

Patients with inhibitors are complex and their management should be directed in consultation with a hematologist. Inhibitors may be “low-responding” and can be overcome with large doses of factor concentrate. Patients with “high-responding” inhibitors require alternative factor agents. Two available agents for these patients include activated prothrombin complex concentrates, FEIBA-VH (Baxter Healthcare, Deerfield, IL) which contains activated vitamin K-dependent factors (II, VII, IX, X) and NovoSeven (Novo Nordisk Inc., Princeton, NJ), a recombinant activated factor VII. The superiority of one treatment has yet to be clearly established and both are accepted treatments for patients with inhibitors. The theorized underlying mechanism of action is enhanced thrombin generation on activated platelets leads to a more stable fibrin clot and hemostatic plug. Significant trauma or surgical intervention requires a minimum initial FVIIa dose of 120 μg/kg followed by repeat dosing every 2 hours.

The only proven therapy for inhibitors is controversial due to significant cost. Patient with inhibitors may undergo antigen-specific immune tolerance induction to eradicate inhibitors through long-term daily treatment of large doses of coagulation factors (23,25).

Inhibitors also occur de novo in nonhemophiliac patients, those directed against factor VIII being the most common. Treatment of life-threatening bleeding is similar to that described previously, which uses high doses of factor VIII concentrates, aPCCs, and recombinant factor VIIa. To arrest synthesis of the inhibitor, steroids and immunosuppressants, such as azathioprine or cyclophosphamide, are given (10,11).

Patients with complex conditions such as liver disease or DIC usually have deficiencies of multiple coagulation factors and, often, of platelets as well. If laboratory tests confirm these abnormalities and the patient is actively bleeding, fresh-frozen plasma and platelets are given to replace the needed components.

Because so many bleeding disorders are associated with underlying diseases, attention should always be directed to the potential associated condition while immediate lifesaving transfusions of blood components are provided.

CRITICAL INTERVENTIONS

- Initiate platelet transfusion if there is active bleeding that is unresponsive to local measures and the platelet count is $<50{,}000/\mu L$.
- Replace clotting factor to achieve a factor level of 100% of normal for hemophiliacs with suspected bleeding in high-risk sites. Give 50 U/kg of factor VIII or 100 U/kg of factor IX, depending on which factor deficiency exists. Initiate therapy before confirmatory testing.

DISPOSITION

Life-threatening bleeding in a patient with a bleeding disorder requires admission, often to a monitored setting. An acutely bleeding patient should be transferred to another facility only if a service unavailable at the initial hospital can be provided at the second facility. A patient with minor bleeding may be managed as an outpatient if the patient is reliable with good resources and if management can be closely coordinated with the patient's hematologist.

Common Pitfalls

- Failure to initiate treatment early (before imaging) in bleeding disorders.
- Failure to begin treatment with mild symptoms in severe hemophilia.
- Failure to recognize inhibitors and adjust management appropriately
- Failure to recognize how underlying coagulation disorders complicate the management of common injuries.
- Failure to involve pharmacy and hematology in complicated replacements or surgical procedures.

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CHAPTER 197

Disseminated Intravascular Coagulation, Thrombotic Thrombocytopenic Purpura, and Hemolytic–Uremic Syndrome

David Beran

Several disease processes lead to thrombus formation in the microvascular circulation with resultant consumption of clotting components and, ultimately, organ dysfunction. The underlying pathologies of these conditions differ, but the clinical presentation of multisystem involvement with hemorrhage and thrombosis may be very similar. Careful history, physical examination, and laboratory analysis enable the emergency physician (EP) to differentiate these conditions and begin appropriate treatment and referral.

The unique pathophysiology, laboratory findings, and treatments of each condition are discussed in the following sections.

DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation (DIC) is a condition where the clot-forming and clot-dissolving pathways are activated leading

to a state of simultaneous thrombus formation and hemorrhage. DIC does not occur alone, but secondary to other diseases which share the feature of causing the release of procoagulant substances. In the emergency department, commonly seen examples of such diseases include trauma (such as head injuries, burns, and crush injuries), sepsis, malignancy, obstetric conditions such as abruptio placenta or amniotic fluid embolism, and intravascular hemolysis, as with transfusion reactions (1,2).

The clot-forming coagulation cascade is activated through the release of tissue factor, leading to the formation of thrombin. Tissue factor is released in response to bacterial endotoxin, by tumor cells and secondary to severe trauma, intravascular hemolysis, and obstetric conditions (3–5).

Once generated, thrombin plays its normal pivotal role in coagulation, cleaving fibrinogen to form fibrin, activating the intrinsic pathway and platelets. Thrombin is also involved in the body's normal method of terminating the clotting process. As procoagulants are continuously released into the circulation, they drive the coagulation cascade and the coactive inhibitory mechanisms, yielding both fibrin clots throughout the vascular system and large amounts of inactivated factors. Further, inhibitors of the coagulation cascade such as antithrombin III (AT III) and tissue factor inhibitor are reduced via consumption and decreased synthesis leading to an even greater increase in coagulation and fibrin mesh formation. The fibrin mesh caused by the activated coagulation cascade traps circulating platelets, leading to concomitant hemorrhage.

Simultaneous with the coagulation cascade is the activation, then suppression, of the fibrinolytic system. Plasminogen activator release from endothelial cells activates plasmin which attacks fibrinogen-producing fibrin degradation products (FDPs) such as D-dimer. FDPs are significant as they interfere with the polymerization of fibrin, which is necessary to create functional clots. This further contributes to the hemorrhagic features of DIC.

This profibrinolytic response leads to a sustained increase in plasminogen-activator inhibitor type 1 (PAI-1), the major regulating enzyme of the fibrinolytic system. High levels of plasma PAI-1 has been shown as a strong predictor of mortality in select patient populations with DIC (6). Consequently, fibrinolysis cannot keep pace with intravascular coagulation and the microvasculature fills with occlusive thrombi—simply, the patient forms clots faster than they bleed but both are ongoing.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

DIC occurs in an acute, fulminant form and in a low-grade, chronic form. The acute form usually is associated with sepsis, trauma, and acute obstetric events where the chronic form is associated with underlying malignancy. The incidence of DIC in severe sepsis is 18% and in septic shock, 38% (5) with a prevalence of up to 50% in gram negative sepsis (7). Excessive bleeding in these clinical settings should cause suspicion of DIC. Petechiae, purpura, hemorrhagic bullae, and subcutaneous hematomas can be seen along with gastrointestinal, urinary tract, and pulmonary bleeding. Although hemorrhage may be impressive, it is organ failure that is the usual cause of death in DIC. This is caused at least partially by microvascular fibrin deposition in end organs (1,8).

The differential diagnosis for DIC includes other microangiopathic hemolytic anemias such as thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) as well as primary hemostatic disorders and liver disease.

ED EVALUATION

The EP's initial role in evaluating the patient with DIC involves identifying disease processes associated with DIC. An appropriate clinical setting with a typical physical examination suggestive of DIC should spur the physician to seek laboratory evidence of the secondary diagnosis.

Readily available laboratory tests that confirm depletion of coagulation factors include the prothrombin time (PT), PTT, and fibrinogen level (1,8). The PT and PTT are prolonged in only about 50% of cases of DIC, because activated factors and degradation products may interfere with these tests. Therefore, PT and PTT testing cannot confirm or exclude the diagnosis. The fibrinogen level is less than 150 mg/dL in only 70% of cases, probably because it is an acute-phase reactant and is elevated in acute illness. Examination of the peripheral blood smear will show schistocytes in 50% of patients with fulminant DIC, as well as large platelet forms (1). Platelet counts range from 20,000 to 100,000/μL, averaging about 60,000/μL.

The consumption of coagulation inhibitors can be measured directly by checking the AT III level, which is decreased in 89% of patients with DIC; but this information is rarely available to the EP.

Activation of the fibrinolytic system can be assessed by measurement of FDPs and D-dimer levels. In one study, using a D-dimer assay for the diagnosis of DIC gave a sensitivity of 98%, specificity 86%, negative predictive value 99%, and positive predictive value 66%. The value of D-dimer in the evaluation of DIC thus rests in its high negative predictive value (9).

Because there is no single laboratory test that is diagnostic for DIC, scoring systems have been developed that assign points for clinical criteria and abnormal values for platelet count, PT, FDPs, and fibrinogen.

The system proposed by the International Society of Thrombosis and Haemostasis (ISTH) is designed to identify overt DIC. It has a sensitivity of 91% to 93% and a specificity of 97% to 98% (10). It must be applied to patients with an underlying disorder known to be associated with DIC and is calculated as follows:

Platelet count: $>100{,}000 \rightarrow 0$; $<100{,}000 \rightarrow 1$; $<50{,}000 \rightarrow 2$

FDP, D-dimer: no increase $\rightarrow$ 0; moderate increase $\rightarrow$ 2; strong increase $\rightarrow$ 3

Prolongation of PT: by <3 sec $\rightarrow$ 0; by >3 but <6 sec$\rightarrow$ 1; by >6 sec $\rightarrow$ 2

Fibrinogen level: >1.0 g/L $\rightarrow$ 0; <1.0 g/L $\rightarrow$ 1

$\rightarrow$

Scores ≤ 5 are compatible with overt DIC and are associated with a 28-day mortality rate of 40% to 70%. Those <5 are suggestive of nonovert DIC and portend a 25% to 35% mortality. The score should be repeated daily.

A scoring system for nonovert DIC has been developed by the Japanese Association for Acute Medicine. This system has been shown to detect DIC earlier in the disease process than the ISTH score and may therefore allow for earlier intervention (11). In this system, the clinician must first exclude confounding conditions prior to applying the score.

Once these are excluded the score is calculated as follows.

Number of Systemic Inflammatory Response Syndrome criteria:

3 or greater $\rightarrow$ 1; 2 or less $\rightarrow$ 0

Platelet count ($\times 10^9$/L):

<80 or $>50\%$ decrease in 24 hours $\rightarrow$ 3; >80 but <120 or $>30\%$ decrease in 24 hours $\rightarrow$ 2; >120 $\rightarrow$ 0

PT (value of patient/normal value):

>1.2 $\rightarrow$ 1; <1.2 $\rightarrow$ 0

Fibrin/FDPs (mg/L):

>25 $\rightarrow$ 3; >10 but <25 $\rightarrow$ 1; <10 $\rightarrow$ 0

A score ≤ 4 indicates a diagnosis of DIC.

Laboratory test results such as increased serum LDH or creatinine may reflect end-organ damage and be supportive of the diagnosis. Other useful tests are hemoglobin and hematocrit, urinalysis, pregnancy test, and imaging studies as guided by history and examination to search for the inciting illness.

KEY TESTING

- Complete blood count

- Comprehensive metabolic panel
- D-dimer
- International normalized ratio, PT/PTT
- Fibrinogen
- Serum pregnancy test
- Lactate dehydrogenase
- Peripheral blood smear
- Imaging as dictated by the presumed underlying disease process (eg. chest x-ray for presumed pneumonia, computed tomography (CT) for head trauma, etc.)
- If available, Antithrombin III level
- Cultures of blood and urine, as appropriate

ED MANAGEMENT

There is one area of universal agreement in DIC treatment: The underlying illness must be aggressively attacked. Early surgery, antibiotics, chemotherapy, or other appropriate therapy to stop the continuous activation of the coagulation cascade must be carried out (1,3,4,8). The EP's responsibility rests in the management of the underlying disease state and identification of illnesses associated with DIC. The EP should obtain laboratory data for their own guidance but recall that they may have the ability to order tests such as AT III or fibrinogen levels earlier, which may be useful to their consultants.

Indications for transfusion of blood products are similar in DIC and non-DIC patients. Transfusion of packed red blood cells, platelets, and fresh frozen plasma (FFP) follow standard indications. Although some clinicians fear "fueling the fire" of coagulation by giving FFP or cryoprecipitate to patients with DIC, this event has not been shown to occur in most cases (3,8). FFP should be given in patients with an international normalized ratio greater than 2, a twofold increase in aPTT or fibrinogen level less than 100 mg/dL, but will rarely be sufficient by itself to replete fibrinogen (12).

Heparin can partly inhibit the activation of coagulation in patients with DIC but has never been shown to have a significant

beneficial effect on survival in controlled trials. Its use in DIC is recommended in patients with obvious thromboembolic disease such as purpura fulminans and acral ischemia.

AT III has largely been studied in patients on the sepsis spectrum. Various studies have shown a decreased duration of symptoms, improved coagulation parameters, improved oxygenation, or a decrease in intensive care unit (ICU) and ventilator days, but none have demonstrated an actual mortality benefit.

CRITICAL INTERVENTIONS

- Early recognition and aggressive management of conditions associated with DIC
- Transfusion of blood products according to usual indications
- Early involvement of hematology and subspecialists needed to manage underlying disease state

DISPOSITION

The primary role of the EP is to stabilize these patients and obtain the necessary laboratory and imaging studies to screen for and identify the presence of DIC. The importance of immediate specialty consultation once DIC is suspected cannot be overemphasized, owing to the importance of treating the underlying cause. Further, antibiotics and replacement of blood component therapy should be initiated in the emergency department to best prepare the patient for the next phase of their care, be it surgical, medical, or oncologic. The prognosis in patients with DIC is poor and they will require intensive care. They should not be transferred from an institution that has facilities to care for them and their underlying disease process.

Common Pitfalls

- Failing to consider DIC as a complication of the conditions it is most frequently associated with. DIC should be sought in all patients at risk.

- Allowing bleeding to distract the physician from the search for and treatment of the underlying causative illness. Any therapeutic plan that fails to include measures directed against the underlying cause is likely to be unsuccessful.

THROMBOTIC THROMBOCYTOPENIC PURPURA AND HEMOLYTIC–UREMIC SYNDROME

TTP and adult HUS appear to be similar disorders clinically—each presents with some of the elements of the classic pentad of thrombocytopenia, neurologic abnormalities, fever, and renal dysfunction. In TTP, neurologic abnormalities predominate, and renal dysfunction is seen less often; the opposite is characteristic of HUS. Pathophysiologically, however, they are distinct.

Most cases of TTP occur in previously healthy patients. Acquired idiopathic TTP is most often a single episode seen in older children and adults. TTP is also seen in association with the use of drugs such as ticlopidine, clopidogrel, cyclosporine, mitomycin, quinine, and combinations of chemotherapeutic agents. It also occurs concurrently with other conditions, such as pregnancy; autoimmune diseases; cancer; bone marrow transplantation; and bacterial and viral infections, including HIV and HTLV-1 (13–16). HIV was present in 4% to 50% of TTP cases in various series (17).

The pathophysiology of idiopathic TTP involves the formation of occlusive small vessel thrombi made up of platelets held together by unusually large von Willebrand factor (ULvWF) multimers with little or no fibrin. These large multimers are produced by and released from endothelial cells. Normally, a metalloprotease enzyme referred to as ADAMTS 13 cleaves these large multimers into smaller vWF molecules. This enzyme is synthesized in the liver and has a binding site on endothelial cells. During an episode of TTP, ADAMTS 13 activity is undetectable in the plasma, probably due to the action of IgG inhibitory antibodies. The lack of ADAMTS 13 activity leaves the ULvWF multimers uncleaved. Their large size and configuration induce active adhesion and aggregation of platelets, leading to thrombus formation which leads to the occlusion of

microvasculature. These clots are composed of aggregated platelets; fibrin is not detected in them.

In HUS, the toxin released from the causative *Escherichia coli* and *Shigella* strains is transported by neutrophils to target organs such as the brain and kidney where they cause endothelial damage. About 90% of cases of pediatric HUS are associated with *E. coli* enterocolitis (18). The toxin activates platelets and induces the secretion of ULvWF from the endothelial cells. However, unlike patients with TTP, those with HUS have normal metalloprotease activity and microthrombi in HUS contain fibrin and platelets with little or no vWF (17,19,20). Only smaller, not ultra-large, vWF fragments are found in the plasma of HUS patients (17). A prothrombotic state with biochemical evidence of thrombin generation and inhibition of fibrinolysis has been detected as early as the fourth day of diarrheal illness in children who go on to develop HUS (21).

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Although the pentad of symptoms and laboratory findings is considered classic in these diseases, it is important to realize that only about 40% of patients manifest all five criteria. There are no pathognomonic physical findings specific for TTP or HUS. In those with TTP, less than 15% have severe renal dysfunction with creatinine greater than 5 mg/dL (14,15). Only about one-third of HUS patients have neurologic dysfunction. Fever has been reported in approximately 50% of patients (22). Most patients with TTP present with vague symptoms of abdominal pain, nausea, vomiting, and weakness (23).

The most frequent initial neurologic abnormality is altered mental status, which may be manifested by subtle personality change, lethargy, agitation, or confusion. Seizures, hemiplegia, aphasia, paresthesia, and visual disturbances occur in less than half of patients and more often in the later stages of the disease.

Although 20% of patients may complain of gross hematuria, renal dysfunction is usually discovered only in laboratory studies. Bleeding, secondary to thrombocytopenia (e.g., epistaxis, hematuria, gastrointestinal or vaginal hemorrhage), is seen in about 30% to 40% at initial presentation. Anemia or thrombocytopenia may present as pallor, jaundice, or petechiae.

This type of multisystem symptomatology requires the EP to entertain a broad differential diagnosis that includes DIC, CNS infection, collagen vascular disease, bacterial endocarditis, eclampsia, HELLP syndrome, and malignant hypertension, among others. Laboratory studies can be very helpful in confirming the diagnosis of TTP or HUS, as the laboratory abnormalities of the pentad are more consistently present than the clinical symptoms.

ED EVALUATION

The patient's initial presentation will yield a broad differential diagnosis. The EP will begin their laboratory evaluation directed toward the etiology of fever, bleeding, and neurologic abnormalities. Complete blood count, platelet count, PT, PTT, fibrinogen, FDPs, D-dimer, lactate dehydrogenase, and examination of the peripheral blood smear often suggest the diagnosis. All patients with TTP–HUS are anemic; 90% have hemoglobin less than 10 g/dL, and 40% have less than 6 g/dL. The peripheral smear reveals schistocytes and a decreased number of platelets; 50% of patients have a platelet count less than 20,000/μL. The PT and PTT are normal in 90%, and fibrinogen is less than 100 mg/dL in only 5% of TTP–HUS patients. In DIC, by contrast, D-dimer and tests reflective of coagulation factor consumption are usually abnormal (15).

The LDH, blood urea nitrogen (BUN), creatinine, electrolytes, blood cultures, and CT scan of the head can provide further important diagnostic information. Lumbar puncture should be considered, but severe thrombocytopenia may lead the clinician to defer this procedure. Serum LDH is uniformly and greatly elevated in TTP patients; median levels are often six times normal. The

combination of a greatly elevated LDH, microangiopathic hemolytic anemia, and thrombocytopenia is often considered sufficient to make a diagnosis of TTP, even in the absence of fever and renal or neurologic abnormalities.

Abnormalities of BUN and creatinine are universal in patients in whom HUS is diagnosed, and are seen in 40% to 50% of patients with TTP.

KEY TESTING

- Complete blood count
- Comprehensive metabolic panel
- D-dimer
- International normalized ratio, PT and PTT
- Fibrinogen
- Lactate dehydrogenase
- HIV test
- Peripheral blood smear
- CT of the brain
- Lumbar puncture, if no contraindication

ED MANAGEMENT

As always, airway, breathing, and circulation should receive primary attention. In febrile patients in whom infection is suspected, antibiotic therapy should be initiated after obtaining appropriate cultures in the emergency department. The EP should be aware that despite significant thrombocytopenia and clinical bleeding, platelet transfusions are contraindicated in TTP (15). The exception to this is with patients with evidence of intracranial bleeding on CT where platelet transfusions are sometimes given as a stopgap measure.

The mainstay of current therapy for TTP is plasma exchange with FFP. Plasma exchange removes metalloprotease inhibitors and ULvWF and provides active ADAMTS 13 (13,24). The hematologist will determine infusion amounts and durations but will usually begin with an exchange of 1 to 1.5 plasma volumes per day (23).

Response to plasma therapy generally follows a predictable pattern in TTP. Neurologic abnormalities are the first to resolve, usually within 3 days where renal function may take 14 days to normalize. LDH levels normalize in about 5 days, and platelet counts in 10 days. It usually takes about nine plasmapheresis treatments to produce sustained improvement (25). Exchange therapy is generally continued for a minimum of 2 days after the platelet count returns to normal (23).

Prednisone in doses of 1 mg/kg/d or greater is often given on the basis of historic precedent (23). Patients who do not respond to plasmapheresis may be candidates for either splenectomy or cryopoor plasma (plasma with cryoprecipitate and therefore vWF removed).

Since the advent of plasma therapy, overall survival in patients with TTP has been about 90% (20). Recovery from neurologic, hematologic, and renal abnormalities is usually complete.

PEDIATRIC HEMOLYTIC&NDASH;UREMIC SYNDROME

E. coli O157:H7 is now recognized as the leading cause of HUS in the United States, Canada, and Europe (18). However, cases associated with other bacterial, viral, or fungal infections, HIV infection, chemotherapeutic agents, and radiation therapy continue to be reported.

E. coli O157:H7 is transmitted by contaminated food and water. Recently, there have been outbreaks related to frozen food products, organic spinach, and fast food establishments. Person-to-person spread is also reported in institutions, childcare centers, and within families (18).

Two to seven percent of children with *E. coli* O157:H7 infection develop HUS. HUS is usually evident 5 to 13 days after onset of the diarrheal illness. Most laboratory abnormalities resolve within 2 weeks. Twenty-five percent of patients will have severe HUS with more than 7 days of anuria, more than 14 days of oliguria, or stroke. Five to nine percent die, usually from thrombotic CNS involvement, which occurs in about 30% of pediatric HUS cases. Thirty-five to

fifty percent of survivors have chronic kidney damage; 3% have end-stage disease (18).

All patients should receive supportive care with careful management of fluids, electrolytes, and blood pressure, and dialysis when needed. Plasma exchange is generally reserved for those more severe cases that resemble TTP with CNS involvement (18,20). In patients with HUS secondary to Shiga-like toxins, there is no clear role for antibiotics or binding resins. Should these patients progress to end-stage renal disease, they become candidates for renal transplant, with a 10% recurrence rate. In contrast, patients with non–Shiga-like toxin-induced HUS, plasma exchange may be initiated by the hematologist accepting the patient.

CRITICAL INTERVENTIONS

- Avoid platelet transfusions in TTP–HUS except as a stopgap measure in patients with intracranial bleeding demonstrated on CT since administration of platelets is associated with deterioration in TTP–HUS.
- Involve hematology and nephrology services early when the disease process is suspected.
- In TTP, initiate plasma infusion with FFP and arrange for plasmapheresis.
- In HUS, carefully manage fluids and electrolytes.

DISPOSITION

Patients with TTP–HUS require high levels of nursing care and blood bank support, and should be admitted to an ICU. If plasmapheresis is not available, transfer to another institution should be arranged while plasma infusion therapy is begun.

Common Pitfalls

- Only about a third of patients have all five criteria of the classic diagnostic pentad of TTP–HUS at the time of presentation.
- Despite its rarity, TTP–HUS should always be considered in patients with neurologic, renal, or hemostatic abnormalities.

- The combination of microangiopathic hemolytic anemia, thrombocytopenia, an extremely high LDH, and normal PT/PTT is characteristic of TTP and distinguishes it from DIC.

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CHAPTER 198

Complications of Antithrombotic Therapy

Michael Ganetsky

The antithrombotics have multiple life-saving indications and life-threatening complications. In acute coronary syndromes (ACS), venous thromboembolism, and acute ischemic stroke both treatment and prevention, the antithrombotics save lives. Patients may present to the ED with life-threatening complications related to outpatient use or develop iatrogenic complications while receiving antithrombotic therapy as part of ED care. Emergency physicians must understand the basic mechanisms, indications, and complications of antithrombotic therapy. This chapter provides a practical review of the complications of common antithrombotic therapy including the antiplatelet, anticoagulant, and fibrinolytic agents.

ANTIPLATELET AGENTS

Aspirin

Originally discovered by Hoffman in the late 1800s, aspirin remains the most effective, safest, and least expensive of all antithrombotic drugs. At doses as low as 75 mg, aspirin irreversibly blocks platelet synthesis of thromboxane A2, a potent inducer of platelet aggregation and vasoconstriction (1). Aspirin is commonly prescribed for the prevention and management of cerebrovascular and coronary artery disease and for the prevention of stroke in low-risk patients with atrial fibrillation or with contraindications to anticoagulant

therapy. Other indications include the treatment of pain, rheumatic fever, pre-eclampsia, and Kawasaki disease. Nonenteric-coated aspirin is rapidly absorbed in the stomach and inhibits platelet function within 1 hour versus 3 to 4 hours for enteric-coated. Antithrombotic effects last the 10-day life span of the individual platelet with 50% replacement of the platelet pool within 5 days (1). Given the significant benefit in ACS, occult gastrointestinal (GI) bleeding requires close monitoring but is not an absolute contraindication to aspirin therapy.

ADP Inhibitors

The thienopyridines, ticlopidine, clopidogrel, ticagrelor, and prasugrel selectively inhibit adenosine diphosphate (ADP)-induced platelet aggregation. Delayed onsets and significant side effects, such as thrombotic thrombocytopenic purpura and neutropenia, have limited the use of ticlopidine. FDA indications for clopidogrel include unstable angina, non-ST segment elevation myocardial infarction (NSTEMI), ACS with aspirin intolerance, and reduction of secondary atherosclerotic events in patients with recent MI, recent stroke, or peripheral vascular disease. Clopidogrel is commonly prescribed after stent placement with aspirin in the prevention of atherosclerotic disease (2). Prasugrel was approved by the FDA in 2009 and ticagrelor approved in 2011 as alternatives to clopidogrel for patients undergoing percutaneous coronary intervention (PCI) for ACS.

Glycoprotein IIb/IIIa Receptor Inhibitors

Studies of a rare bleeding disorder, Glanzmann thromboasthenia, led to the discovery of the glycoprotein IIb/IIIa receptor. Fibrinogen binding to the IIb/IIIa receptor is the “final common pathway” of platelet activation and aggregation. Several glycoprotein IIb/IIIa receptor inhibitors (GPI) have been developed within three broad categories; abciximab (ReoPro) is a monoclonal antibody, eptifibatide (Integrilin) is a synthetic peptide, and tirofiban (Aggrastat) is a nonsynthetic peptide. GPIs have been extensively studied and proven to be beneficial in patients with unstable angina

or NSTEMI undergoing PCI (3). Use in low-risk patients with unstable angina who are not undergoing PCI is not recommended. However, in high-risk patients in whom PCI is not possible, GPIs, specifically eptifibatide or tirofiban, may be considered in consultation with the admitting cardiologist.

ANTICOAGULANTS

Heparin

Heparin, derived from the Latin "hepar," meaning liver, was first discovered by McLean in 1916 from a liver extract. By inducing a conformational change in antithrombin III (ATIII), heparin produces a very rapid inhibition of thrombin (4). This complex inactivates several enzymes of the coagulation cascade's intrinsic system including IXa, XIa, and XIIa and highly sensitive enzymes of the common pathway Xa and IIa (thrombin). In addition, heparin inhibits platelet function and binds to endothelial cells. In contrast to fibrinolytics, heparin has no effect on clot already present but prevents new clot formation and existing clot propagation. Intravenous heparin is indicated in the ED for acute deep venous thrombosis (DVT), pulmonary embolism (PE), atrial fibrillation, and ACS. In hospitalized patients, intravenous heparin is used for those undergoing cardiac bypass, vascular surgery, or coronary angioplasty and for select patients with disseminated intravascular coagulopathy (DIC) (4). In contrast to warfarin, both heparin and low-molecular-weight heparin (LMWH) are safe to use in pregnancy as neither crosses the placenta.

Low–Molecular-Weight Heparins and Pentasaccharides

In the 1970s, work to improve heparin's anticoagulant effect while minimizing hemorrhagic side effects led to the depolymerization of heparin into fragments approximately one-third the size producing the LMWHs. Most unfractionated heparin molecules have the required long saccharide units needed to form a tertiary complex with ATIII and thrombin compared to only 25% of LMWH molecules (4). In addition, LMWH has less of an effect on platelet function and

vascular permeability, theoretically further reducing hemorrhagic complications. Clinical effects of these differences are summarized in Table 198.1.

TABLE 198.1
Clinically Significant Differences of Heparin and LMWH

Characteristic	Heparin	LMWH	Clinical Advantage
Nonspecific protein binding	High	Minimal	Improved consistency, safety, and decreased need for laboratory monitoring with LMWH
Dose response	Poor	Predictable	
Bioavailability	30%	>90%	
Platelet binding	More	Less	Theoretically decreased bleeding complications and HIT syndrome with LMWH
Inhibition of platelet function	More	Less	
Vascular permeability	Increased	No effect	
Half-life	30–150 min	12–24 hrs	Lack of therapeutic "Off Switch" and poor reversibility with LMWH
Protamine reversal	Good, predictable	Poor	

LMWH, low–molecular-weight heparin.

Multiple studies have compared LMWH to heparin in the management of ACS, DVT, and PE and have found it to be safe and effective (4). Outpatient enoxaparin has been shown to be safe, efficacious, and cost-effective when compared with inpatient heparin in the management of DVT (5). Enoxaparin is renally cleared and studies have shown that patients with a creatinine clearance less than 30 mL/min treated with standard dosing (1 mg/kg bid) have an increased risk of major bleeding; empirical dose reduction of 50% (1 mg/kg qd) reduces this risk (4).

The FDA has approved several LMWHs, each with unique pharmacokinetic profiles resulting from different depolymerization

techniques that prevent easy interchangeable use. Current FDA indications include acute management of DVT with or without PE with enoxaparin, outpatient DVT with enoxaparin, postsurgical DVT prophylaxis with enoxaparin or dalteparin, and unstable angina and NSTEMI with enoxaparin or dalteparin.

The minimum heparin fragment necessary for ATIII binding has been demonstrated to be a pentasaccharide; this led to the development of fondaparinux, a synthetic analog of the heparin ATIII-binding pentasaccharide. Similar to enoxaparin, it is administered subcutaneously and can be used for treatment of DVT, PE, and ACS (4).

Warfarin

In 1941, Link isolated dicumarol from moldy sweet clover that was later developed and marketed as a rat poison by the Wisconsin Alumni Research Foundation. Coumadin, the brand name of sodium warfarin, is the most commonly prescribed oral anticoagulant. Warfarin inhibits regeneration of the vitamin K cofactor required for hepatic carboxylation of factors II, VII, IX, and X and the anticoagulant proteins C and S. The coagulation cascade's extrinsic system and common pathway are thereby blocked. The relatively short half-life of the anticoagulant Protein C (6 to 8 hours) compared to the four coagulation factors (6 to 60 hours) results in an iatrogenic hypercoagulable state for 24 to 36 hours, necessitating anticoagulation with heparin or LMWH as a bridge while beginning therapy with warfarin (6). In addition to this hypercoagulable state, physicians must be aware of the dissociation of laboratory response and the clinical response to warfarin. Reduction in factor VII (half-life 6 hours) results in an increased international normalized ratio (INR) within 24 to 36 hours. However, a reduction in thrombin levels (half-life 60 hours) and hence a reduction in significant clot formation does not occur until the fifth day of warfarin therapy, necessitating continued effective anticoagulation with IV heparin or LMWH therapy during the initial 5 days of management of acute thrombosis (6).

Warfarin is most commonly indicated for the management of venous thromboembolism and prevention of embolism with prosthetic heart valves or atrial fibrillation. Warfarin is completely absorbed from the GI tract, achieving peak levels within 4 hours with a mean effective half-life of 40 hours. Adjustments in warfarin dosing are made based on the INR, a standardized measurement of prothrombin time (PT) that corrects for differing laboratory reagents. The typical therapeutic range is 2 to 3 for most indications with the exception of mechanical valves requiring a higher INR of 2.5 to 3.5. Frequent monitoring is necessary to determine the ideal dose in each patient as many factors such as age, use of other medications, diet, comorbidities, and even race may affect patient response. Table 198.2 provides a brief listing of factors that may increase or decrease the response to warfarin. Warfarin crosses the placenta and may cause multiple birth defects and spontaneous abortions, so it is categorized as class X in pregnancy.

TABLE 198.2
Factors that may Increase or Decrease INR/PT Response to WARFARIN

Increase	Decrease
Medications • Multiple antibiotics including azithromycin, cephalosporins, and fluoroquinolones, tetracyclines, metronidazole • NSAIDs including ibuprofen, indomethacin, celecoxib, naproxen, acetaminophen, and aspirin • Cardiovascular drugs including amiodarone, propranolol, streptokinase, TPA • Prednisone, cimetidine • Influenza virus vaccine **Alternative Medicine** • Ginkgo biloba, garlic **Diet** • Dietary deficiency or malabsorption of Vitamin K • Altered intestinal flora by antibiotics **Patient Factors** • Cancer, collagen vascular disease, congestive heart failure, diarrhea, hyperthyroidism, steatorrhea, advanced, age, liver disease, fever	**Medications** • Carbamazepine, haloperidol • Nafcillin, dicloxacillin, prednisone, ranitidine **Alternative medicine** • St. John's Wort **Diet Changes** • Excess dietary vitamin K **Patient Factors** • Edema, hereditary warfarin resistance, hyperlipidemia, hypothyroidism

INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; PT, prothrombin time.

Direct Thrombin Inhibitors

Leeches were first used in the middle ages to rid the body of "black humors." Derived from a salivary extract of the leech *Hirudo medicinalis,* hirudin tightly binds to and inactivates thrombin. Currently used direct thrombin inhibitors (DTIs) include bivalirudin, argatroban, and dabigatran. DTIs inhibit both free and clot-bound thrombin and reduce platelet aggregating effects of thrombin. Dabigatran, an orally administered DTI, was approved by the FDA in 2010 for stroke prevention in patients with nonvalvular atrial fibrillation. Dabigatran has several advantages over warfarin: It has very few drug–drug and drug–food interactions and has a stable hematologic response thus not requiring frequent laboratory monitoring. Dabigatran has a fairly short duration of action

(elimination half-life of 12 to 17 hours), is predominately renally cleared, and a large portion can be removed via hemodialysis. In trials comparing dabigatran to warfarin, rates of major bleeding episodes tend to be similar, while dabigatran tends to cause less intracranial hemorrhages (ICHs) (7). Argatroban and bivalirudin are intravenous DTIs used in patients with ACS undergoing PCI or who have thrombotic complications and are at risk for or have confirmed heparin-induced thrombocytopenia (HIT) syndrome.

Factor Xa Inhibitors

Two orally administered direct factor Xa inhibitors have received recent FDA approval: rivaroxban in 2011 for stroke prophylaxis in patients with nonvalvular atrial fibrillation and in 2012 for treatment of DVT and PE; apixaban in 2012 for stroke prophylaxis in patients with nonvalvular atrial fibrillation. These factor Xa inhibitors are reversible and highly selective; they inhibit free and clot-bound factor Xa and prothrombinase activity without direct effect on platelet aggregation. Rivaroxaban has a short elimination half-life of 7 to 13 hours but factor Xa activity does not normalize for 24 hours after a dose. It is largely hepatically metabolized while one-third is renally excreted unchanged. Rivaroxaban has a predictable, dose-dependent anticoagulation effect; so routine monitoring of anticoagulation markers is not recommended. In clinical trials, bleeding rates are similar between rivaroxaban and enoxaparin (7).

Fibrinolytics

Streptokinase (SK) was the first fibrinolytic agent to be discovered by Tillett and Garner in 1932. The first use of fibrinolytics for reperfusion in acute MI was not reported until 1958 (8). Today's many different agents have one common mechanism: the conversion of plasminogen to plasmin, which then degrades fibrin and hence thrombus. First-generation, less fibrin-specific agents include SK, anistreplase, and urokinase. Second-generation, more fibrin-specific agents include recombinant tissue plasminogen activator (TPA;

alteplase) and several mutants of TPA including reteplase and tenecteplase (TNK-TPA).

SK is a purified preparation of a bacterial protein of group C β-hemolytic streptococci. SK binds to plasminogen, forming an activator complex that activates both fibrin-bound plasminogen and free circulating plasminogen producing localized thrombus breakdown and a generalized "systemic lytic state." Anistreplase is a modified SK molecule with a longer half-life (100 minutes) allowing for single-bolus dosing. IV or SQ heparin therapy is typically delayed 4 hours after SK and anistreplase to reduce bleeding complications.

Vascular endothelial cells produce TPA. Alteplase is a commercially produced recombinant TPA molecule. Alteplase has several advantages compared to SK, including increased fibrin specificity, resulting in less systemic fibrinolysis; a lower rate of allergic reactions; and an ability to lyse more highly linked fibrin clots, theoretically resulting in increased effectiveness in patients with prolonged symptoms. Reteplase is a deletion mutation of TPA with less fibrin specificity but a longer serum half-life of 18 minutes (vs. 5 minutes for recombinant TPA) allowing for bolus administration. No antigenicity has been reported with reteplase. Tenecteplase (TNK) is a triple substitution variant mutant of TPA with improved fibrin specificity and a longer half-life, again allowing bolus administration. Mortality benefits have not been demonstrated, but a significant reduction in bleeding with TNK compared to TPA was demonstrated in one study (8). Current indications for thrombolytic therapy includes ST-elevation MI (STEMI), acute ischemic stroke, and PE with signs of hemodynamic instability.

CLINICAL PRESENTATION

Patients with complications related to antithrombotic therapy may present to the ED in many different ways. Presentations may be occult, or dramatic, reported by the patient, or detected only during a meticulous history, physical examination, and workup. Regardless of the presentation, a high index of suspicion is necessary to rule out life threats in the patient on antithrombotic therapy.

GI bleeding is the major complication of aspirin therapy. Patients taking antiplatelet agents such as aspirin or clopidogrel may present with occult or massive GI bleeds. Although risk of bleeding is dose-dependent, bleeding may occur even with low-dose therapy.

Warfarin has been a main-stay of oral anticoagulant therapy for decades. Up to 15% of patients will suffer bleeding complications each year, 4.9% major bleeding complications, and up to 0.8% fatal, most commonly ICH (9). The risk of bleeding is directly related to the INR, increasing above 4, and is inversely related to the amount of time spent in the therapeutic range. Risk factors for bleeding include age greater than 75, past GI bleeding, hypertension, cerebrovascular disease, severe heart disease, renal insufficiency, alcoholism, known malignancy, and occult GI and genitourinary malignancies (10). Recent changes in drug doses, diet, and addition or discontinuation of other drugs may interact with warfarin, as described in Table 198.2.

Several types of skin lesions may result from anticoagulation therapy. The classic lesions of warfarin skin necrosis begin on the third to eighth day of therapy, resulting from capillary thrombosis in subcutaneous fat. Commonly associated with protein C deficiency, skin necrosis may also occur with protein S deficiency and in patients with normal levels. Unique skin lesions may occur with heparin and less commonly LMWH. An urticarial rash secondary to local histamine release is becoming less common owing to improved heparin purification techniques. Well-circumscribed plaques may occur at injection sites up to 20 days later, typically in obese or pregnant women. Heparin skin necrosis may occur within 1 day but typically at 1 week after starting therapy, often in patients without prior heparin exposure. The lesions start as an erythematous plaque before becoming hemorrhagic, necrotic, and often pruritic and painful. Biopsy often reveals antibodies, and thrombocytopenia may occur as part of the HIT syndrome (11). Skin necrosis with LMWH typically occurs in patients with prior heparin exposure, often without thrombocytopenia, and with fewer thrombotic complications.

In the ED, patients treated with antithrombotic medications require frequent re-evaluation. Minor bleeding, such as bleeding from puncture sites, or life-threatening GI or ICH must be detected and treated early to minimize further harm. For IV heparin, the risk of bleeding is $<6\%$ (10). Bleeding risk with heparin is directly related to dose and patient response as indirectly measured by the activated partial thromboplastin time (APTT). Dose adjustments based on every-6-hour APTT have been the traditional method of reducing hemorrhagic complications, but bleeding can occur even within the therapeutic range. Risk factors for bleeding complications include recent surgery or trauma, renal failure, aspirin use, GPIs, fibrinolytics, and age older than 70 years. LMWH has been associated with more bleeding complications after subcutaneous administration when compared with subcutaneous heparin and unusual bleeding episodes such as intrahepatic and psoas hematoma (11).

ED patients started on GPI or DTI may develop bleeding from vascular puncture sites, GI bleeding, or ICH, especially when treated with fibrinolytic therapy. Lower adjunctive heparin dose reduces the risk of bleeding with GPIs and fibrinolytics. Rates of life-threatening bleeding and intracranial bleeding for GPIs and DTIs are low as compared to fibrinolytics in ACS. Risk factors for bleeding from dabigatran include older age, baseline renal insufficiency, and acute kidney injury (7).

Patients started on fibrinolytic therapy in the ED may develop transient hypotension, mild-to-severe allergic reactions, and mild-to-life-threatening bleeding complications. In the absence of contraindications, risk factors for fibrinolytic-associated bleeding include older age, female gender, lower body weight, and hypertension.

ED EVALUATION

Many chief complaints are complicated by anticoagulation. The emergency physician should question the patient and family about the reason for anticoagulation, compliance with recent INR testing, other prescriptions, any potential recent medication adjustments, and over-the-counter and alternative medicines. Discussions with primary

care physicians and medical record reviews often help fill in historical blanks. The ED physician should also question the family about subtle changes in mental status, recent “minor falls,” or bleeding. Changes in vital signs may be evidence of early hemorrhagic shock or ICH. Hypertension may be secondary to Cushing response in ICH. Examine carefully for pallor, contusions, abrasions, ecchymosis, and other skin lesions. Perform a rectal examination with any suspicion of bleeding and in any patient beginning anticoagulation in the ED.

In patients with complaints related to antithrombotic therapy, check hemoglobin, platelets, PTT, INR, and other tests as indicated. Patients with bleeding related to aspirin therapy may have normal platelet levels but functional platelet deficits. Medication noncompliance, medication changes, diet factors, and concurrent illness may affect the adequacy of anticoagulation, necessitating laboratory screening in the ED.

GPI therapy may have mild or dramatic effects on platelet levels. Mild thrombocytopenia occurs in 5% of patients that are treated. Severe thrombocytopenia ($<$50,000) occurs in 2% of patients receiving abciximab versus 1% of eptifibatide and tirofiban. Acute profound thrombocytopenia ($<$20,000) occurs within 24 hours of administration of abciximab in 0.7% of patients but is rarer with eptifibatide and tirofiban. Platelet counts must be checked daily in patients receiving GPI to detect this rare but life-threatening complication (12).

Similarly, heparin and LMWH may have mild or dramatic effects on platelets. An early nonimmune-mediated transient thrombocytopenia occurs in 25% of patients, resolving in the majority within 3 days despite ongoing treatment. HIT syndrome develops in up to 3% of patients, typically presenting 5 days after initial heparin exposure but earlier in patients with prior exposure. The clinicopathologic syndrome is characterized by HIT antibody formation accompanied by a fall in the platelet count of $>$50% or skin lesions at injection sites. A hypercoagulable state may result in producing both venous and arterial thrombosis and DIC. The HIT antigen is platelet factor IV conformationally modified by interaction

with medium-chain heparin molecules accounting for the reduced incidence of HIT with low-molecular-weight shorter-chained heparins (11).

The DTIs and factor Xa inhibitors have various effects on coagulation parameters that impact on assessing degree of anticoagulation. Ecarin clotting time has a linear dose–response correlation with dabigatran; however it is not readily available. Thrombin clotting time is overly sensitive and the aPTT has a nonlinear response to dabigatran concentrations. Therefore, a normal thrombin clotting time or aPTT can be used to qualitatively exclude dabigatran-induced anticoagulation; however, when elevated, are not useful to determine degree of anticoagulation (7). The PT and HepTest are sensitive markers of the degree of anticoagulation with apixaban. For rivaroxaban, conventional PT/INR assays are not useful; anti-Factor Xa chromogenic assays or specialized PT assays with rivaroxaban calibrators are recommended and have recently become commercially available (13).

A low threshold for imaging of patients on antithrombotic therapy is required to detect occult but life-threatening bleeding. Even with minor mechanisms of blunt head trauma without loss of consciousness or blunt abdominal trauma without significant tenderness, head and abdominal computed tomography (CT) scans are recommended to diagnose occult life-threatening bleeding in patients on daily warfarin therapy (14,15).

For patients started on fibrinolytic therapy in the ED, repeat physical examinations are essential for the detection of bleeding. The majority of bleeding will occur at vascular puncture sites. Check laboratory values every 6 hours for 24 hours after therapy to detect occult blood loss. A fall in hemoglobin without an obvious source of blood loss necessitates a more diligent search. Repeat rectal examinations and a CT scan of the abdomen and pelvis may be necessary. Any change in mental status requires discontinuing therapy and an immediate head CT.

KEY TESTING

- CBC, serum chemistries (to assess for renal function)

- Type and screen/cross if transfusion of blood products is expected
- Routine coagulation studies (PT/PTT/INR)
- Focused coagulation studies and drug concentrations (i.e., thrombin time, bleeding time, ecarin clotting time, clotting factor concentrations, HepTest) are typically not routinely available nor are currently recommended to guide ED management
- Focused assessment of bleeding site (i.e., CT head, CT abdomen, GI consultation for endoscopy/colonoscopy)

ED MANAGEMENT

In the anticoagulated patient with bleeding, several factors must be considered. What is the severity of this bleeding episode? Is the bleeding into a closed space? Why is the patient on anticoagulation, and what is the risk of reversal? What other modalities such as endoscopy and proton pump inhibitors may be efficacious? If the risk of reversal is high (i.e., mechanical valve), can the patient be managed with just transfusions?

Patients with GI bleeding related to outpatient antiplatelet agents such as aspirin and clopidogrel require standard treatment including large-bore IV access, volume replacement and packed red blood cell replacement as indicated, proton pump inhibitor therapy, and specialty consultation for endoscopy. Despite normal levels, a functional platelet deficiency exists, requiring platelet transfusion of 5 to 10 U of random donor platelets to raise functional platelet levels by 50,000. Use of DDAVP (desmopressin), in addition to platelet transfusion, has been advocated for reversal of aspirin and clopidogrel. The standard dose is 0.3 to 0.4 μg/kg in 100 mL saline over 30 minutes (16). A summary of the management of bleeding complications from antithrombotic therapy is presented in Table 198.3.

TABLE 198.3
Management of Bleeding Complications Related to Antithrombotic Therapy

Aspirin or Clopidogrel	
Major[a]	Transfuse 5–10 U of random donor platelets to raise platelet levels by 50,000 DDAVP 0.3–0.4 μg/kg in 100 mL saline over 30 mis.
Glycoprotein IIb/IIIa Inhibitors	
Major or reversal for CABG	Abciximab: Discontinue all antithrombotics. Infuse 5–10 U of random donor platelets to raise platelet levels by 50,000 Eptifibatide and Tirofiban: Discontinue all antithrombotics. Platelets ineffective
Heparin	
Minor bleeding	Hold heparin Close observation and serial APTT
Major bleeding	Hold heparin Protamine 1 mg/100 mg of heparin in last 2–3 hrs
LMWH	
Major bleeding	Protamine 1 mg/1 mg of enoxaparin, 1 mg/100 U dalteparin, or 1 mg/100 U ardeparin Repeat protamine dosing often needed at 0.5 mg/1 mg of enoxaparin, 1 mg/100 U of dalteparin, or 1 mg/100 U ardeparin
Warfarin	
INR <4.5 without bleeding	Lower or omit next dose Recheck INR in 24–48 hrs
INR 4.5–10 without significant bleeding	Omit next one or two doses Recheck INR in 24 hrs Recent recommendations suggest against routine use of Vitamin K (17)
INR >10 without significant bleeding	Hold doses Vitamin K 2.5–5 mg PO Recheck INR in 24 hrs Resume therapy at lower dose once INR is at therapeutic level
Serious or life-threatening bleeding at any INR	Vitamin K 10 mg SLOW IV infusion FFP 2–4 U Consider PCC per hospital guidelines and in consultation with specialist, especially if intracranial or closed-space bleeding
Pentasaccharides	
Major	rVIIa 90 μg/kg; however routine use is still considered experimental
Direct Thrombin Inhibitors	
Major	Discontinuing therapy. No reversal agent is available, but half-life is short. Consider 2 U of FFP if suspect concomitant coagulation factor deficiency Factor VIIa is controversial but successful in some case reports. Dabigatran can be eliminated via dialysis so should be considered for life-threatening closed-space bleeding
Factor Xa Inhibitors	
Major	PCC have been shown to completely reverse rivaroxaban-induced prolongation of coagulation markers in health volunteers; however routine use is still considered experimental and should be balanced against prothrombotic risks of PCCs
Fibrinolytics	
Major bleeding	Start with 10 U of cryoprecipitate and 2 U of FFP Persistent bleeding or ICH: Above with 5–10 U of platelets and aminocaproic acid: loading dose of 5 g or 0.1 g/kg over 30–60 min followed by continuous infusion of 0.5 to 1 g/hrs

FFP, fresh-frozen plasma; PCC, prothrombin concentrate complex; rVIIa, recombinant factor VIIA.
[a]Major complications: life-threatening, ICH, or requiring blood transfusion.

Rapid reversal of GPI blockade may be necessary in patients who need emergent coronary artery bypass grafting or develop significant bleeding. Abciximab is a long-acting receptor blocker with 50% receptor blockade and platelet inhibition at 24 hours. Fortunately, the plasma half-life of the drug is only 15 to 30 minutes. Discontinuation of infusion and platelet transfusion are effective in reversing abciximab. Eptifibatide and tirofiban are competitive dose-dependent receptor blockers with return of normal hemostasis after only 4 hours. Reversal of these two agents requires discontinuation of the drug and time for clearance. With renal failure, hemodialysis

may be necessary. Platelet transfusion is of little use, as the high number of drug molecules will easily saturate new glycoprotein receptors on transfused platelets. Treatment of GPI thrombocytopenia includes discontinuation of the GPI and heparin and platelet transfusion (12).

Careful consideration must be given to the appropriate management of the anticoagulated patient even without bleeding. A subtherapeutic INR may require anticoagulation with heparin or LMWH while the warfarin dose is increased depending on the indication for warfarin. For the 50-year old with a mechanical valve who "ran out of warfarin a week ago" and now has an INR of 1, simply restarting warfarin may result in an iatrogenic hypercoagulable state and breakthrough thromboembolism. A supra-therapeutic INR may require little more than holding the next dose. Specific management depends on the degree of elevation, presence of bleeding, and the reason for anticoagulation. Methods to lower the INR include withholding or lowering the next dose, vitamin K (Phytonadione), and replacement products such as fresh-frozen plasma (FFP), prothrombin concentrate complex (PCC), or recombinant Factor VIIa (rFVIIa). The American College of Chest Physicians' evidence-based guidelines for the asymptomatic patients with an elevated INR are included in Table 198.3 (17). Major bleeding has not been clearly defined in the literature but for practical purposes may be considered to be any life-threatening bleeding, bleeding into a closed space, or bleeding requiring transfusion or surgical intervention.

Vitamin K is not without risk. A classic concern is anaphylaxis, which may occur at any dose when given IV and IM; however, anaphylaxis is very rare with modern preparations of Vitamin K (16). Subcutaneous absorption is unpredictable. Intramuscular administration may result in hematoma formation. Complete correction of the INR may result in breakthrough thromboembolism. High-dose vitamin K risks prolonged warfarin resistance and may precipitate thromboembolism for up to 1 week. Of the three routes, oral administration is considered the safest and most predictable, with effects beginning in 6 to 10 hours. Oral vitamin K (1 mg) lowers

an elevated INR between 4 and 10 in an asymptomatic patient more rapidly than 1 mg subcutaneously without an increased risk of thromboembolism (18). However, a randomized controlled trial did not find a difference in bleeding rates in nonbleeding patients with an INR between 4.5 and 10 treated with Vitamin K or placebo (19). Slow IV infusion over 10 minutes to prevent anaphylaxis is recommended only for life-threatening active bleeding with effects beginning in 1 to 2 hours. However, up to 24 hours may be needed for the full effects of Vitamin K, so doses typically need to be repeated and either FFP or PCC should be administered if immediate effects are desired. Vitamin K is not effective in advanced liver failure when coagulation factors are no longer synthesized.

The treatment of life-threatening bleeding related to warfarin requires administering vitamin K (10 mg) by slow IV infusion, along with factor replacement with FFP, PCC, or recombinant factor VIIa (rVIIa). Traditionally, 2 to 4 U of FFP are given for immediate control of bleeding; however, this may lead to volume overload, allergic reactions, and there is often a delay in thawing and delivering the blood products (13).

PCC provides a more rapid reversal of warfarin-associated coagulopathy than FFP and are recommended by many national guidelines (13). First used to treat hemophilia B, PCC is a fractionation product of FFP containing various amounts of factors II, VII, IX, and X. Long shelf-life and easy reconstitution into a highly concentrated volume (500 to 1,000 U/20 mL vs. 1 L of FFP per dose) allow for rapid and quick reversal without volume overload or infectious risk. Available PCCs include Bebulin VH, Profilnine, Octaplex, and Beriplex. However, until 2013 only 3-factor PCCs were available in the United States, which are less effective in reversing INR than the 4-factor concentrates. In 2013, the FDA approved Kcentra, a 4-factor concentrate marketed as Beriplex internationally for use in the United States. PCCs carry risk of thrombotic complications and DIC and are very expensive; therefore use should be limited to life-threatening bleeding (13). Also, outcome studies of PCC for ICH do not have control groups, so strength of evidence is mostly based on consensus. Emergency physicians should become

familiar with their hospital's availability of PCCs and guidelines for reversal of warfarin-associated bleeding as there is significant variability amongst institutions. rVIIA has also been shown to reverse INR value but not restore normal hemostasis in patients with warfarin-associated coagulopathy; therefore, PCCs or FFP are preferred agents (13).

Management of heparin-associated bleeding begins with stopping heparin therapy (half-life of 30 to 150 minutes for doses of 25 to 400 U/kg). With life-threatening bleeding, protamine may be used to reverse heparin anticoagulation in a dose of 1 mg/100 U of heparin administered in the previous 2 to 3 hours. As with vitamin K, there are risks associated with protamine administration. Hypotension, bradycardia, flushing, and fatal anaphylactic reactions have been reported. Dose is limited to 50 mg and must be given slowly over 10 minutes. As the duration from last treatment with heparin increases, heparin activity decreases, requiring less protamine for reversal. Although reversal is rapid, the half-life of protamine is shorter than heparin, necessitating repeat dosing if rebound bleeding occurs. In contrast to heparin, LMWHs cannot simply be turned off after subcutaneous administration. The long half-life must be weighed against the benefits when deciding on LMWHs versus heparin. The dose of protamine is compound-specific: 1 mg/1 mg of enoxaparin, 1 mg/100 U dalteparin, or 1 mg/100 U ardeparin. Repeat dosing is often needed at 0.5 mg/1 mg of enoxaparin, 1 mg/100 U of dalteparin, or 1 mg/100 U ardeparin. To date, only a few case reports of neutralization of LMWH have been published with relatively poor efficacy in comparison to heparin neutralization (11).

Management of HIT syndrome and warfarin skin necrosis includes discontinuing all heparin or warfarin products and administration of a rapid-acting anticoagulant such as danaparoid, a mixture of anticoagulant glycosaminoglycans with predominant antifactor Xa activity, or a DTI such as bivalirudin or argatroban.

Bleeding rates with the pentasaccharide fondaparinux are similar to enoxaparin. Use of rVIIa in healthy volunteers given fondaparinux will normalize prolonged coagulation parameters and there is anecdotal evidence of rVIIa controlling fondaparinux-induced

bleeding. The recommended dose of rVIIa is 90 μg/kg intravenously; however routine use is still considered experimental and further clinical experience is necessary before these can be recommended as standard of care (16).

Optimal reversal of the DTI dabigatran is still controversial and no effective reversal agent has been established. Given dabigatran's relatively short half-life, most bleeding episodes can be managed expectantly with supportive care and transfusion of red blood cells. However, closed-space bleeding (i.e., ICH) will likely not respond to this approach. Transfusion of FFP is controversial and is often recommended for repletion of any possible concomitant factor deficiency. Animal studies suggest rVIIa can decrease bleeding times from dabigatran. However, anecdotal experience with bleeding from the DTIs melagatran and lepirudin showed mixed results with rVIIa. In animals given dabigatran, PCCs have improved clotting time and bleeding, but in healthy volunteers given dabigatran, PCC did not reverse coagulation parameters (20). Given the thrombogenic risks of PCCs, routine use for reversal of dabigatran is not recommended. Dialysis can rapidly increase serum dabigatran elimination and thus, theoretically reverse the anticoagulated state. Dialysis may be an effective therapy for dabigatran-induced closed-space bleeding if it can be initiated quickly, but has not be studied clinically as of yet (13,16,21).

Factor Xa inhibitors such as rivaroxaban and apixaban are fairly novel and there is not much experience as of yet with reversal. In animal models, PCC has been shown to reverse anticoagulation induced by rivaroxaban (13) In healthy human volunteers given rivaroxaban, a single dose of PCC completely reversed prolonged coagulation markers (20). Therefore, PCCs seem the most promising reversal agent for Factor Xa inhibitors, but further clinical experience is necessary before these can be recommended as standard of care.

The best way to reduce complications from fibrinolytic therapy is to carefully review indications and contraindications before administration. Each institution should create protocols for STEMI, acute ischemic stroke, and massive PE with easy-to-follow pathway of indications, contraindications, patient consents, consultants to

notify, adjunctive medications, and treatment of complications. Avoid unnecessary procedures and blood draws. Nasal intubation and nasogastric tubes may precipitate massive epistaxis. Arterial lines are rarely essential for ED management. If central access is absolutely required, femoral vein cannulation is preferred as manual pressure of a missed jugular or a subclavian site and a chest tube for an iatrogenic pneumothorax are unnecessarily challenging.

The bulk of fibrinolytic bleeding will occur from puncture sites requiring only direct point pressure to the wound without discontinuing fibrinolytic therapy. Management of life-threatening GI bleeding requires aggressive volume replacement with crystalloid and packed red blood cells as indicated, reversal of fibrinolytic therapy, and adjunctive measures including proton pump inhibitors and endoscopy. Management of ICH requires cryoprecipitate, FFP, platelets, an antifibrinolytic agent, and neurosurgic evaluation. Most life-threatening hemorrhage related to fibrinolytic therapy responds to the administration of 10 U of cryoprecipitate and 2 U of FFP (22). With persistent bleeding or ICH, administer 5 to 10 U of platelets and an antifibrinolytic agent such as aminocaproic acid with a loading dose of 4 to 5 g or 0.1 g/kg over 30 to 60 minutes followed by continuous infusion of 0.5 to 1 g/hr until bleeding is controlled. Be careful to avoid antifibrinolytics in the patient with DIC.

With either SK or anistreplase, allergic reactions may occur typically with mild symptoms of chills, fever, and rigors but in severe forms may include anaphylaxis. Treat with standard therapy including antihistamines, epinephrine, steroids, and airway management. Although controversial, repeat dosing or readministration within 1 year is not recommended (8). Hypotensive episodes secondary to bradykinin generation respond well to decreasing rate of infusion, vasopressors, and IV fluids.

CRITICAL INTERVENTIONS

- Inquire about recent changes in drug doses, diet, and addition or discontinuation of other drugs that may interact with warfarin.
- Maintain a low threshold for imaging the head or abdomen in patients with minor trauma on antithrombotic therapy to detect

occult, but life-threatening, bleeding.
- Administer reversal agents for major bleeding complications associated with antithrombotic therapy (Table 198.3).

DISPOSITION

Most patients who present with or develop complications related to antithrombotic therapy will require hospitalization, especially if they have signs of active bleeding. They will typically need monitoring of hematocrit, coagulation factors, and extent of their bleeding. They may need endoscopic or surgical intervention dependent on the site of bleeding. They may also need replacement of significant blood loss or reversal of anticoagulation dependent on which agent they are taking.

The sub-therapeutic patient on warfarin often requires adequate anticoagulation with heparin or LMWH to prevent a paradoxical hypercoagulable state and breakthrough thromboembolism. Outpatient enoxaparin therapy followed by increased warfarin with close follow-up prevents unnecessary hospitalization.

The asymptomatic patient with a supra-therapeutic INR need not be an automatic admission for "coagulopathy." Although the rate of serious bleeding increases with an INR >4, the overall rate remains low. The indication for anticoagulation, reason for supra-therapeutic level, underlying comorbidities, overall risk of bleeding, fall risk, social situation, reliability, and availability of follow-up must all be considered. Holding warfarin doses, discharge to home, and repeating an INR in the next 24 to 48 hours are typically sufficient for patients with good follow-up who are not at increased risk of falling. HIT syndrome and skin lesions require admission for anticoagulation with alternative agents in consultation with a hematologist.

Anticoagulated patients with bleeding may have an underlying disorder that has been unmasked by the anticoagulant. GI or GU bleeding after starting anticoagulation requires aggressive evaluation for malignancy. Up to 25% of these patients will have an otherwise occult malignancy detected during evaluation for anticoagulant-related bleeding.

For the asymptomatic anticoagulated patient with minor trauma, therapeutic INR, stable hemoglobin, normal imaging studies, and reliable caretakers, discharge with close follow-up is appropriate. The symptomatic anticoagulated trauma patient with evidence of active bleeding requires aggressive management including reversal of anticoagulation, blood replacement, early surgical consultation for operative intervention, and hospitalization. These patients often require transport to a level-one trauma center after initial stabilization for definitive care.

Patients treated with fibrinolytic therapy require admission to an intensive care unit for treatment of the primary disease; close observation and treatment of complications; and cardiology, neurology, and/or neurosurgery consultation.

Common Pitfalls

- Failing to ask about anticoagulation; indication for, changes in dose, timing, and result of last INR, compliance, bleeding or skin lesions, comorbidities, new medicines, changes in diet, and changes in mental status or back pain.
- Failure to realize a patient's medication is actually an anticoagulant or specifically ask about novel anticoagulants. There has been a significant number of oral anticoagulants and antiplatelet agents recently approved by the FDA (i.e., dabigatran, rivaroxaban, apixaban, prasugrel, ticagrelor) and clinicians must add these to their mental list of medications that increase bleeding risk when evaluating a patient with trauma or bleeding.
- Inappropriate use of vitamin K, protamine, or PCCs. These have serious potential complications. High-dose vitamin K may result in prolonged warfarin resistance for up to 1 week. PCCs carry risk of thrombotic complications and DIC and are very expensive.
- Clinicians should become familiar with their institution's guidelines on reversal of anticoagulation. Many institutions are adopting use of PCCs for warfarin-induced life-threatening bleeding and the clinician should learn ahead of time which product is available and the recommended dose.

- The safest place for an asymptomatic supra-therapeutic patient may be at home "resting on their couch." Decide on admission versus close follow-up on a case-by-case basis in consultation with the patient's primary physician.
- The patient with a mechanical valve who ran out of warfarin a week ago with an INR of 1 cannot simply be sent home with a "little extra" warfarin. Adequate anticoagulation with heparin or enoxaparin is necessary in conjunction with restarting warfarin.

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CHAPTER 199

Sickle Cell Disease

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Sickle cell disease (SCD) is a hereditary disorder due to a genetic mutation in the hemoglobin protein. Hemoglobin S (for “sickle”) differs from the normal hemoglobin A in that valine is substituted for glutamic acid in position 6 of the globin beta chain. Both hemoglobin A and C function similarly in the oxygenated state, but deoxygenated hemoglobin S tends to polymerize leading to red cell sickling. Erythrocytes with less total hemoglobin or less hemoglobin S are more resistant to sickling, as are younger and small cells.

Individuals who are homozygous for the sickle cell gene (SS) have *SCD*. Their erythrocytes contain at least 90% hemoglobin S. Patients who are heterozygous for the sickle cell gene (SA) have *sickle cell trait*. Their erythrocytes contain both hemoglobin A (50% to 60%) and hemoglobin S (30% to 40%). *Common sickle variants* include *SC disease* (in which patients are heterozygous for both hemoglobin S and hemoglobin C which is caused by a different mutation of the beta globin chain) and *sickle-thalassemia*. These variants display lower red blood cell (RBC) levels of hemoglobin S and are associated with less morbidity than SCD. Most patients with sickle trait or variants have a normal life span and rare crises, although there is an increased risk for sudden death during exertion (1).

The anemia of SCD is due to both chronic and acute hemolysis. The red cell membranes are damaged with repeated episodes of sickling. During an acute painful vaso-occlusive crisis (VOC), the involved red cells undergo sickling. Initially, this may be reversible, but eventually the RBCs become irreversibly sickled and are destroyed. Sickled cells slow and obstruct the microvascular

circulation, compounded by the increased viscosity and the increased endothelial adherence of RBCs. Local tissue ischemia and acidosis lead to further sickling, and ischemic organ damage occurs.

The clinical severity of SCD is variable. Some patients follow a mild clinical course with infrequent VOCs, but others are more severely affected. An increased frequency of painful crises, particularly chest crises (see later), is associated with a shorter life expectancy (1). Most homozygous patients develop painful events before the age of 1 year, and by 5 years nearly all patients have experienced a VOC. Sickle cell patients diagnosed with concomitant asthma have an increased SCD morbidity and mortality (2).

Infection is a leading cause of mortality in patients with SCD. The life expectancy of these patients is increasing because of aggressive medical therapy, particularly treatment of infection. Currently, most sickle cell patients survive into middle adulthood (1). Sickle trait, SC, and sickle-thalassemia patients all have near normal life expectancies and suffer far fewer symptoms.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Painful VOCs are the most common presenting problem for sickle cell patients in the emergency department (ED). Many triggers have been identified, including infection, systemic acidosis, dehydration, hypoxia, cold exposure, pregnancy, and physical or emotional stress. Episodes of painful sickle events commonly last 48 hours to several days. Notably, many patients who present have an exacerbation of a long-standing pain syndrome—perhaps caused by previous ischemia and organ damage—but less triggered by acute sickling, though this is hard to distinguish from a VOC.

Bony pain is very common during acute VOCs. Adults usually complain of back and proximal extremity pain (2,3). When evaluating a patient with suspected bony VOC pain, other causes, such as trauma or infection, must be considered. The association between sickle cell anemia and *Salmonella* osteomyelitis is well described, yet *Staphylococci* remain the most common pathogen

causing osteomyelitis. Repeated episodes of bony ischemia can lead to aseptic necrosis, particularly in the femoral head (4) and carpal navicular areas, causing persistent pain frequently mistaken for acute vaso-occlusion.

Abdominal pain, nausea, and vomiting are common with episodes of vaso-occlusion. Local ischemia is thought to be the cause of these symptoms. However, a careful evaluation to rule out other causes of abdominal pain is mandatory in these patients. Because of the persistent hemolysis, sickle cell patients develop calcium bilirubinate gallstones and symptomatic cholelithiasis. In addition, other causes of acute abdominal pain, including pancreatitis, appendicitis, renal colic, and peptic ulcer disease should be considered before concluding that a vaso-occlusive event is the sole cause. The presence of active bowel sounds and a lack of high fever or signs of peritonitis favor a nonsurgical etiology. The risk of infectious hepatitis is higher in older sickle cell patients if they have received previous transfusion therapy or injected drug abuse. Jaundice does not necessarily indicate liver disease, as it is commonly due to chronic hemolysis.

The pregnant sickle cell patient with abdominal pain is a diagnostic and therapeutic challenge. Identifying appendicitis or cholecystitis is more difficult because of the anatomic changes associated with pregnancy. Pre-term labor, placental ischemia and abruption, and spontaneous abortion are also more common in sickle cell patients than in the general population.

Low-grade fever during a vaso-occlusive episode is common; however, when the temperature exceeds 38°C, seek an infectious source. Viruses account for most infections, but because of functional asplenia, these patients are at a higher risk than others for localized bacterial infection or bacteremia, especially with encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae.* The functional asplenia of sickle disease is due to autoinfarction of the spleen, which is usually completed by school age in those with homozygous disease. Patients with sickle trait or sickle cell variants generally have normal splenic function and immunity.

The *acute chest syndrome* (ACS) is a leading cause of death in patients with SCD. Patients with ACS present similarly to those with pneumonia. They have fever, chest pain, cough, and hypoxia and have new infiltrates on chest x-ray. Although the exact cause is unknown, ACS is thought to be caused by many mechanisms, from infection and fat embolism from infarcted bone to pulmonary microvascular sludging and infarction. The most common infectious etiologic agents of ACS are *Chlamydia pneumoniae, Mycoplasma pneumoniae,* and respiratory syncytial virus (5).

Chest pain is common in vaso-occlusive events (1). Sickle cell patients have a higher frequency of hypercoagulable diseases and thrombotic events, including pulmonary embolism and infarction. Thus, pleuritic pain can be due to vaso-occlusion (red cell micro-occlusion) with or without pulmonary infarction (platelet and coagulation protein-based clot) or due to infectious etiology. A productive cough, high fever, elevated total and immature neutrophil count, or Gram stain evidence of infection supports the diagnosis of pneumonia. The best clinical indicator of infarction is the absence of these infectious clues and the presence of occlusive symptoms in another area. *S. pneumoniae* and *H. influenzae* are the most frequent causes of bacterial pneumonia in sickle cell patients. It is also important to remember that in adults, chest pain can result from myocardial ischemia.

Focal or generalized neurologic signs and symptoms (including seizures) can follow vaso-occlusion in the cerebral circulation, with both small and large vessels affected. Acute retinal ischemia with visual loss and “floaters” from vitreous hemorrhages secondary to vessel disruption are also reported in sickle cell patients.

Priapism is a manifestation of local sequestration and vaso-occlusion and may present in all age groups. It often responds to vigorous medical therapy, including hydration, analgesia, local ice packs, or exchange transfusions. In refractory cases, surgical decompression is indicated. Testicular or ovarian ischemia can also result from vaso-occlusion, presenting with pain in the affected area.

Besides painful VOCs, the patient with SCD is subject to other less common episodic hematologic crises. These include sequestration,

hemolytic, megaloblastic, or aplastic crises. In *sequestration crisis,* acute anemia, hypotension, and potential shock occur because of sequestration of RBCs in the spleen. This often follows a viral illness and usually occurs in older adults with sickle cell variants. *Hemolytic crisis* can occur during a fulminant vaso-occlusive episode when large numbers of irreversibly sickled cells are lost. Severe anemia with increased reticulocytosis and jaundice is found. Marrow failure, resulting from either *megaloblastic crisis* (often from folate deficiency) or *aplastic crisis,* presents with a gradually falling hematocrit and deficient reticulocytosis.

In addition to the organ ischemia induced by RBC sickling, SCD patients frequently have enhanced coagulation, leading to arterial and venous thrombotic events. This is due to a variety of procoagulant syndromes seen more often in these patients, including protein C and S deficiency and circulating antiphospholipid antibodies (6).

ED EVALUATION

The diagnosis of an uncomplicated VOC is one of exclusion but common; a dangerous error is to attribute all pain in sickle cell patients to this cause. The initial investigation should seek evidence of an acute infection or other precipitating events. Chest pain can result from ACS, pneumonia, pulmonary embolism, pulmonary infarction, or myocardial ischemia; abdominal pain may reflect a surgical emergency. By the third decade of life, many sickle cell patients have undergone cholecystectomy and appendectomy, either because of demonstrable pathology or because abdominal pain during a previous vaso-occlusive crisis suggested an acute abdominal emergency. This eases the task of evaluating later episodes of acute abdominal pain by eliminating certain possibilities.

A focused history and examination are the cornerstones of the evaluation of sickle cell patients. Knowledge of the frequency and severity of past pain events and complications, the medication

history, and baseline laboratory values are helpful in tailoring the initial evaluation and treatment of patients with acute pain.

A complete blood count (CBC) and reticulocyte count (RC) are commonly ordered in sickle cell patients presenting for ED care. These can help screen for marrow failure, sequestration crisis, or infection. However, in a clinically uncomplicated VOC that is similar to previous episodes, these tests add little to the clinical management. In other patients, especially those with suspected infection or nonocclusive crisis, the CBC and RC can aid evaluation.

Most sickle cell patients have a persistent mild leukocytosis and a moderate anemia. The total leukocyte count is best adjusted for nucleated RBCs to avoid factitious elevation. Because of ongoing hemolysis and anemia, the RC should be elevated (usually to 8% or greater) compared to normal subjects. An abrupt drop in the hematocrit suggests a sequestration or hemolytic crisis, whereas an abnormally low RC suggests marrow failure.

Screen the urine for evidence of infection or infarction in patients with fever, pelvic, or back pain. If symptoms of urinary tract infection are present with pyuria or bacteriuria, obtain a urine culture in these immunocompromised patients to help guide follow-up therapy.

Fever, chills, or any pulmonary symptoms or signs suggesting a new abnormality mandate chest radiography to identify ACS or pneumonia. Because of the risk of bacteremia and sepsis, blood cultures should be obtained when there is evidence of pneumonia or pyelonephritis or when high fever or leukocytosis occurs without an apparent source.

Other tests may have a role depending on the clinical presentation. An electrocardiogram can aid when chest pain or other symptoms suggestive of myocardial ischemia exist. Serum electrolytes, blood urea nitrogen, and creatinine determinations can help assess hydration and renal function, but are not mandatory in clinically uncomplicated VOCs. In cases of unexplained abdominal pain, a serum amylase, lipase, liver enzymes, abdominal x-rays, gallbladder ultrasound, or CT scan may be indicated. Helical CT can help detect pulmonary embolism in patients in whom pneumonia or

vaso-occlusion do not explain the findings. A D-dimer is not usually helpful in given the high propensity of false-positive results.

In those patients with stroke, myocardial ischemia, pulmonary embolism, or other arterial/venous thrombotic findings, many begin an evaluation for hypercoagulability, beginning with prothrombin and partial thromboplastin time tests plus other specific tests for coagulopathies though these are not needed in other sickle crises and do not alter ED management.

An assessment of oxygen saturation is important, especially if any pulmonary or chest symptoms or abnormal physical examination findings exist. Arterial blood analysis is reserved for those with a suspected acid–base abnormality, inadequate oximetry signal, or severe hypoxemia (as a confirmatory test).

KEY TESTING

- CBC and RC if concern about worsening anemia
- Urinalysis if fever, abdominal, or back pain
- CXR if fever/chest complaints
- Pulse oximetry

ED MANAGEMENT

In unstable patients, airway and circulatory assistance are the primary immediate concerns. Once addressed, routine ED management can proceed with a diagnostic workup based on the previous recommendations. Treatment is usually supportive, as definitive treatment of vaso-occlusive pathophysiology is still lacking. The best treatment is rehydration with analgesia.

The choice of fluids is controversial; those with orthostasis or hypotension should receive isotonic solutions. In the absence of significant volume depletion, hypotonic fluids may have theoretical benefits. There are no clinical outcome data to support routine parenteral hypotonic solutions in VOCs. Irrespective of the fluid chosen, it is important to pay attention to the total volume administered to avoid iatrogenic pulmonary edema.

Traditionally, all sickle cell patients received supplemental oxygen during painful crises. Although oxygen reverses some sickling in vitro, it can depress erythropoietin levels and reticulocytosis, potentially interfering with a natural compensatory response (7). Currently, there are no outcome data supporting or refuting the routine use of oxygen, although pragmatism suggests that those with clinically important hypoxemia may benefit. An ambient oxygen saturation of $<90\%$ or a drop of $>5\%$ from known baseline is often used to initiate therapy.

Achieving adequate pain control in VOCs is challenging. By late adolescence, many patients with sickle disease require opioid analgesics to gain relief. Complicating the management of these patients are physician and nursing fears of drug abuse and secondary gain. Subjectively reported pain is generally the only tool available to measure discomfort; it is not possible to reliably identify "feigned" pain on clinical grounds or to separate VOC pain from an exacerbation of a long-standing pain syndrome. Optimal treatment of vaso-occlusive pain is based on multifaceted, inexpensive regimens that offer the best chance of timely relief with a minimum of complications. In addition, the patient must be educated to actively participate in the process of pain relief rather than reinforcing a passive approach. This means a frank discussion about the goals of therapy (pain relief, although not always immediate pain extinction, without harm) and the need for nonpharmacologic adjuncts including counseling and behavior modification. Therapy must be individualized based upon patients' previous clinical experiences (8).

Oral analgesics are the mainstays for most patients with mild to moderate pain, with parenteral regimens reserved for those who cannot tolerate oral agents or who are in severe pain. Most patients presenting for care in the United States receive opioids in addition to hydration and acetaminophen. Because the pain of vaso-occlusion is incited by ischemia, the analgesic effects of nonsteroidal anti-inflammatory drugs (NSAIDS) are less prominent than in other syndromes wherein prostaglandin excess is the major biochemical trigger (9). In addition, the risk of renal failure may be higher than

in non–sickle cell patients. A single NSAID dose is unlikely to cause harm, however, and can provide some additional analgesic effect.

Hydrocodone, oxycodone, morphine, and hydromorphone are good opioid choices for those with refractory or more intense pain. For those who require parenteral therapy, the key is choosing an adequate dose and regimen based on individual patient response; the ceiling dose is whatever relieves pain or causes side effects. Many of these patients have tolerance and require high doses of morphine or hydromorphone; conversely, treating all with high doses risks respiratory depression if opioid exposure has been rare. Intravenous regimens (either by repeated injections, continuous infusion, or patient-controlled administration) offer ease of titration, rapid analgesia, and less risk of side effects. Intramuscular injections should be rare and reserved for selected cases when oral therapy is impractical and venous access unobtainable.

A minority of sickle cell patients are opioid abusers. This has led some centers to initiate “contracts” with their patients in an effort to limit abuse while ensuring prompt and humane treatment when a painful crisis occurs. Commonly, the patient agrees in writing to take oral opioids only for severe pain and to contact a designated physician and ED during a crisis. The patient also agrees not to seek alternate opioid sources. This provides adequate care while limiting the total amount of opioid prescribed over a specified period.

For documented or suspected bacterial infections, a broad-spectrum antibiotic should be administered early. Sickle cell patients should take folic acid supplements daily to avoid megaloblastic crisis.

Transfusion therapy is indicated in selected sickle syndromes. In patients with priapism or aplastic, sequestration, or hemolytic crisis, exchange transfusion is preferable to simple transfusion to avoid the risk of iron overload and is generally more effective. Anemia alone is not an indication for emergency transfusion in the absence of signs or symptoms of deficient oxygen delivery to the heart or brain.

Some longer-term approaches to the treatment of SS disease are available. Hydroxyurea disrupts RBC endothelial adhesion, enhances hemoglobin F production, promotes the formation of hemoglobin S

polymers, may mediate nitric oxide release (see further), and can diminish the frequency and severity of crises (10,11). The long-term safety of this treatment is still not completely defined, with marrow failure a limiting side effect, and the drug has mutagenic and carcinogenic properties. It may also cause nausea, vomiting, and skin rashes. Hydroxyurea therapy can decrease mortality in patients (12). To date, bone marrow transplant remains the only curative therapy for sickle cell disease.

Inhaled nitric oxide may increase the oxygen affinity of hemoglobin S in humans both in vivo and in vitro. Therapeutic inhalation is thought to exert direct effect on the pulmonary vasculature to increase oxygenation through diminished shunting and reduce pulmonary hypertension (13). Clinical experience is limited, and its long-term efficacy and toxicity are unknown. It has been found to provide pain relief, especially with chest syndromes, when used with standard therapies but remains investigational (14).

CRITICAL INTERVENTIONS

- Seek evidence of an acute infection or another precipitating event in patients with vaso-occlusive events.
- Rehydrate and treat VOC pain using oral regimens rather than parenteral, when possible.
- Initiate broad-spectrum antibiotics for documented or suspected bacterial infection.

DISPOSITION

Patients with uncomplicated VOCs who are adequately hydrated and obtain sufficient pain relief in the ED can be discharged with close follow-up. There is no absolute rule to determine how long an “adequate” analgesia and hydration trial in the ED should be. If pain relief is obtained in uncomplicated VOCs, oral analgesics can be prescribed for 3 to 5 days to treat milder recurrence, a common phenomenon. Each patient should be encouraged to obtain further care from the same institution or a single physician (or group) to ensure continuity.

The inability to control pain is the most common indication for admission in adults. Patients with proven or suspected sequestration, aplastic, or hemolytic crisis require admission. The presence of any new neurologic sign or symptom, priapism, or an acute abdomen also mandates hospitalization.

In general, the presence of an invasive bacterial infection mandates admission, because it is largely through the aggressive treatment of infections that the life expectancy for SS patients has been increased. The exception would be that adults with a minor pharyngeal or respiratory tract infection may be discharged with treatment if close outpatient follow-up within 24 hours can be arranged (15). Besides these specific instances, admission is indicated for patients with fever, unexplained leukocytosis (especially with immature forms), or uncertain compliance with follow-up schedules.

A new alternative is use of a daytime care center to deliver fluids and analgesia under physician guidance and with nursing staff, akin to oncology outpatient infusion care; these are often adjacent to the ED or hospital and can serve to limit admission.

Finally, patients should be counseled to avoid any sympathomimetic drugs (including over-the-counter decongestants and illicit cocaine) and alcohol (which may suppress a stressed marrow). Pneumococcal and influenza vaccines can be offered or made available in follow-up, along with potential long-term oral penicillin prophylaxis for those with frequent bacterial infections.

Common Pitfalls

- Do not assume that abdominal pain is due to a vaso-occlusive event without considering other causes.
- Be careful not to overlook pneumonia or pulmonary infarcts in sickle cell patients.
- Osteomyelitis and aseptic necrosis of bone can be mistaken for “crisis” pain in this population.
- Exchange transfusion therapy is often not started early enough in the setting of neurologic changes or priapism.

- Give sickle cell patients with pain the benefit of the doubt while being prudent with the total number of doses of pain medication. In those with frequent visits, develop a clear plan to be used by all ED providers, and have the patient enter into a written treatment contract with the primary care provider, if possible.
- Educate sickle cell patients about avoiding triggers, maintaining hydration, and initiating early self-titrated analgesia to limit the need for recurrent ED visits.

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CHAPTER 200

Anemia

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Anemia is defined as a decrease in the number of circulating red blood cells, with a concomitant decrease in the capacity of the blood to carry oxygen to tissues. Anemia is a manifestation of disease rather than a diagnostic entity in and of itself.

Anemia can be classified into disorders of decreased red cell production, disorders of increased red cell destruction, and anemia resulting from blood loss (1–3). Each of these diagnostic groups has its own clinical presentation and differential diagnosis (Table 200.1) and, in general, requires its own approach to emergency department (ED) evaluation and management.

TABLE 200.1
Differential Diagnosis of Anemia

Anemia Secondary to Blood Loss (Acute or Chronic)

Intraperitoneal

Retroperitoneal

Pelvic

Urinary tract

Gastrointestinal tract

Gynecologic (vaginal bleeding, placenta previa, abruption)

Epistaxis

Hemoptysis

External bleeding

Drug-related (coumadin, heparin)

Traumatic

Anemia Secondary to Decreased RBC Production (Insidious-Onset, Decreased Reticulocyte Count)

Hypochromic/microcytic

Iron deficiency

Thalassemia

Sideroblastic (including lead)

Chronic disease (infection, chronic inflammation, neoplasm, diabetes, liver failure, uremia, thyroid disease)

Macrocytic

Hypothyroidism

Folic acid deficiency

Chemotherapy, radiotherapy, immunosuppressive therapy

Liver disease

Vitamin B_{12} deficiency

Scurvy

Normocytic

Primary bone marrow disorder (aplastic anemia, myeloid metaplasia, myelofibrosis, myelophthisic anemia)

Secondary bone marrow disease (endocrinopathy, uremia, chronic inflammation, liver disease, ethanol ingestion)

Anemia Secondary to Increased RBC Destruction (Increased Reticulocyte Count, Free Hemoglobin, RBC Fragmentation)

Intrinsic

Enzyme defect (G6PD, pyruvate kinase)

Membrane abnormality (spherocytosis, elliptocytosis, spur cell, paroxysmal nocturnal hemoglobinuria)

Hemoglobin abnormality (hemoglobinopathy, thalassemia)

Extrinsic

Immunologic (alloantibody, autoantibody, cold agglutinins [e.g., mononucleosis])

Neoplastic (especially leukemia, lymphoma)

Collagen vascular (lupus, rheumatoid arthritis, periarteritis nodosa)

Infections (mycoplasma, syphilis, malaria, Bartonella, viral)

Other (thyroid disease, ulcerative colitis)

Mechanical (microangiopathic hemolytic anemia, prosthetic valve)

Abnormal sequestration (hypersplenism)

Environmental (drugs, toxins, hyperthermia, drowning)

RBC, red blood cell.

Anemia of any cause may present acutely or chronically, and the aggressiveness of intervention and management depends on the acuteness of onset and on the severity of the clinical presentation. For example, anemia secondary to acute gastrointestinal blood loss may require vigorous fluid resuscitation, transfusion therapy, and intensive care management; anemia secondary to chronic occult gastrointestinal bleeding leads to a well-compensated iron-deficiency anemia that can be evaluated and treated on an outpatient basis (4,5).

Defective red blood cell production may be due to interruption in the availability or synthesis of any of the three moieties of the hemoglobin molecule: iron, heme, and globin. Hence, anemia may result from iron deficiency, from toxins or enzymatic deficits that interfere with heme synthesis, or from genetic defects in globin synthesis. Disorders and deficiencies that affect the proliferation of erythroid stem cells in the bone marrow may also result in anemia from decreased red cell production (6–8).

Red cell destruction may result from either intrinsic or extrinsic causes. Intrinsic abnormalities of hemoglobin, enzymes, or red cell membranes may result in hemolytic anemia. Extrinsic destruction may be due to immunologic, mechanical, or environmental causes or to hypersequestration (hypersplenism) (1–3,8).

Blood loss resulting in anemia may be acute or chronic and may originate from intraperitoneal, retroperitoneal, pelvic, pleural, gynecologic, or gastrointestinal sources (3).

CLINICAL PRESENTATION

Patients with anemia secondary to acute blood loss present with hypovolemia. A source of blood loss may be readily identifiable on clinical evaluation; menstrual and gastrointestinal tract blood loss are the most common reasons for occult bleeding (9). A history of underlying disease (e.g., cirrhosis, bleeding diathesis, malignancy, or infection) or of medication use (e.g., use of salicylates, nonsteroidal anti-inflammatory drugs, or anticoagulants) may be

useful in guiding initial evaluation and management. Hypovolemia may be relatively well tolerated in the young patient without underlying disease but can be a significant stress to elderly or chronically ill individuals whose compensatory mechanisms may be overwhelmed and whose tissue perfusion may be marginal at baseline (10,11).

Patients with anemia secondary to chronic blood loss or to decreased red cell production often present with signs and symptoms involving several systems due to hypoperfusion and decreased oxygen-carrying delivery:

- Constitutional symptoms—progressive fatigue, malaise, or dizziness
- Integumentary symptoms—pallor of the skin or mucous membranes, jaundice (from hemolysis), petechiae or purpura (with thrombocytopenia), or glossitis (from vitamin deficiency) (1,2,12)
- Pulmonary symptoms—dyspnea on exertion or decreased exercise tolerance
- Gastrointestinal symptoms—anorexia or nausea, hepatomegaly (from extramedullary hematopoiesis, sequestration or autoimmune process) (1,3,13)
- Cardiovascular symptoms—angina pectoris, claudication, syncope, tachycardia with widened pulse pressure, hyperdynamic precordium from increased cardiac output, or systolic ejection murmur (1,2,14,15)
- Genitourinary symptoms—dark urine (from hemolysis) or decreased urine output (16)
- Neurologic symptoms—focal neurologic deficits, stocking glove anesthesia or impaired position or vibratory sense (due to vitamin B_{12} deficiency) (6,12)

Other important historic information includes ethnicity and family history (predisposition to certain hemoglobinopathies and pernicious anemia), drug use, dietary history, use of ethanol, recent hospitalization (anemia of chronic disease is common in hospitalized patients), and history of underlying disease (renal,

hepatic, thyroid, collagen vascular, or neoplastic disease; previous anemia; or recurrent jaundice) (3,17). Chronic rheumatologic, endocrine, hepatic, or neoplastic disease may manifest with lymphadenopathy, rash, thyromegaly, myxedema, or the stigmata of liver failure (15,16).

The symptoms, signs, and laboratory findings of anemia may be the initial presenting manifestations of pancytopenia (1). The etiology of pancytopenia is multifactorial. Pancytopenia is most commonly idiopathic (50%) but may result from chemical and physical agents, autoimmunity, or vitamin B_{12} or folic acid deficiency. Pancytopenia may follow viral illness, including upper respiratory infection, hepatitis, Epstein–Barr infection, and human immunodeficiency virus infection (1,18). It may also be associated with hypersplenism, myelodysplasia, bone marrow failure, or marrow replacement (3). Clinically, pancytopenia may present as a viral illness, preceding the symptomatic presentation of anemia over several weeks, or as an insidious presentation of anemia with clinical evidence of thrombocytopenia (petechia, purpura, or mucous membrane bleeding) (1).

Patients with anemia secondary to acute hemolysis are likely to present with signs and symptoms similar to those seen with mild chronic anemia. In more severe presentations, there may be jaundice and dark urine. Fever, prostration, abdominal and back pain, and hemoglobinuria suggest acute intravascular hemolysis, similar to that associated with transfusion reaction (1,8). A family history of anemia suggests an intrinsic cause of hemolysis, whereas exposure to drugs or toxins suggests an extrinsic cause (1,3). Immunologic destruction of red blood cells may be due to autoantibodies (8). Mechanical destruction is seen in some patients with prosthetic heart valves (3). Disseminated intravascular coagulation leading to microangiopathic hemolytic anemia is suggested by diffuse bleeding (13,15).

DIFFERENTIAL DIAGNOSIS

A complete differential diagnosis is presented in Table 200.1.

ED EVALUATION

Patients presenting to the ED with hypovolemic shock due to acute blood loss need to be rapidly evaluated and stabilized. Cases of chronic anemia can be evaluated on a less emergent basis, and some patients may continue their evaluation as an outpatient. In-patient evaluation may include further laboratory evaluation for specific diseases as well as a bone marrow biopsy in some cases (3).

Potential diagnostic errors of importance include the following:

- Not suspecting acute blood loss and impending hypovolemic shock with any unexplained normocytic normochromic anemia
- Confusing anemia with other entities that also cause constitutional symptoms (e.g., uremia, collagen vascular disease, fluid and electrolyte imbalance, infections, drug effects)
- Confusing iron-deficiency anemia, which presents with low iron, increased total iron-binding capacity (TIBC), and low ferritin, with anemia of chronic disease, which presents with low iron, low TIBC, and normal ferritin associated with a chronic disease or recent hospitalization (1,3,10)
- Confusing hemolytic anemia with other entities that also cause acute jaundice (particularly acute hepatitis)
- Overlooking pancytopenia by focusing on a clinical picture of anemia and low hemoglobin while neglecting findings of leukopenia and thrombocytopenia

KEY TESTING

Initial testing in the ED should include the following:

- Complete blood count
- Red blood cell indices and reticulocyte count
- Peripheral smear (hemolyzed cells, basophilic stippling, ringed sideroblasts, or hypersegmented leukocytes may be seen) (1,4,7,16)
- Additional focused laboratory analysis for specific conditions
- Serum iron, TIBC, and serum ferritin for hypochromic microcytic anemia (3)

- Folate and vitamin B_{12} levels, liver-function tests, and thyroid-function tests for macrocytic anemia (3,12)
- Indirect Coombs tests, fractionated serum bilirubin count, and lactate dehydrogenase (LDH) and haptoglobin levels in hemolytic anemia (8,12,19)

ED MANAGEMENT

Anemia of pregnancy is treated with prenatal vitamins (one daily) and iron replacement (ferrous sulfate 325 mg three times per day), and hypochromic microcytic anemia associated with an identified source of blood loss (presumed to be due to iron-deficiency anemia) is treated similarly, with iron replacement therapy (5,10,20). These patients should be re-evaluated after 4 to 6 weeks to assess the adequacy of the therapeutic response (5,10).

In megaloblastic anemia, presumed to be due to folic acid or vitamin B_{12} deficiency, treatment may be initiated with 1 mg/d of oral folic acid or with vitamin B_{12} intramuscularly at a dose of 1 mg weekly for 8 weeks (6,10,12,17,18). High doses of oral vitamin B_{12} daily for 90 to 120 days (1 to 2 mg) have been shown to be as effective and safe as intramuscular administration (12). In mild or asymptomatic anemia of chronic disease, therapy is generally directed to control the underlying disease (3).

For severe or sympatomatic anemia, transfusion may be indicated, sometimes in the ED. There is still uncertainty regarding the "transfusion threshold" for critically ill or septic patients or patients experiencing a STEMI. Recent literature suggests that a threshold hemoglobin of 7 may be associated with better outcomes for critically ill adults and children and for patients with acute myocardial infarction (MI) (19,21,22).

In many cases of newly identified anemia, drug therapy and other interventions including the use of erythropoietin have been shown to be beneficial but are frequently not indicated in the ED setting, and patients are referred to a consultant for further evaluation and management (5,7,9,14,16,18,23).

In children, the most common causes of anemia are nutritional deficiencies or hereditary or acquired primary hematologic disorders (3). Treatment is directed toward the underlying cause (2).

CRITICAL INTERVENTIONS

- Recognize clinical signs and symptoms of anemia
- Initiate laboratory investigation for the underlying etiology of anemia

DISPOSITION

Consultation or referral for follow-up, in most cases, is to the patient's primary care physician. Most anemic adult patients have iron-deficiency anemia, vitamin B_{12}- or folic-acid–deficiency anemia, or anemia of pregnancy; these cases can be treated and followed up on an outpatient basis. Children who are symptomatic or severely anemic should receive a transfusion and be admitted to the hospital for further evaluation (2). Stable patients or those with mild anemia may be treated on an outpatient basis.

Urgent consultation and hospital admission should be sought for the following indications (3,10,17):

1. Hypovolemia or ongoing bleeding
2. Need for urgent transfusion, generally because of a hemoglobin level <7 g/dL in a bleeding or symptomatic patient (19,21), or to hemoglobin of 10 g/dL in septic patients in the first 6 hours or patients with acute MI (19,21)
3. Severe symptoms (e.g., chest pain, dyspnea, syncope) that impair the patient's ability to function at home
4. Pancytopenia requiring diagnostic evaluation (1,18)
5. Anticipated need for extensive diagnostic or therapeutic intervention

Unless active bleeding is present or the patient is hemodynamically unstable, there is usually no contraindication to routine transfer for specialized evaluation.

Common Pitfalls

- Failure to suspect and identify bleeding and hypovolemia.
- Failure to appreciate the possibility of anemia from the clinical presentation and, hence, not ordering a hemoglobin or hematocrit determination. This is especially likely in hemolytic anemia or when chest pain, dyspnea, dizziness, or claudication is the presenting complaint.
- Failure to identify and treat the underlying cause of the anemia.
- Failure to ensure referral or appropriate follow-up for evaluation of therapeutic response or the need for additional diagnostic testing.

ACKNOWLEDGMENT

The authors gratefully acknowledge the contributions of Louis S. Binder to the contents of this chapter.

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CHAPTER 201

Transfusion Reactions and Complications

Gregory W. Hendey

Each year, approximately 24 million units of blood components are transfused to patients in the United States (1). The overall incidence of reported transfusion reactions is 0.25%, with only 0.09% being severe (1). The exceptionally low rate of serious transfusion reactions is mainly due to strict adherence to blood banking techniques, careful transfusion practices, and extensive testing of donated units.

Although life-threatening reactions are rare, it is critical that physicians recognize them quickly and respond appropriately to avert a disastrous outcome. Transfusion reactions may be divided by severity and time of onset (Table 201.1).

TABLE 201.1
Blood Transfusion Reactions and Complications

Acute, severe reactions
- Acute hemolysis
- Anaphylaxis
- Septic
- Transfusion-related acute lung injury
- Congestive heart failure

Acute, minor reactions
- Simple febrile
- Allergic

Delayed reactions
- Delayed hemolysis
- Graft-versus-host disease
- Hepatitis
- HIV
- CMV
- Other infections: Epstein–Barr virus, cytomegalovirus, syphilis, trypanosomiasis, babesiosis, malaria, toxoplasmosis, brucellosis, West Nile virus

Massive transfusion
- Coagulopathy
- Hypothermia
- Hypocalcemia (citrate toxicity)
- Hyperkalemia
- Lactic acidosis

CLINICAL PRESENTATION

Acute, Severe Reactions

Acute Hemolysis

One of the most serious (and most preventable) blood transfusion reactions is acute hemolysis caused by incompatibility between recipient and donor ABO blood groups. The incidence is approximately 1 in 600,000 components transfused (1). The resulting IgM–antigen complex fixes complement, leading to rapid intravascular hemolysis, with massive release of hemoglobin, acute renal failure, disseminated intravascular coagulopathy (DIC), and cardio-vascular collapse.

The most common cause is mislabeling or clerical error—the wrong unit is given to the wrong patient. For that reason,

painstaking efforts must be taken to double-check every step in the identification process prior to a transfusion.

The clinical signs of an acute hemolytic reaction are usually not subtle in patients who are awake but may be difficult to recognize quickly in unconscious, intubated patients. In an acute reaction, patients experience a rapid onset of fever, chills, back pain, vomiting, tachycardia, and hypotension.

Anaphylaxis

Anaphylaxis is fortunately a rare occurrence during a blood transfusion, but when it does occur, it is often in IgA-deficient individuals who react to the IgA present in the plasma of the transfused unit. The incidence has been estimated to be between 1 in 20,000 and 1 in 150,000 transfusions (2,3). Although these reactions are not predictable, they may be prevented in a patient with a history of anaphylaxis by minimizing plasma transfusions and transfusing products that are washed or derived from IgA-deficient donors (2).

The onset is generally within the first minutes of transfusion and presents as sudden flushing, pruritus, laryngospasm, bronchospasm, and hypotension.

Sepsis

Another potentially fatal transfusion reaction occurs when a contaminated blood product is transfused. This is a rare event with packed red blood cells (PRBC) transfusions, with only one reported fatality per year reported to the Food and Drug Administration (FDA) (4). The most common bacterium in PRBC units is *Yersinia enterocolitica,* which grows well under refrigerated conditions (4,5).

Platelet transfusions carry a higher risk of fatal sepsis due to bacterial contamination (approximately 1 in 700,000 units) because they are stored at room temperature to maintain platelet activity (1,4,5). Single-donor apheresis platelet units carry a slightly lower risk for bacterial contamination than do pooled random donor platelets as do fresher units with less storage time (4,5). Many bacteria have been implicated in platelet contamination, including *Staphylococcus aureus* and *Enterobacteriaceae.*

When the contaminated unit is transfused, it may produce the acute onset of a sepsis syndrome, with fever, chills, and hypotension. A septic reaction, especially when caused by a gram-negative organism, could easily be confused with the early stages of a hemolytic or anaphylactic reaction.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is a noncardiogenic pulmonary edema occurring unpredictably in 1 in 50,000 units transfused (1,2,5). TRALI has emerged as the leading cause of transfusion-related fatality, with 91 cases reported to the FDA from 2007 to 2011, representing over 40% of reported fatalities (6). Antileukocyte antibodies in the donor unit (often fresh frozen plasma [FFP]) react with the patient's white blood cells, resulting in the release of cytokines. This reaction leads to increased pulmonary capillary permeability and produces an adult respiratory distress syndrome during or just after transfusion. It should be differentiated from acute congestive heart failure (CHF) by the patient's history and the typical chest x-ray (CXR) finding of diffuse interstitial edema without cardiomegaly. An association between TRALI and female plasma donors has been noted and is thought to reflect increased antibody production during pregnancy. For this reason, some blood banks now restrict plasma donations to males.

Congestive Heart Failure

The cardiovascular systems of most patients can easily accommodate the rapid change in intravascular volume that a blood transfusion provides. Elderly patients, however, and those with preexisting cardiomyopathy or diastolic dysfunction may have difficulty handling an acute change in volume and preload, and the result is pulmonary edema. Acute, progressive dyspnea and rales may develop during or soon after a blood transfusion, which some refer to as transfusion-associated circulatory overload (TACO).

Acute, Minor Reactions

Simple Febrile Reactions

Simple febrile reaction is the most common transfusion reaction, with an incidence of 0.1%. It is thought to be due to antileukocyte and antiplatelet antibodies or to transfused pyrogenic cytokines that accumulate in stored blood as leukocytes break down. It is characterized as an isolated fever during transfusion, without any of the more serious signs and symptoms of vomiting, back pain, hypotension, or evidence of hemolysis.

Allergic Reaction

Minor allergic reactions occur largely in response to transfused plasma proteins. The incidence is estimated to be 0.1%, but it may be underreported (2). The reaction is more common with platelet or plasma transfusions, but PRBC units also carry some residual plasma. The patient develops urticaria or flushing and pruritus, without the dyspnea or hypotension that may signify a more serious anaphylactic reaction.

Delayed Reactions

Adverse transfusion reactions may occur days to months after the transfusion. These include delayed hemolysis, graft-versus-host disease (GVHD), and a number of infections. Many infectious diseases may be transmitted by blood transfusion, including the human immunodeficiency virus (HIV), hepatitis, syphilis, malaria, cytomegalovirus (CMV), Epstein–Barr virus, trypanosomiasis, toxoplasmosis, babesiosis, brucellosis, and West Nile virus (1,7). The most clinically significant in the United States are hepatitis, HIV, and CMV.

Delayed Hemolysis

Delayed hemolysis is unusual but may occur 5 to 10 days after transfusion. The incidence is approximately 1 in 29,000 units transfused (1). It is most commonly caused by reactivation of antibodies to the minor RBC antigen systems such as Rh, Kell, Kidd, and Duffy. Clinically, it presents in a less severe and dramatic way than the acute hemolytic reaction in most cases (2). Low-grade hemolysis and progressively worsening anemia are the most common clinical findings of this reaction.

Graft-Versus-Host Disease

GVHD occurs when lymphocytes from a donated unit of blood attack an immunocompromised host who is unable to combat the foreign cells or when lymphocytes from an immunologically similar donor are not recognized as foreign by the host. Signs and symptoms may include fever, rash, nausea, and vomiting as well as elevation of transaminases and pancytopenia occurring 7 to 10 days after transfusion (2). This is a particular danger in neonates and bone marrow transplant recipients.

Hepatitis

Transfusion-associated hepatitis was a major problem in the 1970s and 1980s. It has been estimated that during the early 1970s, transfusion-associated hepatitis occurred in up to 33% of transfusions (8). Since then, aggressive screening of donors and the development of specific assays for hepatitis B (HBsAg and anti-HBc) and C (anti-HCV and nucleic acid amplification) have greatly reduced the risk.

Donahue et al. (9) reported a decrease in the risk of posttransfusion hepatitis C from approximately 1 in 200 during 1985 to 1 in 3,300 in 1991, after hepatitis C testing became available. With further advances in testing, the current estimated risk of transfusion-transmitted hepatitis B is 1 in 200,000, and that of hepatitis C is 1 in 2,000,000 (1,3,10).

Human Immunodeficiency Virus

Although it is now exceedingly rare, the transfusion complication that has received the most public attention is HIV infection. It has been estimated that the risk of HIV transmission in some metropolitan areas was as high as 1 in 100 units transfused in 1983 before HIV testing was available to blood banks in March 1985 (5). Now, thanks to aggressive predonation screening along with testing for HIV-1 and HIV-2 antibodies, p24 antigen testing, and nucleic acid amplification testing (NAT) technology for HIV, the current risk is estimated to be 1 in 2 million units of blood (1,10). NAT technology allows for the detection of viral genetic materials prior to the antibody response.

The use of concentrated pooled plasma products resulted in a majority of hemophiliacs in the 1980s contracting the acquired immunodeficiency syndrome or hepatitis. Highly purified, lyophilized factor VIII concentrate and recombinant products have eliminated these tragic complications of therapy.

Cytomegalovirus

Although CMV is generally not a significant pathogen in immunocompetent individuals, the immunosuppressed, especially premature neonates, HIV patients, and bone marrow and organ transplant recipients are especially susceptible to CMV infection transmitted by blood transfusion. The risk may be greatly reduced through the use of blood collected from CMV-negative donors or by using leukocyte-reduced or frozen-deglycerolized units of blood.

Massive Transfusion

Several alterations are present in stored blood that are insignificant in small transfusions but may become clinically relevant in the setting of massive transfusion. *Massive transfusion* is usually defined as transfusion of the equivalent of one blood volume, or 10 to 12 units of PRBC, within 24 hours (11). Although this situation is unusual in the emergency department (ED), it may be encountered in the setting of major trauma or gastrointestinal (GI) bleeding when definitive care is delayed for whatever reason. A more recent and relevant definition of massive transfusion may be the transfusion of 6 units of PRBC within 3 hours, with ongoing hemorrhage.

Hyperkalemia and lactic acidosis may result from the transfusion of multiple units of older stored blood, but the effects tend to be relatively mild and transient. Hypocalcemia due to citrate toxicity was a significant clinical issue in the past when it was common to transfuse whole-blood units. However, in the era of component therapy, whole blood is rarely available or indicated, and PRBC units contain far less citrate. Transfusing large amounts of cold blood may also cause hypothermia, which in turn may worsen coagulopathy. Blood warmers lessen this problem, but may also slow the rate of

transfusion. Mixing PRBC units with heated crystalloids, making the transfusion both faster and warmer, has been described (12,13).

The coagulopathy associated with massive transfusion is multifactorial. Dilutional effects play a part, as the multiple units of PRBC transfused contain only negligible amounts of clotting factors and platelets. Trauma patients who receive more than 10 units in 24 hours are more likely to develop serious coagulopathy, especially in the presence of hypothermia, acidosis, or hypotension (14). Although platelet counts fall during massive transfusion, the decrease is less than would be predicted from dilution alone (15). This may be due to an "auto-transfusion" effect from platelets stored in the spleen or bone marrow.

DIFFERENTIAL DIAGNOSIS

The patient who develops any adverse symptoms early in a blood transfusion must be carefully evaluated for the possibility of one of the acute, severe reactions. However, many patients who receive emergent transfusions have underlying disease that may have symptoms in common with transfusion reactions. For example, when trauma patients or those with GI bleeding become hypotensive during a transfusion, the hypotension may represent either increasing hemorrhage or an acute, severe transfusion reaction. Sepsis and some drug overdoses (i.e., salicylates) may also present with symptoms that are similar to those of a transfusion reaction. Hypotensive reactions to platelet transfusions have also been reported (16). These are not thought to be allergic in origin but may initially lead the clinician to suspect anaphylaxis. These reactions appear to be uncommon and resolve quickly with cessation of the platelet transfusion (16). Patients with fever may have infectious causes unrelated to the blood transfusion, and those with allergic symptoms may be reacting to an allergen other than a blood product.

Although many of the signs and symptoms of transfusion reactions are nonspecific and can be confused with many disease processes, most transfusion reactions occur during or soon after a transfusion. The temporal relationship is less clear with the delayed reactions. A delayed hemolytic reaction must be differentiated from other causes

of jaundice and anemia, but the indirect hyperbilirubinemia should cue the physician that hemolysis has occurred. A new diagnosis of hepatitis or other transmissible diseases may be traceable to the blood supply but may also have occurred independently.

ED EVALUATION

In the patient with an acute reaction, the clinician must immediately *stop the transfusion* and rapidly decide whether the signs and symptoms are consistent with one of the severe reactions or one of the more benign febrile or allergic reactions (Fig. 201.1). Differentiation may sometimes be done clinically by evaluating the constellation of findings, without extensive testing. One may also employ quick, simple testing, such as observing the serum (after centrifugation of a blood sample) or the urine for pink discoloration during a hemolytic reaction.

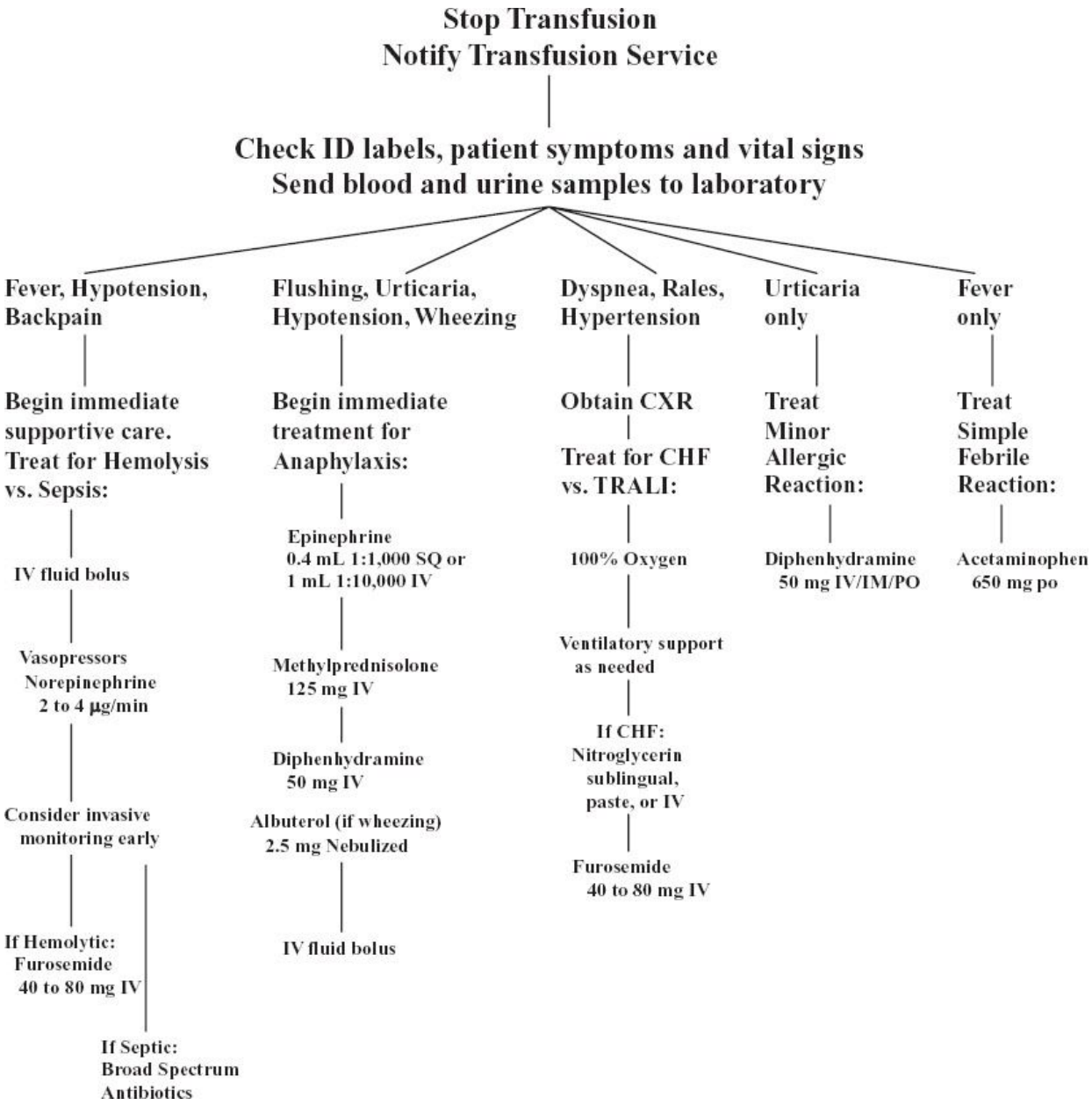

FIGURE 201.1 Clinical algorithm for suspected transfusion reaction. Many hospitals have developed policies and guidelines for actions to be taken in case of a transfusion reaction. Physicians should be informed regarding local hospital policy. TRALI, transfusion-related acute lung injury.

The evaluation should also involve immediate reporting to the laboratory and sending blood samples for testing. Based on the clinical setting, the laboratory will often confirm the ABO types of

the patient and donor unit, perform a direct Coombs test, and search for evidence of hemolysis (an elevated indirect bilirubin, decreased haptoglobin, schistocytes on a peripheral smear, or hemoglobinuria). Testing may also include Gram staining and cultures, especially after platelet transfusions, if bacterial contamination is suggested.

The transfusion must be stopped during this critical evaluation period until the clinician is certain that a severe reaction has been excluded. In many cases of minor reactions, the clinician may choose to treat the symptoms and restart the transfusion, although this remains controversial and varies by institutional policy. One should quickly involve the laboratory and transfusion service for consultation when a reaction occurs. Most institutions have policies or guidelines to help the clinician in evaluating and reporting transfusion reactions.

KEY TESTING

- Send samples of patient's blood and transfusion component to lab
- Type and screen, direct Coombs test, hemoglobin, urinalysis, bilirubin, haptoglobin, peripheral smear

ED MANAGEMENT

Treatment depends on which type of reaction has occurred (see Fig. 201.1). The first step is always to stop the transfusion and carefully evaluate the patient to determine whether a transfusion reaction is occurring and, if so, which type.

The treatment of *acute hemolysis* is largely supportive, with special attention to maintaining renal perfusion. In hemodynamically unstable patients, early use of invasive monitoring is warranted, along with vasopressors and forced diuresis with crystalloids and loop diuretics (e.g., furosemide). Other treatments, such as steroids, mannitol, or heparin for DIC, are more controversial.

Anaphylaxis should be treated with epinephrine, steroids, diphenhydramine, and IV fluids. Patients with a history of serious allergic reactions to blood products may be given washed RBCs or frozen-deglycerolized RBCs in an effort to prevent allergic reactions.

IgA-deficient donors are often available when the transfusion can be planned in advance.

Sepsis from bacterial contamination requires aggressive supportive care, including IV fluids, vasopressors, and broad-spectrum antibiotics. Antibiotic coverage for a contaminated platelet transfusion should include an antistaphylococcal agent as well as a third-generation cephalosporin. Coverage for a contaminated PRBC transfusion must include a third-generation cephalosporin or quinolone to cover *Yersinia.*

CHF is treated with nitrates, diuresis, and ventilatory support as needed. Transfusions must be given carefully in elderly patients and in those with a history of CHF or renal failure. It may be sufficient to transfuse each unit slowly (over 3 to 4 hours) and allow a period of time between subsequent units transfused, usually in the inpatient setting. Administration of a loop diuretic (e.g., furosemide) between units may also be helpful. In high-risk patients, invasive monitoring of right or left ventricular filling pressures in the ICU may be necessary, and transfusions may be accomplished during dialysis for renal failure patients.

TRALI, or noncardiogenic pulmonary edema, has no specific treatment and may require supplemental oxygen, continuous positive airway pressure (CPAP or BiPAP), or intubation and ventilatory support. In many cases, the pulmonary edema resolves spontaneously over hours to days. Limiting plasma donors to males might reduce the incidence of TRALI.

Simple febrile and *allergic* reactions are treated with acetaminophen and diphenhydramine, respectively, but must be differentiated from the more dangerous transfusion reactions. Patients who receive frequent transfusions or who have a history of minor reactions may be given leukocyte-reduced units to reduce the risk of a febrile reaction or pretreatment with diphenhydramine to reduce allergic symptoms. There is controversy about whether the transfusion may be carefully resumed after clinical observation and appropriate laboratory testing have ruled out a more serious reaction.

For GVHD, there is no specific treatment beyond supportive care, but some preventive measures exist. Irradiation of PRBC and platelet

units suppresses white blood cells that may be transfused along with the desired component and may prevent GVHD in high-risk immunocompromised patients.

The many problems associated with *massive transfusion* may be dealt with in several ways. Prevention of hypothermia and monitoring for hyperkalemia and hypocalcemia are important. In cases of massive transfusion over many hours or days, coagulopathy may be monitored with serial laboratory testing. When massive transfusion occurs more quickly, a formulaic approach to the prophylactic administration of FFP and platelets is appropriate. For example, 10 units PRBC → transfuse 4 units FFP and 1 apheresis platelet unit. Many authors now recommend early, aggressive replacement of FFP and platelets during massive transfusion (17).

CRITICAL INTERVENTIONS

- With any sign of a transfusion reaction, stop transfusion immediately and closely monitor vital signs.
- Administer IV fluid bolus if hypotension is present.
- Send samples from patient and transfusion unit to lab.

DISPOSITION

Most patients receiving blood transfusions in the ED are ultimately admitted to the hospital, regardless of whether they have a transfusion reaction. However, acute, severe reactions usually necessitate ICU admission, regardless of the patient's original disposition. Simple febrile or allergic reactions do not necessarily require a change in the patient's treatment plan.

Common Pitfalls

- Failure to carefully identify patients when drawing pretransfusion blood samples and to carefully match identities of blood components, their paperwork, and the recipient. This is the most frequent cause of fatal hemolytic reactions.
- Failure to adequately evaluate a patient who develops symptoms during a blood transfusion. The large majority of reactions are

simple febrile or allergic reactions, but the few dangerous reactions must be recognized and treated immediately.

- Failure to recognize a severe reaction in an intubated patient. Because the patient cannot complain of symptoms, it is more difficult to differentiate a transfusion reaction from underlying disease. An acute, severe reaction may initially appear as isolated hypotension, fever, or hematuria.
- Rapidly transfusing an elderly patient who is inadequately observed. CHF can be avoided by slow, intermittent transfusion and diuresis.

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CHAPTER 202

The Cancer Patient in the Emergency Department

Gwendolyn M. Schillo and Joanne Williams

Cancer is the second leading cause of death in the United States. In fact, one in every four deaths in the United States is a result of cancer or related illnesses. A new diagnosis of cancer may occur during an emergency department (ED) visit, but a more common scenario is one wherein the emergency physician treats an individual with a history of malignancy who suffers a complication of the disease or its treatment.

ED visits for cancer and related complications have increased, not only as a result of disease prevalence, but from changes in treatment. More aggressive chemotherapy regimens have improved patient survival and cure rates but have also resulted in an increased number of complications related to therapy. Common oncologic emergencies facing the emergency physician include metabolic abnormalities (e.g., hypercalcemia and tumor lysis syndrome [TLS]), superior vena cava syndrome, malignant pleural effusion, and neutropenic fever. The emergency physician must be prepared to assess and begin lifesaving treatments for these conditions.

SHORTNESS OF BREATH

Airway Obstruction

The first priority in assessing the patient with shortness of breath is to assess the airway, seeking evidence of obstruction. Most cases of upper airway obstruction involve advanced cases of cancers of the

larynx or the hypopharynx, neck, and mediastinum. Patients with head and neck malignancies will typically present with a history of gradual dyspnea progressing over the course of weeks to months. Additional symptoms may include hoarseness or stridor, dysphagia, and hemoptysis.

Tumors, most commonly carcinoma of the lung, esophagus, thyroid, and lymphoma, cause dyspnea by direct invasion or compression and mass effect of the trachea. Midline shift of the trachea may be apparent on physical examination or radiograph. Obtaining an emergent and definitive airway on these patients may be difficult, as tumors can block the view of the vocal cords or can be subglottic in location, making passage of an endotracheal tube impossible. Tracheostomy is often necessary, as endotracheal intubation can be unsuccessful.

Bronchial obstruction is usually the result of primary lung carcinoma. Rarely, endobronchial metastasis from other primaries such as breast, colon, and renal carcinoma cause significant bronchial obstruction. Typically, there must be more than 75% obstruction before a patient becomes symptomatic. The patient may present with dyspnea on exertion, cough, hemoptysis, wheezing, and rhonchi.

Initial assessment may include x-rays of the chest and soft tissues of the neck. Unfortunately, these are rarely diagnostic; thus, contrast computed tomography (CT) scan with contrast of the neck and chest with three-dimensional airway reconstruction is more helpful. Direct laryngoscopy or nasopharyngeal approaches with fiberoptic scopes are often used to assess the size of the airway lumen and involvement of the vocal cords when upper airway obstruction is suspected. Unfortunately, tumors causing acute airway compromise from edema, infection, hemorrhage, or excessive secretions do not allow time for imaging and determination of anatomic changes. In such situations, one must be prepared to establish an emergent surgical airway. Early involvement of an ear, nose, and throat surgeon is recommended, as the local anatomy of the airway can be greatly distorted. This is particularly true if the patient has been treated previously with tumor resection or radiotherapy or if the

patient has untreated bulky masses. Interventions prior to intubation could include high-flow supplemental oxygen or bag-valve-mask ventilation, heliox, intravenous steroids, racemic epinephrine, and antibiotics.

Pneumonia

When patients present with dyspnea, fever, and sputum production, pneumonia should be suspected. Patients with pulmonary obstructing lesions such as primary lung cancer, lymphomas, or metastasis to the lung are more prone to pneumonia. Other populations at increased risk for pneumonia are those with a history of head and neck cancer, with or without previous surgical treatment, with secondary aspiration, and those with hematologic malignancies or neutropenia who are on chemotherapeutic drugs. Diagnosis is made easily by chest x-ray or CT, and appropriate antibiotic therapy should be started promptly. Patients with postobstructive pneumonia may require bronchial stenting or radiotherapy to definitively treat the pneumonia.

Malignant Pleural Effusion

Malignant pleural effusions are caused most commonly by lymphoma, lung, or breast cancer and less commonly from ovarian and gastrointestinal cancers. Malignant effusions arise from various mechanisms, including tumor emboli seeding the visceral and parietal pleural surfaces, direct tumor invasion, and lymphatic obstruction. Local inflammatory changes in response to tumor invasion may also result in effusion. Rarely, an effusion can be due to congestive heart failure resulting from cardiomyopathy caused by certain chemotherapeutic agents.

It is estimated that up to 30% of cancer patients develop malignant pleural effusion. Patients typically present with dyspnea on exertion or orthopnea or may complain of a dry cough. Examination typically reveals decreased breath sounds on the affected side, dullness to percussion, and occasionally a pleural friction rub.

Chest x-ray or CT confirms the diagnosis. Approximately 300 cm^3 of fluid is needed for an effusion to be seen on an upright chest x-ray and only 100 cm^3 on a decubitus film. For a small effusion with mild hypoxemia, only supplemental oxygen may be needed. Thoracentesis may be required for intractable hypoxemia due to moderate or massive effusion. Pleural fluid obtained during thoracentesis should be sent for cytology, gram stain, culture, cell count and differential, protein, amylase, and lactate dehydrogenase (LDH) determinations. If infection is suspected, antibiotics should be started after a sample of pleural fluid is obtained. For recurrent effusions, an oncologist should be consulted for more definitive therapeutic modalities such as pleurodesis, pleurectomy, or chemotherapy.

Pericardial Effusion

Pericardial effusion occurs most commonly in patients with lung and breast cancer, but virtually any tumor can involve the pericardium. Pericardial effusions leading to tamponade are usually the result of long-standing processes that evolve into critical problems over the course of a few hours. The severity of tamponade is related to the rapidity with which fluid accumulates (see Chapter 88). Slowly increasing effusions allow time for the pericardium to stretch and slowly accommodate the increased volume. If the pericardium is thickened by fibrosis and therefore less compliant, as is often the case in patients who have received radiotherapy to the mediastinum, even a small effusion can cause tamponade. In such cases, chest radiograph may show a small heart, and cardiac tamponade can be confirmed only by the use of a bedside echocardiogram.

Nonconstricting pericardial effusion usually does not cause specific symptoms. However, as the pericardium distends and compression worsens, patients may develop dyspnea, orthopnea, chest pain relieved by leaning forward, cyanosis, dysphagia, hoarseness, epigastric discomfort, or hiccups. On physical examination, the patient is typically apprehensive and diaphoretic,

with a decreased systolic blood pressure and a narrowed pulse pressure. The lungs are usually clear, the neck veins distended, and the heart sounds distant. An increased pulsus paradoxus and inspiratory swelling of the neck veins may be noted. If the effusion is a long-standing one, patients may also have peripheral edema, hepatojugular reflux, hepatomegaly, and even ascites, giving the impression that congestive heart failure is present.

The chest x-ray shows cardiomegaly or a globular cardiac silhouette with clear lung fields. The most common electrocardiogram (ECG) findings are sinus tachycardia and low-voltage QRS complexes or occasionally global ST elevation. Electrical alternans is pathognomonic for pericardial effusion but is commonly missed as it can disappear as compression worsens. Definitive diagnosis is made by echocardiography or CT when ultrasound is unavailable. Bedside ultrasonography may also be used to guide pericardiocentesis in the decompensated tamponade patient. Treatment of frank tamponade also includes the administration of intravenous fluids to increase the right ventricular filling pressure. This alone may provide time to get the patient to surgery for a pericardial window procedure. If emergent pericardiocentesis is performed for shock, cyanosis, or decreased level of consciousness, the fluid should be sent for cytology.

Pulmonary Embolism

Patients with malignancy are in a hypercoaguable state and therefore are at risk of thromboembolic disease such as pulmonary embolism. Venous thrombosis can also form from external compression or direct invasion of vascular structures by tumors. Approximately 10% of all patients with cancer develop thromboembolic disease, and for patients with certain malignancies such as pancreatic, renal cell, and ovarian carcinomas, the incidence can be as high as 50%. As such, pulmonary embolism must always be considered a potential cause of dyspnea in cancer patients. Likewise, patients not known to have malignancy who are

diagnosed with thromboembolic disease, specifically those with recurrent thrombosis, should be screened for malignancy.

Treatment options include anticoagulation with heparin or, when there is a concern for heparin allergy or heparin-induced thrombocytopenia, with nonheparin-based anticoagulants such as direct thrombin inhibitors. The nonheparin-based anticoagulants should be administered in consultation with hematology. When starting anticoagulation in an oncology patient, particular attention should be given to the extent of metastatic disease, especially the presence of brain metastasis. Current opinion supports anticoagulation in the presence of brain metastasis, except possibly in cases of renal cell carcinoma or melanoma, which are more likely to develop hemorrhagic complications. For patients who cannot be treated with anticoagulants, an available option is placement of an inferior vena cava (IVC) filter. The risks of IVC filter placement include complications related to the insertion process, venous thrombosis at the site of insertion, filter migration or erosion into the IVC wall, and IVC obstruction. The risks of placement should be considered prior to insertion.

Superior Vena Cava Syndrome

Superior vena cava (SVC) syndrome is a result of the acute or insidious obstruction of blood flow in the SVC, resulting in elevated venous pressure or venous hypertension. The severity of illness is related to the rapidity of obstruction; the more rapid the onset of obstruction, the shorter the time available for development of collateral circulation. Structures drained by the SVC include the lower airways, upper extremities, neck, face, eyes, and brain. SVC obstruction therefore leads to dyspnea and hoarseness from edema of the airways, dysphagia, chest fullness, blurred vision, and headache. Common physical findings include venous distension of the neck and facial and upper extremity rubor and swelling. The patient's symptoms can usually be exacerbated by a change in position, such as bending forward, stooping, or lying down. As

venous hypertension increases, increased intracranial pressure (ICP) can develop and can lead to syncope.

Obstruction from malignancy is the most common etiology of SVC syndrome, accounting for up to 85% to 95% of cases. Patients have evidence of a mass on chest radiograph only 10% of the time. Chest CT is more sensitive for diagnosing a mass that is causing compression. When a mass is found, it is usually located in the right superior mediastinum. Other causes of SVC syndrome include mediastinal fibrosis from prior radiotherapy, tuberculosis, or thrombosis around indwelling venous catheters. Elevation of the head of the bed, diuretics, and steroids may reduce venous pressure and provide some temporary relief of symptoms. Definitive treatment, however, may include radiotherapy, antineoplastic agents, or percutaneous transluminal stent placement. Emergent radiotherapy is indicated when there is compromised cardiac function, significant upper airway edema leading to respiratory dysfunction, or cerebral dysfunction secondary to brain edema.

MASSIVE HEMOPTYSIS

Massive hemoptysis represents one of the most challenging conditions in clinical practice and this condition is potentially lethal. Patients die from asphyxiation or exsanguination.

Clinically, airway bleeding leading to life-threatening anemia, aspiration, airway obstruction, or hypovolemic shock is considered massive hemoptysis.

The most common cause of massive hemoptysis in cancer patients is bronchogenic carcinoma. Melanoma, breast, kidney, laryngeal, and colon cancers may cause hemoptysis secondary to lung metastases. Esophageal cancers may cause massive hemoptysis by direct extension into the tracheobronchial tree.

Patients with massive hemoptysis may present with hypotension, tachycardia, cold and clammy skin, dyspnea, cough, chest pain, or frank respiratory distress. These patients are true oncologic emergencies. Asphyxiation is the most frequent complication of massive hemoptysis. In that regard, these patients need

endotracheal intubation with the largest possible endotracheal tube, preferably 8-mm catheter or larger to facilitate bronchoscopy. Hypovolemic shock should be treated emergently. Once the airway is secure, the site of bleeding must be identified. A chest x-ray may show which side of the lung is bleeding. If bleeding site is known, place the patient in the lateral decubitus position with the affected lung in the dependent position which may be helpful to prevent aspiration to the unaffected side.

In unstable patients, unilateral intubation by way of a bronchoscope should be performed. The left mainstem bronchus is intubated over the bronchoscope for massive right-sided hemoptysis. The risk of right upper lobe occlusion is to be avoided. Therefore, unilateral intubation of the right lung with massive left-sided bleeding is not recommended. Another option is the utilization of a double lumen endotracheal tube introduced over the bronchoscope isolating the unaffected lung. Further treatment should be deferred to pulmonary or thoracic surgery specialists while resuscitation in the ED continues.

HEADACHES, SEIZURES, AND ALTERED SENSORIUM

Brain Metastasis

Melanoma and lung, breast, colon, and rectal cancers are the most common tumors that spread to the brain. Forty percent to 50% of patients with brain metastasis complain of headache. The headache is typically worse on awakening and improves during the course of the day. As 80% of metastases are located in the cerebrum, patients may additionally present with a history of progressive lethargy, memory loss, cognitive dysfunction, aphasia, paresis, or sensory disturbance. Cerebellar metastases, which account for $<10\%$ of metastases, usually cause dysmetria or gait disturbance. Papilledema is seen in $<10\%$ of patients, and a new seizure may be the first presenting complaint in about 15%. Of patients found to have brain metastasis without a known primary, 60% will be found to have pulmonary malignancy, either primary or metastatic. Diagnosis of

brain metastasis can be made with CT scan, ideally with contrast, or magnetic resonance imaging (MRI).

A cooperative effort between neurosurgery and medical and radiation oncology is needed to manage patients with both primary and metastatic brain tumors. However, immediate treatment is often needed in the ED to alleviate symptoms and reduce ICP. Corticosteroids reduce headache and improve function in 60% to 75% of patients with brain metastasis. Dexamethasone, the steroid of choice because of its high central nervous system (CNS) penetration, should be given as a 10 mg IV loading dose followed by 4 mg four times a day. Additionally, when there are physical or radiographic signs of increased ICP, the following interventions should be initiated: head of bed elevated to at least 30 degrees, fluid restriction, and administration of mannitol IV, 0.75 to 1 g/kg bolus followed by 0.25 to 0.5 g/kg every 3 to 5 hours. Consideration should also be given to radiotherapy and surgical decompression. Diuretics and hyperventilation are also effective short-term measures to reduce ICP.

When a patient has had a seizure, anticonvulsant therapy should be started promptly to prevent further seizure activity. Patients who present with seizures due to a brain tumor should be treated with a first-line anticonvulsant such as phenytoin, carbamazepine, or valproic acid. The agents should be given at the lowest effective dose. Additionally, in patients who are currently undergoing chemotherapy, levetiracetam, lamotrigine, or topiramate should be considered to avoid potential drug interactions, as these agents do not induce hepatic cytochrome P450 enzymes. The decision to administer anticonvulsants to patients with brain metastasis who have not had a seizure should be left to the oncologist or neurosurgeon. However, all patients with brain metastasis have the potential to have a seizure and so should be warned against driving or operating machinery.

Meningitis

When patients with a predisposing cancer present with headache, lethargy, or other vague CNS symptoms, meningitis, including carcinomatous meningitis, should be considered. After obtaining a CT scan to ascertain that there are no brain masses, a spinal tap should be performed. An opening pressure >16 cm H_2O, cerebrospinal fluid (CSF) leukocytosis, increased CSF protein concentration, and decreased CSF glucose concentration should raise suspicions about the presence of meningitis. An additional tube of CSF should be obtained for cytology.

Cancer patients with impaired cellular immunity, like patients with leukemia, lymphoma, or recent steroid use, can also have meningitis caused by atypical pathogens such as *Cryptococcus neoformans* or *Listeria monocytogenes.* Listeria is treated with ampicillin, as the organism is resistant to third-generation cephalosporins and Cryptococcus with amphotericin B. Encephalitis due to herpes simplex virus or varicella zoster virus should also be considered in this population when patients present with headache, low-grade fever, or bizarre behavior. Intravenous acyclovir is used for treatment of these infections. Patients with other bacterial infections such as sinusitis, otitis, or dental abscesses are at risk for contiguous CNS infections, including brain abscess.

Carcinomatous meningitis, or leptomeningeal metastasis, represents a malignancy that has arisen outside of the CNS and has seeded the dura, arachnoid, or pia mater of the brain or spinal cord. It is seen most commonly as a complication of breast and lung cancers, leukemia, and lymphoma. The symptoms of carcinomatous meningitis usually develop gradually and can be general or focal. There may be spinal cord involvement, with pain, headache, and radicular symptoms. Approximately 40% of patients with carcinomatous meningitis show evidence of cranial nerve dysfunction, such as diplopia or facial numbness referred to as “numb chin syndrome.” Evaluation includes CT or MRI to ascertain that there are no brain masses, followed by spinal tap. The classic CSF findings of carcinomatous meningitis include a high opening pressure (>16 cm H_2O), low glucose and high protein

concentrations, lymphocytic pleocytosis, and positive cytology for malignant cells. Although most patients do not have all of these features, an entirely normal CSF examination is uncommon. Treatment should be guided by neurosurgery and oncology consultants.

METABOLIC DISTURBANCES

Hypercalcemia

Hypercalcemia is relatively common in patients with cancer, occurring in about 20% to 30% of cases (see Chapter 212). The most common cancers associated with hypercalcemia include breast, lung and prostate cancers with bony metastasis, multiple myeloma, renal cell carcinoma, and lymphoma. The mechanisms for development of hypercalcemia include local matrix destruction by metastasis via cytokine release, tumor secretion of parathyroid hormone–like peptide, and tumor-mediated calcitriol secretion. Hypercalcemia of malignancy carries a poor prognosis, as the 30-day mortality is approximately 50%.

The severity of symptoms depends on the acuity with which one develops hypercalcemia. Although serum calcium levels may be as high as 15 mg/dL, symptoms of chronic hypercalcemia may be vague and include anorexia, nausea and vomiting, constipation, fatigue, and memory loss. An acute rise in the serum calcium level causes marked CNS effects including lethargy, somnolence, and even coma. When hypercalcemia is acute, severe symptoms may be seen at lower serum levels than chronic hypercalcemia. In general, serum levels of calcium >13 mg/dL are considered medical emergencies and should be treated as such. Assessment of hypercalcemia in the ED includes evaluation of other electrolytes and renal function and an ECG. ECG changes seen with hypercalcemia include a shortened QT interval.

Treatment of hypercalcemia depends on the calcium level and the patient's clinical status. Serum levels below 13 mg/dL, with mild symptoms, may be treated with oral or IV hydration alone. Patients with higher serum concentrations or more profound symptoms

should be treated with IV fluids, loop diuretics, and bisphosphonates. Patients are generally volume-depleted because of poor oral intake and depressed mental status and require aggressive hydration to achieve euvolemia or mild hypervolemia and are then given diuretics. Loop diuretics such as furosemide increase calcium excretion, whereas thiazide diuretics increase reabsorption and should be avoided. Pamidronate, a bisphosphonate, works by inhibiting bone resorption and is given as a continuous infusion of 90 mg over 4 hours. Additional treatments can include glucocorticoids, mithramycin, calcitonin, and dialysis. Patients should be admitted to a telemetry or intensive care unit bed, and potassium, magnesium, and phosphorus levels should be checked every 4 to 6 hours and repeated as needed.

Hyponatremia

Hyponatremia is another metabolic disturbance that can cause depressed mental status in cancer patients and is usually a result of the ectopic secretion of an antidiuretic hormone or syndrome of inappropriate antidiuretic hormone (SIADH) (see Chapter 210). It most commonly occurs with lung (especially small-cell), pancreatic, and ovarian cancer, lymphoma, thymoma, and brain tumors. SIADH causes hyponatremia by interfering with urinary dilution and thus preventing the excretion of ingested water. Patients with hyponatremia often do not have symptoms unless there is an acute drop in the sodium level or the serum sodium falls below 120 mEq/dL. Symptoms can include muscle twitching, seizures, and coma. The initial treatment of SIADH in the ED always includes fluid restriction.

In the emergency setting, correcting hyponatremia too rapidly may result in central pontine myelinolysis (CPM) with permanent neurologic deficits. In that regard, aggressive treatment of hyponatremia should always be weighed against the risk of inducing CMP. Patients who are actively seizing owing to hyponatremia should receive hypertonic saline solution (3% saline), which should be administered at 25 to 100 mL per hour until the seizure stops.

Additionally, furosemide can be given to reduce total body fluid volume. In cases of chronic hyponatremia, correction of the serum sodium should proceed slowly, at rates no faster than 10 to 12 mEq/dL/d. Use of hypertonic and isotonic solutions to rapidly increase the serum sodium levels in patients with long-standing hyponatremia can result in osmotic demyelination or central pontine myelinolysis.

Hypernatremia

An altered sensorium can also be the result of hypernatremia in cancer patients (see Chapter 210). Causes include reduced water intake or excessive gastrointestinal fluid loss related to chemotherapy. Generally, in cases of acute hypernatremia, sodium correction can be achieved rapidly without problems, but if the patient is chronically hypernatremic, correction should be gradual, especially in children. Patients with a history of congestive heart failure should be monitored for volume overload. Diuretics may be required in this patient population.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is most commonly associated with hematologic malignancies and solid tumors with a high rate of cell turnover or rapid tumor necrosis. The release of intracellular products (e.g., uric acid, phosphates, calcium, potassium) overwhelms the body's homeostasis mechanisms. The disorder can result in fatigue and altered mental status as a result of multiple homeostatic derangements including acidosis, acute renal failure due to urate nephropathy, hyperphosphatemia, hypocalcemia, and hyperkalemia. TLS typically presents within 1 to 5 days after irradiation or chemotherapy but can occur independent of treatment regimen. The incidence is significantly reduced by pretreatment with allopurinol and fluids before chemotherapy or radiotherapy.

The diagnosis should be suspected in patients with a large tumor burden who develop acute renal failure in the presence of marked hyperuricemia (>15 mg/dL) and hyperphosphatemia (>8 mg/dL).

Treatment in the ED includes IV hydration, administration of allopurinol or uricase, and urinary alkalinization. Hemodialysis should be used in patients in whom diuresis cannot be induced and volume overload is a concern. Hyperkalemia is the most dangerous component of TLS because it can cause sudden death due to cardiac dysrhythmias and should be addressed emergently with the standard treatment for hyperkalemia.

MUSCULOSKELETAL COMPLAINTS

Spinal Cord Compression

Any vertebral pain in patients with a history of cancer should alert the emergency physician to the possibility of vertebral or epidural metastasis and the potential for spinal cord compression (SCC). The incidence of SCC in cancer patients is estimated at 5% to 10%, regardless of tumor type. Metastatic tumor from any primary site can produce cord compression, but the most common are metastases from prostate, breast, or lung, and renal cell carcinoma; non-Hodgkin lymphoma; and multiple myeloma. Sixty percent of cases occur in the thoracic spine, 30% in the lumbosacral spine, and 10% in the cervical spine. Approximately 20% of cord compressions are the first manifestations of malignancy.

Pain is the initial symptom of SCC in 80% to 95% of patients and may have been present for several weeks to months prior to onset of neurologic symptoms. On average, pain precedes other neurologic symptoms by 7 to 8 weeks. It is usually exacerbated by lying flat, sneezing, coughing, or bearing weight, and abrupt worsening may herald a pathologic compression fracture.

Neurologic findings vary with the location of the tumor and the degree and duration of cord impingement. Motor findings are present in 60% to 85% of patients at the time of diagnosis. As they may be subtle, a thorough examination should be performed, including assessment of gait and the ability to walk on heels and toes. About half of patients present with sensory findings. Bladder and bowel dysfunction is a late finding of SCC.

Patients with cancer and even those with a remote history of a malignancy that has been associated with SCC that present with back pain or new-onset back pain should be evaluated for SCC as soon as possible. Plain radiographs provide information about bony destruction, collapse, and calcification but do not provide adequate information about the spinal cord. MRI, with a sensitivity of 93%, a specificity of 97%, and an overall accuracy of 95% remains the gold standard to evaluate the vertebrae, spinal cord, and epidural space. If MRI cannot be performed, CT myelography provides another option. ED treatment includes pain control and corticosteroids. Patients with neurologic findings should receive a bolus of 10 mg of dexamethasone, followed by 4 mg every 6 hours. Cord compression may also be treated with radiotherapy or tumor debulking, and thus prompt neurosurgical and radiation oncology consultation should be obtained when SCC is suspected.

Bony Metastasis

The sudden onset of pain in the cancer patient, commonly in the extremities, pelvis, or spine, may be due to pathologic fracture. At particular risk are patients with prostate, breast, or lung cancer and those with multiple myeloma. Minor trauma, an unusual mechanism of injury, or a transverse fracture line should heighten suspicion for a pathologic fracture. Recent negative bone scans can often be misleading, especially in patients with cancers such as myeloma and some prostate cancers that may produce purely lytic lesions. Plain radiographs establish the diagnosis, and emergent orthopedic consultation is required for immediate care as well as follow-up. Adequate analgesia must be provided to these patients.

COMPLICATIONS OF CANCER THERAPY

Neutropenia with Fever

Neutropenia is a common oncologic emergency. It may represent natural disease progression in patients with hematologic malignancies or with advanced disease in patients with metastatic solid tumors. Much more commonly, however, neutropenia develops

as a result of myelosuppression from cancer chemotherapy. Neutropenia is defined as absolute neutrophil count (ANC) <500 cells/μL or as a count $<1{,}000$ cells/μL and a predicted nadir of <500 cells/μL. The ANC is the total number of white blood cells (WBCs) multiplied by the percentage of neutrophils plus bands. As the total number of neutrophils decrease, the incidence of occult infection increases; the highest incidence of infection is in patients with an ANC <100 cell/μL. The nadir in ANC occurs 5 to 10 days after the last dose of outpatient chemotherapy. In the case of inpatient therapy, most notably those used in the treatment of hematologic malignancies, the decline in the ANC tends to be of greater depth and duration.

Fever in the cancer patient can be a result of transfusions, antineoplastic drugs, tumor necrosis and, more commonly, infection. Fever, defined as a single temperature >38.3°C or a temperature of at least 38°C for more than 1 hour, is a medical emergency in the neutropenic patient. Fever should be presumed to have an infectious etiology in these individuals, and they should be started on antimicrobials immediately. The 48-hour mortality associated with untreated infection in the neutropenic patient can be as high as 20% to 50%. Historically, infections were due predominantly to gram-negative bacilli, particularly *Pseudomonas aeruginosa.* However, with the use of indwelling catheters there has been an increase in gram-positive infections. Other factors increasing the risk of infection in the cancer patient include poor nutritional status, debilitation from recurrent hospitalization, and skin and mucous membrane disruption from chemotherapy, radiation, or tumor invasion.

Neutropenic patients may have only subtle signs of infection or may present only with hypothermia or hypotension. Thus, a thorough examination should be performed. Careful attention should be paid to the skin, indwelling catheters, and the perianal area. Laboratory evaluation includes a complete blood count (CBC), electrolytes, urinalysis, blood urea nitrogen, Cr, urine culture, chest x-ray, and at least two sets of blood cultures, including samples from any indwelling catheters.

Treatment regimens include initial empiric antibiotic therapy with two antibiotics (an extended spectrum beta-lactam with antipseudomonal activity, such as piperacillin or ceftazidime, plus an aminoglycoside). Monotherapy is also frequently used and may consist of ceftazidime, meropenem, imipenem, cefepime, or piperacillin–tazobactam. Vancomycin should be added for patients with catheter site infection, methicillin-resistant *Staphylococcus aureus* infection, or hypotension or when there has been recent prophylaxis with fluoroquinolones. Fungal, viral, and parasitic infections should also be considered as possible infectious causes of fever. Empiric coverage for these organisms is generally not provided unless there are history or examination findings suggesting such an infection. Colony-stimulating factors should be added only for critically ill patients with pneumonia, hypotension, or organ dysfunction.

CHEMOTHERAPY-INDUCED VOMITING AND DEHYDRATION

From the cancer patient's point of view, one of the most feared side effects of cancer treatment is nausea and vomiting. Promethazine or prochlorperazine are indicated for mild to moderate nausea and vomiting; for more severe cases, serotonin receptor antagonists such as ondansetron are given, as can high-dose metoclopramide. Additionally, the administration of dexamethasone in conjunction with metoclopramide or a serotonin receptor antagonist has been shown to significantly reduce nausea and emesis. For patients who are receiving the most emetogenic chemotherapeutic agents, neurokinin-1 receptor antagonists may be used in conjunction with serotonin receptor antagonists and dexamethasone.

HEMATOLOGIC MALIGNANCIES

Acute Leukemia

Acute leukemia develops as a result of alterations in the normal growth and development of hematopoietic cells. Populations of immature cells that are incapable of differentiating into mature,

functional hematopoietic cells are overproduced in the bone marrow, causing a reduction of normal red blood cells, neutrophils, and platelets. Leukemic patients therefore often present with symptoms related to pancytopenia, such as infection, anemia, and bleeding. Patients generally complain of weakness and fatigue and may have gingival bleeding, petechiae, ecchymoses, epistaxis, or menorrhagia and, less commonly, lymphadenopathy, splenomegaly, or bone tenderness. A provisional diagnosis can be made on the basis of a CBC with differential and a peripheral blood smear that shows blast cells constituting more than 5% of the circulating white cells. Possible morphologic features may include Auer rods, which are seen in acute myeloid leukemia. Definitive diagnosis and characterization of subtype is made by evaluation of the bone marrow.

Infection

The most common complication of leukemia seen in the ED is infection. When fever is present in a leukemic patient, a site of infection must be immediately and vigorously sought and the patient treated empirically with broad-spectrum antibiotics. Because most patients with leukemia tend to have qualitative defects of the circulating neutrophils, febrile patients should be presumed to be septic. Monotherapy using a broad-spectrum anti-pseudomal antibiotic (ceftazidime, meropenem, or cefepime), or dual therapy using an extended spectrum beta-lactam (piperacillin or ceftazidime) and an aminoglycoside, may be administered. There should be a low threshold for adding vancomycin in frequently hospitalized patients and in those with indwelling catheters.

Hemorrhage

Bleeding may occur from absolute thrombocytopenia or from coagulopathy associated with hematologic malignancies. Thrombocytopenic patients may develop petechiae and ecchymoses but typically do not suffer fatal hemorrhagic complications without first developing extensive mucous membrane bleeding such as

epistaxis, bleeding gums, hematuria, GI bleed, and/or bleeding from catheter or surgical sites. A threshold platelet count of 10,000/μL can be used to guide transfusion in patients with no signs of bleeding or just petechiae and ecchymoses. More aggressive therapy is indicated for active bleeding and in patients with risk factors such as fever, coagulation abnormalities, hyperleukocytosis, or recent minor surgery. The threshold in such patients should be at least 20,000/μL. Prophylactic transfusion to 50,000/μL to 100,000/μL is indicated for patients who are about to undergo a major invasive procedure. One unit of platelets usually raises the total platelet count by about 5,000/μL; platelet units are usually pooled in packs of five or six. Patients who have had previous transfusions may require HLA-matched platelets. Leukoagglutinin reaction, a common complication of transfusion that is manifested by fever, rigors, body aches, or shortness of breath, can be prevented or treated by giving acetaminophen and diphenhydramine prior to transfusion and using leukocyte-reduced blood products.

Disseminated intravascular coagulation (DIC) occurs not infrequently in this patient population. Some studies suggest that as many as 49% of cases of acute leukemia are complicated by DIC. DIC prolongs both the prothrombin and partial thromboplastin times, decreases fibrinogen levels, and increases the concentration of fibrinogen degradation products. Patients with DIC are at risk of complications from both increased clotting and bleeding (see Chapter 197). Treatment includes supportive management of coagulopathy until further treatment of the underlying malignancy can be given.

Hyperleukocytotic Syndrome

Hyperleukocytosis and leukostasis occur in acute leukemias as the total WBC count rapidly exceeds 50,000/μL to 100,000/μL and blood flow in the microcirculation becomes progressively impeded by the more rigid and adherent blast cell forms. There is local hypoxemia from the high metabolic activity of the leukemic cells, with resultant endothelial damage and hemorrhage. In chronic

myelogenous leukemia, a WBC count of >250,000/μL is often needed for leukostasis to occur, and problems related to leukostasis may not develop until the WBC count exceeds 1 million/μL.

Although the pulmonary and cerebral vascular beds are the most clinically relevant targets of leukostasis, the coronary circulation can also be affected as well as any other organ system. Cerebral involvement can range from very subtle confusion and somnolence to frank coma. Early pulmonary involvement presents with mild dyspnea and respiratory alkalosis. Typical chest x-ray findings include diffuse interstitial or alveolar infiltrates, but can be normal in early stages.

The management of hyperleukocytosis and leukostasis is centered on cytoreduction and maximizing vascular flow through supportive measures. Ideally, this is achieved by induction chemotherapy, which can dramatically reduce the WBC within 24 hours. As these patients are at very high risk for TLS, they should be closely monitored for electrolyte imbalance and treated prophylactically with allopurinol or rasburicase depending on renal function and fluid resuscitation. The use of leukapheresis is a widely accepted initial treatment but has never been shown convincingly to reduce the risk of developing leukostasis or to reduce early mortality. The urgent institution of induction chemotherapy is the most definitive therapy.

Hyperviscosity Syndrome

Hyperviscosity syndrome is seen in approximately half of patients with macroglobulinemia and in about 2% of the patients with multiple myeloma. The normal range of relative serum viscosity is 1.4 to 1.8. As values exceed 4, symptoms such as epistaxis, purpura, GI bleeding, visual impairment, and neurologic deficits begin to appear. For symptomatic patients, emergent plasmapheresis is necessary.

Polycythemia

Overproduction of erythrocytes or platelets may also precipitate medical emergencies. A hemoglobin level >17 g/dL, or a hematocrit >55% in women or 60% in men, may signal polycythemia vera, an uncontrolled clonal overproduction of erythrocytes. Other conditions that present with a high hematocrit include volume depletion, hypoxia, and polycythemia due to cigarette smoking or exposure to high altitudes. Patients with polycythemia vera are usually middle-aged and generally have a normal arterial oxygen saturation (>92%) and splenomegaly. They often have leukocytosis (>12,000 WBCs per &b.mu;L), as well as thrombocytosis (>400,000 platelets per &b.mu;L).

Emergencies due to polycythemia are related to hypervolemia and hyperviscosity. Patients may present with headache, vertigo, angina, or claudication. Other clinical features include generalized pruritus, especially after a shower or bath, and erythromelalgia (burning in the feet or hands with erythema). Thirty percent of patients with polycythemia vera suffer thrombotic episodes, and stroke is a common complication and cause of death. Elevated hematocrit findings can also interfere with platelet function; thus, some patients with uncontrolled polycythemia suffer hemorrhagic complications, most commonly in the GI tract. Many patients with polycythemia also have thrombocythemia (platelet counts >600,000/μL), a finding that is also associated with abnormal bleeding.

Polycythemic patients with signs or symptoms of hyperviscosity or thrombotic complications should have their blood volume and hemoglobin concentration reduced to normal as quickly as possible. Even without symptoms, a hemoglobin level of 18 g/dL, or a hematocrit 60% or higher, is also an indication for emergent phlebotomy or cytapheresis. Patients who are otherwise healthy can usually tolerate a rapid phlebotomy of 500 mL, although more gradual treatment may be required in the elderly or in those with known coronary artery disease. With the attainment of a normal hematocrit, the platelet defect that gives rise to thrombosis and bleeding is eventually corrected, but this can take weeks to occur. Elective surgery and dental procedures in polycythemic patients should thus be delayed until the red cell mass and platelet count

have been normalized for at least 2 months. Polycythemic patients in need of emergency surgery require emergent phlebotomy or cytapheresis. Low-dose aspirin should be administered if not contraindicated for other reasons. Antihistamines are indicated for pruritus. Other chemotherapeutic agents may be used with the guidance of a hematologist.

Thrombocytosis

Primary thrombocytosis, also known as essential thrombocytosis, is a subgroup of chronic myeloproliferative disorders in which there is chronic thrombocythemia that is not due to infection, inflammation, reactive thrombocytosis, or other myeloproliferative disorders. Patients do not usually become symptomatic or require treatment until the platelet count is >1,000,000/μL. Patients with a count >1.5 million/μL and age older than 60 are at higher risk.

About 25% to 50% of patients have splenomegaly and many have vasomotor symptoms or thrombohemorrhagic complications. Vasomotor manifestations include headache, lightheadedness, syncope, chest pain, acral paresthesia, visual disturbance, or erythromelalgia. Despite the high platelet count, patients may present with varying degrees of bleeding. Thrombotic events include strokes and transient digital ischemia. Treatment includes low-dose aspirin; other chemotherapeutic agents as hydroxyurea and anagrelide may be used with the guidance of a hematologist.

CRITICAL INTERVENTIONS

- Administer broad-spectrum antibiotics to patients with neutropenia and fever, after obtaining the appropriate cultures.
- Administer adequate analgesia for patients with severe pain related to oncologic conditions.
- Involve an oncologist or hematologist early in the course of treatment of the cancer patient.

Common Pitfalls

- Failing to recognize functional neutropenia, especially in cancer patients receiving chemotherapy.
- Failing to adequately treat pain and vomiting in patients receiving therapy.
- Failing to seek out treatable causes of mental-status changes or personality changes in cancer patients.
- Failing to recognize that back pain in a cancer patient may reflect SCC.
- Failing to adequately resuscitate patients who have significant therapeutic options and are not documented to have advanced refractory disease.

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SECTION XXI
Endocrine and Metabolic Emergencies

Section Editor: JEFFREY J. SCHAIDER

CHAPTER 203 Acid–Base Disturbances

Robert Shesser

Severe acid–base disturbances, particularly those that develop rapidly, can be associated with diffuse cellular dysfunction and may require rapid treatment. Cerebral edema, seizures, cardiac dysrhythmias, and vascular dysfunction may result from an acid–base disturbance itself, from its underlying cause, or both. Precise analysis of a patient's acid–base status will help stratify disease severity, and help identify the disturbance's underlying cause(s). A thorough understanding of the principles of acid–base pathophysiology permits the physician to expand the diagnostic considerations from the history and physical examination to identify an additional, previously unsuspected disease process.

BASIC PHYSIOLOGY

Pure water at 25°C is a neutral solution with a pH of 7.0 and concentrations of both H^+ and OH^- of 100 mEq/L. Solutions of biologic importance share two important characteristics: They are all aqueous (water-based) and alkaline (greater concentration of OH^- than H^+ ions) (1). Plasma is a complex aqueous solution of a variety of electrolytes and proteins. Plasma's water component provides a limitless supply of hydrogen ion, but its H^+ concentration at any moment is determined by the relative concentrations of electrolytes, dissolved gas (primarily CO_2), and proteins that influence water's dissociation (1).

For the past century, pH, the logarithm of (1/hydrogen ion concentration), not the actual hydrogen ion concentration, has been used as the main clinical measure of acid–base status. The use of this

mathematically cumbersome surrogate marker arose because pH was the best measure obtainable by the available technology of the time. Cellular enzyme systems function optimally over a narrow range of hydrogen ion concentrations, and prolonged, significant deviations of hydrogen ion concentration from normal are not well tolerated (2). The body's homeostatic systems normally maintain a stable internal milieu, so any significant deviation from normal indicates the presence of disease (3).

For years, the Henderson–Hasselbach equation ($pH = pK \times \log HCO_3^- (0.03 \times pCO_2)$) has been viewed as the core concept governing clinical interpretation of acid–base balance (4,5). This model emphasizes the centrality of bicarbonate as a marker of the patient's metabolic status and considers changes in the nonvolatile buffers as effects rather than cause. The concept of base excess (BE) (or base deficit) was advanced as a way to quantitate the patient's metabolic acid–base status. Base excess was originally defined as the number of milliequivalents of acid (or alkali in the case of base deficit) required to return systemic pH to normal while maintaining the pCO_2 at 40 mm Hg at a temperature of 37°C. This model is useful in simple clinical situations, but fails because it assumes normal plasma proteins, perturbations of which can significantly affect the pH. The BE is also unable to identify situations with several coexisting metabolic acid–base disorders (4,6).

A more nuanced, but clinically complicated, model described by Stewart (4) posits that three independent variables determine the pH by influencing the degree that water dissociates into its components (H^+ and OH^-). The three variables are the strong ion difference (SID), the total weak acid concentration (A_{TOT}), and the dissolved carbon dioxide.

The Strong Ion Difference

The principle of electrical neutrality requires that equal numbers of ions with positive charge (cations) and ions with negative charge (anions) are dissolved in any solution. Dissolved ions differ in their tendency to be in either their completely dissociated (charged) form

or in a combination of charged and uncharged forms. The commonly measured electrolytes Na^+, Ca^{2+}, Mg^{2+}, K^+, Cl^-, etc., and lactate are said to be *strong ions,* meaning that they are fully dissociated in physiologic solutions (e.g., Na^+ and Cl^- do not exist in physiology solutions as uncharged NaCl). Weak ions, including plasma proteins, phosphate, NH_4^+, H^+, and HCO_3^-, are found in physiologic solutions in both their charged and uncharged forms. Although electroneutrality (the total number of cations and anions) is maintained at all times, there is normally a difference between the numbers of strong cations and strong anions in plasma. The SID is the sum of all the strong cations minus the sum of all strong anions. Its value is 40 to 42 mEq/L in healthy individuals with the difference represented by weak anions. Strong anions are conjugate bases (resulting from the addition of acids), and strong cations are conjugate acids (resulting from the addition of bases).

An increased SID from baseline results in a lower concentration of H^+ (alkalemia), and a decreased SID, an acidemia (6,7).

The Total Weak Acid Concentration

A less important metabolic determinant of plasma pH is A_{TOT}. Most of the weak acids are plasma proteins such as albumin, which can exist in their dissociated (A^-) form or undissociated (AH) forms, depending on the pH. Loss of weak acid from the plasma space (e.g., hypoalbuminemia, as seen in cirrhosis or nephrotic syndrome) raises pH independent of the pCO_2 and SID. Increased weak acids such as the hyperphosphatemia seen in renal failure help contribute to the metabolic acidosis seen in those patients. Normally, the kidney and intestines regulate the SID, whereas the liver is the primary regulator of A_{TOT} (4).

Dissolved Carbon Dioxide

About 220 mL/min of carbon dioxide is produced by cellular metabolism and by the interaction of bicarbonate and metabolic acids through carbonic anhydrase ($H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O$

+ pCO_2). Cellular production accounts for the bulk of this (15,000 mM/d), which is more than 30 times the daily normal production of nonrespiratory acids. CO_2 is excreted via the lungs, which can increase minute ventilation to excrete large volumes of CO_2. Hyperventilation will remove H^+, providing an effective, open-ended, homeostatic mechanism to reduce the effects of endogenous or toxin-induced metabolic acidosis. Hyper or hypoventilation can also lead to acid–base changes from a primary disturbance of respiration.

The major differences between the Stewart and traditional model are as follows (8):

1. Bicarbonate is not always viewed as an independent variable that directly influences plasma hydrogen ion concentration (pH).
2. There is clearer acknowledgement of the obligatory dissociation of water into its component parts, its ability to provide a large supply of hydrogen ion, and the effect that other electrolytes have on water's dissociation.
3. Other plasma variables such as plasma proteins whose concentrations independently affect the pH are identified and quantified.

PATHOPHYSIOLOGY

Pathologic processes disturb the body's acid–base equilibrium either by adding to (or subtracting from) the body's soluble hydrogen ion activity (a metabolic disturbance) or through an increase or decrease in ventilation (a respiratory disturbance). The disruption of acid–base equilibrium by a single disease process is termed a *primary disturbance*. Any disruption initiates a series of compensatory responses that tend to return the pH toward normal. A compensatory response to a primary disturbance rarely returns the pH to the normal range and never overshoots the normal range (1,2).

The response to a primary metabolic disturbance is an initial, rapid adjustment of the respiratory rate (altering the pCO_2) followed by a slower renal adjustment mediated through changes in renal chloride excretion. In response to a metabolic acidosis, renal chloride ions are

excreted with ammonium (NH_4^+) (rather than Na^+ or K^+), which, because Cl^- is a strong cation and NH_4^+ is a weak anion, will increase the SID and raise the pH. In this clever manner, the kidney can regulate sodium balance (and thus intravascular volume) independently of chloride (9), which is central to renal response to metabolic acid–base perturbations.

The response to a primary respiratory disturbance relies exclusively upon renal adjustments of chloride excretion (*metabolic compensation*). As described in **Tables 203.1** and **203.2**, the relatively slow speed of the renal response to a primary respiratory disturbance allows clinical differentiation between *acute* respiratory disturbances and those processes that have been operative for several days which are termed *chronic*.

TABLE 203.1
Formulae Describing Expected Compensatory Response to Primary Acid–Base Disturbances

Simple Metabolic Acidosis
Predicted decreased pCO_2 mm Hg = $1.2 \times \Delta(HCO_3^-)$ mEq/L
Predicted pCO_2 mm Hg = $1.5(HCO_3^-)$ mEq/L + 8 ± 2
Anticipated pCO_2 approximates last two digits of arterial pH

Simple Metabolic Alkalosis
Predicted increased ΔpCO_2 mm Hg = $0.67 \times \Delta(HCO_3^-)$ mEq/L

Simple Acute Respiratory Acidosis
Predicted decreased ΔpH units = $0.8 \times \Delta pCO_2$ mm Hg
Predicted increased $\Delta(HCO_3^-)$ mEq/L = $0.1 \times \Delta pCO_2$ mm Hg

Simple Chronic Respiratory Acidosis
Predicted decreased ΔpH units = $0.3 \times \Delta pCO_2$ mm Hg
Predicted increased $\Delta(HCO_3^-)$ mEq/L = $0.35 \times \Delta pCO_2$ mm Hg

Simple Acute Respiratory Alkalosis
Predicted increased ΔpH units = $0.8 \times \Delta pCO_2$ mm Hg
Predicted decreased $\Delta(HCO_3^-)$ mEq/L = $0.2 \times \Delta pCO_2$ mm Hg

Simple Chronic Respiratory Alkalosis
Predicted increased ΔpH units = $0.17 \times \Delta pCO_2$ mm Hg
Predicted decreased $\Delta(HCO_3^-)$ mEq/L = $0.5 \times \Delta pCO_2$ mm Hg

TABLE 203.2
Primary Disturbances and Compensatory Responses in Terms of Changes in Carbonic Acid Constituents

	Usual pH	Hydrogen Ion Concentration	Serum Bicarbonate (Measured as Total CO_2 Content)	pCO_2
Metabolic acidosis	<7.38	Primary increase	Immediate decrease	Rapid compensatory decrease
Metabolic alkalosis	>7.42	Primary decrease	Immediate increase	Variable compensatory increase
Acute respiratory acidosis	<7.38	Secondary increase	Immediate small compensatory increase	Primary increase
Chronic respiratory acidosis	<7.38	Secondary increase	Slow larger compensatory increase	Primary increase
Acute respiratory alkalosis	>7.42	Secondary decrease	Immediate small compensatory decrease	Primary decrease
Chronic respiratory alkalosis	7.40–7.42	Secondary decrease	Slow larger compensatory decrease	Primary decrease

Although the degree and rapidity of compensatory responses to primary acid–base disturbances varies among patients, empiric data have defined a range of the expected compensatory response for each type of primary disturbance. Table 203.2 lists the anticipated compensatory responses for the different types of primary acid–base disturbances (5). Patients with profiles falling outside the predicted compensation range for a primary disturbance may have either a mixed disorder (wherein the primary disease process induces two distinct acid–base disturbances) or multiple primary disturbances from two or more independently acting disease processes.

Tables 203.3 and **203.4** list the causes of the primary and mixed acid–base disturbances most commonly seen in the emergency department (ED) patient. The emergency physician must be able to differentiate simple and mixed acid–base abnormalities and to identify and treat the underlying disease processes operative in a given patient.

TABLE 203.3
Causes of Primary Acid–Base Disturbances

Primary Metabolic Acidosis

Elevated anion gap (ACAT MUDPILES)
- Alcohol ketoacidosis
- Cyanide, CO
- Acetaminophen; antiretrovirals (NRTI)
- Toluene
- Methanol
- Uremia/renal failure
- Diabetic ketoacidosis/alcoholic ketoacidosis/starvation
- Paraldehyde/propylene glycol
- Iron/INH
- Lactic acidosis
- Ethylene glycol
- Salicylates

Normal anion gap (FUSED CRASH)
- Fistulas
- Uteroenteric conduits
- Saline
- Endocrine (hyperparathyroidism)
- Diarrhea
- Carbonic anhydrase inhibitor therapy
- Renal tubular acidosis
- Arginine/lysine/chloride (e.g., TPN)
- Spironolactone
- Hydronephrosis

Primary Metabolic Alkalosis

Vomiting/gastric suctioning

Volume depletion

Diuretic therapy

Corticosteroid therapy

Primary Respiratory Acidosis

CNS lesion

Sedative therapy/overdose

Neuropathies

Myopathies

Chest wall abnormalities
- Trauma
- Kyphosis

Pleural disease

Obstructive airway disease

Primary Respiratory Alkalosis

Anxiety

Progesterone therapy/increased exogenous progesterone

Sympathomimetic therapy

Fever

Hyperthyroidism

Hypoxia

Liver disease

CNS, central nervous system; INH, isoniazid; TPN, total parenteral nutrition.

TABLE 203.4
Mixed Acid–Base Disturbances

Metabolic Acidosis–Respiratory Alkalosis
Salicylate ingestion
Liver disease
Sepsis
Pulmonary embolism or pulmonary edema with hypotension
Pulmonary–renal syndrome
Metabolic Acidosis–Respiratory Acidosis
Cardiopulmonary arrest
Pulmonary edema
Drug overdose
Metabolic Alkalosis–Respiratory Alkalosis
Critical illness
Pregnancy
Mechanical ventilation-induced chronic hypercapnia
Metabolic Alkalosis–Respiratory Acidosis
Chronic hypercapnia with:
Diuretic overuse
Dehydration
Hypokalemia
Metabolic Acidosis–Metabolic Alkalosis
Diarrhea/vomiting
Organic acidosis/vomiting
Metabolic acidosis with excessive bicarbonate administration

ED EVALUATION

Acid–base disturbances should be suspected when a patient appears critically ill, has abnormal vital signs, respiratory rate, an abnormal mental status, and complains of vomiting, diarrhea, or changes in urine output. A blood gas and complete serum electrolytes (including albumin and phosphate) should be obtained. A venous blood gas suffices for measuring the pH and pCO_2 for acid–base analysis purposes in most clinical situations.

A thorough clinical evaluation is mandatory before considering the acid–base status, because the physician must first formulate a set of preliminary hypotheses about the disease processes most likely and

then analyze the patient's observed acid–base parameters. The physician should then ask three questions:

1. Does the patient have an acidemia or an alkalemia? *Acidemia* is defined as a pH <7.38 and *alkalemia* as a pH >7.42. An *acidosis* is any process that causes acid to accumulate, whereas an *alkalosis* is a process that causes hydrogen ion depletion. If the patient is acidemic, at least one of the processes present should be an acidosis.
2. Is the primary disturbance respiratory or metabolic? Look at the serum bicarbonate, BE, and pCO_2. Patients with a primary metabolic acidosis have a low bicarbonate, negative BE, and a pCO_2 below normal. Similarly, patients with a primary respiratory disturbance have an abnormal pCO_2 with a pH that varies with the disease's chronicity (Table 203.5).

TABLE 203.5
Respiratory Versus Metabolic Acidosis/Alkalosis

	pH	pCO_2	HCO_3
Metabolic acidosis	Decrease	Decrease	Decrease
Metabolic alkalosis	Increase	Increase	Increase
Respiratory acidosis	Decrease	Increase	Increase
Respiratory alkalosis	Increase	Decrease	Decrease

3. Is the acid–base disturbance primary or nonprimary? To identify a multiple or mixed disturbance, the physician should compare the observed parameters to a series of formulae that quantify the compensatory responses anticipated for any primary disturbance. When the appropriate formula (see Table 203.1) is applied, a significant deviation from the anticipated compensatory response parameters suggests the presence of either a mixed disorder or two primary disorders. These formulas were developed in populations that had been in a steady state for 12 to 24 hours (5). Accordingly, the emergency physician should avoid the rigid application of these formulas in situations where the clinical situation is rapidly changing.

Metabolic Acidosis and Anion Gap(s)

Primary metabolic acidosis is the most common acid–base disturbance in hospitalized patients and is often present in ED patients (14). Calculation of the *anion gap,* defined as (sodium + potassium) − (chloride + CO_2 content), is used to develop the differential diagnosis of the various causes of a metabolic acidosis (described in Table 203.3) allowing the clinician to divide the causes of primary metabolic acidoses into those with either a normal or elevated anion gap. As plasma's electric neutrality is always maintained, there are always equal numbers of cations and anions. The term "gap" is a misnomer because the "gap" is the difference between the cations and anions that are measured by commonly used clinical laboratory assays. The normal range for the anion gap is 5 to 12 ± 3 mEq/L (2).

Typically, cation concentrations are more tightly regulated and anion concentrations have a greater tendency to fluctuate. Decreased plasma proteins (mainly albumin) and phosphate concentrations (both anions) are frequently seen in critically ill patients. Their decrease would tend to artificially decrease the anion gap and might therefore artifactually mask an anion gap created by an organic acid accumulation caused by a disease process. The anion gap correction for hypoalbuminemia would be as follows:

$$AG_{corr} = AG_{calculated} + 2.5\ (\text{reference albumin-measured albumin})\ (6,7)$$

Increases or decreases of serum phosphate have the same effect as changes in albumin concentration on the anion gap.

An elevated anion gap, primary metabolic acidosis, results from an excess of either endogenous or exogenous organic acids. A moderate increase in the anion gap (12 to 20 mEq/L) may be seen in situations other than a metabolic acidosis, including dehydration, spurious laboratory values, and treatment with citrate, lactate, or certain antibiotics. In cases of slight anion gap increase, the clinician must confirm the presence of a metabolic acidosis by analyzing the pH and pCO_2. Anion gaps >25 mEq/L most often indicate a severe condition such as ketoacidosis, lactic acidosis, or the toxin-associated acidoses

(10). In these cases, the pH and pCO_2 should be checked to assess the severity of the academia and adequacy of respiratory response.

Strong Ion Gap

There has been much concern in the critical care literature that diagnostic reliance on either the BE or standard anion gap may fail to identify some critically ill patients. The Stewart system describes a *Strong Ion Gap (SIG)* which provides the clinician with another tool to identify patients with organic metabolic acidosis where elevated concentrations of unmeasured strong anions such as lactate, formate, ketoacids, or salicylate may be present (8) (Fig. 203.1). This "gap" can be calculated from the results of tests that are available on most critical care patients. The data needed to calculate the SIG include Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, CO_2 content, albumin, and phosphates.

$$SIG = SID_{app} - SID_{eff} = XA^-$$

$$SID_{app} = Na^+ + K^+ + Ca^{2+} + Mg^{2+} - Cl^-$$

$$SID_{eff} = HCO_3^- + 0.28\ (\text{albumin g/L}) + 1.8\ (PO_4^-)$$

FIGURE 203.1 Strong ion gap formula.

The SIG is calculated as the difference between the apparent strong ion difference (SID_a) = ($Na^+ + K^+ + Ca^{2+} + Mg^{2+}$) − ($Cl^-$) and the effective strong ion difference (SID_e) that is estimated as (HCO_3^-) + 0.28 (albumin [g]/L]) + 1.8 (phosphate [mmol/L]). The SIG would then be equal to the plasma concentration of organic acids: $XA^- = SIG = SID_a - SID_e$. The SIG is normally 0. Readers should note that the SIG and SID are two very different measurements. An increased SIG is indicative of an organic acid-induced metabolic acidosis and actually results from a decrease in the SID. The SIG has been suggested to be a superior predictor of mortality than the standard anion gap (2).

The serum potassium level should rapidly be assessed in all patients with a suspected metabolic acidosis by seeking electrocardiographic evidence of hyperkalemia and ordering a

bedside electrolyte analysis. In general, the serum potassium level increases as a patient becomes more acidemic. This increase may result from the interaction of the excess hydrogen ion with intracellular buffer systems (11). There is no completely reliable formula to estimate the expected change in serum potassium arising from a given change in pH. Inorganic acidoses (hydrochloric acid, toxins) tend to increase the serum potassium more than organic acidoses such as ketoacidosis and lactic acidosis (1).

Primary Metabolic Alkalosis

Metabolic alkalosis results in an elevated serum bicarbonate and increased SID. Most metabolic alkaloses are initiated by a combination of volume, potassium, and chloride depletion. Patients with mild metabolic alkalosis generally require both normal saline and potassium chloride administration to correct the acid–base disturbance.

The ventilatory response to metabolic alkalosis is severely limited the patients defense against hypoxia since it would require that the patient hypoventilate. Most of the compensatory responses to a primary metabolic alkalosis would therefore be renal, and the kidney cannot alkalize the urine if the patient is hypokalemic or significantly volume-depleted (12). Metabolic alkaloses, therefore, tend to be self-perpetuating if not treated by aggressive rehydration and potassium administration (5).

Patients with a pH >7.6 from metabolic alkalosis are at risk for cardiovascular and cerebrovascular ischemia and hypoventilation and require rapid reduction of the serum bicarbonate to <40 mmol/L. The most common causes of this condition are chloride-responsive and include loss of gastric acid and loop diuretics (11). Severe metabolic alkalosis often leads to a decrease in bicarbonate's space of distribution (contraction alkalosis) resulting in high extracellular bicarbonate levels in the presence of massive peripheral edema and total body chloride depletion.

Primary Respiratory Disturbances

Primary respiratory abnormalities are classified according to their duration as “acute” or “chronic.” Because the renal compensatory process is delayed by 48 to 72 hours, patients with primary acute respiratory disturbances experience a larger change in pH for a given change in pCO_2 than do patients with primary chronic respiratory disturbances. Chronic respiratory alkalosis is alone among the primary acid–base disturbances in that the compensatory renal response will sometimes return the pH into the normal range (5).

The immediate treatment of a severe, primary respiratory disturbance involves a mechanical airway intervention, such as increasing ventilation in respiratory acidosis or decreasing the minute ventilation for patient with respiratory alkalosis who are being mechanically ventilated. Longer-term treatment involves identifying and treating the disturbance’s underlying cause. The physician must avoid a treatment that suddenly normalizes the pCO_2 in a patient with chronic respiratory disturbance. In instances where renal compensatory mechanisms have corrected the pH, rapid normalization of the respiratory parameters risks a dangerous overshooting of pH until the kidneys adapt to the new respiratory situation.

Patients with respiratory acidosis require emergent intervention, because the increase in pCO_2 can cause life-threatening acidemia and increased somnolence (CO_2 narcosis) (13). A blood gas determination is mandatory for patients with abnormal mental status, especially if they manifest any history of or clinical evidence of ventilatory dysfunction.

Acute respiratory alkalosis is the most common primary respiratory acid–base disorder in emergency practice being caused by such common conditions as fever, anxiety, or pregnancy. Although this acid–base abnormality requires treatment infrequently, its presence may require a search for its underlying cause.

Multiple Acid–Base Disturbances

When multiple acid–base disturbances are present, the patient may be acidemic, alkalemic, or have a “normal” pH. Most combinations

of primary acid–base disturbances can be seen clinically. As mentioned above, clinical context should be established before performing the analysis to search for the presence of a mixed or multiple primary disturbances.

Metabolic acidosis with respiratory acidosis or alkalosis is diagnosed when the pCO_2 deviates significantly from that predicted (see Table 203.1) for a primary metabolic acidosis. Combined metabolic acidosis and respiratory acidosis is seen in situations such as cardiac arrest or the postictal state, in which the pCO_2 is either normal, above normal, or the decrease is less than would be predicted for the degree of metabolic acidosis. Combined metabolic acidosis and respiratory alkalosis are commonly noted in salicylate poisoning, where the salicylate (an exogenous organic acid) causes a metabolic acidosis and while directly stimulating the brainstem to increase ventilation more than would occur from the compensatory response along to the metabolic acidosis.

One should be cautious in diagnosing the presence of mixed or multiple disturbances in patients with a rapidly changing clinical status, because the formulae for the expected responses were derived from patients in a steady state. Thus, there is an increased chance of over-diagnosing multiple disorders in an acutely ill patient with a changing clinical situation (5).

The combination of *metabolic acidosis* and *metabolic alkalosis* is seen in a patient with a relatively normal pH and an anion gap elevation significantly greater than the decrease in bicarbonate from normal (14). A common example of this mixed disturbance is the patient with alcoholic ketoacidosis who has been vomiting or a patient with both vomiting and diarrhea. The presence of a mixed or multiple acid–base disturbance may become evident only after one of the deficits is corrected. In the vomiting and diarrhea example, rapid volume correction with normal saline but without concomitant bicarbonate replacement will “unmask” the metabolic acidosis, with the serum bicarbonate decreasing as volume is restored.

CONTROVERSIES IN MANAGEMENT OF METABOLIC ACIDOSES

The rationale for aggressive treatment of metabolic acidosis with exogenously administered alkaline therapy (most frequently sodium bicarbonate) is that the acidosis per se disrupts cellular function and can lead to decreased cardiac contractility, predisposition to cardiac arrhythmias, peripheral vasodilation, impairment in glucose regulation, and stimulation of inflammatory mediators (8). The presumption of treatment benefit is based primarily on extrapolation from animal studies from which expert recommendations have been derived in the absence of good human treatment data. There is greater concordance among physicians about the benefits of chronic alkali administration to patients with normal anion gap (hyperchloremic) acidosis, particularly those that result from chronic renal bicarbonate loss. Treatment of the underlying disorder in both lactic acidosis and ketoacidosis can rapidly replenish bicarbonate stores.

Diabetic Ketoacidosis

Insulin administration, rehydration, and close monitoring and replacement of potassium are the mainstays of emergent therapy of diabetic ketoacidosis (DKA), and little benefit has been documented from adding bicarbonate to this regimen. Adverse effects of excessive bicarbonate administration in DKA include tissue hypoxia from bicarbonate's leftward shift of the oxyhemoglobin dissociation curve; augmentation of hepatic ketogenesis; hypertonicity and sodium overload; hypokalemia; and late alkalemia, when bicarbonate is regenerated from ketoacids (15). Some patients have deteriorated after aggressive bicarbonate treatment from either a "paradoxical" central nervous system acidosis (15), as bicarbonate does not cross the blood–brain barrier, or cerebral edema from activation of a membrane Na^+–H^+ exchanger by the organic acidosis (16). A recent study showed no benefit from bicarbonate administration in patients with a pH <6.9 (17).

Sepsis and Lactic Acidosis

Most patients with lactic acidosis have either tissue hypoxia leading to lactate overproduction (e.g., hypoperfusion, sepsis, cyanide poisoning, etc.) or the inability to metabolize tissue-generated lactate as seen in patients with liver disease. Bicarbonate therapy is not recommended and may be dangerous in hypoperfusion-induced lactic academia (18). In other cases of lactic acidosis, such as that induced by metformin, bicarbonate therapy may be indicated in patients with very severe acidemia. Common causes of lactic acidosis are listed in Table 203.6.

TABLE 203.6
Common Causes of Lactic Acidosis

Hypotension
Sepsis
Methanol, ethylene glycol
Metformin, nitroprusside, beta-agonist, reverse transcriptase inhibitors
Diabetes mellitus
Alcoholism
Congenital
Thiamine deficiency
Short bowel syndrome
Hematologic malignancies

The treatment of patients with lactic acidosis should focus on improvement of tissue oxygenation and identification and treatment of its underlying cause. As a temporizing measure in the presence of severe lactic acidemia (pH <7.0), 1 to 2 mEq/kg of bicarbonate can be administered by slow infusion, with frequent re-evaluation of the clinical and metabolic situation (6).

Emergency physicians should be aware of cases of potentially life-threatening lactic acidosis in HIV patients taking nucleoside-analog reverse transcriptase inhibitors.

Cardiac Arrest

Neither animal nor human data have demonstrated the effectiveness of bicarbonate in increasing survival after cardiac arrest, and there have been reports of severe hyperosmolality, alkalosis, hypernatremia, and even pediatric intracerebral hemorrhage from injudicious bicarbonate administration.

The 2010 American Heart Association's *Advanced Cardiac Life Support* guidelines (19) support the use of bicarbonate in critically ill patients with a pre-existing metabolic acidosis, hyperkalemia, or tricyclic overdose but not in the "undifferentiated" cardiac arrest patient.

Toxin-Induced Acidosis

Methanol and ethylene glycol are two low–molecular-weight alcohols that produce severe metabolic acidoses when ingested. Parenteral sodium bicarbonate is recommended as an adjunctive therapy because the organic acids generated in these poisonings cannot be converted back to bicarbonate by the liver.

The physician should administer 1 to 2 mEq/kg of bicarbonate to patients with pH <7.10 (<7.2 if the patient has underlying cardiovascular disease) by isotonic drip at a rate of 0.1 mEq/kg/min, and gauge the quantity and frequency of further doses by the response. Definitive treatment includes administration of ethanol or 4-methylpyrazole (fomepizole, Antizol) to delay the formation of toxic intermediates, as well as hemodialysis for removal of the ingested alcohol and its toxic metabolites. In these intoxications, elevations in the anion and osmolar gaps may not be present simultaneously. Patients may present initially with only an elevated osmolar gap, and then the anion gap increases as alcohol is metabolized into a variety of intermediate forms (20).

Salicylate ingestion produces a characteristic picture of metabolic acidosis–respiratory alkalosis. Unless the serum is highly alkaline, judicious administration of sodium bicarbonate to alkalinize the urine, while keeping the blood pH <7.50, will trap the salicylate ion in the renal tubules. With the addition of forced diuresis, urinary alkalinization will enhance excretion of the ingested salicylate.

CRITICAL INTERVENTIONS

- Rapidly test the serum potassium level and place all patients with potential, severe acid–base changes on a continuous cardiac monitor.
- Arterial or venous blood gasses and standard serum electrolytes will suffice to diagnose most acid–base abnormalities.
- Initially evaluate the patient and determine the most likely condition(s) present; by analyzing a discordance between the patient's actual acid–base status and the acid–base changes that should result from the suspected conditions, the clinician can expand the differential diagnosis and identify hitherto unsuspected conditions.

Common Pitfalls

- In a patient with a chronic respiratory acidosis, avoid rapid normalization of the pCO_2, as this may lead to a dangerous overshoot alkalosis.
- Use caution in diagnosing mixed disturbances in patients with a rapidly changing clinical status. The formulas for the expected response to primary acid–base disturbances were developed in patients who had achieved a steady state.
- Be sure to check the pCO_2 in all appropriate patients with abnormal mental status.

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CHAPTER 204 Diabetes Mellitus

Scott R. Votey and Anne L. Peters

Diabetes affects an estimated 8.3% of the US population, or approximately 25.8 million people (1), and this is expected to rise to 33.5 million by 2050 (2). Management of diabetes and its complications is disproportionately resource-intensive. In 2012, the per-capita cost of health care was $13,741 for people with diabetes as compared to $3,495 for those without the disease. The emergency department (ED) utilization rate by people with diabetes is twice that of the unaffected population (3). This chapter focuses on the ED evaluation and treatment of the acute and chronic complications of diabetes other than those directly associated with hypoglycemia and severe metabolic disturbances.

Approximately 90% of patients with diabetes have type 2 (or ketosis-resistant) diabetes (T2DM), and the remainder have type 1 (ketosis-prone) diabetes (T1DM). Although the pathophysiology of the disease differs between the types of diabetes, most of the complications, including microvascular, macrovascular, and neuropathic, are similar regardless of the type of diabetes.

Microvascular complications of diabetes include retinopathy and nephropathy. Macrovascular complications are peripheral vascular, cerebrovascular, and coronary artery disease (CAD). Hypertension eventually occurs in approximately 50% of patients with diabetes. Chronic, poorly controlled hyperglycemia, in addition to the metabolic consequences associated with glycosuria, can lead to impaired immune function and delayed wound healing. The development of complications is related to the duration of diabetes and the degree of glycemic control.

ED EVALUATION

In addition to the history and physical examination related to the presenting complaint, the assessment of patients with diabetes includes the following.

History

Type of Diabetes

Type 1 diabetes mellitus (T1DM) generally occurs in younger, lean patients and is characterized by an autoimmune process that leads to the marked inability of the pancreas to secrete insulin (Table 204.1). The distinguishing characteristic of a patient with T1DM is that if insulin is withdrawn, ketosis, and eventually ketoacidosis, develops. These patients are therefore insulin-dependent (i.e., insulin is life-sustaining), because they produce no endogenous insulin. Although the onset of T1DM often occurs in childhood, 30% of patients with new-onset T1DM are older than 18 years of age. In adults, T1DM tends to have a slower course to total islet-cell failure than it does in children. In addition, rates of obesity in individuals with type 1 diabetes are similar to that in the general population, which means that among adults, one-third is normal weight, one-third is overweight, and one-third obese. Newer antibody tests have allowed for the identification of more people with this slower-onset adult form of T1DM, which has been called *latent autoimmune diabetes of the adult* (LADA).

TABLE 204.1
Metabolic and Clinical Characteristics of the Two Major Types of Diabetes Mellitus

Characteristic	Type 1 Diabetes (T1DM)	Type 2 Diabetes (T2DM)
Synonyms	Juvenile-onset diabetes, IDDM	NIDDM
Age of onset	Usually <30 yrs; up to 30% present above the age of 18	Usually >40 yrs; sometimes in younger persons, even children
Genetic predisposition	Moderate (requires environmental factor[s] for expression); only 50% of identical twins develop DM1 if one sibling affected	A strong family history of T2DM and Hispanic, African American, or Native American heritage make the diagnosis of type 2 diabetes more likely, regardless of age 80–100% of identical twins develop DM2 if one sibling is affected
Precipitating factors	Viral/toxic/other trigger precipitating autoimmune response	Obesity, age, inactivity
Findings at diagnosis	Antibodies include ICA-512, IA2, insulin and zinc transporter 8 (ZnT8) at diagnosis in children. Positive anti-GAD antibodies in adults	Most patients had asymptomatic diabetes for 4–7 yrs prior to "diagnosis"
Endogenous insulin levels	Very low to none. Measurable initially, undetectable over time	Present
Insulin resistance	Can be present if genes for type 2 diabetes, obesity, infection	Present
Response to prolonged fast	Hyperglycemia, ketoacidosis	Normal blood glucose levels
Response to stress, withdrawal of insulin	Ketoacidosis	Hyperglycemia without ketosis
Response to diet alone	Negligible	Always present to some degree

IDDM, insulin-dependent diabetes mellitus; NIDDM, non–insulin-dependent diabetes mellitus; ICA, islet cell antibody.

Type 2 diabetes mellitus (T2DM) typically occurs in older (>40 years of age) patients who have a family history of diabetes. However, T2DM is occurring in younger and younger individuals. Children as young as 2 years old have been diagnosed with T2DM, and increasingly teenagers of Hispanic, Native American, and African American descent are developing prediabetes and diabetes (4). Patients who develop T2DM have a genetic predisposition to do so and develop insulin resistance along with insufficient pancreatic β-cell secretion of insulin. Most patients (90%) who develop T2DM are obese, and obesity itself is associated with insulin resistance, which further worsens the diabetic state. Because patients with T2DM retain the ability to secrete some endogenous insulin, those who take insulin rarely develop diabetic ketoacidosis (DKA) when insulin is stopped. Therefore, they are considered insulin-requiring, not insulin-dependent. Moreover, patients with T2DM often do not require treatment with oral or injectable antidiabetic medication if they lose weight.

Differentiating between the two types of diabetes on the basis of age has become less reliable and cannot always be done in the ED, but a good clinical history often allows the distinction to be made. A strong family history of T2DM, obesity, and Hispanic, African American, or Native American heritage all make the diagnosis of type 2 diabetes more likely, regardless of age.

The presence of anti-GAD65 antibodies confirms the diagnosis of T1DM, and the presence of an elevated or even normal C-peptide

level in patients who have been treated with insulin for several years confirms a diagnosis of T2DM. The presence of measurable C-peptide levels at the time of diagnosis is not usually helpful as C-peptide levels can be elevated or absent in both new-onset type 1 and type 2 diabetes, depending on the level of hyperglycemia and other clinical circumstances. Although neither of these tests is likely to be available on a stat basis in the ED, an understanding of their results may be useful to emergency physicians. When in doubt, use insulin therapy as needed in the ED and defer to the patient's primary care provider to follow up on testing and diagnosis.

Duration of the Diagnosis of Diabetes

The chronic complications of diabetes are related to the length of time the patient has had the disease. Patients with T2DM have often had diabetes for 5 to 7 years before the diagnosis is made and can present with the complications of diabetes at the time of diagnosis (5).

Blood Glucose Levels

Patients should be asked if they self-monitor their blood glucose levels and what their usual and recent blood glucose levels have been. Recent changes in the frequency of high and low blood sugar levels should be noted.

Diabetes Medications

Patients should be asked the names and doses of their diabetes medications. A sense of patients' level of knowledge about managing their diabetes is useful, as it may indicate their degree of adherence with their treatment plan.

Hemoglobin A1c Level

The date and value of the most recent level is a useful indicator of both the quality of glycemic control and the patients' monitoring of their disease.

Symptoms of Diabetes

Symptoms of hyperglycemia (polyuria, polydipsia, nocturia, weight loss) and hypoglycemia (see Chapter 206) should be elicited, with their time course and severity.

Complication of Diabetes

Although complications are often diagnosed by physical examination or by laboratory testing, the presence of known complications of diabetes should also be sought in the history: retinopathy, nephropathy, vasculopathy (hypertension and coronary, peripheral, and cerebrovascular disease), neuropathy, or diabetic foot complications (ulcers and amputations).

Physical Examination

Vital Signs

Orthostatic vital signs may be useful in assessing volume status and in suggesting the presence of an autonomic neuropathy. If the respiratory rate and pattern suggest Kussmaul breathing, DKA must be immediately considered and appropriate tests ordered.

Fundoscopy

Include a careful view of the retina, visualizing both the optic disc and the macula. If hemorrhages or exudates are seen, the patient should be seen by an ophthalmologist as soon as possible. Nonophthalmologists tend to underestimate the severity of retinopathy, especially if the pupils have not been dilated. In general, if patients have not been seen by an ophthalmologist within the past year, they should be encouraged to follow up for an annual retinal examination.

Foot Examination

Foot deformity and abnormal nails can be a sign that follow-up with a podiatrist is needed and attention given to foot care. The dorsalis pedis and posterior tibialis pulses should be palpated and their presence or absence noted. This is particularly important among patients with foot infection, because poor lower-extremity blood flow can delay healing and increase the risk of amputation. Documenting lower-extremity sensory neuropathy is also useful, because decreased sensation limits the patient's ability to protect the feet and ankles. If peripheral neuropathy is found, the patient should be made aware that foot care (including daily foot examinations) is very important

for the prevention of foot ulcers and possible subsequent lower-extremity amputation.

DIABETES MEDICATIONS

The number and variety of medications available for the treatment of diabetes, particularly T2DM, continues to increase (Table 204.2). These drugs allow for the use of combination oral therapy, including the combination oral agents plus a noninsulin injectable and the combinations of nearly any oral or noninsulin injectable with insulin (6,7).

TABLE 204.2
Properties of Currently Available Glucose Lowering Agents Used in the Treatment of Patients with Type 2 Diabetes Mellitus

Class	Compound(s)	Cellular Mechanism	Primary Physiologic Action(s)	Advantages	Disadvantages	Cost
Biguanides	• Metformin	Activates AMP-kinase	• ↓ Hepatic glucose production	• Extensive experience • No weight gain • No hypoglycemia • Likely ↓ CVD events (UKPDS)	• Gastrointestinal side effects (diarrhea, abdominal cramping) • Lactic acidosis risk (rare) • Vitamin B_{12} deficiency • Multiple contraindications: CKD; acidosis, hypoxia, dehydration, etc.	Low
Sulfonylureas	• Glibenclamide/ Glyburide • Glipizide • Gliclazide[a] • Glimepiride	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • Blunts myocardial ischemic preconditioning • Low durability	Low
Meglitinides (Glinides)	• Repaglinide • Nateglinide	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• Postprandial glucose control • Dosing flexibility	• Hypoglycemia • Weight gain • Blunts myocardial ischemic preconditioning • Frequent dosing schedule	High
Thiazolidinediones	• Pioglitazone • Rosiglitazone[b]	Activates the nuclear transcription factor PPAR-γ	• ↑ Insulin sensitivity	• No hypoglycemia • Durability • HDL-C • Triglycerides (pioglitazone) • ↓ CVD events (ProACTIVE, pioglitazone)	• Weight gain • Edema/heart failure • Bone fractures • LDL-C (rosiglitazone) • ↑ MI (meta-analyses, rosiglitazone) • ↑ Bladder cancer (pioglitazone)	High[c]
α-glucosidase inhibitors[d]	• Acarbose • Miglitol	Inhibits intestinal α-glucosidase	• Slows intestinal carbohydrate digestion/absorption	• Nonsystemic • Postprandial glucose • ↓ CVD events (Stop-NIDDM)	• Generally modest A1c efficacy • Gastrointestinal side effects (flatulence, diarrhea) • Frequent dosing schedule	Moderate
DPP-4 inhibitors	• Sitagliptin • Vildagliptin[d] • Saxagliptin • Linagliptin	Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations	• Insulin secretion (glucose-dependent) • ↓ Glucagon secretion (glucose-dependent)	• No hypoglycemia • Well tolerated	• Generally modest A1c efficacy • Urticaria/angioedema • Pancreatitis	High
GLP-1 receptor agonists	• Exenatide • Exenatide extended release • Liraglutide	Activates GLP-1 receptors	• Insulin secretion (glucose-dependent) • Glucagon secretion (glucose-dependent) • Slows gastric emptying • ↑ Satiety	• Weight reduction • Potential for improved β-cell mass/function (preliminary data) • Cardiovascular protective actions	• Gastrointestinal side effects (nausea/vomiting) • Acute pancreatitis • C-cell hyperplasia/ medullary thyroid tumors in animals (liraglutide) • Injectable • Training requirements	High
SGLT2 inhibitors	• Canagliflozin	Inhibits sodium-glucose cotransporter 2 (SGLT2)	• Blocks glucose reabsorption in renal tubules increasing glycosuria	• Reduction in plasma glucose levels • Possibly results in weight loss	• Risk for urinary tract infection • ↑ Vaginal and penile fungal infections • Dehydration • Electrolyte disturbances • ↑ Serum creatinine levels	
Bile acid sequestrants[d]	• Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production; activation of farnesoid X receptor (FXR) in liver	• Unknown • ↓ Hepatic glucose production • ↑ Incretin levels	• No hypoglycemia • ↓ LDL-C	• Generally modest A1c efficacy • Constipation • Triglycerides • May ↓ absorption of other medications	High

Class	Compound(s)	Cellular Mechanism	Primary Physiologic Action(s)	Advantages	Disadvantages	Cost
Dopamine-2 agonists[d]	• Bromocriptine (quick-release)[e]	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• No hypoglycemia • ↓ CVD events (Cycloset Safety Trial)	• Generally modest A1c efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	High
Amylin mimetics[d]	• Pramlintide[e]	Activates amylin receptors	• Glucagon secretion • Slows gastric emptying • ↑ Satiety	• Dampens PPG excursions • Weight reduction	• Generally modest A1c efficacy • Gastrointestinal side effects (nausea/vomiting) • Hypoglycemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule	High
Insulins	• Human NPH • Human regular • Lispro • Aspart • Glulisine • Glargine • Detemir • Premixed (several types)	Activates insulin receptors	• Glucose disposal • ↓ Hepatic glucose production	• Universally effective • Theoretically unlimited efficacy • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • Mitogenic effects • Injectable • Training requirements • "Stigma" (for patients)	Variable[f]

AMP, adenosine monophosphate; CVD, cardiovascular disease; CKD, chronic kidney disease; UKPDS, United Kingdom prospective diabetes study; PPAR, peroxisome proliferator-activated receptor; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ProACTIVE, prospective pioglitazone clinical trial in macrovascular events; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.
[a]Not licensed in the United States.
[b]Prescribing highly restricted in the United States.
[c]To be available as a generic product in 2012, with expected significant reductions in cost.
[d]Limited use in the United States/Europe.
[e]Not licensed in Europe.
[f]Depends on type (analogs >> human insulins) and dosage.
Modified from ADA/EASD guidelines.

The biguanides (e.g., metformin) primarily decrease hepatic glucose production and may also slightly lower insulin resistance. These drugs commonly cause nausea, abdominal cramping, and diarrhea. Rarely, they can cause severe lactic acidosis, especially among patients with renal insufficiency.

The sulfonylurea agents (e.g., glyburide, glipizide, glimepiride) and meglitinides (e.g., repaglinide and nateglinide) increase insulin secretion and are considered long- and short-acting insulin secretagogues, respectively. Their most common serious adverse reaction is hypoglycemia, which can be severe and may limit use of these agents.

The thiazolidinediones (rosiglitazone and pioglitazone) act as insulin sensitizers. Both increase plasma volume and can cause fluid retention. The most common side effect is mild-to-moderate pedal edema. Both can result in congestive heart failure (CHF) in patients who are at risk. The thiazolidinediones should not be used in patients with CHF and in patients who have a baseline alanine

aminotransferase three times the upper limit of normal. Pioglitazone and rosiglitazone differ in terms of their effect on lipids (pioglitazone decreases triglyceride levels and raises high-density lipoprotein (HDL) levels; rosiglitazone causes a lesser increase in HDL cholesterol levels and has no effect on triglyceride levels). Rosiglitazone may cause an increased risk of myocardial infarction (MI) and heart-related deaths (8) and is only available as a restricted use agent. Pioglitazone appears to be safe from a cardiovascular event perspective (9). Finally, thiazolidinediones increase the risk of bone fracture and should be used with caution in individuals with advanced osteoporosis.

The α-glucosidase inhibitors (e.g., acarbose and miglitol) decrease intestinal absorption of carbohydrate, often producing flatulence and, rarely, causing small bowel obstruction. These agents produce a relatively small fall in A1c (approximately 0.5% compared to 1% to 2% for most other agents). They are most effective in patients consuming a high carbohydrate diet and are commonly used in Asia, where rice is a staple.

Dipeptidyl peptidase-4 (DPP-4) inhibitors increase circulating levels of GLP-1 (glucagon-like peptide-1), which is an incretin hormone secreted from the gut that helps improve insulin secretion and lower blood sugar levels. There are four available DPP-4 inhibitors: Sitagliptin, saxagliptin, linagliptin, and alogliptin. All except for linagliptin must be dose reduced for renal dysfunction.

Glucagon-like peptide receptor agonists (GLP-1 RAs) are injectable agents that directly act upon GLP-1 receptors. These agents tend to cause a greater HbA1c lowering than DPP-4 inhibitors and often cause weight loss, owing to an increase in satiety. Currently marketed agents include short-acting exenatide (given twice daily), long-acting exenatide (given once weekly) and liraglutide (once daily). GLP-1 RAs commonly cause nausea, vomiting, and diarrhea. Both GLP-1 RAs and DPP-4 inhibitors are associated with pancreatitis.

Sodium-glucose cotransporter 2 (SGLT2) blocks glucose reabsorption in renal tubules, increasing glycosuria and leading to a reduction in plasma glucose levels and possibly weight loss.

Canagliflozin is the first such agent available in the United States. Side effects include an increased risk for urinary tract infection and vaginal and penile fungal infections. SGLT-2 inhibitors can also cause dehydration, electrolyte disturbances, and an increase in serum creatinine levels.

Bromocriptine (a dopamine-2 agonist) and colesevelam (a bile acid sequestrant) are both approved for the treatment of T2DM, but cause only mild reductions in A1c and are not widely used.

Insulin remains the therapy for patients with T1DM and patients with T2DM for whom oral agents do not achieve adequate glycemic control. The amylin analog pramlintide is an adjunctive therapy for patients with T1DM and insulin-treated T2DM.

ABNORMALITIES CAUSED BY HYPERGLYCEMIA

Acute hyperglycemia, even when not associated with DKA or the hyperglycemic hyperosmolar syndrome (HHS) is harmful for a number of reasons. If the blood glucose level exceeds the renal threshold for glucose (>240 mg/dL in a healthy person, but diminished with advancing age, renal insufficiency, and pregnancy), an osmotic diuresis ensues, with loss of glucose, electrolytes, and water. Hyperglycemia impairs leukocyte function through a variety of mechanisms. Patients with diabetes have an increased rate of wound infection, and hyperglycemia may also independently impair wound healing.

Chronic hyperglycemia is associated with an increased risk for the development of the microvascular and neuropathic complications of diabetes, as elegantly demonstrated in the Diabetes Control and Complications Trial (DCCT) for T1DM (10) and the United Kingdom Prospective Diabetes Study (UKPDS) for T2DM (11). In the DCCT, intensive therapy designed to maintain normal blood glucose levels greatly reduced the development and progression of retinopathy, microalbuminuria, proteinuria, and neuropathy as assessed over a 7-year period. Intensive therapy was not associated with increased mortality or major macrovascular events and did not decrease the quality of life, although it did increase the likelihood of severe hypoglycemic episodes. In addition, when patients enrolled in the

DCCT were followed over the next 12 years in the Epidemiology of Diabetes Interventions and Complications study, there was a significant reduction in rates of cardiovascular disease in those who had been intensely treated (12). In the UKPDS, aggressive treatment of blood glucose levels and hypertension was shown to decrease the risk of microvascular complications in patients with T2DM.

More recent studies, however, such as ACCORD, ADVANCE, and VADT have shown that in older patients with more advanced type 2 diabetes further intensifying control might cause harm (6). In the ACCORD trial those in the intensively treated group (target A1c of less than 6%) had an increased rate of mortality compared to those in the control group. The reasons for this increase in mortality is not well understood, but in all trials, in both intensive and control arms, episodes of severe hypoglycemia were associated with an increased risk for poorer outcomes, including death. Therefore, current guidelines suggest individualizing targets with a particular focus on decreasing the risk of severe hypoglycemia (6,7).

Among patients with known diabetes that is poorly controlled, there is no absolute level of blood glucose elevation that necessitates admission to the hospital or the administration of insulin. Admission is appropriate for the following:

1. *DKA* (see Chapter 205). Plasma glucose >250 mg/dL (>13.9 mmol/L) with (a) arterial pH <7.30 and serum bicarbonate level <15 mEq/L and (b) moderate ketonuria or ketonemia. DKA can occur in patients with normal blood glucose levels, particularly if they are vomiting frequently. Therefore, any blood sugar level in the setting of ketoacidosis can be indicative of DKA, even though an elevated blood sugar level is most common.
2. *HHS* (see Chapter 205). Impaired mental status and elevated plasma osmolality in a patient with hyperglycemia. This usually includes severe hyperglycemia (e.g., plasma glucose >600 mg/dL [>33.3 mmol/L]) and elevated serum osmolality (e.g., >320 mOsm/kg [>320 mmol/kg]).
3. Hypoglycemia (see Chapter 206). Only those patients with prolonged, severe or recurrent hypoglycemia require

hospitalization.

4. Severely symptomatic patient. Patients with T1DM who cannot tolerate oral fluids require hospitalization. Likewise, if the patient is severely symptomatic or the precipitating cause of hyperglycemia cannot be adequately treated in the ED, the patient needs to be admitted.

Generally, lowering the blood glucose level acutely in the ED in individuals without DKA or HHS has little benefit. It does not correct the underlying cause of hyperglycemia and has no long-term impact on the patient's blood glucose levels. Therefore, a plan must be formulated as to how the patient's blood glucose level will be lowered over time and how glycemic control will be maintained. The adequacy of follow-up is an extremely important consideration. Whether to give insulin in the ED is of lesser consequence and can be decided on an individual basis.

ED MANAGEMENT

New-Onset Diabetes

Most patients with diabetes have T2DM, and most of those are asymptomatic at diagnosis. The initial treatment for patients with newly discovered, asymptomatic diabetes is a trial of medical nutrition therapy (MNT; diet therapy) along with initiation of metformin therapy. Therefore, if an asymptomatic patient is noted incidentally to have an elevated blood glucose level in the ED, this can be followed up by the patient's outpatient physician. Patients who have mild-to-moderate symptoms of poorly controlled diabetes but have not previously been diagnosed can usually be treated on an outpatient basis, often with the initiation of low-dose oral antidiabetic agent therapy.

Controversy exists over the management of markedly symptomatic patients with newly discovered T2DM and blood glucose levels over 400 mg/dL. If close follow-up can be arranged, these patients can be started on maximal doses of a sulfonylurea agent and treated as outpatients. Generally, the patient feels better within 1 to 2 days, and, within a week, the blood glucose levels are markedly lower

(13). Their sulfonylurea dose can be tapered as they comply with MNT and metformin is added. In some, diabetes can be controlled with diet alone. However, patients who cannot drink adequate amounts of fluid, who have serious coexisting medical conditions (e.g., MI or systemic infection), or who do not have reliable follow-up should generally be hospitalized for initiation of therapy.

Patients with new-onset T1DM need to be started on lifelong insulin therapy. Many present with DKA. An occasional patient with new-onset T1DM who presents with mild manifestations and is judged to be very compliant can be started on insulin as an outpatient. T1DM patients begun on insulin as outpatients require basic education on insulin administration, self-monitoring of blood glucose, and close follow-up. Patients should be seen as soon as possible to receive thorough diabetes and nutrition self-management education.

MANAGEMENT OF HYPERGLYCEMIA DURING MEDICAL ILLNESS AND SURGERY

Serious medical illness and surgery produce a state of increased insulin resistance and relative insulin deficiency. Hyperglycemia can occur, even in nondiabetic patients, because of stress-induced insulin resistance plus the administration of dextrose-containing intravenous fluids. Increases of glucagon, catecholamines, cortisol, and growth hormone antagonize the effects of insulin, and insulin secretion is itself inhibited by the α-adrenergic effect of increased catecholamine levels. The counter-regulatory hormones also directly increase hepatic gluconeogenesis.

Although it was previously thought that inpatients did better with tighter glycemic control more recent data refutes this concept. Thus, inpatient target blood sugar levels are 140 to 180 mg/dL (14). When managing patients in the hospital with pre-existing diabetes, it is necessary to modify treatment regimens to compensate for both decreased caloric intake and increased physiologic stress.

It is strongly recommended that continuous intravenous infusions of dextrose and insulin be used in patients who are undergoing general anesthesia or are critically ill. Crucial to prevent ketosis in

patients with T1DM, this technique probably benefits patients with T2DM as well. Blood glucose levels must be measured with a glucose meter every hour, and the rates of insulin and dextrose infusion must be adjusted accordingly to prevent hypoglycemia or persistent hyperglycemia. Algorithms are available for insulin infusions, and the use of preprinted orders facilitates drug administration and reduces dosing errors.

- Frequent blood glucose monitoring is not always possible nor necessary for every patient, and patients with less serious illness or those undergoing minor surgery may do just as well with subcutaneously injected insulin. *A basal bolus insulin regimen rather than sliding-scale regular insulin should be used in these patients* (14). In patients going to surgery who have not received their dose of long/intermediate acting insulin for the day, giving 50% to 80% of the daily dose prior to surgery is often effective. At the same time, an intravenous infusion containing 5% dextrose should be started at a rate of 125 mL/hr. Blood glucose levels should be checked every 2 hours during surgery, and small doses of regular or rapid-acting insulin (lispro [Humalog], aspart [NovoLog], or glulisine [Apidra]) insulin should be given if values are >150 mg/dL.

The same principles of providing a constant source of insulin and carbohydrate apply to patients with T1DM who are not going to surgery but who must remain NPO owing to medical reasons. Patients should receive an injection of basal insulin (either glargine [Lantus] or detemir [Levemir]), with additional correction doses using regular insulin or a rapid-acting insulin (e.g., lispro), based on blood glucose levels. To avoid hypoglycemia, regular insulin should not be given more often than every 3 to 4 hours because a dose is effective for up to 6 hours. Rapid-acting insulins may be given every 3 hours. Once the patient is eating, a preprandial insulin dose can be added.

Patients with T2DM who are on insulin can follow similar guidelines. However, because patients with T2DM secrete some endogenous insulin and do not tend to develop ketosis, they can often be managed for brief periods without either insulin or dextrose.

However, if the blood glucose is <100 mg/dL, or >180 mg/dL, appropriate treatment is required.

Patients who have been taking an oral insulin secretagogue (such as a sulfonylurea agent or meglitinide) should have their blood glucose levels monitored when oral intake is not allowed, and intravenous dextrose with or without insulin should be given to keep blood glucose levels between 140 and 180 mg/dL. Metformin should not be given to hospitalized patients until it is clear that their renal function is stable. In general, for the initially hospitalized patients, oral antidiabetic medication should be held and then restarted once the patient is less acutely ill. The exceptions are DPP-4 inhibitors, which can be used in the hospital setting, with dose adjustments as needed based on renal function.

The emergency physician caring for the patient with diabetes who requires emergent surgery must notify the surgeon and the anesthesiologist of the patient's condition, obtain medical consultation when appropriate, and promptly initiate a thorough medical evaluation so as not to delay surgery.

Infections

Infections cause considerable morbidity and mortality among patients with diabetes. Infections may precipitate metabolic derangements and, conversely, the metabolic derangements of diabetes may facilitate infection. Depending on the population studied, infections have been identified as the precipitant in 26% to 77% of cases of DKA. A few infections, such as malignant otitis externa, rhinocerebral mucormycosis, and emphysematous pyelonephritis, occur almost exclusively in patients with diabetes. Certain infections, such as staphylococcal sepsis, occur more frequently and result in greater mortality among patients with diabetes, whereas others, such as pneumococcal pneumonia, affect diabetic patients no differently than the general population.

Although diabetes can compromise all aspects of host defenses against infection, all diabetic patients are nevertheless not equally susceptible to infection. Impairments in humoral immunity and polymorphonuclear leukocyte and lymphocyte function are

exacerbated by hyperglycemia and acidemia but are substantially, if not entirely, reversed by normalization of pH and blood glucose levels. Although the exact level above which impaired leukocyte function occurs has not been well defined, in vitro evidence suggests that glucose levels above 200 mg/dL impair leukocyte function (15).

Patients with long-standing diabetes also tend to develop microvascular and macrovascular disease, with resulting poor tissue perfusion and an increased risk of infection. The ability of skin to act as a barrier to infection may also be compromised when the diminished sensation of diabetic neuropathy results in unnoticed injury.

Ear, Nose, and Throat Infections

Two head and neck infections that are associated with high morbidity and mortality—malignant otitis externa and rhinocerebral mucormycosis—are seen almost exclusively in diabetic patients.

Malignant or necrotizing otitis externa principally occurs in older patients with diabetes and is almost always caused by *Pseudomonas aeruginosa*. The infection starts in the external auditory canal and spreads to the adjacent soft tissue, cartilage, and bone. Patients typically present with severe ear pain and otorrhea and, although they often have a pre-existing otitis externa, the progression to invasive disease is usually rapid. Examination of the auditory canal may reveal granulation tissue, but spread of infection to the pinna, the preauricular tissue, and the mastoid often makes the diagnosis apparent. Involvement of cranial nerves, particularly the facial nerve, is common; when there is extension to the meninges, the outcome is often fatal. Computed tomography (CT) is useful to define the extent of disease.

Prompt surgical consultation is mandatory for malignant otitis externa, because surgical debridement is often an essential part of therapy. Intravenous antipseudomonal antibiotic therapy should be started at once in patients with invasive disease. Diabetic patients with severe otitis externa but no evidence of invasive disease can be treated with an otic antibiotic drop and oral ciprofloxacin, but they require close follow-up.

Mucormycosis is the name given collectively to the infections caused by various ubiquitous molds (16). Invasive disease occurs in poorly controlled diabetic patients, especially in conjunction with DKA although it can occur in individuals with type 2 diabetes, as well. In these patients, the organism colonizes the nose and paranasal sinuses, spreading into adjacent tissues by invading blood vessels and causing soft tissue necrosis and bony erosion. Patients usually present with periorbital or perinasal pain and various degrees of swelling and induration. There may be a bloody nasal discharge. Involvement of the orbits, with eyelid swelling, proptosis, and diplopia, is common. The nasal turbinates may appear dusky red or frankly necrotic. The appearance of black necrotic tissue is an important visual clue. As the illness progresses, there is invasion of the cranial vault through the cribriform plate, which may result in cerebral abscess, cavernous sinus thrombosis, or internal carotid artery thrombosis. Wet smears of the necrotic tissue often reveal broad hyphae and distinguish mucormycosis from a severe facial cellulitis.

CT helps to delineate the extent of disease. Treatment consists of control of the predisposing hyperglycemia and acidemia, intravenous amphotericin B, and immediate surgical debridement. Until the diagnosis is confirmed, treatment with antistaphylococcal antibiotics is appropriate.

Urinary Tract Infection

Patients with diabetes have a 60% increased risk of urinary tract infection compared to individuals without diabetes (17). More importantly, people with diabetes are increased risk for serious upper urinary tract infection. Intrarenal bacterial infection should be considered in the differential diagnosis of any patient with diabetes who presents with flank or abdominal pain.

The treatment of cystitis is essentially the same as in nondiabetic patients, although individuals with a neurogenic bladder due to diabetic neuropathy may not empty the bladder well and may require urologic referral. Sulfonamide antibiotics can cause hypoglycemia among patients taking sulfonylurea agents by

displacing the sulfonylurea agents from their binding sites and increasing their hypoglycemic effect.

The principles of treatment of pyelonephritis do not differ for diabetic patients, but a lower threshold for hospital admission is appropriate for at least two reasons. First, pyelonephritis makes control of diabetes more difficult by causing insulin resistance; in addition, nausea may limit the patient's ability to maintain normal hydration. The ensuing hyperglycemia further compromises the immune response. Second, diabetic patients are more susceptible to the complications of pyelonephritis, including renal abscess, emphysematous pyelonephritis, renal papillary necrosis, and gram-negative sepsis.

Emphysematous pyelonephritis can occur in patients with diabetes (18). This is an uncommon necrotizing infection of the kidney caused by *Escherichia coli, Klebsiella pneumoniae,* or other organisms capable of fermenting glucose to carbon dioxide. The presentation is usually similar to that of uncomplicated pyelonephritis. The diagnosis is established by identifying renal gas on plain radiography, ultrasonography, or noncontrast helical CT urography. Management consists of intravenous antibiotics and supportive care plus percutaneous drainage or emergency nephrectomy in more severe cases.

Skin and Soft Tissue Infections

Sensory neuropathy, atherosclerotic vascular disease, and hyperglycemia all predispose diabetic patients to skin and soft tissue infections. These can affect any skin surface but most commonly involve the feet. Even the smallest wound can be complicated by cellulitis, lymphangitis and, more ominously, staphylococcal sepsis. Minor wound infections and cellulitis are typically caused by *Staphylococcus aureus* or hemolytic streptococci and generally can be treated with a penicillinase-resistant synthetic penicillin or a first-generation cephalosporin. Diabetes, however, is a risk factor for the development of MRSA infections. Severe skin and soft tissue infections, and even minor purulent infections, should be treated with an antibiotic effective against MRSA, such as vancomycin for

serious infections, and clindamycin or cephalexin plus trimethoprim-sulfamethoxazole for less severe infections.

Outpatient treatment of minor infections is appropriate if the patient is reliable, performs self-monitoring of blood glucose levels (and urine ketones for T1DM patients), and has close follow-up available. Wounds and, in particular, cutaneous ulcers can also be complicated by necrotizing infections of the skin, subcutaneous tissues, fascia, or muscle. These infections are typically polymicrobial, involving group A streptococci, enterococci, *S. aureus,* Enterobacteriaceae, and various anaerobes. Radiographs should be taken of any spreading soft tissue infection in a diabetic patient to look for the soft tissue gas that characterizes these infections. Surgical debridement is necessary for necrotizing infections. Gram stains and surface cultures are not helpful; antibiotic coverage should reflect the range of potential pathogens.

Osteomyelitis

Contiguous spread of a polymicrobial infection from a skin ulcer to adjacent bone is common in diabetic patients. In one study, osteomyelitis was found underlying 68% of diabetic foot ulcers, and physical examination and plain radiographs each failed to make the diagnosis in one-half of patients. The consensus guidelines for diagnosing osteomyelitis recommend an aseptically obtained bone sample with histopathologic findings of inflammation and microorganisms found on culture (17). Other diagnostic tests for osteomyelitis are probing to bone, the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), sequential x-rays, and MRI. CT and nuclear medicine scans and are less helpful.

In the ED, where physical examination, ESR, and plain radiographs are the commonly employed diagnostic modalities, the diagnosis is more frequently suspected than definitively established. If osteomyelitis is apparent by radiograph or physical examination (e.g., if wounds are deep enough to expose tendons or bone, or probes to the bone), the patient should be admitted for intravenous antibiotics. If osteomyelitis is suspected but admission is not

necessitated by the soft tissue infection or metabolic disturbances, the patient can be discharged to have an outpatient workup.

Other Infections

Although cholecystitis is probably no more common in patients with diabetes than in the general population, severe fulminating infection, especially with gas-forming organisms, is. The early clinical manifestations of emphysematous cholecystitis are indistinguishable from those of usual cholecystitis. The diagnosis can be made by finding gas in the gallbladder lumen, wall, or surrounding tissues. Even with immediate surgery, mortality is high. Clostridial species are found in more than 50% of cases.

Diabetic patients have a greater incidence of staphylococcal and *Klebsiella* pneumonia than do persons without diabetes. Diabetes is also a risk factor for reactivation of tuberculosis. Cryptococcal infections and coccidioidomycoses are more virulent in diabetic patients.

Ophthalmologic Abnormalities

Visual complaints by diabetic patients should be taken very seriously. Diabetes can affect the lens, the vitreous, and the retina, causing visual symptoms that may prompt the patient to come to the ED. Visual blurring may develop acutely as the lens changes shape with marked changes in blood glucose concentrations. This effect, which is caused by osmotic fluxes of water into and out of the lens as the blood glucose concentration varies, usually occurs as hyperglycemia increases, but it may also be seen when high blood glucose levels are lowered rapidly. In either case, recovery to baseline visual acuity can take up to a month, and some patients are almost completely unable to read small print or do close-up work during this period.

Rarely, patients with T1DM who are in extremely poor control (e.g., those with frequent episodes of DKA) can acutely develop a “snowflake” (or “metabolic”) cataract. Named for their snowflake or flocculent appearance, these cataracts can progress rapidly and

create total opacification of the lens within a few days. Surgery is often required to restore vision. Patients with diabetes also tend to develop senile cataracts at a younger age than do persons without diabetes, although not in relation to the degree of glycemic control.

Diabetic retinopathy remains the leading cause of blindness among persons aged 20 to 64 in the United States (19). Some degree of diabetic retinopathy can be expected to develop in nearly all patients with TIDM and approximately 60% of patients with T2DM who have had the disease for 20 years or more. Patients with T2DM may already have diabetic retinopathy at the time their diabetes is diagnosed.

There are five stages in the progression of diabetic retinopathy:

1. Dilation of the retinal venules and formation of retinal capillary microaneurysms
2. Increased vascular permeability
3. Vascular occlusion and retinal ischemia
4. Proliferation of new blood vessels on the surface of the retina
5. Hemorrhage and contraction of the fibrovascular proliferation and the vitreous

The first two stages of diabetic retinopathy are known as “background” or nonproliferative retinopathy. Initially, the retinal venules dilate, then microaneurysms, which appear as tiny red dots on the retina and cause no visual impairment, develop. As the microaneurysms or retinal capillaries become more permeable, hard exudates appear, reflecting the leakage of plasma. These are sharply defined yellow deposits composed mostly of lipid material. Rupture of intraretinal capillaries results in hemorrhage. If these ruptures occur deep in the retina, they appear as “dot blot” hemorrhages that can be difficult to distinguish from microaneurysms. If a more superficial capillary ruptures, a flame-shaped hemorrhage appears. Hard exudates are often found in partial or complete rings (circinate pattern), which usually include multiple microaneurysms. These rings usually mark an area of edematous retina.

No change in visual acuity may be noted by the patient, unless the center of the macula is involved. Macular edema can cause visual loss, however, so it is extremely important to refer patients with

suspected macular edema to an ophthalmologist for evaluation and possible laser therapy. Laser therapy is effective in decreasing macular edema and preserving vision, but it is less effective in restoring vision once it is lost. The advent of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has added a new dimension to the treatment of diabetic retinopathy, particularly macular edema where it is considered by many to be first-line therapy (20).

Preproliferative and proliferative diabetic retinopathy are the next stages in the progression of the disease. Cotton-wool spots can be seen in preproliferative retinopathy. These represent retinal microinfarcts owing to capillary occlusion and are off-white to gray patches with poorly defined margins.

Proliferative retinopathy is characterized by neovascularization, the development of networks of fragile new vessels that are often seen on the optic disc or along the main vascular arcades. The vessels undergo cycles of proliferation and regression. During proliferation, fibrous adhesions develop between the vessels and the vitreous. Subsequent contraction of the adhesions can result in traction on the retina and retinal detachment. Contraction also tears the fragile new vessels, which hemorrhage into the vitreous. Patients with T2DM do not develop proliferative retinopathy as often as those with T1DM.

Often, the first hemorrhage is small and is noted by the patient as a fleeting, dark area, or “floater,” in the field of vision. Because subsequent hemorrhages can be larger and more serious, the patient should be referred immediately to an ophthalmologist for laser therapy anti-VEGF treatment, or both. Patients with retinal hemorrhage should be advised to limit their activity and keep their head upright (even while sleeping), so that the blood settles to the inferior portion of the retina, thus obscuring less central vision.

Patients with active proliferative diabetic retinopathy are at increased risk for retinal hemorrhage if they receive thrombolytic therapy, so this condition is a relative contraindication to the use of thrombolytic agents.

Diabetic Nephropathy

Diabetes is the leading single cause of end-stage renal failure in the United States. Although the prevalence of diabetic nephropathy varies with the duration of diabetes and can be substantially reduced by improved glycemic and hypertension management, all patients with diabetes should be considered to have the potential for renal impairment unless proven otherwise. Potentially nephrotoxic drugs should be avoided whenever possible. Renally excreted or potentially nephrotoxic drugs should be given at reduced dosage as appropriate to the patient's serum creatinine level, creatinine clearance, or estimated glomerular filtration rate (eGFR).

The use of contrast media, including ionic and nonionic contrast can cause reductions in renal function, and precipitate acute renal failure in patients with underlying diabetic nephropathy. While most patients recover within 10 days, some develop irreversible renal failure. Caution should be used when contrast-enhanced studies are being considered in patients with diabetes with an eGFR) <60 mL/min or a serum creatinine level ≤ 1.5 mg/dL. In general an ultrasound or a noncontrast study should be performed.

Patients with diabetes who must undergo contrast medium–enhanced studies should be well hydrated before, during, and after the procedure and should have careful monitoring of renal function. Data are mixed both with regard to the use of isotonic saline versus a sodium bicarbonate containing fluid for hydration, and the utility of oral N-acetylcysteine to reduce nephrotoxicity (21). The appropriate selection of contrast agents may also reduce nephrotoxicity. Iso-osmolar iodixanol or a nonionic low osmolal agent (e.g., iopamidol or ioversol) are preferable to iohexol (22).

In contrast, the administration of gadolinium-containing contrast agents used in MRI scanning are of concern only in patients with chronic kidney disease (CKD), in whom there is a risk of a serious adverse reaction termed nephrogenic systemic fibrosis. Since many patients with long-standing diabetes have CKD, caution is warranted in those in whom gadolinium contrast is being considered. Because chronic blood pressure elevation contributes to the decline in renal function, it is extremely important that patients with diabetes who are found to be hypertensive be referred for chronic blood pressure

management. If antihypertensive therapy is to be started in the ED, an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) is a good choice because these agents have been found to reduce the rate of decline in renal function, independent of their effect on blood pressure. They also decrease proteinuria among patients with diabetic nephropathy. It should be kept in mind, however, that ACE inhibitors and ARBs tend to increase the serum potassium level and should thus be used with caution in patients with renal insufficiency or somewhat elevated serum potassium levels.

Diabetic Neuropathy

Diabetic neuropathy is common, and distal symmetric sensorimotor polyneuropathy (in a "glove-and-stocking" distribution) is the most frequent pattern. In addition to the pain often experienced in its early stages, this type of neuropathy eventually leads to loss of sensation. The combination of decreased sensation and peripheral arterial insufficiency often leads to foot ulceration and eventual amputation.

A variety of acute-onset neuropathies occur in diabetic patients, including acute cranial mononeuropathies, mononeuropathy multiplex, focal lesions of the brachial or lumbosacral plexus, and radiculopathies. Of the cranial neuropathies, third oculomotor nerve palsy is the most common, followed by sixth (abducens) and fourth (trochlear) nerve palsies. Patients can present with diplopia and eye pain. In diabetic third-nerve palsy, the pupil is usually spared, whereas in third-nerve palsy owing to intracranial aneurysm or tumor, the pupil is affected in 80% to 90% of cases. It is important to consider nondiabetic causes for cranial nerve palsies, including intracranial tumors, aneurysms, and brainstem stroke (23). Evaluation should, therefore, include either nonenhanced and contrast medium–enhanced CT or, preferably magnetic resonance imaging. Neurologic consultation is recommended. Acute cranial nerve mononeuropathies usually resolve within 2 to 9 months. Acute thrombosis of the blood vessels supplying the nerve involved is thought to be the cause.

Autonomic dysfunction can involve any part of the sympathetic or parasympathetic chains and produce myriad manifestations (24). Patients likely to seek care in the ED include those with diabetic gastroparesis and vomiting, severe diarrhea, bladder dysfunction and urinary retention, and symptomatic orthostatic hypotension. Symptoms tend to wax and wane over time. Treatment is only symptomatic. Patients with gastroparesis may benefit from the use of metoclopramide or erythromycin. Before these therapies are started, the degree of dehydration and metabolic imbalance must be assessed, and other serious causes of vomiting must be excluded. In severe cases, gastric pacing has been used. Patients with disabling orthostatic hypotension may be treated with salt tablets, support stockings, or fludrocortisone. Alleviating the functional abnormalities associated with the autonomic neuropathy is often difficult and frustrating for both doctor and patient. The patient's primary physician, and often an appropriate subspecialist, should be involved in devising a long-term treatment plan.

The Diabetic Foot

Fifty percent to 70% of all nontraumatic lower-extremity amputations occur in patients with diabetes (25). The insensate, poorly perfused foot is at risk for ulcers from pressure necrosis or inflammation from repeated skin stress and unnoticed minor trauma. Either can evolve into cellulitis, osteomyelitis, or nonclostridial gangrene and end in amputation.

Wounds, infections, or ulcers of the feet demand particular attention in the diabetic patient. In addition to appropriate use of antibiotics, it is mandatory to avoid further trauma to the healing foot through use of crutches, a wheelchair, or bed rest. If bone or tendon is visible, osteomyelitis is present, and hospitalization for intravenous antibiotics is often necessary. Many patients need a vascular evaluation in conjunction with local treatment of the foot ulcer, because, in some cases, a revascularization procedure may be required to provide adequate blood flow for wound healing. For patients who may be discharged, every attempt should be made to ensure frequent follow-up, optimally with a podiatrist or an

orthopedist with experience in the care of a diabetic foot. If such follow-up is not available, hospitalization may be necessary for initial treatment.

Because curing ulcers and foot infections is difficult, their prevention is extremely important. At one clinic, the rate of amputation was halved after patients were required to remove their shoes and socks at every visit. The emergency physician can contribute to prevention by briefly inspecting the feet of each patient with diabetes and by educating them about the need for proper foot care and maintenance of near-normal blood sugar levels. Patients who have a loss of sensation and/or structural abnormalities, who smoke, or have a history of prior lower-extremity complications should be referred to a foot care specialist for ongoing preventive care and lifelong surveillance.

Macrovascular Complications

Macrovascular disease is the leading cause of death in patients with diabetes. It is responsible for approximately 65% to 75% of deaths in patients with diabetes, compared with approximately 35% of deaths in the general population. Subtle differences in the pathophysiology of atherosclerosis in patients with diabetes result in both earlier development and a more malignant course. The presence of diabetes causes a twofold increase in MI in men and a fourfold increase in women. The risk of stroke is doubled, and the risk of developing peripheral vascular disease is increased fourfold. In fact, it has been shown that patients with T2DM who have never had an MI have the same risk of having an MI as patients without diabetes who have had a prior MI.

Patients with diabetes may have an increased incidence of silent ischemia. However, silent ischemia is common in many patients with CAD, and the apparently increased incidence may be because patients with diabetes are more likely than others to have CAD to begin with. Nevertheless, electrocardiography is prudent in patients with diabetes and a serious illness or who present with generalized weakness, malaise, or other nonspecific symptoms that are not expected to be due to myocardial ischemia.

Hypertension, which also increases the risk of atherosclerosis, is twice as common among patients with T2DM. Because of their high-risk profile, most patients with type 2 diabetes should be taking a daily aspirin (81 mg to start), an HMG-CoA-reductase inhibitor (statin), and an ACE inhibitor or an ARB agent. Aggressive global risk reduction, reinforced by all health care providers, is needed to lower the morbidity and mortality associated with diabetes.

CRITICAL INTERVENTIONS

- Maintain the blood glucose levels of patients with wounds or active infections <180 mg/dL.
- Provide adequate hydration to patients with mild diabetic nephropathy before contrast material is given to avoid precipitating acute renal failure.

Common Pitfalls

- Failure to provide patients who have T1DM with a continuous source of insulin and glucose when they are unable to tolerate oral intake.
- Underestimating the severity of diabetic retinopathy on funduscopic examination through undilated pupils. Any patient with lesions near the macula should be referred urgently to an ophthalmologist.
- Failure to examine the feet; overlooking small ulcers or underestimating their seriousness.
- Failure to consider myocardial ischemia in patients with nonspecific symptoms.

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CHAPTER 205

Hyperglycemic Crises

Scott R. Votey and Anne L. Peters

Diabetic ketoacidosis (DKA) is the syndrome defined by the biochemical presence of hyperglycemia, ketonemia, and acidemia. Hyperosmolar hyperglycemic state (HHS) is a closely related disorder in which hyperglycemia occurs in the absence of significant ketonemia and acidemia. HHS and DKA are often collectively referred to as **hyperglycemic crises**. The underlying cause of both conditions is insulin deficiency and concomitant elevation of counterregulatory hormones, and the two syndromes represent different points along a single biochemical and clinical spectrum although DKA occurs primarily, but not exclusively, in people with type 1 diabetes and HHS mostly in people with type 2 diabetes. The American Diabetes Association (ADA) diagnostic criteria are useful in establishing the diagnosis of DKA and distinguishing it from HHS (Table 205.1) (1). Individual patients may present with DKA and HHS at different times, and a single episode may have features of both syndromes. However, there are important differences in the management of DKA and HHS.

TABLE 205.1
Diagnostic Criteria for Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

Diagnostic Criteria and Classification	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00 to <7.25	<7.00	>7.30
Serum bicarbonate (mEq/L)	15–18	10 to <15	<10	>15
Urine ketone[a]	1–3+	3–4+	3–4+	Trace to 1+
Serum ketone[a]	Positive	Positive	Positive	Small
Effective serum osmolality[b]	Variable	Variable	Variable	>320 mOsm/kg
Anion gap[c]	>10	>12	>12	<12
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

[a]Nitroprusside reaction method.
[b]Calculation of effective serum osmolality: 2[measured Na^+ (mEq/L)] + [glucose (mg/dL)]/18.
[c]Calculation of anion gap: (Na^+) – [Cl^- + HCO_3^- (mEq/L)].
DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state.
Modified from Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care*. 2009;32(7): 1335–1343.

DKA affects 0.5% to 0.8% of patients with diabetes annually, resulting in approximately 140,000 hospitalizations per year in the United States or 4% to 9% of diabetes admissions (2). Hospitalizations for DKA are increasing, and the estimated annual cost has risen to $2.4 billion (1). DKA encompasses a spectrum of severity from minimally symptomatic to critically ill and can be graded as mild, moderate, and severe (1). This grading facilitates the tailoring of evaluation and management to the needs of the individual patient.

Although the majority of DKA cases occur in patients with type 1 diabetes mellitus, it is increasingly recognized as a complication of type 2 diabetes, particularly in the setting of new-onset diabetes among obese African American and Hispanic young adults, teens, and children (3). DKA is more common in adults (approximately 80% of cases) than children, with 37% of patients older than 50 years (4).

Although the per-episode mortality in published series has declined since 1980, it remains significant at approximately 1% (5). Mortality is higher in persons >65 years of age and in the presence of major chronic comorbidities, such as end-stage renal disease, or acute comorbidities, such as myocardial infarction or sepsis (1).

HHS has been known by several other names in the past, including hyperosmolar nonketotic state and hyperosmolar coma. HHS is the

term currently endorsed by the ADA because it more accurately reflects the clinical and biochemical features of the illness; specifically, mild ketosis is common in HHS, and coma is present in only $<30\%$ of cases (6,7).

HHS is primarily a complication of type 2 diabetes but may also occur in type 1 diabetes. Thirty percent to 40% of episodes occur in the absence of a prior history of diabetes, although most previously undiagnosed patients will prove to have mild type 2 diabetes. HHS is less common than DKA and accounts for $<1\%$ of diabetes admissions (7). The mean age of patients suffering HHS has been approximately 65 years, but the incidence is increasing in young adults, adolescents, and children as the prevalence of type 2 diabetes increases in these age groups.

The mortality rate of HHS is 5% to 20% (1), substantially higher than that of DKA. Patients with major acute or chronic comorbidities and more severe illness on presentation as indicated by coma, hypothermia, or hypotension have higher mortality rates (6,7); older age and higher osmolality have been associated with increased mortality in some (8) but not all series.

CLINICAL PRESENTATION

The clinical presentation, diagnostic evaluation, and management of the hyperglycemic crises can be best understood through an appreciation of the pathophysiology. DKA and HHS occur as a result of insufficient effective circulating insulin. In healthy individuals, glucose homeostasis is maintained by a balance between circulating insulin levels and the counterregulatory hormones: glucagon, catecholamines, cortisol, and growth hormone. Insulin acts to increase glucose utilization and to suppress gluconeogenesis, glycogenolysis, and ketogenesis. Without adequate insulin, glucose cannot be utilized as energy substrate. The counterregulatory hormones have the opposite effect, decreasing glucose uptake and utilization and promoting gluconeogenesis, lipolysis, and ketogenesis. The ketones acetoacetate and β-hydroxybutyrate can be used as substrate by the brain and other tissues but, in excess, cause ketonemia and metabolic acidosis. Insufficient insulin effect results

in an elevated blood glucose, ketonemia, and ketoacidemia. Functional insulin deficiency may result from the absence of insulin (absolute insulin deficiency) or elevated counterregulatory hormones that overwhelm insulin's effect in the presence of normal or even high circulating insulin levels (relative insulin deficiency). Episodes of DKA and HHS are typically the result of the simultaneous occurrence of both insufficient insulin and elevated counterregulatory hormones.

Hyperglycemic crises, including both DKA and HHS, are associated with high levels of circulating proinflammatory cytokines, oxidative stress and circulating adhesion molecules promoting platelet aggregation (9). These abnormalities may play a role in the cerebral edema seen in DKA, and the high rate of myocardial infarction and stroke seen in association with hyperglycemic crises in older patients. Treatment of hyperglycemic crises with insulin and normalization of the serum glucose corrects these abnormalities.

The biochemical abnormalities and clinical features of the hyperglycemic crises are the direct product of insulin deficiency (Fig. 205.1). Insulin deficiency results in gluconeogenesis, glycogenolysis, and decreased glucose utilization with resultant hyperglycemia. Hyperglycemia produces an osmotic diuresis that accounts for the polyuria and polydipsia seen early in the course of hyperglycemic crises and the dehydration with tachycardia and hypotension that develop later in the course. Water and electrolyte deficits are variable but are typically quite large (see Table 205.2).

TABLE 205.2
Typical Total Body Deficits in DKA and HHS

Typical Deficits	DKA	HHS
Total water (L)	6	9
Water (mL/kg)	100	100–200
Na^+ (mEq/kg)	7–10	5–13
Cl^- (mEq/kg)	3–5	5–15
K^+ (mEq/kg)	3–5	4–6
PO_4^- (mmol/kg)	5–7	3–7
Mg^{2+} (mEq/kg)	1–2	1–2
Ca^{2+} (mEq/kg)	1–2	1–2

DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state.
Adapted from Ennis ED, Stahl EJVB, Kreisberg RA. The hyperosmolar hyperglycemic syndrome. *Diabetes Rev*. 1994;2:115–126; *and* Kreisberg RA. Diabetic ketoacidosis: An update. *Crit Care Clin*. 1987;3:817–834.

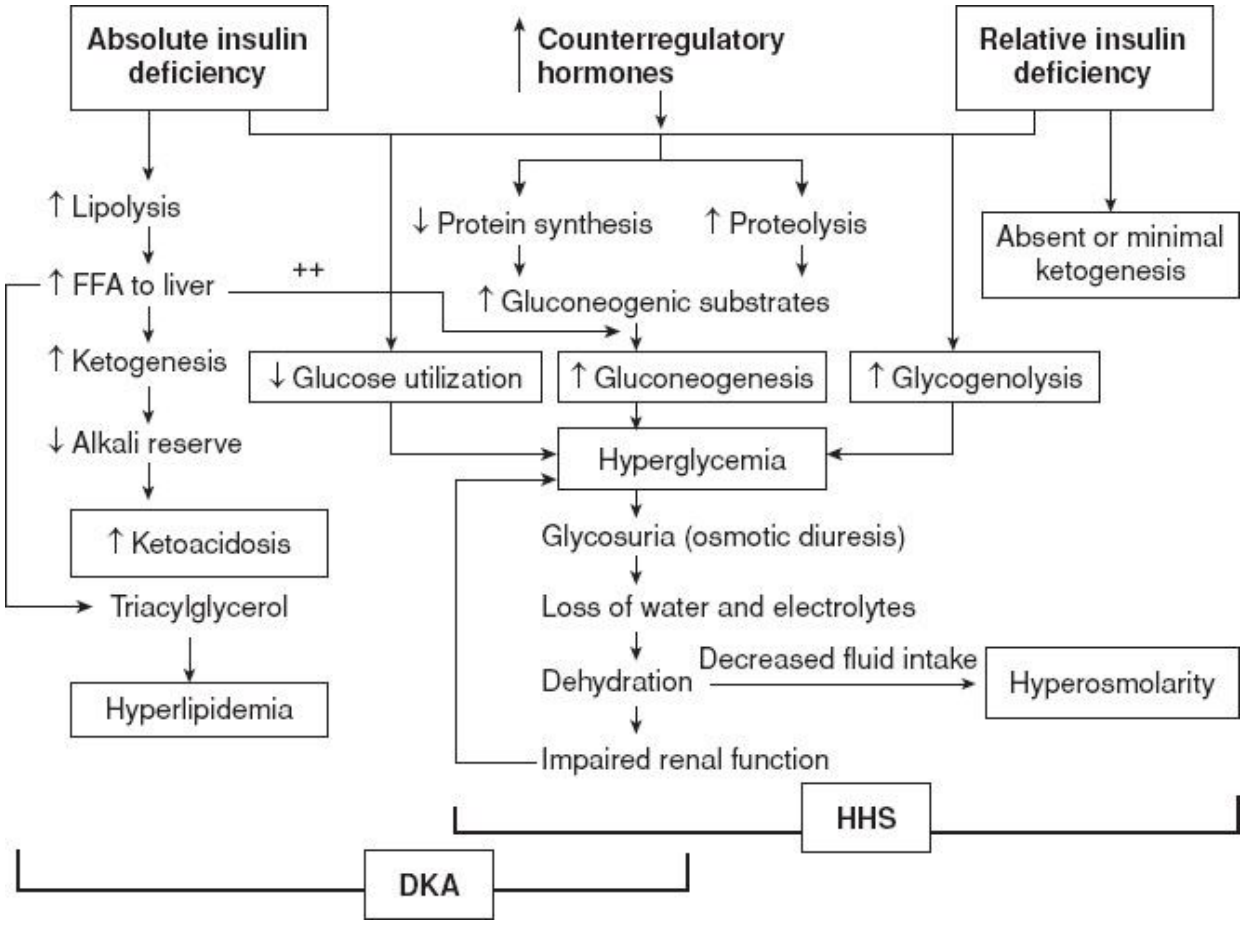

FIGURE 205.1 Pathogenesis of DKA and HHS. FFA, free fatty acid. (Reproduced with permission from Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care*. 2009;32(7):1335–1343.)

Diabetic Ketoacidosis

If insulin deficiency is more severe, ketogenesis accelerates and ketoacids are generated, resulting in DKA. Ketonemia gives rise to nausea, vomiting, and abdominal pain. If these symptoms inhibit fluid intake, dehydration worsens, urine output diminishes, and, in the absence of brisk osmotic diuresis, ketoacid and glucose levels climb and result in acidemia and hyperosmolarity, which in turn engender altered mentation. Respiratory alkalosis with tachypnea is the compensatory response to the ketoacidemia.

Inadequate insulin therapy (nonadherence or an insufficient regimen) resulting in absolute insulin deficiency is a common precipitant of DKA, especially in populations with low income, no health insurance, and low educational levels (Table 205.3) (10). Psychological issues, including eating disorders, are common factors in younger patients. Continuous subcutaneous insulin infusion devices (CSII, insulin pumps) have been associated with a higher incidence of DKA, but with technological improvements this may no longer be the case (11).

TABLE 205.3
Common Precipitants of Diabetic Ketoacidosis

Insufficient Insulin

- Nonadherence (~30%); low income, no health insurance, psychological issues, low educational attainment
- New-onset diabetes (~20%); in both type-1 and type-2 diabetes

Insulin Resistance

- Infection (pneumonia, urinary tract infection, sepsis) (~35%)
- Other medical illness (myocardial infarction, stroke, pancreatitis) and surgery (~15%)
- Medications; corticosteroids, sympathomimetics, second-generation (atypical) antipsychotics (clozapine, olanzapine, and others)

Major illness, most commonly infections but also myocardial infarction, stroke, pancreatitis, and other illnesses that provoke high levels of counterregulatory hormones and insulin resistance, are common precipitants of DKA. New-onset diabetes is identified in

approximately 20% of cases (1,7). Medications, including corticosteroids and second-generation antipsychotics (12), can precipitate DKA, even in patients without a history of diabetes.

DKA develops in hours or more commonly in days, with the onset more rapid in the presence of low circulating insulin levels and more severely elevated counterregulatory hormones, as occurs in the presence of major illness. The ability to consume fluids and maintain a high urine output and thereby an osmotic diuresis of glucose and ketoacids is an important compensatory mechanism as DKA develops. Conversely, the inability to consume fluids and the presence of impaired renal function, particularly anuric renal failure, accelerate the development and exacerbate the severity of DKA.

Polyuria, an early symptom, diminishes as the patient becomes dehydrated. Signs of dehydration (dry mucous membranes, poor skin turgor, tachycardia, positional dizziness, and hypotension) and catecholamine response (tachycardia) may be prominent. Patients typically progress from polydipsia to anorexia, nausea, and vomiting. Abdominal distention, diminished bowel sounds, and abdominal tenderness are present in 50% to 75% of DKA cases (13). Gastric distention and evidence of ileus may be seen on abdominal radiography. All of these abdominal abnormalities may be ascribed to ketosis, but if abdominal pain and tenderness are prominent or fail to improve as metabolic abnormalities resolve, other intra-abdominal pathology should be considered.

Ketoacidosis presents as hyperpnea (an increase in both the rate and depth of breathing) and with the odor of acetone on the breath. In the absence of severe hypotension, altered mentation—lethargy, confusion, or even coma—correlates with, and has been attributed to the severity of the hyperglycemia and hyperosmolarity (7) or the acidosis (14).

Symptoms of a precipitating illness may dominate the clinical presentation or may be obscured by the symptoms of the metabolic derangements of DKA. Signs and symptoms of infection should be sought. Fever is an unreliable sign of infection in patients with DKA and HHS. In fact, DKA and HHS patients presenting with

hypothermia often have a serious underlying infection, and hypothermia is associated with a higher mortality rate (1).

Hyperosmolar Hyperglycemic State

The essential pathophysiologic difference between DKA and HHS is in the severity of insulin deficiency (Fig. 205.1). Higher levels of effective circulating insulin are required to maintain glucose homeostasis than to suppress ketogenesis. HHS develops when circulating insulin levels are adequate to suppress ketogenesis but inadequate to promote glucose utilization or suppress gluconeogenesis. HHS is, therefore, primarily found in patients who secrete some insulin but have insulin resistance at baseline (and may have a diagnosis of type 2 diabetes) and are experiencing a concurrent illness that elevates counterregulatory hormones, exacerbating insulin resistance and resulting in hyperglycemia.

Even more than with DKA the clinical features of HHS are the result of hyperglycemia. Hyperglycemia produces an osmotic diuresis of glucose, which accounts for the polyuria and polydipsia seen early in the course of HHS and the physical signs of dehydration including dry oral mucosa, poor skin turgor, weight loss, generalized weakness, postural dizziness, tachycardia, and hypotension that develop later. HHS develops insidiously over several days to weeks in contrast to DKA, which commonly develops over hours to 1 to 2 days. Water and electrolyte losses are large and typically exceed those found in DKA (Table 205.2), presumably owing to the prolonged diuresis that results in a gradual decline and frequently a delayed diagnosis. Ingestion of fluids to replace fluids lost is an important compensatory mechanism as HHS develops. Impaired thirst, the inability to consume fluids, or a lack of access to fluids accelerates the development of HHS.

As net water and solute loss worsens, hyperosmolarity in the extracellular space promotes movement of water out of the intracellular space, resulting in intracellular hyperosmolarity and cellular dysfunction. Although this process occurs in all tissues, alterations in brain function dominate the clinical presentation and correlate with rising osmolarity. The most common reason patients

with HHS are brought to medical attention is a decreased level of responsiveness. Although there is substantial individual variation, confusion and lethargy are increasingly common as the effective osmolarity exceeds 320 mOsm/L, obtundation with an osmolarity of >340 mOsm/L, and coma with an osmolarity of >350 mOsm/L (7). Hyperosmolarity may also cause a variety of other neurologic signs and symptoms. Seizures, both focal and generalized, have been reported in 15% of cases (15). Focal weakness, aphasia, dysphagia, myoclonic jerks, and chorea may also occur. Neurologic findings may mimic an acute stroke, yet resolve with treatment of the HHS. Conversely, recrudescence of the signs of a prior stroke may occur during an episode of HHS, and an acute stroke may coexist with or precipitate HHS.

Nausea is common with HHS, but repeated vomiting and abdominal pain are less common with HHS than DKA, presumably because the ketosis is less severe. Prominent abdominal symptoms should prompt consideration of possible coexisting intra-abdominal pathology.

Major illnesses, most commonly infection but also myocardial infarction, stroke, pancreatitis, and other illnesses that provoke high levels of counterregulatory hormones and insulin resistance, are common precipitants of HHS (1). Pneumonia, urinary tract infection, and sepsis are the most common infections. Symptoms of a precipitating illness may dominate the clinical presentation, or may be difficult to discern due to altered mental status (AMS).

Medications such as corticosteroids, thiazide, and other diuretics and second-generation antipsychotics (particularly clozapine and olanzapine) can precipitate HHS (1). Reduced thirst and decreased water intake commonly contributes. Tube feedings and parenteral nutrition have also been implicated. Among patients with known diabetes, noncompliance with medications, failure to monitor blood glucose, and poor diabetes education can also contribute to the development of HHS.

DIFFERENTIAL DIAGNOSIS

There is significant overlap in the clinical and biochemical features of DKA and HHS. Depending on the criteria used and the population studied, one-third to one-half of patients have a mixed disorder with features of both conditions (6,16), either hyperosmolarity in patients who meet diagnostic criteria for DKA or mild ketoacidosis in patients whose presentation otherwise is consistent with HHS. The essential action is to exclude moderate-to-severe ketoacidosis in the setting of hyperglycemia. Patients with DKA tend to be younger, to have become ill more rapidly, and to demonstrate the signs and symptoms of ketoacidosis: nausea, vomiting, abdominal pain, rapid deep breathing, and an odor of acetone on the breath. The presence of 3 to 4+ ketonuria on urinalysis supports the diagnosis of DKA, so urinalysis should be performed early in the assessment. By definition, patients with HHS have a serum pH $\leq$7.3, a serum bicarbonate $>$18 mEq/L, and low levels of ketonemia and ketonuria. However, a mild anion gap metabolic acidosis is common in HHS, probably owing to the contributions of ketoacids, lactic acid, and renal insufficiency with accumulation of fixed acid metabolites. A venous or arterial blood gas (ABG) can exclude severe acidosis in the critically ill. The measurement of serum electrolytes and calculation of the anion gap is sufficient in less severely ill patients.

In addition to DKA, ketosis may result from any physiologic starvation state, including fasting, hyperemesis of pregnancy, and ketotic hypoglycemia. The causes of metabolic acidosis are numerous, including lactic acidosis and uremic acidosis (see Chapter 203). It is the simultaneous convergence of hyperglycemia, ketosis, and metabolic acidosis that establishes the diagnosis of DKA (Fig. 205.2). In the case of a patient known to have diabetes who presents with the typical signs and symptoms of the metabolic derangements of DKA, it is enough to establish the presence of hyperglycemia, ketosis, and acidosis to be confident of the diagnosis. In cases where the history is less definitive, particularly when there is a severe metabolic acidosis, it is important to consider alternative causes.

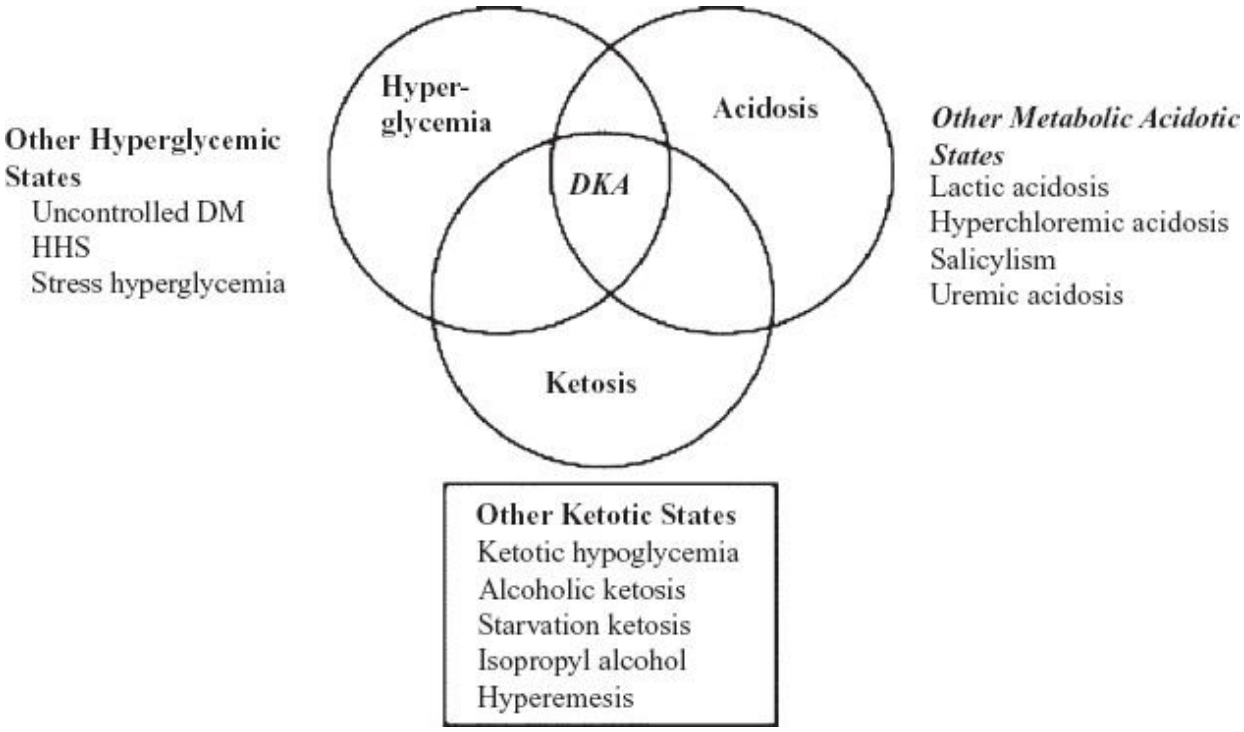

FIGURE 205.2 Differential diagnosis of diabetic ketoacidosis. (Adapted from Kitabchi AE, Fisher JN. Diabetes mellitus. In: Glew RA, Peters SP, eds. *Clinical Studies in Medical Biochemistry*. New York, NY: Oxford University Press; 1987:105.)

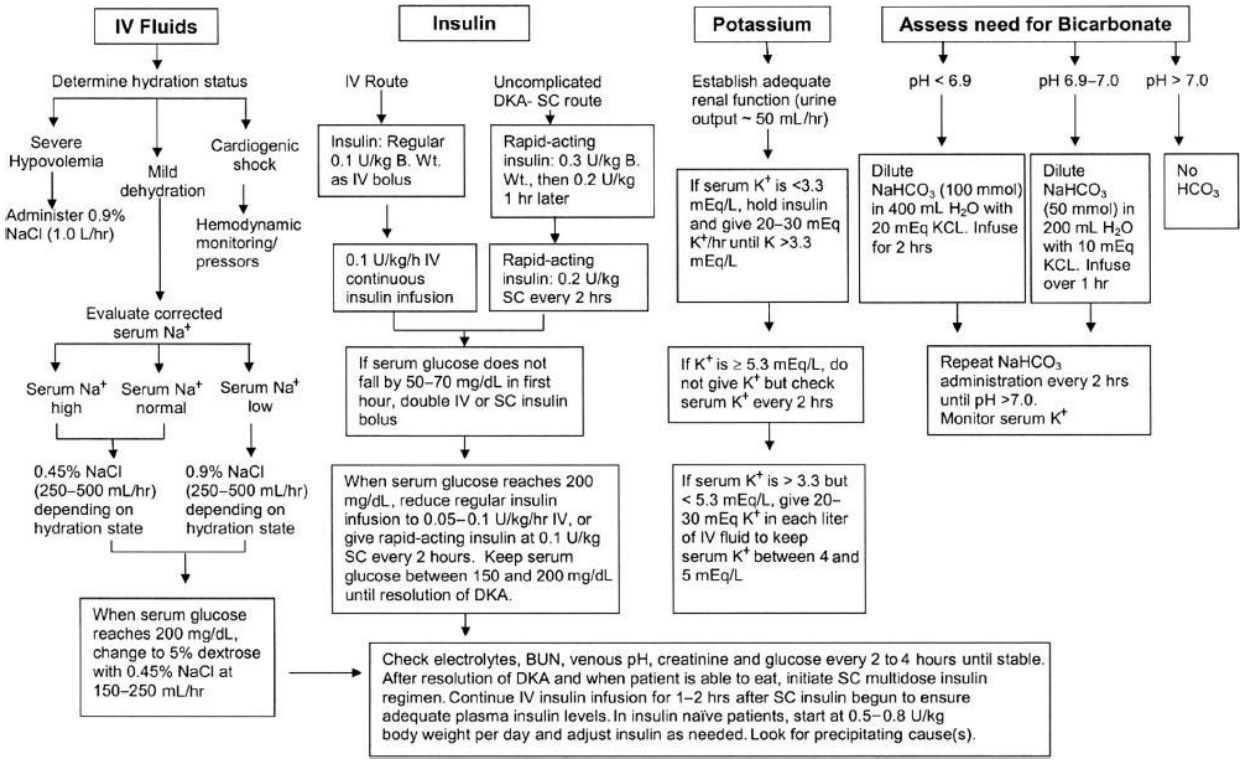

FIGURE 205.3 Management of DKA or HHS in adults. (Reproduced from Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care*. 2009;32(7):1335–1343.

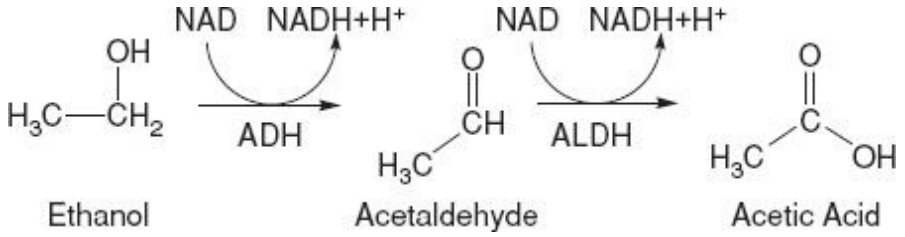

FIGURE 207.1 Alcohol is oxidized by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) to acetic acid, generating reduced NADH.

Alcoholic ketoacidosis (AKA) most closely resembles DKA but can usually be distinguished by history and the absence of the hyperglycemia typically present in DKA (see Chapter 207). Lactic acidosis arising from intra-abdominal pathology, and metabolic

acidosis resulting from toxic ingestions (salicylates, methanol, or ethylene glycol) are particularly important diagnoses to consider.

Because DKA and HHS are often precipitated by illnesses that result in high levels of stress hormones, an important consideration is whether a hyperglycemic crisis accounts for the entirety of the patient's condition or whether a concurrent acute condition is present. The coexistence of infection should be considered in essentially all patients in DKA and HHS; myocardial infarction should be considered in adults, and intra-abdominal pathology should be considered in all patients for whom abdominal complaints are prominent.

The differential diagnosis of the AMS that is typical of HHS, but may also occur with DKA, falls within the much broader differential diagnosis of AMS and decreased level of consciousness (see Chapter 11). The prompt measurement of a bedside glucose is appropriate for essentially all patients with AMS.

ED EVALUATION

Initial evaluation and management should begin simultaneously. If the patient appears critically ill, the ABCs (airway, breathing, and circulation) must be assessed and stabilized as electrocardiogram (ECG) and pulse-oximetry monitoring is begun. Oxygen administration can be guided by the physical assessment and pulse oximetry. Blood pressure should be measured, intravenous (IV) access should be established, and blood should be drawn for analysis. IV normal saline can be started if indicated by blood pressure, heart rate, and the brief physical assessment, if it is not contraindicated by a history of severe kidney disease or heart failure. A bedside blood glucose should be measured on any patient with AMS or in whom either hyper- or hypoglycemia is suspected. Only after these actions are rapidly initiated, which are appropriate for any seriously ill patient, should diagnosis-specific evaluation and treatment begin.

In many cases, a tentative diagnosis of a hyperglycemic crisis can be made within minutes of the patient's arrival. A history of diabetes, a bedside glucose >250 mg/dL, or both generally initiates the diagnostic investigation. Any patient with a history of diabetes

should be promptly questioned regarding medications, current adherence to the regimen, results of recent home glucose and urine-ketone monitoring, prior episodes of DKA or HHS, symptoms of DKA or HHS, self-treatment with oral fluids or additional insulin, and an estimate of oral fluid intake and urine output. In the setting of AMS, a baseline mental status and level of function should be determined. Eliciting a history of kidney or heart disease is also important to subsequent fluid management.

Because approximately 10% to 20% of cases of DKA and 30% to 40% of cases of HHS occur in patients without a history of diabetes, symptoms of a hyperglycemic crisis should be elicited from all patients whose presentation suggests the diagnosis. It is particularly important to try to identify the underlying precipitant, so that it can be addressed specifically, whether it is an infection, a myocardial infarction, a financial problem, a behavioral issue, or the failure of the caregiver to provide sufficient fluids to an immobile patient dependent on others for care. If the patient is unable to give the necessary history, other available sources, including family, caregivers, and paramedics, should be questioned.

A bedside glucose >250 mg/dL is highly sensitive but poorly specific for DKA. "Euglycemic DKA" has been described, but a presenting glucose was <180 mg/dL in only 1% of cases in a series of 722 consecutive episodes (17). A bedside glucose >500 mg/dL, particularly in the context of a history of diabetes, AMS, or both generally suggests HHS. On the other hand, most patients with an elevated glucose have uncontrolled diabetes and not a hyperglycemic crisis so additional evidence is necessary.

Hyperpnea in the presence of clear lungs and normal oxygen saturation support the diagnosis of DKA. The presence of level 3 to 4+ ketonuria on urinalysis greatly improves the specificity of the diagnosis (18), so urinalysis should be performed early in the assessment. In most cases, the history, physical examination, bedside glucose, and urine ketones are sufficient to guide therapy until lab results provide further confirmation. Newer alternative diagnostic strategies include use of venous blood gas electrolytes (19) and bedside measurement of capillary blood ketones using a ketone

meter (20). Both have acceptable sensitivity and specificity for initial screening, and available resources may dictate which modality is preferable at a given institution.

For many years, an ABG has been used to quickly establish the presence of acidosis. In DKA, the pH on a VBG and an ABG correspond closely, so a VBG may be substituted (21). An ABG is preferable only if there is concern for other conditions, such as ventilatory failure or salicylate intoxication, in which an arterial partial pressure of carbon dioxide (pCO_2) is useful. In less severely ill patients, the presence of the expected anion-gap metabolic acidosis of DKA can be determined using the serum bicarbonate and the calculated anion gap [$Na^+ - (Cl^- + HCO_3^-)$], and a blood gas is unnecessary.

Although a tentative diagnosis of HHS can often be inferred at the bedside, the diagnosis can be confirmed only on the basis of the biochemical data. In addition to hyperglycemia >600 mg/dL, the definition of HHS requires an *effective* serum osmolality >320 mOsm/kg (see Table 205.1). Osmolarity in mOsm/L is often calculated using the following formula: 2[Na (mEq/L)] + [glucose (mg/dL)]/18 + [BUN (mg/dL)]/2.8, with a normal value of 290 ± 5. This calculation includes urea, which diffuses freely across cell membranes and, therefore, does not create an osmotic gradient between the intracellular and extracellular spaces nor contribute to the pathogenesis of HHS (16). The calculated *effective* osmolarity excludes urea from the calculation: effective osmolarity (mOsm/L) = 2[Na (mEq/L)] + [glucose (mg/dL)]/18, with normal being 285 ± 5. With normal renal function, the contribution of the blood urea nitrogen (BUN) to osmolarity is small, and the difference between osmolarity and effective osmolarity is insignificant.

The initial laboratory evaluation should include STAT measurement of electrolytes, urea nitrogen, creatinine, glucose, serum osmolarity, serum ketones, and a urinalysis. The mean serum glucose of patients with HHS has been reported to be 930 mg/dL, which is much greater than the maximum measurable by a bedside glucose meter (~600 mg/dL), so the value must be confirmed by laboratory measurement (6). The anion gap should be calculated:

anion gap = [Na^+ − (Cl^- + HCO_3^-)]. The normal is 7 to 9 mEq/L. Serum magnesium, calcium, and phosphate are often measured but are less immediately essential.

Because of the simultaneous loss of water and electrolytes, admission laboratory data (Table 205.4) may not fully reflect the deficits. The osmotic diuresis and dehydration of DKA and particularly HHS may cause hypernatremia, but this may not be apparent from the measured serum sodium concentration. Hyperglycemia causes water to move from the intracellular into the extracellular space, thereby reducing the measured sodium concentration by dilution. This effect resolves as the hyperglycemia is corrected. It is common practice to "correct" for this dilutional effect by adding a factor of 1.6 to 2.4 mEq to the reported sodium concentration for every 100 mg of glucose >100 mg/dL. The corrected serum sodium is commonly used to guide fluid therapy. Dehydration also results in poor renal perfusion, which is reflected in an elevated BUN and creatinine. Also, underlying chronic renal insufficiency is common in HHS patients and older adult DKA patients.

TABLE 205.4
Typical Admission Biochemical Data in Patients Who Have Hyperglycemic Hyperosmolar Syndrome and Diabetic Ketoacidosis

Laboratory Test	HHS	DKA
Glucose (mg/dL)	930 ± 83	616 ± 36
Na^+ (mEq/L)	149 ± 3.2	134 ± 1.0
K^+ (mEq/L)	3.9 ± 0.2	4.5 ± 0.13
BUN (mg/dL)	61 ± 11	32 ± 3
Creatinine (mg/dL)	1.4 ± 0.1	1.1 ± 0.1
pH	7.3 ± 0.03	7.12 ± 0.04
Bicarbonate (mEq/L)	18 ± 1.1	9.4 ± 1.4
BOHB (mmol/L)	1.0 ± 0.2	9.1 ± 0.85
Total osmolality (mOsm/kg)	380 ± 5.7	323 ± 2.5
Anion gap	11	17

Data are presented as mean ± SEM.
HHS, hyperglycemic hyperosmolar syndrome, DKA, diabetic ketoacidosis.
Adapted from Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care*. 2001;24:131–153.

Urine and serum ketones aid in distinguishing HHS from DKA. The direct measurement of the serum β-hydroxybutyrate, the predominant ketone in DKA, is preferred over the older nitroprusside test. The nitroprusside test provides a semiquantitative estimate of acetoacetate and acetone but does not measure β-hydroxybutyrate, resulting in an underestimation of the severity of ketoacidosis.

A complete blood count (CBC) is routinely ordered, often with the intent of using the white blood cell count (WBC) to determine if infection is present. Unfortunately, an elevated WBC is typical in hyperglycemic crises. In DKA, only a WBC $>25{,}000$ or an elevated band neutrophil count has been shown to support a diagnosis of infection (22). A chest radiograph, urinalysis, blood and urine cultures, and sometimes a lumbar puncture are appropriate to evaluate for infection in HHS and in cases of DKA where infection is suspected as a precipitant or a comorbidity. Hemoconcentration can be expected to elevate the hemoglobin and hematocrit.

Additional laboratory testing should be individualized:

- An ECG is indicated if hyper- or hypokalemia, a dysrhythmia, or an acute coronary syndrome is suspected. A serum troponin is appropriate for select patients.
- The ordering of urine and blood cultures should be based on a reasonable suspicion of infection in cases of DKA, but is routine

when evaluating the typically elderly patient presenting in HHS.
- Chest radiography is only indicated if pulmonary or cardiac disease is suspected in DKA, but is almost uniformly indicated in HHS.
- The serum amylase and lipase are frequently elevated in DKA, even in the absence of clinical pancreatitis. Abdominal computed tomography (CT) findings correlate much better with clinical outcomes, making CT the test of choice for patients with severe or persistent abdominal pain. Intravenous contrast should generally be avoided.
- CT scan of the brain is indicated if there is AMS or focal neurologic abnormalities.
- A liver profile and toxicologic studies are sometimes useful.

KEY TESTING

- Bedside glucose (Accucheck)
- Urinalysis
- VBG or ABG
- Basic metabolic profile including electrolytes, BUN, creatinine, glucose
- CBC
- Serum ketones
- Serum osmolarity

ED MANAGEMENT

The management of hyperglycemic crises is directed at correction of the metabolic derangements and treatment of comorbidities (Fig. 205.3). Although the specifics of the individual patient's presentation should guide fluid, electrolyte, and insulin therapy, adherence to written protocols decreases variability of care and improves patient outcomes. Published protocols for the management of hyperglycemic crises are broadly available and have been adopted by many hospitals and health care organizations.

DIABETIC KETOACIDOSIS

Although the components of therapy remain the same across the spectrum of DKA, the aggressiveness of treatment depends on the severity. Patients in severe DKA typically require rapid infusion of large volumes of fluids and IV insulin. At the other end of the spectrum, patients with mild DKA may do well with only oral rehydration and subcutaneous (SC) insulin.

Fluid deficits average 6 L in DKA, making rehydration an essential first step. A liter of normal saline (0.9% NaCl) should be infused in 30 to 60 minutes. For most patients, the first liter should be followed by an additional 1 to 2 L of normal saline (0.9% NaCl) during the next 2 to 4 hours, with the infusion rate dictated by the patient's homodynamic stability and response to therapy, as reflected by the vital signs and urine output (1). This fluid restores circulating volume and tissue perfusion, which decreases circulating counterregulatory catecholamines and begins to reduce serum glucose and osmolality by restoring an osmotic diuresis. Water deficits are typically greater than the corresponding sodium and chloride deficits, so it is appropriate to change to 0.45% NaCl at 250 mL/hr after the initial 2 to 3 L saline infusion as blood pressure, pulse, and signs of tissue perfusion normalize. Patients found to have hypernatremia should be changed to 0.45% NaCl when the serum sodium results are obtained. This usually occurs after the first liter of normal saline has already infused. When the glucose has decreased to $<$250 mg/dL, IV fluids should be changed to dextrose 5% in 0.45 NaCl (D_5 0.45 NaCl) to prevent hypoglycemia. The infusion rate can be further reduced once the patient begins to drink, provided there is a brisk urine output and the metabolic derangements are resolving. The remaining fluid deficits are corrected in 1 to 2 days.

All patients should be reassessed frequently during treatment. The need for adequate fluid replacement must be balanced against the risk of volume overload, and particular caution is warranted in the elderly and patients with cardiac or renal compromise. Fluid management in pediatric DKA is controversial and is typically less aggressive than in adults (see Chapter 274). This caution is caused by concerns about clinically significant cerebral edema, which occurs in

approximately 0.7% to 1% of pediatric DKA episodes, but is rare in adults.

Insulin inhibits ketogenesis independent of its effects on glucose production and utilization and is essential for the correction of ketoacidosis and hyperglycemia. Treatment goals are the inhibition of ketone production and correction of hyperglycemia at a rate of 50 to 75 mg/hr. Although there are recent reports of the successful use of SC rapid-acting insulin (23) and intramuscular insulin was used in the past, IV insulin is preferred for the treatment of moderate to severe DKA. IV insulin provides predictable and titratable insulin levels. SC insulin, which is adequate for mild DKA, may be poorly absorbed in the setting of severe dehydration and hypotension. Patients using an insulin pump should remove the device when being treated with IV insulin.

Once hydration has begun, physiologic doses of insulin (regular insulin at 1 to 5 U/hr IV) are generally all that is required. Higher doses of 10 to 15 U/hr or more may be necessary in the setting of infection or other states in which there are high levels of counterregulatory hormones. Because of this variability, the recommended initial insulin-infusion rate is 0.1 U/kg/hr. If the decline in serum glucose is <50 mg/dL/hr, the insulin-infusion rate may be doubled.

Guidelines for the care of adult patients with DKA recommend an initial bolus of regular insulin 0.1 U/kg IV (1). On the other hand, pediatric guidelines no longer recommend an initial bolus, citing concern about excessively rapid correction of serum glucose (>100 mg/dL/hr) and osmolarity (>3 mOsm/kg/hr), and a potential increased risk of cerebral edema. If no insulin bolus is to be given to an adult patient, data suggest that a slightly higher insulin infusion rate of 0.14 U/kg/hr may reduce the number of patients who require supplemental insulin to achieve the target rate of decrease in glucose levels (24). Whether this is sufficient ground to justify either an initial bolus or a higher infusion rate is controversial. Insulin should be withheld until hypokalemia ($K^+ <3.3$ mEq/L) has been excluded. If hypokalemia is noted, an insulin bolus should be not be given and

the insulin infusion should be delayed until correction of the serum potassium is under way.

Ketonemia typically takes longer to resolve than hyperglycemia. To correct ketosis and avoid hypoglycemia, it is typically necessary to simultaneously infuse insulin and glucose. Protocols vary in the specifics of how this should be done, but it is common to change the IV fluids to dextrose 5% in 0.45 NaCl (D_5 0.45 NaCl) at 150 to 200 mL/hr when the blood glucose decreases to <250 mg/dL, and continue the insulin infusion at the same or a reduced rate of 0.5 U/kg/hr. It may be necessary to temporarily suspend insulin infusion to avoid impending or actual hypoglycemia, but prolonged withdrawal of insulin should be avoided since it almost invariably results in relapse of DKA.

Standard criteria for the resolution of DKA are a glucose <200 mg/dL, and two of the following: a serum bicarbonate ≤ 15 mEq/L, a venous pH >7.3, or an anion gap <12 mEq/L (1). Once DKA has resolved and the patient is able to eat, SC insulin is started. Patients should receive both long-acting (basal) insulin and rapid- or short-acting insulin given before meals or restarted on their insulin pump. The prior insulin dose, if known, provides a basis for restarting SC insulin, with the dose, time of administration, and caloric intake matching the patient's usual pattern. If the prior dose is unknown or if the patient was not previously on insulin, consultation with the physician who will be providing ongoing care is indicated.

A multiple daily-insulin regimen, using a basal/bolus approach of rapid-acting premeal insulin (aspart [NovoLog], lispro [Humalog], or glulisine [Apidra]) plus a basal insulin (glargine [Lantus] or detemir [Levemir]), or use of continuous SC insulin infusion (CSII or insulin pump therapy) with rapid-acting insulin is now common. Regular insulin plus neutral protamine Hagedorn (NPH) insulin, which is less expensive but may cause more hypoglycemia, is an alternative. To ensure adequate insulin levels and avoid relapse, SC insulin should be administered before stopping IV insulin. A delay of 30 to 60 minutes is recommended when using aspart or lispro insulin and 1 to 2 hours when administering regular insulin.

Most, but not all, patients with DKA are potassium-depleted, and deficits of 2 to 5 mEq/kg are common. The initial serum potassium is usually elevated, caused by acidosis and insufficient insulin effect, both of which result in intra- to extracellular potassium shift. Administration of IV fluids and insulin cause a decline in the serum potassium, caused by dilution, diuresis, and cellular uptake. To avoid serious symptomatic hypokalemia with dysrhythmias and respiratory-muscle weakness, insulin should not be administered until the potassium is known to be >3.5 mEq/L. IV potassium replacement is indicated for all DKA patients whose potassium is <5.3 mEq/L and who are urinating >50 mL/hr. A replacement rate of 10 mEq/hr is often sufficient to maintain a serum potassium of 4 to 5 mEq/L, but higher rates are indicated for a potassium level <3.5 mEq/L or when treating symptomatic hypokalemia. Patients who have consumed large amounts of potassium or who are in renal failure may not be potassium-depleted and may present with severe hyperkalemia. For this reason, potassium should generally not be administered until the serum potassium is known and the patient is urinating.

Three mechanisms contribute to the resolution of acidosis in DKA: (a) the suppression of the ketogenesis by insulin, (b) the diuresis of ketoacids via hydration, and (c) the oxidation of ketoacids by skeletal muscle, brain, and kidneys. Additionally, hyperventilation-induced respiratory alkalosis is an important compensatory mechanism. There is no clear evidence that the administration of sodium bicarbonate improves outcome even in severe DKA in adults or children. Bicarbonate corrects the arterial acidosis but not the intracellular or central-nervous-system acidosis. Bicarbonate also decreases tissue oxygen uptake, exacerbates hypokalemia, and is an osmolar load, thereby potentially contributing to the development of cerebral edema. It is broadly agreed that bicarbonate has no role in the management of mild to moderate DKA, and its use in severe DKA is controversial (1,25). If, despite these concerns, bicarbonate is administered, it should be diluted and administered as an infusion, not given in bolus injections.

Like potassium, phosphate is lost with the osmotic diuresis, so that patients in DKA have a phosphate deficit despite normal or increased initial serum levels. The deficit only becomes apparent if the phosphate is rechecked during the course of therapy. Eating replenishes phosphate, and randomized trials of IV phosphate replacement have not demonstrated benefit (1). Rapid administration of phosphate can cause hypocalcemia. Nonetheless, phosphate replacement is widely recommended in severe (1 mg/dL) or symptomatic hypophosphatemia. If it is to be given, potassium phosphate 20 to 30 mEq should be administered slowly in a dilute solution.

Infections, principally pneumonia, urinary tract infections, and sepsis, complicate approximately 35% of episodes of DKA. Other serious acute medical illnesses, including myocardial infarction and stroke, complicate an additional 15% of episodes. Comorbidities may precipitate DKA or be a consequence of its metabolic derangements. In either case, these conditions increase morbidity and mortality in DKA, and their effective management is essential.

The management of DKA in patients with renal failure is particularly difficult. Hyperglycemia and ketoacidosis may be severe even though fluid and electrolyte deficits are minimal or absent. Hemodialysis is often the only effective way to correct these abnormalities. The nephrology service should be consulted and arrangements should be made for hemodialysis in an ICU setting as soon the patient is recognized to have simultaneous renal failure and DKA.

Monitoring is an important component of the management of DKA, and is facilitated by using standardized protocols and flow sheets. Vital signs, fluid balance (IV fluid administration and urine output), insulin and other therapeutic interventions, and serial laboratory studies should be recorded. Glucose and potassium should be measured every 1 to 2 hours, and sodium and bicarbonate should be measured every 2 to 4 hours. There is generally no need to repeat serum ketones or blood gases after the initial assessment, if the patient is improving. Magnesium and phosphate should be assessed 4

to 8 hours after initiating therapy. If phosphate is given, calcium should be rechecked after treatment.

Most of the complications of the treatment of DKA are predictable and largely preventable. Hyperchloremic metabolic acidosis is frequently noted during treatment, but is generally clinically insignificant. Hyperchloremic metabolic acidosis can be minimized by switching the IV fluids to 0.45 NaCl after replenishing the intravascular space with normal saline. Hypokalemia can be minimized by replacing potassium aggressively, omitting an insulin bolus if the potassium is low, and avoiding bicarbonate. Hypoglycemia can be avoided by changing to D_5 0.45 NaCl when the glucose declines to <250 mg/dL. Fluid overload can be prevented by monitoring fluid balance and frequently reassessing the patient.

Neurologic deterioration during treatment of DKA, particularly in children, should prompt consideration of cerebral edema. Diminishing the risk of DKA-associated cerebral edema is problematic because the mechanism is complex and prevention strategies have not been prospectively validated. Nonetheless, the incidence of cerebral edema can probably be reduced and outcomes can be improved when it occurs by correcting hyperosmolarity slowly, monitoring mental status, and treating aggressively when cerebral edema is recognized. A confirmatory brain CT should not delay therapy.

HYPEROSMOLAR HYPERGLYCEMIC STATE

The management of HHS is directed at the replacement of fluids and electrolytes, the correction of hyperglycemia at a rate of 50 to 75 mg/hr, correction of hyperosmolarity at a rate not to exceed 3 mOsm/kg/hr, and the treatment of comorbidities. As noted previously, the ABCs should be assessed and stabilized as monitoring is initiated, vital signs measured, intravenous access established, and blood drawn for laboratory studies including bedside measurement of the blood glucose.

Fluid deficits average 9 L in HHS, making rehydration an essential first step. A liter of normal saline (0.9% NaCl) should be infused over an hour unless known congestive heart failure or severe renal

insufficiency dictate more cautious administration. Expansion of the intravascular volume with normal saline diminishes the serum glucose and osmolarity by dilution and reinitiates the osmotic diuresis curtailed by severe dehydration and poor renal perfusion. Patients who remain hypotensive after the first liter of fluid should continue to receive normal saline (0.9% NaCl), with the infusion rate dictated by the patient's response to therapy, as reflected by the vital signs and urine output. Fluid administration after the stabilizing resuscitation should be guided by the corrected serum sodium. Intravenous fluids should be changed to 0.45% NaCl for patients whose corrected serum sodium is normal or elevated. Patients who are hyponatremic should continue to receive 0.9% NaCl. When the glucose decreases to <300 mg/dL, intravenous fluids should be changed to D_5 0.45 NaCl to prevent hypoglycemia and a too-rapid decline of osmolarity.

The goal of fluid therapy is to replace half of the fluid deficit over 12 to 24 hours and the remainder over the next 24 hours. Even after an initial infusion of 1 to 2 L, subsequent infusion rates of 250 to 500 mL/hr are necessary to achieve this goal. The infusion rate can be reduced once the patient begins to drink if there is brisk urine output and the metabolic derangements are resolving. As with DKA, fluid management in pediatric HHS is less aggressive than in adults. This is due to concerns about clinically significant cerebral edema, which has been described as a complication of HHS in children.

Patients with HHS are typically significantly potassium depleted, with deficits commonly in the range of 4 to 6 mEq/kg. The initial serum potassium level, however, is usually normal or elevated. This is due to the relative insulin deficiency and mild metabolic acidosis that are often present in HHS, both of which result in intra- to extracellular potassium shift.

Administration of intravenous fluids and insulin cause a decline in the serum potassium and phosphate owing to dilution, diuresis, and cellular uptake. The ADA recommends managing potassium and phosphate in HHS according to the same guidelines used for DKA.

Insulin therapy should not be initiated until fluid resuscitation is well under way and the serum potassium is known. In HHS,

hyperglycemia and hyperosmolarity result in the net movement of water into the extracellular space, maintaining intravascular volume despite severe dehydration. Insulin administration results in the intracellular shift of both glucose and, with the resulting decline in extracellular osmolarity, water. Fluid therapy alone will result in decline of glucose averaging 25 to 50 mg/dL/hr and up to 200 mg/dL/hr, often achieving the target goals for the resolution of hyperglycemia and hyperosmolarity. The optimal insulin regimen in HHS has not been definitively determined. In the absence of definitive data, the ADA recommends the same insulin regimen for HHS as DKA.

Infections, principally pneumonia, urinary tract infections, and sepsis, complicate approximately half of HHS episodes, and it is appropriate to have a low threshold for initiating broad-spectrum antibiotics in the emergency department. Other serious acute comorbidities to consider include myocardial infarction and stroke.

Monitoring is also an important component of the management of HHS. Standardized protocols and flow sheets improve outcomes in DKA, and similar benefit is likely with HHS.

As with DKA, the complications of the treatment of HHS are predictable and largely preventable. Fluid overload is a potential complication of fluid replacement, particularly in patients with pre-existing heart failure or renal insufficiency. Patients should be reassessed frequently, and the need for adequate fluid replacement must be balanced against the risk of fluid overload. Particular caution is warranted in the elderly and patients with cardiac or renal compromise. Careful monitoring of fluids infused, urine output, vital signs, and laboratory parameters is essential. Hypokalemia can be minimized by replacing potassium aggressively and electing not to give an insulin bolus if the potassium is low. Hypoglycemia can be avoided by changing to D_5 0.45 NaCl when the glucose declines to $<$250 to 300 mg/dL. HHS-associated cerebral edema is managed in the same manner as DKA-associated cerebral edema.

CRITICAL INTERVENTIONS

- Assess and stabilize ABCs.

- Check a bedside glucose on all patients with AMS.
- Promptly begin aggressive fluid replacement, typically 2 L in the first 4 hours for DKA; fluid replacement can be more moderate in HHS, particularly in the presence heart failure or moderate to severe kidney disease.
- Provide sufficient potassium replacement, beginning when the patient is making urine and the serum potassium is ≤ 5.3 mEq/L for DKA.
- Avoid hypoglycemia and an excessive decline in osmolarity by changing IV fluids to D_5 0.45 NaCl when the serum glucose declines to 250 mg/dL.
- Maintain continuous insulin infusion until the anion gap is normal for DKA patients.
- Identify and treat comorbidities and precipitants.
- Monitor frequently until hyperglycemic crisis resolves and the patient resumes routine medications and is eating and drinking normally.

DISPOSITION

Patients with severe DKA, as indicated by pH <7.1, hypotension, anuria, coma, or need for intubation, should be admitted to an intensive care unit (ICU). Serious comorbidities and age >65 years increase mortality and should lower the threshold for ICU admission.

Location in the hospital for a patient with DKA often depends on where an insulin drip can be given and whether or not frequent monitoring of blood glucose levels is possible outside of an ICU setting. A monitored bed is appropriate for patients with moderate DKA and patients whose DKA was initially severe but has improved with ED therapy. A floor bed is appropriate only for patients whose episode is minor or has almost fully resolved. Patients whose DKA was initially only mild or moderate and was resolved in the ED may be considered for discharge home, if there are no important comorbidities. Safe discharge depends not only on the resolution of the metabolic derangements and the absence of ongoing precipitants

but also on the patient's level of competence for self-care, the available social support, and the availability of close follow-up.

Patients with severe HHS, as indicated by a decreased level of consciousness, seizures, hypotension, or hypothermia, should also be admitted to an ICU. A monitored bed setting is appropriate for awake patients with moderate HHS and for those in whom HHS has substantially improved with ED therapy. A floor bed is appropriate only for patients whose episode has almost fully resolved. Comorbidities should be considered when selecting a level of care. Patients with serious infections, cardiac or renal disease generally require an ICU admission.

Because of the need for immediate and closely monitored treatment for at least 24 hours, it is usually preferable to avoid transfer of hyperglycemic crises patients to another facility until after the metabolic derangements have been substantially corrected and any serious underlying illness has been fully stabilized.

Common Pitfalls

- Failure to check a bedside glucose on all patients with AMS.
- Failure to give adequate volumes of appropriate fluids, starting with 1 L of normal saline in the first hour for adult patients.
- Failure to give adequate IV insulin in severe DKA (0.1 to 0.14 U/kg/hr).
- Failure to manage potassium appropriately, either by administering insulin in the setting of hypokalemia, failing to adequately replace potassium as hypokalemia develops, or administering excessive potassium to patients who are anuric.
- Failure to monitor the blood glucose frequently and to switch to glucose-containing IV fluids when the blood glucose level declines to <250 mg/dL.
- Reliance on sodium bicarbonate to correct the acidosis of DKA.
- Failure to search for and treat precipitating causes and other comorbidities.

ACKNOWLEDGMENT

The authors gratefully acknowledge the contributions of Abbas E. Kitabchi to the content of this chapter.

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CHAPTER 206 Hypoglycemia

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The *clinical syndrome* of hypoglycemia is defined as a low plasma glucose value (usually <55 mg/dL) accompanied by signs and symptoms of adrenergic excess (sweating, nervousness, tachycardia, shakiness) or alterations in mental status (or both) that are relieved by the administration of carbohydrate. The more recent realization that asymptomatic plasma glucose levels of 65 to 70 mg/dL impair defenses against subsequent more severe hypoglycemia in patients with diabetes mellitus has resulted in the broadening of the definition of hypoglycemia to a glucose level of <70 mg/dL (1). This definition, which includes both symptomatic and asymptomatic patients, is intended to include everyone for whom there is potential harm from the low glucose level. The glucose concentration at which *clinical* hypoglycemia occurs varies. Completely healthy women may have glucose levels <45 mg/dL during a fast without symptoms of hypoglycemia. Conversely, adrenergic symptoms of "hypoglycemia" may occur in patients without low blood glucose levels. Therefore, though the diagnosis of the clinical syndrome of hypoglycemia must be based on the presence of both biochemical hypoglycemia and concomitant hypoglycemic symptoms, physicians should be aware that glucose values of 55 to 70 mg/dL have important implications for patients with diabetes.

A balance between glucose utilization and production maintains normal blood glucose levels. In healthy individuals, preprandial blood glucose levels are usually 70 to 100 mg/dL, with a small postprandial rise peaking 1 hour after eating and returning to baseline within 4 hours. The major glucose-requiring tissues are the

brain and red blood cells. Muscle, fat, and a variety of other tissues take up glucose but are also capable of utilizing other fuels. The brain, with its absolute requirement for glucose, is what drives the need to maintain adequate blood levels of glucose. During fasting, glucose production occurs through hepatic glycogenolysis (breakdown of glycogen) and gluconeogenesis (biosynthesis of glucose from nonglucose substrates). Insulin levels are high in the postprandial period and fall with fasting.

Glucoreceptors in the hypothalamus sense low blood glucose levels and cause the secretion of counterregulatory hormones. Glucagon is the primary counterregulatory hormone in nondiabetic patients. Patients with established type 1 diabetes (T1DM) or advanced type 2 diabetes (T2DM) lose their glucagon response to hypoglycemia (2).

The onset of action of glucagon is rapid, and it acts by enhancing glycogenolysis and gluconeogenesis. If glucagon is not present, epinephrine serves as the major counterregulatory hormone. Epinephrine also has a rapid onset of action and acts by inhibiting glucose utilization by muscle, increasing gluconeogenesis, and inciting carbohydrate ingestion (2). Cortisol and growth hormone are secreted as part of normal hypoglycemic counterregulation, but their release is delayed, and they do not contribute to the acute recovery from hypoglycemia.

Although there are many causes of hypoglycemia, the vast majority of episodes encountered in the emergency department (ED) occur as complications of the treatment of diabetes with insulin, sulfonylureas, or meglitinides. Hypoglycemia is an important and growing concern for the approximately 26 million individuals with diabetes in the United States. The Diabetes Treatment and Control Trial (3) in 1993 and the United Kingdom Prospective Diabetes Study (4) in 1998 found that tight control of blood glucose delays the development and progression of microvascular complications in patients with both type 1 and type 2 diabetes, and 7- to 10-year follow-up from these studies has shown a reduction in cardiovascular events as well. From these and subsequent studies came a greater emphasis on maintaining tight glycemic control.

Unfortunately, tight glycemic control also increases the frequency of hypoglycemia, especially in patients treated with insulin (5,6). More recent data suggest that hypoglycemia increases the risk of cardiovascular death, potentially negating the benefits of tight control. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial published in 2008 demonstrated an increased risk of death from any cause and cardiovascular events in the intensively treated patients (7). The higher rate of death in the tight control group was possibly due to the increased use of insulin, very low HbA1c target (<6.0%), and higher rates of hypoglycemia. On the basis of these data and subsequent trials, it is reasonable to conclude that patients at highest risk for cardiovascular death (e.g., older, longer duration of diabetes, existing cardiovascular disease [CVD], or high risk for CVD) may not benefit from intensive therapy, and treatment should be individualized (8).

Goals for emergency physicians in the diagnosis and management of hypoglycemia are:

1. Recognition of each episode of hypoglycemia
2. Prompt and adequate treatment
3. Identification of the cause of the episode
4. Identification of the need for hospital admission to prevent recurrent episodes
5. Establishment of a plan to prevent future episodes for patients being discharged from the ED

CLINICAL PRESENTATION

The signs and symptoms of hypoglycemia fall into two categories: Adrenergic (those caused by increased activity of the sympathetic autonomic nervous system) and neuroglycopenic (those caused by depressed activity of the central nervous system [CNS]; Table 206.1). Although there is much individual variation, the adrenergic symptoms of hypoglycemia typically start as the blood glucose falls below 70 mg/dL, and evidence of neuroglycopenia occurs as the blood glucose falls below 55 mg/dL. Symptoms vary from person to person but, within an individual, remain fairly constant from episode to episode.

TABLE 206.1
Signs and Symptoms of Hypoglycemia

Adrenergic	Neuroglycopenia
Weakness	Headache
Tremor	Mental dullness
Sweating and warmth	Confusion
Tachycardia and palpitations	Amnesia
Nervousness	Incoordination
Irritability	Visual disturbances
Tingling of face and fingers	Seizures
Hunger	Coma
Nausea	Focal neurologic deficits

Patients may not experience the adrenergic symptoms of hypoglycemia (2). Patients who are recurrently hypoglycemic, particularly patients with tightly controlled T1DM or advanced T2DM, may not have symptoms until the blood glucose is <50 mg/dL and neuroglycopenic symptoms develop. This phenomenon, termed *hypoglycemia-associated autonomic failure* (HAAF), is the combined result of a downregulation of the adrenomedullary and sympathetic neural responses to hypoglycemia, owing to intensive insulin therapy or recent hypoglycemia (2,9). HAAF can develop in patients without symptomatic hypoglycemia as a result of glucose levels of 55 to 70 mg/dL. Patients who lack adrenergic symptoms often fail to recognize impending hypoglycemia and are at increased risk for severe neuroglycopenia. In many patients with HAAF, the epinephrine response to hypoglycemia can be restored by the careful avoidance of hypoglycemia for as little as 2 to 3 weeks (9). Because the CNS is almost entirely glucose-dependent for function, hypoglycemia manifests neurologically within minutes. Measurable cognitive deficits commonly begin at blood glucose levels <55 mg/dL, but some patients remain awake and alert at much lower levels (10). Patients may fail to perceive their cognitive dysfunction and deny having any CNS symptoms. The blood glucose at which seizures occur varies, but a seizure at a glucose of >40 mg/dL should prompt investigation for an alternative cause. Focal

neurologic deficits, including hemiparesis, are the presenting symptoms in a small percentage of patients (11).

Mild episodes of hypoglycemia (defined as episodes recognized and treated by the patient) consisting only of adrenergic symptoms should not dissuade patients from adequately treating their diabetes. On the other hand, recurrent severe episodes (involving altered mentation and requiring assistance to treat), particularly those resulting in loss of consciousness or seizures, may be associated with cumulative cognitive impairment in children (12) and adults (13).

Time to recovery and completeness of recovery depend on the severity and duration of hypoglycemia. Young children, the elderly, and patients with a history of prior brain injury, such as a stroke, appear to be at higher risk for a prolonged or incomplete recovery. Although not every episode of severe hypoglycemia will result in measurable cognitive decline, the potential for permanent injury mandates prompt diagnosis and treatment.

DIFFERENTIAL DIAGNOSIS

Although chronic treatment of diabetes with insulin, a sulfonylurea agent, or both is the root cause of the vast majority of hypoglycemic episodes encountered in the ED, there is invariably an acute precipitant perturbing the patient's usual glucose homeostasis. The key to preventing future hypoglycemic episodes is the identification of the precipitant of the current episode. A good history is the principal tool in achieving this goal and will identify the precipitant in approximately 50% of cases. Common precipitants can be grouped according to their physiologic mechanisms (Table 206.2). Inadequate glucose availability is the most commonly identified cause of hypoglycemia, followed by increased caloric utilization, medication error, and diminished excretion of a glucose lowering medication. Recurrent asymptomatic or minimally symptomatic hypoglycemia and the resultant HAAF are important risk factors for severe hypoglycemia (1,2,9).

TABLE 206.2
Precipitants of Hypoglycemia in Patients with Diabetes

Inadequate Glucose Availability

Decreased caloric consumption: Missed or delayed meal, fasting

Decreased hepatic gluconeogenesis: Suppression by alcohol, hepatic failure

Insufficient counterregulatory hormones: Glucagon, epinephrine, cortisol

Increased Caloric Utilization

Exercise

Illness and injury

Medications—Increased Insulin Effect

Accidental overdose: Poor vision, misunderstanding, change in syringe size, change in insulin concentration, pharmacy error

Intentional overdose

Diminished Excretion or Metabolism

Renal insufficiency: Insulin and sulfonylurea agents undergo renal excretion

Hepatic failure: Sulfonylurea agents undergo hepatic metabolism

Patients who take oral sulfonylurea agents can have prolonged periods of hypoglycemia (sometimes lasting up to a week) because of the long elimination half-life of many of these agents; this phenomenon occurs particularly in elderly patients and those with kidney disease or heart failure (14). The possibility of declining renal function should be assessed in any patient who develops recurrent or unexplained episodes of hypoglycemia while taking these agents. These individuals often require admission to the hospital. In addition, ingestions of even small doses of sulfonylurea agents may produce severe hypoglycemia in young nondiabetic children, and any sulfonylurea ingestion in these patients should be taken seriously (15).

The remaining antidiabetic agents vary in their propensity to cause hypoglycemia. The meglitinides repaglinide and nateglinide are short-acting insulin secretagogues that increase insulin secretion and may cause hypoglycemia. The hypoglycemia associated with these agents is of shorter duration than the hypoglycemia associated with the sulfonylurea agents; nevertheless, repaglinide and nateglinide can cause severe symptoms (e.g., seizure) if given after, instead of before, a meal (16).

Pramlintide, a synthetic analog of the human hormone amylin, suppresses postprandial glucagon secretion, slows gastric emptying,

and promotes satiety. Used in combination with insulin in type 1 and type 2 diabetes, it increases the risk of severe hypoglycemia if the premeal insulin dose is not appropriately reduced. Therefore, in all patients starting pramlintide, the instructions in the packet insert should be followed and premeal insulin doses reduced by 50%.

Conversely, metformin; the α-glucosidase inhibitors (acarbose and miglitol), the thiazolidinediones (rosiglitazone and pioglitazone); and the dipeptidyl peptidase IV (DPP-4) inhibitors (sitagliptin, saxagliptin, linagliptin, and alogliptin) rarely cause hypoglycemia when used alone. In combination with insulin or a sulfonylurea, however, these drugs may exacerbate an episode of hypoglycemia. Glucagon-like peptide (GLP-1) receptor agonists (short- and long-acting exenatide and liraglutide) are used solely as an adjunct to other antidiabetic medications. GLP-1 receptor agonists increase the risk of hypoglycemia when used with a sulfonylurea agent or insulin, but only rarely in conjunction with metformin.

Owing to frequent miscommunication among patients, pharmacists, and medical care providers about the currently available types of insulin, it is necessary to be familiar with these products (Table 206.3). Patients often confuse the type of insulin with the brand name, referring to their insulin as "Humulin," for instance, when they mean the "Lilly brand of human Neural Protamine Hagedorn (NPH) insulin." If patients have their insulin vials with them, it helps to look at them. If not, and they cannot name the insulins they take, it is helpful to remember that all the rapid- and short-acting insulins are clear, as are insulin detemir (Levemir) and insulin glargine (Lantus). NPH insulin and mixtures that contain NPH insulin are cloudy.

TABLE 206.3
Time Course of Action of Insulins[a]

Type	Onset	Peak	Duration
Rapid-Acting			
• Aspart (NovoLog)	5–15 min	30–90 min	3–5 hrs
• Glulisine (Apidra)	5–15 min	30–90 min	4 hrs
• Lispro (Humalog)	5–15 min	30–90 min	4 hrs
Short-Acting			
• Regular (Humulin R, Novolin R)	30–60 min	2–4 hrs	4–6 hrs
Intermediate-Acting			
• NPH (Humulin N, Novolin N)	3–4 hrs	8–14 hrs	16–24 hrs
Long-Acting			
• Detemir (Levemir)	2–4 hrs	None	6 (low dose)–24 (high dose) h
• Glargine (Lantus)	4–6 hrs	No discernible peak effect, but an increased effect may occur at 10–20 hrs	24–28 hrs
Mixtures			
• 70/30 (Two mixtures are marketed: 70% NPH + 30% regular, and 70% NPH + 30% Aspart)	Actions based on components of the mixture		
• 75/25 (75% NPH + 25% Lispro)			
• 50/50 Varies (50% X and 50% Y)			

[a]Times are approximate, as insulins may act differently in different individuals.

Some patients, particularly the elderly, are not aware that they are being treated for diabetes. Therefore, it is helpful to review all medications the patient is currently taking when investigating the cause of an unexplained episode of hypoglycemia. Surreptitious use of medication is a consideration in healthy-appearing patients with unexplained hypoglycemia, especially if it is severe or recurrent.

Aside from insulin and sulfonylurea agents, a number of other drugs can precipitate hypoglycemia, either at therapeutic doses or in overdose (Table 206.4). Patients taking β-blockers are at increased risk for severe hypoglycemia owing both to a blunted counterregulatory response and to diminished adrenergic symptoms when hypoglycemia does develop. Salicylate overdoses occasionally precipitate hypoglycemia, particularly in children.

TABLE 206.4
Selected Causes of Hypoglycemia

Fasting
Healthy-Appearing individuals
Drugs
Exogenous insulin
Oral hypoglycemic agents: Sulfonylurea agents, meglitinide agents
β-adrenergic blocking agents
Salicylates
Disopyramide
Quinine
Pentamidine
Others
Ethanol and other alcohols
Insulinomas and non–β-cell tumors
Inherited disorders of metabolism
Ill-Appearing individuals
Liver failure: Depleted glycogen stores and impaired gluconeogenesis
Chronic kidney disease
Adrenal insufficiency
Sepsis
Shock
Malnutrition, including anorexia nervosa
Congestive heart failure, especially severe right heart failure
Pregnancy
Fed (reactive)
Impaired glucose tolerance
Alimentary
Idiopathic reactive

Many serious illnesses may result in hypoglycemia in nondiabetic patients; the most common are sepsis, chronic kidney disease, liver failure, pneumonia, and congestive heart failure (16). Malnutrition, including anorexia nervosa and cancer-associated cachexia is another cause. The etiology is often multifactorial. Adrenal insufficiency itself rarely causes symptomatic hypoglycemia, but it may be a contributing factor during times of physiologic stress. Cortisol is

necessary for gluconeogenesis and, without it glucose levels (especially fasting levels) fall (see Chapter 209).

Ethanol ingestion can precipitate hypoglycemia in patients with or without diabetes by suppressing gluconeogenesis, usually in association with inadequate intake of food. This phenomenon occurs most commonly in children, malnourished chronic alcoholics, binge drinkers, and diabetics who neglect to eat adequately when consuming alcohol.

Insulinomas are a rare cause of hypoglycemia. Patients with these tumors have recurrent episodes of hypoglycemia, typically presenting with neuroglycopenic rather than adrenergic symptoms. Insulinomas often go undiagnosed for years. Weight gain from eating large amounts of food to self-treat the hypoglycemia is common. Non–β-cell tumors, including mesenchymal tumors, hepatocellular carcinomas, adrenal carcinomas, and others, can also produce hypoglycemia.

Newborns, especially premature infants, are at risk for hypoglycemia during times of physiologic stress owing to small glycogen stores and limited hepatic gluconeogenesis. In addition, several inborn errors of metabolism can cause hypoglycemia in children. These include glucose-6-phosphatase deficiency, galactosemia, hereditary fructose intolerance, and carnitine deficiency. Inborn errors of metabolism usually present in the first year of life. Infants experiencing unexplained hypoglycemia should be hospitalized and evaluated for these disorders.

Although hypoglycemia occurs most commonly in the fasting state, there are several causes of fed, or postprandial reactive hypoglycemia (18). Alimentary hypoglycemia occurs in patients who have undergone gastrointestinal surgery, most commonly gastrectomy and gastric bypass bariatric surgery (19). Patients have symptoms of hypoglycemia 30 to 120 minutes after eating. The hypoglycemia is thought to occur because of a more rapid emptying of food into the duodenum, leading to both an accelerated absorption of glucose and an exaggerated insulin response.

Some patients with “mild” diabetes, including patients treated with diet alone and those with risk factors for type 2 diabetes but

who have not yet been diagnosed as having diabetes, experience postprandial hypoglycemia. The insulin response to food is initially delayed; the enhanced insulin secretion that follows produces postprandial hypoglycemia.

Idiopathic reactive hypoglycemia is a rare disorder that is substantially over-diagnosed, particularly in young women. In general, patients with this diagnosis have adrenergic symptoms on fasting or postprandially but are rarely documented to have a glucose <50 mg/dL.

ED EVALUATION

In the ED, the biochemical diagnosis of hypoglycemia is usually made by using a bedside glucose meter. A blood glucose level should be checked immediately on any patient presenting with adrenergic or neuroglycopenic symptoms, including behavioral abnormalities, decreased level of consciousness, and acute focal deficits. An immediate check should be done on patients with syncope and trauma patients in whom hypoglycemia as a precipitant may be overlooked.

Most glucose meters are now calibrated to give results that are consistent with plasma glucose levels, but plasma glucose levels measured in the laboratory are still considered the most accurate determination of the blood glucose level, particularly in critical care settings (20). In addition, arterial blood has a glucose level 5% to 10% higher than that of venous blood. Test strips and meters are highly sensitive for the diagnosis of hypoglycemia but may give falsely *high* readings in the setting of severe anemia and hypotension.

A number of substances interfere with glucose measurement. The severity of interference varies with the specific meter (20,21). For example, in the setting of high levels of acetaminophen glucose measurements using meters which rely on the glucose oxidase method may be falsely low, whereas meters which utilize the glucose dehydrogenase method may be falsely elevated (20).

Test strip accuracy also deteriorates with prolonged storage, so strips should not be used beyond their printed expiration date.

Despite all of these potential confounders, meters are sufficiently accurate so that the laboratory confirmation of hypoglycemia diagnosed by bedside testing is usually not necessary, when the results are consistent with the clinical picture.

After the patient has recovered adequately, a focused history should be taken, investigating the cause of the episode, including the timing and doses of medications, food eaten, and activity. For diabetic patients, the history should include an assessment of diabetic control, whether home glucose monitoring is performed, usual values, and the frequency and severity of hypoglycemic episodes. The presence of comorbidities, including kidney disease, liver disease and heart failure, should be ascertained.

Additional laboratory testing, including measurements of the serum creatinine or hepatic transaminases, is necessary only if the history fails to reveal the cause of the episode and contributory comorbidities are suspected.

Hypoglycemia has been associated with silent and symptomatic myocardial ischemia and infarction in diabetic patients both with and without known coronary artery disease (22). The possibility that an episode of hypoglycemia has induced myocardial ischemia should be considered in all diabetic patients at risk for coronary artery disease.

Nondiabetic patients who are suspected of having hypoglycemia, but for whom the diagnosis was not established in the ED can be referred for an outpatient diagnostic workup.

KEY TESTING

- Bedside glucose

ED MANAGEMENT

Hypoglycemia should be considered in every patient with an altered sensorium or any acute neurologic deficit. Ideally, a fingerstick blood glucose level should be obtained to confirm the diagnosis before treatment with glucose is initiated, but glucose should be given empirically if the level cannot be obtained immediately. Although

animal studies and retrospective human studies have found a correlation between hyperglycemia and poor neurologic outcome among patients with stroke and severe brain injury, there is no evidence that the doses of glucose given to correct hypoglycemia are harmful. Only 20 g of carbohydrate is generally required to restore euglycemia, although, occasionally, more is required. Glucose can be administered orally or intravenously, depending on the patient's level of consciousness.

The initial treatment for a confused or comatose adult with hypoglycemia is a 50-mL bolus of 50% glucose intravenously. Less concentrated glucose solutions are recommended for children (25%) and neonates (10%) owing to concerns about hyperosmolality. The mean increase in the serum glucose level after this bolus is 150 mg/dL, but it varies greatly and is not predictable (23). The bolus should be followed by the continuous infusion of 5% or 10% glucose at a rate sufficient to keep the glucose level over 100 mg/dL until the patient is capable of eating. If there is any reason to suspect thiamine deficiency, thiamine 100 mg intravenously should be given concomitantly with glucose to avoid precipitating Wernicke–Korsakoff syndrome.

Patients who are alert enough to eat may be treated with glucose tablets or gel, orange juice, hard candy, or any form of concentrated sugar. If a patient is taking an α-glucosidase inhibitor (acarbose or miglitol), absorption of oral carbohydrate may be inhibited. These patients must be treated with dextrose (which is in glucose tablets) as opposed to sucrose (which is in table sugar). They can also be effectively treated with milk, because the drug does not inhibit lactase.

Adults with hypoglycemia who are unable to eat and in whom intravenous access cannot be secured can be given glucagon 1 mg intramuscularly. Children should receive 0.5 mg. Available data have shown glucagon to be safe and effective in restoring euglycemia (24), with neurologic recovery occurring generally within 10 minutes.

Adrenergic symptoms respond to glucose therapy within minutes. The time to recovery of neuroglycopenic symptoms is more variable, ranging from minutes to (in rare cases) days (10). A patient failing to

show clear signs of neurologic recovery within 10 minutes should have the glucose level rechecked to verify that euglycemia has been restored, because an additional bolus of glucose is occasionally needed. Alternative etiologies should be considered if there are no signs of neurologic recovery within 30 minutes.

To prevent recurrence, a meal or snack should be given after treatment. The simple carbohydrate given to raise the blood glucose level quickly does not produce a sustained elevation of blood glucose (50 mL of D50 and an 8-oz glass of orange juice contain only about 100 calories each), so a more complete meal, containing protein, fat, and complex carbohydrate, should be given to produce a more sustained rise in blood glucose levels. If hypoglycemia is due to administration of a long-acting insulin or a sulfonylurea agent, low glucose levels will typically last for an extended time. It is important to continue treatment and close observation to prevent relapse.

Octreotide, a synthetic peptide analog of somatostain, is a useful supplement to dextrose for the treatment of sulfonylurea-induced hypoglycemia in patients who are experiencing refractory or recurrent hypoglycemia despite routine management (25). Octreotide has no established role in the management of hypoglycemia caused by insulin overdose.

Long-term therapy depends on the cause of the hypoglycemia. If the hypoglycemia is secondary to a disorder such as hepatic failure or adrenal insufficiency, treatment of the underlying disorder is necessary to prevent recurrent hypoglycemia.

Dietary therapy is the treatment of choice for reactive and alimentary hypoglycemia. Patients should avoid sugars and eat frequent small snacks that contain a mixture of carbohydrate, fat, and protein. Restricting carbohydrate intake to 40% of total calories also may help.

In insulin-treated patients who become hypoglycemic, whether the usual insulin dose should be adjusted depends on the severity of the reaction. If the reaction is minor (easily detected and treated by the patient) and there is an explanation for the reaction (e.g., a missed meal or increased exercise), no insulin dose adjustment is indicated. However, if the reaction is more severe or is unexplained or if there

is a pattern of hypoglycemia occurring at the same time each day, the insulin dose should be decreased. Close monitoring of blood glucose levels is necessary to prevent hypoglycemia or hyperglycemia when the insulin dose has been changed.

Because recurrent hypoglycemia acutely downregulates the adrenergic response to additional episodes of hypoglycemia, a moderately severe episode of hypoglycemia will induce hypoglycemia unawareness on subsequent days, resulting in a more severe episode. Therefore, on the day after a moderate-to-severe hypoglycemic episode, the insulin dose should be reduced by 25%. Patients should be instructed to contact their primary care provider as soon as possible regarding subsequent insulin dosing.

CRITICAL INTERVENTIONS

- Administer glucose based on patients' symptoms rather than waiting for laboratory confirmation of hypoglycemia.
- Feed patients in the ED after a response to intravenous glucose.
- Administer glucagon to any hypoglycemic patient with neuroglycopenic symptoms who is unable to take oral glucose and in whom intravenous access has failed.
- Admit patients with hypoglycemia secondary to sulfonylurea agents or long-acting insulin preparations.

DISPOSITION

Most patients seen in the ED for hypoglycemia meet discharge criteria (Table 206.5). Hospital admission is indicated for patients failing to meet these criteria. Hypoglycemic patients with type 2 diabetes require hospitalization more frequently owing to the need for monitoring in patients with sulfonylurea-induced hypoglycemia, poor general condition, and a higher rate of concomitant disease requiring treatment (14).

TABLE 206.5
Discharge Criteria After a Symptomatic Hypoglycemic Episode

Brief episode
Full neurologic recovery
Able to eat
No major comorbidities that require hospital admission
Cause of the episode found and addressed
Treatment plan to prevent future episodes understood by the patient
Hypoglycemia accidental
Relapse unlikely—no long-acting insulin or oral agent nor prolonged excretion or metabolism
Ability to do home glucose monitoring[a]
Responsible person to be with the patient[a]
Follow-up arranged[a]

[a]Imperative for severe episodes requiring assistance for recovery.

Patients who are discharged should receive specific instructions on how best to avoid recurrent episodes (most commonly by increasing caloric intake or decreasing the insulin dose), should be instructed to perform self-monitoring of blood glucose, and should carry some form of oral glucose at all times. Family members of patients who have experienced a severe episode requiring assistance should be instructed in how to recognize and treat hypoglycemia, including use of a glucagon emergency kit. All patients with diabetes who take medications that predispose to hypoglycemia should be encouraged to wear a medical alert bracelet.

Common Pitfalls

- Failure to consider hypoglycemia in all patients with acute neurologic or psychiatric symptoms, including stroke-like symptoms, regardless of any history of diabetes.
- Failure to consider hypoglycemia in any physiologically stressed infant.
- Failure to follow a bolus of intravenous glucose with a continuous glucose infusion in patients who remain unable to eat.
- Prematurely discharging a patient whose episode of hypoglycemia is due to a long-acting insulin or a sulfonylurea agent.
- Failure to consider intentional overdose as the cause of hypoglycemia.

- Failure to consider that hypoglycemia may have induced clinically significant myocardial ischemia.
- Failure to reinforce the need for self-monitoring of blood glucose and, in particular, failure to discuss the need for monitoring blood glucose levels before driving.

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CHAPTER 207 Alcoholic Ketoacidosis

Sage W. Wiener and Robert S. Hoffman

Americans consume 6.8 L of pure alcohol (ethanol) per capita each year, equivalent to more than 30 gallons of beer. A total of 15 to 20 million are problem drinkers, and alcohol is responsible for the death of 100,000 people each year in the United States (13). Alcohol dependency commonly results in malnutrition and toxicity to multiple organ systems. When alcohol-dependent patients become ill and are unable to tolerate oral intake, they are at greater risk than other patients because of their underlying diseases and the recent metabolism of alcohol. Alcoholic ketoacidosis (AKA) is a common result.

The chronic consumption of alcohol leads to substantial metabolic derangements. Unlike most drugs and toxins, alcohol is itself an energy source, and alcoholic patients may come to depend on this source for as much as half of their daily caloric intake (13). This leads to nutritional deficiencies, most notably of vitamin B_1 (thiamine) (3). Because the two-carbon molecule of alcohol cannot be utilized for anything other than energy production or fatty acid synthesis, these patients become glycogen-deficient.

AKA is a condition that results from these derangements, typically during a period of alcohol abstinence that immediately follows a drinking binge. As in diabetic ketoacidosis (DKA), the lack of glucose substrate leads to the production of the “ketone bodies” acetoacetate and β-hydroxybutyrate as alternate energy sources. Unlike in DKA, the underlying problem is not the absence of insulin preventing glucose utilization (although relative insulin deficiency

may play a role), but rather the absence of glucose substrate because of malnutrition and lack of glycogen. Alcohol metabolism shifts the redox state of the body toward a more reduced state by generating nicotinamide adenine dinucleotide (NADH) (Fig. 207.1). High concentrations of NADH cause the equilibrium between lactate and pyruvate to shift, favoring lactate (Fig. 207.2). Gluconeogenesis is inhibited in alcoholics, further limiting available glucose, because pyruvate is the initial substrate. Low glucose concentrations lead to low concentrations of insulin, so hormone-sensitive lipase is disinhibited. The result is lipolysis, releasing free fatty acids that are broken down to acyl-coenzyme A, subsequently forming ketone bodies (10,12,13).

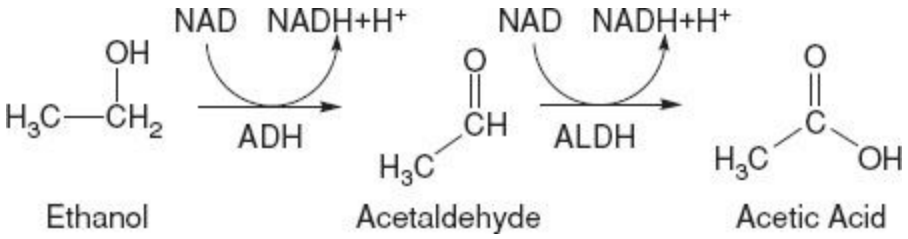

FIGURE 207.1 Alcohol is oxidized by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) to acetic acid, generating reduced NADH.

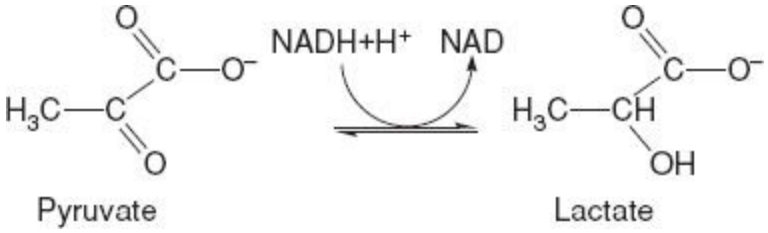

FIGURE 207.2 The relative concentrations of pyruvate and lactate are also governed by the redox state (the ratio of NAD to NADH). When the body is reduced (high levels of NADH), there is insufficient pyruvate for gluconeogenesis.

Although significant morbidity may result from coexisting medical disorders (6,7), once recognized, AKA generally responds well to therapy and has a low mortality rate in the hospital.

However, sudden cardiac arrest may occur even after initiation of medical care (23). A Danish prospective study of medicolegal autopsies in alcoholics found that 7% of deaths in their population could be attributed to AKA (18). This suggests that overall mortality from this disorder is higher than previously thought, possibly because many patients do not come to medical attention.

CLINICAL PRESENTATION

Patients generally present with nausea and vomiting and have abdominal pain suggestive of gastritis or pancreatitis. Vital signs are significant for tachypnea, tachycardia, and orthostatic hypotension. Patients tend to have significant volume depletion (several liters or more) caused by decreased oral intake, vomiting, osmotic diuresis from ketone bodies, and increased insensible losses from tachypnea, a compensatory response to metabolic acidosis (10). Their breath may have a characteristic fruity odor of ketosis. Although metabolic acidosis with an elevated anion gap (caused by the presence of unmeasured ketoacid anions) is always present, the serum pH may be normal or even elevated (22). This is because mixed acid–base disorders are common, including metabolic alkalosis from vomiting, contraction alkalosis from volume depletion, and compensatory respiratory alkalosis (10). Severe acidemia with a serum pH as low as 6.7 has been reported in fatal cases (6). Serum or urine ketones are typically only weakly positive, even in severe AKA (6). This is because the nitroprusside reaction used to measure ketones can only detect the functional ketone group of acetone or acetoacetate. Although often called a “ketone body” because it is in equilibrium with acetoacetate, β-hydroxybutyrate is not a true ketone and is missed by this test (Fig. 207.3). As in the case of the lactate–pyruvate ratio, the reduced redox state of the alcoholic patient causes the equilibrium to favor β-hydroxybutyrate. As patients improve with treatment, the NADH/NAD^+ ratio shifts to favor the production of acetoacetate, and ketones may actually appear to rise (4).

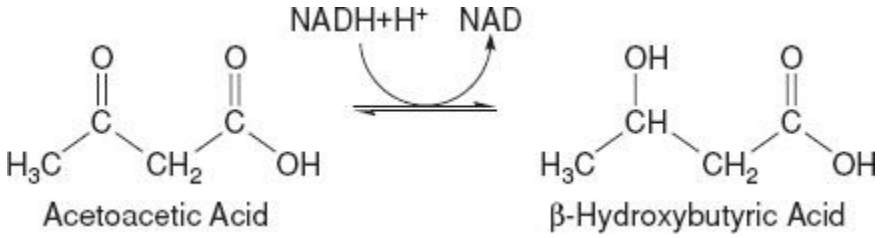

FIGURE 207.3 The relative concentrations of the "ketone bodies" acetoacetate and β-hydroxybutyrate depend on the redox state (the ratio of NAD^+ to NADH) of the body. Note that β-hydroxybutyrate is not a true ketone.

Electrolyte abnormalities are also common, particularly hypomagnesemia, hypophosphatemia, hypocalcemia, and hypokalemia (10,15,22). Hypoglycemia may be profound. If hypoglycemia is unrecognized, it may lead to substantial morbidity (11). Other abnormalities on laboratory evaluation (e.g., liver enzymes, pancreatic lipase and amylase), although common, are typically a result of associated illness, rather than being primary manifestations of AKA.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of anion-gap metabolic acidosis in the alcoholic patient is extensive. The familiar, although incomplete, MUDPILES mnemonic for causes of anion-gap acidosis includes methanol, metformin, uremia, DKA and other ketoacidoses, such as starvation ketosis and AKA, paraldehyde, phenformin, iron, isoniazid, ibuprofen, lactate, ethylene glycol, and salicylates. Common causes of acidosis in the alcohol-dependent population include elevated lactate from seizures or sepsis, AKA, and (much less frequently) toxic alcohols such as methanol and ethylene glycol.

Metabolic acidosis with an elevated lactate concentration, a marker of anaerobic metabolism, may be produced by many disorders including infections, ischemia, or hypoxia, which can lead to decreased oral intake and precipitate AKA. Illnesses such as pancreatitis, pneumonia, sepsis, Wernicke encephalopathy, and hepatic dysfunction are associated with an elevated lactate

concentration, and are therefore commonly seen in the alcoholic, as in other patients (8).

The distinction between alcoholic and other ketoacidoses is primarily based on history. A history of diabetes mellitus in the setting of ketoacidosis suggests DKA. Serum glucose elevation also suggests DKA, although hyperglycemia sometimes occurs in AKA, and DKA may rarely present with euglycemia (9). Significant acidosis caused by starvation is uncommon in the developed world and is usually a result of hyperemesis gravidarum, hunger strikes, or other similar causes of prolonged decrease in oral intake. A history of alcohol dependence should immediately suggest a diagnosis of AKA in the ketotic patient. Rubbing alcohol (isopropanol) ingestion also causes ketosis because it is metabolized to acetone. Because acetone does not undergo further metabolism to an organic acid, isopropanol ingestion does not cause a metabolic acidosis (see Chapter 283).

Methanol and ethylene glycol (see Chapters 299 and 300) are metabolized to the carboxylic acids formate, glycolate, and oxalate and may cause an anion-gap metabolic acidosis in the alcohol-dependent patient. Late findings in methanol poisoning include visual changes ranging from blurred vision to total blindness. In ethylene-glycol poisoning, acute kidney injury is the feared late complication. Unless the patient presents late enough to have end-organ toxicity, or there is a known history of ingestion of these substances, this diagnosis is difficult to establish, because timely concentrations are not available in most hospitals.

The serum alcohol concentration provides important information but is frequently misinterpreted. Most importantly, an undetectable alcohol concentration does not exclude a diagnosis of AKA; rather, it supports the diagnosis. Patients generally do not develop AKA until oral intake ceases. In contrast, the presence of any significant alcohol concentration (~100 mg/dL or more) almost excludes toxic alcohols as a source of metabolic acidosis because alcohol blocks alcohol dehydrogenase and prevents the metabolism of toxic alcohols to their carboxylic acid metabolites. Except in the rarely reported event of a patient drinking a toxic alcohol, waiting several

hours, and drinking alcohol before presenting, patients with significant alcohol concentration should not be able to generate a metabolic acidosis.

A further source of confusion is the osmol gap, a screening test for toxic alcohols. The serum osmolality can be significantly elevated in AKA, and an elevated osmol gap does not necessarily indicate the presence of a toxic alcohol (1,17). Toxic alcohol poisoning should be considered if there is a known history of ingestion, if there are signs of end-organ toxicity with acidosis (although temporary blindness has also been reported in association with AKA), or if other causes of an increased anion gap have been excluded.

Rapid improvement following intravenous fluids and dextrose is typical of AKA, and the anion gap generally returns to baseline after several hours (7,10,22). Such a response does not occur in toxic alcohol poisoning and most other conditions causing anion-gap acidosis (except reversible elevations of lactate concentration that might occur with a seizure or transient hypoperfusion). Without specific therapy, the anion gap would be expected to rise after toxic alcohol ingestion.

ED EVALUATION

The history should include the time, amount, duration, and pattern of prior alcohol consumption; circumstances that prevented continued consumption; the time of onset, nature, and severity of symptoms; prehospital treatment; and past medical history. The physical examination should focus on the vital signs, cardiopulmonary and neurologic status, assessment of the abdomen, and hydration status. If the patient's mental status is abnormal, as occurs in 15% of AKA patients (10), the bedside rapid reagent glucose should be checked early, because alcohol inhibits gluconeogenesis and is frequently associated with hypoglycemia (11,14). The patient should also be assessed for clinical signs of Wernicke's encephalopathy. Electrolytes, including calcium, magnesium, and phosphate, and an alcohol concentration should be sent, and a urinalysis should be performed.

AKA is usually first considered once the electrolytes reveal an elevated anion gap (4,16,21). The next step is to send a blood gas with lactate, because causes of an elevated lactate concentration occur commonly with metabolic acidosis. The blood gas is often performed on arterial samples, although a venous sample is probably adequate (2). If the lactate concentration does not account for the anion-gap elevation, urine or serum ketones should be checked. Once the diagnosis of AKA is established, it is important to look for any precipitating factors that led to the patient's condition. Further evaluation (see Key Testing) should be guided by the patient's signs and symptoms.

KEY TESTING

- Serum chemistry (electrolytes, BUN, creatinine, glucose)
- Serum calcium and magnesium (if not included in chemistry panel)
- Liver enzymes
- Serum lipase
- Serum ketones
- Complete blood count (CBC)
- Blood gas (venous or arterial)
- Serum or blood lactate
- Blood cultures
- Urinalysis
- Urine culture
- Stool guaiac
- Chest radiography
- Consider lumbar puncture (if suggested by the patient's signs and symptoms)
- Consider computerized tomography of the abdomen (if suggested by the patient's signs and symptoms)

ED MANAGEMENT

Advanced life support measures should be instituted as needed. Airway and breathing difficulties are rarely caused by AKA,

although associated alcohol withdrawal or severe respiratory infections may warrant endotracheal intubation. Specific therapy includes fluids, glucose, and thiamine administration. Intravenous crystalloids should be given to restore intravascular volume and to promote the renal clearance of ketones from the blood. In severely ill patients, a central venous catheter or ultrasound may be helpful in assessing volume status and response to treatment, particularly in those patients with underlying cardiac, hepatic, or renal disease.

Glucose is given to correct the underlying cause of AKA, which is primarily the lack of glucose and glycogen stores and relative insulin deficiency. Glucose provides energy substrate and stimulates insulin release from the pancreatic β-islet cells (6,7,10,12). Insulin, once released, inactivates hormone-sensitive lipase. This process leads to decreased release of free fatty acids, the substrates for ketogenesis. Thus, glucose is able to stop ketone formation. In the rare cases of AKA with significant hyperglycemia, dextrose may be withheld, but is necessary with euglycemia to invoke a brisk insulin response. The rapid reagent glucose should be followed closely, and insulin should be considered (9). Glucose should initially be given intravenously as 5% dextrose, unless the patient is significantly hypoglycemic, in which case a 50% dextrose bolus is indicated. Food should be given as soon as tolerated.

Thiamine is required for the utilization of glucose in the Krebs cycle, and the chronic administration of dextrose without thiamine has been reported to precipitate or worsen acute Wernicke encephalopathy (20). A dose of 100 to 200 mg should be administered intravenously (3) because alcohol-dependent patients do not absorb oral thiamine well (19).

Associated problems may require additional therapy. Abnormal electrolytes (potassium, phosphate, and magnesium) should be corrected. Although patients may have significant acidosis, sodium bicarbonate is unnecessary and should be avoided. The acidosis typically resolves rapidly once fluids and glucose are repleted (6,7,15,22). Insulin is an unnecessary intervention, unless the patient has a known history of diabetes mellitus or persistent hyperglycemia (which would suggest relative insulin deficiency and

impaired clearance of ketones) (6,7,10,22). Treatment of underlying or intercurrent medical problems should be instituted.

CRITICAL INTERVENTIONS

- Administer intravenous crystalloids to correct salt and water depletion.
- Administer intravenous dextrose to provide nutritional substrate and reverse ketosis unless the patient is severely hyperglycemic; feed patients who are able to eat.
- Administer parenteral thiamine (100 to 200 mg).
- Correct electrolyte abnormalities such as hypokalemia, hypomagnesemia, and hypophosphatemia.
- Avoid the use of sodium bicarbonate and insulin.
- Identify and treat associated precipitating medical illness (e.g., infections, pancreatitis, gastritis, alcoholic hepatitis).

DISPOSITION

In the hospital, AKA has low morbidity and mortality and responds well to treatment. The symptoms and metabolic derangements of mild AKA may often be corrected in a short time in the emergency department. Because of this prognosis, some authors have advised that most patients can be safely discharged with close follow-up. In one series, only 54% of patients with AKA were admitted (22). However, AKA occurs only in patients with a significant degree of alcohol dependence and nutritional deprivation. These patients are at high risk and cannot be relied upon to follow up appropriately. Coexisting medical illness is common. Rapid discharge from the emergency department without an evaluation for precipitating factors may be potentially dangerous. In the absence of severe electrolyte abnormalities, most patients with symptoms that do not resolve or whose precipitating event cannot be determined should be admitted to an observation or low-acuity bed.

Common Pitfalls

- Failure to appreciate that patients with AKA may have an undetectable serum alcohol concentration and trace or absent serum and urine ketones.
- Failure to identify and treat associated or precipitating medical illness (e.g., infection, pancreatitis, and hepatitis).
- Underestimating the degree of salt and water depletion.
- Failure to administer supplemental dextrose.
- Failure to recognize that the normal anion gap is diminished in hypoalbuminemia.
- Misdiagnosing AKA as DKA, usually because of incomplete history.
- Failure to administer thiamine or failure to appreciate that thiamine may not be absorbed by the oral route in patients with AKA.
- Inappropriately using insulin or sodium bicarbonate to treat AKA.

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CHAPTER 208 Thyroid Emergencies

Adam G. Field

Recognizing thyroid disorders in the emergency department can be a diagnostic dilemma as the presentation can often be very subtle with vague symptoms such as depression, constipation, mild dyspnea, cough, weight gain or loss, anorexia, and palpitations. With more severe thyroid illness like thyroid storm, the diagnosis can also be elusive as the symptoms can often mimic other life-threatening diseases that present with clinical signs of a hyperadrenergic state including sympathomimetic toxidromes, sepsis, severe opiate or alcohol withdrawal. With severe hypothyroidism, the symptoms may mimic several medical conditions including hypothermia, septic shock, congestive heart failure, primary central nervous system (CNS) events, or a variety of other toxic metabolic syndromes. It is important not to have an anchoring bias to your first diagnosis, as life-threatening stressors such as infection, stroke, or myocardial infarction can either mimic or independently precipitate the onset of a thyroid emergency. A thorough review of the vital signs as well as a complete history and physical examination are imperative to identifying thyroid disease.

THYROID PHYSIOLOGY

Thyroid hormones regulate basal metabolic rate, protein synthesis, bone growth, and increase the body's sensitivity to catecholamines. The thyroid is made up of follicular cells that produce thyroid hormone and parafollicular cells that secrete calcitonin. Calcitonin and parathyroid hormone, which are made by chief cells in the

parathyroid gland, control plasma calcium and phosphate levels. Patients therefore, after thyroidectomy, often present to the emergency department with signs and symptoms of hypocalcemia.

There are two biologically active thyroid hormones: thyroxine (T_4) and triiodothyronine (T_3). T_4 and T_3 are both produced by the thyroid gland, but the majority of T_3 (approximately 60% to 80%) is produced by deiodination of the outer phenyl ring of T_4 in peripheral tissues. Several physiologic and pathologic stimuli influence thyroid hormone synthesis as well as conversion of T_4 to the more biologically active compound T_3. T_3 is three to four times more potent than T_4 and is therefore administered with more caution during severely decompensated hypothyroidism.

T_4 and T_3 are stored in the protein thyroglobulin and readily synthesized and released from the thyroid when needed. T_4 and T_3 that are bound in the serum to TBG (thyroxine-binding globulin) are referred to as total T_4 and T_3. Approximately 1% of T_4 and T_3 is free T_3 and free T_4 which are unbound thyroid hormones. Free T_3 and T_4 are the active hormones and subsequently these are the values that, in addition to TSH, are most often measured in the emergency department evaluations for thyroid dysfunction. TBG is affected by many factors including medications, disease states, and pregnancy. If one uses total T_3 and T_4 levels as a measure of thyroid function, this could lead to many false positives and negatives as these values are directly related to the amount of TBG available.

Sufficient iodine stores are necessary for the production of thyroid hormone. Iodine is transported into follicular cells which then oxidizes and binds to thyroglobulin. The iodinated thyroglobulin forms monoiodotyrosine and diiodotyrosine, which are then coupled to form T_3 and T_4. Iodine has several effects on thyroid function. Iodine deficiency and excess can cause hyper- or hypothyroidism. The effect of iodine depends on whether a patient is previously iodine-deficient, the etiology of thyroid dysfunction, and the rate and amount of iodine administered. As a clinician, one must be aware of potential sources of excess iodine so as not to precipitate

thyroid dysfunction in a patient with previously existing thyroid disease. Exogenous iodine may come in the form of amidarone, over-the-counter cold medications, or iodinated contrast material. The use of any of these products can decrease the effectiveness of nuclear thyroid imaging and therefore delay definitive diagnostic and treatment options (1,2). The use of iodinated contrast has also been shown to precipitate thyroid storm.

Thyroid hormone production is regulated by two mechanisms. The first mechanism is a feedback loop between the hypothalamic–pituitary axis and the thyroid gland. Thyroid stimulating hormone (TSH), which is secreted from the pituitary gland, increases production and secretion of T_4 and T_3 by the thyroid gland. Secretion of TSH from the pituitary is stimulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. Extra thyroidal conversion of T_4 to T_3 is regulated by nutrition, other hormones, concomitant illness, and by the need for the body to increase its basal metabolic rate.

The hypothalamic–pituitary–thyroid access is considered a negative feedback loop as TSH and TRH levels decrease if more T_4 and T_3 is produced, and secreted, and increases with decreased levels of thyroid hormone. Hence, with primary hyperthyroidism, there is a high T_3 and/or T_4 with a low TSH, and with primary hypothyroidism, a low T_3 and T_4 with a high TSH. There are some exceptions with TSH levels when thyroid dysfunction is due to disease in the pituitary and the feedback loop is disrupted.

Thyroid function in the emergency department is assessed by measuring TSH and free T_4 (Table 208.1). Free T_3 measurement is only rarely indicated if there is a high clinical suspicion for thyrotoxicosis with normal free T_4 levels. This is referred to as T_3 thyrotoxicosis.

TABLE 208.1
Interpretation of Thyroid Function Tests

TSH	Free T_4	Disease State
Normal	Normal	None
Normal	Low	Euthyroid hypothyroxemia; severe nonthyroidal illness
Normal	High	Euthyroid hyperthyroxemia
Low	Normal	Subclinical hyperthyroidism; T_3 toxicosis (rare)
Low	Low	Central hypothyroidism; euthyroid sick syndrome
Low	High	Thyrotoxicosis
High	Normal	Subclinical hypothyroidism
High	Low	Primary hypothyroidism
High	High	TSH-mediated hyperthyroidism

Adapted from Supit EJ, Peiris AN. Interpretation of laboratory thyroid function tests for the primary care physician. *South Med J*. 2002;95(5):481–485.

HYPERTHYROIDISM

Hyperthyroidism is due to an increased production of thyroid hormone from the thyroid gland. Thyrotoxicosis refers to any state with increased circulating thyroid hormone whether it is from overproduction, excess release, or exogenous ingestion. The prevalence of hyperthyroidism in the United States is approximately 1% to 2%. The incidence of thyroid storm is about 1% to 2% of all patients with thyrotoxicosis. The incidence of hyperthyroidism is higher in areas with low iodine intake. In areas of high or normal iodine intake, the most common etiology is Graves disease, whereas in low iodine intake areas it is nodular goiter.

Graves disease is associated with increased circulating thyroid-stimulating antibodies which bind to thyroid receptors and increase the production of thyroid hormone. It is more common in females by a ratio of 10:1. It is often associated with several unique physical characteristics including Graves ophthalmopathy and dermopathy (see Clinical Presentation section). Graves disease is the most common thyroid illness associated with thyroid storm.

Toxic adenoma is a single thyroid nodule that excretes excess amounts of thyroid hormone, whereas multinodular goiter (TMNG) is associated with at least two or more thyroid nodules that produce excess thyroid hormone. Patients with a toxic adenoma as well as TMNG may present with thyrotoxicosis, subacute hyperthyroidism,

or euthyroid. TMNG is more common with advanced age and is the number one cause of hyperthyroidism in adults over 55 years of age. It can occur in younger patients but usually in areas where there is significant iodine deficiency. TMNG accounts for over 50% of cases of thyrotoxicosis in iodine-deficient areas (3). The symptoms are typically more gradual in onset than those of Graves disease. Like Graves disease however, it is more common in women than in men.

Thyroiditis is an inflammatory process that causes follicular disruption and release of thyroglobulin and stored thyroid hormone without de novo synthesis. Thyrotoxicosis is usually transient and is followed by hypothyroidism and then recovery. Hyperthyroidism does not usually persist since ongoing synthesis of thyroid hormones is inhibited due to TSH suppression. There are several etiologies of thyroiditis. Subacute thyroiditis and infectious thyroiditis are associated with acute illness with thyroid pain. Painless thyroiditis is associated with no pain as well as thyroid dysfunction and/or goiter (4).

Subacute thyroiditis is usually post viral and is thought to have an autoimmune basis. It often presents with hoarseness, dysphagia, and a painful goiter. As mentioned above, the hyperthyroidism is transient and usually progresses to a euthyroid and then hypothyroid phase. The hyperthyroid phase only lasts about 2 to 6 weeks. About 15% of patients remain hypothyroid, whereas others return to a euthyroid state if all of the thyroid gland has not been destroyed. This cycle typically takes about 6 to 12 months (4). It often follows an upper respiratory infection, tends to be seasonal, and has been associated with adenovirus, coxsackie, Epstein–Barr, and influenza viruses. It occurs more often in females and is more common in the 40- to 50-year age range. It is often associated with an elevated sedimentation rate and C-reactive protein (3).

Painless thyroiditis is associated with mild transient symptoms that typically resolve without treatment. It is due to lymphocytic infiltration of the thyroid gland and is usually associated with a painless goiter. There are several causes of painless thyroiditis including drug induced and Hashimoto thyrotoxicosis.

Hashimoto thyrotoxicosis is a form of painless thyroiditis. This disease process is typically associated with hypothyroidism (discussed below) but may have a transient hyperthyroid phase which is referred to as hashitoxicosis. In one study of patients with autoimmune thyroiditis, only 11% developed hashitoxicosis and the range of symptoms lasted from 31 to 168 days (3). A small percentage of these patients may develop hashitoxicosis encephalopathy, which is characterized by a subacute onset of confusion with altered level of consciousness, seizures, and myoclonus. This complication typically responds to corticosteroids and immunosuppressive therapy.

Thyroiditis can also be induced by medications, acute bacterial infections, iodine, radiation, trauma, as well as a postpartition state. Suppurative thyroiditis is a bacterial infection in the thyroid gland that can rarely be a life-threatening cause of thyroiditis. It can occur by direct inoculation through intravenous drug use, esophageal rupture, interventional procedures, and hematogenous spread. Patients that are predisposed include immunocompromised, elderly, and those with neck trauma, thyroid malignancy, and anatomic variants in the thyroid (3,4).

Common drugs that may precipitate thyroiditis include lithium, amiodarone, interferon-alpha, and interleukin-2 (Table 208.2). Iodine-induced thyroiditis can be in the form of amiodarone or radiographic contrast media. Radiation-induced thyroiditis occasionally occurs when a patient with Graves disease is being treated with radiation which can lead to destruction and inflammation of follicular cells. This may be associated with transient worsening of hyperthyroidism and a painful thyroid. Trauma-induced thyroiditis can occur after parathyroid surgery or direct blunt trauma to the neck. This usually presents as neck pain with transient hyperthyroidism. Other causes of thyrotoxicosis include exogenous ingestion, TSH pituitary secreting adenomas as well as primary and metastatic tumors within the thyroid that cause a destruction-induced thyrotoxicosis (2). A more extensive list of all the causes of thyrotoxicosis is listed in Table 208.3.

TABLE 208.2
Drugs Causing Alteration in Thyroid Function Testing

Decrease TSH Secretion

Glucocorticoids: inhibit TSH release

Dopamine: blocks TSH release

Octreotide: inhibits TSH release

Alter Thyroid Hormone Secretion

Decrease thyroid hormone secretion: iodide, amiodarone, lithium

Increase thyroid hormone secretion: iodide, amiodarone

Decrease T_4 Absorption

Cholesystramine, colestipol, sucralfate, ferrous sulfate, aluminum hydroxide, omeprazole

Alter T_4 and T_3 Transport in Serum

Increase serum TBG: estrogens, heroin, methadone, mitotane, fluorouracil

Decrease serum TBG: androgens, anabolic steroids

Displacement from protein-binding sites: furosemide, salicylates, heparin

Alter T_4 and T_3 Metabolism

Increase hepatic metabolism: phenobarbital and rifampin

Increase hepatic metabolism and displace from binding proteins: phenytoin and Carbamazepine

Cytokine Mediated

Interferon (5)

TABLE 208.3
Causes of Thyrotoxicosis

Graves disease
Toxic multinodular goiter
Toxic adenoma
Gestational hyperthyroidism
Chorionic gonadotropin induced
Physiologic hyperthyroidism of pregnancy
Trophoblastic tumors
Iodide-induced hyperthyroidism
Struma ovarii
Metastatic functioning thyroid carcinoma
TSH-secreting pituitary tumors
Thyroiditis
Lymphocytic thyroiditis (silent, painful, and postpartum)
Autoimmune: Hashimoto disease with Hashitoxicosis
Subacute thyroiditis (postviral, granulomatous, painful)
Drug-induced thyroiditis (amiodarone, lithium, interferon-α, interleukin-2)
Suppurative or infectious thyroiditis
Exogenous thyroid hormone
Thyrotoxicosis factitia (ingestion of natural products containing thyroid hormone)
Hamburger: thyrotoxicosis (related to using the neck of a cow to make hamburger patties)

Modified from Melmed S, Polonsky KS, Reed Larsen P, et al. Thyrotoxicosis. In: Mandel SJ, Larsen Reed P, Davies TF, eds. *Williams Textbook of Endocrinology*. 12th ed. Philadelphia, PA: Elsevier Saunders; 2011:362–402.

CLINICAL PRESENTATION

Thyrotoxicosis has a wide spectrum of presentations ranging from subclinical and apathetic hyperthyroidism to overt hyperthyroidism and thyroid storm. It affects most organ systems and is also associated with unique physical findings. The severity of concomitant stressors or precipitating infections may determine how dramatic the initial clinical signs and symptoms will be. The classic symptoms typically include tachycardia, weight loss, irritability, excessive sweating, anxiety, and heat intolerance. Please see Table 208.4 for a more complete list of clinical signs and symptoms.

TABLE 208.4
Signs and Symptoms of Thyrotoxicosis

General
- Excessive sweating
- Flushing
- Heat intolerance
- Weight loss
- Gynecomastia
- Irritability
- Dyspnea

Cardiovascular
- Palpitations
- Tachycardia
- Atrial fibrillation
- Systolic hypertension
- Congestive heart failure

Head/Neck
- Ophthalmopathy (Graves)
- Goiter

Gastrointestinal
- Abdominal pain
- Anorexia or increased appetite
- Diarrhea

Neurologic
- Nervousness
- Hyperreflexia
- Tremor

Muscular
- Muscle weakness
- Myalgias, myopathies
- Periodic paralysis (rare)

Dermatologic
- Hair loss
- Velvety skin
- Palmar erythema

These classic symptoms are often more obvious in younger than older patient populations. Older patients may present with vague or isolated symptoms making the diagnosis much more difficult (1). Beware in the elderly as up to 40% of this population with hyperthyroidism exhibit no tachycardia, defined as a heart rate over 100 (6).

Skin manifestations can include loosening of nails from the nail bed (Plummer nails), pruritis and hives (primarily with Graves), hyperpigmentation due to increased ACTH from accelerated cortisol metabolism, vitiligo, hair loss, and palmer erythema. Infiltrative dermopathy occurs in fewer than 5% of patients with Graves disease. These lesions cause hyperpigmented, nonpitting induration of the skin on the legs which are commonly over the pretibial area and dorsa of the feet (1).

Eye examination can demonstrate lid lag and stare. Lid lag is identified on physical examination if the sclera can be seen above

the iris when the patient looks down. Graves disease, which is the most common cause of hyperthyroidism is associated with unique eye findings referred to as Graves ophthalmopathy (Fig. 208.1). Autoantibodies target fibroblasts around the eye resulting in inflammation of the extraocular muscles and orbital fat. This causes proptosis and impairment of extra ocular motor function. Corneal ulcers and diplopia may result from this as well (1).

FIGURE 208.1 Patient with active thyroid-associated ophthalmopathy. Features exhibited include conjunctival hyperemia, periorbital edema, upper-lid retraction, and exophthalmos. (From Gold DH, Weingeist TA. *Color Atlas of the Eye in Systemic Disease*. Baltimore, MD: Lippincott Williams & Wilkins; 2001.)

Neck examination may demonstrate a thyroid goiter, which may be tender in patients with subacute thyroiditis. Massive thyroid enlargement may be found with Graves disease, toxic multinodular goiter, or painless thyroiditis. A small palpable nodule may also be seen with a thyroid adenoma. Associated symptoms with large goiters include dysphagia, mild dyspnea, or stridor.

Examination of the cardiopulmonary system can give several diagnostic clues. Respiratory rate and work of breathing is increased due to increased oxygen consumption and muscle fatigue. Hyperthyroidism can exacerbate underlying asthma. Cardiac and

peripheral vascular examination demonstrates a widened pulse pressure with systolic hypertension and signs of decreased peripheral vascular resistance.

Congestive heart failure can occur with severe hyperthyroidism or may be exacerbated in patients with pre-existing heart failure. Mitral valve prolapse occurs more frequently in patients with Graves and Hashimoto disease. With the use of bedside ultrasound in the emergency department, other findings such as increased left ventricular mass, mitral regurgitation, and signs of pulmonary hypertension may be appreciated (7). Pulmonary hypertension may be secondary to increased sympathetic tone, blood volume, and cardiac output, which can lead to pulmonary vasoconstriction and increased pulmonary arterial pressure (8).

The most common cardiac complications of thyrotoxicosis are atrial fibrillation and other atrial dysrhythmias, which can occur in 10% to 20% of patients with hyperthyroidism. The increased frequency of atrial fibrillation in elderly patients with thyrotoxicosis is thought to be due to the increasing incidence of cardiac disease independently in this age group. Atrial fibrillation can often be the only clinical sign in the elderly and is estimated to be present in up to 20% to 35% of older patients suffering from hyperthyroidism (9). Attempts to cardiovert atrial fibrillation should be deferred until the fourth month of maintaining a euthyroid state, because more than 56% of atrial fibrillation spontaneously reverts to sinus rhythm by this time. Medical or chemical cardioversion is usually successful in the remaining patients once a euthyroid state is obtained, except if there are other secondary causes as may be seen in the elderly (1,10).

Gastrointestinal manifestations include weight loss secondary to increased metabolism, abdominal pain, and vomiting. Occasionally, patients may gain weight with mild cases of hyperthyroidism because of increased appetite stimulation with a lesser degree of increased metabolic rate. Patients may develop symptoms of malabsorption as well as marked increased frequency of bowel movements. Liver function tests may be affected as well.

Many hematologic disorders may be associated with hyperthyroidism. Patients may exhibit a normocytic anemia. Graves disease may be associated with autoimmune hematologic disorders such as idiopathic thrombocytopenic purpura and pernicious anemia. A hypercoagulable state may develop from excess prothrombotic factors. Major thromboembolic complications such as pulmonary emboli are responsible for 18% of deaths caused by thyrotoxicosis (8).

Multiple electrolyte and laboratory abnormalities may exist as a result of the hypermetabolic state associated with thyrotoxicosis. Pre-existing diabetics may have increased difficulty with blood sugar control secondary to increased metabolic demands and associated biochemical changes. Increased lipolysis and ketogenesis can lead to lactic acidosis and ketoacidosis. Sodium, potassium, and chloride levels are not typically affected with hyperthyroidism but rarely hypokalemic periodic paralysis may be seen with thyrotoxicosis. Correction of the thyrotoxic state and hypokalemia will typically correct this process. Renal failure can rarely develop due to accelerated glomerular filtration rate which can lead to glomerulosclerosis and proteinuria. Renal insufficiency can also occur with severe thyrotoxicosis due to rhabdomyolysis or urinary retention from bladder dysfunction (8).

Calcium and phosphorous metabolism may also be affected by thyrotoxicosis. Increased osteoclast activity as well as increased excretion of calcium in the stool and urine can lead to accelerated osteoporosis and increased risk of fractures. Occasionally, hypercalcemia may be present with severe thyrotoxicosis as well.

Alteration in reproductive function as well as sexual maturation is also associated with thyrotoxicosis. Female patients may have altered cycles or amenorrhea. Increased rates of infertility as well as increased risk of miscarriage are associated with thyrotoxicosis. In males, increased conversion of testosterone to estradiol can result in clinical signs of decreased libido, erectile dysfunction, and decreased sperm production (1).

Neuromuscular and psychiatric abnormalities may be mistaken for other disease processes. Patients typically present with personality

changes, anxiety, emotional unstability, psychosis, and depression. These symptoms can sometimes mimic a patient with schizophrenia, manic depression, or attention-deficit disorder (1). Neurologic symptoms may include excessive body movements, hyperreflexia, proximal muscle weakness, and myopathy. Fine muscle tremors may be confused for new-onset Parkinson disease. Seizure activity is increased as well in this patient population (1).

The symptoms of hyperthyroidism may vary depending on the patient population. Two-third of older adults with hyperthyroidism present similarly to young patients with symptoms of sympathetic overactivity. One-third of elderly patients present with apathetic hyperthyroidism characterized by subtle symptoms such as lethargy, weight loss, and constipation. Shortness of breath, poor blood sugar control, leg edema, and heart failure may be the only diagnostic clue. Studies demonstrated a higher proportion of older adults reporting only one or two symptoms versus five or more in the younger patients. The lack of clinical signs of hyperthyroidism in older adults ($\leq$70 years) has been confirmed by several studies. Because of the vague symptoms, other diagnoses are often considered before entertaining the possibility of thyroid disease (9,11).

In pregnancy hyperthyroidism is associated with other pregnancy-specific clinical findings such as spontaneous abortion, premature labor, low birth weight, preeclampsia, and heart failure. Gestational thyrotoxicosis in early pregnancy can occur in 1% to 3% of cases and is associated with elevated HCG levels. It can present as hyperemesis gravidarum with symptoms of severe dehydration, weight loss, and ketonuria. Patients however should have other signs of thyrotoxicosis besides hyperemesis to warrant thyroid function testing (12). Hyperthyroidism can also present as a complication of pregnancy post partum. Postpartum thyroiditis (PPT) is an autoimmune, destructive inflammation of the thyroid gland that typically occurs within 1 year postpartum. The classic presentation of PPT starts with transient hyperthyroidism in the first 6 months postpartum, followed by transient hypothyroidism, then a return to the euthyroid state by 1 year postpartum (12).

One other factor to consider with regard to the pregnant patient with hyperthyroidism is the concomitant presentation of thyrotoxicosis in the neonate. It occurs more commonly in pregnancies complicated by Graves disease. Of the offspring born to women with Graves disease, 1% to 5% are affected with hyperthyroidism. High fetal heart rates, fetal goiter, poor growth, and craniosynostosis are some of the clinical features. With severe thyrotoxicosis in the neonate, high-output cardiac failure may develop (12).

Thyroid Storm

Thyroid storm is a life-threatening form of thyrotoxicosis associated with high temperatures of 104° to 106°F, severe tachycardia (>140), and CNS dysfunction with delirium, agitation, stupor, and coma. Other symptoms include severe dyspnea, abdominal pain, vomiting, and diarrhea. Additional clinical findings are the same as those described above (under Clinical Presentation of thyrotoxicosis) but may be more pronounced. Thyroid storm and severe thyrotoxicosis will be used interchangeably throughout the rest of this discussion.

Thyroid storm is often precipitated by surgery, trauma, infection, childbirth, or any other severe physiologic stressors. Thyroid surgery in patients with uncontrolled hyperthyroidism is used to be the most common precipitant of thyroid storm, but it now appears to be a severe infection (9). Thyroid storm has also been reported with discontinuation of antithyroid drugs, excessive ingestion or intravenous administration of iodine (e.g., radiocontrast dyes, amiodarone), radioiodine therapy (RAI), and even pseudoephedrine and salicylate use. Salicylates may increase free thyroid hormone levels and therefore should be avoided as a treatment option with thyroid storm (Table 208.5) (2).

TABLE 208.5
Precipitants of Thyroid Storm

Infection
Surgery/trauma
Vigorous palpation of the thyroid gland
Thyroid hormone ingestion
Cerebrovascular accident
Congestive heart failure
Pulmonary embolism
Diabetic ketoacidosis
Parturition
Toxemia of pregnancy
Emotional stress
Iodinated contrast dyes
Pseudoephedrine
Amiodarone

In addition to being a precipitant of overt hyperthyroidism, cardiac dysrhythmias, hypercoagulopathy, stroke, and pulmonary embolism may also be the end result of a thyroid storm.

It is important to have a high clinical suspicion for this disease process and to initiate early treatment. If thyroid storm is not recognized and treated on an emergent basis, hypotension and death can occur from cardiovascular collapse. Mortality rate is increased by 20% to 30% in this population. Table 208.6 shows a scoring system to help determine severity of presentation (2).

TABLE 208.6
Diagnostic Criteria for Thyroid Storm

Thermoregulatory Dysfunction	
Temperature (°F)	
99–99.9	5
100–100.9	10
101–101.9	15
102–102.9	20
103–103.9	25
≥104.0	30
Central Nervous System Effects	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizure, coma)	30
Gastrointestinal–Hepatic Dysfunction	
Absent	0
Moderate (diarrhea, nausea/vomiting, abdominal pain)	10
Severe (unexplained jaundice)	20
Cardiovascular Dysfunction	
Tachycardia (beats per minute)	
99–109	5
110–119	10
120–129	15
130–139	20
≥140	25
Congestive heart failure	
Absent	0
Mild (pedal edema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary edema)	15
Atrial fibrillation	
Absent	0
Present	10
Precipitant history	
Negative	0
Positive	10
TOTAL SCORE	
Scoring System	
>45: Highly suggestive of thyroid storm	
25–44: Suggestive of impending storm	
<25: Unlikely to represent thyroid storm	

In patients with severe thyrotoxicosis, points are assigned to the highest weighted description applicable in each category and scores totaled. When it is not possible to distinguish the effects of a concurrent illness from those of the severe thyrotoxicosis, points are awarded to favor the diagnosis of storm and empiric therapy.

With permission from Burch HB, Wartofsky L. Life-threatening thyrotoxicosis: Thyroid storm. *Endocrinol Metab Clin North Am* 1993;22:263–277.

DIFFERENTIAL DIAGNOSIS

As mentioned in the introduction, thyroid storm and severe thyrotoxicosis have similar presentations to many other life-threatening processes including the following: sympathomimetic (i.e., cocaine and methamphetamine) and anticholinergic toxidromes, malignant hyperthermia, salicylate overdose, alcohol, opiate and benzodiazepine withdrawal, multisystem trauma, sepsis, serotonin syndrome, exsanguination from ruptured viscous, pheochromocytoma, and psychotic break. Each of these clinical presentations has unique characteristics that may help differentiate them from a thyroid storm. For example, thyroid storm should not have lack of sweat or hypoactive bowel sounds as with an anticholinergic toxidrome. Patients with alcohol withdrawal or methamphetamine abuse will typically have other sequelae of chronic substance abuse. The only problem is that any of these processes can also precipitate a thyroid storm. A detailed history and examination is imperative to help differentiate these life threats from a thyroid storm.

With more subtle presentations of thyrotoxicosis, the differential diagnosis may include gastroenteritis, hepatitis, asthma exacerbation, anxiety disorder, other causes of high-output congestive heart failure, or pulmonary embolism to name a few. Apathetic hyperthyroidism or hyperthyroidism in the elderly may be confused for dementia, delirium, and other causes of unexplained weight loss.

ED EVALUATION

The diagnosis of thyrotoxicosis as well as thyroid storm is based on history and physical examination, identifying risk factors, and confirmatory TSH and free T_4 tests. Low TSH, less than 0.05–1 mU/L, with elevated T_4 confirms the diagnosis. TSH levels may be normal or elevated with elevated T_4 and T_3 levels in TSH-induced hyperthyroidism due to pituitary adenoma or partial resistance to the feedback loop. The severity of clinical manifestations may not

correlate with the degree of thyroid hormone elevation or TSH suppression.

In subclinical hyperthyroidism, the TSH may be borderline suppressed (>0.05 mU/L) with normal T_3 and T_4. These patients do not need emergent treatment in the emergency department and should follow up with their primary care physician on a routine basis. Follow-up testing for TSH and free T_4 is recommended in 6 to 12 months, especially in elderly patients who are at increased risk of cardiovascular disease, atrial fibrillation, unexplained extensive weight loss, and osteoporosis (13). The primary care physician would need to determine if the patient has a sustained TSH depression on repeat testing and make sure that there are not other nonthyroidal etiologies for depressed TSH (13).

Diagnostic evaluation of thyrotoxicosis depends on the severity of presentation. With less severe presentations such as anxiety, weight loss, or unexplained tachycardia, the evaluation should include electrolytes, complete blood count (CBC), thyroid function tests, and ECG. With more severe cases of thyrotoxicosis as in thyroid storm, a more aggressive approach to find the precipitating cause may include obtaining blood cultures, toxicologic screen, cardiac enzymes, chest x-ray, CT scan, and lumbar puncture (LP), if altered neurologic status and high fevers are present (8).

KEY TESTING

- CBC
- Chemistry panel
- Liver function tests
- Cardiac enzymes
- CPK
- Urinalysis
- ECG
- Core temperature
- Thyroid function tests
- Blood and urine culture
- Toxicologic screen

- Chest x-ray
- CT and LP, if clinically indicated

Other diagnostic tests may be used in follow-up with the endocrinologist to help determine the etiology of hyperthyroidism as well as guide in the treatment. Twenty-four hour radioiodine uptake and scan may be used to differentiate Graves disease with high radioactive uptake from most causes of thyroiditis that have low radioactive uptake. “Hot nodules” are nodules with increased radioactive uptake and they may also be seen with toxic adenoma and multinodular goiter. High radioactive uptake is associated with increased synthesis of new thyroid hormone as the etiology of hyperthyroidism, whereas low uptake is usually associated with little to no de novo synthesis. The pattern of uptake may also differentiate Graves disease from other causes of hyperthyroidism like toxic adenoma or toxic multinodular goiter.

ED MANAGEMENT

Treatment of thyroid storm involves several steps. The first step is to resuscitate the patient with supportive therapies including repletion of excessive fluid losses, rapid cooling of high fever, airway control if necessary, and rapid evaluation and treatment of any underlying precipitants. Dextrose containing IV solutions should also be used in addition to normal saline, supplemental multivitamins, and thiamine as there have been reported cases of Wernicke encephalopathy with severe thyrotoxicosis. Some of the signs and symptoms may not be corrected until definitive antithyroid medication is initiated. For example, rapid atrial fibrillation may be refractory to rate control or cardioversion until antithyroid medication is instituted (2).

The next steps include stopping synthesis of new hormone within the thyroid gland, halting release of stored thyroid hormone from the thyroid gland, preventing conversion of T_4 to T_3, and controlling the adrenergic symptoms associated with thyrotoxicosis (2).

With severe thyrotoxicosis or thyroid storm, a thionamide (methimazole or propylthiouracil [PTU]) should be given about an hour or two prior to giving iodine to block production of new thyroid hormone. Methimazole and PTU reduce the production of thyroid hormones by selectively inhibiting thyroid peroxidase (TPO). There are several risks in giving PTU including liver failure and agranulocytosis. PTU should be given as a second-line drug to methimazole except in first trimester of pregnancy or if the patient does not tolerate methimazole (12). Either agent may be used to treat thyroid storm. PTU has the additional advantage of inhibiting peripheral conversion of T_4 to T_3. On the other hand, the duration of action of methimazole is longer, and can therefore be given less frequently. In the United States, thionamides are typically given orally, but rectal preparations are also available. The powder form of methimazole can be mixed with normal saline and filtered to create an intravenous solution. IV forms of thionamides are available in Europe.

Various forms of iodine are then given to halt the release of thyroid hormone. Inorganic iodine (Lugol solution or saturated solution of potassium iodide [SSKI]) is used 1 hour after the administration of PTU or methimazole to block the release of preformed thyroid hormone. Large doses of iodine will reduce the organification of thyroglobulin. Blocking hormone synthesis must take place first prior to iodine therapy to ensure that the iodine cannot be used for further thyroid hormone production. Alternative therapy with lithium at a dose of 300 mg every 6 hours may be used to block release if the patient has an iodine allergy. Lithium dosage may be adjusted to maintain serum lithium of 0.8 to 1.2 mEq/L (8). The radiocontrast agent ipodate (Oragrafin) may also be used in this step as it inhibits peripheral T_4 conversion and blocks thyroid hormone release.

Corticosteroids are used to decrease peripheral conversion of T_4 and inhibit the release of thyroid hormone. Treatment of thyroid storm with corticosteroids may have the added affect of treating adrenal insufficiency which may occur concomitantly (2). The initial

dose of hydrocortisone is 300 mg followed by 100 mg every 8 hours during the first 24 to 36 hours. Thyroid storm has been reported to recur when steroids had been discontinued after initial clinical improvement (8).

β-Blockade is used to control the peripheral actions of thyrotoxicosis. β-Blockers not only correct tachycardia but also improve agitation, convulsions, psychotic behavior, diarrhea, fever, and excess sweating. Propanolol traditionally is the initial drug of choice as it blocks peripheral β-receptors as well as has the theoretical benefit of blocking the conversion of T_4 to T_3. A significant effect however is only seen at doses of 160 mg/d or greater (8). The dosing for propanolol is 60 to 80 mg every 4 hours. It can also be given intravenously every 10 minutes at a dose of 1 to 3 mg. IV esmolol may also be used in the potentially unstable patient because with its short half-life, it is easier to discontinue without prolonged adverse side effects. Longer-acting cardioselective β-blockers like atenolol or metoprolol may be used as well and have been shown to be just as effective as propanol with less frequent dosing despite not having the benefit of blocking peripheral conversion of T_4 to T_3 (8). β-Blockers are contraindicated with bronchospasm or severe congestive heart failure. If the cause of the heart failure is thought to be high output and due to the tachycardia from the thyrotoxicosis, a short-acting β-blocker may be the best choice. Diltiazem may also be used for rate control but it will not block the other peripheral β-receptor symptoms mentioned above (Table 208.7).

TABLE 208.7
Treatment of Thyroid Storm

(1) PTU 600 to 1,000 mg PO/PR then 200 to 250 mg every 4 hrs or
Methimazole 15 to 30 mg/d
(2) Inorganic iodine (1 hr after PTU)
Lugol solution 8 drops PO/PR every 6 hrs *or*
SSKI 5 drops PO/PR every 6 hrs
(3) Corticosteroids
Dexamethasone 2 mg IV every 6 hrs or
Hydrocortisone 300 mg IV then 100 mg every 8 hrs
(4) β-Blocker (If NO CHF)
Esmolol 250 to 500 µg/kg IV bolus then 50 to 100 µg/kg/min infusion or
Propanolol 60 to 80 mg PO every 4 hrs or
Propanolol 0.5 to 1 mg IV every 1 hr (infuse slowly)
(5) Supportive care
Acetaminophen, cooling blankets, IV fluids
(6) Treat the precipitating event
Broad-spectrum antibiotics if no source identified, treat CHF, MI, stroke, pulmonary emboli, etc.

Along with providing specific treatment for thyroid storm, it is also important to provide supportive care for the clinical manifestations as well as identify and treat the precipitating cause. If no infectious source is identified in the unstable patient, broad-spectrum antibiotics should be administered until a source is identified. When clinical deterioration occurs in thyroid storm, despite the use of all of these medications, removal of thyroid hormone with plasmapheresis, charcoal hemoperfusion, resin hemoperfusion, and plasma exchange has been found to be effective (2).

Therapy for uncomplicated cases of thyrotoxicosis in the emergency department usually consists of initiation of a β-blocker for symptomatic relief. Patient may be given a first dose intravenously or orally depending on the severity of clinical presentation and discharged on an oral regimen of either propanolol or a cardioselective long-acting β-blocker. A thionamide may be started if there is clinical suspicion for Graves disease as well as in cases of toxic adenoma and multinodular goiter, where overproduction of thyroid hormone is the suspected cause of the patient's symptoms. For the reasons mentioned above, methimazole

is the preferred first-line drug except in first trimester of pregnancy. Methimazole is started at 15 to 30 mg/d with maintenance doses of 5 to 10 mg/d. PTU is initiated at a dose of 100 mg every 8 hours and can be reduced to 50 mg two to three times a day once the euthyroid state is reached.

Although definitive treatment is not started in the emergency department, it is important to be able to communicate the potential treatment options to the patient. With Graves disease there are three definitive treatment options: prolonged antithyroid medication with thionamides, iodine therapy, and partial or total thyroidectomy.

The goal of RAI is to create a euthyroid state, but up to 10% may still be hyperthyroid after treatment. Up to 20% may become hypothyroid and have a 3% to5% increased risk of developing hypothyroidism each year. Thyroidectomy is reserved for patients with a severe allergy to thionamides, pregnant patients, or patients suffering from severe compressive symptoms from a large goiter. Antithyroid treatment is the preferred first-line method of treatment during pregnancy.

There has been some success with prolonged thionamide treatment. Up to 40% of patients receiving thionamides will undergo remission after 6 to 18 months of therapy. A fourth treatment option is referred to as block and replace. Patients who are difficult to stabilize are put on a dose of antithyroid medication to block thyroid function, and then given thyroid replacement hormone to normalize thyroid function. It is thought that this option may create more stable thyroid levels and make antithyroid treatment more tolerable.

Management of thyroiditis is typically less complicated and the symptoms are usually transient. With subacute thyroiditis antithyroid medication is not necessary because symptoms are based on release of preformed thyroid hormone, not overproduction. This condition is usually treated with nonsteroidal medication or a prednisone taper. β-Blockers may be needed for symptomatic relief. Other more rare forms of thyroiditis such as medication induced or infectious require treatment of the underlying cause.

Common Pitfalls

- Not recognizing thyrotoxicosis in an elderly patient with apathetic hyperthyroidism.
- Administration of iodinated contrast to a thyrotoxic patient without recognizing the risk of developing thyroid storm.
- Administration of iodinated contrast to a patient who is in the process of workup for thyroid disease, therefore delaying future diagnostic and treatment options.
- Diagnosing and treating thyroid storm without searching for and treating the precipitating event.
- Failure to consider thyroid storm in a patient that presents with hyperadrenergic signs and symptoms (i.e., tachycardia, high fever, tachypnea, agitation).
- Using long-acting β-blockers rather than short-acting β-blockers in an unstable patient presenting with signs of thyroid storm.

CRITICAL INTERVENTIONS

- In an ill patient with a history of thyrotoxicosis or a goiter, suspect and treat thyroid storm early.
- In the treatment of thyroid storm, administer a thionamide 1 hour before inorganic iodine.
- Administer the short-acting agent esmolol in unstable patients or patients with signs of congestive heart failure.
- Early administration of broad-spectrum antibiotics in a patient with decompensated severe thyrotoxicosis even if a definitive infectious source has not yet been identified.

HYPOTHYROIDISM

Hypothyroidism is one of the most common endocrine disorders. It is more common in women and the elderly. The incidence is about 0.5% in the United States and increases to 2% to 3% in the elderly. Primary hypothyroidism occurs as a result of undersecretion of thyroid hormone from the thyroid gland.

Secondary hypothyroidism may occur as a result of damage or disease of the pituitary or hypothalamus. Secondary hypothyroidism may be masked by other endocrine deficiencies such as hypogonadism and adrenal insufficiency (14). Almost 95% of hypothyroidism is primary, whereas secondary hypothyroidism is very rare.

Causes of Primary Hypothyroidism

Iodine deficiency is the most common cause of hypothyroidism worldwide. Chronic autoimmune (Hashimoto disease) thyroiditis, which is mentioned earlier in the chapter, is the most common cause in iodine-sufficient areas (15). It is associated with antibodies against TPO and/or thyroglobulin as well as lymphocytic infiltration of the gland. As discussed above, Hashimoto disease may have transient hyperthyroid phases but the typical course is slow destruction of the gland that eventually results in hypothyroidism. There can often be alternating periods of hyperthyroid and hypothyroid symptoms, which is characteristic of Hashimoto disease.

Another common cause of hypothyroidism is a total thyroidectomy with clinical signs typically developing within 2 to 4 weeks. The majority of patients with subtotal thyroidectomy for Graves disease are typically euthyroid after 1 year, but approximately 1% becomes hypothyroid each year after their surgery (16).

Radiation and radioactive iodine are both associated with hypothyroidism. After I-131 treatment, the majority of patients will be hypothyroid after 1 year and the remaining patients at a rate of about 2% per year (16). Radiation for other head and neck cancers as well as exposure to nuclear accidents has an increased risk of hypothyroidism.

Medications have multiple effects that can lead to a hypothyroid state. Drugs such as lithium, amiodarone, interferon, and interleukin-2 have been associated with hypothyroidism. Cholestyramine, proton pump inhibitors, calcium carbonate,

phosphate binders, and ferrous sulfate can decrease absorption in hypothyroid patients taking T_4. The end result may be a patient on thyroid placement with persistent symptoms of hypothyroidism despite adequate thyroxine dosing (15). A more extensive list of all the causes of hypothyroidism is given in Table 208.8 (16).

TABLE 208.8
Causes of Hypothyroidism

Autoimmune thyroiditis (Hashimoto)
Subacute, silent or postpartum thyroiditis
Systemic illness
Neonatal
- Thyroid agenesis
- Genetic disorders affecting thyroid hormone synthesis
- Transplacental passage of TSH receptor blocking antibody

Radioablation with I^{131} for hyperthyroidism and thyroidectomy
Iodine deficiency or excess
Radiation exposure
Medications
- Lithium
- Amiodarone
- Iodine deficiency or excess or iodinated contrast
- Sulfonamides
- Phencyclidine
- Antithyroid medications

Causes of secondary hypothyroidism:
Infiltrative processes (both primary and secondary)
- Neoplasia (lymphoma)
- hemochromatosis
- Sarcoidosis
- Tuberculosis
- Reidel thyroiditis (fibrous)
- Histiocytosis
- Amyloidosis
- Scleroderma

Tumors, infarcts, or trauma
Sheehan syndrome (postpartum pituitary necrosis)
Lymphocytic hypophysitis
Infection and medication (14,15)

CLINICAL PRESENTATION

Hypothyroidism may affect all organ systems. Signs and symptoms depend on the degree of thyroid deficiency as well as whether the etiology is primary or secondary. Generalized fatigue, cold intolerance, and weight gain are common. Patients typically present with gradual onset of symptoms over months to years. The spectrum of clinical presentations ranges from subclinical hypothyroidism

with no symptoms to severely decompensated hypothyroidism. Because the symptoms are usually vague, they often mimic signs and symptoms of other euthyroid illness (15). As in hyperthyroidism, there should be detailed attention to vital signs as well as general appearance. Patients may be lethargic with slow movement and slow speech. Thick and hoarse speech is thought to be due to myxedema of the tongue and larynx. Generalized muscle stiffness is present especially when exposed to cold (17).

Decreased cardiac output can lead to narrowed pulse pressure with cool pale extremities. Alterations in the cardiovascular system manifest as ECG changes which include sinus bradycardia, low amplitude, and flattening or inverted T waves. Echocardiography may demonstrate small pericardial effusions as well as findings of left ventricular diastolic dysfunction (17). Distant heart sounds may be appreciated on examination and enlarged cardiac silhouette can be seen on chest x-ray. Many of these clinical findings may mimic congestive heart failure. In patients with no underlying heart disease, treatment with thyroxine will reverse most if not all of these changes (14).

Respiratory symptoms may include shortness of breath and decreased exercise capacity. Hypoventilation can occur with more severe hypothyroidism. Rarely, pleural effusions may be appreciated on chest x-ray. Reversible obstructive sleep apnea is not uncommon.

Constipation is the most common gastrointestinal sign with hypothyroidism. Ileus may be confused with bowel obstruction. Decreased taste sensation has also been reported. Other autoimmune gastrointestinal-related diseases such as pernicious anemia from antiparietal antibodies and celiac disease are more prevalent especially in those patients with hypothyroidism due to autoimmune thyroiditis (14,17).

Neurologic manifestations may include mild symptoms such as numbness and tingling in extremities and carpal tunnel syndrome from glycosaminoglycan deposits on the median nerve (17). Deep tendon reflexes may be delayed in the relaxation phase. Some of the more severe neurologic symptoms include problems with memory, night blindness, hearing loss, dementia, stupor, syncope, and rarely

seizures in more severe cases. Evaluation of a new paranoia or depression should include thyroid functions tests (TFTs) looking for hypothyroidism (14,17).

Multiple cutaneous manifestations are found in patients with hypothyroidism. Hylauronic acid accumulates in soft tissue, which leads to mucinous edema that is responsible for the thickened features, pretibial edema, and puffy appearance, which is referred to as myxedema. Decreased production by sweat glands is associated with hyperkeratosis and ruff dry skin. Growth of hair is slowed and nails are brittle. Wounds also tend to heal slowly (17).

Metabolic abnormalities include hyponatremia, hypoglycemia, reversible increases in serum creatinine, increased triglycerides and free fatty acids, and elevation in creatine kinase. Delay in secretion of water due to decreased perfusion of the kidney may contribute to hyponatremia and decreased renal function (8).

Changes in sexual and reproductive function in women may include amenorrhea or abnormal menses. Alteration in cycles may contribute to decreased fertility. In pregnancy, there is also an increased risk of abortion in women with hypothyroidism. Galactorhea may develop from overstimulation of the hypothalmus by TRH. Other findings due to undersecretion of the pituitary gland may also be seen in secondary hypothyroidism. In men, decreased libido, erectile dysfunction, and altered sperm morphology may contribute to infertility as well. This is partially reversible with treatment (17).

Table 208.9 summarizes the more common signs and symptoms of hypothyroidism.

TABLE 208.9
Signs and Symptoms of Hypothyroidism

Appearance

- Puffy and pale facies
- Dry, brittle hair
- Sparse eyebrows
- Dry, cool skin
- Thickened and brittle nails
- Myxedema—fluid infiltration of tissues

Energy and nutrient metabolism

- Cold intolerance
- Weight gain
- Fatigue

Nervous system

- Headache
- Paraesthesias (including carpal tunnel syndrome)
- Cerebellar ataxia
- Delayed relaxation of deep tendon reflexes

Cognitive/psychiatric

- Reduced attention span
- Memory deficits
- Depression

Cardiovascular

- Bradycardia
- Diastolic hypertension
- Pericardial effusion
- Decreased exercise tolerance

Musculoskeletal

- Myalgias
- Arthralgias

Gastrointestinal

- Anorexia
- Constipation

Reproductive system

- Irregular or heavy menses
- Infertility

Additional investigations

- Hypercholesterolemia (statin therapy in hypothyroid patients increases risk of rhabdomyolysis)
- Raised creatine kinase
- Hyponatremia
- Mild anemia (15)

ED EVALUATION AND MANAGEMENT

Diagnosis of hypothyroidism in the emergency department should consist of screening with TSH and free T_4 based on the clinical clues listed above. Elevated TSH (>10 mU/L) with low T_4 should indicate the need for treatment with levothyroxine. Low TSH and low T_3 and T_4 suggest secondary hypothyroidism. Low TSH can also occur when the adrenal gland is stressed as well. If there is suspicion for secondary hypothyroidism, further testing should include prolactin level, FSH, LH, ACTH, and cortisol levels. If there is a high index of suspicion for secondary hypothyroidism, adrenal function must be tested prior to initiating thyroid replacement therapy. Starting patients on thyroid replacement with a cortisol deficiency prior to starting glucocorticoids could precipitate an Addisonian or adrenal crisis.

An elevated TSH with a normal free T_4 is referred to as subclinical hypothyroidism. This is detected in 4% to 8% of the general population and in up to 15% to 18% of women aged more than 60 years. The benefit of treating subclinical hypothyroidism is somewhat controversial. The potential risks of not initiating therapy include progression to overt hypothyroidism, cardiovascular effects, worsening lipid profiles, and neuorpsychiatric effects (15,18). This is especially true when treating subclinical hypothyroidism in pregnancy as this could potentially prevent long-term psychomotor and auditory development in the neonate (13).

A recent Cochrane review found that in nonpregnant patients, thyroxine versus no treatment for subclinical hypothyroidism did not affect overall survival but did improve markers for cardiovascular disease such as lipid profile (15,18). Most of the literature still recommends treatment however if patients have a TSH over 10 with a normal free T_4. No treatment is indicated with TSH between 5 and 10 mU/L with a normal free T_4 unless patients exhibit signs of hypothyroidism. In this case, the patient may be given a 3- to 6-month trial with synthroid to see if symptoms improve. All other patients can be referred to their primary

physician for risk stratification to determine if treatment is needed (13,16,19).

The recommended approach to treating hypothyroidism is to titrate thyroxine therapy against the TSH concentration while assessing clinical response to treatment. It is important to note especially in the emergency department setting that repeat TSH levels should not be obtained until about 3 to 4 weeks after therapy is initiated. Checking the levels too early can lead to unnecessarily increasing the dosage of thyroid replacement. Furthermore, it also takes patients several weeks for their symptoms to improve after starting treatment (13).

The recommended starting dose for the majority of patients is 50 to 100 μg of thyroxine. Higher doses may be indicated in patients post-thyroidectomy. Doses should be increased in 25 to 50 μg increments with the TSH repeated every 4 to 6 weeks after each change. Most patients will become clinically euthyroid in the range of 75 to 150 μg/d (1.6 μg/kg on average based on ideal body weight). In elderly patients, especially those with ischemic heart disease, the initial dosage should be 25 μg with increases of 25 μg rather than 50-μg increments (13).

During pregnancy, there is an increased need for thyroxine especially in women with pre-existing hypothyroidism. Furthermore, absorption of thyroxine may also be decreased with pregnancy requiring increased dosing. Hypothyroid pregnant patients receiving thyroxine therapy should get an additional 25 to 50 μg per day to maintain normal serum TSH levels. About 2 to 4 weeks after delivery, the dosage can usually be decreased back to prepregnancy levels depending on the TSH level (13).

Untreated hypothyroidism in pregnancy has been associated with several adverse maternal and fetal outcomes including early miscarriage, intrauterine fetal demise, placental abruption, gestational hypertension, postpartum hemorrhage, gestational diabetes, and delayed neurologic development as well as lower IQ in the neonate (14).

Several preparations of levothyroxine are available including synthroid, levothyroid, unithyroid, levoxyl, and generic. They all

appear to be equivalent in terms of thyroid replacement (20). Some patients have reported having more improvement of symptoms with preparations that combine T_4 and T_3 or just use T_3 alone. These preparations include the products triiodothyronine (Cytomel) or desiccated thyroid (Armour). Several studies have actually shown subjective improvement of symptoms with combined therapy versus synthroid alone (21). Larger studies have not confirmed the benefit of combined therapy however.

Common Pitfalls

- Failure to consider hypothyroidism in elderly patients with cognitive deficits or patients with an unexplained pleural effusion or anemia.
- Failure to consider the effect of many commonly prescribed drugs and pregnancy on thyroid function.
- Expecting the rapid return of the TSH level to normal in a patient recently started on hormone replacement for hypothyroidism.

MYXEDEMA COMA

Myxedema coma is defined as severe hypothyroidism presenting as decreased mental status, hypothermia, and other signs and symptoms of a decreased metabolic rate. It is extremely rare with an incidence of 0.22 per million per year. It is most common in elderly women with long-standing hypothyroidism and other comorbidities (8).

CLINICAL PRESENTATION

Myxedema coma most commonly occurs with severe infection, sepsis, myocardial infarction, cold exposure, or administration of sedatives, antidepressants, or opioids (Table 208.10).

TABLE 208.10
Precipitants of Myxedema Coma

Infection
Trauma, burns
Cerebral vascular accident
Congestive heart disease
Gastrointestinal bleeding
Lung disease/CO_2 retention
Hypothermia
Hypoglycemia
Untreated hypothyroidism
Discontinuation of thyroid replacement
Medications
- Drug overdose
- Diuretics, amiodarone, β-blockers
- Sedatives, lithium, phenytoin

Physical findings include all those mentioned in Clinical Presentation of hypothyroidism, with bradycardia, macroglossia, hoarseness, cachexia, hypoventilation, severe hypothermia (often profound to 80°F [26.7°C]), and decreased level of consciousness. Hypotension may exist in up to 50% of cases from decreased cardiac contractility. Coma is misleading as mental status changes may range from slowing of speech to unconsciousness. Seizures may occur in up to 25% of these patients and are often due to hypoglycemia or hyponatremia. Severe tongue and laryngeal swelling may create a difficult airway. Puffiness of the hands and face with nonpitting edema are also common signs of myxedema (Fig. 208.2). Myxedema however does not need to be present to have severely decompensated hypothyroidism (8).

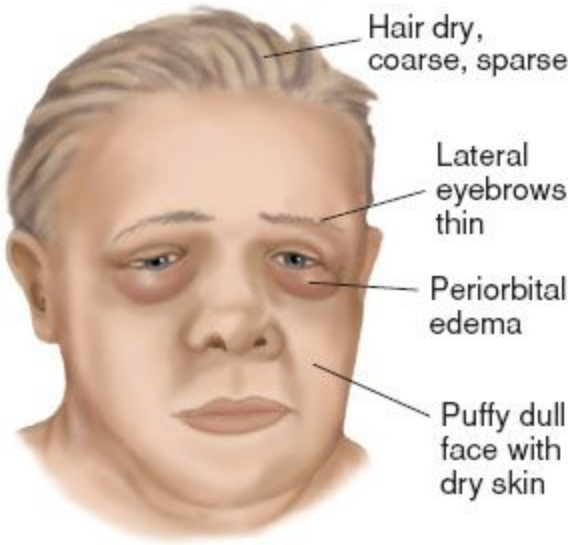

FIGURE 208.2 Myxedema: The patient with severe hypothyroidism (myxedema) has a dull, puffy facies. The edema, often particularly pronounced around the eyes, does not pit with pressure. The hair and eyebrows are dry, coarse, and thinned. The skin is dry. (From Bickley LS Szilagyi P. *Bates' Guide to Physical Examination and History Taking*, 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

DIFFERENTIAL DIAGNOSIS

With a diverse array of symptoms including hypotension, hypothermia, and altered mental status, the differential diagnosis for myxedema coma is broad. In addition, other findings associated with panhypopituitarism and adrenal insufficiency with secondary hypothyroidism may cloud the picture even more. The differential diagnosis of myxedema includes sepsis, meningitis, cold exposure, stroke, SIADH and seizure disorder, intracranial hemorrhage, prolonged hypoglycemic reaction, ingestion of sedative hypnotics, gastrointestinal bleed, as well as numerous other metabolic disorders. The presentation may also be mistaken for acute heart failure with the presence of increased heart size, peripheral edema, pleural effusions, and hypotension. Furthermore, any of these illnesses may occur concomitantly with myxedema and may actually be the precipitant.

ED EVALUATION

Laboratory testing should include TSH, free T_4, urine and blood cultures, electrolytes with glucose, coagulation panel, cortisol level, ECG, and cardiac enzymes. Imaging should include a chest x-ray and head CT when indicated. A LP should be performed if suspicious for meningitis. Severe hyponatremia may contribute to the comatose state. Renal failure with rhabdomyolysis is not uncommon. In contrast to mild hypothyroidism where thrombosis is more likely, severe hypothyroidism is associated with a higher risk of bleeding due to acquired von Willebrand syndrome (type 1) and decreases in factors V, VII, VIII, IX, and X (8). Patients with myxedema coma may have elevated opening pressures in the CSF as well as elevated CSF protein (8).

ED MANAGEMENT

Myxedema coma should be treated very aggressively as the mortality is 30% to 40%. Patients with the greatest risk are elderly patients as well as those with cardiac complications, altered level of consciousness, hypothermia, and sepsis. Table 208.11 shows an algorithm for the treatment of myxedema coma.

TABLE 208.11
Treatment of Myxedema Coma

1. Levothyroxine 200 to 500 µg IV followed by 75 to 100 IV/PO µg per day
2. IV fluids, pressors, and mechanical ventilation as needed; caution with pressors
3. Passive rewarming. Try to avoid active rewarming to avoid excess vasodilation
4. Hydrocortisone 100 mg IV or dexamethasone 6 mg IV an hour prior to thyroxine
5. Treat any precipitants with special attention to a potential infectious etiology

Treatment should consist of thyroid replacement, supportive measures, and recognizing and treating the precipitating cause. Patients must be treated with stress dose steroids prior to thyroid replacement until concomitant adrenal insufficiency has been ruled

out. Hydrocortisone 100 mg should be given intravenously every 8 hours. Initial treatment should involve airway management as the patient's comatose state may be worsened by hypoventilation and severe respiratory acidosis. Mechanical ventilation may be required for the first 36 to 48 hours and in some cases up to 2 to 3 weeks. Patients should not be extubated until they are fully awake as hypoxia may persist even after the respiratory acidosis has been corrected (8).

The emergency physician is sometimes hesitant to give IV thyroxine especially if thyroid function testing results are not yet available or the patient has underlying cardiac disease. Although there may be some risk of precipitating a myocardial infarction, these risks have to be weighed against the benefits of treating the myxedema coma. One study looked at administration of 500 μg of thyroxine as an IV loading dose followed by 100 μg daily and found this regimen to have a lower mortality than with 100 μg daily without a loading dose (22). There will be no immediate signs of clinical improvement after initial administration of thyroxine, as it must be converted to the more active form T_3 first. Initial effects may not be seen for over 24 hours.

Administration of T_3 alone is not considered safe. High T_3 concentrations during treatment have been associated with increased mortality (16,21). It is controversial as to whether T_3 should be administered with T_4 to patients with severely decompensated hypothyroidism. Patients with myxedema have decreased conversion of T_4 to T_3, which is thought to be a protective mechanism against the more biologically active T_3. Although most clinicians treat with thyroxine alone due to a better safety profile (23), combination therapy of T_4 and T_3 has been reported. Instead of administering 300 to 500 mg of T_4, the T_4 dose is reduced to 200 to 300 mg and is given with an initial bolus of 10 mg of T_3. An additional dose of 100 mg T_4 is given 24 hours later and T_3 is continued at 10 mg every 8 to 12 hours until the patient is conscious and able to take maintenance T_4.

Additional supportive measures include treating the underlying cause with early broad-spectrum antibiotics until a source is identified, correcting electrolyte abnormalities, supporting blood pressure, and correcting hypothermia. Passive rewarming is preferred over active rewarming, as there may be an increased risk of vasodilation and worsening hypotension. Hypotension is often corrected with thyroid hormone replacement. If fluids are indicated, dilute preparations should be avoided to avoid worsening hyponatremia.

Severe symptomatic hyponatremia associated with seizures or altered mental status may require administration of small amounts of hypertonic saline. A vasopressin antagonist, conivaptan, has also been used to treat hypothyroid patients with hyponatremia. Conivaptan is thought to work due to high vasopressin levels seen with hyponatremia in the setting of severe hypothyroidism (8).

Vasopressors should be used but with caution as there is an increased risk of an ischemic event in a patient with a long-standing depressed metabolic state. Steroids, as mentioned above, may also be of benefit if hypotension is due to adrenal insufficiency (8). Additional dextrose may be added to intravenous fluids with persistent hypoglycemia.

In addition to treating potential underlying infections, other precipitating events must be addressed as well including myocardial infarction, stroke, congestive heart failure, or any other potential precipitating events as well as a thorough review of medications and dosing.

DISPOSITION

Patients with myxedema coma typically require prolonged ICU stays. Mortality ranges from 15% to 30%. Factors that increase mortality include coma, advanced age, core temperature $<93^{\circ}F$, bradycardia <44 beats/min, hypotension, and concomitant sepsis or myocardial infarction (24).

Common Pitfalls

- Failure to consider the diagnosis of myxedema coma in a patient with altered mental status and a history of hypothyroidism.
- Failure to administer hydrocortisone or dexamethasone prior to giving thyroxine in order to avoid precipitating an adrenal crisis.
- Use of active rewarming that may precipitate hypotension.
- Failure to search for and treat precipitating events, especially infection.

CRITICAL INTERVENTIONS

- IV levothyroxine should be administered prior to thyroid test results in patients with suspected myxedema coma.
- Vasopressors should be used with caution in the treatment of myxedema coma.
- Passive rewarming should be instituted in myxedema patients, because active rewarming may precipitate hypotension.

THYROID NODULES

Thyroid nodules are estimated to be present in about 50% of the population based on postmortem and ultrasound studies. Only about 5% of nodules are cancerous. Typically, thyroid nodules do not require emergency department ancillary testing except for thyroid function tests if clinically indicated. Other diagnoses should be considered in evaluating thyroid nodules, including branchial cleft cyst, thyroglossal duct cyst, neck abscess, lymphoma, reactive lymphadenopathy, and Hodgkin disease.

In nontoxic patients, where there is low clinical suspicion for overt hyperthyroidism, hypothyroidism, acute infection, or airway compromise, outpatient workup is all that is required. Even though these tests are not performed in the emergency department, it is important to understand the diagnostic process for the evaluation of a thyroid nodule so as to communicate better with your consultant and give your patients reassurance as well as a more informative treatment plan. If a patient presents with clinical findings of a nontoxic goiter, thyroid asymmetry, or palpable nodules, follow-up thyroid ultrasound should be arranged. Fine-needle aspiration

biopsy of a goiter is indicated if there is a rapid growth, pain, as well as suspicious findings on ultrasound.

Patients with thyroid nodules associated with an initial low TSH and elevated T_4 require an outpatient thyroid scan rather than a thyroid ultrasound. Thyroid nodules that absorb radioiodine are referred to as “hot nodules” and are typically not cancerous. Nodules that do not take up radioiodine are referred to “cold” nodules and have a 5% chance of being cancerous and require further workup.

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CHAPTER 209

Adrenal and Pituitary Disorders

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The adrenal gland is made up of two distinct glands, the cortex and the medulla. The adrenal cortex is made up of three zones. The outer zone, which is referred to as the zona glomerulosa, secretes the mineralocorticoid aldosterone which maintains salt balance and regulates blood pressure. The intermediate zone, the fasciculata, secretes cortisol, which is a key factor in the body's response to stress. More specifically, it helps to regulate immune function, vascular tone, and metabolism. The inner zone, the reticularis, secretes androgens (sex hormones and their precursors). The adrenal medulla produces the catecholamines epinephrine and norepinephrine. Important adrenal disorders that need to be identified in the emergency department (ED) include the following: inadequate cortisol production (adrenal insufficiency), excess cortisol production (Cushing disease), and excess catecholamine release (pheochromocytoma) (1).

ADRENAL INSUFFICIENCY

Primary adrenal insufficiency or Addison disease is the result of direct destruction of the adrenal cortex which leads to decreased secretion of cortisol, aldosterone, and androgens. Secondary or tertiary adrenal insufficiency arises from failure of the hypothalamic–pituitary axis (HPA) to produce sufficient adrenocorticotropic hormone (ACTH) or corticotropin-releasing

hormone (CRH), which stimulates the adrenal glands to produce cortisol. With secondary adrenal insufficiency, the renin–angiotensin–aldosterone system remains intact. Aldosterone primarily stimulates the kidney to reabsorb sodium and excrete potassium and hydrogen ions. Patients with secondary adrenal insufficiency, therefore, do not have the salt wasting, hyperkalemia, and hypovolemia seen in primary adrenal insufficiency and less often present with hypotension (2). Patients with secondary adrenal insufficiency therefore only require cortisol replacement, whereas patients with primary adrenal insufficiency need both glucocorticoid and mineralocorticoid replacement.

Androgen replacement is typically only needed in preadolescent females for proper development of secondary sex characteristics as well as women with signs of androgen deficiency such as dry itchy skin, decreased libido, and mood instability. The majority of androgens in males are produced in the testes, not in the adrenal gland.

Primary adrenal insufficiency is an uncommon disorder, affecting approximately 100 persons per million (2). When Thomas Addison first described the disease, bilateral adrenal destruction by tuberculosis was the most common cause. Now tuberculosis accounts for $<10\%$ of cases in Western countries, whereas autoimmune disease is responsible for 70% to 90%. The remaining etiologies include other infectious diseases, replacement by metastatic cancer, adrenal hemorrhage or infarction, and drugs (Table 209.1). Autoimmune adrenalitis or "idiopathic" primary adrenal insufficiency is a process involving both humoral and cellular immune mechanisms that are directed at the adrenal cortex. This process is often associated with autoimmune destruction of other endocrine glands and is part of autoimmune polyendocrine syndrome (APS) type I or type II (3). In type I APS, hypoparathyroidism or chronic mucocutaneous candidiasis often precedes the onset of adrenal insufficiency. Type II APS is often associated with autoimmune thyroid disease and type I diabetes mellitus. Hypogonadism, pernicious anemia, vitiligo, and other autoimmune processes may be associated with both types of APS.

Primary adrenal insufficiency associated with APS is more common in females (70%); isolated autoimmune adrenalitis is more common in males in the first two decades of life, and later in life occurs predominantly in females.

TABLE 209.1
Causes of Primary Adrenal Failure

Autoimmune disease: associated with autoimmune polyglandular syndromes
Metastatic cancer: lung, breast, colon, kidney, pancreas, leukemia
Infection: tuberculosis, fungal, viral (CMV, HIV/AIDS), bacteremia, sepsis (Waterhouse–Friderichsen syndrome)
Infiltrative diseases: sarcoidosis, amyloidosis, hemochromatosis
Hemorrhage: anticoagulant therapy, abdominal trauma, post-liver transplantation
Adrenal infarction: hypercoagulable states, adrenal vein thrombosis, arteritis
Drugs: ketoconazole, etomidate, high-dose fluconazole, rifampin, aminoglutethimide, metyrapone, mitotane
Miscellaneous causes: adrenalectomy, adrenomyeloneuropathy, congenital adrenal hyperplasia

Adapted from Kruse JA, Carlson-Fink MP. *Manual of Critical Care.* 1st ed. Philadelphia, PA: WB Saunders; 2003.

With the exception of autoimmune adrenalitis and tuberculosis, other causes of primary adrenal insufficiency are rare (see Table 209.1). Adrenal metastasis is often found on autopsy but rarely causes adrenal insufficiency, as more than 90% of the cortex must be involved to become symptomatic (4). Primary acute adrenal insufficiency may occur as a result of infarction caused by hemorrhage or adrenal vein thrombosis. Adrenal hemorrhage can be associated with sepsis, coagulopathy, thromboembolic disease, hypercoagulable states, trauma, and (rarely) after liver transplantation. When adrenal hemorrhage is associated with meningococcemia, it is referred to as *Waterhouse–Friderichsen syndrome.* It can occur at any age but is somewhat more common in children. Prompt diagnosis and treatment with the appropriate antibiotics is imperative or the patient may die within hours to days. Other pathogens associated with this syndrome include *Pseudomonas*

aeruginosa, Escherichia coli, Streptococcus pneumoniae, Haemophilus influenzae, Neisseria gonorrhoeae, and *Staphylococcus aureus* (5).

The most common cause of secondary adrenal insufficiency (inadequate pituitary ACTH reserve) is suppression of the HPA axis by exogenous glucocorticoids. The likelihood of suppression is related to the dose of glucocorticoids and the duration of treatment. Suppression is unlikely with doses equivalent to <5 mg/d of prednisone and duration of <2 weeks (4).

Depending on the dose and duration of therapy, it may require several months to 1 year after withdrawal of glucocorticoids before the HPA axis again functions normally. Adrenal suppression has also been reported infrequently with prolonged inhaled and topical corticosteroid use (4).

Secondary adrenal insufficiency is otherwise caused by disorders that destroy or compromise pituitary or hypothalamic integrity, such as pituitary or parasellar tumors (prolactinoma, acromegaly, meningioma, craniopharyngioma); hypothalamic tumors; head trauma; infarction (pituitary apoplexy); cranial radiation; infiltrative or inflammatory processes; and hemorrhage (Sheehan syndrome). With the exception of trauma, infarction, and hemorrhage, pituitary and hypothalamic disease tends to result in gradual rather than sudden loss of function.

Adrenal insufficiency is seen in patients with human immunodeficiency virus (HIV) and AIDS at a rate higher than in the general population. Patients with HIV can have both primary and secondary adrenal insufficiencies. Patients with AIDS often have elevated basal serum cortisol levels but have a decreased adrenal reserve as measured by serum cortisol response to prolonged ACTH stimulation. The diagnosis is often overlooked because the vague symptoms are attributed to the patient's medications or to the virus. It appears that many factors contribute to adrenal insufficiency in this population, including HIV itself, opportunistic infections, malignancy, and medications frequently used by HIV-infected patients (6).

Adrenalitis is caused by cytomegalovirus, atypical mycobacterium, or disseminated fungal infection and infiltration

from Kaposi sarcoma. Some drugs used to treat opportunistic infections in AIDS (e.g., ketoconazole) inhibit cortisol synthesis (4,6). Unlike ketoconazole, fluconazole in standard doses is not thought to interfere with cortisol production, although in higher doses adrenal insufficiency has been reported as well (6). Rifampin, which increases cortisol metabolism, may precipitate adrenal crisis in patients with subclinical adrenal insufficiency. Concomitant use of these as well as other drugs that affect cortisol metabolism may require dose adjustment of steroids in patients with adrenal insufficiency. Steroids used for the treatment of *Pneumocystis carinii* pneumonia or in combination with other HIV therapy may lead to secondary adrenal insufficiency. Cases of Cushing syndrome have been described with the concomitant use of fluticasone and ritonavir, as well as severe adrenal insufficiency with discontinuation of fluticasone. Rare case reports of interactions between ritonavir and budesonide or ritonavir and intra-articular triamcinolone have also been reported. Long-term steroid replacement is usually necessary until the HPA recovers (6).

Megestrol acetate, an appetite stimulant used in patients with weight loss related to cancer or AIDS, has also been associated with secondary adrenal insufficiency (6). It was also recently reported that infants of human immunodeficiency virus 1 (HIV-1) infected mothers who were treated before and after birth with the protease inhibitor lopinavir–ritonavir were more likely to experience adrenal dysfunction, including life-threatening adrenal insufficiency in premature infants, compared with a zidovudine-based regimen (7).

Adrenal insufficiency has been observed in 30% to 70% of patients with septic shock. There has been controversy as to whether administration of intravenous steroids is helpful or harmful in the setting of septic shock. In the Surviving Sepsis Campaign, it was concluded that patients with fluid and vasopressor refractive shock should be presumed to have adrenal insufficiency and treated as such, pending the results of confirmatory laboratory data (8).

Etomidate, which is an excellent induction agent for critically ill hypotensive patients, can also have adverse effects on the HPA axis, leading to decreased cortisol production and adrenal insufficiency.

Recent literature has argued that the excellent safety profile of single-bolus etomidate may outweigh the often transient effects of adrenal insufficiency. A large, prospective, randomized control trial of single-dose etomidate (0.3 mg/kg) versus midazolam (0.1 mg/kg) used for rapid sequence intubation of patients meeting sepsis criteria demonstrated no difference in mean hospital stay, ventilator days, or hospital mortality. Prolonged administration of etomidate in the intensive care setting is not recommended, however, because of the potential for adrenal suppression (9).

CLINICAL PRESENTATION

The clinical features of adrenal insufficiency are related to the rate of onset and severity of adrenal deficiency. In most cases, the disease has a gradual onset, and a diagnosis is made only when the patient presents with an acute crisis from an inadequate rise in cortisol secretion during a physiologic stress (10). Adrenal crisis can also occur in patients who are receiving physiologic doses of glucocorticoid if their mineralocorticoid requirements are not met. Acute stressors include, but are not limited to, severe infection, sepsis, alcohol withdrawal, trauma, surgery, myocardial infarction, and other toxic metabolic disease processes. In newborns, traumatic delivery or prolonged and difficult labor may precipitate adrenal crisis (11).

Acute adrenal insufficiency or “addisonian” crisis is a medical emergency that typically presents with altered mental status and hypotension out of proportion to the severity of concurrent illness and may not correct as readily as expected with pressors and fluids. Gastrointestinal symptoms including anorexia, nausea, vomiting, diarrhea, and abdominal pain are the most common initial presenting symptoms. The abdominal pain may suggest an acute abdomen. Unexplained fevers may also occur. Other associated autoimmune endocrine deficiencies may present concomitantly, such as hypothyroidism or gonadal failure.

The presentation of chronic adrenal insufficiency is more subtle, with symptoms of weakness, fatigue, weight loss, intermittent

vomiting, diarrhea or constipation, muscle cramps, arthralgias, and postural hypotension. Low-grade fever and salt craving may also be present. The classic physical finding that differentiates primary from secondary adrenal failure is skin hyperpigmentation or the “suntan that doesn’t fade.” With both acute and chronic primary adrenal insufficiency, pigmentation is seen in sun-exposed areas and in recent scars, palmar creases, nipples, axillae, mucous membranes (vaginal, buccal, and anal), nail beds, and pressure points. This skin manifestation is felt to be due to overproduction of ACTH, which stimulates increased production of melanin.

Patients with secondary adrenal insufficiency may have additional symptoms and signs related to hypothalamic or pituitary disease, such as loss of libido, menstrual disturbances, headache, visual disturbances, galactorrhea, features of acromegaly, or hypothyroidism. Compression of structures near the optic chiasm by the pituitary typically presents as visual-field deficits which are discussed below under pituitary disorders. Hyperpigmentation is rare, because circulating levels of ACTH and related peptides are low (1).

Adrenal crisis is much less common in patients with secondary adrenal insufficiency because the function of the renin–angiotensin–aldosterone system is generally preserved (2). Rarely, adrenal crisis can occur when there is sudden loss of pituitary function because of infarction or hemorrhage. Hypotension can result from sudden loss of ACTH secretion and concomitant decrease in cortisol levels. Although mineralocorticoids play a greater role in the maintenance of volume status, glucocorticoids have a role in maintaining peripheral vascular adrenergic tone as well (2).

The laboratory findings of primary adrenal insufficiency include hyponatremia, hyperkalemia, hypercalcemia, mild metabolic acidosis, hypoglycemia, anemia, lymphocytosis, and eosinophilia. Hypoglycemia is a common presentation in children and infants. Type I diabetics with adrenal insufficiency have a higher incidence of hypoglycemia than type I diabetics without cortisol deficiency. This occurs due to loss of the counter-regulatory effects of the adrenal gland, including loss of gluconeogenesis and lack of the

hyperglycemic effects of epinephrine (4). Hyponatremia is found in approximately 90% of patients and is due to sodium loss and volume depletion secondary to aldosterone deficiency. Mild hyponatremia may still be present in secondary adrenal insufficiency because of increases in vasopressin. Hyperkalemia associated with a mild hyperchloremic metabolic acidosis is also due to mineralocorticoid deficiency and occurs in about 60% of patients. In secondary adrenal insufficiency, the potassium level is usually normal because mineralocorticoid function is intact. One final potential laboratory abnormality is a rapid drop in hemoglobin, which may be seen with adrenal hemorrhage.

DIFFERENTIAL DIAGNOSIS

Because of the high mortality associated with acute adrenal insufficiency, the diagnosis should be considered and therapy instituted prior to confirmatory laboratory data. Hypovolemic shock that is refractory to standard resuscitation and unexplained changes in mental status should increase the clinician's suspicion for acute adrenal insufficiency. Abrupt discontinuation of steroids in the setting of chronic glucocorticoid use should prompt consideration for steroid administration in a patient who presents with other physiologic stressors.

The differential diagnosis of acute adrenal crisis includes other causes of cardiovascular collapse and shock including myocardial infarction, heart failure, hypovolemia, sepsis, and pulmonary embolism. Adrenal insufficiency should be in the differential diagnosis for any potential etiology of the acute abdomen and other gastrointestinal disorders. It should also be in the differential for fever of unknown etiology and altered mental status.

Chronic adrenal insufficiency is difficult to diagnose because the symptoms are more gradual in onset. It is often confused with a "flu-like" illness. The examination is often unremarkable. Laboratory evaluation may not be particularly revealing in all cases, especially with secondary insufficiency. The differential diagnosis includes psychiatric illness, chronic fatigue syndrome, and anorexia nervosa

(12). It should also be in the differential diagnosis for the evaluation of chronic "wasting syndromes," unexplained weight loss, and nonspecific arthralgias and myalgias.

ED EVALUATION

The first steps in the evaluation of adrenal insufficiency are a thorough history and a physical examination. The diagnosis may be overlooked because attention is often focused on the precipitating physiologic stressor or illness. Laboratory studies should include electrolytes, blood urea nitrogen (BUN), creatinine, glucose, complete blood count (CBC), baseline ACTH level, cortisol level, and thyroid function tests. Coagulation factors should be obtained with suspected adrenal or pituitary hemorrhage, especially in the setting of anticoagulant use or suspected disseminated intravascular coagulopathy. Chest x-ray, electrocardiogram, urinalysis, blood cultures, urine cultures, and any other test to rule out other potential stressors for an adrenal crisis should be obtained in the proper clinical setting.

The diagnosis of adrenal insufficiency cannot typically be made on the basis on a random single cortisol level. A low level, especially in the clinical setting of physiologic stressors, may suggest adrenal insufficiency. An early morning (8 AM) plasma cortisol level lower than 3 μg/dL confirms adrenal insufficiency, whereas a value higher than 15 μg/dL makes the diagnosis highly unlikely. Cortisol levels in the range of 3 to 15 μg/dL may be seen in patients with primary, secondary, or tertiary adrenal insufficiency.

Although it is not necessary in the ED, adrenocortical function can be evaluated with a Cortrosyn (Cosyntropin) stimulation test. Cortrosyn is a synthetic derivative of ACTH. This test only assesses the ability of the adrenal cortex to increase cortisol production in response to the ACTH derivative. It does not test the integrity of the HPA axis. The metyrapone test blocks cortisol synthesis which should increase ACTH production and can therefore be used to test hypothalamic and pituitary function. Differentiating between primary and secondary adrenal insufficiency may also be done by

measurement of basal plasma ACTH levels. An elevated ACTH level with a low cortisol level is consistent with primary adrenal insufficiency, and a low or normal ACTH level with a low cortisol level is consistent with secondary or tertiary adrenal insufficiency.

For the standard Cortrosyn stimulation test, 250 μg of IV or IM cortrosyn is administered and then cortisol levels are checked at 0, 30, and 60 minutes. Using absolute cortisol levels in critically ill patients to diagnose adrenal insufficiency is controversial as total cortisol levels may be affected by circulating proteins. Hypoproteinemia may lead to false-positive ACTH stimulation tests and overtreatment with steroids. Some authors have suggested using free cortisol or at least calculated free cortisol rather than total cortisol levels. Adrenal failure is likely if the peak post-cosyntropin cortisol level is <15 μg/dL. Cortisol levels >18 μg/dL are usually interpreted as excluding adrenal failure; however, cortisol levels <25 mg/dL may be inadequate in some critically ill patients. In sepsis, adrenal insufficiency is likely when baseline cortisol levels are <10 μg/dL or when the cortisol rises by <9 μg/dL after stimulation by 250-μg cosyntropin (2,8).

Abdominal computed tomography (CT) scan may demonstrate adrenal hemorrhage, metastasis, or calcification (seen with fungal adrenalitis and 50% of tuberculosis adrenalitis). These are incidental findings that are typically seen when these patients are being evaluated for potential causes of an “acute” abdomen. Head CT may demonstrate pituitary hemorrhage, infarction, or adenoma. Head CT is typically done in these patients when they present with altered mental status, severe headache (as with pituitary hemorrhage), or new visual disturbances (12).

KEY TESTING

- Electrolytes, BUN, creatinine, glucose
- CBC
- ACTH level
- Cortisol level
- Thyroid function tests

ED MANAGEMENT

Initial management of an adrenal crisis should include reversal of shock with vasopressors and isotonic saline as well as treatment of the precipitating illness. After fluid resuscitation, attention should be directed at treating hypoglycemia and other electrolyte abnormalities (Table 209.2). In severe cases, it may be necessary to treat hyperkalemia. The total body potassium level however is often low and total serum potassium value can decrease even more after glucocorticoids are administered. Symptomatic hyponatremia should also be corrected, generally with fluid restriction after the patient had been fluid resuscitated to a euvolemic state. There has been some success with the use of vasopressor receptor antagonists for the treatment of severe hyponatremia with primary adrenal insufficiency since ADH is increased due to salt wasting and excessive water losses from decreased aldosterone production. Hypertonic saline may rarely be indicated if the patient is symptomatic with altered mental status or persistent seizures from the hyponatremia. Monitoring of SvO_2 and central venous pressure through central venous access may be necessary, especially in the clinical setting of sepsis with hypotension.

TABLE 209.2
Treatment of Acute Adrenocortical Insufficiency (Adrenal Crisis)

1. Obtain adequate IV access. Central access to assist hemodynamic monitoring
2. Normal saline boluses to correct hypovolemia. Monitor carefully for signs of fluid overload
3. Obtain glucose level and replace accordingly
4. Send additional laboratory studies including electrolytes, creatinine, and baseline cortisol and ACTH levels
5. Hydrocortisone 100 mg IV (use dexamethasone 6–8 mg IV if ACTH stimulation test to be performed later for diagnostic purposes)
6. General supportive measures as indicated
7. Further evaluation to determine potential cause of crisis (electrocardiography, chest x-ray, blood and urine cultures)

Stress-dose steroids should be given prior to laboratory confirmation if adrenal insufficiency is suspected especially in the setting of vasopressor-resistant shock (8,13). Dexamethasone 10 mg IV is recommended for glucocorticoid replacement because it does not interfere with the cosyntropin test. Alternatively, an immediate intravenous bolus injection of hydrocortisone 100 mg should be followed by approximately 200 mg over 24 hours. Different dosing regimens have been suggested to mimic circadian rhythm variation in cortisol levels. Hydrocortisone 200 mg/d can be divided in doses every 8 hours or as a continuous infusion for 48 hours. Once the patient is stable, parenteral dosing can be changed to an oral dose of 50 mg every 8 hours for six doses, then taper to 30 to 50 mg/d in divided doses. When adrenal insufficiency presents concomitantly with hypothyroidism, steroids should be administered before giving levothyroxine so as not to precipitate adrenal crisis (14).

Glucocorticoid use has been studied extensively as a therapeutic agent in patients with sepsis. Although a short course of high-dose glucocorticoids (methylprednisolone 30 mg/kg) has been shown to be potentially harmful and ineffective in patients with sepsis, recent studies have demonstrated that a lower dose (hydrocortisone 200 to 300 mg/d) has been associated with decreased mortality and organ dysfunction in patients with vasopressor-resistant shock and relative adrenal insufficiency. Lower-dose steroids are, therefore, recommended in goal-directed therapy of sepsis patients presenting with hemodynamic instability (8,13).

Patients with known chronic adrenal insufficiency or chronic steroid use typically take a daily dose of 15 to 25 mg/d (15 mg in the morning and 10 mg at night) with slightly higher doses for primary than secondary adrenal insufficiency (20 to 25 mg vs. 15 to 20 mg). Adjustments should also be made based on patient's body surface area as well as other medications, which may affect cortisol metabolism. Patients with hyperthyoidism or using exogenous thyroxine may need to have the dosage of cortisol increased as well. Mineralocorticoids are usually only replaced in primary adrenal insufficiency with a fludrocortisone dose of 0.1 (0.05 to 0.25) mg/d taken as a single dose in the morning. Increased mineralocorticoids

may be needed in infants and neonates and may have to be adjusted in tropical climates (14). Hydrocortisone has some mineralocorticoid activity, whereas decadron and prednisolone have very little. When hydrocortisone is therefore administered at higher doses, additional mineralocorticoids may not be necessary. Dosing of steroids can be adjusted based on symptoms. Fatigue, nausea, myalgia, lack of energy, and weight loss may indicate underreplacement, whereas weight gain, central obesity, osteoporosis, impaired glucose tolerance, and hypertension may suggest overreplacement (14).

The most important component of crisis prevention is "*sick-day rules*" training for the patient and their families. They should be aware of stress-related glucocorticoid dose adjustments. Patients should have a hydrocortisone emergency kit which should contain 100 mg of solu-cortef to be given as an intramuscular injection (14). Intercurrent illness, such as respiratory infection associated with fever, requires doubling of the daily glucocorticoid dose until recovery. In the event of vomiting or diarrhea, the hydrocortisone dose should be doubled; if the medication is not kept down due to vomiting, glucocorticoids should be administered parenterally. For major stress events, such as surgery, trauma, or childbirth, 100- to 200-mg hydrocortisone should be administered over 24 hours (14).

DISPOSITION

Patients with acute adrenal insufficiency require admission to an intensive care unit. Subspecialty consultation should be requested. Patients in whom chronic adrenal insufficiency is suspected should be admitted to the hospital for evaluation. Rarely, patients with known chronic adrenal insufficiency who present with mild physiologic stressors may be discharged from the ED if the concomitant illness is addressed and the patient is started on stress-dose steroids with an appropriate taper. This approach requires appropriate consultation and very close follow-up.

Common Pitfalls

- Failure to consider the diagnosis of adrenal insufficiency in critically ill patients with septic shock or hypotension refractory to intravenous fluids and vasopressors.
- Failure to increase the steroid dose (to two to four times the usual regimen) in patients on chronic steroid therapy who have concurrent illness or physiologic stress.
- Failure to provide steroid replacement and adequate fluid resuscitation before performing an ACTH stimulation test.
- Failure to administer stress-dose steroids in a suspected case of myxedema coma before administering thyroxine as this could potentially precipitate an adrenal crisis.

CUSHING SYNDROME

Cushing syndrome is characterized by glucocorticoid excess secondary to increased adrenal cortisol production or chronic glucocorticoid therapy. The syndrome as originally described by Harvey Cushing in 1932 includes truncal obesity, hypertension, proximal muscle weakness, and striae. Pituitary oversecretion of ACTH, adrenal neoplasms, and ectopic ACTH production by a nonpituitary tumor are potential etiologies. The most common cause of Cushing syndrome is prolonged exogenous steroid administration.

Cushing disease, which is specifically due to excessive ACTH secretion from the pituitary, accounts for 70% of individuals with naturally occurring Cushing syndrome (15). Cushing disease typically occurs in women between 20 and 40 years of age and has a gradual onset. Most of these patients have pituitary microadenomas. When macroadenomas are responsible, patients may present with headaches or visual changes due to pressure on the optic chiasm.

Cushing syndrome can be caused not only by an ACTH-secreting carcinoma (e.g., small-cell bronchogenic carcinoma, pancreatic cancer, bronchial carcinoid, or carcinoma of the thymus) but rarely by nonpituitary tumors that secrete corticotropin-releasing hormone (16).

Adrenal neoplasms are another cause of Cushing syndrome, comprising about 20% of cases. In children, the most common

adrenal tumors just involve symptoms of access androgens. Among adults, Cushing syndrome alone is the most common followed by a mixed clinical presentation of both glucocorticoid and androgen excess. Adrenal tumors are usually unilateral, and approximately 50% are malignant (4).

CLINICAL PRESENTATION

Obesity and weight gain are common findings in Cushing syndrome (Table 209.3). Seventy-five percent of patients have deposition of fat in the face, described as “moon facies,” and around the neck and shoulders, known as a “buffalo hump.” Other fat accumulation occurs within the mesentery, producing truncal obesity. Half of patients have skin atrophy and abdominal striae which are characteristically reddish purple and wider than 1 cm. Other skin findings include easy bruising, poor wound healing, edema, acne or pigmentation, hirsutism, and a flushed appearance to the face. Old photographs are useful in showing the progression of changes, especially the development of moon facies, truncal obesity, and hirsutism. Patients also complain of fatigue and weakness. A proximal myopathy can be detected in about 60% of patients (15).

TABLE 209.3
Clinical Features of Cushing Syndrome

Feature	Percent
Truncal obesity	90–95
Thoracocervical/facial fat deposits (buffalo hump/moon faces)	80–85
Gonadal dysfunction	75–80
Menstrual irregularities	—
Loss of libido	—
Hirsutism	75–80
Hypertension	65–75
Psychiatric abnormalities	40–60
Ranging from depression to psychosis	—
Skin atrophy/striae formation	50–60
Proximal muscle weakness	50–60
Glucose intolerance/diabetes mellitus	50–60
Osteoporosis	40–50
Infection	—
Tuberculosis	—
Fungal	—
Ophthalmologic complications	20–30
Elevated intraocular pressures	—
Exophthalmos	—

Osteoporosis develops from mobilization of calcium, resulting in vertebral compression and pathologic fractures. Glucose intolerance and insulin resistance are other features, but overt diabetes is seen in only about 20% of patients. Hypertension is common. Menstrual abnormalities, sexual dysfunction, psychosis, emotional lability, and paranoia may also occur. Weight gain and growth retardation may be clinical signs in children (16).

Laboratory findings are generally nonspecific. The hemoglobin and hematocrit are high to normal, and the white blood cell count usually shows a leukocytosis with a predominance of neutrophils. The electrolytes are often normal, but there may be hypokalemia, hypochloremia, hyperglycemia, and hypercholesterolemia. Hypokalemic metabolic alkalosis may be present in cases of extreme cortisol excess (15).

Certain populations of patients with Cushing syndrome may have slightly different clinical presentations. Patients with ectopic ACTH syndrome caused by small cell lung carcinoma lack many of the

typical clinical features of Cushing syndrome such as obesity and weight gain. These patients may have a more dramatic presentation due to the rapid course of the malignancy as well as high ACTH levels and cortisol. Hyperpigmentation, myopathy, glucose intolerance, and hypokalemic alkalosis may predominate. Female patients with primary adrenal carcinomas may present with signs and symptoms of excess androgens which include hirsutism, acne, breast atrophy, deepening of the voice, temporal hair recession, and clitoral enlargement in addition to symptoms of glucocorticoid access (15). In contrast to nonmalignant causes of Cushing syndrome, adrenal carcinoma also has a more rapid onset and progression, with hypokalemia and abdominal pain as common symptoms.

Cushing syndrome during pregnancy deserves special mention, as it is associated with increased mortality owing to preeclampsia, hypertension, diabetes, wound breakdown, opportunistic infections, and fractures. Increased cortisol effects on the fetus include an increased rate of spontaneous abortion, perinatal death, premature birth, and intrauterine growth retardation. The diagnosis is difficult because of the physiologically increased cortisol levels during the second and third trimester of pregnancy (11).

DIFFERENTIAL DIAGNOSIS

Because many features of Cushing syndrome, such as obesity, hypertension, amenorrhea, and weakness, are common in other illnesses and thus nonspecific, the diagnosis can be difficult. Differentiation of Cushing syndrome from pseudo-Cushing syndrome can sometimes be a challenge. A pseudo-Cushing state is defined as having some of the clinical features and biochemical evidence of Cushing syndrome. Patients with chronic alcoholism may exhibit some characteristics suggestive of Cushing syndrome, but these abnormalities resolve after discontinuation of alcohol. Increased glucocorticoids may also lead to depression or emotional liability, which may make it difficult to differentiate between depression or other psychiatric illness and mild Cushing syndrome.

ED EVALUATION

It is difficult and most often not necessary to make a definitive diagnosis of Cushing syndrome in the ED. A single midnight serum cortisol level >7.5 mg/dL can be an early but not definitive finding. Several factors can affect random cortisol levels however. Diurnal variation makes random measurements of serum cortisol have little diagnostic value. Random serum cortisol levels during pregnancy and in females taking estrogens can also be falsely elevated as well.

Screening for Cushing syndrome can be done by a 24-hour urinary free cortisol determination, 1-mg dexamethasone suppression test, or midnight salivary cortisol. The 24-hour free cortisol can give cortisol levels lower than the true cortisol if the patient has a decreased GFR and higher levels with excess fluid intake. False-positive dexamethasone suppression test can occur with concomitant use of other medications such as dilantin, phenobarbital, and rifampin, as they can increase clearance of dexamethasone (15). Patients should be referred to an endocrinologist if the constellation of symptoms suggests the diagnosis.

KEY TESTING

- Electrolytes, BUN, creatinine, glucose
- CBC
- ACTH level
- Cortisol level—midnight cortisol level most helpful; random measurements are of little diagnostic value

ED MANAGEMENT

From the ED point of view the most important thing about managing Cushing syndrome is to first recognize the disease and then be aware of the potential increased mortality associated with it. Cushing syndrome is associated with increased risks of opportunistic infections as well as excess steroids masking a febrile illness or an acute abdomen. It is also important in the ED to be aware that these patients with a “Cushingoid” appearance from

exogenous steroid use may require excess steroids during an acute illness.

The treatment of Cushing syndrome for the endocrinologist focuses on reducing cortisol secretion, particularly surgical removal of a causative tumor. Complications of treatment that may be seen in the ED include postoperative diabetes insipidus (DI) and hypothyroidism, although hypothyroidism may take some time to present.

Patients who undergo bilateral adrenalectomy may develop Nelson syndrome, the effect of an enlarging pituitary tumor that secretes high levels of ACTH. This syndrome presents with hyperpigmentation and visual changes due to tumor encroachment on the optic chiasm. Up to 25% of patients who undergo bilateral adrenalectomy develop Nelson syndrome within 10 years of surgery.

When surgery is not successful or when it is not an option, as in metastatic adrenal carcinoma or ectopic ACTH production, hypercortisolism may be treated by medications that inhibit steroidogenesis. They include ketoconazole, metyrapone, mitotane, aminoglutethimide, and etomidate. Patients using these medications may require glucocorticoid replacement to avoid adrenal insufficiency. Rarely, when medication is not successful for hypercortisolism secondary to ectopic ACTH production, bilateral adrenalectomy may be necessary.

DISPOSITION

Well-appearing stable patients may be discharged with appropriate follow-up. Patients with impending adrenal crisis or any complications such as sepsis, or uncontrolled diabetes should be admitted to the hospital for monitoring and initiation of appropriate therapy.

Common Pitfalls

- Because the symptoms are common and nonspecific, the clinician may fail to consider the diagnosis of Cushing syndrome.

- Failure to recognize that patients with Cushing syndrome may have an immunocompromised state which can predispose them to developing opportunistic infections, reactivation of fungal infections and tuberculosis, as well as dissemination of otherwise self-limited viral disease such as herpes and chickenpox.
- Excess glucocorticoids may mask fever and other systemic signs of infection, including pain from an acute abdomen.
- Patients with Cushing syndrome from exogenous steroids may be at risk of adrenal crisis if they do not receive stress-dose steroids during an acute illness.

PHEOCHROMOCYTOMA

Pheochromocytomas are catecholamine-producing tumors that originate from chromaffin cells of the adrenal medulla. Tumors that arise from outside the adrenal gland are referred to as extra-adrenal pheochromocytomas or paragangliomas (17). They secrete norepinephrine, epinephrine, and occasionally other vasoactive peptides, but norepinephrine is usually predominant. The "rule of 10s" for pheochromocytomas is the following: 10% are extra-adrenal, 10% involve both adrenal glands, 10% are malignant, 10% are familial, 10% occur in children, and 10% are multiple (other than bilateral adrenal) (16).

Pheochromocytoma is present in $<1\%$ of hypertensive patients but is a potentially treatable cause of hypertension. If symptomatic pheochromocytomas are not treated, they may lead to acute myocardial infarction, congestive heart failure (CHF), stroke, or death. Pheochromocytoma may also however be completely asymptomatic. A retrospective study by the Mayo Clinic reported that 50% of diagnoses were identified at autopsy. Approximately 10% are discovered incidentally on CT (18). Pheochromocytomas may also occur in familial syndromes, including multiple endocrine neoplasia 2A and 2B, neurofibromatosis, and von Hippel–Lindau disease. Family history may be an important clue to the diagnosis, and family members of individuals with these syndromes should all be screened (10).

CLINICAL PRESENTATION

All patients with persistent uncontrollable hypertension should be screened for the diagnosis of pheochromocytoma. The clinical manifestations of pheochromocytoma are caused by the physiologic effects of the catecholamines and may be extremely variable (18). The classic triad of episodic headache, excessive sweating, and tachycardia occur together in less than 50% of these patients. Hypertension is the most common finding and may be sustained or paroxysmal, with varying frequency and duration. Sudden paroxysms of hypertension may cause the patient to feel a throbbing palpitation or headache. As an individual symptom, headache is the most common occurring in about 90% of symptomatic pheochromocytomas. Focal neurologic symptoms, blurred vision, and altered mental status may develop as well. Symptoms may be transient, lasting minutes or several hours. They may occur once a month or several times a week, but they usually increase in frequency as the tumor grows.

Attacks may occur in the absence of stimuli or with precipitating factors such as trauma, childbirth, exercise, abdominal pressure, or postural changes. These patients may have a hypertensive response to various medications and other agents including but not limited to the following: glucagon, steroids, droperidol, anesthesia induction, cocaine, amphetamines, tricyclic antidepressants, MAO inhibitors, certain cold medications, nasal decongestants, reglan, compazine, radiographic contrast, naloxone, and tyramine-containing foods (18,19). If a patient is being treated with beta-blockade alone in the ED for unexplained tachycardia, hypertension, or pulmonary edema and has a sudden spike in blood pressure, pheochromocytoma should be added to the differential diagnosis as well.

Other symptoms of catecholamine excess may be more subtle and persistent. These may include heat intolerance, increased sweating, weight loss, nausea, weakness, anxiety, dyspnea, orthostatic hypotension, and signs of hyperglycemia such as polyuria and polydipsia. In pregnancy, the symptoms may be positional as well. The gravid uterus may compress the tumor in a supine position

leading to normal blood pressure with sitting or standing and hypertension when lying flat (11).

Chronic constriction of the arterial and venous beds may decrease the total intravascular volume, resulting in orthostatic symptoms despite a baseline increase in blood pressure. Acute arterial vasospasm from elevated catecholamine levels may rarely lead to limb ischemia (17).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of pheochromocytoma is broad and includes most conditions in which there is a hyperadrenergic state and any disease processes associated with a hypertension.

Pheochromocytoma should be included in the differential diagnoses of any acute cardiovascular or cerebral vascular process presenting with refractory hypertension or orthostatic hypotension. Other hyperdynamic states commonly seen in the ED include hyperventilation, panic attacks, premenopausal hot flashes, hypoglycemic reaction, acute alcohol or opiate withdrawal, drug reaction, illicit drugs, hyperthyroidism, labile essential hypertension, carcinoid syndrome, serotonin syndrome, altered mental status, pulmonary embolus, and toxemia of pregnancy (18). Abrupt withdrawal of clonidine or beta-blockers as well as patients on MAO inhibitors who ingest tyramine-containing food may have a similar presentation as well. The absence of proteinuria may differentiate pheochromocytoma from hypertension associated with preeclampsia. Pheochromocytoma in pregnancy is associated with a markedly increased fetal and maternal morbidity and mortality if an antenatal diagnosis is not made (11).

ED EVALUATION

The ED evaluation typically does not involve immediate testing for pheochromocytoma. With a high clinical suspicion, as in patients with a family history of an MEN 2, von Hippel–Lindau, or imaging that is highly suggestive of a pheochromocytoma, fractionated plasma metanephrines may be ordered during the initial ED

evaluation. Outpatient 24-hour urine collection for catecholamines and their metabolites can be ordered if the patient is considered to have a low risk for pheochromocytoma such as with an asymptomatic adrenal mass or paroxysmal self-limiting hyperadrenergic symptoms. Overall, the 24 hour urine collection for fractionated metanephrines and catecholamines has a high sensitivity and specificity (98% sensitivity and specificity). An elevated fractionated plasma metanephrine level has a highest sensitivity (96% to 100%) but a lower specificity (85% to 89%) (20). The sensitivity is lower in patients over 60 years and also in patients with dopamine-secreting neoplasms. Most laboratories now measure fractionated metanephrines and catecholamimes rather than total plasma levels due to decreased false-positive and negative tests with the newer methods. Patients may still have inaccurate results if they are concomitantly taking certain antipsychotic medications, antihypertensive medications, or were recently administered contrast agents. The method of obtaining plasma and urine samples may also still lead to false-positive or negative testing even with the more sensitive tests (20).

Both magnetic resonance imaging and CT scan have about a 98% to 100% sensitivity. The specificity is only about 70% however due to the high prevalence of incidental adrenal tumors. MRI is more accurate than CT scan at differentiating pheochromocytoma from other adrenal tumors. CT with IV contrast has been demonstrated to precipitate a hypertensive crisis, so it is suggested to use a lower-osmolarity contrast agent if there is a high clinical suspicion for pheochromocytoma. A low-osmolarity contrast agent may increase diastolic blood pressure but does not increase plasma catecholamine levels and is not associated with hypertensive crises (21). Scintigraphy using a norepinephrine analog can also be used to identify extra-adrenal pheochromocytomas (16). These tests are not necessary for initial management in the ED.

KEY TESTING

- MRI or CT scan image of adrenal gland

ED MANAGEMENT

The priority for the emergency physician is to treat the hypertensive emergency, if present, and volume expansion. Sodium nitroprusside (starting at 1 to 3 μg/kg/min) helps to control hypertension through its arterial and venous dilating effects. If pheochromocytoma is suspected or hypertension is resistant to treatment with nitroprusside, alpha-blockade can be achieved with intravenous phentolamine (2.5- to 5-mg bolus IV at 1 mg/min followed by a continuous infusion titrated to effect). Because of phentolamine's short half-life, doses may be repeated every 3 to 5 minutes. Parenteral beta-blockade is used to treat dysrhythmias and resistant hypertension but should be given only after alpha-blockade so as to avoid paradoxical hypertension from unopposed alpha effects (16). Labetalol has been used as an alternative, but its use is controversial because it has much greater beta- than alpha-blockade. The use of labetalol has been associated with some case reports of paradoxical hypertension (18). Newer antihypertensive drugs such as Carvedilol (Coreg) have similar side effects to labetalol and should be avoided in the preoperative treatment of a pheochromocytoma. Nicardipine may also be used with a starting dose of 5 mg/hr and titrated up to 15 mg/hr with increases of 2.5 mg/hr every 15 minutes.

Any patient who is already diagnosed with a pheochromocytoma should undergo surgical resection after appropriate medical management. There has been a lack of consensus regarding the recommended preoperative drug regimen. Oral alpha-agonists, calcium channel blockers, and angiotensin inhibitors have all been recommended. For tachyarrhythmias, oral beta-blockers or calcium channel blockers are recommended after appropriate alpha-agonist blockade. Typically, patients will be placed on an oral alpha-agonist such as prazosin, doxazosin, terazosin, or phenoxybenzamine 2 to 3 days before starting beta-blockers. In most cases, this medication regimen is started 7 to 14 days prior to surgery to normalize blood pressure and to avoid a catecholamine-induced crisis during surgery. Various oral calcium channel blockers may be used as well including amlodipine, nicardipine, nifedipine, and verapamil.

Calcium channel blockers can supplement alpha-blockers in patients who do not have adequate blood pressure control as well as replace alpha-blockers in patients that are having adverse side effects such as orthostatic hypotension (19).

It has also been suggested that the patient should be put on a high-salt diet preoperatively as well (if no contraindication such as CHF) to help expand the contracted blood volume. In addition, there is an extensive list of medications which is mentioned above that should be avoided as they may precipitate release of catecholamines (19).

DISPOSITION

Typically, patients with uncontrolled hypertension and symptoms suggesting hypertensive crisis require admission. Stable patients who are asymptomatic should be referred for prompt follow-up with an endocrinologist for further evaluation and testing.

Surgical resection is the definitive treatment of choice once a pheochromocytoma has been identified and located. The recurrence rate after surgical resection is $<10\%$, and the 5-year survival after surgery is approximately 95%. About 25% of patients continue to have hypertension after removal of the pheochromocytoma; the cause is believed to be irreversible vascular damage from previous uncontrolled catecholamine excess, or underlying essential hypertension, but the blood pressure in these patients is usually readily controlled with standard antihypertensive regimens.

Common Pitfalls

- Be aware of certain medications (listed earlier in the text) and higher-osmolarity contrast media, as potential precipitants of hypertensive crisis in patients with pheochromocytoma.
- Pheochromocytoma should be considered in patients who complain of transient symptoms that have resolved by the time of ED evaluation. These patients may benefit from appropriate referral and outpatient evaluation.

- Because patients with pheochromocytoma are often hypovolemic, sudden blood loss or sudden loss of vascular tone can result in precipitous and severe hypotension.

PITUITARY DISORDERS

The pituitary gland is divided into an anterior and posterior lobe. The anterior pituitary hormones are regulated by hypothalamic releasing and inhibitory hormones and by negative feedback of the target glands' hormone production. Prolactin, which affects lactation, is the only pituitary hormone not directly increased by hypothalamic regulation but may be inhibited by PIF (prolactin-release inhibitory factor). Antidiuretic hormone (also referred to as ADH or vasopressin) and oxytocin are produced in the hypothalamus and travel through the pituitary stalk to the posterior pituitary gland where they are stored and released. ADH regulates blood pressure, stimulates water reabsorption, and reduces excretion of urine. Oxytocin helps to regulate uterine contraction and lactation as well (22).

In addition to prolactin, ADH, and oxytocin, the pituitary gland secretes TSH (thyroid-stimulating hormone), FSH and LH (follicle stimulating hormone and luteinizing hormone), ACTH (adrenocorticotropic hormone), and GH (growth hormone) in response to corresponding hypothalamic releasing hormones. In turn, these stimulating hormones affect the secretions of the thyroid, gonads, and adrenal glands.

Tumors of the pituitary may present with hypofunction, hypersecretion, or mass effect. Pituitary hemorrhage, infiltration, destruction, injury, or necrosis more often presents with hypofunction. Hyperfunctioning pituitary adenomas may be the cause of Cushing disease or secondary hyperthyroidism, as discussed above, as well as prolactinomas and acromegaly (22).

Prolactinomas typically present as lactation in males and females but may be associated with other symptoms such as hypogonadism, headaches, or visual-field deficits secondary to mass effect. If there are no signs of mass effect or headaches, the ED evaluation would

typically only involve a pregnancy test (for females), a review of the patient's medication list, and an endocrinology referral if no other obvious cause of lactation is identified. Multiple medications have been associated with increased lactation and discontinuation of them may prevent the need for a more exhaustive laboratory workup and imaging. The presence of severe headache and/or signs of mass effect with lactation however may warrant a CT or MRI to rule out more serious pathology such as an inflammatory process, malignancy, or aneurysm.

The evaluation for acromegaly, which is typically due to a growth hormone–secreting pituitary macroadenoma, can be referred to an endocrinologist for further confirmatory testing unless there is other secondary pathology requiring ED evaluation such as CHF or hyperglycemia. In order to properly recognize and refer a patient with potential acromegaly, the following typical characteristics of this disease process are listed: coarse facial features, thick coarse skin, enlargement of limbs, fingers, and ears, macroglossia and malocclusion of teeth with gaps, hypertension, CHF, arrhythmias, diabetes mellitus, carpal tunnel syndrome, neuropathic joints, signs of pituitary mass effect, and pituitary insufficiency (22).

Evaluation of pituitary disease in the ED most often focuses on hypopituitarism as this clinical spectrum of disease more often requires immediate interventions. Hypopituitarism is a decreased production of one or more of the regulatory hormones which leads to decreased end-organ function.

CLINICAL PRESENTATION

The clinical manifestations of hypopituitarism include end-organ hypofunction such as hypothyroidism, hypogonadism, and adrenal insufficiency. Pituitary adenomas are the most common cause of acquired hypopituitarism. Hypogonadism is the most frequent manifestation of the endocrine abnormalities.

Pituitary adenomas can cause headache and vision loss when larger tumors compress the optic chiasm or optic nerve. The most common visual defect is bitemporal hemianopsia which is a loss of

vision in the outer half of both right and left visual fields. If the tumor extends lateral to the sella where the pituitary sits, cavernous sinus involvement can lead to impingement of cranial nerves III, IV, V1, V2, and VI. Patients with a sellar mass pressing on the optic chiasm should have a Humphrey visual-field testing by an ophthalmologist. Pituitary adenoma is found in about 10% to 20% of autopsies, but the incidence of clinical symptoms attributed to pituitary tumors is quite low at about 2 to 8 per 100,000 persons per year (23).

Pituitary insufficiency may also be caused by other intrasellar and parasellar tumors, ischemic necrosis secondary to sickle cell anemia, vasculitis, or diabetes, granulomatous disease (sarcoidosis, tuberculosis, Wegener granulomatosis), cavernous sinus thrombosis, infections (fungal, meningitis, syphilis), empty sella syndrome, aneurysmal dilation of the internal carotid, autoimmune destruction, surgical removal, radiation-induced destruction of pituitary tissue, traumatic brain injury, subarachnoid hemorrhage, or postpartum pituitary necrosis (Sheehan syndrome). Secondary hypopituitarism may be due to abnormalities of the hypothalamus or pituitary stalk and compression by an aneurysm or tumor (16).

Hypopituitarism occurring in the postpartum patient after an episode of hypotension or shock is known as *Sheehan syndrome.* These patients may fail to lactate in the postpartum period and may develop amenorrhea, gonadal atrophy, and symptoms of hypothyroidism and adrenal insufficiency. Some, however, remain undiagnosed until a later exposure to stress triggers an adrenal crisis.

When hypopituitarism occurs from an acute loss of pituitary function, it is referred to as *pituitary apoplexy*. Infarction or hemorrhage of an enlarged pituitary gland or pituitary tumor is the most common cause. The presenting signs are sudden onset of severe headache, visual changes, meningismus, decreased level of consciousness, and cranial nerve palsies. Headache is the most common symptom and it often mimics the presentation of a subarachnoid hemorrhage (22).

Destruction of at least 90% of the pituitary is required before complete panhypopituitarism becomes clinically apparent, and chronic or partial hypopituitarism may present with subtle signs of single or incomplete hormone deficiencies. When a patient with known hypopituitarism presents to the ED because of a concurrent illness unrelated to the endocrine system or the central nervous system, he or she should continue to receive usual hormonal replacement therapy, including stress doses of corticosteroids, if necessary.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hypopituitarism is so broad because of the wide spectrum of endocrine functions that the HPA regulates. Growth hormone deficiency may initially present as lack of energy or decreased exercise tolerance. Gonadal dysfunction may present with amenorrhea in a menstruating woman or with impotence in a man. Hypothyroidism may often be initially misdiagnosed as depression or chronic fatigue. ACTH deficiency typically presents in later stages and may present with a spectrum from fatigue and vague gastrointestinal symptoms, with or without hypoglycemia, to adrenal crisis from an intercurrent stressor (16). Posterior pituitary involvement may present with polydipsia and polyuria secondary to decreased antidiuretic hormone from DI. Patients with DI may also have seizures, headaches, and visual-field defects in addition to evidence of volume contraction.

ED EVALUATION AND MANAGEMENT

The diagnosis of hypopituitarism is generally made after extensive testing by an endocrinologist, including measurement of specific hormone levels and magnetic resonance imaging of the pituitary. The treatment of hypopituitarism consists of lifelong hormone replacement.

Emergency hormone replacement is rarely needed in the ED. Suspected deficiencies in growth hormone as well as gonadotropin hormones can be referred to an endocrinologist. Blood samples

should be sent for measurement of plasma cortisol, prolactin, ACTH, and TSH levels, and thyroid function studies before instituting cortisol replacement if the patient is stable and pituitary disease is suspected. As mentioned above, decadron can be given initially to the unstable patient with suspected adrenal insufficiency rather than hydrocortisone, so as not to interfere with the ACTH stimulation test. Glucocorticoid replacement should precede administration of levothyroxine if myxedema coma is also suspected, because thyroxine accelerates the metabolism of cortisol and can precipitate an adrenal crisis (22).

Electrolyte panels should also be obtained looking for hypernatremia if central DI is suspected when the patient has symptoms of excess thirst or urination. It is also important to rule out other causes of polyuria and polydypsia such as new-onset diabetes mellitus. With central DI, the patient will have a very dilute urine with a low specific gravity despite the presence of increased serum osmolality and elevated sodium (16). Typically, patients with central DI can drink enough fluids to replace urinary loss. If hypernatremia is severe, patients may require fluid replacement with dextrose containing hypotonic IV fluids. Do not correct the sodium more than 0.5 mmol/L/hr. In central DI, the drug of choice is desmopressin which is a synthetic analog of ADH. It can be given IV, subcutaneous, intranasal, or orally two to three times a day. Carbamazepine, chlorpropamide, thiazide diuretics, and nonsteroid anti-inflammatory agents may control polyuria in mild cases by enhancing the effect of antidiuretic hormone on the renal tubules and collecting duct (16).

KEY TESTING

- Electrolytes, BUN, creatinine, glucose
- Cortisol
- Prolactin
- ACTH
- TSH/TFT

DISPOSITION

Patients with evidence of shock or hemodynamic instability should be admitted to an intensive care unit setting and have prompt endocrine evaluation if hypopituitarism is suspected. Other patients should be referred to an endocrinologist for further testing and diagnosis.

Common Pitfalls

- Most hypopituitarism is chronic and difficult to diagnose. Some patients may have been given psychiatric diagnoses.
- Acute loss of pituitary function is also difficult to diagnose unless a pituitary abnormality is apparent on an imaging study.

CRITICAL INTERVENTIONS

- In suspected but unconfirmed acute adrenal insufficiency, administer dexamethasone rather than hydrocortisone, as it will not interfere with the ACTH (cosyntropin) stimulation test; do not wait for cosyntropin test to give patient steroids
- If pheochromocytoma is suspected or hypertension is resistant to treatment with nitroprusside, administer IV phentolamine (2.5- to 5-mg boluses)
- Beta-blockade is used to treat tachyarrhythmias and resistant hypertension but should be used only after alpha-blockade has been accomplished, to avoid paradoxical hypertension from unopposed alpha-effects
- Patients with Cushing syndrome may require exogenous steroids during stress to avoid an adrenal crisis

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of Christine A. Kletti, Clare T. Sercombe, and Louis J. Ling to the content of this chapter.

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CHAPTER 210 Disorders of Sodium and Water Metabolism

Sandra A. Craig

Serum sodium concentration and serum osmolality are normally maintained within a narrow range by homeostatic mechanisms involving thirst, antidiuretic hormone (ADH), and renal handling of sodium.

Sodium and chloride ions are normally separated from the glomerular filtrate in the ascending limb of the loop of Henle, leaving behind a hypotonic filtrate, and resulting, in the absence of ADH, in the net excretion of free water. Increases in serum osmolality above the normal range of 280 to 300 mOsm/L are detected by osmoreceptor neurons in the hypothalamus and cause an increase in thirst and in circulating levels of ADH. ADH acts on the collecting ducts of the renal tubules, increasing free-water reabsorption. This reabsorption results in the excretion of low volumes of urine of relatively high osmolality and a return of the serum osmolality toward normal. ADH is also secreted in response to decreases in intravascular volume and in response to noxious stimuli such as pain, fear, nausea, hypoxia, and surgical procedures (1).

Sodium balance is regulated independently of ADH by atrial natriuretic peptide–mediated changes in the degree of sodium reabsorption in the renal tubule. Hypovolemic states such as those caused by hemorrhage or dehydration are associated with increased sodium absorption in the renal tubule and decreased delivery of sodium to the tubular diluting sites. Conversely, increases in intravascular volume and glomerular filtration rate suppress

proximal tubular sodium reabsorption, resulting in increased delivery of sodium to diluting sites.

Disorders of water balance can be traced to abnormalities of thirst or water acquisition, glomerular filtration rate, renal sodium transport, or ADH metabolism.

HYPONATREMIA

CLINICAL PRESENTATION

Hyponatremia is physiologically significant insofar as it reflects a state of extracellular hypo-osmolality in which free water shifts from the vascular space to the intracellular space (see Fig. 210.1). Although the resulting cellular edema is well tolerated by most tissues, the brain is sensitive to changes in cell volume. The clinical manifestations of hyponatremia, usually associated with serum sodium levels <130 mEq/L, are related primarily to cerebral edema. Symptoms include headache, difficulty in concentrating, confusion, lethargy, agitation, nausea, vomiting, and seizures. Anorexia and muscle cramps are also common.

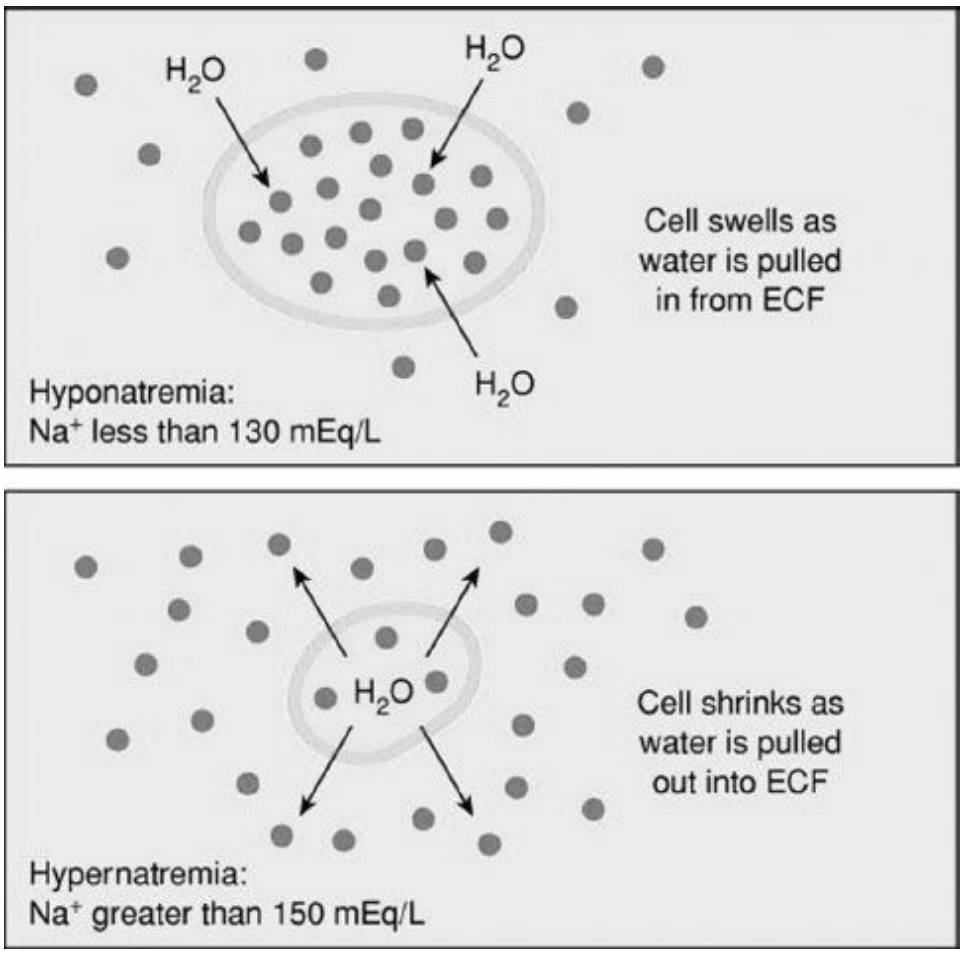

FIGURE 210.1 Effect of extracellular sodium on cell size.

The incidence and severity of manifestations increase not only with the degree of hyponatremia but also with the rate at which it develops. When the serum sodium level falls gradually over a period of days or weeks, the brain can compensate via active extrusion of solutes and passive movement of water into the extracellular space. Serum sodium values as low as 110 mEq/L may thus be reached with minimal symptomatology. However, a rapid fall in the serum sodium, for example, from a normal level to $<$125 mEq/L within 48 hours, exceeds the capacity of these compensatory mechanisms and can lead to profound cerebral edema, causing coma or brainstem herniation (1).

DIFFERENTIAL DIAGNOSIS

The diagnosis of hyponatremia rests entirely on the ability to obtain and measure accurately the concentration of sodium in the patient's serum. The possibility of erroneous sampling should always be considered, especially when the reported value does not seem consistent with the clinical situation. Was the specimen properly labeled? Was it drawn from a venous site proximal to an infusion of hypotonic saline or dextrose 5% in water (D_5W)? Is there an error in laboratory measurement or recording? When an error of some kind is suspected, a fresh sample should be obtained and tested before diagnostic or therapeutic procedures are initiated.

There are several clinical conditions in which an accurately measured, low serum sodium concentration does not represent a true hypo-osmolar state. The most common is moderate to severe hyperglycemia. Extracellular glucose accumulation causes movement of free water into the extracellular space, resulting in hyponatremia and a normal or increased serum osmolarity. The serum sodium value decreases by approximately 2.4 mEq/L for each 100-mg/dL increase in the serum glucose value (2). This hyponatremia is not physiologically significant, and it resolves as normoglycemia is reestablished. This phenomenon, termed hypertonic hyponatremia, is also noted in patients treated with mannitol, glycerol, sorbitol, radiocontrast media, or IVIG suspended in 10% maltose solution (1).

Pseudohyponatremia refers to a falsely low serum sodium measurement in patients whose plasma contains excessive amounts of lipid or protein. In this situation, the plasma water in which sodium is dissolved occupies a smaller proportion of the blood specimen. Laboratory methods that measure sodium content per unit of plasma report low sodium levels, even though the concentration of sodium in serum water is normal. This situation occurs when the serum sodium concentration is measured by the flame emission spectrophotometry or indirect potentiometry method but not with direct potentiometry. Indirect potentiometry is performed in approximately 66% of chemistry laboratories in the United States (3). The emergency physician must remain aware of this phenomenon. Because serum osmolarity is normal, water metabolism is completely undisturbed. Hyperlipidemia severe enough to produce

pseudohyponatremia is almost always associated with a lipemic appearance of the serum. Hyperproteinemia of a sufficient degree to cause pseudohyponatremia is commonly caused by multiple myeloma or administration of intravenous immune globulin. Point-of-care testing utilizes direct potentiometry, and serum sodium results remain accurate in the setting of hyperlipidemia or hyperproteinemia.

Measurement of serum osmolality will distinguish true hypotonic hyponatremia from these other states.

ED EVALUATION

The ED evaluation of true hyponatremia has two goals. The first is to define the chronicity of the hyponatremic state, which must be based primarily on historic clues. Patients with a paucity of symptoms despite sodium levels <125 mEq/L are likely to have chronic hyponatremia. Acute hyponatremia is less common than chronic hyponatremia and should be suspected in patients with a history of sudden free-water loading (e.g., patients with schizophrenia who may exhibit psychogenic polydipsia, infants given only tap water for 1 to 2 days, and postoperative patients who have received hypotonic IV fluids, enemas, or bladder irrigation fluids) (1).

The second goal in the evaluation of the hyponatremic patient is to establish the cause. Hyponatremia should be classified as hypovolemic, euvolemic, or hypervolemic based on the history and physical examination (Fig. 210.2). Classification helps to narrow the list of causes and aids in the selection of therapy. Hypovolemic patients demonstrate signs of volume depletion, such as tachycardia, orthostasis, dry mucous membranes, diminished skin turgor, oliguria, or azotemia. A low fractional excretion of sodium (<0.5%) and low fractional excretion of urea (<55%) may be helpful in identifying subtle cases of hypovolemia (4). Hypervolemia is manifested by the presence of congestive heart failure, peripheral edema, or ascites. Patients who appear neither volume depleted nor volume overloaded are classified as having euvolemic hyponatremia.

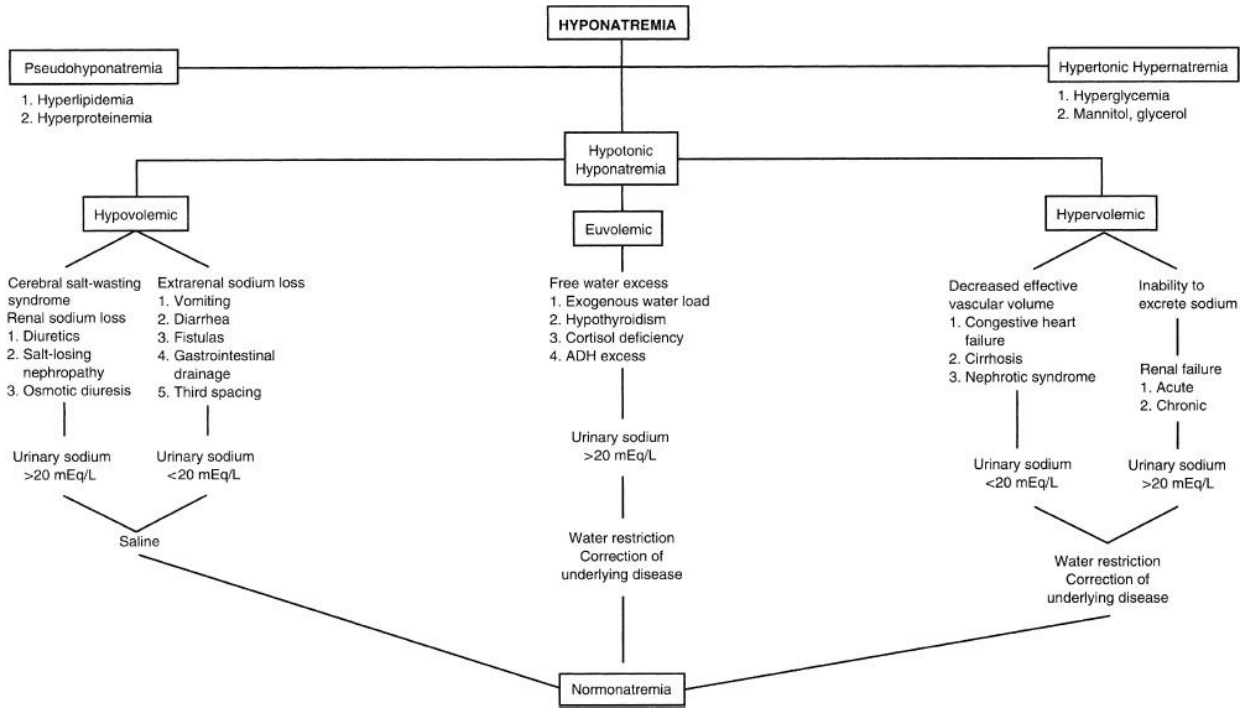

FIGURE 210.2 Algorithm for diagnosis and treatment of hyponatremia.

Hypovolemic Hyponatremia

Patients with hypovolemic hyponatremia have decreased total body sodium stores. Nonrenal causes of sodium depletion include vomiting, diarrhea, fistulas, gastrointestinal drainage tubes, excessive sweating, and third spacing of fluids from peritonitis, pancreatitis, or burns. Cerebral salt-wasting syndrome should be considered in patients with intracranial disease such as traumatic brain injury, tumor, stroke, meningitis, or intracranial surgery (1). Renal causes of sodium loss include osmotic diuresis and salt-wasting nephropathies such as medullary cystic disease and obstructive uropathy. Thiazide diuretics (hydrochlorothiazide, metolazone, indapamide) are one of the most common causes of severe hyponatremia, especially in the elderly population. Hyponatremia typically occurs between 5 and 25 days after initiating therapy. The precise mechanism remains unknown.

The nonrenal causes of hypovolemic hyponatremia are associated with a urine sodium value of <20 mEq/L, and renal causes are

associated with a urine sodium value of >20 mEq/L. As a general principle, hyponatremia does not develop unless free-water intake exceeds free-water excretion. In these hypovolemic conditions, hyponatremia is maintained by low glomerular filtration rates that preclude adequate free-water excretion and by high levels of ADH secreted in response to hypovolemia.

Hypervolemic Hyponatremia

Hyponatremic patients with clinical signs of total body sodium excess, usually evidenced by the presence of edema, are classified as having hypervolemic hyponatremia. Two situations are associated with inappropriate increases in body sodium stores. The first is renal retention of sodium in response to states of decreased effective intravascular volume (e.g., congestive heart failure, cirrhosis, and nephrotic syndrome). The second is an inability of the kidney to excrete ingested sodium loads because of acute or chronic renal insufficiency.

In patients with hypervolemic hyponatremia, the evaluation should include a search for signs of decreased cardiac output, increased portal vein pressure, nephrotic range proteinuria, or renal insufficiency. Patients with decreased effective vascular volume caused by heart failure, cirrhosis, and nephrotic syndrome typically have urine sodium values that are <20 mEq/L; those with renal insufficiency typically have values >20 mEq/L.

Euvolemic Hyponatremia

Patients who appear neither dehydrated nor edematous are considered to have euvolemic hyponatremia. As with the other types of hyponatremia, the low serum sodium concentration implies that free-water intake has occurred at a rate that exceeds the kidneys' ability to excrete it. This disorder can occur in patients with psychogenic polydipsia (who, if renal function is normal, must drink at least 15 L of water per day), but it has also been noted in patients who have been given tap water enemas or in infants given tap water bottle feedings. This group is identified by the history of excessive

free-water administration and by a urine osmolality that is appropriately low, generally <100 mOsm/L (5). Hyponatremia in association with a grossly normal volume status may also be seen in some patients with renal failure who have ingested more free water than can be promptly excreted, given their decreased glomerular filtration rate.

An often considered but uncommon cause of euvolemic hyponatremia is the syndrome of inappropriate ADH secretion (SIADH) (Table 210.1), in which ADH is secreted in excessive amounts despite the presence of hyponatremia and adequate intravascular volume. This syndrome is associated with a variety of pulmonary and central nervous system (CNS) conditions, malignancy, acquired immunodeficiency syndrome (AIDS), and the use of a number of medications (Table 210.2) (1). The diagnostic criteria for SIADH are as follows:

- Hypotonic hyponatremia
- Inappropriately concentrated urine (UOsm >100 mOsm/L)
- Normal renal excretory function
- Normal adrenal and thyroid function
- Absence of hypovolemia and dehydration
- Absence of edema

Measurement of ADH levels is not helpful in making the diagnosis, because the ADH level is also commonly elevated when hyponatremia is linked to other causes.

TABLE 210.1
Causes of Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH)

Diseases of the Central Nervous System
Infection
Trauma
Neoplasm
Vascular
Degenerative diseases
Psychosis

Pulmonary Disease
Pneumonia
Active tuberculosis
Abscesses
Asthma
Aspergillosis

Metabolic Disease
Acute porphyria

Neoplasms
Lung
Pancreas
Duodenum
Lymphoma
Ureter
Ewing sarcoma
Prostate

Stress
Trauma

Drugs
See **Table 210.2**

Idiopathic

TABLE 210.2
Drugs Associated with Hyponatremia

Enhanced Effect of ADH

Nonsteroidal anti-inflammatory drugs
Chlorpropamide
Tolbutamide

Increased Release of ADH

Amiodarone
ACE inhibitors
Aripiprazole
Atovaquone
Bromocriptine
Carbamazepine
Carboplatin
Cisplatin
Clofibrate
Clozapine
Cyclophosphamide
Duloxetine
Felbamate
Haloperidol
Ifosfamide
Interferon
Levetiracetam
Lorcainide
MDMA (ecstasy)
Mirtazapine
Monoamine oxidase inhibitors (moclobemide)
Opiates
Oxcarbazepine
Phenothiazines
Proton-pump inhibitors
Selective serotonin reuptake inhibitors
Sulfonylureas
Tricyclic antidepressants
Venlafaxine
Vinblastine
Vincristine
Thiazides

Impaired Water Excretion Independent of ADH

Acetazolamide
Desmopressin
Eplerenone
Heparin
Oxytocin thiazides

ADH, antidiuretic hormone; ACE, angiotensin-converting enzyme; MDMA, 3,4 methylenedioxy-methamphetamine.

Two additional causes of euvolemic hyponatremia must be excluded before making the diagnosis of SIADH or exogenous water toxicity—hypothyroidism and cortisol deficiency. Hyponatremia caused by cortisol deficiency is rarely associated with a serum sodium level <120 mEq/L, and it corrects promptly after glucocorticoid replacement. Hypothyroidism has been associated with sodium levels as low as 110 mEq/L and is treated by thyroid hormone replacement. The mechanism of hyponatremia in these conditions remains incompletely understood.

Postoperative hyponatremia is a form of euvolemic hyponatremia that deserves special mention because of its iatrogenic nature and potential for serious sequelae. Surgical patients experience multiple

stimuli for ADH secretion such as pain, fear, and nausea. Numerous case reports describe development of acute severe hyponatremia and elevated levels of ADH in otherwise healthy patients who receive hypotonic IV or bladder irrigation fluids after elective surgery. Permanent neurologic sequelae, including brainstem herniation and death, are known to occur. For this reason, hospitalized patients should never be exposed to hypotonic fluid infusions in the immediate postoperative period (1).

KEY TESTING

- Obtain serum sodium level from correct patient, correct site
- Serum osmolality is low in cases of true hypotonic hyponatremia
- Obtain serum glucose and calculate corrected serum sodium if hyperglycemic
- Check serum protein and lipids if lack of symptoms suggests pseudohyponatremia

ED MANAGEMENT

The treatment of hyponatremia depends on the severity of symptoms and the rate at which hyponatremia has developed. It is important to distinguish between acute and chronic hyponatremia, because the pathophysiology and appropriate treatment are different.

Patients with acute hyponatremia (i.e., developing in <48 hours) are at risk for severe CNS effects, such as obtundation, seizures, and brainstem herniation, at levels of 125 mEq/L or less. Cerebral edema develops as free water shifts from the vascular space to the intracellular space within a period too short to allow the neurons to compensate by extruding cellular solutes. Cardiopulmonary arrest may occur secondary to brainstem herniation (1,6). Meticulous attention must be given to maintaining adequate airway and oxygenation. The source of excess free water must be immediately identified and eliminated. Patients with obtundation or seizures should receive hypertonic (3%) saline to increase the serum sodium rapidly but only enough to arrest the progression of symptoms. An increase of 4 to 6 mEq/L is usually sufficient to reverse cerebral

edema and terminate hyponatremic seizures. Further correction should proceed at an overall rate of 8 to 10 mEq/L in the first 24 hours, and serum sodium levels should be closely monitored. In theory, acute hyponatremia can be corrected more rapidly without risk of adverse consequences, but, in practice, it may be difficult to be certain of the time course over which hyponatremia developed and the degree of cellular compensation that may already have occurred.

Chronic hyponatremia must be managed especially carefully. Overaggressive therapy is potentially more dangerous than the condition itself. In these patients, the brain cells have had time to reduce their solute content to match that of the hypo-osmotic serum and are relatively protected from cerebral edema. When patients such as these have the serum sodium concentration increased rapidly, a significant number develop an osmotic demyelination syndrome, characterized by focal myelin destruction in the pons and extrapontine areas (6,7). Symptoms begin 1 to 7 days after overly rapid correction of the serum sodium and consist of dysarthria, dysphagia, seizures, altered mental status, quadriparesis, and hypotension (6,7). The diagnosis is confirmed by magnetic resonance imaging (MRI) of the brain, although lesions may not be seen until 10 to 14 days after the onset of symptoms. The condition is typically associated with permanent sequelae. The risk of osmotic demyelination syndrome appears to be low in patients whose chronic hyponatremia is corrected at a rate of <0.5 mEq/L/hr. In order to stay well clear of correction rates that risk osmotic demyelination, the goal should be to increase serum sodium by 8 to 10 mEq/L in the first 24 hours, 14 to 16 mEq/L in the first 48 hours, and 16 to 18 mEq/L in the first 72 hours (6). Osmotic demyelination syndrome is rarely associated with rapid correction of hyponatremia of <24 hours duration (5,7).

Hypertonic saline is indicated only for the initial correction of severely symptomatic acute or chronic hyponatremia. The appropriate volume of hypertonic saline required to produce a given change in the serum sodium level may be estimated using the following formula:

$$\text{Required volume} = \frac{(Na_{desired} - Na_{current})\ (TBW)}{Na_{IV\ fluid} - Na_{current}}$$

For a 50-kg woman with 60% total body water (TBW) and serum sodium of 113 mEq/L, the volume of 3% NaCl (513 mEq/L) required to raise the serum sodium by 4 mEq/L would be

$$\frac{(4\ \text{mEq/L})\ (50\ \text{kg} \times 0.6)}{(513 - 113)} = 0.3\ \text{L or } 300\ \text{mL}$$

One might give 100-mL boluses of 3% NaCl every 10 minutes, repeated up to a total of 300 mL until resolution of seizures and then proceed with other steps to increase the serum sodium by a total of 8 to 10 mEq/L for the first 24 hours. Hypovolemic hyponatremia should be treated with normal saline. Hypervolemic hyponatremia is often difficult to treat, because the underlying disorders are usually not readily reversible. Sodium and water restriction is usually the best alternative. Diuretics may result in transient loss of sodium and water but may ultimately decrease the glomerular filtration rate and limit free-water excretion. Patients with euvolemic hyponatremia should have their free-water intake restricted, and any identifiable underlying cause should be treated. Diuretic-induced hyponatremia responds to withdrawal of the offending medication, liberalized sodium intake, and repletion of total body potassium.

The parenteral ADH (arginine vasopressin) receptor blocker conivaptan (Vaprisol) was developed and Food and Drug Administration (FDA) approved it in 2008 for the treatment of euvolemic hyponatremia such as SIADH and hypervolemic hyponatremias resulting from congestive heart failure, cirrhosis, or the nephrotic syndrome. Several double-blind placebo-controlled trials demonstrated that conivaptan is more effective than water restriction alone in increasing serum sodium in hospitalized patients with serum sodium of 115 to 130 mEq/L. More recently, a V2 selective receptor antagonist, tolvaptan, has been FDA-approved for oral use in patients with euvolemic and hypervolemic hyponatremia. At this time, the FDA has limited its use to 30 days in patients without known liver dysfunction, due to early reports of severe liver

injury. Further research is needed to define the appropriate clinical indications and safety profile of these agents (6,8–10).

CRITICAL INTERVENTIONS

- Distinguish acute from chronic hyponatremia based on history and mental status.
- Intervene immediately in cases of severe hyponatremia with obtundation or seizures.
- Correct chronic hyponatremia at < 0.5 mEq/L/hr in order to avoid osmotic demyelination syndrome.
- Monitor serum sodium closely during therapy to avoid overly rapid correction.

DISPOSITION

Evidence-based guidelines for disposition of patients with hyponatremia do not exist, so admission decisions must be made case by case based on thorough understanding of underlying physiology. Decisions should be based on the chronicity of hyponatremia and the severity of symptoms more than on the absolute serum sodium level. Essentially all patients with acute hyponatremia should be admitted. These patients usually present with severe neurologic signs: obtundation, seizures, or cardiopulmonary arrest caused by brainstem herniation. Patients with chronic hyponatremia and significant symptoms such as lethargy, vomiting, seizures, or obtundation should also be admitted, so that serial sodium levels can document improvement of serum sodium at the appropriate rate. Patients with asymptomatic or minimally symptomatic chronic hyponatremia (nausea without vomiting or altered mental status) in whom a clear cause of hyponatremia is identified (e.g., thiazide use) can be discharged with instructions to discontinue the offending agent and have serum sodium levels rechecked in 24 to 48 hours.

Common Pitfalls

- Consider the possibility of sampling error, hyperglycemia, hyperlipidemia, or hyperproteinemia before making the diagnosis

of hypotonic hyponatremia.
- Consider the possibility of hyponatremia in high-risk groups, including elderly patients on diuretics, psychiatric patients, infants given only tap water, postoperative patients receiving hypotonic fluid therapy, and patients with malignancy or AIDS.
- Acute symptomatic hyponatremia should be recognized and treated quickly to avoid cerebral edema and brainstem herniation. Chronic hyponatremia should be corrected at an overall rate less than 0.5 mEq/L/hr to minimize the risk of osmotic demyelination syndrome.
- Accidental overcorrection of serum sodium is common. Follow serum sodium levels closely during therapy.

HYPERNATREMIA

Hypernatremia is considerably less common than hyponatremia, because even a small increase in the serum sodium concentration is a potent stimulus to thirst. Elevated serum sodium levels develop only in patients who are unable to experience thirst or are unable to gain access to water. Hypernatremia is most often seen at the extremes of age.

CLINICAL PRESENTATION

Hypernatremia reflects a state of intravascular hyperosmolarity that results in the efflux of water from the intracellular space to the extracellular space. Signs and symptoms are primarily related to CNS dehydration. Mental status changes range from irritability to lethargy, confusion, delirium, seizures, and coma. Muscle tone tends to be increased, as are deep tendon reflexes. CNS hemorrhage into the subarachnoid, intracerebral, or subdural space is seen in severe cases and is thought to be caused by tearing of bridging veins as they are stretched by shrinkage of brain tissue (11).

As with hyponatremia, the severity of symptoms correlates with the severity of hypernatremia and the rate at which it develops. When the serum sodium value increases gradually over several days or weeks, neurons respond by retaining excess quantities of

osmotically active solutes. This retention minimizes the efflux of free water from the cells and delays the onset of symptoms until relatively extreme levels of hypernatremia are achieved. When hypernatremia develops rapidly (in <48 hours), this adaptive mechanism is overwhelmed, and symptoms develop at a lower serum sodium level.

ED EVALUATION

It is helpful to classify hypernatremia as hypovolemic, hypervolemic, or euvolemic on the basis of clinical signs of dehydration or volume overload. Classification helps to narrow the list of causes and aids in the selection of therapy (Fig. 210.3).

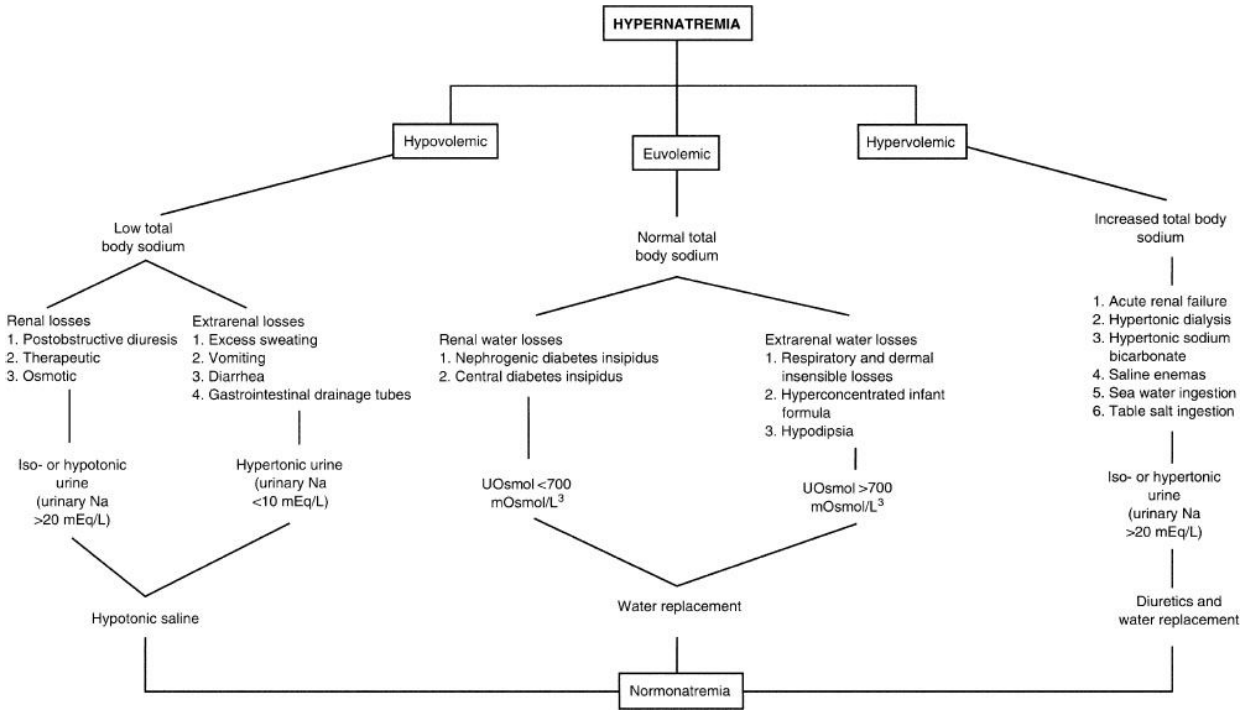

FIGURE 210.3 Algorithm for diagnosis and treatment of hypernatremia.

Hypovolemic Hypernatremia

Patients with hypovolemic hypernatremia exhibit signs of dehydration such as tachycardia, orthostasis, dry mucous membranes, diminished skin turgor, oliguria, and azotemia.

Hypovolemia implies that total body sodium stores are decreased, and hypernatremia implies that free water has been lost to a greater degree than sodium. There are nonrenal and renal causes. Nonrenal causes of hypovolemia include excessive sweating, protracted vomiting, diarrhea (hyperosmotic nasogastric feedings, acute gastroenteritis, lactulose), and gastrointestinal drainage tubes; the urine sodium concentration is <10 mEq/L. Renal causes include postobstructive, osmotic, or therapeutic diuresis or cerebral salt-wasting syndrome; the urine sodium is >20 mEq/L. To achieve a hypernatremic state, the loss of hypotonic fluids must be coupled with inadequate free-water replacement (1).

Hypervolemic Hypernatremia

Patients with signs of fluid overload (e.g., pulmonary edema or peripheral edema) are classified as having hypervolemic hypernatremia. This group has increased total-body sodium stores with a smaller increase in total-body free water. The differential diagnosis includes acute renal failure, use of hypernatremic dialysate solutions, seawater or soy sauce ingestion, and excessive administration of sodium in the form of hypertonic saline, sodium bicarbonate, hyperalimentation, or saline enemas or emetics. An enteral overdose of as little as 4 teaspoons of table salt can result in a serum sodium concentration of 160 mEq/dL in the average adult. Patients who have taken an overdose of table salt but have had no intake of water may not have overt signs of hypervolemia. The urine sodium value is >20 mEq/L in these cases.

Euvolemic Hypernatremia

Patients who appear neither dehydrated nor edematous are considered to have euvolemic hypernatremia, implying normal total body sodium stores and an isolated loss of free water. This condition may occur in comatose or intubated patients whose insensible free-water losses are not adequately replaced. It is common in patients whose insensible losses are accelerated because of tachypnea or fever. Euvolemic hypernatremia is seen in infants whose powdered

formula is inadequately diluted or, rarely, in persons with an intrinsic defect in the hypothalamic thirst drive, a condition known as essential hypernatremia. In all of these cases, the urine osmolarity is appropriately >700 mOsm/L during water deprivation.

Diabetes insipidus causes euvolemic hypernatremia due to inappropriate loss of free water in the urine. In this condition, there is an inability to maximally concentrate urine during periods of water deprivation. This may be due to inadequate hypothalamic secretion of ADH (central diabetes insipidus) or an inability of the kidneys to respond adequately to circulating ADH (nephrogenic diabetes insipidus). In either case, hypernatremia is accompanied by inappropriately dilute urine (UOsm <700 mOsm/L[3]), even during water restriction.

KEY TESTING

- Obtain serum sodium in patients with altered mental status, especially at extremes of age
- Urine sodium distinguishes renal from nonrenal causes of hypovolemic hypernatremia
- Euvolemic hypernatremia with urine osmolarity <700 suggests diabetes insipidus
- Consider brain CT in those with severe hypernatremia to identify CNS hemorrhage

ED MANAGEMENT

The underlying cause of hypernatremia should be identified and eliminated. When choosing the concentration and volume of fluid used to correct serum sodium, as with the treatment of hyponatremia, it is important to distinguish between acute hypernatremia (<48 hours duration) and chronic hypernatremia (>48 hours duration), because cell physiology and the response to therapy are different.

Acute hypernatremia is less common and usually develops in the setting of inadvertent sodium administration. Severe neuronal dehydration develops, and the cells are unable to rapidly adapt by

retention of additional cellular osmoles. Subarachnoid, intracerebral, and subdural hemorrhage may occur. Acute hypernatremia should be corrected rapidly, using D_5W or oral administration, until acute manifestations begin to improve. Diuretics should be added for patients with clinical signs of volume overload.

More commonly, hypernatremia develops over several days or weeks because of slower loss of hypotonic fluid or insensible free-water loss. Neurons adapt by retaining cellular solutes, minimizing movement of free water out of the cell. Rapid administration of hypotonic saline or D_5W in these patients carries a risk of cerebral edema. Chronic hypernatremia should be normalized at a steady rate of <0.5 mEq/L/hr (12).

Hypotensive patients should receive 0.9% normal saline (154 mEq/L) until they are normotensive and can be started on hypotonic fluids. The free-water deficit can then be estimated using the following formula:

$$\text{Water deficit} = \frac{\text{TBW}\ (\text{Na}_{\text{actual}} - \text{Na}_{\text{desired}})}{\text{Na}_{\text{actual}}}$$

where total body water (TBW) is 60% of the usual body weight. Replacement fluids can be administered as D_5W or oral water, with 30% of fluids given over the first 24 hours, and 70% of fluids given over the next 48 hours (1).

Patients with diabetes insipidus should receive DDAVP in addition to free-water replacement. Hypervolemic patients with chronic hypernatremia may require diuretic therapy in addition to free-water replacement.

CRITICAL INTERVENTIONS

- Distinguish acute from chronic hypernatremia based on history and mental status.
- Intervene immediately in cases of acute hypernatremia to avoid CNS hemorrhage.
- Correct chronic hypernatremia at less than 0.5 mEq/L/hr so as to avoid cerebral edema.

DISPOSITION

Evidence-based guidelines for disposition of patients with hypernatremia do not exist. Admission decisions must be made case by case based on a thorough understanding of underlying physiology. Decisions should be based on the chronicity of hypernatremia and the severity of symptoms more than on the absolute serum sodium level. Factors such as underlying illness, age, and ability to sense thirst and acquire water should be considered. Essentially all patients with acute hypernatremia should be admitted. These patients often experience severe neurologic signs: irritability, lethargy, confusion, delirium, seizures, and coma. Computed tomography (CT) of the brain is indicated in severely symptomatic patients to look for subarachnoid, intracerebral, or subdural hemorrhage, which would mandate neurosurgical consultation.

Patients with chronic hypernatremia and significant symptoms, such as irritability, lethargy, confusion, seizures, or coma, should be admitted so neurologic status can be monitored. Patients should be admitted until serial sodium levels document improvement of serum sodium steadily over 48 to 72 hours. Patients with asymptomatic chronic hypernatremia in whom a reversible cause of hypernatremia is addressed (i.e., fever, dehydration, access to water) can be discharged and have serum sodium levels checked in 24 to 48 hours.

Common Pitfalls

- Consider the possibility of hypernatremia in high-risk patients: infants and demented, comatose, or intubated patients without access to free-water replacement.
- Chronic hypernatremia should be corrected gradually in order to minimize the risk of cerebral edema.

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CHAPTER 211 Disorders of Potassium Metabolism

Daniel J. Combs and Robert G. Buckley

OVERVIEW OF POTASSIUM HOMEOSTASIS

Potassium is the body's major intracellular cation. The average 70-kg person has approximately 3,500 mEq of potassium—98% of which resides intracellularly—primarily within muscle cells (1). The remaining 2% is located extracellularly, where the potassium plasma concentration is maintained within a narrow range of 3.5 to 5 mEq/L (2). Because of this enormous intracellular-to-extracellular gradient, potassium serves as the main determinant of resting cell membrane potential, wherein small shifts can result in important alterations in nerve and muscle depolarization (1). Therefore, both hypo- and hyperkalemic states can lead to life-threatening impairments in neuromuscular and cardiac function.

The average adult takes in roughly 100 mEq of dietary potassium daily, with 90% renally excreted. The remaining 10% is excreted in stool, and that amount can increase dramatically in diarrhea, where concentrations as high as 90 mEq/L can be reached (2). Similarly, sweat contains only a negligible amount of potassium (roughly 5 mEq/L) but may lead to clinically significant losses in warm climates.

The sodium-potassium-ATPase pump (Na/K-ATPase) is a key controller of intracellular and extracellular potassium. By pumping 2 potassium ions into the cell and 3 sodium out, it exerts a crucial effect in maintaining a negative resting membrane potential (1). The Na/K-ATPase pump is activated by a number of factors such as

increases in extracellular potassium, insulin, catecholamines, and aldosterone (3) (Fig. 211.1). Na/K-ATPase pump activation by catecholamines or insulin in skeletal muscle results in huge, rapid intracellular shifts. Acidosis leads to increased plasma potassium as hydrogen ions shift into cells and potassium shifts out. Similarly, hypertonicity (e.g., diabetic ketoacidosis [DKA] or mannitol infusion) leads to a shift of water and potassium out of the cell.

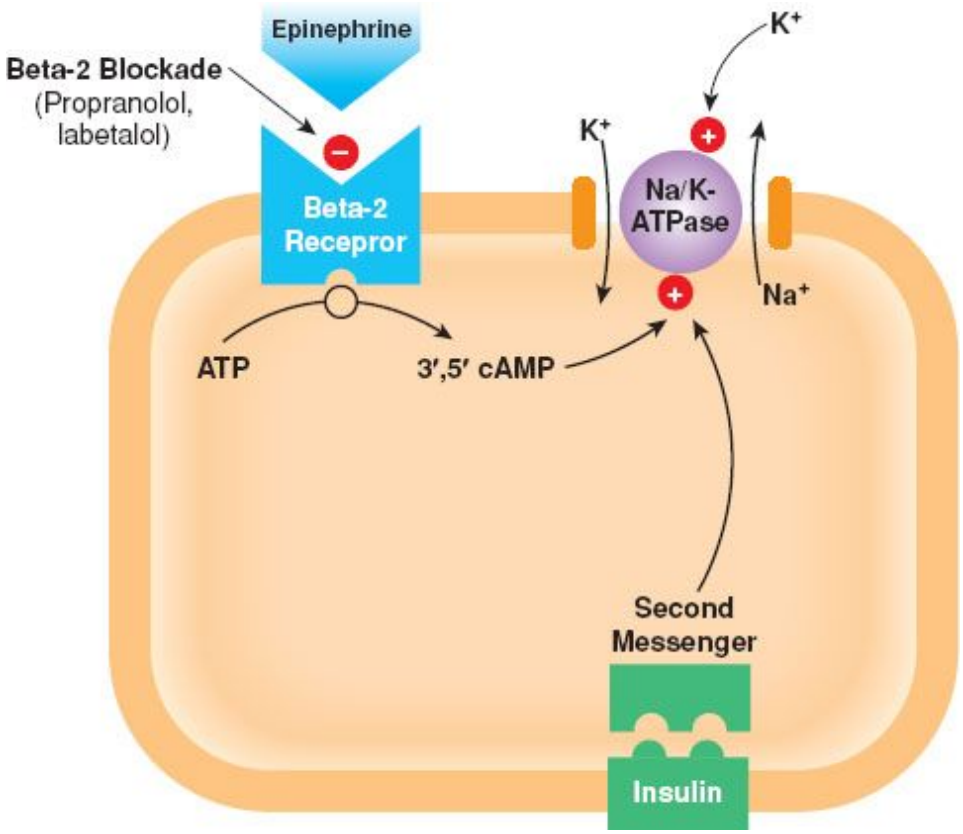

FIGURE 211.1 Schematic depiction of various endogenous and exogenous modulators of intracellular potassium. (Graphics courtesy of Judy A. Christensen, Medical Graphics Division, Naval Medical Center San Diego.)

HYPERKALEMIA

CLINICAL PRESENTATION

Hyperkalemia is defined as a serum potassium concentration >5 mEq/L. Pseudohyperkalemia due to red blood cell hemolysis during

venipuncture is probably the most common emergency department (ED) presentation (4,5), whereas true, life-threatening hyperkalemia most commonly presents in patients with renal failure (6). Clinical signs or symptoms are rarely apparent with mild-to-moderate hyperkalemia and are nonspecific (e.g., generalized weakness, muscle cramps, or vague gastrointestinal symptoms) (7,8). The most critical presentation involves impairment of cardiac conduction including asystole or ventricular fibrillation (8). Hyperkalemia generally becomes apparent only when a characteristic electrocardiographic (ECG) pattern (9) or cardiac rhythm is encountered, or a blood chemistry panel detects the elevated level. It is, therefore, imperative to maintain a low threshold for obtaining serum electrolytes in all patients presenting with nonspecific muscular weakness or any ECG abnormalities compatible with the diagnosis of hyperkalemia.

DIFFERENTIAL DIAGNOSIS

Apart from pseudohyperkalemia, the various causes of true hyperkalemia are due to one of the three disorders: Increased potassium intake, transcellular shifts, or impaired renal excretion (Table 211.1). All of these disorders should be considered when attempting to explain an elevated serum potassium level.

TABLE 211.1
Common Causes of Hyperkalemia in Emergency Department Patients

Disorder	Etiology
Pseudohyperkalemia	Hemolysis (in vitro or venipuncture)
	Extreme leukocytosis or thrombocytosis (e.g., leukemia)
Increased potassium intake	Increased oral intake
	Potassium-containing medications (e.g., penicillins)
	Massive transfusion
Transcellular shift of potassium	Insulin deficiency (e.g., DKA)
	Beta-2 blockade (e.g., propranolol)
	Acidosis
	Cell breakdown (e.g., DIC, crush, burns, tumor lysis syndrome)
	Hyperkalemic periodic paralysis
	Drugs (e.g., digoxin toxicity, succinylcholine)
Impaired renal excretion	Oligoanuric renal failure
	Severe volume depletion
	Hypoaldosteronism (e.g., addisonian crisis)
	Type 4 RTA
	Drugs
	Potassium-sparing diuretics
	ACE inhibitors
	Trimethoprim
	Pentamidine
	NSAIDs

DKA, diabetic ketoacidosis; DIC, disseminated intravascular coagulopathy; NSAIDs, nonsteroidal anti-inflammatory drugs.

ED EVALUATION

A serum potassium level should be obtained on all patients who present with even minimal symptoms and any of the disorders listed in Table 211.1. This is particularly true in the dialysis-dependent patient. Once an elevated potassium level is suspected, an ECG should be obtained immediately. If pseudohyperkalemia is suspected and the ECG is normal, blood should be redrawn (if possible without a tourniquet) and the patient kept on a cardiac monitor until a normal level is confirmed.

ECG changes (Fig. 211.2) are classically described as evolving in a stepwise fashion: Starting with symmetrical T-wave peaking, followed by P-wave flattening, QRS widening, and, if untreated, a

sinusoidal ECG pattern (9). In one early investigation, ECG abnormalities were found in 64% of 39 patients with potassium levels of 5.5 mEq/L or more and in all patients with levels >6.7 mEq/L (10). Though ECG changes generally do not occur with potassium levels below 6.5 mEq/L, there is no absolute correlation between the severity of cardiac conduction abnormalities and potassium elevation (11). For example, Acker et al. (12), in a study of 127 hyperkalemic episodes, found that only 46% of all patients with serum potassium levels <6.8 mEq/L had typical ECG abnormalities, whereas nearly half of those with higher levels lacked any characteristic ECG changes. Therefore, though the ECG is too insensitive to rule out hyperkalemia, all hyperkalemic patients who have typical changes on ECG should be aggressively managed (13).

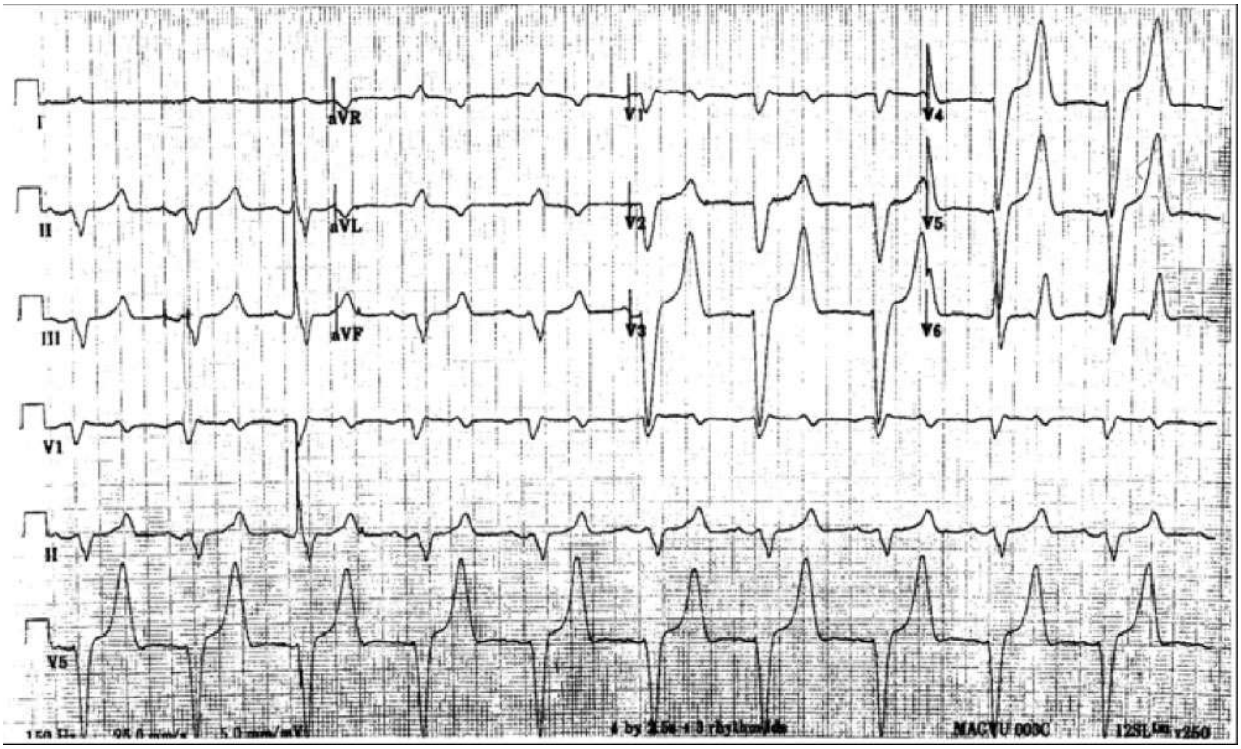

FIGURE 211.2 ECG in patient with potassium level of 7.3 mEq/L. Hyperkalemia-related findings in this ECG include peaked T-waves, prolonged PR intervals, decreased amplitude of P-waves, and widening of QRS complex.

The initial ED workup of hyperkalemia should also include a complete blood count, chemistry panel, serum ketones, if DKA is suspected, and a digoxin level if applicable. Arterial blood gas analysis may also help explain the cause of hyperkalemia when an obvious diagnosis is not apparent.

ED MANAGEMENT

All patients with hyperkalemia should be placed on a cardiac monitor. The need for therapy and urgency with which therapy is given is based primarily on the severity of ECG alterations, the degree and chronicity of the potassium elevation, the severity of neuromuscular dysfunction, the presence of underlying cardiac disease, and, finally, when apparent, the underlying cause of the hyperkalemia. The emergency treatment of hyperkalemia follows four strategies: (a) directly antagonize the membrane destabilizing effects of hyperkalemia (e.g., calcium salts); (b) translocate extracellular potassium into cells (e.g., insulin, glucose, albuterol, and sodium bicarbonate [$NaHCO_3$]); (c) remove potassium from the body (e.g., cation exchange resins and dialysis); and (d) treat the underlying cause of hyperkalemia (e.g., Fab fragment antidotal therapy for digoxin toxicity, hydrocortisone for addisonian crisis, or discontinuation of drugs associated with hyperkalemia, such as potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, or trimethoprim-sulfamethoxazole).

Calcium salts should be given immediately to all patients with QRS widening on ECG or dysrhythmias. The typical regimen is calcium gluconate 10%, one to two 10-mL ampules (2 mL/kg in children) infused over 2 minutes each, and repeated in 5 minutes if no effect is noted on ECG (2,14). Calcium chloride 10%, which contains roughly three times the amount of elemental calcium per 10-mL ampule, may be infused in roughly equimolar amounts to calcium gluconate (13). Calcium gluconate, however, is safer when infused through a peripheral vein because it causes less venous irritation, and calcium chloride causes severe tissue necrosis if tissue infiltration should inadvertently occur.

There is a time-honored caution that calcium should be avoided in patients taking digoxin. Digoxin's chief effect on cardiac myocytes is to antagonize the Na/K-ATPase pump. The subsequent rise in intracellular sodium results in an increase in intracellular calcium through a number of mechanisms, one of which is a sodium-calcium exchange pump. This rise in intracellular calcium, in turn, prolongs calcium's binding to contractile proteins. Exogenous calcium administration may theoretically lead to a potentiation of this effect, but recent studies have questioned the validity of this concern (15,16). Pending further study, it remains prudent to use calcium with caution in patients with hyperkalemia specifically due to acute digoxin toxicity. In this setting, Fab fragment is considered a first-line therapy (17).

Insulin stimulates Na/K-ATPase activity via an intracellular second messenger and has an onset of action of 20 to 30 minutes, lowering serum potassium levels by roughly 0.5 to 1 mEq/L in 1 to 2 hours (2). Among the immediate treatments for hyperkalemia, insulin is considered the most efficacious and reliable (8). The typical dose is regular insulin 0.1 U/kg up to a 10-U bolus. In euglycemic patients, 25 to 50 g of dextrose should be given. Glucose should be avoided in hyperglycemic patients ($>$200 mg/dL), as extracellular hypertonicity leads to a shift of free water and moves potassium out of the cell. For the same reason, some authors advocate giving insulin and glucose more slowly (e.g., 500 mL of D_{10} W with 10 U of regular insulin infused over 60 minutes). This slow infusion is probably prudent in stable patients with mild ECG changes, with bolus therapy reserved for more severely symptomatic patients with advanced ECG alterations. In all instances, close monitoring (i.e., hourly) of fingerstick and serum glucose should be done to avoid hypoglycemia (13).

$NaHCO_3$ leads to a shift of potassium into cells as hydrogen ions shift extracellularly. Alkalemia leads to increased potassium in the distal convoluted tubules (DCTs) as hydrogen ions are conserved (5). Its effects are most beneficial in the acidotic patient and should generally be avoided in the dialysis-dependent patient with hyperkalemia (13). The standard bolus is one 50-mEq ampule

infused over 5 minutes, (2 to 3 mL/kg in children) (14). The onset of action occurs in 5 to 10 minutes and lasts for roughly 2 hours. $NaHCO_3$ can lead to acute fluid overload in patients with congestive heart failure (CHF) or renal failure and may lead to tetany and seizures in hypocalcemic patients when alkalosis induces increased calcium-protein binding and decreased ionized calcium. Current literature has called into question the efficacy of $NaHCO_3$ as treatment for hyperkalemia although it remains an accepted treatment and has a role as adjunctive therapy for some patients (8,18).

Nebulized albuterol (10 to 20 mg) can be used as an immediate therapy to shift potassium intracellularly via beta-2 receptor stimulation (13,19). There appears to be a dose-related response and the treatment may be repeated after 120 minutes. Combining albuterol with insulin-glucose therapy seems to reduce potassium levels more effectively than either treatment alone (18). The onset and duration of action of albuterol are similar to those of $NaHCO_3$. Though only modest increases in heart rate and blood pressure occur, albuterol should be used with caution in patients with known cardiac disease. It is generally not needed in mild cases.

As the most common presentation of hyperkalemia in most EDs is in the patient with chronic kidney disease who has missed a scheduled dialysis session, a renal consultant should be contacted when hyperkalemia is detected. Hemodialysis is highly effective in reducing extracellular potassium, with standard coils removing roughly 40 mEq over the first hour. Comparatively, peritoneal dialysis can remove only 5 mEq of potassium per liter of dialysate per hour.

Sodium polystyrene sulfonate (SPS) is a cation exchange resin that can remove up to 1 mEq of potassium for each gram used. Its onset of action is 4 to 6 hours (20); therefore, it has generally been reserved for stable patients with less severe ECG abnormalities who are not undergoing emergent hemodialysis. The standard oral regimen is 30 g mixed with 50 mL of 20% sorbitol solution to induce diarrhea. Alternatively, a 1-hour retention enema using 50 g of SPS

and 200 mL of 20% sorbitol can be given just prior to the patient's hospital admission.

However, recent reviews have called into question not only the efficacy of SPS, but also its safety when given with sorbitol (20). The FDA has issued a warning against the use of sorbitol with SPS in light of reports of colonic necrosis and other gastrointestinal adverse events (21). Given the weak evidence of benefit and the potential for complications, SPS is currently being used much less commonly for hyperkalemia. Certainly, its use concomitantly with sorbitol would certainly be contraindicated in patients with suspected bowel obstruction, ileus, or recent abdominal surgery.

Hyperkalemia in the euvolemic or hypovolemic patient with normal renal function should be treated with volume expansion to optimize the glomerular filtration rate. All hyperkalemic ED patients who require emergent treatment should have continuous intravenous access and cardiac monitoring. They should have glucose and electrolytes measured after the first hour of treatment, then at least every 2 hours thereafter.

The specific cause of hyperkalemia should be considered in all patients, with particular attention paid to medications. Digoxin and other medications mentioned earlier, as well as others—the most obvious being oral potassium supplements—should be considered.

CRITICAL INTERVENTIONS

- Obtain an ECG in all suspected cases.
- If characteristic hyperkalemic abnormalities are found (peaked T-waves, P-wave flattening, QRS widening), initiate treatment immediately with
  - calcium gluconate 10%, 10 mL over 2 minutes if ECG reveals widened QRS or dysrhythmias (may repeat in 5 minutes);
  - regular insulin 0.1 U/kg up to 10 U IVP. Add 25 g of D_{50} W if serum glucose <200 mg/dL;
  - albuterol 20 mg with 5-mL saline nebulized over 15 minutes in severe cases with ECG abnormalities refractory to standard treatment.
- Repeat potassium level if ECG normal and hemolysis is suspected.

- Consult nephrology for emergent hemodialysis in all dialysis-dependent patients or those with acute renal failure.

DISPOSITION

Admit all patients with characteristic ECG abnormalities to a monitored setting. All others with potassium levels >6 mEq/L should be admitted, or, in the case of patients with chronic kidney disease, transferred directly to a dialysis unit. For asymptomatic patients without ECG abnormalities suggestive of hyperkalemia with a potassium level <6 mEq/L and an identifiable cause that is not associated with ongoing potassium elevation, discharge with urgent outpatient follow-up is acceptable.

Common Pitfalls

- Failure to recognize and treat ECG abnormalities characteristic of hyperkalemia.
- Failure to consult nephrology for all dialysis-dependent patients.
- Causing volume overload by giving too much $NaHCO_3$ to a patient who is dialysis-dependent or has advanced CHF.

HYPOKALEMIA

CLINICAL PRESENTATION

Hypokalemia is defined by a serum potassium level <3.5 mEq/L. As in patients with hyperkalemia, hypokalemia can present with vague symptoms of muscle weakness, generalized malaise, or paresthesias (2,3,22). Alternatively, even moderate hypokalemia (2.5 to 3 mEq/L) may predispose patients with underlying cardiac disease to life-threatening dysrhythmias and present as cardiac arrest. One unique cause of hypokalemia is hypokalemic periodic paralysis (HPP), which typically presents with recurrent bouts of profound muscular weakness that may progress to respiratory paralysis. Because of the vague presentation and potential for catastrophic sequelae if not detected, all patients who have an underlying disorder, acute illness, or medication profile that predisposes them to hypokalemia and who

present with such symptoms should have a basic electrolyte panel obtained. HPP should be distinguished from the hyperkalemic variety.

DIFFERENTIAL DIAGNOSIS

The most common cause of hypokalemia in ED patients is diuretic-induced renal or diarrhea-induced gastrointestinal losses of potassium. Nonetheless, the finding of low serum potassium should bring to mind a number of other diagnostic considerations (5–7,23–27). Table 211.2 summarizes common causes of hypokalemia in ED patients according to the underlying mechanism of (a) decreased potassium intake, (b) increased potassium loss, or (c) transcellular shifts without total body potassium deficit.

TABLE 211.2
Common Causes of Hypokalemia in Emergency Department Patients

Disorder	Etiology
Inadequate intake	Low dietary content
	Clay ingestion (pica)
Excessive loss	Renal loss
	Diuretics
	Vomiting (contraction alkalosis)
	Hypomagnesemia
	Tubular disorders (type 1 RTA, drugs)
	Renal artery stenosis
	Severe hypertension
	Cushing syndrome
	Primary hyperaldosteronism
	Licorice ingestion
	GI loss (diarrhea)
	Skin loss (profuse sweating, burns)
Transcellular shifts	Metabolic or respiratory alkalosis
	Beta-2 adrenergic stimulation
	Sympathomimetics (cocaine, albuterol)
	Myocardial infarction
	Delirium tremens
	Theophylline
	Thyrotoxicosis
	Exogenous insulin administration
	Endogenous insulin in nondiabetics w/ glucose load
	Barium poisoning
	Hypokalemic periodic paralysis

Thiazide and loop diuretics cause an increased delivery of sodium to the DCT where potassium is lost in exchange as sodium is resorbed. Vomiting and nasogastric suction induce a metabolic alkalosis and selectively decrease chloride. A so-called “chloride-sensitive contraction alkalosis” results leading to an increase in potassium loss at the DCT (2). The mechanism by which hypomagnesemia leads to hypokalemia is unclear but is thought to be related to magnesium’s role as a cofactor for Na/K-ATPase function (3). It is well established that potassium replacement is ineffective if significant hypomagnesemia is not concurrently corrected.

The key effect of transcellular shifts from insulin and beta-2 adrenergic stimulation (albuterol, delirium tremens) was previously covered in this chapter. Overdose with methylxanthines, such as theophylline and caffeine, which are not sympathomimetics, is thought to cause hypokalemia by increasing Na/K-ATPase activity by inhibiting cellular phosphodiesterase or by the attendant hyperadrenergic state accompanying these overdoses (24). Similarly, thyroid storm is often accompanied by hypokalemia as a result of sympathetic outflow combined with a direct effect of increased Na/K-ATPase synthesis. Barium overdose is thought to block potassium's exit from cells (23,26).

Finally, a rare but dramatic presentation of hypokalemia is familial HPP, an autosomal-dominant disorder that results from sudden, rapid shifts of potassium into skeletal muscle. A nearly identical disorder, thyrotoxic periodic paralysis, is the most common form of periodic paralysis reported in Asian populations (25). Both can present with profound muscular paralysis and both respond quickly to IV potassium replacement. Total body potassium stores are normal, so judicious potassium replacement and monitoring are advised to avoid rebound hyperkalemia. Thyroid studies should be obtained in all patients presenting with HPP who are of Asian descent or lack a clear history of familial HPP.

ED EVALUATION

As discussed, a serum potassium level should be obtained in all patients who are acutely ill or who present with vague symptoms of fatigue, weakness, a muscular cramping with any reason to suspect hypokalemia from decreased intake, excess loss, or transcellular shifts as outlined in Table 211.2. Once hypokalemia is detected, a 12-lead ECG should be obtained and the patient maintained on a cardiac monitor if any signs of ectopy are present. A targeted search for the specific causes of the hypokalemia that are outlined in Table 211.2 should be undertaken based on the patient's history and clinical presentation. Along with a standard electrolyte panel, a serum magnesium level should be obtained.

The characteristic ECG abnormalities found in hypokalemia include U-waves, T-wave flattening, and ST-segment depression. Patients with severe hypokalemia (<2.5 mEq/L) or patients with cardiac disease with mild-to-moderate hypokalemia may suddenly develop more severe dysrhythmias—as the relatively hyperpolarized state leads to a prolonged refractory state—predisposing to ventricular fibrillation.

ED MANAGEMENT

The cornerstone of therapy for hypokalemia is potassium replacement and treatment of the underlying cause. Since even mild hypokalemia is often associated with total body deficits of 100 to 200 mEq, replacement is typically slowly over many hours or even days. Though relatively straightforward, the risks of iatrogenic hyperkalemia must be weighed against the need for rapid parenteral replacement. Patients with concomitant hypomagnesemia should have magnesium replaced concurrent with potassium replacement as outlined in Chapter 212.

Most cases of mild-to-moderate (2.5 to 3.5 mEq/L) hypokalemia can be corrected by oral replacement therapy and correction of the underlying cause. Most patients prefer the taste of slow-release tablets compared to liquid preparations, although both wax matrix and microencapsulated formulations carry a slightly increased risk of gastric ulceration (28). A typical oral dose is 40 mEq while in the ED, supplemented with at least 20 mEq daily. Higher daily doses may be needed depending on ongoing losses and dietary supplementation. Patients with hypertension, CHF, or dysrhythmias should ideally have their potassium levels maintained above 4 mEq/L (29). For more severe cases (<2.5 mEq/L) and all cases with cardiac ectopy, profound weakness, ileus, or other severe illness, IV potassium replacement should begin in the ED, and the patient should be admitted to a monitored setting until resolved.

The rate at which potassium can be infused intravenously depends on both the site (peripheral vs. central) and the urgency of the underlying clinical condition (cardiac ectopy, profound muscular weakness, and respiratory depression) for which it is being replaced.

In general, patients with peripheral IV access should not have potassium infused at a rate >20 mEq/hr or 0.2 to 0.3 mEq/kg/hr in children (1,14). In a review of 495 potassium infusion sets of 20 mEq/hr, Kruse and Carlson (30) found a mean increase of 0.25 mmol/L, with only 10 instances of mild hyperkalemia and no temporally related life-threatening dysrhythmias. Though replacement rates of 40 mEq/hr by central line are reported to be safe, this rate should be reserved for cases of severe hypokalemia with sustained, life-threatening cardiac dysrhythmias. In all instances, patients receiving potassium supplementation at rates of 20 mEq/hr or greater should have continuous cardiac monitoring and hourly checks of electrolyte levels.

DISPOSITION

Most cases of mild-to-moderate uncomplicated hypokalemia can be safely discharged with close outpatient reassessment once adequate oral replacement has been initiated. Patients displaying clinical effects of hypokalemia or those with levels <2.5 mEq/L requiring ongoing parenteral correction should generally be admitted.

Common Pitfalls

- Failure to maintain a low threshold for checking potassium levels in all patients who have potential for ongoing potassium loss (diuretic use or diarrhea) or underlying cardiac disease.
- Initiation of potassium replacement therapy before adequate renal function is confirmed.
- Failure to detect and treat concomitant hypomagnesemia.
- Overzealous parenteral potassium replacement, resulting in hyperkalemia, particularly in conditions where hypokalemia is due to transcellular shifts, such as HPP, adrenergic excess, or metabolic alkalosis.
- Inadequate oral replacement for patients with ongoing potassium loss due to diuretic therapy, in whom a minimum of 40 mEq of KCl per day is generally required.

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CHAPTER 212

Disorders of Calcium, Phosphate, and Magnesium Metabolism

John W. Love and Robert G. Buckley

OVERVIEW OF CALCIUM METABOLISM

Calcium is a critically important ion. Not only does it comprise the main mineral component of bone, it plays a key role in neuromuscular transmission and serves as a cofactor in numerous extracellular and intracellular processes. Serum calcium levels are tightly regulated within a normal range of 8.5 to 10.5 mg/dL or an ionized level of 1.0 to 1.15 mmol/L. Roughly half of serum calcium is protein-bound, and half is the form of physiologically active free ionized calcium (1–4).

Parathyroid hormone (PTH) is the key controller of serum calcium concentration. As calcium levels fall, PTH is secreted from the four tiny parathyroid glands in the anterior neck, leading to a rapid increase in calcium resorption from bone and reabsorption in the distal renal tubules (5,6). PTH also stimulates renal production of 1,25-dihydroxyvitamin D that leads to increased absorption of calcium in the gut. Rising calcium levels lead to a decrease in PTH release with subsequent calcium bone deposition, renal excretion, and diminished gastrointestinal (GI) uptake (3,6).

HYPERCALCEMIA

CLINICAL PRESENTATION

Hypercalcemia is defined as a serum calcium concentration of >10.5 mg/dL. The signs and symptoms of mild hypercalcemia (up to 12 mg/dL) are generally vague and include changes in cognitive function, depression, and fatigue (1,7). Higher levels are more frequently associated with GI symptoms (nausea, anorexia, constipation, and abdominal pain), muscle weakness, and more profound changes in mental status. The electrocardiograph (ECG) may reveal QT_c shortening and PR or QRS widening (3). As with other electrolyte abnormalities, the nonspecific nature of the clinical presentation calls for a low threshold in ordering calcium levels. Hypercalcemic crisis may occur when levels reach 14 mg/dL or greater, resulting in paralysis or coma (1,3,7).

DIFFERENTIAL DIAGNOSIS

Although a number of disorders lead to hypercalcemia (Table 212.1), the most common cause in ambulatory patients is primary hyperparathyroidism, which is often detected during laboratory screening of asymptomatic or minimally symptomatic patients. In hospitalized patients, cancer is the most common etiology (3,7). Humoral hypercalcemia of malignancy is due to tumors secreting PTH-related protein (e.g., squamous cell carcinomas) or calcitriol (e.g., B-cell lymphomas). A separate mechanism of hypercalcemia in cancer patients is due to local osteolytic hypercalcemia that occurs when tumor within the bone itself (e.g., multiple myeloma) causes cytokine release and increased osteoclastic calcium resorption from bone (7). Other causes such as granulomatous disease (e.g., sarcoidosis), medications (e.g., lithium and thiazide diuretics), endocrine disorders, or factious hypercalcemia should also be considered (1,3,7).

TABLE 212.1
Causes of Hypercalcemia

Hyperparathyroidism (e.g., adenoma, hyperplasia, or carcinoma)
Malignancy-associated hypercalcemias
Humoral hypercalcemia of malignancy (e.g., squamous cell carcinomas of lung, oropharynx, kidney, cervix, or ovary)
Local osteolytic hypercalcemia (e.g., multiple myeloma, breast cancer, or lymphoma)
Granulomatous diseases (e.g., sarcoidosis, tuberculosis, or histoplasmosis)
Medications (e.g., vitamin A or D supplements, antacids, lithium, or thiazide diuretics)
Factitious hypercalcemia (e.g., hyperproteinemias)
Thyrotoxicosis
Adrenal insufficiency

ED EVALUATION

Once an elevated calcium level has been detected, the serum protein or albumin level should be measured. The "corrected" level of calcium is obtained by lowering the measured serum concentration by 0.8 mg/dL for every 1 g/dL of protein or albumin above the normal reference range (e.g., multiple myeloma). Alternatively, an ionized calcium level can be quickly obtained from most arterial blood gas analyzers (1,3,6–8).

Because hypercalcemia is associated with a number of malignancies, granulomatous diseases, endocrinopathies, and medications, further investigation to detect these disorders should be initiated in the emergency department (ED) based on accompanying clinical findings. At a minimum, a complete blood count, comprehensive metabolic panel (to include magnesium and phosphate levels and renal and liver function studies), urinalysis, ECG, and chest radiography should be obtained in all patients. The most important next step in investigating hypercalcemia in a patient without an obvious neoplastic etiology is to obtain a serum PTH concentration. This is generally best coordinated with the primary provider following up the ongoing care of the patient (1,3,6).

ED MANAGEMENT AND DISPOSITION

Most cases of mild or even moderate hypercalcemia in an otherwise well-hydrated, minimally symptomatic patient require no immediate

ED treatment. Those with more profound symptoms and higher levels—typically found in patients with known malignancy—should have treatment to lower calcium levels initiated in the ED and be admitted.

Virtually all cases of severe hypercalcemia are associated with some degree of volume contraction. Therefore, the first step is to give at least 1 L of normal saline to reexpand the extracellular space. After the volume status has been corrected with 1 to 2 L of normal saline, furosemide 40 mg IVP should be given to enhance calcium excretion (1,3,6).

Repeat electrolyte and calcium levels should be obtained roughly 2 hours after initiating ED treatment and generally show a decrease in the serum calcium level by 1 to 2 mg/dL. Patients who fail to respond adequately to IV hydration and diuresis should have further therapy aimed at decreasing calcium mobilization (1,3,6). Bisphosphonates (pamidronate 60 to 90 mg IVPB over 4 hours or zoledronate 4 mg IVPB over 15 minutes) are the mainstay of treatment for cancer-related hypercalcemia (7). Alternative therapies such as mithramycin (25 μg/kg over 4 hours), which directly inhibits osteoclastic activity, or calcitonin (4 IU subcutaneously or IM), which has the most rapid onset, are both limited by a higher incidence of side effects. Glucocorticoids (e.g., hydrocortisone 200 mg IV or its equivalent) are beneficial in patients with hematologic cancers, granulomatous diseases, or vitamin D toxicity but are ineffective in nonhematologic tumors or parathyroid adenomas (7).

Patients with symptomatic hypercalcemia require admission for IV fluids, parenteral therapy, and careful monitoring of fluid status. Minimally symptomatic or asymptomatic patients with mild to moderate hypercalcemia (corrected calcium level <13.0 mg/dL) and no known malignancy should have a PTH level ordered and close outpatient follow-up arranged.

CRITICAL INTERVENTIONS

- Measure a calcium level in all patients with known or suspected malignancy who present with fatigue, weakness, or change in mental status.
- Treat all cases of hypercalcemia with profound fatigue, muscle weakness, altered mental status, cardiac dysrhythmias, or serum calcium level of 14 mg/dL or greater.
- Restore the intravascular volume with 1 to 2 L of normal saline before initiating loop diuretic therapy.

Common Pitfall

- Failure to repeat serum calcium levels 2 hours after initiation of treatment to gauge effectiveness.

HYPOCALCEMIA

CLINICAL PRESENTATION, DIFFERENTIAL DIAGNOSIS, AND ED EVALUATION

Hypocalcemia is generally defined by a serum calcium level <9 mg/dL, with severe hypocalcemia defined as serum calcium ≤ 7.0 mg/dL. Neuromuscular irritability is the hallmark of true hypocalcemia. Tetany, muscle cramps, and spasms commonly ensue at adjusted corrected calcium levels <7.5 mg/dL. In extreme cases, cyanosis from glottic and diaphragmatic spasm can ensue (2,3,6).

The two classic physical findings of hypocalcemia, Chvostek and Trousseau signs, when present, are useful in corroborating the presence of ionized hypocalcemia (2–4,6). Chvostek sign is facial musculature twitching elicited by percussion over the facial nerve in the preauricular region. Trousseau sign is carpal spasm after inflation of a brachial blood pressure cuff above the patient's systolic blood pressure for 3 minutes. Unfortunately, neither sign has adequate accuracy to detect or completely exclude significant hypocalcemia. Therefore, as with almost all electrolyte disorders, a low threshold for obtaining calcium levels should be maintained

when evaluating patients with neuromuscular abnormalities or complaints.

The concentration of bioactive calcium is best obtained by measuring an ionized calcium level, which can be obtained from most blood gas analyzers (8). If the ionized calcium level cannot be obtained, then measure the serum calcium and albumin concentrations. Calculate the corrected calcium level by adding 0.8 mg/dL to the serum calcium level for each decrease of 1 g/dL of serum albumin <4 g/dL. The corrected QT interval is characteristically prolonged in hypocalcemia and may rarely progress to ventricular dysrhythmias, such as torsades de pointes, or heart block (3,6).

Although the most common cause of a low serum calcium level is pseudohypocalcemia due to reduced serum protein states, a number of causes should be considered when a true reduction in ionized calcium is encountered (Table 212.2). The vast majority of cases of true hypocalcemia are due either to an insufficiency in the production or bio-effectiveness of either PTH or vitamin D metabolites (2,3,6). Additionally, symptomatic hypocalcemia can be found in a number of disease states in which chelation with organic anions leads to decreased ionized calcium levels (6). Examples include hyperphosphatemia in rhabdomyolysis, saponification with fatty acids in severe pancreatitis, and citrate chelation with massive transfusion of preserved blood products. Hypocalcemia is well reported in severe hydrofluoric acid burns and is generally considered secondary to precipitation of calcium fluoride, though the precise mechanism remains under investigation (3,9). Alkalosis increases calcium binding to plasma proteins and can lead to a decreased ionized calcium level despite the presence of a normal serum calcium level—a common result of tetany in acute hyperventilation (3,6).

TABLE 212.2
Causes of Hypocalcemia

Parathyroid Hormone Insufficiency
Iatrogenic (e.g., surgical or radiation)
Infiltrative (e.g., hemochromatosis, Wilson disease)
Autoimmune
Magnesium deficiency
PTH resistance

Vitamin D Insufficiency
Nutritional deficiency (e.g., rickets, osteomalacia)
Malabsorption (e.g., gastrectomy, inflammatory bowel disease)
Altered vitamin D metabolism (e.g., hepatic or renal disease)

Medications
Bisphosphonates
Phosphates (e.g., cow's milk hypocalcemia in neonates)
Calcitonin
Plicamycin

Other Conditions
Pseudohypocalcemia (e.g., hypoalbuminemic states)
Acute pancreatitis
Rhabdomyolysis
Tumor lysis syndrome
Massive transfusion of citrated blood
Osteoblastic metastases (e.g., breast or prostate cancer)
Neonatal hypocalcemia (high phosphate cow's milk)
Ethylene glycol poisoning (due to calcium oxalate precipitation)
Hydrofluoric acid burns

ED MANAGEMENT AND DISPOSITION

Treatment with IV calcium salts should be initiated immediately in all patients with neuromuscular excitability and true hypocalcemia (adjusted for serum albumin or from direct measurement of ionized calcium). The goal of therapy is to eradicate all signs or symptoms of neuromuscular excitability by attaining a serum calcium level of roughly 8 to 9 mg/dL. To do this, an initial dose of 200 to 300 mg of elemental calcium should be slowly infused over 5 to 10 minutes while the patient is maintained on a cardiac monitor (2,3,6).

Either calcium chloride 10% (360-mg calcium per 10-mL ampule) or calcium gluconate 10% (93-mg per 10-mL ampule) may be used

(10,11). However, calcium chloride much more commonly leads to localized pain and thrombophlebitis at the infusion site and, thus, should only be used peripherally if calcium gluconate is not available. Repeat boluses or an infusion rate of 0.5 to 2.0 mg/kg/hr of elemental calcium may be required if symptoms recur (3,6). For infants and young children, the recommended initial dose of calcium gluconate 10% is 0.5 to 1.0 mL/kg (3).

Parenteral calcium administration should be performed with extra care in patients taking digoxin, owing to a proarrhythmic effect that has been reported (2,3). Calcium salts should never be given through the same infusion site as sodium bicarbonate owing to precipitation of calcium bicarbonate. Patients with concomitant hypomagnesemia should have magnesium replaced as outlined later in this chapter. Repeat calcium and magnesium levels should be obtained every 1 to 2 hours.

All patients requiring ongoing parenteral calcium replacement should be admitted to a monitored setting. Those patients with minimal associated symptoms and without QT prolongation can generally be discharged with early outpatient follow-up. The decision to initiate supplemental oral calcium and vitamin D therapy, as well as further specific diagnostic testing, is best made in concert with the patient's primary provider prior to discharge.

CRITICAL INTERVENTIONS

- Exclude pseudohypocalcemia by confirming the ionized calcium level or adjusting the serum calcium level for hypoproteinemia.
- Obtain a 12-lead ECG to rule out QT_c prolongation, particularly in patients with underlying heart disease.
- Infuse one 10-mL ampule of calcium gluconate over 2 minutes in symptomatic patients with confirmed hypocalcemia, repeating up to three doses and initiating a continuous infusion if the patient has persistent or recurrent symptoms.
- Measure and replace magnesium when the serum magnesium level drops below 1.0 mEq/L.

Common Pitfall

- Do not rely on the absence of Chvostek and Trousseau signs to exclude the possibility of hypocalcemia. Obtain serum calcium levels on patients suspected of having hypocalcemia.

PHOSPHORUS METABOLISM

Phosphate is a crucial substance for all cells, forming a major component in phospholipid cell membranes and in high-energy compounds such as adenosine triphosphate. Roughly 85% of the body's phosphorous is stored in bones as hydroxyapatite and is controlled by PTH and vitamin D similar to calcium. The recommended daily allowance is 800 mg, which is found in high concentrations in meats and dairy products. More than 90% is renally excreted. The normal range of serum phosphate is 2.5 to 4.5 mg/dL (6).

Isolated phosphorous abnormalities requiring treatment in the ED are exceedingly rare. Nonetheless, a basic understanding of phosphorous abnormalities remains important for EM practice, as mild to moderate abnormalities are fairly regularly encountered particularly in patients with diabetes, alcoholism, cancer, chronic obstructive pulmonary disease (COPD), and renal failure. Furthermore, severe abnormalities occasionally present needing immediate intervention (12).

HYPERPHOSPHATEMIA

CLINICAL PRESENTATION, DIFFERENTIAL DIAGNOSIS, AND ED EVALUATION

Mild to moderate hyperphosphatemia is defined by levels roughly between 5 and 14 mg/dL and is generally asymptomatic. Levels above 14 mg/dL or those with symptoms associated with hypocalcemia (as previously described) define severe hyperphosphatemia (12).

Hyperphosphatemia is most commonly encountered in patients with chronic renal failure but may also be found in hypoparathyroid states, after excess exogenous administration, or owing to cell breakdown in rhabdomyolysis, cancer, or hemolysis (3,6,13). Pseudohyperphosphatemia results from inorganic phosphate measurement during laboratory analysis in cases such as multiple myeloma, hyperlipidemia, hemolysis, and hyperbilirubinemia. Evaluation of hyperphosphatemia is generally directed at the underlying cause and associated hypocalcemia. Calculation of the calcium–phosphate product (serum calcium multiplied by serum phosphorous) is an important step, as values >70 are associated with accelerated myocardial, vascular, and other soft-tissue calcification.

ED MANAGEMENT AND DISPOSITION

Treatment of hyperphosphatemia rarely needs to be initiated in the ED. Emergency treatment, rather, is directed at the accompanying hypocalcemia, as previously described.

Patients with normal renal function, who have hyperphosphatemia from exogenous sources (such as rhabdomyolysis), generally respond to saline diuresis. Patients with renal failure with moderate phosphate elevation or whose calcium–phosphate product exceeds 70 are usually managed as outpatients with a diet low in protein and dairy products and with calcium- or aluminum-containing phosphate binders (6,13). Dialysis is only transiently effective in lowering serum phosphate levels and should be reserved for overtly symptomatic patients with reduced renal function (3,6,13).

HYPOPHOSPHATEMIA

CLINICAL PRESENTATION, DIFFERENTIAL DIAGNOSIS, AND ED EVALUATION

Hypophosphatemia is a relatively common finding, with a prevalence of roughly 1% to 3% in unselected hospitalized

populations. Moderate hypophosphatemia is defined by a serum phosphate concentration of 1.0 to 2.5 mg/dL. Symptoms generally are manifest only with severe hypophosphatemia, defined as levels <1.0 mg/dL (12). As phosphate is a cardinal element in cellular metabolism for processes such as oxidative phosphorylation and glycolysis, symptoms related to impaired skeletal and myocardial muscle function are most common. In addition, hypophosphatemia can decrease 2,3-diphosphoglycerate (2,3-DPG) in red blood cells which leads to a decrease in hemoglobin oxygen release, most importantly in the myocardium and central nervous system, which may lead to signs of encephalopathy and coma (6).

The differential diagnosis of hypophosphatemia, shown in Table 212.3, is grouped according to the underlying mechanism: renal loss, decreased absorption, or transcellular shifts of phosphate into the cell. Hypophosphatemia is common in chronic alcoholics, with a prevalence of up to 50% in admitted Veteran's Administration hospitals (11). As with hypokalemia, patients with diabetic ketoacidosis almost universally have some degree of phosphate depletion owing to extracellular shifts and osmotic renal losses and initially present with normal phosphate levels that rapidly decrease as phosphate shifts intracellularly once insulin is administered (14). All disease states presenting with alkalosis or catecholamine excess can have some degree of hypophosphatemia (3,11).

TABLE 212.3
Causes of Hypophosphatemia

Renal Loss
Renal tubular dysfunction
Diuretic therapy
Hyperosmotic states (DKA, HONK hyperglycemia)
Hyperparathyroidism
Decreased Intake
Malnutrition (e.g., alcoholism)
Phosphate-binding antacids
Chronic diarrhea
Inflammatory bowel disease
Vitamin D deficiency
Transcellular Shifts
Respiratory alkalosis (COPD, sepsis, ASA poisoning)
Hyperadrenergic states (Etoh withdrawal)
Hyperglycemia
Insulin therapy

ASA, acetylsalicylic acid; COPD, chronic obstructive pulmonary disease; DKA, diabetic ketoacidosis; HONK, hyperosmolar nonketotic coma.

ED MANAGEMENT AND DISPOSITION

Phosphate replacement rarely needs to be initiated in the ED. Intravenous replacement therapy is almost never needed in the ED and is only necessary for patients with profound muscle weakness, respiratory insufficiency, or myocardial dysfunction or those patients with a serum phosphate level <1.0 mg/dL (11,15). The typical infusion rate for IV replacement calls for no more than 1 g of elemental phosphate infused over a 24-hour period (11,15). (One millimole of phosphate is equivalent to 31 mg of elemental phosphorous.) An acceptable rate to initiate in the ED is 4.5 mmol/hr for the first 3 hours, and phosphate should never be infused with lactated Ringer owing to precipitation with calcium. Patients receiving IV replacement should be monitored for tetany from attendant hypocalcemia or hypotension. All patients requiring IV replacement of phosphate should be admitted.

Asymptomatic patients with mild to moderate hypophosphatemia can be treated orally as outpatients with sodium phosphate (Neutra-Phos) or, in patients with concomitant hypokalemia, as in diabetic

ketoacidosis, with potassium phosphate (K-Phos). The typical dose is one 250 mg capsule four times daily (12).

CRITICAL INTERVENTIONS

- Measure serum phosphate levels in groups who are at high risk for hyperphosphatemia (renal failure, malignancy, severe rhabdomyolysis), hypophosphatemia (alcoholism, diabetic ketoacidosis, COPD, sepsis), or coexisting electrolyte, calcium, or magnesium abnormalities
- Initiate treatment for hyperphosphatemia only when the level exceeds 14 mg/dL; direct treatment at the underlying cause
- Initiate IV phosphate therapy only for symptomatic patients with serum phosphate levels <1.0 mg/dL—all others may have phosphate replaced orally

Common Pitfalls

- Failure to recognize, initiate treatment, and obtain close follow-up for renal failure patients with a calcium–phosphate product >70. These patients are at long-term risk for accelerated calcium deposition in vital organs, arteries, and soft tissues.
- Failure to recognize that serum phosphate levels may drop precipitously once patients with malnutrition (e.g., alcoholics receiving glucose therapy) or acidosis (diabetic ketoacidosis patients receiving IV insulin therapy) are treated.
- Failure to monitor patients receiving IV phosphate therapy for hypotension or tetany owing to accompanying acute hypocalcemia.

MAGNESIUM METABOLISM

Magnesium is the second most abundant intracellular cation. It is involved in numerous physiologic processes, including cardiac and neural depolarization, energy storage, nucleic acid stability, and enzyme activation (16). The average healthy adult contains approximately 25 g of magnesium. Of this amount, 50% is complexed in bones and not readily exchangeable, whereas 49% is

distributed to the intracellular soft-tissue space. Only 1% of body stores are found in the extracellular space and are thus available to be detected by routine electrolyte laboratory testing (6). Despite the fact that total serum levels are an insensitive determination of actual body magnesium stores, they remain the clinically most common standard for defining magnesium status. Normal plasma concentrations range from 1.8 to 2.5 mg/dL.

In contrast to sodium, potassium, and calcium, there is little evidence suggesting direct hormonal control of magnesium homeostasis. Instead, magnesium balance is the result of intestinal absorption, obligatory secretion, and renal excretion. The average adult consumes 250 to 300 mg of magnesium per day. Under normal conditions, net absorption by the intestine is approximately 100 mg/d via a saturable transport system and passive diffusion process, regardless of serum levels. In contrast, the kidney adjusts the rate of magnesium excretion depending on serum levels. Under normal conditions, the kidney excretes approximately 5% (100 mg) of the filtered load per day and can decrease the excreted amount to 0.5% or increase it to 80% of the filtered load. Hypermagnesemia develops during renal failure because of the lack of a feedback mechanism to regulate intestinal absorption. Hypomagnesemia occurs with prolonged poor dietary intake, malabsorption syndromes, or renal wasting, despite renal compensatory mechanisms (1,3,7).

HYPERMAGNESEMIA

CLINICAL PRESENTATION, DIFFERENTIAL DIAGNOSIS, AND ED EVALUATION

Hypermagnesemia is uncommon in the ED in the absence of renal insufficiency or treatment for preeclampsia. As such, most cases of hypermagnesemia can be anticipated. During acute renal failure, hypermagnesemia develops because intestinal absorption continues despite elevated serum magnesium levels. Many over-the-counter medications contain a significant amount of magnesium,

particularly antacids and laxatives. Renal failure patients should not receive inappropriate medications containing magnesium. Nonrenal risk factors associated with hypermagnesemia include advanced age, the misuse of magnesium-containing medications, and narcotic or anticholinergic medications, which decrease GI tract motility and enhance magnesium absorption. The typical hypermagnesemic patient with normal renal function is an elderly individual taking a narcotic or anticholinergic medication with a history of laxative use for constipation (3,6,17). Several pediatric fatalities from the inappropriate use of over-the-counter magnesium-containing medications have been reported.

Hypermagnesemia results in neuromuscular depression by inhibiting acetylcholine release at the neuromuscular junction (18). In addition, magnesium acts as a calcium-channel blocker and can impair cardiovascular function. Common initial ECG findings include PR and QRS interval prolongation. Symptoms are unusual until the serum magnesium level exceeds 4 mg/dL. A serum magnesium level is diagnostic. Initially, the presentation is nonspecific and includes nausea, vomiting, and weakness. As the serum magnesium level increases above 7 mg/dL, loss of deep-tendon reflexes, muscle paralysis, respiratory insufficiency, and cardiac arrest may occur.

ED MANAGEMENT AND DISPOSITION

In the mildly symptomatic patient with normal renal function, discontinuing the additional magnesium alone will rapidly result in normal serum levels, although GI tract decontamination may be needed to prevent ongoing absorption in magnesium oxide overdose (17). Renal excretion is enhanced by first expanding the extracellular space with IV fluids followed by furosemide 40 mg IVP. Treatment with IV calcium can rapidly reverse the calcium-channel blocking effect from severe magnesium toxicity. Use either 5 to 10 mL of calcium chloride 10% or one to two 10-mL ampules of calcium gluconate 10% over 5 minutes. The pediatric dose of calcium gluconate 10% is 0.5 to 1.0 mL/kg (3,6). The ECG and

hemodynamic parameters should guide repeat IV calcium therapy. Peritoneal dialysis or hemodialysis with a low-magnesium dialysate is also very effective in decreasing toxic serum magnesium levels. Finally, transvenous cardiac pacing has been reported to be effective in hypermagnesemic asystole that is refractory to calcium chloride (19).

CRITICAL INTERVENTION

- Administer IV calcium to counter the effects of severe hypermagnesemia.

Common Pitfalls

- Failure to remember that renal failure is the main risk factor for developing hypermagnesemia.
- Failure to consider hypermagnesemia in symptomatic elderly patients taking magnesium-containing laxatives.

HYPOMAGNESEMIA

CLINICAL PRESENTATION, DIFFERENTIAL DIAGNOSIS, AND ED EVALUATION

Magnesium deficiency can be categorized into three main areas: increased losses either renal or intestinal, inadequate intake, or cellular redistribution. Table 212.4 lists the most common specific causes. Hypomagnesemia is routinely encountered in the ED and is defined as a total serum magnesium concentration of <1.5 mg/dL. It rarely occurs as an isolated metabolic abnorm-ality as the predisposing conditions also lead to other electrolyte imbalances (3,6).

TABLE 212.4
Causes of Hypomagnesemia and Magnesium Deficiency

Increased Losses	Gitelman syndrome
Intestinal	Bartter syndrome
Diarrhea	Dietary
Laxatives	Chronic alcoholism
Malabsorption syndromes	Anorexia nervosa
Inflammatory bowel disease	Malnutrition
Short bowel syndrome	**Redistribution**
Renal	Metabolic acidosis
Drugs	Insulin (DKA)
Loop diuretics	Acute pancreatitis
Aminoglycosides	Parathyroidectomy/hungry bone syndrome
Amphotericin B	Refeeding syndromes after starvation
Cisplatinum	**Miscellaneous**
Cyclosporine	TPN
Pentamidine/Foscarnet	Hyperthyroidism
Tubular defects	Cardiopulmonary bypass
Osmotic diuretics (glycosuria)	Diabetes
Diuretic phase of ATN	
Postobstructive diuresis	
Ethanol	

ATN, acute tubular necrosis; DKA, diabetic ketoacidosis; TPN, total parenteral nutrition.

Severe symptomatic hypomagnesemia depends on the rate of development but is rare unless serum levels are below 1.0 mg/dL. Predisposing conditions that lead to hypomagnesemia include chronic alcoholism, diuretic use, and renal toxic drugs such as cisplatinum. The most common clinically recognizable manifestations are cardiac dysrhythmias and neuromuscular irritability, similar to those described for hypocalcemia. The most immediate life-threatening concern is ventricular dysrhythmias, particularly torsades de pointes. Predisposing conditions include myocardial ischemia and QT/QT_c prolongation, regardless of cause. Common ECG changes are similar to those encountered in hypocalcemia and hypokalemia. Neuromuscular symptoms include ataxia, tetany, and seizures (3,6,15).

ED MANAGEMENT AND DISPOSITION

All patients with symptomatic magnesium deficiency require immediate IV access, an ECG, and continuous cardiac monitoring. The initial focus is to prevent and stabilize cardiac dysrhythmias (10). Current Advanced Cardiac Life Support guidelines consider IV magnesium as the antidysrhythmic of choice for torsades de pointes or ventricular fibrillation–pulseless ventricular tachycardia in the known or suspected hypomagnesemic patient. The recommended adult dose for life-threatening dysrhythmias or severe neuromuscular symptoms is 2 g IV over 30 to 60 seconds (25 to 50 mg/kg in children, 2 g maximum). The rate of infusion should be slowed for less severe conditions. Side effects depend on the rate of infusion and include flushing, bradycardia, hypotension, and dysrhythmias. After the appropriate clinical response, follow up the bolus with a continuous infusion of 0.5 to 1 g/hr for several hours in patients with normal renal function. It is important to note that the kidneys will excrete the majority of the administered IV magnesium. Although serum levels will rapidly normalize, total body intracellular stores require several days to correct. Loss of deep-tendon reflexes and progressive weakness are early clinical indicators of magnesium toxicity.

Magnesium has been extensively studied in the treatment of acute myocardial infarction (AMI). Proposed theoretical benefits include an antidysrhythmic effect, limiting the influx of calcium into ischemic myocytes, and decreasing vascular smooth muscle tone. Several early small trials supported the use of IV magnesium as an adjuvant treatment for AMI. The ISIS-4 and Magnesium in Coronaries trial studied more than 64,000 patients with suspected AMI and IV magnesium initiated after reperfusion therapy. The study, the largest prospective investigation to date, found no benefit for mortality or dysrhythmias in the magnesium group, indicating no clear routine role for magnesium in the treatment of AMI. Moreover, the Intravenous Magnesium for Acute Myocardial Infarction Cochrane meta-analyses review included 26 previous clinical trials, and concluded that it is unlikely that magnesium is beneficial in reducing mortality. Magnesium may reduce the incidence of severe arrhythmias needing treatment, but it may

increase the incidence of profound hypotension, bradycardia, and flushing. The evidence does not support the use of IV magnesium in the treatment of AMI (20).

Animal studies indicate that IV magnesium has a relaxant effect on smooth muscle and acts as a bronchodilator, and early human clinical trials suggested that IV magnesium could produce additional bronchodilation when added to standard asthma treatment. A meta-analysis from the Cochrane Airway Review Group concluded that current evidence does not support the routine use of IV magnesium in ED patients presenting with mild to moderate asthma exacerbations, but subgroup analyses in the severe asthmatic group revealed a decreased admission rate and a small improvement in peak expiratory flow rate. The absolute FEV_1 improved by 10% of predicted. The authors concluded that magnesium appears to be safe and beneficial for patients who present with severe acute asthma (17). Adult study participants received magnesium 1.2 to 2 g IV over 20 minutes after standard albuterol therapy. In the pediatric studies, children received 25 or 100 mg/kg (maximum 2 g) IV over 20 minutes (21).

Magnesium is also used in several other clinical scenarios. Decades of experience support the use of magnesium in preeclamptic and eclamptic patients. Magnesium deficiency is a common finding in chronic alcoholism and alcohol withdrawal. Although IV replacement in the ED is a common practice, routine parenteral administration of magnesium is not recommended because existing controlled data do not demonstrate improvement in alcohol withdrawal severity, delirium, or seizures (22).

CRITICAL INTERVENTIONS

- Place patients with suspected hypomagnesemia on a cardiac monitor and perform an ECG.
- Administer IV magnesium for patients with dysrhythmias (torsades de points) due to magnesium deficiency.

Common Pitfalls

- Total magnesium serum levels are an inaccurate indicator of actual intracellular body stores.
- Failure to appreciate that predisposing conditions that lead to magnesium deficiency commonly lead to other electrolyte abnormalities.
- The kidneys rapidly excrete the majority of an IV magnesium bolus, while replenishing body stores takes days.

ACKNOWLEDGMENTS

The views expressed in this chapter are those of the authors and do not reflect the official policy or position of the Department of the Navy, the Department of Defense, or the United States government.

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CHAPTER 213
Rhabdomyolysis

Mark T. Steele

Rhabdomyolysis is a clinical syndrome resulting from injury to skeletal muscle. The most common causes in hospitalized adults are alcohol and drugs (illicit and prescribed), followed by muscle diseases, muscle trauma, neuroleptic malignant syndrome, seizures, immobility, metabolic, infection, exercise, and heat-related causes (Table 213.1) (1–3). It is common for there to be multiple causes of a given episode. Viral myositis and trauma are the most common etiologies in the pediatric age group (4). The final common pathway of all these etiologies is damage to the muscle cell membrane, or sarcolemma, which results in an influx of calcium and the liberation of intracellular contents such as creatine, myoglobin, **alanine aminotransferase, aspartate aminotransferase,** lactate dehydrogenase (LDH), aldolase, potassium, uric acid, and phosphorus (2).

TABLE 213.1
Causes of Rhabdomyolysis

Direct Trauma

Crush injury

Burns

Child abuse

Electrical injury

Muscle Overuse/Prolonged Exertion

Jogging/contact sports

Seizures

Status asthmaticus

Alcohol withdrawal syndrome

Dystonia

Psychosis

Drugs and Toxins

See Table 213.3

Infections

See Table 213.4

Metabolic Abnormalities

Diabetic ketoacidosis

Nonketotic hyperosmolar conditions

Hypokalemia

Hypo- or hypernatremia

Hypophosphatemia

Hypo- or hyperthyroidism

Muscular Ischemia

Prolonged immobility with external compression

Vascular obstruction (e.g., emboli, thrombosis)

Shock

Sickle cell disease

Hypo- or Hyperthermia

Malignant hyperthermia

Neuroleptic malignant syndrome

Heat stroke

Immune Disorders

Dermatomyositis

Polymyositis

Genetic Disorders

Disorders of glycolysis or glycogenolysis, including myophosphorylase deficiency (McArdle syndrome)

Disorders of lipid metabolism, including carnitine and carnitine palmitoyltransferase deficiency

Idiopathic

CLINICAL PRESENTATION

The presenting symptoms and signs of rhabdomyolysis are variable and generally reflect the underlying cause. The classic triad of muscle weakness, tenderness, and swelling is uncommon. Symptoms may be vague or absent in up to 50% of patients with rhabdomyolysis. About half of the patients in one series had muscle pains primarily involving the thighs, calves, and lower back (1). The physical examination is likewise often of limited value in making the diagnosis. In a pediatric cohort of patients, 45% complained of muscle pain and about 40% had a fever and symptoms of viral infection (5).

Because the history and physical examination can be nonspecific, a high index of suspicion should be maintained, particularly in the setting of seizures, unconsciousness, or agitation. The prehospital history may be helpful, particularly if the patient has an altered mental status: There may be a history of suspected overdose, seizure, or prolonged immobilization. There may also be a history of drug abuse or recent strenuous exercise or a family history of muscle dysfunction. The history should also include current medical problems and medications, any recent trauma or compression, bites and stings, infections, excessive exertion, electrical shock, or temperature extremes. Rarely, patients may report that their urine is dark reddish-brown (port-wine–like color). This symptom can occur if myoglobin levels exceed 100 mg/dL (1).

The major complications of rhabdomyolysis are listed in Table 213.2. Hyperkalemia is the most serious complication, because it can result in cardiac arrest and death if not diagnosed and treated promptly, particularly following crush-related disasters like earthquakes (6,7).

TABLE 213.2
Major Complications of Rhabdomyolysis

Hyperkalemia/cardiac dysrhythmias
Acute renal failure
Compartment syndrome
Disseminated intravascular coagulation
Respiratory dysfunction

Hyperphosphatemia, hypocalcemia, hyperuricemia, and hypoalbuminemia are also potential complications. Hypocalcemia, the most commonly encountered metabolic abnormality, is believed to be caused by calcium entering damaged muscle cells and from deposition of calcium phosphate in necrotic muscle (2). Hyperuricemia is related to the release of intracellular purines from damaged muscle tissue, and hypoalbuminemia is related to leakage of protein from injured muscle vessels. Release of organic acids from dying muscle cells may produce an elevated anion gap metabolic acidosis.

Acute renal failure is a major complication of rhabdomyolysis, with the reported incidence ranging from 4% to nearly 50% in retrospective studies (1,2,8,9). In an undifferentiated population of pediatric patients the rate of acute renal failure was 5% (5); the incidence was 13% in a pediatric trauma patient population (10). There are no well-designed prospective studies, so the true incidence of acute renal failure is unknown. In this setting, there is decreased glomerular filtration rate (GFR), the exact mechanism of which is unclear. Experimental evidence suggests increased renal vascular resistance secondary to intrarenal vasoconstriction, which may be due to microthrombi, activation of the renin–angiotensin system, vasopressin, or prostaglandins. Cellular release of myoglobin can lead to tubular obstruction and leakage of free radicals which also can cause cellular damage (2). The exact role of myoglobin is unclear, but it is known that hypovolemia and acid urine are required for myoglobin to result in renal injury. Likely predictors of renal failure in rhabdomyolysis include the degree of elevation of serum creatine phosphokinase (CPK) and the presence of sepsis or dehydration (3).

Compartment syndrome may be either a cause or a complication of rhabdomyolysis. In the latter case, this is more likely to occur in the setting of crush injuries (1). Fluid accumulates in the interstitial space, resulting in swelling and an increased intracompartmental pressure, leading to further muscle damage and necrosis. Compartment syndrome should be anticipated in patients with rhabdomyolysis, and compartment pressures measured if it is suspected. Fasciotomy should be strongly considered in patients with pressures >35 mm Hg.

There are other potential complications. Disseminated intravascular coagulation (DIC) is believed to be the result of the liberation of activating substances such as thromboplastin from necrotic muscle. Respiratory dysfunction can occur as a result of involvement of the respiratory musculature. Myocardial damage can also occur, resulting in manifestations ranging from isolated electrocardiographic (ECG) changes to heart failure and death (1).

DIFFERENTIAL DIAGNOSIS

Rhabdomyolysis should be considered in patients with muscle injury (direct trauma, burns, or compartment syndrome), known muscle disease, or exceptional muscular activity. Besides overt trauma, rhabdomyolysis can be seen in comatose patients or anesthetized surgical patients who remain in the same position for a prolonged period of time. In addition, rhabdomyolysis must always be part of the differential diagnosis of acute renal failure.

Drugs and toxins (Table 213.3) are the most common causes of rhabdomyolysis in adults. Ethanol, the most commonly implicated of these, has a direct toxic effect on the muscle cell membrane. More importantly, severe intoxication with alcohol or sedative–hypnotic drugs can result in prolonged immobilization and compression of the extremities, with resulting compromise of the blood supply to muscle. Metabolic complications of alcoholism, such as hypokalemia, hypophosphatemia, and hypomagnesemia, may also increase the risk of rhabdomyolysis. Alcohol-withdrawal seizures and delirium tremens can cause excessive muscular activity, with resultant rhabdomyolysis (11).

TABLE 213.3
Drug- and Toxin-Associated Rhabdomyolysis

Drugs of Abuse

Amphetamines/methamphetamine
Bath salts (mephedrone or methylenedioxy pyrovalerone [MDPV])
Barbiturates/sedative hypnotics
Cocaine
Lysergic acid diethylamide (LSD)
Opioids
Phencyclidine hydrochloride (PCP)

Alcohols

Ethanol
Ethylene glycol
Isopropyl alcohol
Methanol

Psychiatric Drugs

Antipsychotics
Lithium
Antidepressants (all classes)

Antiretrovirals

Didanosine
Lamivudine
Tenofovir
Zidovudine
Integrase inhibitors (e.g., Raltegravir)
Maraviroc

Anesthetics/Neuromuscular Blocking Agents

Inhaled gases (e.g., halothane)
Ketamine
Propofol
Succinylcholine

Antihistamines

Diphenhydramine
Doxylamine

Sympathomimetics (e.g., phenylpropanolamine)

Lipid-Lowering Agents

Statins
Fibric acid derivatives (fibrates)
Niacin

Other Drugs

Acetaminophen
Amiodarone
Amphotericin B
Anticholinergics
Azathiopine
Baclofen
Colchicine
Cyclosporine
Cyclobenzaprine
Daptomycin
Diuretics
Epsilon aminocaproic acid
Erythromycin
Glucocorticoids and anabolic steroids
Isoniazid
Laxatives
Leflunomide
Linezolid
Phenytoin
Promethazine
Proton-pump inhibitors
Quinidine
Salicylates
Terbutaline
Theophylline
Trabectedin
Trimethoprim sulfamethoxazole
Valproic acid
Vasopressin

Other Toxins

Arsenic
Carbon monoxide
Toluene
Mercuric chloride
Quail eating
Haff disease
Wild mushrooms (*Tricholoma equestre*)
Peanut oil

Poisonous Insect/Reptile Bites

Snake bites
Spider bites
Massive bee stings
Fire ant bites

Cocaine-induced rhabdomyolysis is not uncommon. At least some degree of skeletal muscle injury and CPK elevation appears to be common in emergency department (ED) patients who present after using cocaine (11). The exact etiology is unclear but may be related to excessive energy demands placed on the muscle cell, cocaine-induced vasospasm with resultant muscle ischemia, direct toxicity to the cell membrane, seizure activity, or agitation associated with cocaine toxicity. In addition, adulterants used to "cut" cocaine may be myotoxic (11).

Phencyclidine hydrochloride (PCP) and amphetamine intoxication cause similar toxicity. In a retrospective series of 367 patients identified in a California ED with rhabdomyolysis, the majority had toxicological evidence of illicit drugs and alcohol, with 43% testing positive for methamphetamine (12). Only 11% of the patients in this series developed acute renal failure. Excessive physical activity appears to be associated with rhabdomyolysis related to PCP abuse. It is not clear if PCP is directly toxic to the myocyte (11). Amphetamines are not known to be directly myotoxic but, like cocaine, have vasoconstrictive properties that can cause myocytes to become ischemic. They additionally raise levels of norepinephrine and dopamine, which increase the adenosine 5′ triphosphate (ATP) demands of the cell membrane (11). Amphetamine-intoxicated individuals also often present as agitated, requiring physical and chemical restraint, which may contribute to the development of rhabdomyolysis. Hyperthermia and DIC may also be factors contributing to the development of rhabdomyolysis in these patients. Rhabdomyolysis associated with heroin injection has been linked to adulterants such as quinine. Opioids may also have direct cell toxicity, and heroin users tend to be stationary for prolonged periods of time, placing them at further risk to develop rhabdomyolysis (11).

In a series of 475 hospitalized patients with rhabdomyolysis, neuroleptic drugs led the list of prescribed drugs most commonly associated with rhabdomyolysis, followed by statin agents (3). The statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are associated with mild CPK elevations, myalgia with and without elevated CPK levels, muscle weakness, muscle cramps,

myositis, and rhabdomyolysis. Myalgias can affect up to 10% of patients taking statins (4). The exact mechanism of muscle cell injury is unknown, but statins appear to reduce the production of small regulatory proteins that are important in maintaining the integrity of the myocyte. Clinically significant rhabdomyolysis with statins is uncommon, with an overall reported incidence of fatal rhabdomyolysis of 0.15 deaths per million prescriptions (13). The occurrence of renal failure with statin-induced rhabdomyolysis appears to be related to the magnitude of muscle injury, the patient's hydration status, and possibly other factors, such as concomitant medications or genetic predisposition. The risk of rhabdomyolysis appears to be dose-dependent, with the risk of myopathy increasing with higher serum concentrations of the statins.

Medications that inhibit the cytochrome P-450 3A4 system, such as the macrolide antibiotics, azole antifungals, and cyclosporine, increase the serum concentrations of selected statins and the risk of rhabdomyolysis. Other medications that increase the risk of statin-associated myopathy include the fibric acid derivatives (especially gemfibrozil), niacin, human immunodeficiency virus (HIV) protease inhibitors, verapamil, diltiazem, and amiodarone. Impaired renal or hepatic function, diabetes, hypothyroidism, heavy exercise, or surgery also appear to increase the risk of rhabdomyolysis in patients on statins (13).

Rhabdomyolysis due to strenuous or prolonged exercise can be seen in both untrained and trained athletes, especially if the exercise is conducted in extremely hot or humid conditions. Sickle-cell trait has been associated with exertional rhabdomyolysis; several fatalities have been reported (14). Survivors of high-voltage electrical injury or lightning strikes may develop rhabdomyolysis (7). Direct thermal cellular injury or electrical disruption of the sarcolemmal membrane is believed to be the etiology in these instances. Hyperpyrexic states can also outstrip cellular energy supplies, resulting in cell membrane dysfunction (15).

Infections (Table 213.4) may induce rhabdomyolysis by direct muscle injury or by inducing tissue hypoxia. Influenza is the most commonly reported viral etiology, followed by HIV infection and

enteroviral infection. Legionella species have been the most commonly reported bacterial organisms, followed by streptococcus species, *Francisella tularensis,* and *Salmonella* species (7). The myotoxic effects of *Legionella* are mediated through an endotoxin.

TABLE 213.4
Infectious Etiologies of Rhabdomyolysis

Bacterial
Legionnaire disease
Staphylococcus toxin
Streptococcus
Mycoplasma pneumoniae
Shigellosis
Salmonellosis
Tetanus
Gas gangrene
Septic shock
Q fever
Viral
Influenza (most common) A & B
Epstein–Barr virus
Cytomegalovirus
Echovirus
Coxsackievirus
Herpes virus
Adenovirus
Hepatitis
Human immunodeficiency virus (HIV)
Varicella-Zoster
Rickettsial
Rocky Mountain spotted fever
Parasitic
Trichinosis
Other
Reye syndrome

Other toxins, such as carbon monoxide and mercuric chloride, are directly toxic to the muscle cell membrane. Snake envenomations and stings from Africanized bees and honeybees can cause rhabdomyolysis via direct myotoxins. The eating of quail fed with hemlock has been associated with outbreaks of rhabdomyolysis (15). Haff disease is a syndrome of unexpected rhabdomyolysis related to the consumption of certain types of fish. Recent US cases have been associated with buffalo fish (*Ictiobus cyprinellus*), a bottom-feeding species found mostly in the Mississippi River and its tributaries (16). Cases of rhabdomyolysis due to the ingestion of wild mushrooms (*Tricholoma equestre*) have been reported (17).

Certain genetic defects, such as McArdle syndrome (absence of muscle phosphorylase) or carnitine palmitoyltransferase deficiency, prevent the effective use of carbohydrates or lipids as energy substrates. These entities can cause recurrent episodes of reversible rhabdomyolysis (2). Finally, in immunologically mediated diseases (e.g., polymyositis and dermatomyositis), muscle cells may be injured by inflammation.

ED EVALUATION

Evaluation, as always, begins with confirmation of hemodynamic stability. The history should be directed at identifying any possible etiologic factors, including exposure to alcohol, cocaine, or other toxins. On physical examination, look for signs of focal or generalized muscular tenderness or swelling, and note any obvious trauma. Laboratory evaluation should include electrolytes, blood urea nitrogen (BUN), creatinine, glucose, CPK, calcium, magnesium, and phosphate. Serum albumin, uric acid, and coagulation studies may be helpful in some instances. False-positive elevations of cardiac troponin I have been reported in rhabdomyolysis (18).

CPK is the most sensitive test for rhabdomyolysis. Five times the upper limit of normal, in the absence of cardiac or brain injury, is often considered the threshold for the diagnosis. CPK is an excellent marker because it is present almost immediately following injury, is easily measured, and is not rapidly cleared. Elevations are seen 2 to 12 hours following muscle injury; levels peak in 1 to 3 days and

generally fall off within 3 to 5 days after muscle injury ceases (1). There is a linear correlation between CPK and creatinine levels (3). Investigations suggest a relationship between CPK level and the development of acute renal failure and mortality (3). Renal injury is uncommon with levels of CPK less than 15,000 to 20,000 U/L unless dehydration or sepsis is present (2).

Serum and urine myoglobin determinations have also been used to diagnose rhabdomyolysis. Myoglobin typically rises more quickly than CPK, so it may be helpful in the diagnosis of early rhabdomyolysis, but because its half-life in plasma is only 1 to 3 hours it can also be unreliable because it can completely disappear from plasma within 6 hours of injury (1). Urine tests that use guaiac, orthotolidine, or similar agents can detect myoglobin or hemoglobin in the urine but cannot distinguish between the two. False-negative tests for myoglobinuria can occur because of rapid clearance of myoglobin from the urine (2). In a recent series, urine myoglobin was detected in only 19% of the patients with rhabdomyolysis (3).

KEY TESTING

- Electrolytes
- BUN
- Creatinine
- Blood glucose
- Calcium
- CPK

ED MANAGEMENT

The goals of management are to treat the underlying cause or causes of rhabdomyolysis, to identify and treat complications, and to prevent acute renal failure.

Rhabdomyolysis may continue to proceed or may be exacerbated by excessive exertion, agitation, fighting of restraints, seizures, or abnormal posturing. These should be controlled by aggressive sedation with a benzodiazepine to prevent further muscle breakdown. Rarely, pharmacologic paralysis with nondepolarizing

neuromuscular agents and intubation may be required. Hyperthermia, if present, should also be aggressively treated.

Patients with hyperkalemia require continuous cardiac monitoring and aggressive intervention. Hypocalcemia is generally self-limited and rarely requires specific treatment unless the patient is symptomatic or has severe hyperkalemia (2); the same is true of hyperphosphatemia. As noted previously, the patient should be monitored for the development of compartment syndrome. Coagulopathy can generally be addressed by treating the underlying disease process.

The mainstay of treatment is early repletion of fluids (2). Reports suggest that patients with delayed fluid resuscitation are more likely to suffer renal injury (19). There are no prospective studies comparing aggressive and nonaggressive hydration for the prevention of renal failure in patients with rhabdomyolysis. Uncontrolled studies suggest the efficacy of early, aggressive isotonic fluid administration in preventing acute renal failure in crush-related or traumatic rhabdomyolysis (2,20). In the case of major crush events (e.g., building collapse or earthquake), aggressive fluid repletion should be initiated during extrication if possible and prior to evacuation (6). This treatment results in increased renal tubular flow rates, which facilitate the excretion of substances that may injure or obstruct the renal tubules. A target urine flow rate of 200 to 300 mL/hr has been suggested. The fluid of choice is controversial and there are no definitive studies in this regard. Most experts initially recommend isotonic saline (2). Some have suggested the use of lactated Ringer solution (21) or half-normal saline (15).

Many experts also recommend the use of intravenous sodium bicarbonate to alkalinize the urine, because myoglobin is toxic to the kidneys in acid urine and bicarbonate will reduce the risk of hyperkalemia. *There have not been any large, randomized, and controlled studies to date demonstrating the benefit of bicarbonate* (1,2). Comparative trials have either been retrospective (22) or have been confounded by the concurrent use of saline loading or a combination of alkalinization plus mannitol. Saline and sodium bicarbonate are a reasonable approach, particularly for patients with metabolic

acidosis. One source recommends checking the urine pH, and if less than 6.5, alternating liters of normal saline and 5% dextrose plus 100 mmol of bicarbonate (2).

The role of diuretics such as mannitol and furosemide is also unclear, with no study demonstrating clear benefit (1,2). They should only be considered following adequate fluid repletion. Mannitol (1 g/kg) should probably be considered if urine output is inadequate despite saline infusion, because it may convert oliguric renal failure to nonoliguric renal failure, which has a better prognosis. Mannitol increases renal blood flow and GFR, may reduce muscular swelling by acting as an osmotic agent, increases urinary flow, may prevent obstructive myoglobin casts by acting as an osmotic diuretic, and scavenges free radicals (15). Acute renal failure unresponsive to the aforementioned measures may require dialysis. Indications for dialysis include worsening renal failure, persistent hyperkalemia despite treatment, fluid overload and pulmonary edema, resistant metabolic acidosis, or persistent oliguria or anuria (2). The overall prognosis for ultimate recovery is good (1).

CRITICAL INTERVENTIONS

- Strongly consider rhabdomyolysis in the setting of seizures, unconsciousness, or agitation, particularly if associated with a history of drug use.
- Suspect rhabdomyolysis if the urine dipstick is strongly positive for blood with few or no red blood cells (RBCs) seen on microscopic examination of the urine; confirm the diagnosis by obtaining a CPK level.
- Aggressively hydrate with normal or half-normal crystalloid solution to maintain urine output at 200 to 300 mL/hr.
- Aggressively treat hyperkalemia.

DISPOSITION

Patients with rhabdomyolysis generally require admission to the hospital, as it is not possible to predict which individuals will develop complications. Patients with hyperkalemia, metabolic

acidosis, or evidence of renal failure, and those with other serious comorbid conditions, require hospital admission. Patients with hyperkalemia require admission to a monitored setting, and nephrology consultation is indicated if renal insufficiency develops or if metabolic abnormalities are unresponsive to usual medical treatment. Dialysis is required for some individuals. If renal consultation and dialysis are not available at the treating institution, transfer to a facility with those capabilities should be initiated.

Common Pitfalls

- Failure to consider rhabdomyolysis in patients with alcoholism or drug abuse, on rhabdomyolysis-associated medications, unconsciousness, prolonged immobilization, seizures, hyperthermia, or infection.
- Failure to pharmacologically control agitation, seizures, or abnormal posturing in patients who are at risk for rhabdomyolysis.
- Failure to evaluate for compartment syndrome.
- Failure to realize that the diagnosis of rhabdomyolysis cannot be ruled out on the basis of the serum or urine myoglobin alone.
- Failure to provide adequate hydration and to prevent or treat acidosis in patients with rhabdomyolysis.

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SECTION XXII
Pediatrics

Section Editor: ROBERT L. CLOUTIER

PART 1 • GENERAL PRINCIPLES OF PEDIATRIC EMERGENCY CARE

CHAPTER 214

General Approach to the Pediatric Emergency Patient

Paul Ishimine

Children present frequently to the emergency department (ED) and pose special challenges to providers who are more accustomed to evaluating adult patients. They have different illnesses when compared to adults, and they have different responses to the same diseases. Communication with children can be challenging, and interaction with pediatric patients must involve parents or guardians as well.

Of the 130 million ED visits in 2010, 30 million visits or 23% of all ED visits were by children under the age of 18 years (1). One-quarter of all children under the age of 6 years visited EDs in 2011 (1). Generally, children tend to be less sick compared to adult patients. Children are triaged at lower acuities at the time of ED presentation and are more likely to be discharged home, as compared to adults (2). The two most common reasons for ED visits are cold symptoms and injury, the latter most commonly from falls (1).

While children are generally less ill than adult ED patients, EDs are the most common entry points into the health system for the vast majority of critically ill and injured children. The Institute of Medicine supports the idea of regionalization of pediatric emergency care so that critically ill and injured patients are directed to facilities with the capabilities of taking care of these children (3). This poses a challenge to emergency providers, since critical procedures in

children are infrequently performed in the ED (4). With regionalization, most emergency providers will have fewer opportunities to take care of seriously ill and injured children, and yet, all EDs and emergency providers must be able to assess and stabilize pediatric patients.

INITIAL ASSESSMENT OF THE PEDIATRIC PATIENT

The initial assessment of the pediatric patient can be based largely on observation (5). This clinical gestalt is formed, either consciously or subconsciously, by components of the Pediatric Assessment Triangle (PAT). The PAT is a useful tool to that uses only visual and auditory cues and allows the clinician to rapidly assess the severity of a child's condition. This general impression of the child's condition drives the urgency for treatment (5). The three components of the PAT include appearance, work of breathing, and circulation.

The appearance limb of the PAT is actually a mental status examination. It not only assesses brain function but helps to determine adequacy of circulation, ventilation, and oxygenation. Is the child irritable or lethargic? Does he or she respond to his or her environment in a way that is age-appropriate? Is she or he easily consoled when rocked or cuddled? Does she or he interact appropriately with her environment and caregiver? Is his or her look/gaze age-appropriate? Is the character of the cry weak, high-pitched, muffled, or atypical?

Work of breathing in infants and young children can best be assessed before touching the patient. Listen carefully for both inspiratory and expiratory sounds. Is there audible wheezing, stridor, or grunting? Are there intercostal, subcostal, or supraclavicular retractions? Is there nasal flaring or head bobbing? What is the preferred position of the patient?

Assessment of circulation to the skin can be determined by observing for pallor, cyanosis, or mottling. Frequently, the first objective indicator of compensated shock is a combination of tachycardia and pallor. The pale infant or young child should be considered in shock until proven otherwise. As circulation to the skin

becomes further compromised, patches of erythema or cyanosis interspersed with pallor (mottling) will appear.

Once the initial assessment is complete, a more formal assessment can then proceed, starting with measurement of the vital signs. Vital signs can be highly variable in the same patient and should be interpreted while considering the context in which these vitals were obtained. For example, an anxious child who is crying at triage is more likely to have tachycardia, tachypnea, and high blood pressure.

Normal heart rates for infants and children are age-dependent (Table 214.1) (6). In compensated shock, the first sign will usually be tachycardia. However, tachycardia is a very nonspecific finding and is also increased with pain, fear, and fever. The heart rate must be compared with pulse quality and mental status to determine the significance of either an abnormally fast or slow rate. The most common cause of a slow heart rate is respiratory compromise and hypoxemia. The quality of pulses is an important physical examination tool to monitor during stabilization and resuscitation. Central and peripheral pulse should be compared simultaneously.

TABLE 214.1
Normal Heart Rate and Respiratory Rate (6)

Age	Heart Rate, Beats/min, Median (Interquartile Range)	Respiratory Rate, Breaths/min, Median (Interquartile Range)
0–3 ms	143 (133–154)	43 (40–52)
12–18 mos	123 (112–132)	35 (32–42)
4–6 yrs	98 (89–108)	23 (21–25)
8–12 yrs	84 (75–93)	19 (18–21)
12–15 yrs	78 (69–87)	18 (16–19)

Blood pressure measurements are often difficult to obtain when infants and young children are agitated and crying. Furthermore, blood pressures defined as normal depend on the patient's age, sex, and height (Table 214.2) (7). Improper blood pressure cuff sizes, can cause incorrect readings. To obtain an accurate blood pressure, the cuff width should be at least two-thirds the length of the upper arm

of the child. Time should not be wasted during resuscitation and stabilization with attempts to obtain an accurate blood pressure. If the child is alert, crying, and responding to his or her environment, blood pressure measurements can wait until stabilizing interventions are under way. The lower limits for blood pressure (fifth percentile) are typically considered to be (8):

TABLE 214.2
Normal Blood Pressures by Age and Sex

	Boys		*Girls*	
Age (Years)	Systolic, mm Hg, Mean (Interquartile Range)	Diastolic, mm Hg, Mean (Interquartile Range)	Systolic, mm Hg, Mean (Interquartile Range)	Diastolic, mm Hg, Mean (Interquartile Range)
1	85 (83–87)	37 (46–38)	86 (85–88)	40 (39–41)
3	91 (89–93)	46 (45–47)	89 (88–91)	49 (48–50)
8	99 (97–100)	59 (58–60)	98 (96–99)	57 (56–58)
12	106 (104–108)	62 (61–63)	105 (104–107)	62 (61–63)
16	116 (114–118)	65 (64–66)	111 (110–112)	66 (65–66)

[a]For 50th percentile of height.
National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114:555–576.

- <60 mm Hg in term neonates (0 to 28 days)
- <70 mm Hg in infants (1 month to 12 months)
- <70 mm Hg $+$ (2 $\times$ age in years) in children 1 to 10 years
- <90 mm Hg in children ≤ 10 years of age

Capillary refill time is a cruder measurement of perfusion status and should generally be <2 to 3 seconds when an infant or child is in a neutral–thermal environment. Delays in capillary refill can occur if the ambient temperature is low (9). When an infant compensates for hypovolemia or hemorrhage, early skin signs include not only pallor and decreased peripheral pulses but cool distal skin temperature as well.

Respiratory rates are also age-dependent (Table 214.1) (6). Although rates above 60 breaths/min can periodically be normal for short periods of time in an infant, any rate above this, or any prolonged periods of tachypnea, must be considered abnormal until proven otherwise. Slow respiratory rates must alert the healthcare

provider to consider respiratory failure. The respiratory rate must always be interpreted in conjunction with heart rate and mental status when determining whether ventilatory efforts are adequate or insufficient.

Pulse oximetry is frequently utilized in the assessment of pediatric patients. Normal pulse oximetry values have not been established but are generally accepted to be 97% to 99%. This can vary throughout the day. The oxygen saturation is commonly lower during sleep, when it can be as low as 90% to 93% in normal patients (10). Nonetheless, pulse oximetry may be a useful screening tool in children with suspected respiratory pathology.

Temperature measurements should be obtained in children who present to the ED. Although body temperature can normally fluctuate, the generally accepted average core temperature is 37.0°C (98.6°F). Fever is generally accepted as a temperature of 38.0°C (100.4°F); conversely, hypothermia is commonly defined as a temperature below 35.0°C (95.0°F). Rectal temperature measurements provide the closest approximation to a core temperature measurement, and in young children, for whom a precise measurement of temperature leads to a specific plan of action (e.g., the initiation of an evaluation for sepsis in a young infant), this method is preferred over other, more convenient, means of temperature measurement.

An age-appropriate pain scale should be used to measure pain severity whenever significant pain is a complaint. Although the perception of pain is very subjective, intense pain should always be an issue of concern to the healthcare provider. Finally, a weight, measured in kilograms, should be obtained in pediatric patients. Medications are dosed in units per kilogram, and appropriate equipment size is often linked to patient weight. If an actual weight cannot be measured, weights should be estimated using a length-based measurement system.

AGE-SPECIFIC CONSIDERATIONS

A basic understanding of how developmental age affects child behavior is necessary to get the most out of the emergency

department assessment. Knowledge of language development and the sequence of physical and behavioral milestones can be quite helpful in determining the optimal approach to the assessment of an infant or young child. Table 214.3 summarizes age-related pediatric differences in language development, behavioral activities, and motor-physiologic milestones.

TABLE 214.3
Age-Specific Considerations

Age	Language	Behavioral	Motor/Physiologic
Birth	• Express needs and discomfort by crying	• No/limited eye contact • No social smile • No recognition of caretaker	• Acrocyanosis • Abdominal breathing • Irregular head control
2 mos	• Vowel sounds with pleasure • Babbles • Laughs aloud	• Social smile • Recognizes caretaker	• Tracks light • Grasps objects • Rolls over • Sits with support
6 mos	• Repetitive vowel sounds • Repetitive consonant sounds	• Stranger anxiety • Oral exploration • Imitative behavior • Independent activities	• Sits alone • Increasing mobility • Creeps • Crawls • Stands
12 mos	• Variable and progressive language capabilities • Jargon speech • Speaks in 2- to 3-word phrases	• Increasing curiosity • No fear of danger • Strong opinions • Egocentrism • Problem solve by trial and error	• Walks alone • Stiff running • Climbs stairs
2 yrs	• Comprehension greater than expression • Speaks in short sentences • Rapidly progressing language development	• Development of acceptable social patterns • Toilet training • Nightmares; fears of separation, bodily injury	• Refinement of both fine and gross motor skills
4 yrs	• Good verbal skills	• Cooperative during examination • Gain in independence • Ability to reason with adults • Fear of pain, procedures	• Specialized motor skills emerge (games)
Adolescence	• Expressive and comprehensive language skills mature	• Peer pressures replace parent control • Abstract thinking • Rational thought/analysis • Risk-taking	• Very mobile

Neonates (birth to 1 month) and young infants (1 to 3 months) have a limited behavioral repertoire. A neonate sleeps approximately 20 hours per day in early infancy. The young infant's expression of needs is by crying and is generally a sign of hunger or discomfort. Neonates typically lose weight during their first few days of life, but usually return to their birth weight by 10 to 14 days of age.

Older infants (3 to 12 months) begin appropriate interaction with their environment such as smiling with pleasure and recognition of

familiar faces. Babbling sounds emerge as the beginning of language development and motor activities begin to mature. When performing assessments on infants younger than 6 months of age, emphasis should be on the most important and least traumatic aspects of the examination first. Keeping hands and instruments warm and using distractions and a quiet soothing voice can assist in gaining cooperation and facilitating the examination process. The majority of the examination should be done in the caretaker's arms whenever possible. It is important to be aware of the increased risk of heat loss from a high surface-area-to-weight ratio. Providers should aim to maintain a neutral–thermal environment during the examination process.

Examination of 6-month to 1-year-old infants can be a challenge, especially if they have had previous negative experiences with healthcare providers. Always anticipate and expect separation anxiety and perform as much of the examination on the caregiver's lap as possible. It is often helpful to get at or below eye level of the infant during the examination. Toys and distracting sounds can be used to keep the infant from losing control. The *toe-to-head* approach to examining the infant should always concentrate on the least traumatic aspects of examination first. The ears and mouth should be examined last.

The toddler years (12 to 36 months) are manifested by increasing mobility and curiosity. Toddlers have little fear of danger, and the risk of preventable injury events increases dramatically as mobility progresses. When examining a toddler, obtain as much information as possible through observation, before laying on hands or a stethoscope. Magical games often help with difficult portions of an examination. For example, as the caretaker palpates the abdomen, he can "guess what the toddler had for breakfast earlier." Reassurance and praise goes a long way, and any painful procedure should be explained in very simple terms.

As preschoolers (3 to 5 years) young children begin to understand cause-and-effect relationships and learn to reason with adults. Their increasing independence outside the home becomes evident, but this newfound independence will often crumble during stressful

situations. It is not unusual for a 4-year-old to express plans for complete cooperation during a painful procedure, but when the procedure begins, she or he may lose control and become combative. Information given to a young child can often be misinterpreted and create unwarranted fear and anxiety.

School-aged children (5 to 12 years) have developed a stronger sense of cause-and-effect. It is important to speak directly to the child and obtain information from the child, supplementing that information by parental report. Praise and compliments go a long way. It is best to anticipate questions and address fears with simple and clear explanations during the examination. Always respect the patient's modesty. When there are options in performing a procedure, allow the child limited control. For example, one cannot negotiate the need for a blood draw, but they can negotiate whether the procedure is performed in the left arm or the right arm.

In many ways, adolescent (12 to 18 years) behavior is similar to that of the toddler; both are periods of rapid physical development and developmental changes. Adolescents are very mobile and risk taking and often have no fear of danger. They may not anticipate consequences, and may fail to use common sense before performing risk-taking activities. Peer pressure becomes very important. During a history and physical examination, adolescents should be separated from parents, and information should be obtained from the patient, not the caretaker. Privacy and confidentiality must be respected.

CONSENT AND CONFIDENTIALITY ISSUES

Most children who present to the ED for evaluation are accompanied by a parent or guardian, and usually the parent or guardian provides consent for the evaluation and management of these minors (i.e., persons under the age at which they can provide legal consent) and participates in the child's care. Indeed, the principles of patient- and family-centered care encourage collaboration between the patient, family, and provider (11). However, situations occasionally arise where a parent or guardian is unavailable to provide consent for treatment, when parental consent is unnecessary, or when parental refusal of consent is potentially dangerous.

For those minors who present to the ED unaccompanied by a parent or guardian, a medical screening examination and any life- or limb-saving interventions that cannot be safely delayed (including treatment of severe pain) should be undertaken while attempting to contact the parent or guardian, and should never be delayed because of difficulties obtaining consent. This is mandated by the Emergency Medical Treatment and Active Labor Act and falls under the doctrine of "implied consent." The legal basis for this is known as the "emergency exception rule" (12). If an emergency medical condition is not identified, then the emergency provider should generally seek consent before providing any additional, nonemergent care. The clinician should document attempts to contact the parent or guardian and the rationale for emergency interventions.

There are several situations where a minor, and not a parent or guardian, can consent to treatment. When a child is emancipated, he or she can consent to medical treatment. Criteria for emancipation vary from state to state, but most states recognize minors to be emancipated if they are married, on active duty in the military, or are self-sufficient and living independently. The "mature minor" exception allows a minor, generally over 14 years of age, with sufficient maturity and intelligence, to provide informed consent; the criteria for a "mature minor" also varies from state to state. Additionally, minors can usually consent to evaluation and treatment of certain conditions (e.g., pregnancy-related conditions, mental health issues, sexually transmitted diseases, substance abuse); these conditions also vary from state to state (1).

While a parent or guardian with adequate decision-making capacity may have the right to refuse treatment for his or her child, this authority is not absolute, and the appropriate child protective agency should be consulted if the parent or guardian makes a decision that places a child at significant risk or serious harm when compared to an alternative choice (12,13).

Adolescent patients should be afforded the opportunity to speak and be examined privately by emergency care providers, but they should be informed that the emergency provider may need to breach

this confidentiality if there is a potential danger to self or others or there needs to be a disclosure of abuse (11–13).

CHILDREN WITH SPECIAL HEALTHCARE NEEDS

While most children who present to the ED have a single-system, self-limited illness, some children have chronic medical conditions. Patients may have multiple medical problems, may be taking multiple medications, and may have indwelling medical devices. The involvement of the parents or caretakers of these children is even more imperative than with most children. Parents or caretakers usually can recognize when a child is at his or her baseline health status, and they frequently know why their child's condition has changed. Additionally, parents and caretakers are usually best able to assess the capabilities they have at home to take care of their children; thus, they should be involved in the disposition process. Early engagement of the patient's primary care physician and subspecialists can lead to a more directed evaluation in a child with a chronic medical condition. Both the American Academy of Pediatrics and the American College of Emergency Physicians have advocated the use of an Emergency Information Form, a concise summary of a patient's health status (14,15).

ED PREPARATION FOR CHILDREN

The majority of children seeking emergency care are seen in the EDs of general hospitals, so every ED needs to be prepared to assess and stabilize children. Despite the large numbers of children seen in general EDs, adherence to previously published guidelines for recommended pediatric supplies and equipment has previously been low (16,17).

Although most children can be discharged from the ED to which they initially present, EDs must be prepared to transfer these children to facilities that can provide definitive care, if needed. Guidelines for ED readiness call for the designation of physician and nurse coordinators for pediatric emergency care. Furthermore, these guidelines call for emergency physicians and nurses to have the skills, knowledge, and training to evaluate and treat children who

may be brought to the ED. Furthermore, EDs should have a pediatric patient care review process in place, as well as pediatric policies, procedures, and protocols that address specific pediatric topics, including pediatric-specific safety concerns, patient care, and interfacility transfers. Laboratory and radiology services should be appropriate for the ED services provided. Finally, guidelines endorsed by the American Academy of Pediatrics, American College of Emergency Physicians, and the Emergency Nurses Association make recommendations for the availability of pediatric equipment, supplies, and medications (18).

ACKNOWLEDGMENT

This chapter is a revision of the chapter written by Robert Wiebe, MD. The author gratefully acknowledges Dr. Wiebe's contributions.

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CHAPTER 215

General Approach to Neonates and Infants Less Than 12 Months of Age

Khoon-Yen Tay and Rakesh D. Mistry

While only approximately 3% of the almost 130 million emergency department (ED) visits in 2010 in the United States were for the care of infants less than 12 months of age, this age group offers a particular challenge to emergency medicine providers in all settings (1). For providers who rarely or infrequently care for children, evaluating infants creates significant discomfort and anxiety (2). Here we focus on age-specific differences in the evaluation of infants less than 12 months of age, separately addressing the neonate under 56 days and the infant from 8 weeks to 12 months of age.

The typical "past medical history" for most infants will be sparse, but must include the perinatal, birth, and vaccination history; information from this period may be invaluable in the continuing care of the infant. For example, in an infant presenting with bruising or signs of bleeding, the etiology could range from nonaccidental trauma (NAT), to failure of vitamin K administration in the immediate postnatal period.

In the first months of life, activity and well-being are best monitored by the infant's ability to perform very basic life activities such as feeding, urinating, stooling, and sleeping. Normal performance of even these most primitive functions may often exclude serious illness in young infants. Neonates, especially those who are breastfed exclusively, can lose up to 10% of their

birthweight in the first week of life. By 7 to 10 days of life, once maternal breast milk “let-down” has occurred and feeding regimens have become more regular, most neonates will have regained their birthweight and will gain an average of 20 to 30 g/d.

As infants grow, acquisition of gross motor skills, speech and vocalization skills, and general interaction with their environment become important markers of normal development and growth. The general timeline for developmental milestones in the first year of life is presented in Table 215.1. It should be noted that the range of development is wide, and achievement of milestones may differ from infant to infant.

TABLE 215.1
Examples of Major Developmental Milestones in Neonates and Infants 0–12 Months of Age

	1–2 months	3–4 months	5–6 months	7–8 months	9–10 months	11–12 months
Social and Emotional	Preferential social/responsive smile					
			Stranger anxiety			
			Feeds self			
				Indicates wants		
				Separation anxiety		
Language and Communication	Variation in crying					
	Quiets to voice					
			Turns head to sounds			
					Listens and responds to selective words	
					Uses symbolic jargon	
Fine Motor		Eyes follow 180°				
			Reaches for object			
			Palmar grasp			
			Thumb finger grasp			
				Bangs two objects together		
						Put block in cup
Gross Motor		Sits alone momentarily				
		Rolls back to stomach				
		Sits steadily				
					Stands alone	
				Pulls to standing		
						Walks alone

[a]Appearance and resolution of most developmental milestones occur within a range of ages, as depicted.

Measurement of vital signs, while as important as in older patients, takes on special significance in infants, potentially offering an early clue to occult disease; abnormalities such as fever or tachycardia may be the *only* indication of illness requiring immediate intervention. Evaluation of vital signs may be challenging, as

differences in normal age-appropriate vital signs are not intuitive to all providers. Not only are infant vital signs drastically different from those of adults, they also vary significantly from birth to 1 year of age, and specifically within the neonatal period. The normal ranges of vital signs, by age, are presented in Table 215.2.

TABLE 215.2
Vaccine Schedule for Pediatric Infants

Vaccines	Birth	1 month	2 months	4 months	6 months	9 months	12 months	15 months	18 months
Hepatitis B (HBV)	1st dose	2nd dose			3rd dose				
Rotavirus		1st dose	2nd dose						
Diptheria, tetanus, acellular pertussis (DTaP)		1st dose	2nd dose	3rd dose					
Haemophilus influenza type b (Hib)		1st dose	2nd dose	3rd dose					
Pneumococcal conjugate (PCV13)		1st dose	2nd dose	3rd dose					
Inactivated polio		1st dose	2nd dose	3rd dose					
Influenza					*Annual Vaccination*				
Measles, mumps, rubella (MMR)							1st dose		
Varicella							1st dose		
Hepatitis A							1st dose		

[a]Does not include premature infants or infants with chronic medical illnesses such as congenital heart disease.
Definition of hypotension based on American Heart Association Pediatric Advanced Life Support Guidelines, 2011.
Adapted from Nelson's Textbook of Pediatrics, 19th ed. 2011, and American Heart Association Pediatric Advanced Life Support Guidelines, 2011.

There are many unique aspects of the physical examination of infants. Anterior and posterior fontanelles, and palpable suture lines, are common throughout infancy and are occasionally mistaken for injuries. Primitive reflexes (suck, Moro, grasp) and clonus of the extremities are often the only findings of a normal neurologic examination. Among the more anxiety-provoking examination findings for emergency physicians (and parents) is crying. However, a preverbal infant cries for many reasons, including hunger, discomfort, need for attention; in cases where the infant cannot be consoled, etiologies such as pain and infection should be considered.

A high degree of suspicion for NAT must be maintained in this age group; presenting complaints are often vague, a history of trauma is absent, and external signs of injury are rare. The signs of abuse are often missed, explaining why over 40% of mortality from NAT is in infants less than 12 months of age (3). Injuries incompatible with developmental age accompanied by altered mental status (e.g., lethargy, listlessness, irritability, seizure) *without* a history of trauma

are red flags for possible NAT. Consultation with local child abuse experts must be sought for any child suspected of NAT (see Chapter 290).

GENERAL APPROACH TO THE NEONATE 0 TO 56 DAYS

History and Physical Examination

While the term "neonate" generally refers to patients from birth to 4 weeks of age, infants up to 8 weeks of age are included in this discussion. The history and physical examination must be tailored to assess a number of issues specific to neonates, including (1) the potential exposure to pathogens in utero or peripartum, placing them at risk for early sepsis, (2) an underdeveloped and unvaccinated immune system that is largely dependent on maternal antibodies, and (3) previously undiagnosed congenital anomalies or inborn errors of metabolism (IEM) presenting during this period.

Perinatal and birth history are vital elements of a thorough neonatal evaluation. Knowledge of prematurity or associated sequelae, such as respiratory distress syndrome, meconium aspiration, prolonged intubation, neonatal infections, repaired congenital heart defects, intraventricular hemorrhage, or necrotizing enterocolitis, can help focus evaluation of an acutely ill neonate.

Presence or absence of adequate prenatal care can be helpful: the majority of significant congenital diseases are diagnosed prenatally, including cardiac (e.g., hypoplastic left heart syndrome, transposition of the great arteries, tetralogy of Fallot, etc.), genetic (e.g., trisomy 21, 13, 18), neurologic (e.g., spinal dysraphisms), renal (e.g., renal agenesis, duplicate collecting systems), lung (e.g., lung hypoplasia from congenital diaphragmatic hernias, congenital cystic adenomatoid malformations), and bone (e.g., perinatal fractures often suggest osteogenesis imperfecta) anomalies. Additionally, routine prenatal care involves screening for pathogens potentially transferred from the mother to the fetus transplacentally during gestation or transvaginally at delivery. Herpes simplex virus (HSV), syphilis, cytomegalovirus (CMV), toxoplasmosis, and human immunodeficiency virus (HIV) may result in congenital infections or

major developmental complications postnatally. Perinatal treatment can moderate the risk of infection, such as administration of perinatal parenteral antibiotics for women with known group B streptococci colonization, and antiretroviral treatment for pregnant women with HIV. Absent or incomplete prenatal care in any neonate presenting to the ED should prompt a higher index of suspicion for specific perinatal infections and congenital anomalies. Additional birth history that may be of importance includes birthweight, administration of routine care such as vitamin K injection and erythromycin eye ointment, and results of newborn screening, all of which are routine received in the delivery room.

Social histories should document any prescription medications or illicit drugs that, may cross the placenta or be introduced into breast milk. Neonatal abstinence syndrome, may develop in infants exposed to addictive illegal or prescription drugs in utero, and then abruptly withdrawn at birth. These infants present with classic signs of withdrawal, such as irritability, poor feeding, jitteriness, seizure activity, diarrhea, diaphoresis, and excessive crying (4).

The review of systems for neonates stresses assessment of the five major activities common to this age group: feeding, urinating, stooling, sleeping, and breathing. Deviation from baseline in these activities may indicate distress or acute illness. Certain signs may be unique and should trigger increased concern, including the presence of fever, hypothermia, lethargy, increased fussiness, respiratory distress, intermittent cyanosis, or changes in skin color. Vomiting, diarrhea, rhinorrhea, and cough may be present from typical childhood viral illnesses; though other illnesses should be considered for each of these symptoms.

Neonatal hydration status is assessed by gaining a general sense of formula or breast milk intake and urine output; more specific questions about feeding, including quantity, volume, type of nourishment (breast milk vs. formula) are vital elements of the neonatal history. For neonates receiving formula reconstituted from a powder, it is important to ask caretakers how the formula is prepared. Overdilution of formula will result in an excess administration of free water to a renal system with reduced filtration

ability. This is in turn may lead to severe hyponatremia and refractory status epilepticus, which will only respond to interventions aimed at increasing the concentration of serum sodium such as 3% saline.

The poor sensitivity of the physical examination for detection of serious illness is among the most challenging aspects in the evaluation of infants less than 2 months of age. Multiple studies have shown that physicians are unable reproducibly assess which newborn infants are "well-appearing." The Yale Observation Scale (YOS) is a set of six observations that can be scored by medical providers for young febrile children, including observations such as the quality of the child's cry, color, and social response (5,6). However, in validation studies, the YOS alone was determined to be unreliable in neonates under 8 weeks of age and, conversely, a significant portion of infants with elevated scores had no objective evidence of serious illness (7). Consequently, more objective laboratory data are necessary in the evaluation of many neonates, particularly those presenting with fever. Nonetheless, a thorough head-to-toe physical examination remains of utmost importance, since detection of hallmark physical examination findings may provide useful clues for ED management. These include findings related to general appearance, tone, the anterior fontanel, and quality of cry.

Specific Disease Processes

Emergency providers should be aware of several disease processes exclusive to the newborn period. While many are common and benign, certain conditions are critical, often requiring prompt recognition, and immediate intervention to prevent morbidity and mortality. Thus, these processes should be considered in the general approach to an ill-appearing neonate in the ED; however, details regarding diagnostic workup and management can be found elsewhere in this textbook.

Neonatal sepsis refers to physiologic instability in the presence of an infecting pathogen, usually bacterial or viral, in an infant less than 8 weeks of age (56 days). In neonates, sepsis may originate, or produce meningitis, pneumonia, urinary tract infection (UTI), or

bacteremia (6,8–10). As discussed previously, neonates are at increased risk of invasive infection due to relatively poor host defenses and relatively compromised immune status. Presenting signs of sepsis in this age group are numerous, and include both fever ($\leq$38°C), and even more concerning, hypothermia ($<$36°C). Other presenting signs may include respiratory distress, tachypnea, tachycardia *or* bradycardia, and signs of poor perfusion such as mottling and prolonged capillary refill. Extreme fussiness or irritability, though neither sensitive nor specific, can herald a serious bacterial infection in a neonate, and should not be overlooked by emergency providers. As a result, infants less than 2 months of age are often empirically tested, and sometimes treated, for potential invasive bacterial infections. Further discussion on the workup and management of neonatal sepsis is discussed in Chapter 216.

Jaundice commonly occurs in neonates, and is usually benign in origin. Often, mild unconjugated hyperbilirubinemia is seen physiologically after birth, peaking within 48 to 96 hours of birth and lasting up to 2 weeks. "Breast milk jaundice," which presents around 4 to 7 days of life due to interactions of breast milk hormones with hepatic enzymes is typically self-limited and nonthreatening. "Breastfeeding jaundice," which occurs during the first few days of life before maternal breast milk let-down, results from dehydration, thus increasing the concentration of bilirubin in the serum, and occasionally requiring fluid supplementation. Although a frequent neonatal complaint, emergency providers must consider that (1) severely elevated levels of bilirubin in the blood can be toxic to the neonatal brain (kernicterus) and (2) the presence of conjugated hyperbilirubinemia implies an underlying pathologic process. Therefore, a careful approach to the jaundiced infant is required. In specific cases, when jaundice is present in the entire body, and associated with lethargy, poor feeding, and reduced urine output, evaluation for kernicterus, hepatic dysfunction, sepsis, and ABO incompatibility is necessary. Prompt institution of phototherapy, hydration, or even transfer to a tertiary-care facility may be necessary (11).

Inborn errors of metabolism (IEM), encompasses a group of disorders that result from disruption of the normal enzymatic function within mitochondrial cycles and cascades. The consequence is buildup of toxic precursors and metabolites, or the inability to produce vital proteins and molecules necessary for cellular function. As a result, these disorders often present after the onset of enteral feeding, and largely are diagnosed in the newborn period. Presenting signs of an IEM include poor feeding, vomiting, hypoglycemia, seizures, and lethargy. Histories of sudden decompensation after a prolonged period of fasting, or after initiation of common infant formulas, are helpful clues of a possible IEM diagnosis. Currently, the majority of IEMs are detected via newborn screening, prior to onset of symptoms; perinatal diagnosis allows for institution of specific formula to compensate for metabolic dysfunction. However, providers should not be falsely reassured by a reported normal newborn screen, as these screening tests vary by individual state and local, and are not always comprehensive. In some cases, physical examination findings, such as ambiguous genitalia in the case of congenital adrenal hyperplasia, can also lead to early diagnoses of IEM. Discussion about the diagnosis and treatment of pediatric inborn errors of metabolism is found in Chapter 275.

Congenital heart diseases are among the most feared diagnoses when ED physicians are faced with an in ill neonate. Fortunately, owing to the advent of fetal echocardiography, the majority of *significant* congenital heart lesions are identified in utero, and adverse events are avoided as pediatric cardiac intensivists and neonatologists are able to intervene immediately after birth. Nonetheless, congenital heart defects may elude prenatal or perinatal diagnosis, such as in cases of poor prenatal care or home birth; these situations should alert the emergency provider to the possibility of newly diagnosed congenital heart disease. Congenital heart anomalies, which rely on a patent ductus arteriosus (PDA) to maintain either systemic or pulmonary circulation, so-called “ductal-dependent lesions,” will often present in the first few days of life, as the ductus arteriosus is closing, leading to severely reduced cardiac output. Consequently, these neonates often present with a sepsis or

shock-like picture, with evidence of poor perfusion, decreased mental status, poor or labored feeding, and worsening respiratory distress. Severe hypoxia is usually present and unresponsive to administration of supplemental 100% oxygen. Examples of lesions that rely on a PDA to supply the systemic circulation include hypoplastic left heart syndrome, critical aortic stenosis, and critical coarctation of the aorta; congenital heart disorders that rely on a PDA for maintenance of pulmonary circulation include pulmonary atresia, critical pulmonary stenosis, tricuspid atresia, and tetralogy of Fallot. More subtle presentations of congenital heart disease are possible and subtle signs such as diaphoresis with feeding, irritability, or poor weight gain may manifest, as well as physical findings such as hepatomegaly or intermittent cyanosis. In any infant in whom a diagnosis of congenital heart disease is considered, the physical examination should concentrate on obtaining vital signs (specifically blood pressure and oxygen saturation) in all four extremities (or at the very least, the right upper extremity and a lower extremity), perfusion status, cardiovascular examination (including pulses in the upper and lower extremities), a lung examination, and examination for hepatomegaly. Further discussion on the use of other diagnostic testing and interventions are discussed in Chapter 268.

Abdominal pathology is not common among neonates; however, two notable conditions are unique to infants in the first 2 months of life. Hypertrophic pyloric stenosis is typically a more benign diagnosis in an infant 3 to 6 weeks of age, presenting with nonbilious projectile emesis immediately after feeding. Hypertrophy of the pylorus effectively produces an obstruction, preventing movement of gastric contents to the duodenum, and subsequently large volume, forceful emesis. Patients may require fluid resuscitation if diagnosis is delayed, but surgical correction (pyloromyotomy) is usually performed on an urgent, not emergent, basis. Malrotation with midgut volvulus, on the other hand, is a true abdominal catastrophe, resulting from abnormal rotation of the bowel in utero resulting in an unfixed segment of bowel that can twist, strangulating itself from its blood supply, resulting in bowel ischemia, necrosis, and death. Neonates with bilious emesis have malrotation with midgut volvulus

until proven otherwise. Other common presenting signs are poor feeding, lethargy, and shock. Resuscitation in the ED and immediate surgical consultation is indicated, prior to emergent surgical correction (laparotomy with a Ladd procedure). Discussion on the diagnostic workup and management of these two diagnoses are discussed in Chapters 271 and 272.

GENERAL APPROACH TO INFANTS 2 TO 12 MONTHS OF AGE

History and Physical Examination

The approach to infants between 2 and 12 months of age presenting to an ED differs from that of infants less than 8 weeks of age for several reasons. At 2 months of age, infant immune systems are more robust and most infants have received their first set of vaccinations. Routine vaccination in the first year of life confers protection from the following pathogens: *Corynebacterium diptheriae, Clostridium tetani, Bordatella pertussis, Haemophilus influenza* type B*, Streptococcus pneumoniae,* poliovirus*,* rotavirus, and hepatitis B virus. Infants receive these vaccines in a series at 2, 4, and 6 months of age; evidence has shown that significant immunity is conferred after the first set of vaccines has been administered at 2 months (Table 215.3) (12). Additionally, with continued growth and development, infants interact more with their environment, making assessment easier. More importantly, the physical examination becomes increasingly reliable and more specific allowing practitioners to more frequently and accurately ascertain general appearance and detect disease in specific organ systems (13,14).

TABLE 215.3
Vaccination Schedule for Children from Birth to 18 Months of Age

Vaccines	Birth	1 month	2 months	4 months	6 months	9 months	12 months	15 months
Hepatitis B (HBV)	1st dose	2nd dose			3rd dose			
Rotavirus		1st dose	2nd dose					
Diptheria, tetanus, acellular pertussis (DTaP)		1st dose	2nd dose	3rd dose				
Haemophilus influenza type b (Hib)		1st dose	2nd dose	3rd dose				
Pneumococcal conjugate (PCV13)		1st dose	2nd dose	3rd dose				
Inactivated polio		1st dose	2nd dose	3rd dose				
Influenza					*Annual Vaccination*			
Measles, mumps, rubella (MMR)							1st dose	
Varicella							1st dose	
Hepatitis A							1st dose	

[a]Adapted from Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedule for Persons Aged 0 Through 18 Years—United States, 2013. MMWR, February 1, 2013; 62(01):2–8.

While birth history and past medical history remain important, other historical information is also valuable. Determination of vaccine status will give providers a higher index of suspicion for vaccine-preventable infections if a patient is un- or undervaccinated. The history of present illness in this age range will be of greatest yield in determining the etiology of the infant's presenting complaint. Length and severity of symptoms and a general assessment of the infant's activity, oral intake, and output remain important. Knowledge of ill contacts and exposure to other young children in daycare is helpful as the majority of illnesses in this age group are viruses that are highly contagious. Physical examination findings in this age range are more reliable, including the level of alertness, general tone, and presence of true irritability and meningismus. With respect to specific examination findings, the posterior fontanelle closes during this time period, though the anterior fontanelle remains open until after one year of age, allowing for some protection from increased intracranial pressure. A general sense of whether the infant is functioning appropriately for developmental age is also important. While it is not imperative to remember the specific age range for each developmental milestone (Table 215.1), it is helpful to remember that motor and neurologic development occurs in a cranial to caudal fashion, and has several major milestones, such as when infants are capable of rolling over on their own (~4 to 5 months), then when they can sit up unassisted (~6 months), followed by crawling and cruising (pulling to stand and walking while holding on to solid objects) (~9 months), and finally walking (~12 months). Histories deviating from normal

developmental milestones are important clues in the assessment of injuries potentially attributable to NAT.

A number of chief complaints are common in this age group. More comprehensive descriptions of these disease processes, including diagnostic evaluation and management, are available in other chapters.

Fever is one of the most common ED complaints for infants 2 to 12 months of age (15). In contrast to neonates, the occurrence of occult sepsis in an otherwise well-appearing immunized infant presenting with fever is very uncommon. The overwhelming majority of well-appearing infants with fever have a viral illness. Therefore, historical information should focus on associated symptoms to help direct the diagnostic evaluation should additional testing be required. Even for unusual presentations of fever with nonspecific blanching maculopapular exanthems, physicians can often be assured that these are "viral exanthems" from common viral infections in the setting of a well-appearing infant. Usually with these presentations, no further workup or evaluation is necessary, and owing to vaccination programs, the incidence of occult infections, specifically bacteremia, has diminished to the point where laboratory testing with CBC and blood cultures is *rarely* indicated (16,17). (Refer to Chapter 222.)

Contrary to the incidence of occult blood-borne infection, the incidence of occult UTI, in the setting of specific risk factors, remains appreciable (18,19). In female infants up to 12 months of age, uncircumcised male infants up to 12 months of age, and circumcised male infants up to 6 months of age, presence of a high fever $\leq$2 days without any other symptoms is concerning for presence of a UTI and obtaining a sterile specimen of urine for urinalysis and culture is recommended (20). Diagnostic evaluation and management of UTIs in children is covered in detail in Chapter 288.

Respiratory complaints are extremely common among infants presenting to EDs especially during the winter months. Bronchiolitis is a respiratory viral illness unique to young infants. Patients with bronchiolitis have signs and symptoms of both upper and lower respiratory tract infection: rhinorrhea and congestion with tachypnea, retractions, and scattered wheezes, rhonchi, or crackles

on lung examination. Hypoxia may or may not be present, depending on the severity of the illness. The most significant issue in infants with bronchiolitis is dehydration. Insensible losses are greatly increased in infants with tachypnea, as a small amount of water vapor is exhaled with each breath. This is compounded by increased difficulty feeding, making dehydration and hypoglycemia additional issues guiding treatment. Infants by and large tolerate tachypnea well over long periods of time and do not “fatigue” in the same manner as adult patients.

Croup, or layrngotracheobronchitis, is common in older infants, and typically results from infection of the vocal cords by parainfluenza viruses. Children with croup will often have a history of an antecedent upper respiratory infection that acutely worsens (often in the nighttime) with development of a barky, seal-like cough and inspiratory stridor. Severity of illness is determined by presence of respiratory distress, increased work of breathing, and hypoxia. Croup is often contrasted with epiglottitis, a bacterial infection with high complication rate; however, it should be noted that epiglottitis is extremely rare in the post-HiB vaccination era.

Foreign body aspiration should be considered in infants who are developmentally able to grasp and place objects in their mouths, as well as infants with toddler-age siblings. A history of a choking episode and focal lung examination findings may or may not be present, so a high index of suspicion should be maintained in infants with respiratory distress and no clear infectious etiology. Diagnostic evaluation and management for bronchiolitis, croup, pneumonia, and foreign body aspiration is covered in Chapters 261, 264, and 265, respectively.

Vomiting, with and without diarrhea, is another common complaint presenting in the infant less than 1 year of age. While presentations of malrotation with midgut volvulus are still possible after 2 months of age, it is less common. Gastrointestinal complaints such as nonbilious vomiting, particularly when accompanied by nonbloody diarrhea, are highly indicative of viral gastroenteritis in infants less than 1 year of age. Prior to the addition of the rotavirus vaccine to routine infant immunization schedules in 2006, rotavirus

was a frequent cause of viral gastroenteritis. While the morbidity from viral gastroenteritis has declined significantly since 2006, other gastrointestinal viruses, such as norovirus, continue to produce significant disease (21). In cases of acute gastroenteritis, assessment of the infant's hydration status is paramount. Assessment of dehydration includes obtaining pertinent history of oral intake, urine output, and frequency and volume of the emesis and diarrhea. Special attention on physical examination should be paid to the patient's level of alertness, perfusion and skin turgor, mucous membranes, and evidence of sunken eyes or anterior fontanelle. With respect to vital signs, infants primarily compensate hemodynamically via increasing their heart rate. Therefore, tachycardia is the first sign of dehydration, and will be present well before hypotension in infants who are severely dehydrated. Fortunately, validated measures of dehydration exist, to assist clinicians in assessment and institution of interventions, such as oral rehydration therapy (22–25). Diagnostic evaluation and management of viral gastroenteritis is covered in Chapters 223, 224, and 225.

Parents frequently present their infants for care in the ED with a suspicion of pain localized to the abdomen. Abdominal pain and complaints are largely limited to benign conditions such as acute gastroenteritis and constipation; however clinical suspicion for certain pathologies should be maintained. While intermittent crying episodes, accompanied by a history of drawing his or her knees up to the chest, are often a sign of constipation, even in the setting of history of hard or infrequent stools, and a normal abdominal examination does not preclude consideration of intussusception. An abdominal emergency unique to the older infant and toddler, intussusception is the result of telescoping of one piece of bowel into another, most often the ileum into the cecum. This is followed by mucosal edema, venous congestion, and obstruction which is maniested by severe, intermittent pain. A history of acute, intermittent, severe abdominal pain, bloody stools, and vomiting which spontaneously resolves and that alternates with normal activity is classic. Depending on the time of examination relative to a painful episode, the abdominal examination can range from normal

(soft and nontender) to distended and tympanitic with a tender mass felt in the right lower quadrant (Dance sign). While the classic finding of current jelly stools is a hallmark, the presence of occult blood in the stool should raise the suspicion of intussusception in the setting of possible symptoms. Younger children with intussusception may also present with intermittent altered mental status without any of the classic symptoms described above, and the diagnosis should be considered in young children with lethargy, hypotonia, and altered consciousness. The diagnostic evaluation and management of intussusception is covered in Chapter 270. The highly variable presentation of intussusception truly highlights the challenges of the diagnostic approach to infants under a year of age, and emphasizes the importance of a careful history and examination.

CONCLUSION

It is imperative for emergency physicians to approach infants under 12 months of age more judiciously than older children, and to note the issues and specific pathologies typical of neonates less than 2 months, and infants between 2 and 12 months. Normal changes that occur with growth, such as developing immune systems, continuous exposure to new pathogens, and neurodevelopmental advancement, in addition to the limitations in accurately reporting pain and distress, pose unique challenges to caring for neonates and infants. Adding to the complexity, reassuring physical examination findings in neonates can be misleading and providers should maintain a high index of suspicion for infectious pathologies, as well as abnormalities of the cardiac, abdominal, and metabolic systems in their ED assessments. Physical examination findings (or lack of pertinent physical examination findings) can be used to more reliably assess the older infant; therefore, a history of present illness with a targeted physical examination should allow an ED provider to diagnose the vast majority of illnesses. Familiarity with the general approach to this patient population, as well as knowledge of the disease processes discussed in this textbook, will permit emergency physicians to perform a stepwise, careful, and comprehensive assessment, and

more accurately initiate important evaluation and management strategies.

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PART 2 • GENERAL PRINCIPLES OF RESUSCITATION, PROCEDURAL SEDATION, AND PAIN MANAGEMENT

CHAPTER 216 Newborn Resuscitation

Rodney B. Boychuk

Birth produces major physiologic changes in the newborn, the most important of which concern breathing. It is not surprising, therefore, that approximately 10% of all newborns require some type of resuscitation immediately following birth to establish spontaneous respirations (1–3). The majority respond to simple maneuvers such as drying, suctioning, administration of supplemental oxygen (room air is 21% oxygen), and stimulation ("SOS"). For some, however, more invasive resuscitation efforts may be required. At every delivery, there should be at least one person whose primary responsibility is the newborn and who is capable of performing a complete resuscitation, including tracheal intubation and medication administration.

PATHOPHYSIOLOGY AND PRINCIPLES OF RESUSCITATION

The goal of newborn resuscitation is to facilitate the transition from fetal (intrauterine) to newborn (extrauterine) life. These recommendations are also applicable to neonates who require resuscitation in the first weeks of life beyond delivery. Prior to delivery, the fetal lungs are fluid-filled, with high pulmonary arterial pressure and little pulmonary blood flow. Coexisting with this is fetal systemic hypotension, resulting in preferential high placental flow. Normal fetal blood flow is dependent upon intra- and extracardiac shunts (foramen ovale and ductus arteriosus) whereby blood largely bypasses the lungs and the left side of the heart, and goes to the placenta for gas exchange. After the umbilical cord is clamped

establishment of adequate spontaneous ventilation, or assisted ventilation if needed, is essential for extrauterine survival.

During the first initial respirations, displacement of fetal lung fluid as the alveoli expand and the establishment of functional residual capacity are necessary for a smooth transition. In addition, the introduction of oxygenated gas (room air) into the lung causes pulmonary vascular resistance to decrease. Clamping of the umbilical cord leads to increased systemic vascular resistance, resulting in closure of the foramen ovale and ductus arteriosus and an increase in pulmonary blood flow and the establishment of normal extrauterine circulation (4). This normally smooth transition can be interrupted in the antepartum, intrapartum, or postpartum stages. It is not possible to predict every case of asphyxiation in the newborn; however, certain prenatal factors should alert the emergency physician to the possibility (Table 216.1).

TABLE 216.1
Significant Maternal History

1. Prematurity: many require ventilatory support and possibly surfactant
2. Multiple gestations: multiple resuscitation setups; more personnel required
3. Meconium: suction at perineum/trachea (if nonvigorous) before stimulation.
4. Maternal drug (opiate) abuse: Avoid naloxone; it may precipitate seizures
5. "Maternal" bleeding: may require colloid or O-negative blood resuscitation
6. Maternal fever or prolonged rupture of the membranes

The type of resuscitation necessary depends on when resuscitation is started relative to the onset of asphyxia. Deprivation of ventilation and, therefore, oxygen leads to progressive bradycardia, decreased neuromuscular tone, and finally, primary apnea (5). Room air oxygen, and stimulation induce spontaneous respirations in most newborns at this stage, resulting in an increase in heart rate (HR) to over 100 beats/min. However, if asphyxia continues, irregular, ineffective gasping occurs, with bradycardia and flaccidity, until the newborn takes his or her last gasp and enters into the phase called secondary apnea. Once secondary apnea occurs, death is imminent unless resuscitation with assisted ventilation and oxygen is initiated.

From a practical standpoint, it is difficult to distinguish primary apnea from secondary apnea; therefore, all apneic newborns should be assumed to be in secondary apnea and treated with ventilatory assistance. Unlike adults requiring resuscitation, bradycardia is a secondary manifestation of hypoxemia, and must be treated with ventilation and oxygen.

The most important initial action is to ventilate and expand the partially collapsed, fluid-filled alveoli. This results in expansion of the lungs and clearance of alveolar fluid. Oxygen is a very potent chemical stimulator of the respiratory center in the brain and decreases pulmonary vascular resistance, resulting in increased pulmonary blood flow and improved gas exchange. Once oxygenated blood reaches the bradycardic hypoxic myocardium, HR, myocardial contractility, cardiac output, and tissue perfusion increase.

Too much oxygen, however, can cause oxygen toxicity including lung injury and retinopathy of prematurity (6). In most cases, room air is adequate for successful resuscitation (7,8); within 10 minutes of birth, oxygen saturations of 80% and greater are achieved (9), in healthy preterm and term infants without supplemental oxygen.

The 2010 American Heart Association (AHA/)American Academy of pediatrics (AAP) International Liaison Committee on Resuscitation (ILCOR) (1,3,8) has recommended the use of 100% oxygen if the HR is below 60 after 90 seconds of resuscitation. Further use of supplemental oxygen should be based on pulse oximetry monitoring. The oxygen saturation may remain in the 70% to 80% range for several minutes following birth. Current targeted SpO_2 levels for term infants based on the time after delivery are defined in Table 216.2 Most institutions have modified their previous resuscitation protocols and now utilize no supplemental oxygen for initial resuscitation and use 30% oxygen only for bradycardic newborns of less than 30 weeks' gestation (8). However, hypoxia must be avoided; if lower concentrations of oxygen are utilized during resuscitation but there is no appreciable improvement in the infant's HR or respiratory effort, additional supplemental oxygen must be added.

TABLE 216.2
Targeted Preductal SpO_2 After Birth (Right Arm)

1 min : 60–65%
2 min: 65–70%
3 min: 70–75%
4 min: 75–80%
5 min: 80–85%
10 min: 85–95%

Distention of the alveoli stimulates stretch and other pulmonary receptors, which results in stimulation of the respiratory center to increase ventilation (Hering–Breuer reflex). Thus, ventilation alone, with distention of the alveoli, has a beneficial effect.

To summarize, resuscitation of the asphyxiated newborn should primarily include ventilation for treatment of respiratory depression or gasping, with room air (or oxygen if needed to correct hypoxia).

Newborns may not respond to standard resuscitation measures for a variety of reasons. A key step is recognizing when a newborn is **not** responding to resuscitative efforts. If this occurs, the causes of resuscitation failure or deterioration must be sought and corrective action begun immediately (Table 216.3).

TABLE 216.3
Special Situations Resulting in Nonresponse to Resuscitation

Technical Problems

- Inadequate airway: positioning/ventilation
- Inadequate mask to face seal
- Inadequate pressure
  - Inadequate oxygen
  - Equipment failure
- Obstruction (mucus/meconium)
- ETT in esophagus
- ETT down too far

Unrecognized Pulmonary Problems

- Pneumothorax
- Diaphragmatic hernia
- Intrauterine pneumonia/sepsis
- Hypoplastic lungs
- Pleural effusion(s)/Hydrops Fetalis

Severe Metabolic Problems

- Hypothermia
- Hypoglycemia
- Acidosis

Other Problems

- Extreme prematurity
- Central nervous system
  - Injury
  - Narcosis
- Congenital anomalies
  - Upper airway
  - Lower airway
  - Pulmonary
- Cardiac structural/congenital heart block
- Neurologic sign
- Severe anemia, hypovolemia

Hypothermia and hypoglycemia are common occurrences in newborns requiring resuscitation and must be treated if present. Cooling results in increased oxygen consumption, increased metabolic rate and utilization of glucose and glycogen, increased lactic acid production, and increased acidosis (both respiratory and metabolic); therefore, the newborn must be kept warm (10). It is also important to prevent *hyper*thermia (11).

Practical Aspects of Resuscitation

Every emergency department (ED) delivery should be considered an emergency until proven otherwise. Once notified, the ED resuscitation team sets in motion the following: (1) preparation, (2) assessment, and (3) management. Preparation must occur well in advance of the delivery. The resuscitation of a depressed and asphyxiated newborn requires at least two people, and ideally three: a trained physician, nurse, and respiratory therapist make an ideal team to perform the two basic principles of resuscitation: (1) SOS (suction, oxygen, and stimulation) and (2) do not hesitate to ventilate, (i.e., if not breathing, start positive pressure ventilation [PPV]) (Fig. 216.1).

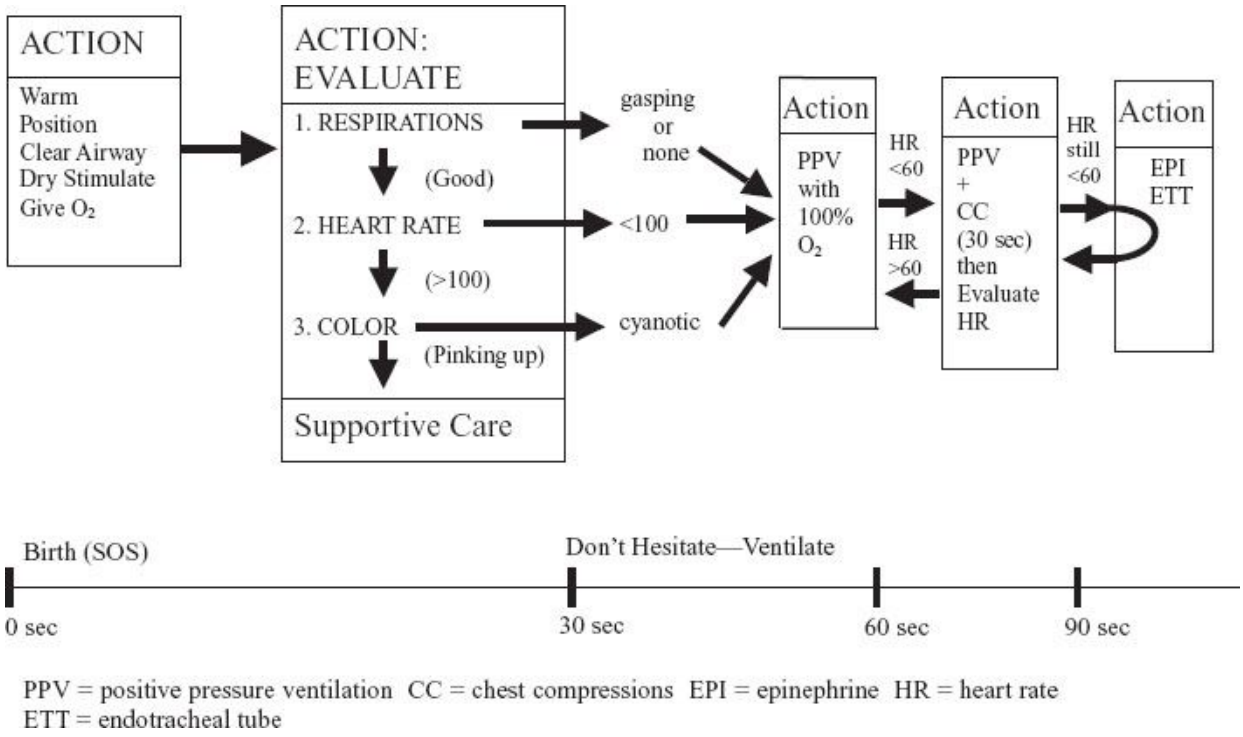

FIGURE 216.1 Neonatal Resuscitation algorithm (excluding nonvigorous meconium birth): Action versus time (seconds).

Table 216.4 outlines equipment that should be maintained and readily accessible at all times. It is advisable that all EDs be equipped with newborn resuscitation tray that includes emergency resuscitation equipment and algorithm charts specific for various

gestational ages or weights. It is essential that all ED personnel familiarize themselves with the resuscitation tray, and that daily checks be made to ensure presence and proper function of all the equipment. In addition, a radiant warmer should be kept on the unit; personnel skilled in newborn resuscitation must be immediately available (5).

TABLE 216.4
Practical Aspects of Resuscitation: Preparation of Equipment

1. Overhead radiant warmer: on and working. Warm blankets, caps.
2. Suction: on and working; catheters (sizes 8 F, 12 F, 14 F) immediately available;(1) blue bulb suction open and ready,(2) meconium aspiration device immediately available.
3. Oxygen supply: on and working. Blender ideal.
4. Laryngoscope and number 0 and 1 straight blades: batteries fresh, bulb secure, light a bright "white" intensity when turned on.
5. Endotracheal intubation tubes: sizes 2–4 mm ready.
6. Pressure-monitored anesthesia bagging apparatus: setup tested and ready. Face masks in premature and newborn sizes. Resuscitation bags: 250 mL for premature, 450 mL for term infant.
7. Nurse: ready to start the timer and monitor the infant's HR.
8. Physician: ready to evaluate, suction, laryngoscope, ventilate, intubate, and carry out further procedures.
9. Respiratory therapist: ready to administer oxygen, suction, and assist with ventilation and intubation.
10. Other equipment: meconium aspirators, umbilical catheters (3.5 F and 5 F), syringes, three-way stopcock, catheterization trays, chest tube trays, and drugs—epinephrine, volume expanders, naloxone, glucose, saline flush—immediately available or drawn up.

ASSESSMENT OF THE NEWBORN

Assessment is the physician's responsibility. If a physician is not available, the most skilled nurse or respiratory therapist must perform this role. From the instant of birth until resuscitation is complete, this individual evaluates the infant repeatedly, assessing the degree of asphyxia and the newborn's response to resuscitation. Even before the cord is clamped, evaluation of the respiratory effort and cry, HR, and color should be started. The term "integrated findings" (compound and ongoing action of all signs) is utilized, with

all signs being evaluated simultaneously as a group (2). The compromised newborn may exhibit any or all of the following: (1) depressed respiratory drive/gasping or apnea, (2) bradycardia; (3) poor muscle tone, (4), cyanosis and/or (5) low blood pressure.

The Apgar score per se plays no roll in determining the need for resuscitation. The components of the score, however, are important; HR being the single most important factor to monitor. Respiratory effort, color and muscle tone serve as guides to help guide further resuscitative efforts.

INITIAL RESUSCITATION OF THE NEWBORN

Figure 216.1 neonatal resuscitation algorithm describes actions that should be taken based on the time from birth. Broadly, the initial steps in a newborn resuscitation are: position under a warmer, clear the airway (including tracheal meconium suctioning if necessary); suction the mouth and nose (in that order); dry; remove wet linen; and reposition. During this time, simultaneously evaluate the newborn's respiratory effort and HR (2). Once placed under a radiant warmer, the newborn is positioned supine, or lying on the side with the head in a neutral or slightly extended position. This will facilitate optimal opening of the airway. Suctioning of the mouth, and then the nose, can be accomplished with a bulb syringe or mechanical suction device. Do not suction for a prolonged period, too deeply or too vigorously. In addition, do not pass the suction catheter into the stomach as vagally mediated apnea and bradycardia may occur (10). Unless meconium is present, the newborn should be thoroughly dried with warm blankets to prevent heat loss and stimulate spontaneous respirations. Wet blankets should be removed immediately. Reposition the infant as needed, and give oxygen as necessary. Stimulation is provided by rubbing the back or flicking the soles of the feet. Following this process again, simultaneously and continuously reevaluate HR and respiratory effort. Spontaneous respiratory effort is adequate if the newborn is able to maintain a HR higher than 100 beats/min and is breathing well or crying.

Newborns who remain apneic throughout the initial steps or who have gasping respirations require PPV with a bag valve mask (BVM)

device. It is important NOT to delay PPV by prolonging free flow oxygen and stimulation. If the newborn remains apneic provide PPV **(do not hesitate to ventilate).** Ventilate for about 30 seconds, then reassess. HR can be assessed by palpating the base of the umbilical cord; if a pulse is not palpable, auscultate the central left chest with a stethoscope. In the well newborn, the HR should remain greater than 100 beats/min. A HR less than 100 needs to be closely monitored and PPV initiated (or continued). If the HR remains less than 60, for greater than 30 seconds, further intervention with oxygen, chest compressions, appropriate diagnostic evaluation, and, infrequently, medications is indicated. Ideally, with a team present, the complex of signs can be evaluated simultaneously, with each individual monitoring a specific one.

A healthy newborn will eventually become and remain pink without supplemental oxygen. Acrocyanosis, or peripheral cyanosis, is not an unusual finding at birth. It is thought to occur secondary to cold stress and initially sluggish circulation; not because of hypoxemia (9). True cyanosis, or central cyanosis, is determined by examining central structures, particularly the oral mucous membranes. Newborns with persistent central cyanosis, regardless of HR and respiratory effort, require supplemental oxygen and may require BVM and endotracheal intubation, depending on the etiology of the hypoxemia.

THE DISTRESSED NEWBORN

Following the initial assessment and resuscitation, the newborn will generally follow one of two paths—either being vigorous and requiring no further intervention other than close observation; or exhibiting signs of “distress,” mandating further resuscitative efforts. One situation that precludes normal resuscitation is that of meconium in the amniotic fluid.

Meconium staining of the amniotic fluid (MSAF) generally implies fetal distress. It is found in approximately 12% of all deliveries, predominantly in small-for-gestational-age (SGA) and post-term–stressed newborns. It is clinically important to avoid meconium aspiration which can result in meconium aspiration syndrome with

the following complications (hypoxemia, acidosis, and persistent pulmonary hypertension) (1,3).

The practice of suctioning the mouth, pharynx, and nose as soon as the head is delivered (intrapartum suctioning) is no longer recommended. The 2010 AHA/AAP/ILCOR guidelines (3) for management of the newborn with MSAF are as follows: After the body delivers, the appropriate management of the airway depends not only on the presence of meconium but especially on the newborn's level of activity (i.e., vigorous vs. nonvigorous). A vigorous newborn is defined as one who has strong respiratory effort, a HR greater than 100 beats/min and good muscle tone (7). In the vigorous infant with meconium, intubation and suctioning of the trachea is no longer recommended. Simply follow the routine postdelivery management protocol. However, if MSAF is noted and the newborn is nonvigorous (i.e., with depressed or absent respirations, depressed muscle tone, and/or a HR less than 100 beats/min) direct suctioning of the trachea is indicated as soon as possible, ideally before respirations have occurred. In this scenario the oropharynx and hypopharynx are first suctioned and then the trachea is intubated under direct visualization, allowing meconium to be suctioned from the lower airway. This is accomplished by utilizing a meconium aspiration device, attached to the endotracheal tube (ETT) on one end, with a suction device attached to the other end. Suction (negative pressure) should not exceed 100 mm Hg when the suction device opening is occluded. Once occluded, the negative pressure is transmitted to the tip of the ETT, resulting in meconium being drawn up into the ETT. The entire device and ETT are then all withdrawn at the same time. Repeated intubation and suctioning can be performed until meconium is no longer recovered. After tracheal suctioning the newborn should be resuscitated like other infants. Because of the complexity of this procedure and the need for two individuals, it is recommended that ED physicians be familiar with the equipment needed, as well as the procedure (1–3).

ADVANCED RESUSCITATION

Distressed newborns may require ongoing resuscitation (Fig. 216.2). Following the initial evaluation, any newborn who has apnea, gasping or ineffective respirations, or HR less than 100 that does not respond to SOS requires ventilation. Remember, do not hesitate, ventilate. Use a BVM with 100% oxygen at 40 to 60 breaths/min. This is the recommended ventilatory rate when chest compressions are not indicated. Because the fetal alveoli are atelectatic and collapsed, the initial BVM "breaths" in a term newborn may require a higher pressure ($>$30 to 40 cm H_2O pressure) to establish adequate lung volumes, but all subsequent breaths should be delivered at the lowest possible pressure. Good chest rise should be observed; if not, reposition the infant's head and attempt ventilation again. It is important to ensure a good seal between the mask and the newborn's face, and if necessary, to use the two-person technique. An 8 F orogastric tube should be placed to prevent gastric distension if prolonged BVM is required. After 30 seconds of PPV, the HR should be reevaluated. If oxygen is not available, initiate PPV with room air, and if a mask is not immediately available mouth-to-mouth and nose ventilation, with appropriate precautions, may be utilized. Remember, however, that the tidal volume required is only about 5 mL/kg weight; air should be puffed from the mouth rather than blown from the lungs. Improvement in the HR should result. The HR is the first sign of adequate ventilation and oxygenation, and will rise immediately. Once the HR is greater than 100, observe for spontaneous, effective respirations and discontinue PPV once they occur. Further resuscitative efforts are based on the HR after 30 seconds of PPV. If the HR remains $<$100 after 30 seconds, continue PPV and note if the HR is less than 60, at which point, chest compressions should accompany PPV with 100% oxygen (11). After 30 seconds of chest compressions and ventilation, stop long enough to determine the HR (palpable umbilicus). Continue ventilation if pulse is palpable. If a pulse is not palpable, check the HR by auscultating the chest. Then continue resuscitation based on HR and ventilatory effort. Adjust oxygen concentration administration based on pulse oximetry.

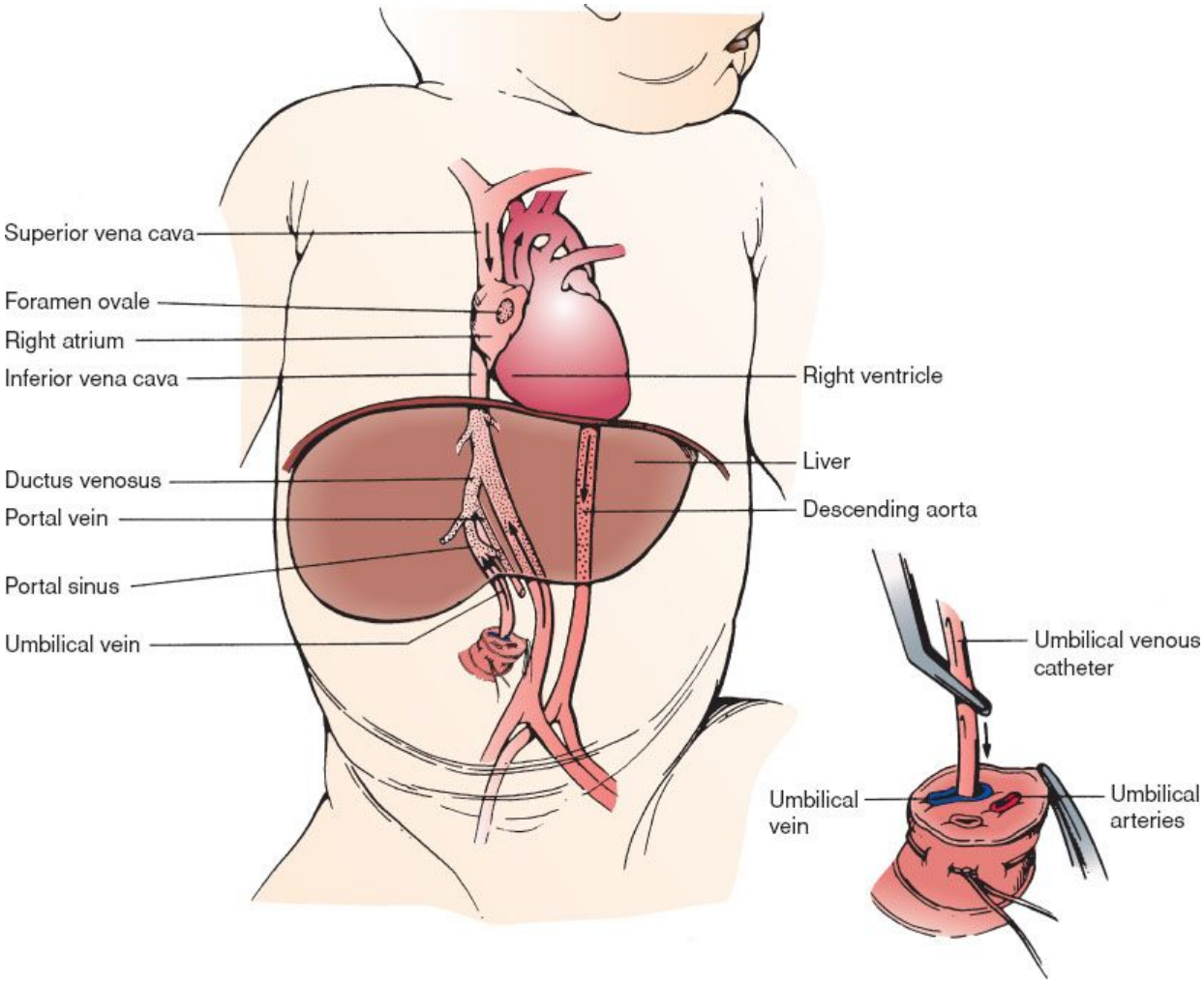

FIGURE 216.2 Insertion of the umbilical venous catheter.

Chest Compressions

Chest compressions should be initiated if: (1) absent HR at any time, (2) HR is less than 60 beats/min despite adequate assisted ventilation for 30 seconds. PPV must always be continued during chest compressions (1–3). The best technique for neonatal chest compression utilizes both thumbs placed on the lower third of the infant's sternum, with the resuscitator's hands encircle the newborn's torso with the fingers supporting the spine. Pressure is applied to the lower third of the sternum, between the nipple line (12). The sternum should be depressed one-third of the total diameter of the chest, accompanied by PPV at a rate of one ventilation for every three compressions; this delivers 90 chest compressions and 30

ventilations per minute. Chest compressions should be smooth, with the thumbs not leaving the infant's sternum between compressions and sufficiently deep to generate a palpable pulse. Care should be taken to avoid applying pressure to the xiphoid process, as this may injure abdominal organs. Compressions may be discontinued when the newborns' spontaneous HR exceeds 60 beats/min. The 2010 ILCOR working group agrees that *ventilation should be the priority in resuscitation of the newborn, and that chest compressions are likely to compete with ventilation.* Therefore, ventilations and compressions should be coordinated to optimize the resuscitation. Note that during chest compressions the ventilatory rate is 30 breaths/min, and not the 40 to 60 breaths/min used before chest compressions are started.

Endotracheal Intubation

Tracheal intubation is necessary: (1) whenever BVM is ineffective or prolonged, (2) when tracheal suctioning for meconium is required, (3) when chest compressions are performed, (4) when a congenital diaphragmatic hernia is suspected, (to avoid gastric distension) and (13) may be indicated after birth of an extremely low–birth-weight premature infant with inadequate ventilatory effort. Equipment size for intubation can be selected based on the infant's estimated weight and gestational age (Table 216.5). In general, premature newborns require a 2.5-mm ETT, whereas term newborns need a 3- to 3.5-mm ETT. A laryngoscope with a straight (Miller) blade (size 0 for premature, size 1 for term infants) is used to visualize the newborn's glottis and vocal cords. If a stylet is used, care must be taken to prevent the tip from protruding beyond the end of the ETT and injuring the airway. After intubation, proper ETT placement should be determined by careful physical examination, capnography or end tidal CO_2 monitoring (exhaled CO_2 detection) (14), and chest radiograph. Lack of chest rise, asymmetry of chest movement, and the lack of an increase in HR and/or color are signs of ineffective ventilation or a misplaced ETT.

TABLE 216.5
Equipment Size Based on Estimated Age and Weight

Age (wk)	Weight (kg)	ETT (mm)	Insertion Depth (cm)	Blade
<28	<1	2.5	7	0
28–34	1–2	3.0	8	0
35–38	2–3	3.5	9	0–1
>38	>3	3.5–4.0	10	1

The laryngeal mask airway (LMA) may be an effective alternative when used by appropriately trained providers in selected newborns (13). Masks that fit over the laryngeal inlet have been developed and found effective for ventilating full-term newborns, but have not been evaluated in small preterm newborns or those with meconium aspiration syndrome.

PHARMACOTHERAPY

Medications are rarely indicated during a newborn resuscitation and are reserved for specific situations (1,3,15). They are only utilized after unsuccessful resuscitative efforts initially focused on ventilation, oxygenation, and chest compressions. Epinephrine is the primary drug for asystole or bradycardia (HR less than 60) when there is a poor response to PPV with 100% oxygen and chest compressions for a minimum of 30 seconds. Occasionally, volume expansion is indicated, utilizing 10 mL/kg of crystalloid (normal saline, lactated Ringer). Volume is given by slow intravenous push, usually over 5 to 10 minutes. Five percent albumin has no advantage over crystalloid (15). The dose may be repeated after further clinical assessment.

Naloxone is no longer recommended when there is severe respiratory depression associated with a history of maternal narcotic administration. Naloxone can precipitate immediate severe withdrawal signs and should not be used in newborns born to mothers suspected of *chronic* opioid use. Current management is standard resuscitative measures, including ventilation.

Sodium bicarbonate (4.2%) is almost never indicated (16). If utilized, it should only be administered during a prolonged arrest unresponsive to standard measures where a severe metabolic acidosis is documented. Sodium bicarbonate may worsen respiratory acidosis and may induce hyperosmolality; it should not be a substitute for adequate ventilation.

Glucose ($D_{10}W$) should be administered in a dose of 2 to 4 mL/kg intravenously (IV) for documented or symptomatic hypoglycemia (less than 30 mg/dL in preterm, less than 40 mg/dL in term newborns).

A dopamine infusion (5 to 20 μg/kg/min IV continuous) should be considered when signs of shock continue despite volume expansion. High-dose epinephrine is not recommended in newborn resuscitations (Table 216.6).

TABLE 216.6
Medications

Medication	Concentration	Dose	Route
Epinephrine	1:10,000	0.1–0.3 mL/kg	IV recommended
Volume expanders	Normal saline Ringer lactate O-negative blood	10 mL/kg	IV
Glucose	$D_{10}W$	2–4 mL/kg	IV
Dopamine	Continuous IV infusion at 5–20 μg/kg/min		

VASCULAR ACCESS

When intravenous access cannot be established, the umbilical vein is the most accessible site. Using sterile technique, a tie is placed around the base of the umbilical stump to control bleeding, and a scalpel is used to cut the cord 0.5 to 1 cm above the skin. *The umbilical vein (always at the 12:00 o'clock position towards the head) is easily distinguished from the two smaller arteries, which are usually constricted.* Flush a sterile 3.5 F (premature) or 5 F (term) umbilical venous catheter with normal saline and attach it to a three-way stopcock. The catheter is advanced into the umbilical vein just below

the skin level until good blood return is obtained (usually of 2 to 4 cm). Wedged hepatic positions are recognized by subsequent failure of free blood return after introduction. If this occurs, the catheter should be withdrawn to a position where blood can be easily aspirated. Secure the umbilical venous catheter to the skin with tape (Fig. 216.2). When other means of vascular access are not available, the intraosseous route may be attempted; however, its use is not common in this age group (17).

FAILURES OF RESUSCITATION: SPECIAL SITUATIONS IN NEWBORN RESUSCITATION

If the newborn is not responding to resuscitative measures, other causes must be considered and sought. Generally, the etiology of the "failures" fall into one (or more) of five categories: (1) technical problems, (2) unrecognized pulmonary problems, (3) congenital anomalies of the organ systems involved, and, (4) severe anemia and (5) severe metabolic problems (Table 216.3).

"Technical Problems" are by far the most common, and of these, inadequate ventilation is the most frequent. This is either because the airway is not opened adequately, poor position of the head, poor seal of the mask to the face, or (if the patient has been intubated) malposition of the ETT. Airway repositioning may solve the problem. In intubated patients, the ETT may be in the esophagus or it may have been advanced into the right main stem bronchus. First, check the tube position by laryngoscopy or reintubating the newborn. If the tracheal tube is in correct position, chest expansion should be seen with ventilation, the HR should rise, and the oxygen saturation should increase. Another possible cause of poor air entry is pneumothorax, which may occur on either side. PPV with esophageal intubation may result in "apparent" air entry when auscultating the lungs; however, the chest will not move and air will be heard entering the stomach. Therefore, one should auscultate both lungs in the axilla and the epigastric area for confirmation of initial ETT placement and position.

Other technical problems include inadequate oxygen flow, pressure, concentration, or a "malfunctioning" ventilation system. If

there is an inadequate response, increase the oxygen concentration to 100%, with enough flow and pressure to generate chest wall movement. Excessive pressures are harmful, yet adequate pressure must be administered for ventilation to occur.

The second category of failures is unrecognized pulmonary problems. Although these must be suspected clinically, many are ultimately confirmed radiologically. Problems such as pneumothorax, diaphragmatic hernia, hypoplastic lungs, intrauterine pneumonia or sepsis, pleural effusion (hydrops fetalis), and other severe restrictive lung problems may result in an "unresuscitatible" infant.

Those born with hypovolemia or severe anemia secondary to placenta previa or abruptio placenta, are frequently unrecognized and may be unresponsive to appropriate resuscitative techniques. The most common problems include hypothermia, hypoglycemia, and severe metabolic acidosis. All will interfere with resuscitative efforts and therefore must be recognized and treated.

Infants born with congenital or acquired conditions involving the lungs, airway, heart, central nervous system, neuromuscular system, or hematopoietic system may not respond to resuscitation. Persistent central cyanosis may be secondary to cyanotic congenital heart disease, whereas persistent bradycardia may be secondary to heart block. Radiographic and other evaluations are frequently required to make the diagnosis.

POSTRESUSCITATIVE CARE AND DISPOSITION

Early consultation (including the physical presence) of a neonatologist or pediatrician is ideal to assist with resuscitation and determine the level of postresuscitative care needed. Depending on the etiology and on the degree of resuscitation required, the newborn will now require 1 of 3 levels of care: routine (standard observation), supportive (frequent evaluation), or ongoing care (continuing evaluation and monitoring in an NICU environment). If transfer is required, it is best accomplished by a tertiary care facility with a newborn transport team.

Following stabilization of the newborn, special care should be taken to maintain temperature and euglycemia, and to monitor

respiratory rate and effort, oxygen saturation, administered oxygen concentration, HR, blood pressure, and muscle tone or activity. Newborns remaining in the ED for any prolonged time should have labs sent, including CBC, arterial blood gas (ABG), glucose and calcium levels. A chest x-ray to assess ETT placement and to rule out occult pathology is recommended. If needed, the newborn can be ventilated at a rate of 40 to 60 breaths/min with end tidal CO_2 and pulse oximeter monitoring until the ABG and results are obtained. Maintenance intravenous fluids can be started with $D_{10}W$ at 80 mL/kg/d, as electrolytes are generally not required in the first 24 hours of life. Lorazepam 0.1 mg/kg (or equivalent) is effective to sedate the intubated newborn if needed. In addition, treatment of possible infection, seizures, or hypotension (with volume expanders or inotropes), and documentation of resuscitation are indicated. The parents must be informed of the newborn's condition and must be allowed to see and touch the baby, with their questions answered as frankly and honestly as possible.

DISCONTINUING RESUSCITATIVE EFFORTS

When the newborn demonstrates no signs of life (no respiratory effort, no heartbeat) after 10 minutes of effective continuous resuscitation, outcomes are dismal. The rare survivor whose heartbeat returns after this period of time will most likely have suffered severe anoxic encephalopathy and hypoxemic tissue and organ damage, with severe morbidity and high likelihood of early mortality (1–3,18).

In most cases it is advisable for the parents to be present in the resuscitation room to become actively involved with the decision to discontinue resuscitation and, if desired, to allow the newborn to die in the arms of the mother.

CRITICAL INTERVENTIONS

- Develop newborn resuscitation preparation plans or policies covering equipment, medications, contact information (NICU,

transport team, labor, and delivery, etc.), mock resuscitation drills, and staff education
- Obtain critical historical elements as soon as possible (multiple births, prematurity, meconium, vaginal bleeding, or maternal drug use)
- Continually reassess HR, respirations, and color after each intervention
- Remember the practical and the resuscitation basics, suction, oxygen, and stimulation (SOS), and do not hesitate—ventilate

Common Pitfalls

- Failure to have specific newborn resuscitation equipment set-up and readily accessible, including a radiant warmer.
- Lack of individuals with the skills required to perform a complete newborn resuscitation
- Failure to recognize the "high-risk" mother or fetus.
- Failure to initiate basic resuscitation techniques, especially ventilation.
- Failure to recognize the newborn with secondary apnea, thus delaying the initiation of PPV.
- Failure to adequately clear meconium from the hypopharynx and trachea before stimulating the nonvigorous newborn.
- Failure to consider "other causes" in a nonresponsive newborn (Table 216.3).
- Delay in initiating SOS and do not hesitate to ventilate!

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CHAPTER 217

Pediatric Resuscitation

Stephanie J. Doniger

The resuscitation of pediatric patients may be especially challenging to emergency care providers. In approaching pediatric resuscitations it is crucial to identify early decompensation and respond promptly. Successfully applied techniques of basic and advanced life support are crucial to reducing childhood mortality. The goal of resuscitation is to urgently re-establish delivery of substrate to meet the metabolic demands of vital organs, particularly the brain (1).

In contrast to adults, the majority of cardiac arrests in children result from a progression of shock and respiratory failure to circulatory arrest. The most common causes of unexpected death in children are trauma, sudden infant death syndrome (SIDS), respiratory causes, cardiovascular causes, and submersion (2). In patients older than 1 year, injury is the most common cause of death. While survival from traumatic arrest is rare, targeted intervention and prevention are emphasized in the newest American Heart Association (AHA) pediatric guidelines (3). It is estimated that in the United States there are 2.6 to 19.7 out-of-hospital pediatric cardiac arrests per 100,000 children each year. The incidence of in-hospital pediatric cardiac arrest is unknown. Reported survival rates to hospital discharge after an out-of-hospital or in-hospital arrest are approximately 6% and 27%, respectively (4). Approximately 50% to 65% of children requiring cardiopulmonary resuscitation (CPR) are less than 1 year of age, and the majority are less than 6 months old.

The year 2010 marked the 50th anniversary of CPR, and its newest guidelines were published. The majority of changes focused on the administration of quality compressions, and the education and

training of providers (5). Training and education can be greatly enhanced by the use of simulation, which has been shown to improve performance during actual resuscitations (5). The previously taught sequence of “ABC” or “airway-breathing-chest compressions (circulation)” was changed to “CAB” or “chest compressions-airway-breathing” to reflect the importance of quality compressions during CPR. This is also because the vast majority of victims requiring CPR are adults in cardiac arrest due to ventricular fibrillation, in whom compressions are crucial. It is also generally easier to start compressions immediately, while administering ventilations requires preparation and patient positioning (6). It is important to note, however, that since the majority of pediatric cardiac arrests are secondary to asphyxial, rather than cardiac causes, it may be prudent to employ the original “ABC” algorithm.

For the lay rescuer, pediatric guidelines are applied to children from 1 to 8 years of age, and adult advanced cardiac life support (ACLS) guidelines to those more than 8 years old. For the advanced provider, pediatric advanced life support (PALS) guidelines can be applied to children 1 year of age through the onset of puberty, which is typically 12 to 14 years of age. The 2010 guidelines further specify that signs of puberty in a female includes breast development, while in males includes the presence of axillary hair (6).

Despite the use of CPR and improved resuscitation techniques, mortality rates resulting from cardiac arrest are as high as 90% to 97% for infants and children. For respiratory arrest alone, the mortality rate is nearly 25%. In cases with survival, children may suffer from severe neurologic deficit.

CLINICAL PRESENTATION AND ASSESSMENT

In contrast to adults who require resuscitation, cardiovascular collapse in children is generally the result of respiratory decompensation. Children may first present with subtle abnormalities in vital signs or may exhibit frank signs of respiratory distress. It is crucial to recognize deviations from age-appropriate vital signs early, so that unanticipated cardiovascular failure can be avoided. (**Tables 217.1–217.3**).

TABLE 217.1
Expected Respiratory Rates, According to Age

Age (yr)	Breaths (per min)
<1	30–60
1–3	24–40
4–5	22–34
6–12	18–30
13–18+	12–16

Adapted from Ralston M, Hazinski M, Zaritsky A, et al. Pediatric Assessment. *PALS Provider Manual.* Dallas, TX: American Heart Association; 2006:1–32.

TABLE 217.2
Expected Heart Rates, According to Age (20)

Age	Rate beats/min (mean)
0–3 mos	80–205 (140)
3 mos–2 yr	75–190 (130)
2–10 yr	60–140 (80)
>10 yr	50–100 (75)

Adapted from Ralston M, Hazinski M, Zaritsky A, et al. Pediatric Assessment. *PALS Provider Manual.* Dallas, TX: American Heart Association; 2006:1–32.

TABLE 217.3
Expected Systolic and Diastolic Blood Pressures According to Age

Age	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)
0 d	60–76	30–45
1–4 d	67–84	35–53
1 mo	73–94	36–56
3 mos	78–103	44–65
6 mos	82–105	46–68
1 yr	67–104	20–60
2 yr	70–106	25–65
7 yr	79–115	38–78
15 yr	93–131	45–85

NOTE: Females have slightly lower systolic blood pressures and slightly higher diastolic blood pressures when compared with males of the same age.
Adapted from Ralston M, Hazinski M, Zaritsky A, et al. Pediatric Assessment. *PALS Provider Manual.* Dallas, TX: American Heart Association; 2006:1–32.

Early signs of respiratory distress in children may include nasal flaring, retractions or accessory muscle use, or irregular respirations. Signs of airway obstruction include breathing difficulty, the inability to speak or breathe, poor air exchange, a silent cough, or poor air exchange. On auscultation of the lungs, abnormal sounds include stridor, grunting, gurgling, wheezing, and crackles.

The assessment of cardiovascular function primarily includes heart rate and rhythm and blood pressure. Indicators of adequate perfusion include peripheral and central pulses, capillary refill time, and skin color and temperature. A delayed capillary refill time (>2 seconds) represents poor peripheral perfusion and may be the result of dehydration, shock, or hypothermia.

Heart rate varies according to the child's age, and the normal range is wide (Table 217.2). Typically, the rate is slower in a sleeping or athletic child. Bradycardia, which is a heart rate less than that expected for a child's age, may be attributed to vagal stimulation, hypoxemia, acidosis, or an acute elevation of intracranial pressure. Other serious etiologies can include first-, second-, and third-degree heart block. Complete heart block, acquired or congenital, is a common cause of significant bradycardia in pediatric patients. However, the most common cause of bradycardia in the pediatric population is hypoxemia.

Tachycardia is defined as a heart rate greater than that expected for a child's age. The vast majority of pediatric tachycardias are supraventricular in origin. Tachycardias of ventricular origin are typically associated with significant hemodynamic compromise.

Normal blood pressures also vary according to age (Table 217.3). Hypotension is defined as below the fifth percentile of expected blood pressures for age. Hypotension may be due to hemorrhage, sepsis, or cardiac failure.

EMERGENCY DEPARTMENT EVALUATION AND MANAGEMENT

The newer 2010 AHA guidelines recommend initiating chest compressions early, as the first step of the resuscitation sequence, except when arrest is caused by asphyxia.

It is important to approach the evaluation and management in a stepwise manner. It has been traditionally taught that the airway is assessed first, then breathing, and finally circulation (ABC). If there is an abnormality at any step of this ABC assessment, intervention must be initiated at that point. The newer 2010 AHA guidelines recommend initiating chest compressions early, as the first step of the resuscitation sequence, except when arrest, is caused by asphyxia. In single bystander rescuer resuscitation, or basic life support (BLS), compressions alone may be sufficient in nonasphyxial arrests. While the traditional teaching for PALS is a stepwise approach, for in-hospital cardiac arrests, there is usually a team present, where each member can perform components of the resuscitation concurrently.

Early initiation of high-quality CPR and early defibrillation appear to improve overall survival from arrest. Only one-third of out-of-hospital cardiac arrest victims receive CPR prior to the arrival of emergency medical service (EMS) (4), and those who do receive it often do not receive effective CPR. Suboptimal CPR is often characterized by chest compressions that are too few, too shallow, and too weak. In addition, patients are often overventilated and there are too many interruptions in chest compressions (7).

CIRCULATION

Either the intravenous (IV) or intraosseous (IO) route is used for vascular access and for the administration of drugs. Peripheral IV placement may be difficult in a critically ill child. An IO line, especially with the advent of rapid guns for their insertion, is preferred to the placement of a central line. Central line placement requires time and expertise. However, the safety and success of central line placement can be improved with the use of ultrasound guidance. When other routes of vascular access are unavailable, lipophilic drug delivery may be performed via the ETT. These drugs include "LEAN": lidocaine, epinephrine, atropine, and naloxone (Narcan) (8). The drugs need to be administered at higher doses, generally two to three times their IV dosing. Epinephrine is recommended to be 10 times the IV dosing, and atropine 0.04 to 0.06 mg/kg. This route, however, is unpredictable and is *not* recommended.

Rhythm abnormalities must be recognized and treated appropriately. The heart rhythm can initially be assessed as either regular or irregular, or too fast or too slow. It is crucial to determine whether a pulse is present with the associated rhythm. Unfortunately, it has been shown that pulse checks are often difficult and unreliable. Bedside ultrasound is helpful in determining the presence of cardiac activity.

For patients with bradycardia, defined as a heart rate <60 beats per minute, providers must support oxygenation and ventilation and perform CPR. One must search for and correct underlying causative abnormalities and promptly initiate pharmacologic therapy as necessary.

For tachycardia, stepwise questioning can help the evaluation. Is the rhythm regular or irregular? Is the QRS narrow or wide? Does every P result in a single QRS? The important tachydysrhythmias to recognize are ventricular fibrillation, ventricular tachycardia, pulseless electrical activity (PEA), asystole, and supraventricular tachycardia. For PEA, it is important to identify and treat possible causes. Bedside ultrasound may readily identify some reversible causes of PEA and arrest, such as cardiac tamponade.

Compressions

Effective chest compressions are crucial in improving survival. Compressions provide blood flow to vital organs such as the heart and brain and allow for the return of spontaneous circulation. The AHA recommends to "push hard and push fast." Interruptions in compressions should be limited to <10 seconds for interventions such as placing an advanced airway or defibrillation. *Interruptions in compressions have been shown to decrease the rate of return of spontaneous circulation.* Rhythm checks should be performed every 2 minutes, or every five cycles of CPR. Once an advanced airway is in place, compressions and ventilations should be performed continuously without interruption.

Previous studies show that 92% of chest compressions delivered during in-hospital resuscitation were less than the recommended depth (9). A recent study further showed that 20% of the time, compressions are administered at double the recommended rates in in-hospital pediatric arrests (10). In order to perform adequate compressions for children, the heel of one or two hands can be used to compress the lower half of the sternum to a depth of at least one-third of the anteroposterior diameter of the chest, or approximately 2 inches (5 cm) in children and 1.5 inches (4 cm) in infants. This depth provides an associated systolic blood pressure >80 mm Hg and diastolic blood pressures >30 mm Hg during CPR in children (11). For infants, the AHA recommends that two thumbs press on the sternum, with the hands encircling the chest. This technique improves coronary artery perfusion pressure and may generate higher systolic and diastolic blood pressures. There is insufficient evidence to suggest an additional circumferential squeeze of the thorax (3). In order to prevent rescuer fatigue, rescuers should be changed after five cycles of CPR, or every 2 minutes. To minimize interruptions in CPR this switch should be performed in less than 5 seconds.

In patients without a pulse, and in children with a heart rate <60 beats per minute, chest compressions should be initiated. Because bradycardia is often a terminal rhythm in children, one should not

wait for pulseless arrest to occur before initiating compressions. For children of all ages, except newborns, compressions should be performed at a rate of 100 per minute. The compression to ventilation ratio is 30:2 for single rescuers, and the ratio is 15:2 for two-rescuer resuscitation (6). These universal rates simplify guidelines for providers, and they allow for sufficient time for adequate chest recoil to permit cardiac filling and venous return (12).

Defibrillation

With witnessed arrest due to ventricular fibrillation, immediate defibrillation is warranted. This action is followed by CPR and drug administration. CPR provides some blood flow, delivering oxygen and substrate to the heart, making reversal of ventricular fibrillation more probable. A single shock should be administered at a dose of 2 J/kg, followed by immediate CPR. Ventricular fibrillation is terminated by the first shock in at least 90% of cases (13). For children less than 1 year of age or less than 10 kg pediatric-specific paddles or pads *must* be used. It is important to use the self-adhesive pad or electrode gel. Do not use saline-soaked pads, ultrasound gel, bare paddles, or alcohol pads. While manual defibrillation is preferred, if unavailable, an automated external defibrillator (AED) with a dose attenuator may be used. If neither are available, an AED may be used and does not lead to myocardial damage (1).

CPR is beneficial immediately post defibrillation. CPR appears to "prime" the heart for the next defibrillation attempt. In cases of prolonged ventricular fibrillation, it has been shown that giving CPR prior to defibrillation increases survival rates from 4% to 22% (14). Defibrillation is performed with energy of 2 J/kg, followed by 4 J/kg for subsequent dosages, regardless of the type of defibrillator. "Stacked" shocks are no longer recommended because of the time required to administer three shocks in a row, during which CPR is not being provided. A single shock, followed by CPR, is recommended. CPR should not be interrupted for a pulse or rhythm check until five cycles or 2 minutes.

The treatment of each rhythm disturbance should proceed according to the tachycardia algorithm (Fig. 217.1); with the presence or absence of a pulse, determining which arm of the algorithm is followed. Sinus tachycardia with adequate perfusion is no longer included in the algorithm. Polymorphic ventricular tachycardia is now considered an unstable rhythm that requires the use of unsynchronized, rather than synchronized, shocks. Low-energy synchronized shocks are felt to risk provoking ventricular fibrillation (1).

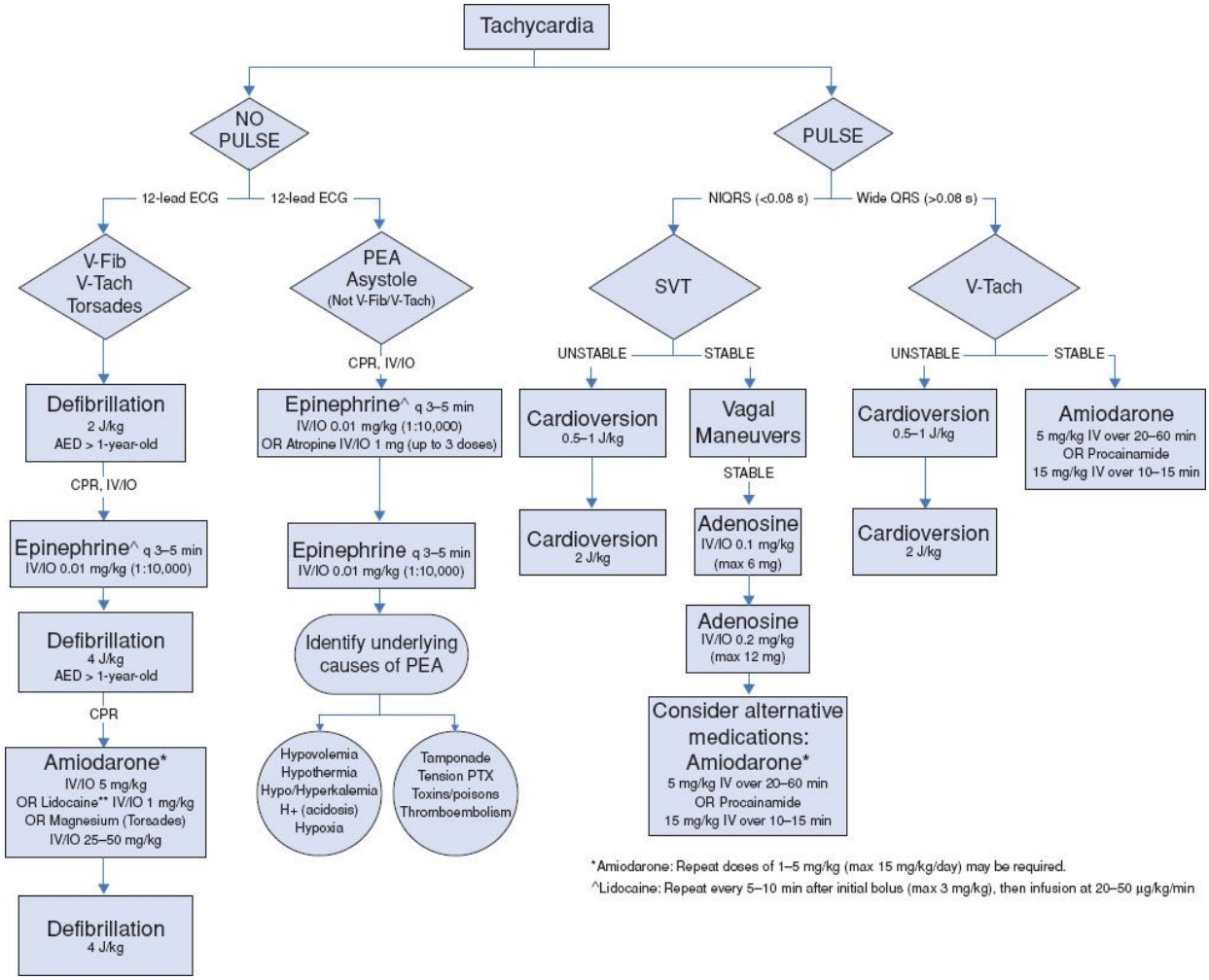

FIGURE 217.1 Tachycardia algorithm. (Adapted from Ralston M, Hazinski M, Zaritsky A, et al. Pediatric Assessment. *PALS Provider Manual*. Dallas, TX: American Heart Association; 2006:1–32.)

Community use of AEDs has been shown to increase survival rates, and there is evidence that they can safely be used in patients greater than 1 year of age (15). The AED should be used as soon as possible after a sudden witnessed collapse. If the collapse is unwitnessed, CPR should be performed for five cycles, or 2 minutes, prior to the use of the AED. Energy levels should be adjusted for age. If the pediatric dose is unavailable, the adult dose is a reasonable alternative.

Pharmacologic Therapy

For the most part, the algorithm drug dosages remain the same in the updated 2010 AHA guidelines. Dosing for medications has been controversial; the current recommendations suggest utilizing the patient's actual weight, rather than the ideal body weight. Tape-based methods (such as Broselow) have been validated and shown to be more accurate than estimation by providers. Drug delivery should not interrupt CPR. The timing of drug delivery is less important than minimizing chest compressions.

For pharmacologic treatment of bradycardia, epinephrine (IV/IO 0.01 mg/kg, ETT 0.1 mg/kg) should initially be administered and can be repeated every 3 to 5 minutes. In situations of a primary atrioventricular (AV) block or increased vagal tone, atropine is recommended (initial dose 0.02 mg/kg, minimum dose 0.1 mg, maximum dose 1 mg) and may be repeated (16). Epinephrine and isoproterenol infusions are no longer recommended to treat refractory bradycardias.

In cases of asystole or PEA, one should initiate immediate CPR. CPR is followed by epinephrine (0.01 mg/kg IV/IO). Alternatively, atropine may be administered (1 mg IV/IO, 0.04 to 0.06 mg/kg ETT). For PEA in particular, it is important to identify and treat underlying causes.

High-dose epinephrine (1:1,000 concentration via IV) is not recommended in any age group and is associated with a worse outcome, especially in cases of asphyxia (17). Therefore, the standard recommended dose is 0.01 mg/kg IV/IO, which correlates to 0.1 cc/kg. Though the preferred routes of administration are IV or IO, it may be given via the ETT at 10 times the IV dose, when other

access is unable to be obtained (0.1 mg/kg ETT) (18). In exceptional cases, such as β-blocker overdoses, high-dose epinephrine may be considered.

Amiodarone is the preferred drug for the treatment for pulseless arrest. Lidocaine is recommended only when amiodarone is unavailable and is no longer listed on the AHA stable ventricular tachycardia algorithm (16), having been replaced by amiodarone and procainamide. Amiodarone and procainamide should not be administered together, as they can lead to severe hypotension and prolongation of the QT interval.

The routine use of calcium and sodium bicarbonate is not recommended. Sodium bicarbonate in particular may impair tissue oxygen delivery, induce electrolyte abnormalities, and decrease the VF threshold. However, both calcium and sodium bicarbonate may be indicated in special situations such as toxidromes (1). Sodium bicarbonate may be indicated for tricyclic antidepressant or sodium channel blocker overdoses, while calcium may be indicated for a calcium channel blocker overdose. Calcium gluconate may be preferable than calcium chloride since it causes a greater increase in ionized calcium.

Airway

The first priority in basic and advanced life support for children is evaluation of the airway. In order to assess upper airway patency, the provider should look for chest rise, listen for breath sounds and air movement, and feel the movement of air at the nose and mouth. It is crucial to determine whether the airway can be maintained by simple maneuvers; if not, advanced interventions are necessary.

If the airway is not patent, simple measures to restore patency should be tried first: changing the patient's position, suctioning, and attempting to relieve foreign body obstruction. For the latter, the recommendation is to perform five back blows and five chest thrusts in infants and to perform the Heimlich maneuver in older children. If a patient is unresponsive, it is recommended to activate EMS and to begin performing CPR. For the lay rescuer, the preferred method of opening the airway is the head tilt–chin lift maneuver. It is

unadvisable to perform blind finger sweeps, and it is not recommended to perform the "jaw thrust" maneuver, because this technique is difficult to learn and perform and is often ineffective, especially for inexperienced providers. In trauma situations, especially when a cervical spine injury is suspected, jaw thrust maneuver without head tilt is the maneuver of choice to open the airway (16).

Patients who do not exhibit adequate breathing should receive rescue breaths. It is recommended to try to deliver two effective rescue breaths. In patients who are not breathing but have a pulse, respirations should be delivered without compressions. The provider should administer 12 to 20 breaths/min (1 breath every 3 to 5 seconds) for infants and children (6). Breaths should be given over 1 second in order to avoid hyperventilation and gastric inflation.

The method of maintaining the airway depends on the provider's skill level. For those untrained in advanced airway skills, the focus must be on effective bag valve mask (BVM) technique. A two-person BVM technique can be utilized in situations of airway obstruction, poor lung compliance, or when the rescuer has difficulty in creating an adequate seal. Airway adjuncts such as oropharyngeal and nasopharyngeal airways may assist in opening the airway and facilitating the delivery of oxygen by bag valve mask.

For those skilled in its use, endotracheal intubation is the preferred way of securing an airway with rapid sequence intubation (RSI) (see Chapter 218). It is now recommended that a cuffed endotracheal tube (ETT) may be used in all ages except neonates. The cuffed tube is especially useful for those patients with poor lung compliance, increased airway resistance, or a large glottic air leak. Attention must be paid to tube size, position, and pressures. For children less than 1 year of age, a 3-mm cuffed ETT may be used. For children 1 to 10 years of age, the endotracheal size can be calculated by the following formula (19).

The size of an uncuffed ETT is determined by:

$$\text{Size (mm internal diameter [ID])} = (\text{age in years}/4) + 4$$

For a cuffed ET, subtract 0.5 from the size to obtain the appropriate-sized tube. The appropriate depth of placement of the ETT is roughly estimated as three times the ID of the ETT. ETT cuff pressure should be maintained at <20 cm H_2O (20).

ETT placement should be confirmed by the auscultation of breath sounds. It is recommended to measure exhaled CO_2 by a colorimetric detector or by capnography. However, these devices are effective only in patients with a perfusing rhythm. In patients weighing more than 20 kg, one may consider use of an esophageal detector device to confirm tube placement (21). It is important to repeatedly verify ETT position immediately after the tube is inserted, during transport, and after movement of the patient as ETTs may become dislodged. When endotracheal intubation is not possible, a reasonable alternative is the placement of a laryngeal mask airway (LMA). However, the placement of LMAs are associated with a higher incidence of complications in children (22).

During the process of providing breaths and intubating a patient, gastric inflation is common with subsequent vomiting. In order to decrease gastric inflation, it is recommended to avoid excessive peak inspiratory pressures, but ventilating slowly and only giving enough tidal volume to create visible chest rise. Cricoid pressure may be utilized, but care must be taken to avoid excessive cricoid pressure, which may cause tracheal obstruction. Finally, a nasogastric or orogastric tube may be utilized to decompress the stomach. In situations where a child has a gastrostomy tube in place, it may be vented to relieve gastric inflation (16).

Breathing

The assessment of breathing includes an evaluation of the respiratory rate and effort, lung sounds, and pulse oximetry. Further factors to assess are adequacy and equality of chest wall excursion and the amount of air movement.

Once an advanced airway is in place, respirations should be administered simultaneously with chest compressions, at a rate of 8 to 10 per minute. Note this rate is markedly lower than previous

recommendations. Hyperventilation is not recommended and can be harmful (23). Increased respiratory rates tend to produce cause increased intrathoracic pressure, which reduces venous return and coronary perfusion pressure. Rescue breaths that are administered at a high rate create increased intrathoracic pressure, which reduces venous return and coronary perfusion pressure. Fewer breaths and smaller volumes are needed for oxygenation and ventilation because there is significantly less blood flow to the lungs during CPR (16). The most recent AHA guidelines discuss the possible adverse effects of hyperoxia; they recommend performing resuscitation with 100% FiO_2, but once the patient is stabilized the FiO_2 may be reduced to maintain oxygen saturations of at least 94% (6).

Positive-pressure ventilation can be provided by the use of a self-inflating bag, a flow-initiating bag, or a T-piece device. The T-piece is a valved device that regulates pressure and limits flow. The best indicator of successful ventilation is an increase in the heart rate. Supplemental oxygen is recommended for patients receiving positive-pressure ventilation and who are breathing spontaneously but are cyanotic.

KEY TESTING

- Laboratory testing is usually not immediately available to impact immediate, life-saving, resuscitative efforts
- When available, point-of-care electrolyte, glucose, and blood gas testing may be helpful
- In PEA arrest, bedside ultrasound may be helpful in determining cardiac activity, cardiac tamponade, or unsuspected pneumothorax
- Postintubation portable radiographs are important to confirm ETT and central line placement
- For sepsis, CBC, blood cultures, and serum lactate may help in guiding therapy
- For traumatic arrests, CBC and type-and-screen may be indicated

CRITICAL INTERVENTIONS

- Effective CPR is crucial with limited interruptions.
- "Push hard, push fast" at 100 compressions/min.
- Universal compression: ventilation 30:2 (lone rescuer), 15:2 (two rescuers).
- Use cuffed or uncuffed ETT with attention to size, position, and pressures.
- Once advanced airway is in place, provide simultaneous ventilations and compressions with ventilation rate of 8 to 10 breaths/min.
- IV/IO is preferable to ETT for drug administration.
- Defibrillation: a single shock is followed by immediate resumption of CPR.
- Amiodarone is preferred for pulseless arrest due to ventricular fibrillation or ventricular tachycardia.

SPECIAL SITUATIONS

The newest AHA recommendations discuss special situations, including shock, trauma, known congenital heart disease, and special pediatric health care needs.

It is common for children to present in shock. However, it is often not recognized early enough. In septic shock, it is important to identify and intervene early, and consider providing early ventilatory assistance. In situations where a child in septic shock is intubated, one may consider the use of etomidate as an induction agent, since it causes minimal hemodynamic effects. However, etomidate has been shown to cause adrenal suppression and may lead to a higher mortality rate in septic shock, so alternative induction agents should be considered (1).

In traumatic arrests, common errors include the failure to open and maintain the airway, failure to provide appropriate fluid resuscitation, and the failure to recognize and treat internal bleeding. It is also important to maintain C-spine immobilization. It is ideal to open the airway with a jaw thrust, but when that is not possible, a head tilt–chin lift may be performed. For patients with maxillofacial trauma or a basilar skull fracture, an orogastric, instead of a nasogastric, tube should be utilized. Contrary to prior teaching, it is

not routinely recommended to hyperventilate, even with head injury. For trauma patients presenting in shock, one should consider and look for intra-abdominal hemorrhage, a tension pneumothorax, tamponade, or spinal cord injury as possible etiologies. A high suspicion for thoracic injury should be maintained with all patients with thoracoabdominal trauma. In those patients presenting with penetrating chest trauma, a thoracotomy should be considered (16). In addition, pressure should be applied to all external signs of hemorrhage and spinal motion should be prevented by securing the thighs, pelvis, and shoulders to an immobilization board. Whenever possible, children should be transported to a pediatric trauma center as rapidly as possible (3).

The newest 2010 AHA guidelines discuss the management for children with single ventricle physiology and pulmonary hypertension. For those children with a systemic to pulmonary artery shunt, or a right ventricle to pulmonary artery shunt, heparin should be considered, since a clotted-off shunt may be the cause of acute decompensation. It is important to maintain a careful balance between systemic and pulmonary blood flow, and to therefore maintain saturations greater than 80%, rather than the 94% target for children without congenital heart disease. It is important to note that $ETCO_2$ may not be reliable since pulmonary blood flow changes rapidly in this patient population. For those patients with a Fontan or hemi-Fontan/bidirectional Glenn, hypoventilation may improve oxygen delivery in those patients in a prearrest state. Finally, for those patients with pulmonary hypertension, standard PALS resuscitation guidelines should be initiated. One may attempt to correct the hypercarbia, and to administer IV fluids to correct preload. Inhaled nitric oxide or aerosolized prostacyclin may be considered in order to reduce pulmonary vascular resistance. When these inhaled agents are unavailable, IV prostacyclin may be considered as an alternative agent (16). In those situations where cardiac arrest is refractory to standard attempts, extracorporeal membrane oxygenation (ECMO) should be considered.

Children with special health care needs present frequently to the emergency department. Those patients requiring resuscitation can

present a particular challenge to providers. Patients with gastrostomy tubes should have the tube vented to prevent gastric inflation during ventilation assistance. In those patients with a tracheostomy or stoma present in respiratory distress, one may consider replacing the tracheostomy tube. When this is unsuccessful, ventilation may be performed directly through the stoma, or the stoma may be occluded while administering BVM breaths from above (16).

DISPOSITION

Postresuscitation goals are to stabilize and preserve neurologic function, and to prevent secondary organ injury. It is important to properly monitor patients (pulse oximetry, $ETCO_2$), assist ventilation, and confirm proper ETT placement, especially when the patient has been moved or transported. In order to reduce oxidative injury, saturations should be maintained greater than 94%, rather than 100%. Once alternative IV access is obtained, an IO line should be removed in order to prevent complications.

New recommendations recognize the probable benefits of vasoactive medications, including ionodilators such as inamrinone and milrinone, to treat postresuscitation myocardial depression. Further, dopamine may be useful for shock that is unresponsive to fluid, and norepinephrine for shock with low peripheral vascular resistance (septic, anaphylactic, spinal cord shock). Other agents include sodium nitroprusside, which increases cardiac output by decreasing the afterload, and dobutamine, which increases contractility and decreases peripheral vascular resistance (16). Norepinephrine and epinephrine are also commonly used inotropes.

Although current evidence is insufficient to recommend the routine use of systemic or selective cerebral hypothermia after resuscitation of children, it is important to avoid hyperthermia, especially in very low–weight infants. However, there are potential benefits of induced hypothermia (32 to 34˚C) for 12 to 24 hours following successful resuscitation, and critical care consultation should be obtained promptly (24).

Evidence suggests that the duration of resuscitation is not an adequate prognostic indicator of survival. Intact survival has been

reported even in cases with prolonged resuscitation and administration of epinephrine doses (25). Unfortunately, there are no reliable predictors of outcome to guide to the terminate resuscitation efforts. One should consider the mechanism of arrest, the duration of resuscitation, and the medications and doses that have been administered.

Common Pitfalls

- Failure to recognize age-appropriate vital signs
- Failure to maintain cervical spine precautions and recognize intra-abdominal or intrathoracic hemorrhage in cases of trauma
- Inadequate CPR with too few, too shallow, or too weak chest compressions, or frequent interruptions in CPR
- Inaccurate medication dosing and failure to use Broselow tape
- Failure to recognize sepsis early and provide early ventilation and support

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CHAPTER 218

Pediatric Airway Management and Rapid-Sequence Intubation

Michele M. Nypaver

The ability to manage infants and children with respiratory distress is a fundamental skill required for emergency medicine (EM) and pediatric emergency medicine (PEM) practice. The conceptual framework of airway evaluation, action, and intervention summarized in previous chapters can be applied to children as well as adults. Hospital-based providers must be adept in the use of both temporary, noninvasive (NIV) airway adjuncts as well as intubation in the context of an infant or child with limited ability to communicate or cooperate. Variations in anatomy, size, morphology, and physiology encountered in young children add incremental complexity to the medical decision-making surrounding pediatric airway management. Despite the frequency of children visiting the emergency department (ED) with respiratory complaints, the need for intubation, even in high-volume pediatric emergency centers, is rare (1). However, infrequent exposure to children with severe respiratory illness represents a challenge for trainees who need this experience to establish initial proficiency and for emergency clinicians who must maintain competency in pediatric critical airway skills (2–4). Successful airway management in children demands a comprehensive approach to system readiness including planning, equipment availability, training, and regular practice to ensure optimal patient outcomes. High-fidelity simulation may play a role in

bridging the gap between the high stakes and low frequency of pediatric acute airway interventions. This chapter stresses the unique differences in the approach to airway management in children as compared to adults (see Chapter 1).

APPLIED ANATOMIC DIFFERENCES AND BASIC AIRWAY SUPPORT

Clinical presentations of respiratory distress in infants and young children are influenced by developmental stage. A rapid assessment of children using a brief visual approach based on a child's level of consciousness, breathing effort, and color is helpful to determine level of distress and initiate interventions (5). Careful interpretation of a child's response to people, surroundings, and examination is useful to guide the timing and level of intervention. Often, children in some distress but maintaining their own airway may be best served by *avoiding* interventions that increase anxiety and agitation which may precipitate decompensation, as in the case of suspected epiglottitis. The mnemonic "TICLS" is a quick bedside tool that has been validated for pediatric clinical assessment (6):

- Tone
- Interactiveness/Consolability
- Look/Gaze
- Speech/Cry

Clinicians should immediately intervene when infants or young children cannot be consoled or do not react appropriately to examination. Babies and toddlers typically cry or are fearful of strangers. Limpness, listlessness, or somnolence in a child should always prompt airway support and ongoing reevaluation of clinical status. Accurate measurement and monitoring of vital signs, including pulse oximetry, is required in every child in respiratory distress. Variation from normal values of vital signs by age should be recognized. Pediatric vital sign reference ranges should be immediately available to staff, particularly in settings where pediatric visits are infrequent.

Pediatric airway management requires recognition of differences in the anatomy and physiology of infants and children compared to

adults (**Tables 218.1** and **218.2**). The differences are most prominent during infancy and progressively become adult-like by approximately 8 years of age. With this in mind, clinicians can develop a systematic approach and anticipate the common challenges that arise during pediatric airway management. Infants and young children are prone to airway obstruction when the soft tissue mass of the tongue and tonsils fall posteriorly with supine positioning or relaxation induced by sedation or paralytic medications. Basic NIV airway support measures to relieve airway obstruction are easily applied, effective and are the foundation of pediatric airway management (8,9). Nontraumatized children demonstrating signs or symptoms of upper airway obstruction by anatomic structures (i.e., tongue and tonsils) who are awake may be less anxious when in a seated upright position. For those children who must remain supine, chin lift and jaw thrust can be used to relieve obstruction with or without a nasopharyngeal airway. Caution must be exercised during chin lift if an opposite hand is used to stabilize the forehead, in order to avoid neck hyperextension which may make obstruction worse. Positioning of young children is an underappreciated but basic and effective method to enhance airway patency. Raising the shoulders relative to the head using a towel or a cushion facilitates airway alignment, improves airflow during bag mask ventilation (BMV), and aligns the visual axes of the operator to the vocal cords (VC) during laryngoscopy. Various equipment sizes of suction tips, masks, and endotracheal tubes (ETTs) (in both larger and smaller sizes than anticipated) should be at the bedside to allow for rapid equipment choices when necessary. Other variations in airway anatomy encountered in children are those associated with congenital anomalies involving the head, face, and neck (Table 218.3). Presence of these conditions should immediately alert clinicians to the potential for a difficult airway.

TABLE 218.1
Anatomic Features of the Pediatric Airway, Clinical Impact, and Countermeasures

Feature	Clinical Impact	Countermeasure(s)
Larger soft tissue mass of tongue/tonsils in infants and young children	Airway obstruction when supine Difficult visualization of larynx/vocal cords (VCs) during laryngoscopy	No trauma: Chin lift, jaw thrust Trauma: Jaw thrust with in-line immobilization of C spine Use of straight laryngoscope blade (Miller) inserted to right side of mouth, sweeping tongue/soft tissue block to left Video laryngoscopy BVM with oropharyngeal (unconscious patient) or nasopharyngeal airway (conscious patient)
Large floppy epiglottis	Floppy epiglottis may partially block view to VCs	Use of straight laryngoscope blade places epiglottis "behind" the blade When using curved or straight blade, correct motion to lift tongue/soft tissues with operator thumb toward feet of patient
Higher positioning of larynx C1–4: Infants-children <7 yrs C4–5: Children >7 yrs to adult	Acute angulation causes difficulty in visualization of VCs during laryngoscopy may result in missed attempt or failure to intubate	Infants: Towel roll under shoulders Young children: Towel under head (sniffing position) Gentle cricoid pressure may be attempted but stopped if visualization is made more difficult "Hockey stick" bend of ETT to direct toward glottic opening Video laryngoscopy if available BVM
Conical shape of larynx compared to adult cylinder: Maximal narrowing subglottic below level of VCs	May be difficult to pass endotracheal tube (ETT) beyond VC Cricoid ring narrowed opening is larger in ant/postdiameter than lateral (elliptical)	ETT ready and available in sizes smaller than anticipated Uncuffed or cuffed tubes acceptable in children. If cuffed tube used, cuff pressure must be confirmed (American Heart Association 2010) Cuffed tubes *not* recommended for neonates (Neonatal Resuscitation Program 2010)
Small cricothyroid membrane size/diameter Infants: Mean 2.6 × 3 mm Adults: Mean 14 × 12 mm	Infants: Too small to accurately identify landmarks and carries laryngeal injury	For children in Can't intubate situations: Attempt BVM ventilation with/without oral airway or supraglottic device Surgical consultation

TABLE 218.2
Physiological Factors and Clinical Impact in Children Compared to Adults

Factor	Clinical Impact
Compliant chest wall	Inability to generate large negative intrathoracic pressure to inflate non compliant lung causes increased work of breathing
Immature musculature of intercostal muscles and diaphragm (less type I muscle fibers)	Limits ability of chest to fully expand Early chest wall fatigue Infants are dependent on functional diaphragms to ventilate
Smaller and narrowed airway causes increased airway resistance	Small changes in diameter of airway due to inflammation or edema cause large increases in airway resistance
Increased oxygen consumption	Infant oxygen consumption is up to twice (6 L/min) that of adults contributes to early/rapid hypoxia
Decreased functional residual capacity (FRC)	Compliant chest wall, small thorax, and large abdomen combine to reduce FRC in infants/young children. This is maximized during supine positioning Reduced FRC = diminished respiratory reserve = decreased time to desaturation during laryngoscopy

TABLE 218.3
Congenital Syndromes and Airway Anomalies

Name	Features
Pierre Robin sequence	Micrognathia (small mandible), glossoptosis, cleft palate
Goldenhar syndrome	Micrognathia (asymmetric), soft palate incomplete development
Treacher Collins syndrome	Micrognathia, small mouth, funnel shaped larynx
Apert syndrome	Midface anomalies, high arched palate, cervical fusion
Hunter/Hurler syndromes	Enlarged tongue due to mucopolysaccharides infiltration
Beckwith–Wiedemann syndrome	Macroglossia
Freeman–Sheldon syndrome	Fibrosis around mouth and microstomia

Emergency physicians must employ a proactive strategy to optimize oxygenation and ventilation early in all ill-appearing children to limit potential decompensation. Children become hypoxic

more quickly than adults because of greater oxygen consumption and a smaller functional residual capacity (FRC). Recognizing respiratory distress across a broad age range and disease spectrum in children is the first step in matching airway interventions to a specific patient at a specific point in their illness. Rapid changes in both respiratory and cardiovascular parameters in ill-appearing children should be anticipated. All children in respiratory distress should receive 100% FIO_2 titrated to pulse oximetry $>95\%$ delivered via the most effective means for a given clinical situation. Nasal cannulas may be used for children requiring minimal support; however any spontaneously breathing child in moderate to severe distress deserves 100% FIO_2 delivered via nonrebreather face mask. A child's clinical course and likelihood for deterioration may also be predicted in the context of age and disease. Young infants with bronchiolitis may present with subtle or mild respiratory symptoms followed suddenly by apnea. Asthmatic children may fatigue more quickly than older patients. Children with chronic lung, cardiac, and neuromuscular diseases may not follow a typical course in the setting of a superimposed respiratory illness given a more limited respiratory reserve. Convention dictates early airway support in children with respiratory distress in the setting of septic shock on the presumption of reducing overall metabolic demand; however there are very limited (and no pediatric) data analyzing the outcome of septic patients as a result of intubation or ventilation (8). While feeding children is an important comfort measure offered by caregivers of an ill child, caution should be exercised in offering food or drink to a child in respiratory distress to reduce potential for vomiting or aspiration should respiratory deterioration occur. Continuous cardiorespiratory monitoring including pulse oximetry is required in all children with difficulty breathing and especially for young infants, patients with chronic cardiac, neurologic or pulmonary conditions, children demonstrating evidence of shock, and those with anomalies that may heighten risk for airway compromise.

Patient size as a function of weight is vital for accurate airway equipment selection and medication calculations; a measured weight in kilograms is best but not always feasible to obtain. Tools and

formulas are available to reliably estimate weight in most circumstances when a child's condition precludes a measured weight (Table 218.4). The length-based color-coded Broselow tape is able to predict weight in children less than 10 years who are normal weight for length and weigh <25 kg; this tape has been validated in US pediatric populations and in other countries (10). Limitations of the Broselow and other length-based tapes include underestimation of weight compared to age-based formulas when children are at the extremes of weight for length, such as in preterm or malnourished infants as well as older and, more commonly, obese children. Age-based formulas to estimate weight are as accurate as the Broselow tape in weight prediction for children 25 to 40 kg. Arm circumference may predict weight more accurately than either age or height in children but evidence is limited and normative values are not readily available (11). The use of cognitive aids such as the Broselow tape to facilitate selection of equipment and drug dosing during airway and resuscitation emergencies is recommended by the American Heart Association Pediatric Advanced Life Support and American College of Emergency Physicians Advanced Pediatric Life Support authors (8). A summary of logistical issues in pediatric airway support is provided in Table 218.5.

TABLE 218.4
Weight/Size Estimation Tools and Formulas

Method	Benefits	Limitations
Length-based tapes (Broselow tape)	Accurate in children <10 yrs who are average height for weight up to 40 kg Recommended for use in all resuscitation/RSI calculations	Underestimate weight in obese and very young infants
Leffler formula, age Weight (kg) = (age in month/2) + 4 Children <1 yr Weight (kg) = (2 × age in years) + 10 Children 1–10 yrs	Accurate as length-based tapes in children 25–40 kg Better than length-based tapes for overweight children	Less accurate than length-based tapes for children <25 kg

TABLE 218.5
Sources of Logistic Issues Particular to Pediatric Airway Management

1. Weight estimation
2. Equipment selection
3. Recall/referencing doses
4. Calculation of doses
5. Calculation of drug volumes
6. Calculation of fluid volumes
7. Calculation of ventilatory volumes

NONINVASIVE AIRWAY SUPPORT

The advent of NIV airway interventions has extended the range of airway support beyond positioning, face mask oxygen, and endotracheal intubation. NIV airway interventions such as humidified high flow nasal cannula (HHFNC) and continuous positive airway pressure (CPAP) are increasingly being used in the care of some children in the ED setting. Although typically these had been reserved for infants and children in the intensive care unit (ICU), recent studies of children with bronchiolitis suggest that these NIV interventions may be valuable in the ED as a way to prevent

intubation (12,13). Data on outcomes such as need for escalation of support, frequency of intubation, and length of stay are still limited to retrospective reports and to prospective observational studies in select populations. There are as yet no randomized clinical trials in pediatric ED populations. Both HHFNC and CPAP require specialized equipment that is correctly sized for children and respiratory therapists and clinicians with clinical experience applying these techniques.

HHFNC is the delivery of humidified oxygen via a nasal cannula, using flow rates greater than the patient's peak inspiratory demand and delivered at temperatures typically between 35° to 37°C. Flow rates are not standardized; initial rates are usually 2 to 4 L/min, but can vary by weight and age up to 40 L/min. The mechanism of action is not completely understood, but may be related to increased airway distending pressure, more consistent flow of oxygen or washout of nasopharyngeal dead space.

NIV airway interventions have resulted in a significant reduction in the number of pediatric patients requiring intubation. Two small single-center pediatric emergency retrospective studies compared rates of intubation between time periods before and after HHFNC system introduction. In a heterogeneous population of ED children with acute respiratory insufficiency, an 8% reduction in intubation rate was noted largely by a reduction in ED intubations. Similar findings, a 7.6% reduction in ED intubations, were reported in patients started on HHFNC in the ED compared to children started on HHFNC in the PICU (18.1%) hours to days after admission (14). McKieranan et al. (12) retrospectively reviewed charts of children $<$24 months admitted to the PICU with bronchiolitis and compared rates of intubation before and after introduction of HHFNC, adjusting for age, weight, and RSV status. A dramatic 68% reduction in intubation during the postimplementation period was noted; however, these results must be interpreted with caution, as almost all patients (88%) received HHFNC in the postintervention period.

The addition of NIV methods requires vigilance on the part of practitioners to recognize when progression to endotracheal intubation may be required. A 2013 study assessed risk factors

associated with HHFNC failure in 498 children <2 years who received HHFNC within 24 hours of triage and included (1) initial venous pH <7.30, (2) triage respiratory rate greater than 90th percentile for age, and (3) PCO_2 >50 mmHg (15). HHFNC has demonstrated feasibility in children with bronchiolitis but has not been well studied in other pediatric ED disease populations. HHFNC may be a reasonable alternative in some children with bronchiolitis not requiring immediate intubation, in facilities where appropriate expertise and equipment are available.

A number of types of ventilation assist modalities are available beyond HHFNC, including CPAP, bi-level positive airway pressure (BiPAP), and nasal intermittent positive pressure ventilation (NIPPV). These methods all work by aerating atelectatic alveoli, increasing FRC, reducing respiratory workload, and improving oxygenation. Differences between these methods relate to the timing and control (patient versus machine) of gas delivery. CPAP delivers a constant flow of gas regardless of the patient's respiratory cycle while BiPAP delivers two distinct pressures delivered at fixed times or can be triggered by the patient's inspiration. NIPPV is essentially a hybrid of CPAP and BiPAP utilizing two flow meters delivering constant, but variable gas pressures; the machine is set to cycle between the two pressures at prescribed intervals (rather than being activated by the patient). The amount of oxygen delivered can be titrated separately or directly within each of the systems.

The most common pediatric emergency clinical application for CPAP is in the management of bronchiolitic children with acute respiratory distress who need more than simple oxygen yet do not require intubation. The major drawback of CPAP use in pediatric ED settings continues to be the requirement of a nasal or tight fitting face mask which may be difficult for an awake infant or young child to tolerate. Characteristics of children with bronchiolitis who require higher levels of airway intervention such as CPAP or intubation have recently been described in a PICU setting. Independent predictors of the need for CPAP/intubation were age <6 months, birth weight <7 lb, maternal smoking during pregnancy, onset of breathing difficulties <1 day before ED visit, presence of apnea, presences of

severe retractions, oxygen saturation <85%, and inadequate oral intake (13). The overall quality of evidence for CPAP use in children with respiratory distress in the ED setting remains very limited (17).

A summary of NIV (HHFNC, CPAP, and BiPAP) airway measures and their clinical application is shown in Table 218.6. The use of these techniques must take into consideration the ED setting, availability, experience of key personnel (i.e., physicians and respiratory therapists), and equipment resources. Complication rates are low, usually related to failure of the method to work (12–16). The method and timing of airway intervention depend on the clinical scenario, including disease process, existing comorbidities, age, and response to treatment. No randomized controlled trials have compared various NIV methods head to head in the ED setting and there are currently no guidelines or recommendations detailing use of these interventions. Decision-making for a child in severe respiratory distress rests with the judgment and experience of the emergency physician using the tools that he or she is most familiar with. NIV methods should not supplant or delay the use of BMV or intubation in any child whose clinical status progressively deteriorates. The ability to temporarily support oxygenation and ventilation through BMV has been shown to be as effective as endotracheal tube intubation (ETI) in children (albeit with increased risk of stomach insufflation and aspiration with prolonged use). In ED settings of care staffed by experienced providers, ETI should be performed in children with respiratory failure rather than subjecting them to prolonged BMV.

TABLE 218.6
Noninvasive Airway Support Methods

Method	Description	Clinical Application
High-flow oxygen (nasal cannula)	Heated and humidified high-flow oxygen delivered via nasal cannula Flow rates Neonates: 1–5 L/min Infants: 7 L/min Children: 7–8 L/min Adults: Max flow rate 50 L/min Flow rates and FIO_2 are titrated to desired oxygen saturation and work of breathing Nasal cannula sizes are chosen by fit; optimum fit allows some flow to escape (never fully occlude nares). Cannula fit directs size of equipment and maximum flow Patients require close monitoring for effect including heart rate, pulse oximetry, and capnography if available	Most evidence from children with bronchiolitis in PICU and some ED settings May reduce need for further escalation of airway support/intubation compared to standard nasal cannula O_2 in children with bronchiolitis Clinical effect should be seen within 60–90 min. Positive effect = decreased respiratory rate, work of breathing, accessory muscle use, and improved oxygenation No published guidelines for use in children in ED setting Requires respiratory therapy and experienced nursing staff
Continuous Positive Airway Pressure (CPAP)	Delivers constant positive airway pressure support Pressure range: Typical 5–10 cm H_2O Up to 15 cm H_2O Changes should be made in 1 cm H_2O steps Attached to oxygen blender Delivered by specific flow device or ventilator connected to flow device Requires delivery through nasal prongs (1 or 2 prongs), nasal mask, or oral nasal mask Patients require close monitoring for effect including heart rate, pulse oximetry, and capnography if available	Data from heterogeneous groups and settings (ED and PICU) bronchiolitis Contraindicated in patients with recent history of upper airway or GI surgery Requires respiratory therapy and experienced nursing staff No published guidelines for use in children in ED setting Patients need time for acclimatization Risk of air leak through prongs/nasal mask Face mask difficult to tolerate Effect should be seen 60–90 min
BiPAP/Bi-level nasal CPAP	Delivers two levels of positive airway pressure Higher pressure for inspiration 2–25 cm H_2O Lower pressure for expiration 2–20 cm H_2O Net pressure support = higher pressure – lower pressure Supplemental FIO_2 can be attached or blended within device Can be set to be triggered by patient breath or timed	Heterogenous population pneumonia, asthma, respiratory distress (ED and PICU) Contraindicated in patients with recent history of upper airway or GI surgery Requires respiratory therapy and experienced nursing staff No published guidelines for use in children in ED setting Risk of air leak through prongs/nasal mask Face mask difficult to tolerate Patients need time for acclimatization

RAPID-SEQUENCE INTUBATION

Rapid-sequence intubation (RSI) has been demonstrated to be both safe and effective in children (18). Inability to maintain or protect the airway, inadequate gas exchange (oxygen or ventilation), worsening clinical status, or potential for deterioration are the primary indications for RSI for children in emergency settings. Clinicians may also use RSI in other pediatric situations where ill or injured children may be unable to cooperate such as during prolonged transport or radiographic imaging procedures. Although no specific pediatric contraindications to RSI exist, clinicians should be aware of particular circumstances in children that signal a need for specific alternative airway plans. A quick algorithm for decision-making is available here (Fig. 218.1).

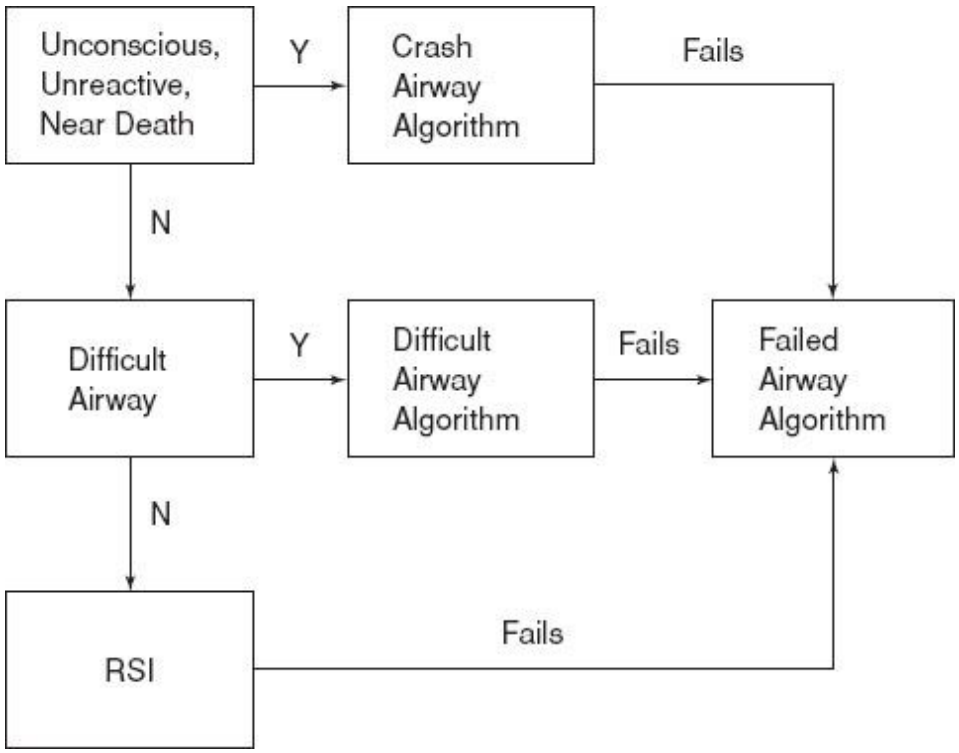

FIGURE 218.1 The universal emergency airway algorithm. (Adapted from Walls RM, Luten RC, Murphy M, et al. National Emergency Airway Management Course Manual. 3rd ed. Wellesley, MA: Airway Management Education Center, 1999.)

As in adults, RSI in children is a complex procedure requiring a mixture of cognitive and technical skill. First attempt success rates of EM physicians performing ETI during RSI of children are lower (53% to 77%) compared to adult RSIs and are positively correlated with operator experience (2,18,19). In a recent retrospective study from a busy children's hospital, ED EM residents' first-attempt success rate was 53% and attending level providers were 10 times more likely to be successful on the first ETI attempt compared to all trainees combined (2). More concerning, in the same study of 114 videotaped RSI procedures, were higher overall rates (including attending physicians and trainees) of first-attempt ETI failure (52%) and adverse effects (61%) compared to previous reports; adverse effects were also not reliably captured in written documentation. As with any infrequently utilized critical skill, pediatric RSI requires advance preparation as well as integration with system improvement

planning; this includes attention to training, maintenance of skill, and ongoing event monitoring to ensure safe practice for optimal patient outcomes. The Advanced Pediatric Life Support and Pediatric Advanced Life Support courses include chapters and skill stations on RSI. Mock codes and practice sessions are invaluable to multidisciplinary team members.

The seven "P's" are a useful cognitive aid to recall the series of actions required to perform RSI. With an emphasis on preparation to avoid complications and mitigate potential aspiration from a full stomach the mnemonic is applicable to both adults and children. The steps of RSI are as follows:

1. Preparation
2. Preoxygenation
3. Premedication
4. Induction and paralysis
5. Cricoid pressure
6. Intubation
7. Postintubation management

Figure 218.2 presents a timed flowchart of the procedure. **Tables 218.7** to **218.10** outline the medications, dosing, and clinical situations that direct used in the scheme.

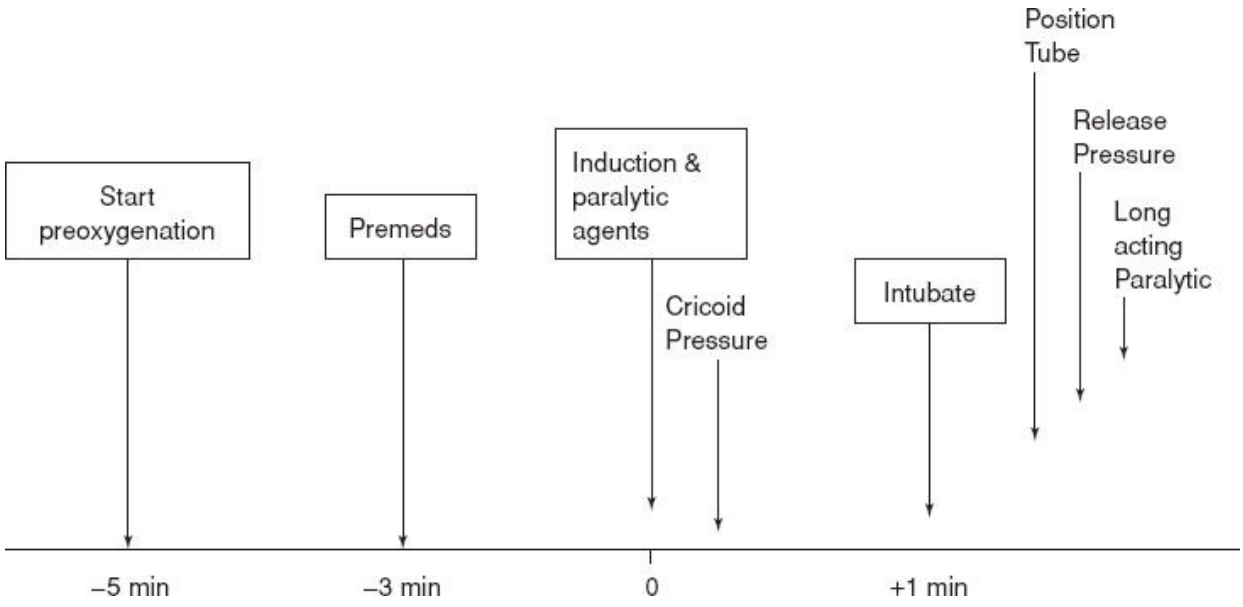

FIGURE 218.2 Rapid-sequence intubation. This chart reflects details of the timed sequence of the procedure in the stable patient. It is important to note that all time intervals may be abbreviated by the clinician, when deemed necessary, owing to less than optimal or deteriorating clinical status.

TABLE 218.7
Common Premedications in Rapid-Sequence Intubation

Drug	Dose (IV)	Action
Lidocaine	1.5 mg/kg	Lowers ICP
Atropine	0.02 mg/kg	May consider to prevent or correct bradycardia associated with airway manipulation and succinylcholine
Pancuronium/vecuronium (defasciculating dose) Defasciculating dose is not recommended for children	0.02 mg/kg	Prevents fasciculations and ICP elevations from succinylcholine (may consider in teenagers and adults)
Fentanyl (optional and usually not recommended in children)	1–5 µg/kg	Attenuates sympathetic discharge and resultant elevations in ICP. Use with caution. May cause respiratory depression or blunt compensatory sympathetic tone

ICP, intracranial pressure.

TABLE 218.8
Suggested Induction Agents for Specific Clinical Conditions

General Sequence	Etomidate, Propofol, Thiopental, Midazolam, Ketamine	Provider Preference
Poor perfusion	Ketamine	Propofol, thiopental, midazolam are more prone to cause hypotension. In the presence of potential septic shock etomidate should not be used due to interference with steroid production.
Elevated ICP	Etomidate, propofol, thiopental, midazolam, consider ketamine	Traditionally ketamine has not been recommended in conditions associated with elevated ICP because of the potential to further exacerbate cerebral pressure levels. Recent evidence, however, suggests a beneficial effect of the drug in these patients. Benefits may be mediated through favorable effects on cerebral perfusion and by conferring protection against humoral mediators of neuronal cell death. The data demonstrating this effect come from the adult literature. Most sources do not recommend ketamine for this indication in children yet and still maintain the cautionary stance to its use in patients with potential ICP elevation
Asthma/ RAD	Ketamine etomidate propofol, midazolam	Thiopental may cause histamine release with resultant bronchospasm
Hyperkalemia risk	Propofol, etomidate, thiopental, midazolam ketamine	

ICP, intracranial pressure.
Adapted from Broselow-Luten Color Coded Management System 2008; Point of Care Guide 3: Rapid Sequence Intubation.

TABLE 218.9
Common Agents for Induction of Unconsciousness in RSI

Drug	Dose (IV)	Onset	Duration
Thiopental	3–5 mg/kg	10–30 sec	10–30 min
Ketamine	1–2 mg/kg	1–2 min	15–30 min
Midazolam	0.2 mg/kg (maximum 5 mg)	1–2 min	30–60 min
Etomidate	0.2–0.4 mg/kg	1 min	3–14 min
Propofol	1.0–2.0 mg/kg	30–60 sec	10–15 min

RSI, rapid-sequence intubation.

TABLE 218.10
Common Agents for Muscle Relaxation in RSI

Drug	Dose (IV)	Onset	Duration
Succinylcholine	1.0–1.5 mg/kg (>10 kg) 1.5–2.0 mg/kg (<10 kg)	30–60 sec	4–10 min
Vecuronium	0.2–0.25 mg/kg (RSI)	60–90 sec	90 min
	0.1 mg/kg (standard dose)	2–3 min	25–40 min
	0.01 mg/kg (defasciculating dose)		
Pancuronium	0.1 mg/kg	2–5 min	45–90 min
	0.01 mg/kg (defasciculating dose)		
Rocuronium	1.0–1.2 mg/kg	30–60 sec	25–60 min

PREPARATION

Preparation for RSI begins with assessment of the child's airway with consideration of the clinical scenario and level of difficulty anticipated. All patients require a basic and contingency RSI plan for failed or unexpected difficult intubation. Histories of prior difficult intubation or expected difficult intubation are critical to contingency planning. Advanced airway supplies in pediatric sizes should be immediately available (and checked at regular intervals) for use in difficult intubation situations such as a videolaryngoscope, lighted stylets, bougies, laryngeal mask airways (LMA), combitube, and surgical trays with materials to facilitate a crash surgical airway. These plans should also integrate larger system protocols to escalate help through alerts to additional advanced personnel (such as anesthesiology) and include procedures for moving a child to the

operating room if necessary. A directed assessment of the airway before RSI and common assessment tools such as the Mallampati score or LEMON evaluation can be applied to children; however data to support their use is limited. History and clinical scenario alone can, typically, direct attention to the likelihood of encountering problems. Extreme caution should be exercised before sedation or paralytic medications are given to any infant or child with craniofacial problems (including injury) that may impede bag-valve-mask (BVM) ventilation; these children may benefit from use of reversible medications with backup support in attendance during RSI or consider moving the patient to the operating room for the procedure.

Equipment required for RSI in children is summarized in Table 218.11; all equipment should be checked prior to the procedure. Both curved (e.g., Macintosh) and straight (e.g., Miller) laryngoscope blades with handles should be available for clinician flexibility particularly when intubating infants and young children <2 years. Choice of curved versus straight blades remains at the discretion and experience of the clinician. Curved blades are often used in children older than 2 years (Figs. 218.3 and 218.4). However, the Miller 2 blade is a reliable blade in children between the ages of 2 and 10. It may be used as a traditional straight blade that lifts the epiglottis or as a curved blade placed in the vallecula.

TABLE 218.11
Equipment Required for Rapid-Sequence Induction

Oxygen source
Bag-valve masks
Face masks (100% nonrebreather)
Oral and nasopharyngeal airways
Laryngoscope handles
Laryngoscope blades
Suction system
Endotracheal tubes: Cuffed and uncuffed
Stylet
Cardiac monitor
Pulse oximeter
Difficult airway cart: Laryngealmask airway (LMA), videolaryngoscope, tracheal tube devices (lighted stylet, ventilated stylet), Bougie
Needle cricothyroidotomy supplies
End-tidal CO_2 detector

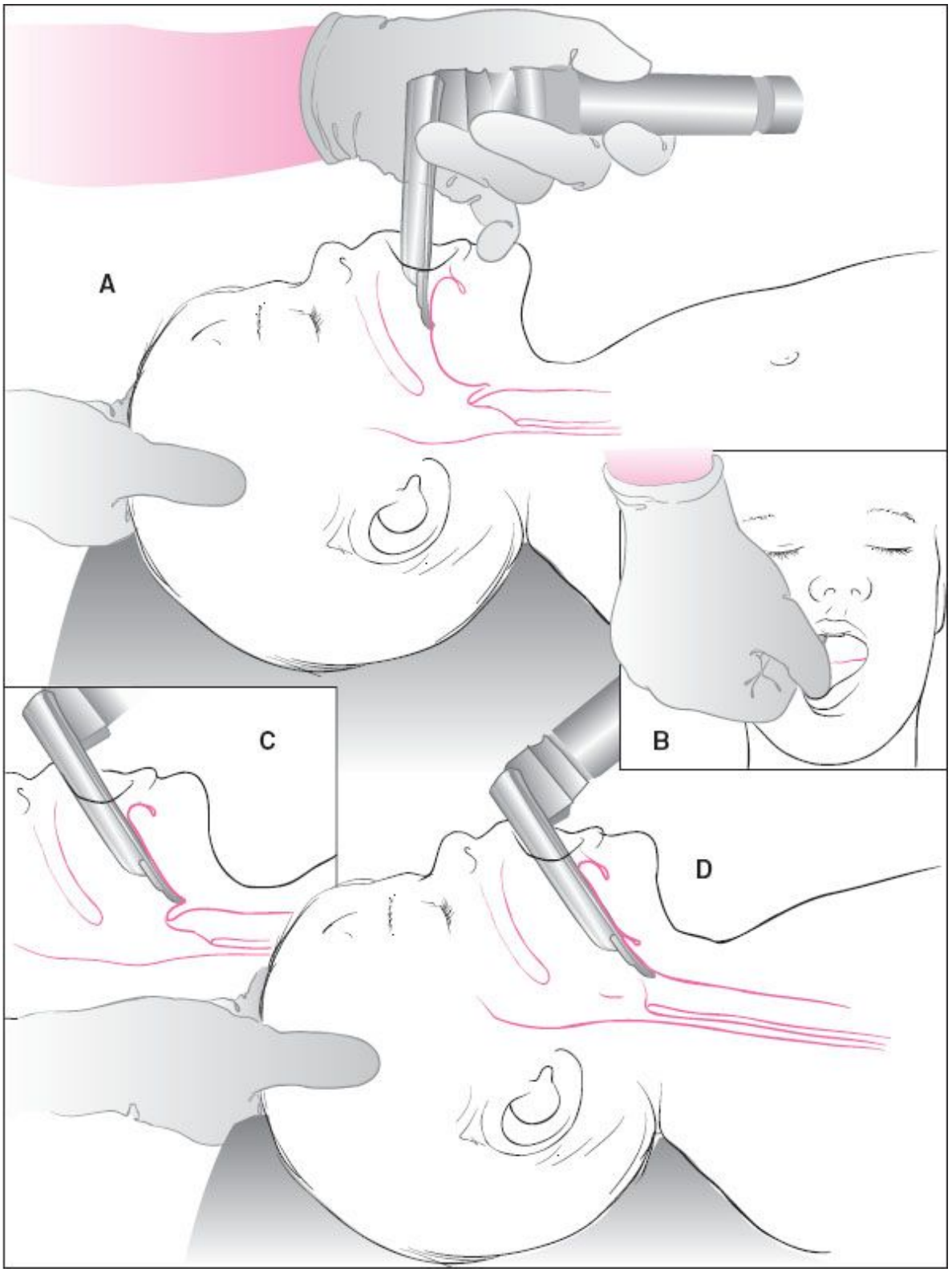

FIGURE 218.3 Direct laryngoscopy using a straight blade. (Reproduced with permission from King C, Rappaport LD. Emergent

endotracheal intubation. In: King C, Henretig FM, eds. *Textbook of Pediatric Emergency Procedures.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008, p168. Copyright © 2008. Lippincott Williams & Wilkins.)

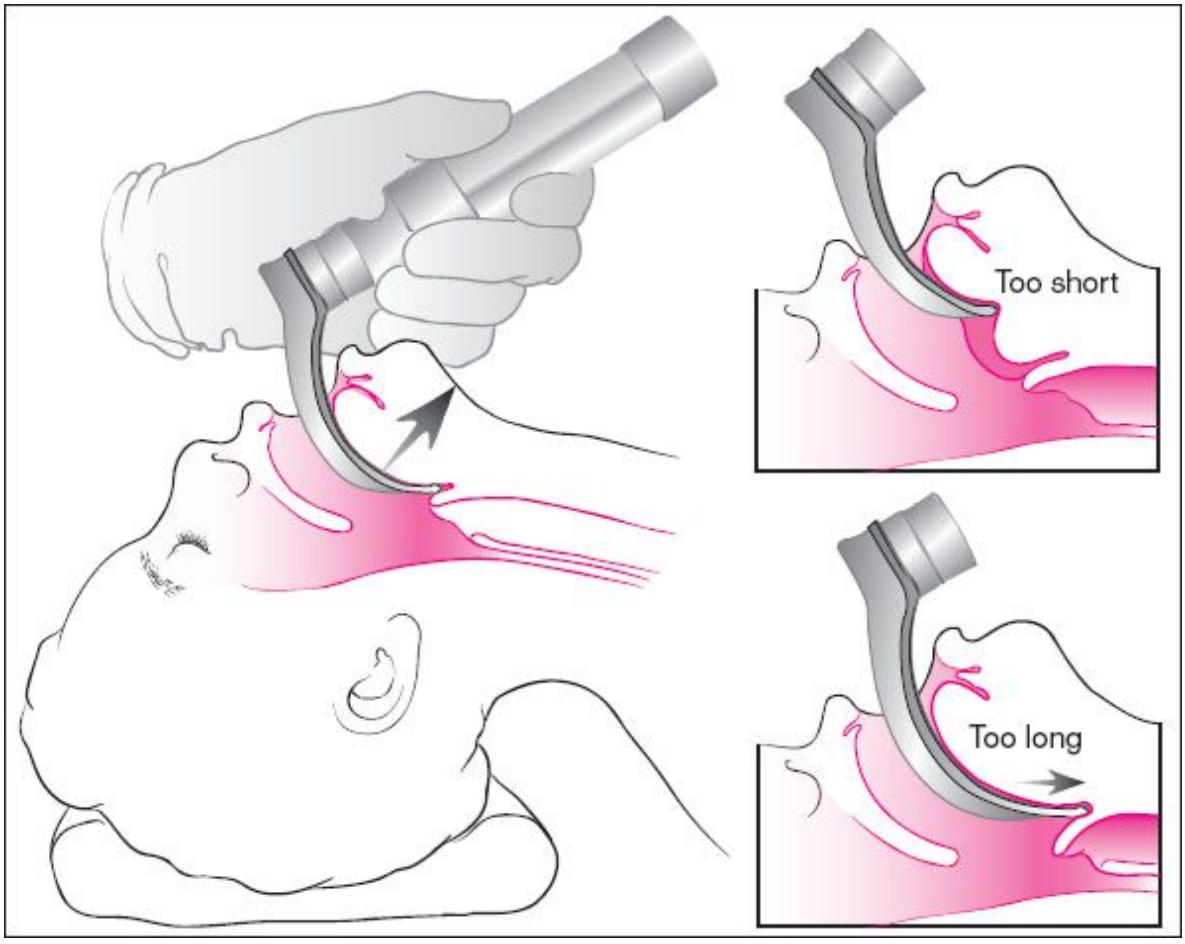

FIGURE 218.4 Direct laryngoscopy using a curved blade. (Reproduced with permission from King C, Rappaport LD. Emergent endotracheal intubation. In: King C, Henretig FM, eds. *Textbook of Pediatric Emergency Procedures.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008, p170. Copyright © 2008. Lippincott Williams & Wilkins.)

Previous RSI instruction directed operators to avoid cuffed ETTs in children under 8 years. However, recent evidence has found cuffed ETTs to be safe and effective in young children and infants. New low-

pressure, high-volume cuffed ETTs have not been associated with tracheal injury or long-term complications (20,21).

Length-based tapes (e.g., Broselow) reasonably predict ETT size selection in most situations, but may not provide guidance for children requiring smaller cuffed tubes (e.g., < 5.5 mm). Suggested formulas for sizing cuffed ETT in young children are listed in Table 218.12 (8). A general rule that may be applied in these situations is to choose the cuffed tube 0.5 to 1 size smaller than the estimated size of an uncuffed ETT. Cuffed tubes may be preferable in situations where children are at risk for aspiration and those requiring potentially higher ventilator pressure settings (such as bronchiolitis or asthma) (8,21). Small stylets are available for infant sized ETT; however, the largest stylet available should be utilized ensuring it does not protrude beyond the end of the tube.

TABLE 218.12
Calculations for Cuffed ETT Sizing in Young Children

Age	Size
Less than 1 yr (>3.5 kg)	ID = 3.0 mm
1–2 yrs	ID = 3.5 mm
Greater than 2 yrs	ID (mm) = Age in years/4 + 3.5

ID, internal diameter.

Cervical spine collars in children with suspected injury restrict laryngoscopy. Opening the collar anteriorly with in-line immobilization to prevent movement of a potential cervical spine injury may facilitate placement of the ETT; however this procedure may still offer incomplete view of the glottis, may not arrest all cervical spine movement, and can result in higher force generated during visualization of the cords (22,23). Operators will need to balance the force generated during laryngoscopy with existing in-line stabilization maneuvers to allow adequate visualization while minimizing cervical spine movement to the greatest degree possible.

Preoxygenation

Two to three minutes of preoxygenation are required in spontaneously breathing children or 1 to 2 minutes of BMV with 100% FIO_2 in an apneic child to allow a "safe" period of apnea by establishing a physiologic oxygen reservoir for laryngoscopy without desaturation. Practitioners should supply the highest level of oxygen to the patient as soon as RSI is contemplated. Patients with respiratory insufficiency or impending failure will be challenging to preoxygenate and may require BMV using small tidal volumes to minimize gastric insufflation and hence the risk of subsequent vomiting and aspiration. Deflation of the stomach with a nasogastric tube is indicated if gastric distention, despite an increased risk of vomiting and aspiration, impedes oxygenation or the effectiveness of BMV before ETI. Chronically ill children with gastrostomy tubes in place can be vented to accomplish the same goal.

Premedications

Premedications, including atropine, lidocaine, and defasciculating doses of neuromuscular blocking agents, may be considered to blunt physiologic responses to laryngoscopy or neuromuscular blockade; however, evidence for the use of the agents listed above is either clinically ineffective or controversial due to limited evidence (Table 218.7).

Atropine has traditionally been administered in pediatric RSI to control reflex vagal stimulation and bradycardia related to laryngoscopy and the use of succinylcholine. These phenomena allegedly occur most often in children under 1 year of age and are attributed to a relative predominance of vagal tone in the immature neonatal ventricle. This predisposes the heart to wider pulse rate variations under stress whose effects are potentially mediated and/or blunted by atropine. This relative parasympathetic/sympathetic imbalance recedes by approximately 6 months of age making the indications for atropine beyond the first year of life less clear. There is no conclusive evidence to either support or refute the use of atropine pretreatment; however, recent evidence suggests a trend away from the routine use of atropine in pediatric RSI across many

specialties including anesthesia and neonatology (Rothrock). In addition, while the AHA, ACEP and the AAP have maintained guidelines for the use of atropine in the following populations: (1) *all* children under 1 year undergoing RSI, (2) children less than 5 years in whom succinylcholine is used as the paralytic agent, and (3) in any child requiring a second dose of succinylcholine during RSI (25). *none of these organizations dictate atropine pretreatment as the standard of care in pediatric RSI* (Rothrock). *Atropine has a number of significant side effects to be considered in the context of the ED patient. These include paradoxical bradycardia if less than the minimum 0.1 mg dose is given, urinary retention, reduction of lower esophageal sphincter pressure, pupillary dilatation, and tachycardia that may last hours beyond the procedure.* These effects could make assessment of head injured patients more challenging and make hypoxemia that presents with bradycardia more difficult to detect. Given the paucity of evidence, no conclusions can be drawn regarding the use of atropine for pretreatment in pediatric RSI. It *may* be useful for infants less than 1 year of age but is not routinely recommended beyond this age.

Lidocaine has a long history in RSI algorithms of adults and children to mitigate the transient increased intracranial pressure (ICP) associated with laryngoscopy and intubation. However, as in adults, its use in the pediatric population is rightly questioned (24).

Defasciculating agents of neuromuscular blocking drugs are not recommended in children. The transient increase in ICP induced by succinylcholine is not considered clinically significant enough to warrant the addition of supplemental agents to the RSI protocol (25).

In conclusion there is no evidence to support premedication of the pediatric RSI patient. Simplicity should be valued over potential of medication errors, side effects, or unclear significance of the treatment.

INDUCTION WITH PARALYSIS

Choice of sedation and neuromuscular blocking agents in children depends largely on the clinical situation and hemodynamic status of the patient (Table 218.8). Controversy exists regarding the optimal sedative in pediatric RSI and no perfect agent exists. Ketamine and

etomidate are the commonly used and well-studied sedatives in RSI algorithms of adults and children. Etomidate is a frequently used and well-studied agent in pediatric RSI. It is a rapid and effective sedative with minimal negative hemodynamic effects and has neuroprotective properties (decreases cerebral metabolic rate and blunts ICP). Its impairment of endogenous corticosteroid synthesis, even after a single dose, is a drawback particularly in septic patients. As a result current recommendations from the American College of Critical Care Medicine and the American Heart Association discourage use of etomidate in the setting of suspected sepsis (8).

Ketamine, a widely used dissociative pediatric deep sedation agent, is also a reasonable choice of sedative for pediatric RSI, given its reliable sedative profile and its positive effects on heart rate and blood pressure. However, a recent report of cardiovascular collapse in two separate cases following a single dose of ketamine during RSI have raised concern (26). The majority of children following ketamine administration experience positive chronotropic cardiac effects and an increased blood pressure secondary to the sympathomimetic catecholamine release, overriding ketamine's lesser direct negative inotropic effects. Thus, the usual hemodynamic protective qualities seen with ketamine depend upon adequate catecholamine stores to balance its negative effects. Patients with depleted catecholamine stores (due to the stress of chronic or critical illness) may be at risk of negative hemodynamic effects such as sudden hypotension and bradycardia.

Clinicians must appreciate the pharmacology of sedative agents in the context of patient characteristics and the clinical situation at hand to choose the safest, most reliable option for sedation and induction. Ketamine is the preferred sedative agent in the child with presumed sepsis unless further evidence emerges to the contrary. Consideration should be given to use of other sedatives in patients with suspected catecholamine deficiency in whom ketamine is being considered.

Other sedatives include midazolam, thiopental, and propofol. While these agents offer value in RSI for their induction properties, either respiratory or myocardial depression or both may limit use in

children, especially for those presenting with hemodynamic compromise prior to RSI. Midazolam may be employed in adult and pediatric RSI but sedation can be unreliable (27). Thiopental is a short-acting barbiturate with neuroprotective characteristics that serves as a first-line induction agent in many institutions but has largely been supplanted by newer agents. Thiopental reduces cerebral oxygen consumption but may also cause vasodilatation, myocardial depression, and hypotension, as well as histamine release. This limits its use in children with hemodynamic instability or asthma. Similarly, propofol offers excellent intubating conditions, but with a trade-off of hypotension and potential hypersensitivity reactions in children with unrecognized egg or soybean allergy.

Paralytic Agents

Depolarizing and nondepolarizing paralytic agents are used to enable laryngoscopy and ETI via general muscle relaxation. Succinylcholine is a commonly used paralytic in adult as well as pediatric RSI; given in doses higher than adults it is attractive for its rapid onset and resolution of symptoms. Succynlcholine does have significant drawbacks including rare instances of bradycardia and even asystole in children. Additionally, hyperkalemia is known to occur immediately as well as in a delayed fashion in children with known or suspected neuromuscular diseases (including burns, muscle injury or atrophy, motor neuron lesions, muscular dystrophies) resulting in cardiac arrest. Of particular importance are the known contraindications to succinylcholine applicable to children including any child with a history of or potential for hyperkalemia, malignant hyperthermia, known injury with crush, burn, or denervation within the last 48 to 72 hours, preexisting denervating neuromuscular disease, or suspected myopathy. Nondepolarizing agents including vecuronium, pancuronium, atracurium, and shorter acting agent rocuronium are frequently used in children but are typically slower in onset and last longer than succinylcholine (Table 218.10). Of these, rocuronium offers the best features most closely resembling succinylcholine in time of onset. In many institutions rocuronium is the first-line agent in children. The RSI team should be prepared for

rapid changes in vital signs and clinical status at all points during the procedure and ensure reliable vascular access with ability to rapidly deliver fluids and/or pressor support when necessary. As in adult patients ongoing sedation and paralysis should be maintained with appropriate agents such as midazolam and vecuronium.

CRICOID PRESSURE

The Sellick maneuver, consisting of digital cricoid pressure to occlude the esophagus and prevent passive regurgitation, has been advocated as part of the required sequence for RSI. Routine use of cricoid pressure has not been shown to prevent aspiration reliably and may interfere with laryngoscopic viewing of the glottic opening (8). Recent evidence based on CT imaging of the neck in children suggest variation in the anatomic position of the esophagus relative to the trachea, noting that the esophagus does not always lie directly behind the cricoid cartilage (28). It is thus reasonable to consider using cricoid pressure initially during pediatric RSI until the ETT is placed or the laryngoscopist requests removal to optimize the view of the VC.

Endotracheal Tube Placement with Confirmation

As in adults, it is vital to confirm tube placement in the trachea. Colorimetric CO_2 detection devices (confirming change from purple to yellow) are very reliable and widely used. Correctly intubated hypotensive patients with poor perfusion may not display a clear color change due to limited exhaled CO_2. In these cases a second laryngoscopy with the tube in place may be performed to confirm proper placement. Auscultation of breath sounds, chest rise, and radiographic confirmation of the ETT in the correct position are important secondary adjuncts to confirm tube placement.

RESCUE TECHNIQUES

Proper patient positioning, aggressive preoxygenation, use of appropriate oral and nasal airway adjuncts, and good BMV technique are the best methods to avoid a failed airway in both children and

adults. For children, the most readily available backup airway technique for the patient who cannot be bagged is placement of an LMA (7,8). LMA placement in children is essentially the same as in adults; however, the larger pediatric epiglottis may fold back into the airway as the LMA is placed, causing obstruction above the glottic opening and resulting in an inefficient seal. Both of these problems can usually be corrected quickly by withdrawing of the tip of the LMA slightly to allow either the epiglottis or the LMA tip to unfold and then reseating the tip.

Specific recommendations for management of the difficult pediatric airway beyond LMA are challenging. Video laryngoscopy is a rapidly emerging technology in pediatric EM and has an established track record in adult EM (see Chapters 1 and 2). Pediatric experience is evolving and pediatric sized laryngoscope attachments are available. Trainees and novice operators were successful in placement of ETTs in a mannequin after brief instruction on the use of videolaryngoscopy (29,30). Nonetheless, no official guidelines for the use of videolaryngoscopy in the difficult pediatric airway are available. More than ever, individual providers must familiarize themselves, practice, and demonstrate proficiency in airway tools available to them in their practice setting.

Needle cricothyrotomy is rarely performed in the pediatric population, but the technical placement of the catheter is very similar to the cannulation of a vein. Although various percutaneous needle cricothyrotomy kits and needles are commercially available, the simplest equipment that is appropriate for use in infants consists of a 14-gauge over-the-needle catheter, a 3.0-mm ETT adapter, and a 3- or 5-mL syringe (31). The trachea is isolated, and the 14-gauge angiocath attached to the syringe is inserted directly inferior to the thyroid cartilage at an angle of approximately 30 degrees. The cricothyroid membrane cannot be palpated in the child, so the catheter is placed through the tracheal rings. Any damage to the tracheal cartilage that may occur during needle insertion can be repaired at a later time. Air is aspirated as the catheter is inserted to ensure proper placement. The catheter is left in as the needle is gently withdrawn. The catheter is then attached to the 3-mm ETT

adapter to which a high-pressure source of oxygen can be attached. The provider should expect significant resistance as the patient is ventilated through the catheter, although some definite airflow with chest rise should occur. Needle cricothyrotomy is a rescue modality to gain time until a definitive airway is established. While oxygenation may be preserved, ventilation is likely to be inadequate and progressive hypercarbia is to be anticipated.

CRITICAL INTERVENTIONS

- Select premedications and sedative and paralytic agents taking into consideration the patient's history, age, and physiologic status.
- Have a plan in place for management of the failed airway that includes a minimum of BMV, LMA, and needle cricothyrotomy.
- Have a quality improvement system in place for pediatric RSI that includes all clinicians, nursing, and technical personnel, and addresses medications, equipment, RSI, and failed airway protocols, as well as provision for simulation education with regularly scheduled training exercises.

Common Pitfalls

- Failure to preoxygenate.
- Failure to obtain an adequate laryngoscopic view due to incorrect size or use of equipment.
- Failure to follow succinylcholine with intravenous sedation and a nondepolarizing agent in patients requiring prolonged mechanical ventilation.
- Failure to verify ETT position both clinically and with an end-tidal CO_2 detector.
- Failure to prepare for unanticipated difficult pediatric airway situations during each RSI.

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CHAPTER 219

Vascular Access in Children

Matt Hansen

Children are a heterogeneous group in regard to vascular access, with unique needs in different age groups. Besides the size and depth of the vessel to be cannulated, challenges include control of the patient's physical motion, while pain, anxiety, and parental concerns are addressed. This chapter reviews peripheral venous access, central venous access, ultrasound-guided access, and intraosseous access in children, and discusses techniques for anxiolysis and analgesia during these procedures.

PERIPHERAL VENOUS ACCESS

Peripheral venous access is a cornerstone of modern medical care. Veins in children are often of small caliber requiring narrow-gauge IV catheters. The skin can be thin, and vessels are often more superficial than in adults. Furthermore, the pain and anxiety associated with peripheral access in children is significant (1). Besides even in neonates, neural pain pathways are well developed and it is believed that pain can condition the patient's future responses to painful events. In this context, it is ideal to obtain access as quickly and efficiently as possible, minimizing the number of IV attempts and the resulting stress to the patient and family. Placing a peripheral IV catheter in children requires more nursing resources, may take longer than in adults, and often requires active management of the patient's position and anxiety by a second

operator. Providers must consider the utility of the catheter and whether there are alternative options. For example, an IV catheter is often placed to check electrolytes and infuse fluid bolus in a child with dehydration from gastroenteritis. However, other than a bedside glucose, laboratory testing is of little utility in this situation, and oral rehydration is equally as effective as IV hydration in most circumstances.

The anatomic locations best suited for peripheral access in children are similar to those in adults, but with a few notable exceptions. First, the saphenous vein is a relatively large vein with a consistent location and can be accessed blindly using anatomic landmarks. It can often be located 1 to 2 cm superior and 1 cm medial to the medial malleolus, and then runs posteriorly toward the popliteal fossa. Use of a tourniquet and careful palpation may assist in locating the vessel. The antecubital fossa is another site which is relatively easy to cannulate in children, but it may be difficult to secure and maintain a line due to inadvertent kinking as a result of elbow flexion.

Several techniques may improve the success in difficult IV access in children. Placing a tourniquet on the extremity may also increase the caliber of the vessel and improve the likelihood of success. Transillumination of the hand or foot is a technique which can improve visualization of veins in these locations. A cool light source is needed in order to avoid damage to the skin. Several types of light source are available, including fiberoptic sources.

ULTRASOUND-GUIDED PERIPHERAL ACCESS

Ultrasound-guided peripheral access is another option in children. Ultrasound has been shown to be more accurate than external landmarks in localizing the saphenous vein in children and has been used to insert IV catheters in infants (2,3). In addition, ultrasound has been shown to reduce the time and number of attempts required in children with difficult access (4,5). However, the experience level of the sonographer 1 is an important factor in actual use 6. The technique for obtaining ultrasound-guided peripheral access in

children are similar to those in adults and are well described (7,8). However, in small children or neonates, in whom some veins may be too close to the ultrasound probe to appropriately visualize, a stepoff pad or small bag of saline may be placed between the probe and patient to provide more distance between the probe and the target vein.

CENTRAL VENOUS ACCESS

Central venous access is rarely required in children in the emergency department (ED), largely because of the advent of powered intraosseous devices (discussed below). However, there are times where pediatric central access may be needed. The common locations for pediatric central access include the femoral vein, internal jugular vein, and subclavian vein, and the anatomic landmarks for obtaining central access in children are similar to those in adults. Complications of central access in children are similar to those in adults as well, though because of the relative proximity of important anatomic structures in children, increased vigilance is needed to avoid serious complications. Furthermore, it is frequently impossible to safely obtain central access in young children and infants who are awake or nonintubated, and in whom movement cannot be otherwise controlled.

The femoral vein is often felt to be the technically easiest location for inserting a central venous catheter and has the advantage of being distant from the heart, lungs, and carotid artery. Femoral lines are often avoided in adults because line infections are more common than with internal jugular and subclavian lines, though this is not necessarily the case in children (9).

One notable circumstance where a femoral line is relatively contraindicated is in diabetic ketoacidosis (DKA), where there is a strong association between femoral vein central line placement and subsequent deep vein thrombosis (9). Intraosseous access is the route of choice in patients with DKA in whom peripheral access cannot be established.

The use of ultrasound for central access has become routine in adults. There is evidence that, as in adults, the use of ultrasound for central access in children also lowers complication rates and improves success rates for both internal jugular and femoral sites (10–13).

INTRAOSSEOUS ACCESS

The intraosseous route provides access to a noncollapsible structure with reliable landmarks and relatively few associated contraindications. Powered intraosseous access has dramatically changed emergency access in critically ill children. Several devices are currently available, the most commonly used in the United States is the EZ-IO. Powered intraosseous access is rapidly obtained (typically in less than 1 minute) and complications are rare. The procedure can be easily learned on models or manikins by a wide variety of practitioners, from paramedic to physician (13,14). The IO has had high success rates in patients of all ages, including neonates, and has the potential to replace umbilical vein access in the ED (15). The most common location for intraosseous access is the proximal tibia, though access at the humeral head, distal femur, and distal tibia are also well described. Sternal osseous access has mostly been used in the military setting.

Proximal tibia placement via the EZ-IO will be described since the EZ-IO is the most frequently used device in the US and the proximal tibia the most common site for placement. In order to avoid the physis, the site on the proximal tibia to be accessed is approximately 2 cm distal to the tibial tuberosity. The needle is placed on the skin perpendicular to the bone. The trigger is depressed and remains engaged until the needle has been passed through the cortex of the bone. The operator should feel a sudden reduction in the pressure required to advance the needle once the needle is through the cortex. Care must be taken to not drill in an oblique manner or to go too deep as the needle could pass through the posterior cortex. After the needle is in place, the stylette is removed from the needle and an IV connector is attached. Placement can be confirmed by

aspiration of bone marrow; however, the needle can be in good position and marrow not aspirated. In this situation, the catheter is flushed while palpating the area around the needle and posterior to the needle to monitor for extravasation. If the line flushes easily it is presumed to be in good position. One must be vigilant during the use of an IO for extravasation. This is the most common complication, and can occur posteriorly or lateral to the site of placement, depending on the angle and depth of the needle. The IO needle can be secured by bolstering with gauze and tape, using tape alone, using commercially available products, or other means. Regardless of the method used, it is important to be able to visualize the area near the hub of the needle and posteriorly.

Anything, including fluids and medications, that is administered by an IV can be given through an IO. Fluids infused by the IO route rapidly reach the central circulation. Although IO needles have a large bore, the medullary cavity of the bone has a somewhat high resistance, and IV pumps or pressure bags are frequently needed to aid in rapid fluid administration. In addition, rapid infusion of fluids into the medullary space can be painful, so lidocaine is often administered (0.5 mg/kg via slow push) prior to rapid fluid boluses. In general, longer use of IO access is likely to lead to more complications; thus, IO access is a temporizing means of access until a more stable route can be established.

Contraindications to IO access include infection at the site of insertion, fracture proximal to the site of insertion, suspicion of compartment syndrome in the extremity, previous IO attempt, or bone abnormalities raising the risk of fracture such as osteogenesis imperfecta. Complications include extravasation, skin necrosis, compartment syndrome, cellulitis, osteomyelitis, air embolism, and fracture (16–21). Most are directly related to extravasation of substances which can cause tissue necrosis due to misplacement or dislodgement of the needle, not due to anything inherent in the IO itself. This reinforces the need for vigilance at the site of placement.

ANALGESIA AND ANXIOLYSIS

Analgesia and anxiolysis for vascular access in children can be improved by using both behavioral and pharmacologic techniques. Behavioral techniques start before the procedure and involve providing information on the procedure in a developmentally appropriate manner. Both patients and parents can be taught coping techniques such as deep breathing. Parents can assist in providing a position of comfort and can be actively engaged in distraction, which can be an extremely powerful tool in mitigating anxiety related to a procedure. For infants, comfort may be improved by swaddling, skin to skin contact, breastfeeding, and sucrose administration. Following the procedure, encouragement and distraction are helpful to further reduce anxiety and anticipation of future events (22).

Pharmacologic techniques for analgesia and anxiolysis are myriad (1). Pharmacologic anxiolysis for IV starts may be achieved by inhaled nitrous oxide, or by midazolam, which can be administered via the intranasal, oral, or buccal routes. Pharmacologic analgesia can be achieved by local infiltration, transdermal creams, and active delivery mechanisms. Local infiltration of lidocaine is less painful than IV cannulation, but does involve a needle stick, and perhaps for this reason is not widely used. The J-Tip (National Medical Products Inc., Irvine, CA) is another option for local infiltration and uses CO_2 to inject lidocaine. Several studies demonstrate that it has rapid onset and is effective, though it was associated with a reduced rate of successful cannulation in one adult study. Lidocaine and prilocaine cream 2.5%/2.5% has been shown to be effective in multiple studies at reducing the pain associated with venipuncture. The time needed for this to be optimally effective is 60 minutes, though 90 minutes is more effective. This product is not intended for use on broken skin, as it may result in systemic absorption. Tetracaine gel, not available in the United States, is also effective and requires less time to achieve its effect than the lidocaine and prilocaine mixture. Liposomal 4% lidocaine has also been shown to reduce pain in children when starting a peripheral IV, but as with similar agents, needs 30–60 minutes to achieve its desired effect.

Complications are few and generally involve local skin irritation. Many other techniques have been described to facilitate delivery of local anesthetics through the skin, including heat and lasers. Finally, vapocoolant sprays have been used as analgesics and act by causing temporary (less than 1 minute) cooling of the skin in the area. Studies evaluating efficacy have been mixed, however, probably due to the extremely short duration of action, which may be insufficient for starting an IV.

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CHAPTER 220

Procedural Sedation, Anxiolysis, and Analgesia

Raymond D. Pitetti

Children often require relief of pain and anxiety when undergoing diagnostic or therapeutic procedures in the emergency department (ED). Despite adequate local anesthesia, distraction techniques, and reassurance, many children are unable to "lie still" during a procedure without being physically restrained. Physically restraining a child may facilitate the successful completion of a procedure but can result in psychological trauma for the child and creates less than optimal procedural conditions for clinicians. As a result, procedural sedation and analgesia (PSA) has become standard practice in the outpatient setting to help optimize care of such patients.

Historically, physicians have done a poor job of alleviating pain and anxiety in children undergoing diagnostic testing and procedures (1,2). Even as recently as 20 years ago, it was a commonly held belief among healthcare professionals that young children undergoing a painful or anxiety-provoking procedure did not experience pain, would be at risk of becoming addicted to opiates if they were used, would retain no memory of the event, and would not experience any lasting effects. Dramatic advances in procedural sedation techniques, a greater understanding of the pharmacodynamics of available sedatives and analgesics, and a greater understanding of the physiology and behavioral aspects of how children experience pain have led to an increase in the use of

procedural sedation and to improved safety practices governing its use.

Providing effective and safe ED PSA requires a well-defined process including (1) preprocedural patient assessment; (2) appropriate selection of pharmacologic agents; (3) careful intraprocedural monitoring; and (4) proper postprocedure evaluation and discharge. In addition, complete and thorough documentation of each aspect of the sedation process should be included in the medical record, since many aspects of the sedation process are important JCAHO requirements.

GUIDELINES FOR PEDIATRIC SEDATION AND ANALGESIA

Guidelines for pediatric PSA (3) were first developed and published in 1985 by the National Institutes of Health and the American Academy of Pediatrics (AAP). These guidelines described patient selection, monitoring, equipment needs, and attempted to define various levels of sedation and analgesia. In 1996, the American Society of Anesthesiology (ASA) Task Force on Sedation and Analgesia by Non-anesthesiologists published similar guidelines. These guidelines sought to bring together consensus opinions proposed by various subspecialty societies (4). A recent revision by the ASA in 2002 and by the AAP in 2006 defined the various states of sedation as follows:

Minimal sedation: Drug-induced state during which patients respond normally to verbal commands; ventilatory and cardiovascular functions are unaffected.

Moderate sedation: Drug-induced depression of consciousness during which patients respond purposefully to verbal commands either alone or accompanied by light tactile stimulation; no intervention is necessary to maintain a patent airway and spontaneous ventilation is adequate; cardiovascular function is usually maintained.

Deep sedation: Drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully

after repeated verbal or painful stimulation; the ability to maintain a patent airway may be impaired, and spontaneous ventilation may be inadequate; cardiovascular function is usually maintained.

General anesthesia: Drug-induced loss of consciousness during which patients are not arousable even by painful stimulation; patients often require assistance in maintaining a patent airway, and positive-pressure ventilation may be required; cardiovascular function may be impaired.

Although most practitioners would undoubtedly feel more comfortable with the idea of moderate sedation, the reality is that most procedures performed in the ED require deep sedation. However, regardless of the level of sedation desired, it is important to stress that these states represent different points on a continuum and that movement along this continuum can occur in either direction at any time. It is therefore imperative for practitioners to have the appropriate training and resources to intervene if a patient moves into a level of sedation deeper than intended. This training should include the ability to manage a compromised airway and use advanced resuscitation techniques.

PATIENT SELECTION AND MONITORING

Administration of sedatives and analgesics should occur in a facility suitable for appropriate evaluation and monitoring of patients, and for performing emergency resuscitative measures if needed. Monitoring and emergency equipment suitable for children of all ages and sizes must be available (Table 220.1). This should include a positive-pressure oxygen delivery system, suction apparatus, blood pressure monitor, pulse oximeter, and an emergency crash cart.

TABLE 220.1
Equipment

Positive-pressure oxygen delivery system
Suction apparatus
Blood pressure and CR monitor
Pulse oximeter
Emergency crash cart

CR, cardiorespiratory.

Capnography should be considered when deep sedation is planned. Capnography allows for continuous assessment of ventilatory status and can provide an early indication of airway or respiratory compromise. In addition, capnography avoids depending on the pulse oximeter's delayed detection of changes in oxygen desaturation.

Reversal agents should also be readily available. The practitioner responsible for monitoring the patient *must be someone other than the one performing the diagnostic or therapeutic procedure* and should be appropriately trained and certified.

A full evaluation of the patient's health and medical history should be performed, with consideration given to the patient's physiologic reserve defined by the ASA physical status classification (Table 220.2). Patients who are ASA class I or II are usually considered appropriate candidates for moderate or deep sedation in the ED. Patients in ASA class III or IV present special problems that involve additional considerations (4).

TABLE 220.2
American Society of Anesthesiologists Physical Status Classification

Class I	A healthy patient
Class II	A patient with mild systemic disease
Class III	A patient with severe systemic disease
Class IV	A patient with severe systemic disease that is a constant threat to life
Class V	An ill patient not expected to survive without an operation

Evaluation of the patient's recent food and fluid intake is recommended. Although there is no evidence supporting a

relationship between preprocedural fasting and incidence of adverse events during procedural sedation, current ASA and AAP guidelines recommend that patients undergoing elective sedation follow the same fasting guidelines as those for general anesthesia (Table 220.3). However, it may not be reasonable or acceptable to follow nil per os (NPO) guidelines in some emergent circumstances. Therefore, clinical judgment should be exercised, and the risks of aspiration versus the benefits of performing the procedure in a timely fashion should be carefully considered.

TABLE 220.3
Anesthesia Fasting Guidelines

Ingested Material	Minimum Fasting Period
Clear liquids	2 hrs
Breast milk	4 hrs
Formula, nonhuman milk	6 hrs
Light meal (BRATT diet)	6 hrs
Heavy meal	8 hrs

Thorough documentation of a PSA event should start with informed consent. During sedation, the patient's vital signs, medications, depth of sedation, and occurrence of unexpected events (Table 220.4) should be recorded. The frequency of documentation varies with the level of sedation. It is recommended that heart rate, blood pressure, and oxygen saturation be recorded prior to the sedation, every 5 minutes during moderate and deep sedation, and once again prior to discharge. After the procedure is completed and sedation is no longer desired, monitoring should continue until the patient has recovered sufficiently to meet the following discharge criteria:

TABLE 220.4
Documentation

Monitor	Document
Oxygenation	Consent
Ventilation	Vital signs
Airway	Oxygen saturation
Level of consciousness	Medications
	Untoward events
	Recovery

1. Cardiovascular function and airway patency are satisfactory and stable.
2. Patient is easily arousable and protective reflexes are intact.
3. Patient can talk and sit up (age-appropriate level).
4. Hydration is adequate and the patient can tolerate PO intake.

In general, patients should be monitored for up to 1 hour following completion of the procedure. During this time, vital signs should be monitored and recorded every 15 minutes. For the very young or special-needs child who is incapable of the usual expected responses, the presedation level of responsiveness or a level as close as possible to the child's baseline should be achieved prior to discharge. Appropriate discharge instructions specifically pertaining to PSA should be given to caretakers and include anticipatory guidance regarding sleep, diet, activity, safety precautions, and specific instructions on how to access care in the event of untoward effects or unexpected complications.

NONPHARMACOLOGIC THERAPY

The involvement of child life specialists in the management of pain and anxiety in the pediatric patient can be invaluable. By providing the patient with age-appropriate information regarding the procedures to be performed and teaching appropriate coping strategies, these specialists often succeed in lessening the child's fear and anxiety, thereby reducing and occasionally eliminating the need for any pharmacologic intervention. Distraction techniques such as listening to music with headsets, singing, or imagery can also be powerful coping strategies. Finally, parental support at the bedside can play a significant role in reducing the child's distress (5).

PHARMACOLOGIC THERAPY

There is currently no single agent available that possesses all of the qualities desired for optimal PSA in children. There are, however, many drugs that, when used alone or in combination for the right indications, are very effective and relatively safe. In selecting an agent, the physician must consider the effects desired, the risks and benefits, and the logistics of administration for each situation. When pure sedation is the desired end-point, agents such as benzodiazepines, barbiturates, and propofol should be considered. These agents do not inhibit perception of pain and should never be used as the sole agent when pain management is needed as part of the PSA. Purely sedative agents, however, can be used for painful procedures when used in conjunction with other agents that provide analgesia.

In contrast, nitrous oxide, ketamine, and sedating analgesics such as opioids are excellent choices for painful procedures. Although they provide varying degrees of sedation, they should rarely be used as single agents for nonpainful diagnostic studies. Combining different classes of agents is a way to produce an effect not present with either agent alone. Such combinations must be used with caution, however, for they may potentiate both desired responses and undesired adverse effects.

Pure Analgesics (Nonnarcotics)

Indications: relief of mild to moderate pain
Complications: gastritis, peptic ulcer disease

Specific Agents

Acetaminophen. Pure analgesic agent with antipyretic properties. The standard dose is 15 mg/kg every 4 hours; the agent can be given orally or rectally and can be combined with narcotics such as oxycodone and hydrocodone.

Ibuprofen: Nonsteroidal anti-inflammatory agent with analgesic and antipyretic properties. The standard dose is 10 mg/kg by mouth every 6 hours.

Ketorolac: Nonsteroidal anti-inflammatory agent best suited for relief of biliary and renal colic. The standard dose is 0.4 to 1.0 mg/kg intravenously (IV) or intramuscularly (IM).

Pure Sedatives

Indications: sedation for nonpainful diagnostic or therapeutic procedures

Complications: dose-dependent respiratory depression, hypotension, "paradoxical" (disinhibitory) effects

Specific Agents

Benzodiazepines

Midazolam: Potent sedative with amnesic and anxiolytic properties, rapid onset, and short duration of action (6).

The standard dose is 0.02 to 0.1 mg/kg IV, 0.5 to 0.7 mg/kg orally or rectally, and 0.3 mg/kg intranasally. Midazolam given orally, rectally, or intranasally is effective in providing anxiolysis. The intranasal route, using an appropriate atomizer, provides excellent and easily administered low-grade anxiolysis for a wide variety of applications, from IV starts and brief imaging studies to minor wound repairs. When titrating intravenously, onset of sedation may take 2 to 5 minutes. Children younger than 5 years of age can become excited and agitated when given midazolam (7). Whether this represents a paradoxical or disinhibitory effect and whether higher doses would eliminate the effect is unknown. IV and oral caffeine has successfully reversed this effect.

Barbiturates

Pentobarbital: Sedative agent best used intravenously for nonpainful diagnostic studies. The onset of action is within 1 to 2 minutes, with duration of 30 to 60 minutes, and the standard dose is 2 to 6 mg/kg IV. It is recommended to start with an initial dose of 2 mg/kg and titrate to effect with subsequent doses of 1 to 2 mg/kg every 30 seconds as needed.

Thiopental: Ultra–short-acting agent that can cause profound respiratory depression and hypotension. Standard dose is 3 to 5 mg/kg IV or 25 mg/kg rectally. In current EM practice it is rarely used.

Methohexital: Ultra–short-acting agent with dose-dependent respiratory depression and apnea but minimal associated cardiovascular side effects. Standard dose is 1 mg/kg IV.

Other Agents

Etomidate is an ultra–short-acting sedative hypnotic with no analgesic properties. It has an onset of action of <1 minute and duration of 3 to 5 minutes; cardiorespiratory effects are minimal. Standard dose is 0.1 to 0.3 mg/kg IV. Several studies have shown that etomidate is safe and effective when used in conjunction with analgesics for brief painful procedures (8).

Dexmedetomidine: Also known as precedex, this is a selective α_2-adrenoceptor agonist similar to clonidine, but with a much higher affinity for α_2-receptors than α_1-receptors. It produces "arousable sedation" in which patients experience clinically effective sedation yet are easily arousable. The initial dose of precedex is 3 μg/kg IV, administered over 10 minutes. This can be followed by a maintenance infusion of 2 μg/kg/hour. Precedex should not be given to infants <6 months of age or those with a history of acquired or congenital heart disease other than ASD, VSD and PDA, stroke, recent seizure, moyamoya disease, significant hepatic or renal failure, use of β-blockers, calcium channel blockers and digoxin, or allergy to clonidine. Episodes of bradycardia, hypotension, and sinus arrest have been associated with dexmedetomidine when administered rapidly IV (e.g., bolus administration) or with patients having high vagal tone. Use caution in patients with heart block, severe ventricular dysfunction, hypovolemia, diabetes, chronic hypertension, and in the elderly patients.

Propofol is an ultra–short-acting sedative hypnotic with no analgesic or amnestic properties. It has a rapid onset and brief

duration of action and is a potent antiemetic agent. It does, however, have a narrow therapeutic range with a slightly higher reported incidence of partial airway obstruction, apnea, and hypotension in comparison to other commonly used sedative agents (8). Standard initial dose is 1 to 2 mg/kg, followed by either additional boluses of 0.5 mg/kg or a constant infusion of 50 to 100 μg/kg/min. It can cause pain at the site of infusion and should not be administered to patients with egg or soy allergy. Multiple studies have shown that propofol is a safe and effective single agent for painless diagnostic studies (8) or in conjunction with opioid analgesics for painful procedures (9).

Chloral hydrate is a sedative hypnotic with a long history of safety in pediatrics. It can be given orally or rectally. Because of its unpredictable and variable onset and recovery profile (onset taking as long as 40 to 60 minutes) its practical utility in the ED is severely limited. It is also a known gastrointestinal irritant with arrhymogenic potential when given in the higher dose ranges. Children <6 months of age appear to be at increased risk of adverse events when compared to older children. The standard dose is 25 to 100 mg/kg orally or rectally with a maximum of 1 g for infants and 2 g for older children. For infants less than 2 months of age who require sedation, a dose of 35 to 50 mg/kg PO is recommended.

Sedative Analgesics

Indications: moderate to severe pain management, painful procedures

Complications: respiratory depression, nausea, vomiting

Specific Agents

Opioids

Morphine is the gold standard against which all other narcotics are compared. The standard dose is 0.1 to 0.2 mg/kg IV. The use of morphine as a single agent is not considered procedural sedation. As with most narcotics, dosing may vary depending on degree and extent of pain.

Fentanyl, the most potent of the conventionally used narcotics, has a rapid onset of action (1 to 10 minutes) and a relatively brief duration of 30 to 60 minutes. It has fewer respiratory and cardiovascular depressive effects than other opioids but can cause severe respiratory depression and apnea when combined with benzodiazepines. The standard dose is 1 to 2 μg/kg IV, administered slowly. Rapid boluses have been associated with chest wall rigidity and should be avoided (10). Although available in transmucosal form as a lollipop, the high incidence of nausea and vomiting has limited its acceptability (11). Fentanyl is an excellent choice as an intranasal agent given at 2 μg/kg via for rapid treatment of pain before an IV is established (e.g., minor partial thickness burn patient). The use of fentanyl as a single agent is not considered procedural sedation. For procedural sedation, fentanyl is often combined with either propofol or midazolam.

Nonopioids

Ketamine is unique among the sedative analgesics in that it produces a dissociative state between the thalamus and limbic systems, which is characterized by four features: sedation, analgesia, amnesia, and catalepsies (12). It possesses positive inotropic and bronchodilatory effects, with preservation of spontaneous respirations and protective airway reflexes. These qualities make it an ideal choice for outpatient procedures, with an excellent safety and efficacy record documented in more than 11,000 children (13). The standard dose is 1 to 2 mg/kg IV, 3 to 5 mg/kg IM, and 10 mg/kg PO. The clinical state produced by ketamine differs from other sedatives; the patient's eyes often remain open but with a disconnected stare and marked nystagmus. This "lights on, nobody home" look can be disconcerting to parents and they should be warned of this prior to administration of the drug. Potential side effects of ketamine may include increased salivary and tracheobronchial secretions and emergence reactions (13). Atropine (0.01 mg/kg; minimum, 0.1 mg; maximum, 0.5 mg) or glycopyrrolate (0.005 mg/kg; maximum, 0.25 mg) may help attenuate increased in secretions. Overall the literature describing increased secretions is not conclusive and

additional suctioning maybe all that is required to manage secretions. Emergence reactions are uncommon in children younger than 8 years. Whether the frequency of emergence reactions can be reduced by premedication with a benzodiazepine (e.g., midazolam 0.05 mg/kg) is controversial. A recent study concluded that the incidence of emergence phenomena was not affected by the addition of midazolam (14). Laryngospasm after administration of ketamine has been documented especially in small infants (younger than 3 months) with respiratory tract infections, and use of ketamine is therefore contraindicated in this patient population. In older patients laryngospasm is noted in approximately 1 in 256 patients (13). It is typically seen shortly after administration of the medication (with in 30 seconds) and can be managed with effective positive pressure ventilation via bag valve mask; the vast majority of episodes of laryngospasm will resolve within 10 to 20 seconds. A very small minority of patients will require paralysis with succinylcholine to terminate laryngospasm. Other contraindications include conditions associated with increased intracranial or intraocular pressure, hypertension, thyroid disease, and porphyria.

Inhalational Agents

Nitrous oxide is the only inhalational agent in common use in EM practice, usually in concentrations of 30% to 70% N_2O mixed with oxygen. Concentrations $<50\%$ generally provide analgesia only, with sedation occurring in concentrations $>50\%$. It is a safe, effective sedative–analgesic with a rapid onset and short duration of action upon withdrawal. Nitrous oxide is inexpensive and easy to administer by experienced personnel. “Setting the scene” is very important when using nitrous oxide in young patients. The patient must be well prepared in terms of expectations and be able to cooperate. This method of sedation is best used in older children and adolescents who are more likely to cooperate with the mask.

Reversal Agents

Reversal agents available for PSA include the following:

Naloxone (narcan): opioid antagonist (dose 0.01 to 0.1 mg/kg IV or IM)

Flumazenil (mazicon): benzodiazepine antagonist (dose 0.01 mg/kg IV, maximum 0.2 mg, repeated every 1 minute to a maximum of 3 mg)

Topical Anesthetic Agents

LET: Topical solution of 4% lidocaine, 0.1% epinephrine, and 0.5% tetracaine. It should be applied directly into the wound and has an onset of action of 20 to 30 minutes. It should not be applied to areas where vasoconstriction is a concern. It can be made into a gel form with the addition of hydroxyethyl cellulose.

EMLA: Eutectic mixture of 2.5% lidocaine and 2.5% prilocaine. It should be applied to intact skin with an occlusive dressing and has an onset of action of 60 minutes.

LMX-4: Formulation of 4% lidocaine in a liposomal delivery system. It should be applied to intact skin with an occlusive dressing and has an onset of action of 30 minutes.

Common Pitfalls

- Insufficient monitoring during and after procedural sedation.
- Failure to assure that the provider responsible for monitoring the patient does not become involved in performing the procedure.
- Providing only a sedative agent for a painful procedure without providing analgesia.
- Giving insufficient medication because of time factors or fears about side effects, especially respiratory depression.
- Selecting an agent that cannot be titrated quickly enough and thus fails to produce the desired state.
- Failing to have reversal agents readily available.
- Failing to anticipate disinhibitory effects with the use of benzodiazepines in small children.
- Failing to prepare parents for the nystagmus and catalepsy seen with ketamine.

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PART 3 • CHIEF COMPLAINTS

CHAPTER 221 Neonatal Jaundice

Margaret Wolff

Jaundice is defined as a yellow discoloration of the skin and sclerae indicative of excessive bilirubin production or disordered bilirubin metabolism or excretion. When the serum concentration of bilirubin exceeds 2 mg/dL, jaundice usually becomes apparent and is best appreciated on the palms and soles (1). The etiologies of neonatal jaundice range from physiologic jaundice to potentially life-threatening conditions. These can be differentiated by a thorough history, physical examination, and laboratory evaluation. This chapter discusses the diagnostic approach to a young infant with jaundice. For the approach to patients greater than 8 weeks of age, see Chapter 102 (jaundice).

Bilirubin is created from the breakdown of hemoglobin and other heme-containing proteins. Bilirubin produced by this degradation process is unconjugated and poorly water soluble. Unconjugated bilirubin is conjugated in the liver with glucuronic acid (which is water soluble) and excreted into the biliary tract and in the stool (Fig. 221.1).

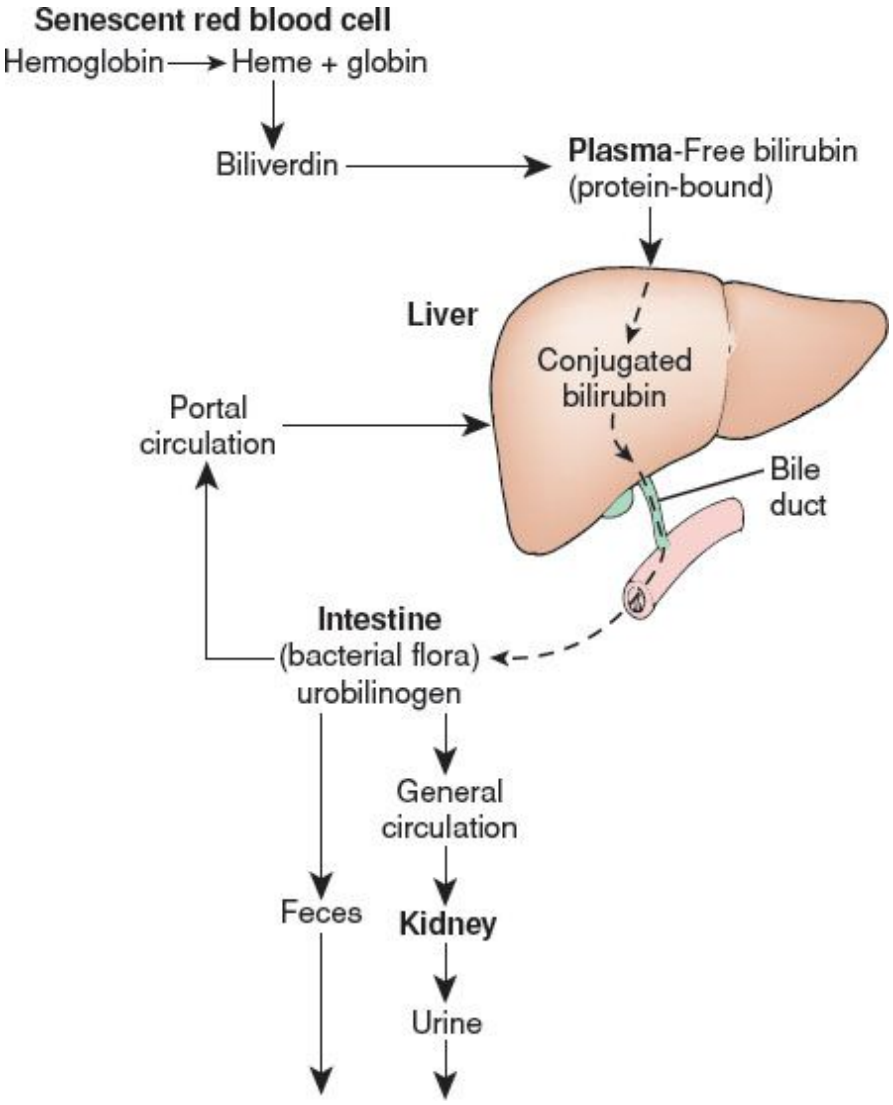


FIGURE 221.1 The process of bilirubin formation, circulation, and elimination. (Image from Porth CM. Pathophysiology: Concepts of Altered Health States. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.)

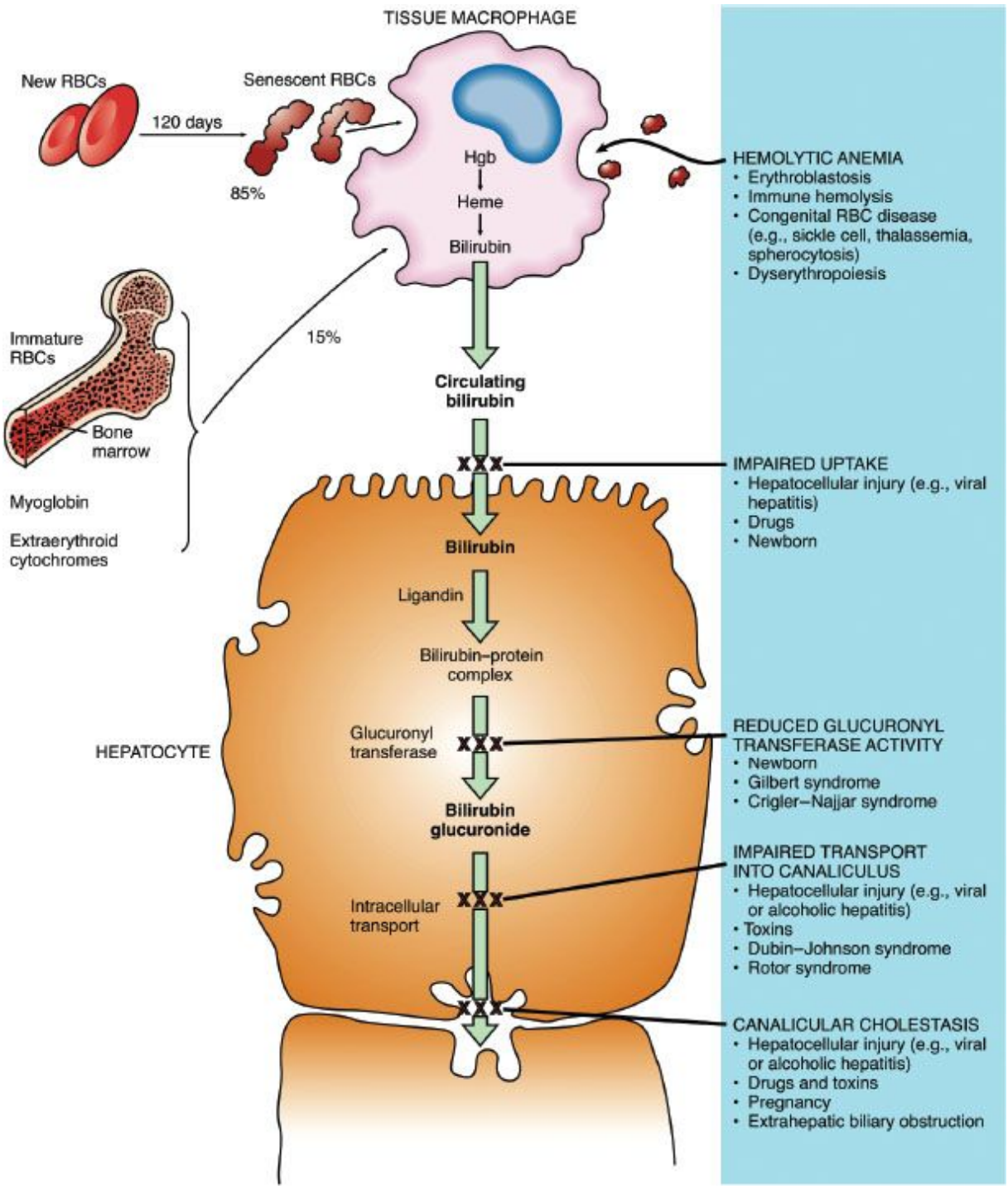
CLINICAL PRESENTATION

Almost all neonates will have some degree of jaundice in the first week of life but are otherwise well appearing (2). Some of these neonates may appear dehydrated or have significant reduction in weight from birth weight suggesting insufficient oral intake. Other findings may suggest a more concerning cause of neonatal jaundice.

- Temperature instability, lethargy, apnea, or poor feeding suggest a serious bacterial infection (3)
- Pallor may indicate anemia
- Jaundice and vomiting suggest upper gastrointestinal obstruction
- Acholic stools suggest biliary tract obstruction
- Hepatomegaly may be associated with liver dysfunction
- Splenomegaly may indicate a hypersplenic state
- Neonates with acute bilirubin encephalopathy (kernicterus) may present with lethargy, hypotonia, and poor suck in the initial stages, and irritability and hypertonia in more advanced stages (4)
- Infants who present after the first 2 weeks of life with jaundice have pathologic jaundice and must be fully evaluated to determine the cause. These infants may be otherwise well appearing without any associated symptoms or they may exhibit any of the above signs and symptoms

DIFFERENTIAL DIAGNOSIS

Jaundice can be grouped based on underlying pathophysiology into the following categories: (1) excessive bilirubin production, (2) disordered bilirubin metabolism, or (3) disordered excretion (cholestasis) (eFig. 221.1). The majority of neonates develop some degree of jaundice due to a relative deficiency of glucuronic acid in the liver until approximately 14 weeks of age (5). In addition, neonates have more red blood cells and a shorter red cell half-life, resulting in increased bilirubin production compared to older children (6). This benign jaundice is termed physiologic neonatal hyperbilirubinemia and results in peak unconjugated bilirubin levels between 3 and 5 days that resolves without treatment. Breastfed neonates may develop breastfeeding-associated jaundice in the first week due to mild dehydration because of a delay in the let-down of breast milk as it transits from colostrum. Breastfed infants may also develop mild jaundice after the first week of life termed breast-milk jaundice due to effects of breast milk on intestinal excretion and resorption of bile (7).



eFIGURE 221.1 Mechanisms of jaundice at the level of the hepatocyte. Bilirubin is derived principally from the senescence of circulating red blood cells, with a smaller contribution from the degradation of erythropoietic elements in the bone marrow, myoglobin, and extraerythroid cytochromes. Jaundice results from overproduction of bilirubin (hemolytic anemia) or defects in its

hepatic metabolism. The locations of specific blocks in the metabolic pathway of bilirubin in the hepatocyte are illustrated. (Image from Rubin E, Farber JL. *Pathology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.)

Nonphysiologic hyperbilirubinemia is defined as jaundice in the first 24 hours of life, a rapidly rising bilirubin level, a bilirubin level exceeding phototherapy thresholds, jaundice that persists after 2 weeks, or conjugated hyperbilirubinemia (Table 221.1). Nonphysiologic jaundice may be caused by an exaggeration of the mechanisms that produce physiologic jaundice, or may be due to pathologic conditions leading to excessive bilirubin production, disordered bilirubin metabolism, or disordered excretion (cholestasis). After the neonatal period, excessive production from hemolysis is the most common cause of unconjugated hyperbilirubinemia (Table 221.2).

TABLE 221.1
Causes of Jaundice in Neonates

Physiologic hyperbilirubinemia

Breastfeeding-associated jaundice

Breast-milk jaundice

Nonphysiologic hyperbilirubinemia

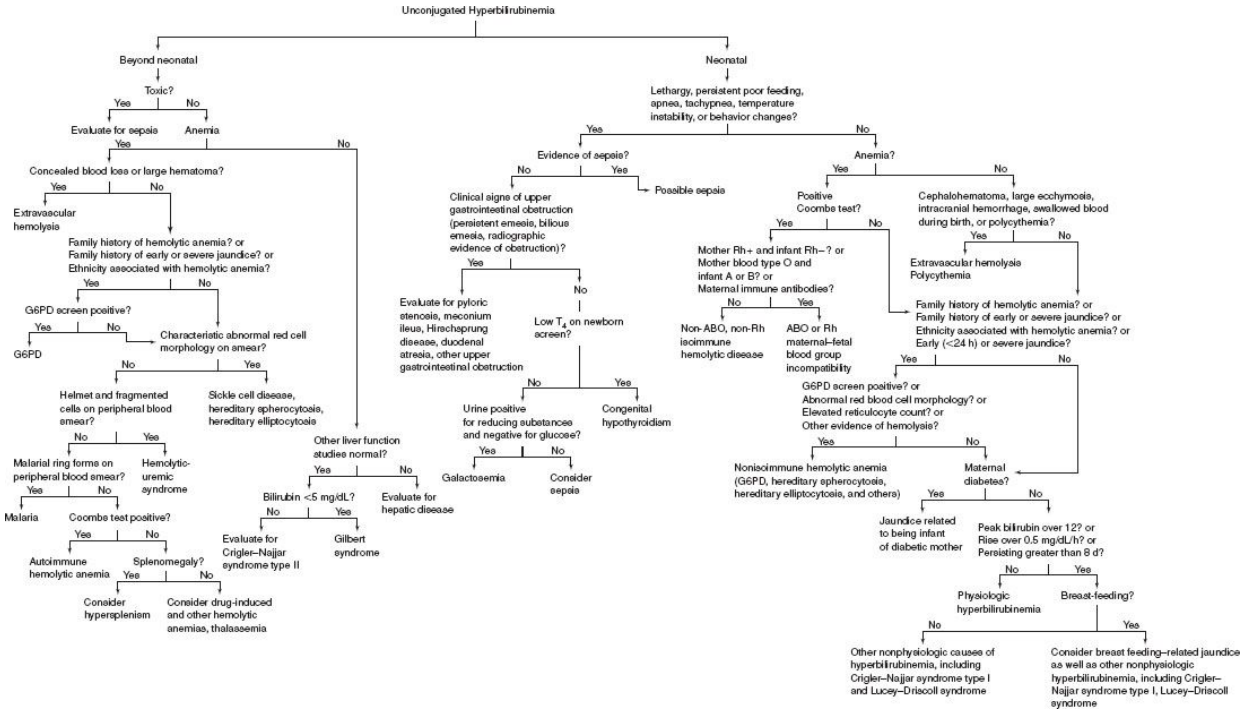
- **Excessive bilirubin production (unconjugated hyperbilirubinemia)**
- Intravascular hemolysis
  - Maternal–fetal blood group incompatibility
  - Polycythemia
- Extravascular hemolysis
  - Extravasated blood (cephalohematoma)
- **Disordered bilirubin metabolism (unconjugated hyperbilirubinemia)**
- Upper gastrointestinal obstruction
  - Hirschsprung disease
  - Pyloric stenosis
- Hypothyroidism
- Inherited disorders
  - Crigler–Najjar syndrome
  - Galactosemia
- **Cholestasis (conjugated hyperbilirubinemia)**
  - Biliary atresia
  - Metabolic disorder
  - Perinatal infections

ED EVALUATION AND MANAGEMENT

The emergency physician must distinguish neonates with nonphysiologic jaundice, who require treatment, from neonates who have benign self-limited causes of jaundice. If left untreated, high levels of bilirubin are associated with kernicterus, a chronic form of bilirubin encephalopathy characterized by permanent neurologic damage (8). Although kernicterus is rare, recent cases demonstrate the need for vigilance when evaluating these infants (9,10). Unfortunately, visual determination of bilirubin levels in neonates is unreliable, making laboratory testing necessary (11,12).

Since the majority of well-appearing neonates will have physiologic jaundice that does not require further treatment (eFig. 221.2), it is reasonable to obtain an initial fractionated bilirubin level from a heelstick capillary sample (13). If this demonstrates

hyperbilirubinemia with predominantly unconjugated bilirubin, the next step is to determine if phototherapy treatment is required, based on AAP Guidelines (Fig. 221.2). Patients requiring phototherapy should have more formal laboratory studies ordered, including a complete blood count, peripheral blood smear, blood type, and Coombs test. Neonates with bilirubin levels below the phototherapy threshold should be risk stratified to determine the near-term risk of hyperbilirubinemia (Fig. 221.3). Follow-up and repeat testing should be arranged as needed (4). In the rare instance that bilirubin levels indicate the need for an exchange transfusion, the decision should be made expeditiously after consultation with a neonatologist (Fig. 221.4). Patients who ultimately require exchange transfusion should be hospitalized and have phototherapy initiated promptly.



eFIGURE 221.2 Approach to the patient with unconjugated hyperbilirubinemia. TORCH, toxoplasmosis, other (infections), rubella, cytomegalovirus (infection), and herpes (simplex) (titer). (From Fleisher GR, Ludwig S, Henretig FM, et al., eds. *Textbook of Pediatric Emergency Medicine*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.)

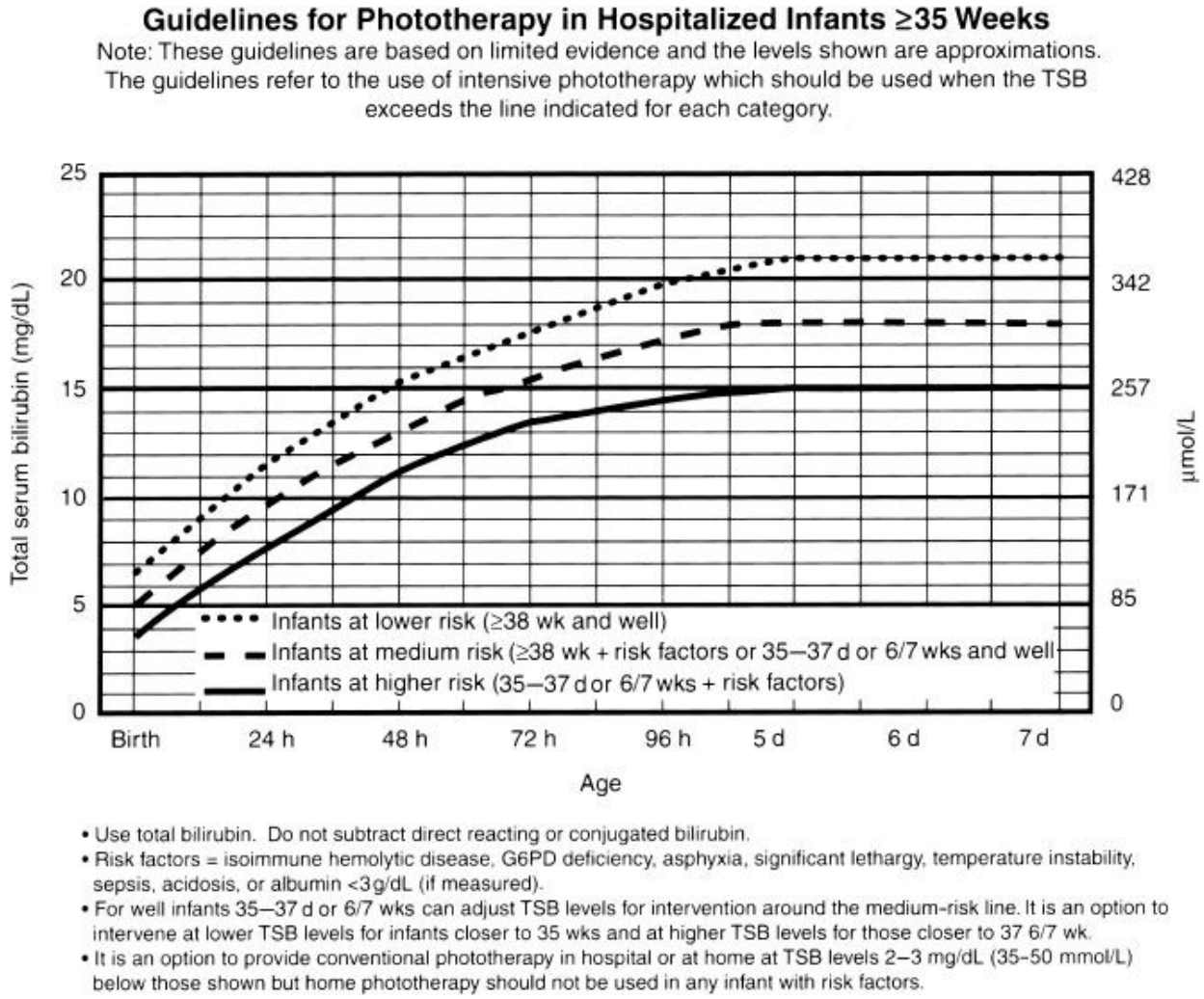


FIGURE 221.2 Management of hyperbilirubinemia in the newborn infant of 35 or more weeks of gestation. AAP guidelines for phototherapy in hospitalized infants of 35 or more weeks of gestation. Note: These guidelines are based on limited evidence and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy which should be used when the TSB exceeds the line indicated for each category. Infants are designated as “higher risk” because of the potential negative effects of the conditions listed on albumin binding of bilirubin the blood–brain barrier, and the susceptibility of the brain cells to damage by bilirubin. (From MacDonald MG, Mullett MD, Seshia MMK. *Avery’s Neonatology: Pathophysiology and Management of the Newborn*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.)

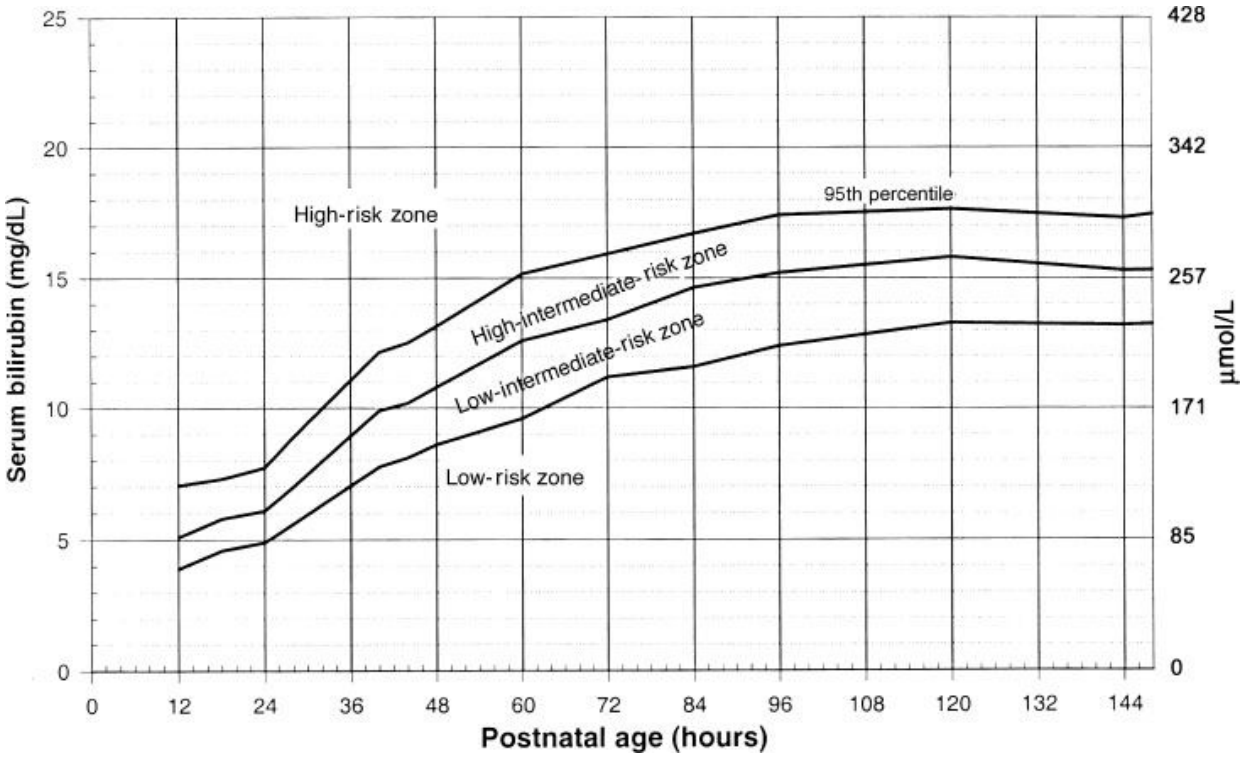


FIGURE 221.3 Nomogram for designation of risk in 2,840 well newborns ≤36 weeks of gestational age with birth weight ≤2,000 g or ≤35 weeks of gestational age and a birth weight ≤2,500 g or more based on the hour-specific serum bilirubin values. The serum bilirubin level was obtained before discharge, and the zone in which the value fell predicted the likelihood of a subsequent bilirubin level exceeding the 95th percentile (high-risk zone). (From MacDonald MG, Mullett MD, Seshia MMK. *Avery's Neonatology: Pathophysiology and Management of the Newborn.* 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.)

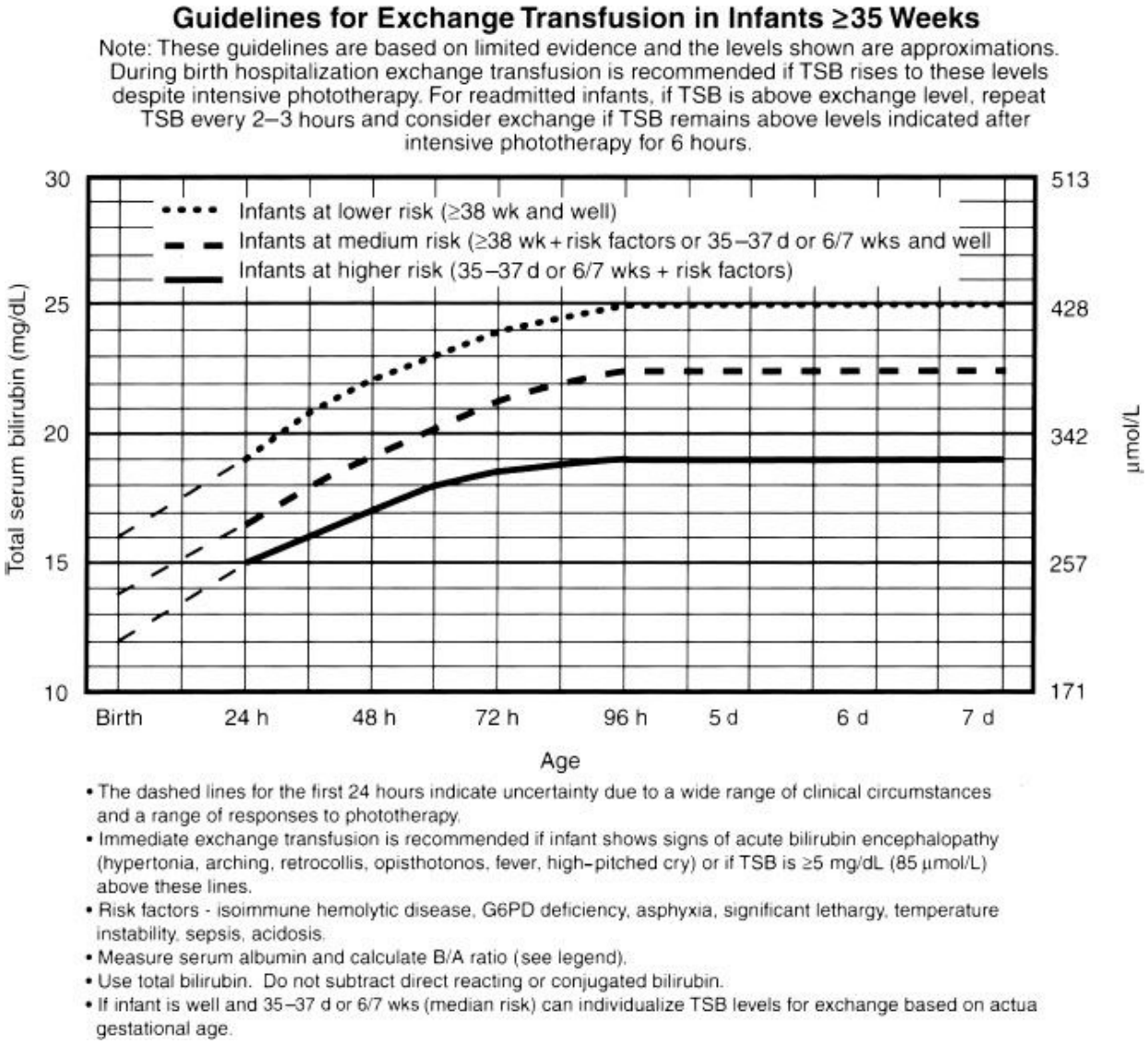
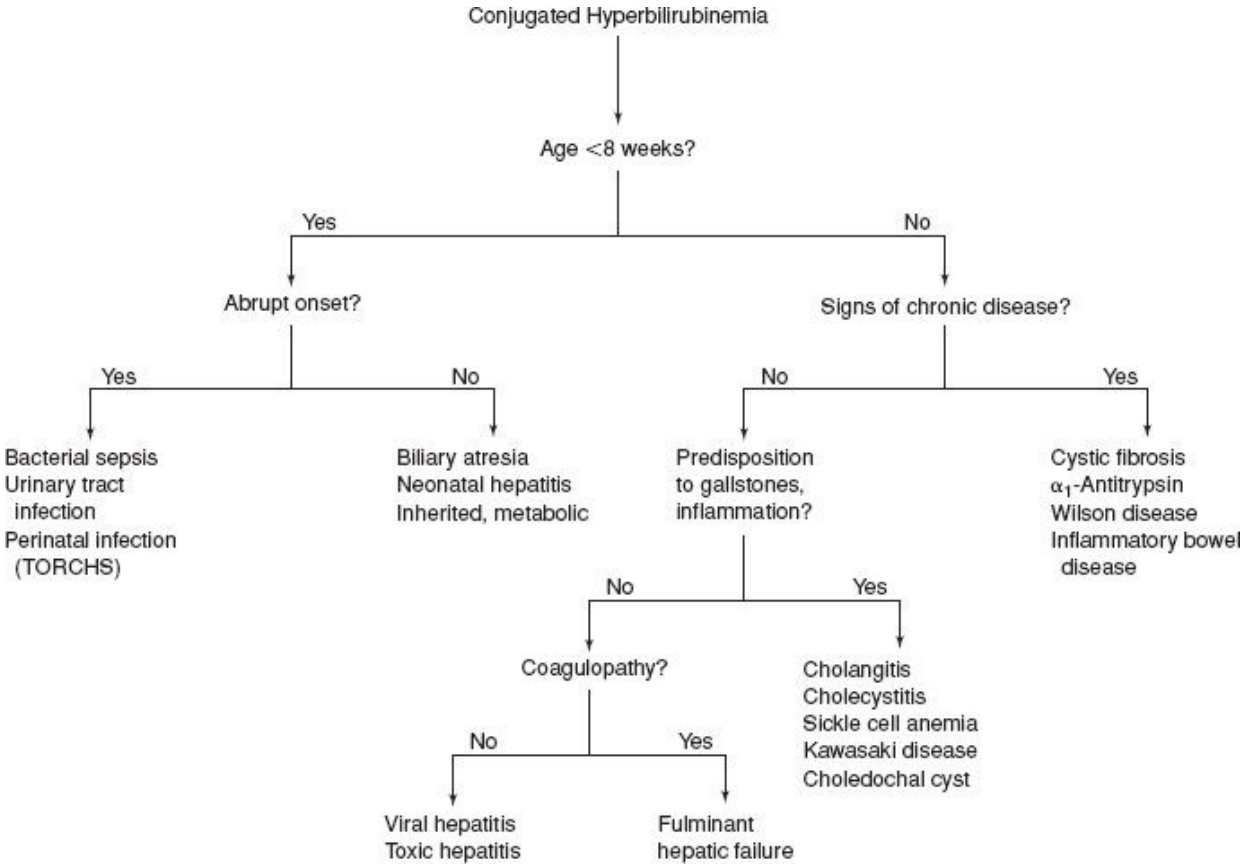


FIGURE 221.4 AAP guidelines for exchange transfusion in infants who are 35 or more weeks gestation. Note that these suggested levels are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if the TSB rises to these levels despite intensive phototherapy. For readmitted infants, if the TSB level is above the exchange level, repeat TSB measurement every 2 to 3 hours and consider exchange if the TSB remains above the levels indicated after intensive phototherapy for 6 hours. (From MacDonald MG, Mullett MD, Seshia MMK. *Avery's Neonatology: Pathophysiology and Management of the Newborn.* 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.)

Laboratory evaluation consistent with conjugated hyperbilirubinemia (conjugated bilirubin >1 mg/dL when total bilirubin is <5 mg/dL or more than 20% of total bilirubin if the total bilirubin is ≤5 mg/dL) should prompt an evaluation for an underlying cause (eFig. 221.3) (14). If the onset was abrupt, consider perinatal TORCHS infections (i.e., toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex, and syphilis), bacterial sepsis, and urinary tract infections (15). If the neonate appears well and does not have evidence of perinatal or bacterial infection, a urinalysis and urine culture should be ordered since a conjugated hyperbilirubinemia may be an early sign of neonatal urinary tract infection.



eFIGURE 221.3 Evaluation of the pediatric patient with unconjugated hyperbilirubinemia. (From Fleisher GR, Ludwig S, Henretig FM, et al., eds. *Textbook of Pediatric Emergency Medicine*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.)

Infants with biliary atresia usually present with gradual onset of jaundice and acholic stools. However, it is important to maintain a high index of suspicion for biliary atresia in *any* neonate presenting with conjugated hyperbilirubinemia (16). Other disorders to consider when there is a more insidious onset of conjugated hyperbilirubinemia include metabolic disorders, and viral hepatitis. Laboratory studies will assist in assessing the degree of hepatocyte injury and biliary dysfunction (serum alanine aminotransferase and aspartate aminotransferase, serum alkaline phosphatase, and gamma-glutamyl transpeptidase) as well as the biosynthetic function of the liver (prothrombin and partial thromboplastin time, serum albumin, glucose, and ammonia). Newborn screening for thyroid disease and galactosemia should be reviewed and an ultrasound of the liver and biliary tract ordered. An extensive evaluation is often required in these patients and consultation with a pediatric gastroenterologist can guide additional testing and treatment. Phototherapy is relatively contraindicated in neonates with conjugated hyperbilirubinemia due to its association with bronze baby syndrome (4).

For infants who present after the first 2 weeks of life with jaundice, measure the total and conjugated bilirubin level to assess for evidence of cholestasis. For exclusively breastfed infants with no history of dark urine or acholic stools, a normal physical examination and reliable follow-up can have this evaluation deferred until 3 weeks of age. If the conjugated bilirubin is elevated, check the results of the newborn screen and evaluate for causes of cholestasis (see above) (4,17). Infants with elevated unconjugated bilirubin levels may be diagnosed with breast-milk jaundice, if they are exclusively breastfed and are otherwise well appearing. For these patients close follow-up should be ensured, however (Table 221.2).

TABLE 221.2
Causes of Jaundice After the Neonatal Period

Excessive Bilirubin Production (Unconjugated Hyperbilirubinemia)
Intravascular hemolysis
Autoimmune hemolytic anemia
Drug-induced hemolytic anemia
Infection
Bacterial sepsis
Malaria
Inherited red blood cell disorders
Microangiopathic hemolytic anemia
Extravascular hemolysis
Hypersplenism
Large hematomas
Disordered Bilirubin Metabolism (Unconjugated Hyperbilirubinemia)
Impaired hepatic bilirubin uptake
Drugs
Heart failure
Viral hepatitis
Impaired bilirubin conjugation
Inherited
Crigler–Najjar syndrome
Gilbert syndrome
Acquired
Drugs
Hyperthyroidism
Liver disease
Cirrhosis
Chronic hepatitis
Cholestasis (Conjugated Hyperbilirubinemia)
Intrahepatic
Hepatotoxins
Viral hepatitis
Metabolic disorders
Nonalcoholic steatohepatitis
Primary biliary cirrhosis
Sepsis
Extrahepatic (biliary obstruction)
Choledocholithiasis
Cholecystitis
Choledochal cyst
Pancreatitis
Primary sclerosing cholangitis

CRITICAL INTERVENTIONS

- Neonates presenting with temperature instability, lethargy, apnea, or poor feeding require prompt evaluation for possible sepsis and initiation of antibiotics and resuscitative efforts, as indicated.
- For neonates who meet phototherapy threshold criteria, intensive phototherapy should be initiated promptly.
- Neonates with severe hyperbilirubinemia who meet criteria for exchange transfusion require emergent transfer to a critical care setting where exchange transfusion can be initiated.

DISPOSITION

Neonates who are ill appearing or meet criteria for phototherapy or exchange transfusion require admission for treatment. Well-

appearing neonates with unconjugated (physiologic) hyperbilirubinemia that do not meet the threshold for phototherapy can be discharged home if close follow-up and repeat testing as indicated by risk assessment can be ensured. The majority of young infants with conjugated hyperbilirubinemia will require hospitalization for further diagnostic evaluation.

Common Pitfalls

- Visual determination of bilirubin level in neonates is unreliable; laboratory evaluation should always be performed to determine bilirubin level.
- Jaundice may be the initial presentation of serious bacterial infections in neonates.
- If a neonate's bilirubin level does not meet the phototherapy threshold, determine risk for subsequent significant hyperbilirubinemia and ensure necessary follow-up prior to discharge.

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CHAPTER 222

Fever

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Fever accounts for up to 30% of all visits presenting to pediatric emergency departments (EDs) or primary care providers, making it one of the most common chief complaints (1,2). Fever as a symptom is steeped in generations of myth and anecdotal folklore that has contributed to persistent misunderstandings and fever phobia. Studies addressing the topic of fever phobia in 1992, 2001, and 2010 touched upon a set of recurring themes (1). Among these were large number (91%) of parents who believed in the potential permanent harm fevers could cause, including brain damage (21%) and death (14%). Most importantly, among the 56% of respondents who considered themselves very worried about fever, there was a higher likelihood of having had a child who had undergone an evaluation for fever in which blood work was drawn and the treating physician seemed very worried about the fever (1). Parents' notions and attitudes regarding fever are often modeled on the attitudes of clinicians who have cared for febrile children. Rational evidence-based approaches to fever in young children are vital to providing care that treats fever like a symptom and not a disease. This chapter presents an approach to fever in otherwise well-appearing or mildly ill children stratified by age: 0 to 28 days, 29 to 56 days, and greater than 8 weeks of age.

CLINICAL PRESENTATION

Fever represents a physiologic response, at the level of the hypothalamus, to bacterial or viral agents and their associated by-products (i.e., endotoxin). An alteration of the body's set point

results in an elevation of core temperature that creates a less hospitable environment for infectious microorganisms. The elevated temperature retards bacterial growth, enhances neutrophilic action, and promotes the acute-phase immune response. Since fever is a natural response to infection, many have questioned the utility of antipyretics. Fever already been stated may promote insensible water loss that leads to frank dehydration. Antipyretics are thus still advocated for children who are symptomatic from the fever, but clinicians should not gauge the likelihood of bacterial illness by the degree of response to antipyretic therapy, since there is no association between the two (7). Fever secondary to infection is not generally harmful unless the temperatures rise above approximately 106.5˚F (1). One of the most significant misconceptions among parents and caregivers concerns what to consider a high fever. Approximately 7% felt that fevers could reach 43.4˚C (110˚F), and 44% felt that a fever of 38.9˚C was a high fever. Fever anxieties also manifest themselves in how antipyretics are used; 44% of caregivers who administered either acetaminophen or ibuprofen did so at too frequent dosing intervals, which could result in either hepatic or renal damage.

Clinicians must educate caregivers on how to appropriately approach and treat fevers in their children. The first step is to prioritize patient appearance over height of fever. A happy and playful infant with a fever of 40˚C is of less concern than a lethargic child who has a fever of 38.5˚C. In evaluating young febrile children, the patient's age and overall appearance, and presence or the absence of a clinically suspected source of infection, are the most important factors in determining the need for further diagnostic testing. Although the degree of fever is important, it *must* be considered within the clinical context and not as the sole factor. The features of an ill appearance include altered mental status, poor eye contact, lethargy, and poor muscle tone. An elevated fever ($>$40˚C, 104˚F) can make a child appear quiet and unhappy but should not necessarily result in an ill appearance. Other important factors to consider are the patient's vaccination history, any underlying

conditions (e.g., HIV, cancer, prematurity), and the availability of follow-up.

Signs of serious illnesses such as meningitis can be subtle. Assessing behavior in young children and infants in particular can be difficult, even for experienced examiners. In a patient with an equivocal presentation, observation of trends in behavior over time, including alertness, consolability, social interactions, and feeding, is the most sensitive means of discerning the presence of a serious infection. When follow-up is uncertain, a more extensive evaluation and a more cautious disposition may be justified.

Traditionally, a rectal temperature (for neonates and young children) of ≤38°C (100.4°F) has been defined as fever. There is some debate surrounding these numbers, but the variation is relatively narrow, within 1 to 2 tenths of a degree. Bundling of an afebrile child should not cause a significant fever when the temperature is taken rectally (3). Axillary temperatures, as well as other methods measuring temperature over the forehead or temporal artery, have been shown to vary widely when compared with rectal temperature (4). Patients frequently present with a history of tactile fever. In one study, patients with reported tactile fever who were noted to be afebrile in the ED were at low risk for fever in the subsequent 48 hours (5). Recent antipyretic use may interfere with the identification of fever, although fever is typically not entirely eliminated, and the antipyretic effects begin to dissipate approximately 2 hours following the most recent dose (6).

DIFFERENTIAL DIAGNOSES

Fever is not always infectious in origin. Noninfectious causes (Table 222.1) must also be considered. Table 222.2 presents an approach to the evaluation of the acutely febrile infant or child based on the child's age and assuming the absence of underlying conditions and reliable follow-up.

TABLE 222.1
Noninfectious Causes of Acute Fever in Infancy and Childhood

Environmental

Overbundling (may raise skin temperature but not rectal temperature to highly febrile range) (13)

Heat stroke

Collagen vascular disease

Rheumatic fever (prolonged fever, recent sore throat, rash, arthralgia)

Juvenile rheumatoid arthritis (prolonged fever, rash, arthritis)

Poisoning

Atropine or other anticholinergics (dry mucous membranes, flushed)

Salicylates (tinnitus, hyperventilation)

Amphetamines (pupillary dilation, agitation, tremor, hypertension, tachycardia, hyperreflexia)

Antidepressants

Other

Kawasaki disease (prolonged fever, conjunctivitis, rash, adenopathy, erythematous mucous membranes)

Drug reaction

Prolonged seizures

Hemolysis

TABLE 222.2
Evaluating the Acutely Febrile Child

Age	
<28 d[b,c]	Septic workup,[d] empiric antimicrobials, supportive care and monitoring, and hospital admission
1–2 mos[b]	Septic workup[d]
	Ill-appearing infants[e] or those with positive septic workup or not meeting Philadelphia, Boston, or Rochester criteria (**Tables 222.4–222.6**) should receive empiric antimicrobials, supportive care and monitoring, and hospital admission
	If nontoxic with a negative septic workup (i.e., meeting low-risk criteria), discharge home with close follow-up with or without intramuscular antibiotics[d]
2–24 mos	Ill-appearing[e] infants and young children should undergo a septic workup and receive empiric antimicrobials, supportive care and monitoring, and hospital admission
	Additional laboratory workup and management considerations in this age group are dependent on general appearance and change over time and specific physical findings, such as meningismus or bulging fontanelle (e.g., lumbar puncture), painful swollen joint (e.g., arthrocentesis), petechial rash (e.g., possible meningococcemia requiring parenteral antimicrobials and hospital admission), or prolonged gastroenteritis (e.g., possible enteric pathogens)
	Additional laboratory workup and management will also be influenced by the child's medical history especially for immunocompromised states such as sickle cell anemia or cancer
	If nontoxic-appearing, temperature >39°–39.5°C,[f] and no source on examination[g] consider:
	UA and UC for girls <2 yrs old and for uncircumcised boys <6–12 mos old
	Chest x-ray if signs of lower respiratory tract disease are present
	If no infectious source is identified, in a well-appearing child, blood cultures and empiric antibiotics are generally no longer recommended in children who have received at least two sets of HiB and pneumococcal vaccinations. For unvaccinated or undervaccinated well-appearing children thought to be at risk of occult bacteremia (e.g., high fever or WBC count), consider blood cultures, with or without empiric antibiotics (e.g., ceftriaxone), and close follow-up
>24 mos	History and physical examination are usually reliable to identify presence of serious (e.g., meningitis or septic shock) or localized infection, and will dictate the extent of laboratory workup and management. UA and UC should be considered for girls if no source found on examination, or if vomiting, abdominal pain, or tenderness exists

[a]Simplified approach to evaluation of fever; many variables must be taken into account, including prematurity, past medical conditions, ability to follow-up.
[b]Fever defined as 38°C in this age group.
[c]Age is defined as postterm age; body weight and past medical conditions should be considered when determining category for workup.
[d]CBC, blood culture, urinalysis (UA), urine culture (UC), stool for WBCs and culture if diarrhea, chest x-ray if symptoms or signs of lower respiratory infection are present. Lumbar puncture and CSF analysis recommended <1 month of age; 1–2 months of age optional but should be strongly considered even if no signs of CNS infection are present, and especially if antimicrobials are to be prescribed.
[e]Ill-appearing infant or young child is defined as having altered mental status, unresponsiveness, poor eye contact, lethargy, or limp tone. Dehydration alone can also present as an ill-appearing child. Highly elevated temperatures can make children appear unhappy but should generally not present as ill-appearance.
[f]The risk of bacterial infection as a cause for the fever increases with the degree of temperature elevation.
[g]Otitis media, upper respiratory infections, and gastroenteritis are not necessarily considered reliable sources of fever, such that other diagnoses can be excluded.

ED EVALUATION AND MANAGEMENT

To understand how febrile infants are risk-stratified, one must appreciate the historical context of our current practice. In the 1980s, prior to the introduction of the *Haemophilus influenzae* type b [HiB] and Prevnar vaccines, all febrile infants, in many cases up to 12 weeks of age, were routinely admitted to the hospital for a complete septic evaluation and treatment. Studies from the late 1980s and early 1990s generated evidence that made it possible to better stratify the risk of serious bacterial infection and narrowed the population of patients at greatest risk to 8 weeks and under; with infants less than 28 days remaining at highest risk (14–17).

All children evaluated for fever should receive a thorough physical examination. The initial examination should start with an evaluation of the child's ABCs. Signs of respiratory distress, hypoperfusion, or shock should be treated immediately. The child's mental status and interaction with the environment are especially important. Febrile children should be undressed to look for skin infections and rashes, including petechiae (e.g., meningococcemia) and vesicles (e.g., *Coxsackie* or *Varicella* infection). Testing the gait of a child who normally is ambulatory will help to evaluate for occult joint infection. Table 222.3 lists key symptoms and signs that should be pursued as part of the emergency evaluation of febrile infants and children.

TABLE 222.3
Key Historical and Physical Findings Relevant to the Evaluation of the Acutely Febrile Infant or Child

History

Behavior: Activity level, consolability, irritability when moved, lethargy

Hydration status: Fluid intake, urine output

Respiratory symptoms: Cough, difficulty breathing

Gastrointestinal symptoms: Vomiting, diarrhea (with blood), travel

Renal symptoms: Abdominal pain, dysuria, frequency, urgency, hematuria

Other: Focal pain (e.g., limp, sore throat, earache, abdominal pain, rash)

Medical history: Immunization status, chronic medical conditions, ill contacts

Physical examination

General appearance: Activity, eye contact, muscle tone, color, consolability

Hydration status: Mucous membranes, fontanelle, capillary refill, skin color, mottling

Respiratory: Respiratory rate, grunting, nasal flaring, rales, bronchial breath sounds, retractions

HEENT: Adenopathy, meningismus, pharyngitis, otitis media

Cardiovascular: Heart rate, murmur

Abdomen: Tenderness, guarding, organomegaly, CVA tenderness

Skin: Rash (including viral, Kawasaki disease, measles, Coxsackievirus, scarlet fever, roseola, Henoch–Schönlein purpura, varicella), petechiae

Musculoskeletal: Bone or joint tenderness, swelling, erythema, ability to ambulate

CVA, costovertebral angle.

Neonates (0 to 28 Days or Younger than 4 Weeks)

Approximately 12% to 28% of febrile neonates presenting to EDs have a serious bacterial illness (SBI) (8). Once a source such as the urinary tract is identified, neonates are at greater risk for hematogenous spread and seeding of distant sites, including the meninges. Because bacterial sepsis and meningitis can present very subtly in neonates, even the slightest changes in behavior or health (e.g., change in sleep or feeding pattern, diarrhea, or jaundice) may be indicators of significant illness. A complete septic workup, including blood and urine cultures, and lumbar puncture (LP) for cerebrospinal fluid (CSF) cultures, should be performed, and hospital admission is generally recommended (9,10). Studies have shown that implementation of a standard protocol in the ED can decrease the time to antibiotic therapy (12). Studies examining the utility of protocols that avoid performing an LP in selected neonates less than

28 days have generally been focused on ambulatory practices where follow-up is assured and contact with the PCP is well established. It has been suggested that some febrile well-appearing neonates with negative initial septic workups can be successfully managed with admission and observation without empiric antibiotic treatment, or even be discharged (13). This, however, is not a standard approach. Baker et al. in 1993, developed the Philadelphia protocol for infants between 29 and 56 days of age, but were not able to successfully apply the protocol to infants less than 28 days (13,17). In most circumstances, neonates should be treated with intravenous antibiotics until culture results are known. Ampicillin and cefotaxime are recommended as initial empiric therapy. Gentamicin can later be substituted for cefotaxime if the CSF is negative. These combinations will provide adequate coverage for the most common bacterial pathogens in this age group, including group B *Streptococcus, Listeria monocytogenes,* and *Escherichia coli.* If the infant is a recent neonatal intensive care unit graduate, the addition of vancomycin is recommended. Treatment with acyclovir for potential herpes infection should be considered for those with maternal history of herpes, vesicular rash, altered mental status, focal neurologic findings, seizures, or CSF pleocytosis with no organisms on Gram stain. In neonates less than 2 weeks of age, transaminitis and low platelet count can also be evidence of herpes infection (11).

Infants (29 to 56 Days or 4 to 8 Weeks)

Febrile infants between 4 and 8 weeks of age remain at risk for serious bacterial infections but to a slightly lesser degree than neonates. This age group continues to show only subtle manifestations of serious infection, and the physical examination continues to be of limited value. Nonetheless, there are significant bodies of evidence supporting the selective discharge of low-risk infants after a suitable ED evaluation. As a general rule, infants between 28 and 56 days should be evaluated, in the same fashion as neonates, with a complete sepsis evaluation. The differences between the Philadelphia criteria and the Boston and Rochester criteria

revolve around which patients undergo an LP and which patients are treated with empiric antibiotics.

The Philadelphia criteria was introduced in 1993 based on a prospective study of 422 infants evaluated for SBI (19). It is distinguished from the Rochester and Boston criteria primarily by not including empiric antibiotics prior to discharge (Table 222.4). This criteria (similar to the Boston protocol—see below) assumes a "well-appearing infant." It requires performing a full septic evaluation (as would be performed for a neonate 0 to 28 days); a chest x-ray is performed if clinically indicated, but a low threshold should be maintained. If the laboratory evaluation (including CSF studies) is negative, the patient may be considered low risk and may be discharged if there is guaranteed follow-up with a medical provider for reevaluation within 24 hours. The patient must remain well appearing throughout the ED stay. If at any point the patient's condition appears less than optimal, there is admission for observation, with or without antibiotics. Other issues to consider are the parents' comfort with discharge. Some parents may not feel comfortable observing the child at home and admission for observation is thus warranted. The notion of the "well-appearing infant" is therefore broader than the patient; it applies to the larger social milieu of the family and their ability to carefully monitor a potentially ill infant.

TABLE 222.4
The Philadelphia Criteria for Evaluating Young Infants with Fever

Well-appearing term infant[a] that remains well appearing through ED stay
WBC count of ≤15,000 (mm^3)
Band to neutrophil ratio of ≤0.2
Urinalysis with <10 WBC/HPF
Urinalysis with few or no bacteria on centrifuged urine specimen
CSF with <8 WBC/mm^3 with negative Gram stain
Chest radiograph negative (obtained on all patients)
Patient has guaranteed follow-up with a medical provider within 24 hrs of ED discharge for reevaluation

[a]Infant Observation Score of 10 or less.

The "Boston criteria" (Table 222.5) is also a well-validated approach to risk-stratify these young patients and is based on a study of 503 infants. The laboratory criteria differ somewhat from the Philadelphia criteria in terms of white blood cell (WBC) count (<20,000 for Boston vs. <15,000 in Philadelphia) but the evaluation includes LP, urinalysis, and blood cultures. Unlike the Philadelphia criteria, the Boston criteria require the use of empiric intramuscular ceftriaxone for infants meeting low-risk criteria prior to discharge. Follow-up for these patients involves returning to the ED in 24 hours for reassessment and a second dose of IM ceftriaxone.

TABLE 222.5
The Boston Criteria for Evaluating Young Infants with Fever

Previously healthy, nontoxic-appearing term infant
No focal infection on examination
WBC count ≤20,000 (mm^3)
CSF with ≤10 WBC/HPF
Stool WBC count ≤5 WBC/HPF when diarrhea present
Chest radiograph negative (if indicated)
Microscopic urinalysis with ≤10 WBCs/HPF or urine dipstick negative for leukocyte esterase

The "Rochester criteria" (Table 222.6) represents the earliest validated set of clinical and laboratory criteria that place infants at low risk for a bacterial infection, and allow them to be managed as outpatients (15,16). Based on these criteria, the estimated risk of

bacteremia and meningitis in low-risk infants is 1.1% and 0.5%, respectively. For children meeting the Rochester criteria, urine and blood cultures are recommended, and routine LP and empirical antimicrobials are considered optional (17,18).

TABLE 222.6
The Rochester Criteria for Evaluating Young Infants with Fever

Previously healthy, nontoxic-appearing[a] term infant
No previous antimicrobial use
No focal infection on examination
WBC count 5,000–15,000 (μL)
Band count >1,500 (μL)
Stool WBC count ≤5 WBC/HPF when diarrhea present
≤10 WBCs/HPF in spun urine

[a]Includes activity, alertness, color, strength of cry, consolability, irritability, eye contact, social responsiveness, and respiratory effort.

Which criterion to follow is driven by three factors: (1) clinician experience, (2) availability of follow-up, and (3) family comfort levels with discharge. If follow-up is likely to be challenging to accomplish or the reliability of follow-up actually taking place is in question, the Boston criteria with a dose of ceftriaxone may be preferred. This is done, however, with the understanding that the patient may not receive the second dose of ceftriaxone if they do not return for follow-up, which risks leaving a partially treated infection unfollowed. Under the vast majority of circumstances, however, reliable follow-up can be established within 24 hours, making the Philadelphia, Boston or Rochester criteria all reasonable approaches.

The key point is to select a method and stick with it. Septic evaluations should be treated as binary for less experienced clinicians, meaning that they should either be done completely or not be done at all (i.e., if the patient is not believed to have had a fever due to an infectious cause). Selective a la carte methods for testing and treatment (if any) risk missing subtle infections or can create confusion for providers who may see the patient on a subsequent visit. The role of the LP in this age group is often debated

and occasionally omitted because of parental preference, but should be considered in the context of the provider's comfort and clinical experience as well. However, the evidence that supports omitting LP from the evaluation is weak, with the possible exception of infants diagnosed with RSV bronchiolitis. In many EDs, viral testing, such as rapid tests for RSV or influenza A or B, is used to decide whether to proceed with blood, urine, and CSF studies in febrile young infants without an identified source of fever (28). The presence of a documented viral infection lowers, but does not eliminate the possibility of a coexisting serious bacterial infection. Several studies have found that febrile young infants who test positive for RSV are at low risk for bacterial infections (29,30). Those bacterial infections that do occur are predominantly urinary tract infections (UTIs), with the rate reported to be from 1.5% to as high as 5% (29,30). The studies are too small to detect differences in the prevalence of meningitis and bacteremia between RSV(+) and RSV(−) infants, but preliminary data show a trend toward lower rates in these infections as well. A number of studies found no cases of meningitis in infants who had CSF testing and who had tested positive for a viral pathogen or had clinical bronchiolitis (29,31).

Infants and Children Greater Than 8 Weeks of Age

In children older than 8 weeks of age "well appearance" becomes more reliable. Between 2 and 4 months, infants begin exhibiting a social smile, making meaningful eye contact, and starting to interact with their environment. Consequently, the contrast between "well" and "ill" becomes more apparent; linking irritability and lethargy more reliable to underlying bacterial infection.

While the evaluation of infants less than 8 weeks of age is based on screening for SBI, in children greater than 8 weeks of age the focus of diagnostic testing is on specific sources of infection such as the urine, lung, CSF and, to a lesser extent, blood. Infections arising from the skin, GI tract, and bone should also be considered under the appropriate circumstances. Table 222.7 outlines common infectious causes of fever based on the associated chief complaint. As a practical point, testing to be considered should primarily include

chest radiograph, urinalysis, and urine culture. Routine use of CBC and electrolyte testing in *well-appearing* febrile infants and children has a low yield, is invasive, and may delay patient disposition.

TABLE 222.7
Common Infectious Processes Causing Fever in Young Children and Their Associated Symptoms

Seizure
Febrile seizure
Meningitis
Encephalitis

Headache[a]
Meningitis
Encephalitis
Sinusitits

Ear Pain
Otitis media
Otitis externa
Mastoiditis

Sore Throat
Pharyngitis/tonsillitis
Gingivostomatitis
Coxsackievirus "hand-foot-and-mouth disease"
Parotitis (viral or suppurative)
Tonsillar/pharyngeal abscess (uncommon)
Peritonsillar cellulitis/abscess (uncommon)

Face or Neck Pain
Periorbital cellulitis
Orbital cellulitis
Facial cellulitis
Cervical adenitis

Rhinorrhea
Common cold/influenza
Sinusitis

Stridor
Croup
Epiglottitis (uncommon)

Cough
Pneumonia
Bronchiolitis
Bronchitis

Chest Pain or Palpitations
Myocarditis (uncommon)
Endocarditis (uncommon)

Abdominal or Pelvic Pain and/or Vomiting
Acute gastroenteritis
Appendicitis
Acute salpingitis
Epididymitis

Dysuria
Urinary tract infection

Joint Pain
Toxic synovitis
Septic arthritis
Osteomyelitis

Rash
Viral exanthem
Roseola infantum
Meningococcemia

Systemic
Bacterial sepsis/bacteremia
Viremia
Rocky Mountain spotted fever
Toxic shock syndrome

[a]Elevated body temperature alone is a common cause of headache. Symptoms should improve with the use of an antipyretic and lowering of the elevated body temperature.

Fever may be the only indication of a UTI in a young child. Up to 7% of febrile young children in whom no source is identified on physical examination have a UTI. In one study, up to 4% of young

febrile children younger than 2 years old who were found to have either acute otitis media or gastroenteritis as a source for fever, also had a UTI (20). A urinalysis and culture is recommended as part of the workup of girls younger than 2 years old, of circumcised boys up to 6 months of age, and of uncircumcised boys up to 12 months. A dipstick and microscopic urinalysis are insufficiently accurate to be used alone to evaluate the presence of UTI in young children and, a urine culture should be ordered as well (21). Enhanced urinalysis, defined as including either a Gram stain or cell count by hemocytometer, has a higher sensitivity and specificity than standard urinalysis for the diagnosis of a UTI; however, this type of testing is not available in all locations (21). (See Chapter 288.)

Pneumonia is rarely present without clinical signs of lower respiratory tract disease (22). Indications for a chest x-ray include tachypnea, retractions, nasal flaring, abnormal auscultatory findings, or a pulse oximeter reading of $<92\%$ (22). Occasionally, occult pneumonia may present only as abdominal pain and fever. (See Chapter 265.)

When no source for a fever is found on physical examination and pneumonia and UTI have been excluded by physical examination and laboratory tests, the possibility of occult bacteremia should be considered. Occult bacteremia is a concern because there is a potential for seeding other areas, and sequelae such as pneumonia, septic arthritis, and meningitis.

Since the late 1980s, three new childhood vaccines (HiB) and two pneumococcal vaccines (PCV-7 and PCV-13) have greatly reduced the incidence of serious bacterial infections, including occult bacteremia, due to these pathogens, and have changed our approach to the young child with significant fever and no apparent source (23,24). Before the advent of these vaccines, the incidence of occult bacteremia rate was 3% to 5%, and even higher in patients with an elevated WBC count or very high temperatures ($>40^{\circ}C$, $104^{\circ}F$). Management included blood cultures and empiric antibiotics until the results of blood cultures were known. Currently, there is increasing evidence that the incidence of bacteremia, and specifically the rate of pneumococcal bacteremia, has decreased to the point that

using testing and empiric treatment may no longer be justified (5,12,23,28).

In an otherwise healthy, well-appearing, febrile young infant or child with just two sets of the HiB and pneumococcal vaccines, blood cultures and empiric antibiotics are not recommended (25). For children with one or no vaccines against these organisms, occult bacteremia must be considered. But even for these "unprotected" febrile infants, lower rates of pneumococcal bacteremia are seen due to "herd" immunity (26).

Biomarkers such as the WBC count, absolute neutrophil count (ANC), and the C-reactive protein (CRP) have long been used to evaluate well-appearing febrile children without an obvious source of infection for the risk of occult infection such as bacteremia. Although of less utility because of the current very low rate of occult bacteremia, CRP appears to be more sensitive than the white count in identifying occult bacteremia and other serious bacterial infections. Procalcitonin appears to have approximately the same performance characteristics as CRP, but may be more sensitive in children who present within the first 6 to 8 hours of fever onset (27).

The decision to consider occult bacteremia also depends on the physician's experience, the infant's birth and past medical history, the prevalence of viral disease in the family or community, the duration of illness, and the family's ability to obtain follow-up.

KEY TESTING

Neonates (0 to 28 Days or Younger than 4 Weeks)

- Complete sepsis evaluation including LP, CBC, electrolytes, urinalysis, blood cultures, and urine cultures

Infants (29 to 60 Days or 4 to 8 Weeks)

- Complete sepsis evaluation including LP, CBC, electrolytes, urinalysis, blood cultures, and urine cultures guided by risk-stratification protocols*

Infants and Children Greater than 8 Weeks of Age

- Urinanalysis if indicated by history and degree of fever (see Chapter 288)

- Chest x-ray if indicated by history and presentation (see Chapter 265)

*Philadelphia, Boston and Rochester protocols.

CRITICAL INTERVENTIONS

- In febrile infants younger than 1 month of age, perform a complete evaluation for the source of the fever, including LP, and administer antibiotics.
- In febrile infants 1 to 2 months of age, perform a complete evaluation for the source of the fever. If empiric antibiotics are to be prescribed, an LP should be done prior to their administration.
- For ill-appearing or immunocompromised febrile infants and children, perform aggressive resuscitation and evaluation for the source of the fever and promptly initiate antibiotic treatment.
- Undress all febrile children: Petechiae may be an early indication of meningococcal disease.

DISPOSITION

Fever control with acetaminophen (15 mg/kg every 4 to 6 hours) or ibuprofen (10 mg/kg every 6 hours); cool, clear liquids; and light clothing are advised. The alternating administration of acetaminophen and ibuprofen for the management of fever is sometimes advocated by parents and health care providers, but no strong evidence supports this practice (32).

Although experimental evidence suggests that fever may be adaptive and stimulate the immune system, fever reduction has not proven to be deleterious and does lead to increased patient comfort and decreased metabolic demands and fluid loss. Control of fever is thus recommended.

Discharge instructions for febrile children should include indications for urgent return (Table 222.8). The most important indications for urgent reevaluation are lethargy and persistent irritability. Even with continued fever, if the child's behavior and disposition improve, urgent reevaluation is unnecessary. A child

younger than 2 months old or a child who has been given empiric antibiotics must be followed up in 12 to 24 hours by a primary care physician or other medical provider.

TABLE 222.8
Indications for Urgent Return for Reevaluation

Behavior
Persistent lethargy or irritability
Hydration Status
Signs of dehydration (decreased urine output, decreased tears)
Respiratory
Worsening cough
Difficulty breathing
Gastrointestinal
Persistent vomiting
Bilious vomiting
Worsening diarrhea
Other
New rash
Pain

Common Pitfalls

- Failing to carefully evaluate and document the child's general appearance.
- Failing to account for an infant's age in determining the extent of the fever evaluation.
- Overrelying on acute-phase reactants such as the WBC count or ANC instead of clinical assessment and observation.
- Failing to consider noninfectious disease processes as a cause for fever.

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CHAPTER 223 Vomiting

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Vomiting is the coordinated action of the pharyngeal, esophageal, stomach, and diaphragmatic musculature to expel gastric contents, directed by the medullary vomiting center within the central nervous system. This center receives input from the chemoreceptor trigger zone in the floor of the fourth ventricle and from higher cortical centers that receive and process external stimuli. Although vomiting may provide a survival advantage by expelling ingested toxins, it frequently occurs with disorders from a variety of organ systems (1).

Infants and children with vomiting commonly present to the emergency department (ED) for diagnosis and treatment. For most pediatric patients, vomiting is associated with relatively minor self-limited conditions, but it may also be a manifestation of serious surgical or medical illness. In the ED, the first priority must be to determine whether clinical stabilization is immediately required and whether an emergent surgical or medical condition exists. If no evidence of serious illness is identified, the next priority becomes recognizing and initiating therapy for the less urgent clinical conditions associated with vomiting.

CLINICAL PRESENTATION

The initial ED history and physical examination should identify and address any evidence of systemic illness or toxicity. Persistent vomiting with severe dehydration or metabolic abnormalities may require treatment prior to establishing a definitive diagnosis. Because pediatric vomiting may be a nonspecific symptom associated with severe systemic illness (e.g., meningitis, sepsis, respiratory distress,

drug overdose, closed head injury, ventriculoperitoneal shunt failure, etc.), the ED evaluation must consider or rule out these possible etiologies, based upon the initial history and physical examination.

The initial history must define whether the emesis is bilious or nonbilious. Bilious vomiting, containing dark green material from the biliary tract, generally indicates a mechanical or functional bowel obstruction below the ampulla of Vater. Nonbilious emesis implies either a more proximal obstruction in the duodenum or a functional disorder with no mechanical bowel obstruction (1). Yellow bile-stained emesis occasionally may occur with persistent vomiting and no bowel obstruction. This emesis is usually caused by a temporary reversal of gastric peristalsis. Fecal material in the emesis indicates a colonic obstruction, as in severe obstipation, Hirschsprung disease, or other large bowel disorders. Although studies have found that only 10% to 38% of infants and children presenting to the ED with bilious (either yellow or green) vomiting will ultimately be diagnosed with an emergent surgical condition, every child with bilious emesis must be assumed to have a bowel obstruction until proven otherwise (2–4).

The duration of vomiting, the number of episodes each day, and any additional gastrointestinal (GI) symptoms should be defined next, including abdominal pain, distention, anorexia, diarrhea, constipation, and presence of blood in the emesis or stools. The history should also note presence of systemic (fever, weight loss, nutritional status, hydration status), neurologic (headache, neck pain or stiffness, coordination or behavioral changes), genitourinary (dysuria, hematuria, change in urine output, vaginal discharge or bleeding), respiratory (cough, evidence of distress), or head and neck (otalgia, sore throat, dysphagia, nasal drainage) symptoms to further direct care and diagnostic evaluation. A past history of similar severe episodes of vomiting may lead to the diagnosis of a recurring condition, such as cyclic vomiting, an inborn error of metabolism, or malrotation with intermittent volvulus; a history of early morning vomiting should raise concerns for an intracranial mass lesion (1).

The physical examination should initially seek evidence of systemic toxicity, including respiratory or cardiovascular instability,

altered mental status, or severe dehydration. A validated pediatric scoring tool for the clinical assessment of dehydration using a combination of four objective physical findings (dry mucous membranes, absent tears, abnormally lethargic or restless appearance, prolonged capillary refill) has proven to be helpful in the recognition of dehydration, with two of four findings present with 5% dehydration, and three or more present with more severe states of dehydration (5–7).

On abdominal examination, auscultation for bowel sounds prior to palpation may reveal diminished activity with ileus arising from surgical or medical illness, or increased activity (borborygmi) with partial bowel obstruction or a diarrheal disorder. Next, palpation for abdominal tenderness, distention, mass, or enlargement of the liver or spleen should be performed. Gentle one- or two-finger percussion, rather than the less accurate gross abdominal wall movement with the compression-rebound technique, may demonstrate peritoneal findings associated with surgical conditions such as appendicitis. Finally, a thorough general evaluation for nonabdominal conditions associated with vomiting, including the head and neck, pulmonary, genitourinary, and neurologic examination, may identify the etiology and direct or obviate further diagnostic workup.

DIFFERENTIAL DIAGNOSIS

While viral gastroenteritis is one of the most common causes of vomiting for infants and children of all ages, the differential diagnosis for vomiting varies according to age at presentation. Table 223.1 outlines an age-based differential diagnosis for surgical and medical etiologies of pediatric vomiting.

TABLE 223.1
Age-Based Differential Diagnosis for Vomiting

All Ages

Surgical

- Appendicitis
- Bowel obstruction (adhesions from previous surgery)
- Malrotation with intermittent volvulus
- Incarcerated inguinal hernia
- Closed head trauma (accidental or abuse)
- Abdominal trauma (accidental or abuse)
- Ventricular peritoneal shunt failure

Medical

- Generalized sepsis
- Meningitis, encephalitis
- Hepatitis
- Toxin ingestion/drug overdose
- Urinary tract infection
- Viral or bacterial gastroenteritis

Infant

Surgical

- Pyloric stenosis
- Congenital GI anomalies (intestinal stenosis or duplication, duodenal or antral webs, annular pancreas, etc.)
- Malrotation with volvulus
- Hirschsprung disease
- Intussusception
- Necrotizing enterocolitis

Medical

- Gastroesophageal reflux
- Head and neck (upper respiratory infections, sinusitis, otitis media, pharyngitis, stomatitis)
- Respiratory distress (bronchiolitis, pneumonia, asthma, pertussis, aspiration in the developmentally impaired)
- Viral or bacterial gastroenteritis
- Urinary tract infection
- Metabolic conditions (inborn errors of metabolism, renal tubular acidosis, congenital adrenal hyperplasia)

Child

Surgical

- Appendicitis
- Intussusception
- Cholecystitis
- Intracranial (occult closed head injury, abuse, hydrocephalus, mass, hemorrhage)

Medical

- Viral or bacterial gastroenteritis
- Metabolic (type 1 diabetes, diabetic ketoacidosis)
- Renal (insufficiency, ureteropelvic junction obstruction, nephrolithiasis)
- Adrenal insufficiency
- Henoch–Schönlein purpura
- Drug/toxin accidental ingestion
- Pancreatitis
- Urinary tract infection
- Inflammatory bowel disease
- Neurologic (migraine headaches, seizure variants)
- Cyclic vomiting
- Peptic ulcer disease

Adolescent

Surgical

- Appendicitis
- Ovarian (torsion, cysts)
- Cholecystitis

Medical

- Pregnancy (ectopic or intrauterine)
- Pelvic inflammatory disease
- Drug/toxin overdose
- Viral or bacterial gastroenteritis
- Metabolic (type 1 diabetes, diabetic ketoacidosis)
- Renal (insufficiency, ureteropelvic junction obstruction, nephrolithiasis)
- Adrenal insufficiency
- Pancreatitis
- Urinary tract infection
- Inflammatory bowel disease
- Neurologic (migraine headaches, seizure variants)
- Cyclic vomiting
- Peptic ulcer disease

For the infant from birth to 2 months of age, the most common condition associated with vomiting is gastroesophageal reflux, often resulting from overfeeding; it typically occurs within 30 to 60 minutes of feeding in an otherwise healthy-appearing infant. Occult gastroesophageal reflux may present as positional fussiness, persistent cough and congestion, or truncal arching (Sandifer syndrome) that may mimic tonic seizure activity. Reflux precautions, including formula thickened with rice cereal, small frequent feedings, and upright positioning for 30 minutes after feedings, will effectively treat the majority of infants. Persistent reflux may require medical therapy (8).

Pyloric stenosis is the most common surgical condition that must be differentiated from gastroesophageal reflux in vomiting infants.

Most affected infants present at 3 to 4 weeks of age, with a history of 1 to 2 weeks of progressive forceful “projectile” nonbilious vomiting. With more advanced disease, there may be weight loss from severe dehydration. While palpation of the hypertrophied pylorus or “olive” is diagnostic, the physical examination is often nonspecific, and an ultrasound is generally required for definitive diagnosis in younger infants (9,10). ED treatment includes prompt evaluation for electrolyte disturbances (the classic presentation with hypochloremic metabolic alkalosis has become increasingly rare) and intravenous (IV) fluid rehydration, with surgical referral for suspected cases (9).

Other emergent surgical causes of vomiting in the first 2 months of life include congenital GI anomalies (intestinal stenosis or duplications, duodenal or antral webs, annular pancreas, etc.), incarcerated inguinal hernia, malrotation with volvulus, and Hirschsprung disease. Most UGI congenital anomalies present within the first few days of life and are infrequently seen in the ED setting. An inguinal hernia may be noted on examination of the diaper area, with the presence of an inguinal, scrotal, or labial mass. Steady and gentle pressure at the external inguinal ring and on the mass can successfully reduce the majority of hernias. However, some patients may require sedation and surgical consultation if the initial ED attempt is unsuccessful.

The young infant presenting to the ED with bilious emesis (even one episode) must, without exception, be assumed to have GI malrotation with volvulus until proven otherwise. Eighty-five percent of patients with volvulus present in the first year of life, and 60% of patients present within the first month of life. The abdominal examination may be normal in up to 75% of cases, but diminished bowel sounds, distention, a palpable mass, or tenderness may be noted in 10% to 25% of infants with volvulus (3). Hypovolemic shock from prolonged intestinal ischemia is uncommon at presentation, but must be considered in the moribund infant. Immediate evaluation with a UGI series (a contrast enema may miss the diagnosis in up to 20% of patients) is required for all suspected cases, with emergent surgical consultation and laparotomy for any symptomatic patient with an identified malrotation (1,3,11).

Hirschsprung disease, or aganglionosis, is a fairly common cause of intestinal obstruction in newborns, infants, or young children. It occurs in 1 in 5,000 live births, and more than 80% of cases are diagnosed within the first year of life. Up to 90% of infants with Hirschsprung disease have a history of failure to pass meconium in the first 24 hours of life, making this an important historical question for any child presenting with abdominal pain. Hirschsprung is due to a congenital absence of ganglion cells in the colonic submucosa, resulting in uncoordinated intestinal contractions which manifest clinically as chronic constipation, abdominal distention, and vomiting. Abdominal radiographs may demonstrate dilated proximal bowel loops with air-fluid levels; a contrast enema may be diagnostic in more than 80% of cases. ED treatment consists of IV fluid resuscitation, nasogastric (NG) decompression, broad-spectrum antibiotics (with anaerobic coverage), and surgical consultation for confirmatory biopsy and corrective surgery (12). Even after corrective surgery, toxic megacolon or enterocolitis remains a significant concern, occurring in more than one-third of Hirschsprung patients because of retained aganglionic segments of bowel. Enterocolitis may present as abdominal distention, foul watery diarrhea, lethargy, or systemic toxicity, and must be recognized and treated early with aggressive supportive care, including broad-spectrum antibiotics and rectal irrigation (12).

Many other medical conditions may cause vomiting in young infants. Infections such as sepsis, meningitis, encephalitis, hepatitis, pharyngitis, stomatitis, or otitis media may present with vomiting as an initial symptom. Gastroenteritis is common year-round, with seasonal peaks during summer and winter viral outbreaks. Urinary tract infection is the most common bacterial source for a fever in infants with a normal physical examination, and may present with vomiting and no diarrhea (13). Respiratory distress from pertussis, pneumonia, asthma, bronchiolitis, or aspiration in the developmentally impaired patient may also be noticed only after the infant has been vomiting.

Intracranial pathology, from occult closed head injury, abuse, hydrocephalus, or hemorrhage may present with neurologic findings

and associated vomiting. Victims of nonaccidental trauma involving occult head trauma or abdominal trauma may present with vomiting. Only with careful history taking and consideration of abuse as an etiology will these cases be detected (see Chapter 290). Patients with indwelling ventricular peritoneal shunts (see Chapter 291) may present with vomiting as their only sign of increasing intracranial pressure (ICP) with shunt failure.

Finally, metabolic conditions such as inborn errors of metabolism, renal tubular acidosis, and congenital adrenal hyperplasia may present as vomiting with metabolic acidosis, hypoglycemia, hyperammonemia, or hyperkalemia in combination with hyponatremia (14,15). While a number of the conditions outlined previously may also affect the older infant or child, gastroesophageal reflux, congenital anomalies, and inborn metabolic disorders become less likely with increasing age.

Two common surgical disorders to consider in the older infant or child with vomiting are appendicitis and intussusception. While only 10% of appendicitis occurs in children younger than 10 years of age, and only 1% in infants younger than 2 years, it remains the most frequent indication for emergent pediatric surgery. The “classic” findings of right lower quadrant abdominal pain, vomiting, and fever are uncommon in younger patients, who may have an atypical history of diarrhea or respiratory distress, evidence of generalized sepsis, or atypical laboratory findings at presentation (16). Because of the nonspecific nature of such symptoms and perhaps a more rapid progression to perforation, appendicitis in the child younger than 4 years of age is often associated with an 80% perforation rate at the time of diagnosis and a significant mortality risk among younger infants. Older children may be more likely to have the classic presentation of appendicitis, and may be appropriate for surgical consultation and clinical diagnosis.

While contrast pelvic computed tomography (CT) scan has been quite accurate for the diagnosis of pediatric appendicitis, recent research has attempted to improve appendicitis diagnostic accuracy, while limiting CT scan utilization and its associated radiation risk. A multicenter-validated prediction rule using an absolute neutrophil

count $\leq 6.75 \times 103$ μL with either no maximal tenderness in the right lower abdominal quadrant, or absence of pain with walking or jumping, was able to identify children at low risk of appendicitis with 98% sensitivity, patients who may be appropriate for further clinical observation (17). If imaging is utilized for the diagnosis of appendicitis, a staged approach using US, followed by CT scan if negative or equivocal, has been found to be both very sensitive for the diagnosis, and cost-effective, while limiting radiation exposure (18,19).

Intussusception, from a spontaneous invagination of the intestine upon itself, compromises the vascular supply to the inner segment or intussusceptum. Approximately 95% of intussusception is ileocolic, beginning at the ileocecal valve; the remaining 5% are ileoileal or occur within the colon or sigmoid. Sixty-five percent of intussusception occurs in infants younger than 1 year of age, most frequently (45%) between 5 and 9 months of age (20). The typical infant presents with sudden onset of intermittent severe abdominal pain and vomiting and may appear well between episodes. Bilious vomiting, lethargy, passage of bloody mucus or "currant-jelly" stool, peritonitis, or evidence of cardiovascular compromise are often late findings that indicate more advanced intestinal ischemia, which may require surgical resection (21). The abdominal examination may identify a palpable mass but is usually normal, often with only a positive stool guaiac test to confirm the clinical suspicion for intussusception; abdominal radiographs are generally normal or nonspecific (22). Ultrasound or air-contrast enema is diagnostic for nearly 100% of cases. Air-contrast enema allows therapeutic reduction of the intussusception, and is associated with successful reduction in up to 90% of pediatric cases (23).

In older infants and children, vomiting may be due to a number of medical conditions, including endocrinologic disorders such as new-onset type 1 diabetes, which may present as diabetic ketoacidosis, or renal and adrenal insufficiency. Henoch–Schönlein purpura (HSP), with its characteristic vasculitic lesions concentrated on the lower extremities, may cause abdominal pain and vomiting associated with HSP's increased risk for intussusception.

A number of other conditions, both common and uncommon, may also need to be considered. In accidental drug ingestion in the exploring toddler or intentional overdose in the adolescent, vomiting may be associated with toxin-specific findings. Pancreatitis, cholecystitis, inflammatory bowel disease, and nephrolithiasis, most often seen in older patients, may also present with frequent vomiting. Migraine, cyclic vomiting, and some seizure variants may cause recurrent vomiting episodes (24). Pregnancy (intrauterine and ectopic), ovarian cysts, torsion, and pelvic inflammatory disease must be considered in the differential of the vomiting adolescent female.

DIAGNOSTIC APPROACH

The initial ED therapy for the vomiting infant or child must focus on identifying and managing any evidence of systemic toxicity. Patients with clinical evidence or concern for increased ICP or occult abdominal injury should be stabilized and imaged emergently. Most well-appearing or mildly ill-appearing children without severe abdominal pain, bilious vomiting, or evidence of medical or surgical emergency can be managed with a trial of oral hydration with clear liquids, facilitated with oral ondansetron. However, in children with evidence of clinical instability, prompt IV access should be established, with fluid administration of 20 mL/kg boluses of isotonic normal saline or lactated Ringers solution, and repeated boluses as needed. Analgesics should be administered early in the child being evaluated for appendicitis or other painful conditions; well-designed prospective pediatric studies have found no adverse effects of ED pain control on diagnostic accuracy or clinical outcomes (25). Surgical consultation should be arranged for all patients with suspected surgical conditions, evidence of peritonitis, or unstable trauma prior to reaching a definitive diagnosis.

Initial diagnostic laboratory studies generally include serum electrolytes, glucose, and renal function tests when there is clinical evidence of moderate to severe dehydration. A bedside glucose measurement should be obtained in unstable patients with altered mental status or in whom undiagnosed diabetes is in the differential

diagnosis. In the mildly dehydrated child the bedside glucose may be the only test needed. Additional tests may also be indicated for more severely ill children including a complete blood count (CBC) with a type and cross-match for surgical patients, liver function tests, lipase test for undiagnosed pancreatitis or gall bladder disease, and a urinalysis and urine culture for the febrile patient with a possible urinary tract infection.

After initial stabilization, diagnostic imaging may be necessary to identify the cause of vomiting. A chest x-ray should be considered in the patient with respiratory symptoms and may lead to the diagnosis of pneumonia. If the infant or child is suspected of having bowel obstruction, ileus, or mass, or with evidence of peritonitis, flat and upright abdominal x-rays may confirm the diagnosis and direct further care. For the young infant with bilious vomiting, the initial test of choice is unquestionably the UGI series, which is more sensitive for the diagnosis of malrotation than contrast enema studies. However, confirmatory studies must not delay an emergent surgical consultation in this situation. The contrast enema may be both diagnostic and therapeutic for the older infant or toddler with a suspected intussusception, although ultrasound is often the preferred initial diagnostic test. A contrast enema may also diagnose Hirschsprung disease in the infant with chronic constipation, demonstrating a funnel-shaped transition zone at the border between the normal and abnormal bowel segments. Ultrasound is often helpful in diagnosing pyloric stenosis, appendicitis, intussusception, ureteropelvic junction obstruction, and gynecologic disorders. Appendicitis may be diagnosed by ultrasound or a pelvic CT scan, though a staged approach with an initial US is recommended to minimize the radiation exposure associated with CT (18,19). CT scan is, however, the test of choice for the evaluation of abdominal masses, nephrolithiasis, abdominal trauma, and intracranial pathology.

CRITICAL INTERVENTIONS

- Address clinical instability prior to efforts at definitive diagnosis.

- Check a bedside serum glucose in the infant or child with altered mental status or other evidence of systemic toxicity.
- Give stress-dose corticosteroids (hydrocortisone 25–100 mg IV bolus) to the ill-appearing steroid-dependent patient as soon as possible.
- Consider bilious vomiting or evidence of peritonitis to be caused by an emergent surgical condition until proven otherwise.

DISPOSITION

For the vomiting infant or child with a self-limited condition, no evidence of serious systemic illness, and only mild or moderate dehydration, ED oral hydration with continued outpatient oral rehydration is appropriate, along with defined discharge instructions and a clear follow-up plan. IV fluid rehydration should be utilized for the vomiting patient who cannot tolerate oral fluids, with demonstrated electrolyte abnormalities, or with more severe illness. Recent well-designed prospective pediatric studies have demonstrated a benefit from the administration of oral or IV ondansetron with ED rehydration, noting a significant reduction in continued vomiting, improved tolerance of oral fluid challenges, and reduced hospital admission rates (26–28). While two 20 mL/kg IV isotonic fluid boluses may improve most mildly dehydrated patients enough to make them safe for discharge, those with persistent vomiting, and significant serum electrolyte or glucose abnormalities may benefit from continued inpatient rehydration and observation.

Common Pitfalls

- Overzealous use of laboratory studies and IV fluids in well-appearing children with vomiting; many can be managed with oral hydration and oral ondansetron as needed.
- Forgetting to assess for hypoglycemia in a vomiting infant or child. A rapid glucose test should be checked with the first blood draw.
- Failing to aggressively evaluate and treat the young infant with bilious emesis, even if physical examination and laboratory

studies appear normal. Do not miss the diagnosis of malrotation.
- Overlooking subtle presentations of occult injury in patients with nonaccidental trauma, accidental or intentional ingestions, and ventriculoperitoneal shunt failures.

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CHAPTER 224
Diarrhea

Jeahan H. Colletti and James E. Colletti

Diarrheal illness continues to be a significant cause of pediatric morbidity and mortality. Worldwide diarrheal illnesses are the second leading cause of mortality in children under 5 years of age, accounting for approximately 1.5 million deaths per year (1).

CLINICAL PRESENTATION

The most common presenting etiology of diarrhea in children is infectious gastroenteritis, with viral agents accounting for 75% of cases. Acute diarrhea typically lasts less than 2 weeks, and the history is one of a distinct change in stool frequency, volume, and color. The stools may be less well-formed and yellowish, loose and green, or watery and voluminous. The presence of bloody, mucoid stools increases the possibility of a bacterial cause. Vomiting is common, especially with viral disorders. However, bilious vomiting requires close attention and raises the possibility of intestinal obstruction. Intussusception may complicate an otherwise mild gastroenteritis. Low-grade fever is common, but fever in excess of 40°C suggests a bacterial etiology.

Important history includes antibiotic use, recent travel, or other exposures such as daycare, pets, or an unsanitary water supply. The patient's prior weight, duration of illness, and associated signs and symptoms, such as fever, abdominal pain, vomiting, rash, seizures, and activity level, can aid in determining the degree and severity of dehydration. A vital component of the history is the type of oral intake given to the child. The use of hyperosmolar fluids, such as carbonated soft drinks, apple juice, or excess sodium due to improper

formula preparation, can result in hypernatremia, whereas hypotonic fluid replacement can result in hyponatremia.

Assessment for signs of dehydration is of vital importance Infants may become critically dehydrated over a period of only a few hours and present with shock. As the vascular space contracts, the extremities become cool with decreased distal pulses, and alterations in mental status occur. Gorelick et al. (2) discovered that the findings of three or fewer of the clinical signs of dehydration correlated with a 5% fluid deficit, three to five signs correlated with 5% to 9% dehydration, and more than six signs with a fluid deficit of 10% or greater. In general, the diagnosis of dehydration is improved by the presence of multiple signs or through the use of clinical scales.

Parental reporting has been found to accurately predict degree of dehydration as well as clinically significant acidosis (3). A parental report of a normal tearing state is associated with a reduced likelihood of significant dehydration and acidosis. Moreover, parental reporting of a sunken fontanelle and decreased tears are associated with an increased likelihood of hospital admission (3).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of diarrheal illness is broad. Diarrhea may accompany almost any pediatric illness at any given point in its course. The differential diagnosis may be categorized as acute or chronic. There may be important diagnostic clues based on the child's age, character of the stool, associated symptoms, and effect on the child's general health.

The most common causes of acute and chronic diarrheal disease are listed in Table 224.1. The vast majority of acute diarrheal illnesses are viral. Before the introduction of the rotavirus vaccines, rotavirus was the leading cause of severe acute gastroenteritis (AGE) in US children less than 5 years of age. Since the introduction of the vaccines in 2006, there has been a significant (60% to 65%) reduction in the number of rotavirus-associated hospitalizations (4). With the reduction in rotavirus-associated diarrhea, the Noroviruses have become the leading cause of AGE in children.

TABLE 224.1
Common Causes of Acute and Chronic Diarrheal Illness

Common Causes of Acute Diarrheal Illness	Causes of Chronic Diarrheal Illness
Bacterial	
Campylobacter	Urinary tract infection
Salmonella	
Shigella	
Yersinia	
Escherichia coli	
Clostridium perfringens	
Clostridium botulinum	
Clostridium difficile	
Cholera	
Staphylococcus aureus	
Aeromonas	
Viral	
Rotavirus	
Norwalk virus	
Adenovirus	
Calicivirus	
Astrovirus	
Torovirus	
Parasitic	
Giardia lamblia	*Giardia lamblia*
Cryptosporidium	
Entamoeba histolytica	
Other	
Medication-induced	Postinfectious disaccharide intolerance
Parenteral: otitis media, upper-respiratory infection, urinary tract infection	Irritable bowel syndrome
Food intolerance	Milk or soy protein intolerance
Psychogenic: anxiety	Food allergy
Necrotizing enterocolitis	Maternal deprivation syndrome
Cystic fibrosis	Cystic fibrosis
Adrenal insufficiency	Celiac disease
Organophosphates	Immunodeficiency disorders
Heavy metals (iron)	Short bowel syndrome (postoperative)
Hirschsprung disease	Inflammatory bowel disease
Intussusception	Tumors (neuroblastoma, carcinoid)
	Stagnant loop syndrome
	Acrodermatitis enteropathica
	Adrenal insufficiency or hyperthyroidism
	Chronic constipation with overflow diarrhea

Adapted from Vanderhoof JA. Chronic diarrhea. *Pediatr Rev*. 1998;19:418–422.

ED EVALUATION AND MANAGEMENT

The goals of diarrhea management include prevention of dehydration by early fluid administration, treatment of dehydration with an oral rehydration solution (ORS), continued feeding during the diarrhea, selective use of antibiotics, and avoidance of antidiarrheal medications (5,6).

A thorough history should determine acute or chronic status. Preliminary studies that may be indicated for chronic diarrhea include a stool examination for blood, parasites, culture, Sudan fat stain, and alpha-1-antitrypsin. If there is significant dehydration or failure to thrive, the child should be hospitalized. Otherwise, the patient should be referred to a pediatrician for further evaluation.

If the diarrhea is acute, the primary concern is for dehydration, acidosis, electrolyte disturbances, shock, or associated sepsis. The physical examination indicates the degree of dehydration (Table 224.2). The serum bicarbonate level may occasionally also prove useful. A bicarbonate concentration of <17 mEq/L, when considered along with clinical parameters may improve accuracy in determining the presence of moderate to severe dehydration (7,8). Conversely, a bicarbonate concentration of >15 or 17 mEq/L decreases the likelihood of dehydration (9). Furthermore, a bicarbonate of ≤ 13 mEq/L is associated with a need for prolonged IV fluid replacement (3,10). Other than a guaiac test or culture, stool studies such as fecal leukocytes, Rotazyme, pH, reducing substances, and ova and parasites are usually not helpful in the emergent setting.

TABLE 224.2
Estimating Degree of Dehydration

Symptom	Minimal or No Dehydration (<3% Loss of Body Weight)	Mild to Moderate Dehydration (3%–9% Loss of Body Weight)	Severe Dehydration (>9% Loss of Body Weight)
Eyes	Normal	Sunken slightly	Sunken deeply
Tears	Present	Diminished	Absent
Mouth and tongue	Moist	Dry	Parched
Thirst	Drinks normally	Eager to drink	Drinks poorly; unable to drink
Heart rate	Normal	Normal to increased	Tachycardia, with bradycardia in most severe cases
Quality of pulses	Normal	Normal to decreased	Weak, thready, or impalpable
Extremities	Warm and well perfused	Cool	Cold; mottled; cyanotic
Capillary Refill	Normal	Prolonged	Minimal
Respiration	Normal	Normal to fast	Deep
Skin fold	Recoils instantly	Recoil in less than 2 sec	Recoil in greater than 2 sec
Level of alertness	Alert	Normal to fatigued or restless, irritable	Lethargic, unconscious
Urine output	Normal to decreased	Decreased	Minimal

Adapted from Duggan C, Santosham M, Glass RI. The management of acute diarrhea in children: Oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep*. 1992;41(No. RR-16): 1–20; World Health Organization. The treatment of diarrhoea: A manual for physicians and other senior health workers. Geneva, Switzerland: World Health Organization; 1995. Available online at http://www.who.int/child-adolescent-health/New_Publications/CHILD_HEALTH/WHO.CDR.95.3.htm; Colletti JE, Brown KM, Sharieff GQ, et al. The mangement of children with gastroenteritis and dehydration in the emergency department. *J Emerg Med*. 2010;38(5):688–698.

KEY TESTING

- Well-appearing child with minimal or no dehydration—no testing
- Ill-appearing child or signs of significant dehydration—electrolytes (serum bicarbonate and glucose levels of particular interest)
- Febrile child with bloody stools—stool culture

Dehydration exceeding 5% to 10%, or significant electrolyte disturbances, are considerations for admission. Rehydration should begin in the emergency department (ED). In children who are mildly to moderately dehydrated and refusing oral intake, a nasogastric tube can be placed to initiate replacement therapy. An investigation by Nager and Wang (11) examined rapid nasogastric hydration and rapid intravenous hydration and determined them to be safe, efficacious, and cost-effective alternatives to standard therapy for moderately dehydrated children. When rapid nasogastric hydration was compared to rapid intravenous hydration, there was no significant difference. In this trial, rapid nasogastric hydration was achieved by administering a continuous infusion of 50 mL/kg of Pedialyte over 3 hours, and rapid intravenous hydration was performed by a continuous infusion of 50 mL/kg of normal saline over 3 hours.

In severely dehydrated children, intravenous normal saline boluses of 20 cc/kg should be initiated, with repeat boluses as needed to restore intravascular volume. It is common to administer 60 to 80

cc/kg in the initial phase of fluid resuscitation. Close monitoring of the pulmonary status and urine output is important in children with underlying cardiac or pulmonary conditions. Once intravascular volume has been restored, dextrose-containing maintenance fluid should be initiated. Potassium replacement should continue until the patient is spontaneously voiding and is known to have normal renal function.

In mild to moderate dehydration, oral rehydration therapy (ORT) should begin with a commercially available ORS. ORT is an inexpensive, effective therapy for dehydration that is underutilized in the United States (12). In mildly to moderately dehydrated children, ORT is as effective as IV therapy. Furthermore, ORT has been found to be associated with higher parental satisfaction and decreases in both length of stay and staff time (6,12).

Homemade solutions and electrolyte-glucose beverages for athletes should be avoided the former because serious errors may be made in preparation and the latter because they contain too little sodium, too much sugar, and almost no potassium. The use of carbonated beverages, apple juice, and Jello water should also be discouraged, as they consist of high concentrations of carbohydrates and low concentrations of required electrolytes. The high osmotic load of these fluids often results in an *increase* in stool output, and their low sodium content may contribute to hyponatremia (13,14). Each liter of a commercial ORS contains about 45 to 75 mEq sodium, 20 to 25 mEq potassium, 2% glucose, and a mixture of chloride and base as anions (Table 224.3). This ratio of electrolytes and glucose promotes the coupled mucosal transport of sodium and glucose, with water absorption following.

TABLE 224.3
Contents of Commercial Oral Rehydration Solutions

Solution	Na (mEq/L)	K (mEq/L)	Other (mEq/L)	Cl (mEq/L)	Base (mEq/L)	Carbohydrate (g/L)
Pedialyte	45	20	—	35	30	25
Rehydralyte	75	20	—	65	30	25
Infalyte	50	25	—	45	34	30
Resol	50	20	8	50	34	20
WHO solution	90	20	—	80	30	20

Adapted from Stone B. Fluids and electrolytes. In: Robertson J, Shilkofski N, eds. *The Johns Hopkins Hospital: The Harriet Lane Handbook*. 17th ed. Philadelphia, PA: Mosby; 2005. King CK, Glass R, Bresee JS, Duggan C. Managing acute gastroenteritis among children: Oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep* 2003;52(RR-16):1–16.

If oral rehydration is chosen, it is best started during an extended period of monitored therapy in the ED, and it may be implemented in any child who can drink and is not in shock. The efficacy of ORT has been established even in the child with emesis accompanying diarrhea. In these children, ORT should be administered in small frequent doses (5 mL q1–2 min) (13,14). Table 224.4 lists a program for mild to moderate dehydration. Table 224.5 lists contraindications to ORT.

TABLE 224.4
Emergency Department (ED) Management of Acute Diarrhea with Mild to Moderate Dehydration

Estimate daily fluid requirements and degree of dehydration

Maintenance: 100 mL/kg for first 10 kg body weight, 50 mL/kg for each additional kg over 11–20 kg, and 20 mL/kg for each kg over 20 kg

Deficit requirement for 5% dehydration is 50 mL/kg

While patient is being monitored in the ED, give 50–100 mL/kg ORS over 4 hrs. ORS is best tolerated as small, frequent volumes rather than larger boluses. If vomiting occurs, give the solution 1–2 teaspoons every 5–10 min

Replace ongoing losses <10 kg body weight: 60–120 cc ORS for each diarrheal stool or episode of emesis; >10 kg body weight: 120–240 cc ORS for each diarrheal stool or episode of emesis

If stable and retaining fluids, the child may be discharged after deficit fluid is replaced, with phone contact 4–6 h later

After initial hydration continue breastfeeding or resumption of an age-appropriate diet

TABLE 224.5
Restrictions to ORT Administration

Hemodynamic shock
Obtunded mental status
Abdominal ileus
Bowel obstruction

ORT consists of two phases of therapy. The first is the rehydration phase, in which fluid and electrolytes are restored. Ideally the first phase is completed within a 3- to 4-hour period. The second phase is the maintenance phase, which includes the replacement of ongoing electrolyte and fluid losses as well as ensuring dietary intake.

After successful oral rehydration, a prompt return to age-appropriate diet is indicated. It should be stressed to parents that the objective is to “feed through” the diarrhea, and that loose stools will persist for a few days but should decrease in volume and frequency (15). Continued feeding is safe and may reduce the duration and volume of diarrhea (14). Early refeeding has not been shown to increase the risk of unscheduled parenteral fluid administration, emesis episodes, or the development of persistent diarrhea (16). In general, smaller but more frequent feedings should be given so that the total daily intake approaches normal (5).

Restricted and progressive diets are no longer recommended (17). Breast-fed infants may continue to feed on demand through both the rehydration and maintenance phases of management. Infants who are bottle-fed should stop feeds during rehydration but should restart them with full-strength formula once the rehydration phase is complete. Restarting full-strength formula allows for a return to full caloric intake. Lactose-free formulas are generally not necessary but may be useful in children who are malnourished, have a severe enteropathy, or have persistent lactose intolerance (17). For older children on a mixed diet, the traditional bland diet of bananas, rice or rice cereal, applesauce, and toast (commonly called the BRAT diet) is no longer recommended. To date, there are no studies to support the use of a bland diet and moreover, the BRAT diet is unnecessarily restrictive and provides suboptimal nutrition (17). Therefore, once hydration has been reestablished, the child’s usual preferred and age-appropriate diet should be resumed, although the

BRAT diet may be incorporated into the child's regular diet if desired. Carbonated soft drinks, juice, gelatin desserts, and foods with significant amounts of simple sugars should be avoided, as the osmotic load may increase the diarrhea.

Most episodes of diarrhea do not require antimicrobial therapy, as the predominant cause of acute diarrhea is viral. Moreover, even when a bacterial etiology is responsible, the majority of acute diarrheal cases are self-limited, and the duration of illness is not shortened by antibiotic therapy. However, antimicrobial therapy should be considered in immunosuppressed children, premature infants, septic infants, those with a toxic appearance, or children with underlying disorders (17).

Bloody diarrhea with PMNs probably represents a bacterial cause, and antibiotic therapy may be considered if *Escherichia coli* O157:H7 and *Salmonella* have been excluded. The association of antibiotic therapy in children with *E. coli* 0157:H7 and the development of hemolytic uremic syndrome (HUS) is controversial. It is currently unknown whether empiric antibiotic therapy increases the risk of HUS (18). A few investigations have reported an increased risk of HUS with empiric antibiotic therapy (19,20). In contrast, others have reported a protective effect or a lack of association (21–23). Therefore, the physician contemplating empiric antibiotic therapy for bloody diarrhea should give careful consideration to the possibility of *E. coli* 0157:H7 infection and the potential for an increased risk of HUS with antibiotics.

Generally, antibiotics should be avoided in *Salmonella* gastroenteritis, but exceptions include certain populations prone to *Salmonella* bacteremia, such as in infants younger than 3 months old and in patients with immunodeficiency, a history of chronic gastrointestinal tract disease, or hemoglobinopathies (5). These high-risk patients should be admitted and given intravenous antibiotics.

In cases where *E. Coli* 0157:H7 and *Salmonella* have been excluded and antimicrobial therapy is required, initial antibiotic selection should be adjusted based on stool culture and sensitivity results (Table 224.6).

TABLE 224.6
Antibiotic Therapy Based on Etiology

Organism	Indications	Therapy
Shigella	Majority are self-limited and do not require antimicrobial agents.	77% of *Shigella* are resistant to ampicillin and 37% resistant to trimethoprim–sulfamethoxazole (TMP/SMX)
	Antibiotics are recommended for: Severe disease	Management depends on susceptibility
	Dysentery	*Shigella* susceptible strains:
	Immunocompromised	TMP/SMX: 8 mg/kg/d divided bid based on the TMP component
		Resistant stain or unknown susceptibility:
		Ceftriaxone: 50–75 mg/kg/d IV divided bid for 5 d
		Azithromycin: 12 mg/kg/d PO for 5 d
Salmonella	Overall antibiotics should be avoided	Ampicillin 200 mg/kg/d IV divided bid for 7–10 d and gentamicin 6–7.5 mg/kg/d IV divided tid
	Antibiotics and hospital admission are recommended for:	
	Infants >3 mos old	
	Immunocompromised	
	Hemoglobinopathies	
C. jejuni		Resistant to TMP/SMX, and should be treated with Erythromycin: 30–50 mg/kg/d divided tid PO for 5–7 d
		Azithromycin for 12 mg/kg/d PO for 5–7 d
Giardia	Presence of *Giardia* on stool testing	Metronidazole: 15 mg/kg/d divided tid for 5–7 d
		Metronidazole has a cure rate of 80–95%.
		Tinidazole: 50 mg/kg once with maximum dose of 2 g
C. difficile	*C. difficile* cytotoxin found in stool	Discontinue any current antibiotics
		In the presence of severe diarrhea or diarrhea that persists despite discontinuation of antibiotics:
		Metronidazole: 30 mg/kg/d divided qid
		Vancomycin: 40 mg/kg/d divided qid for 10 d maximum dose of 500 mg is indicated for cases that do not respond to metronidazole. Vancomycin administration is discouraged secondary to promotion of vancomycin resistant organisms

From American Academy of Pediatrics, Pickering LK, ed. *2006 Red Book: Report of the Committee on Infectious Diseases*, 27th ed. Elk Grove Village, IL: Author; 2006.

The American Academy of Pediatrics does not recommend the use of antiemetic, antisecretory, or antiperistaltic drugs (6). There is a growing body of evidence that *selective* use of antiemetics (particularly ondansetron) may be effective in decreasing the rate of vomiting, improving the success rate of oral hydration, preventing the need for IV hydration, and preventing the need for hospital admission in those receiving IV hydration (see Chapter 223).

The use of narcotic-based agents is specifically contraindicated in bacterial gastroenteritis because they may induce bowel stasis and promote more aggressive bacterial invasion. Some of the adverse events associated with use of such antidiarrhea agents in the pediatric population are ileus, lethargy, and death. A systematic review and meta-analysis found the risks to outweigh the benefits of loperamide, specifically in children less than 3 years of age, in those that are malnourished, moderately or severely dehydrated, or systemically ill, and in the presence of dysentery (24).

Parents should be instructed on hygienic precautions for diaper handling and good hand-washing practices. Strict hand-washing techniques have been demonstrated to reduce the incidence of acute infectious diarrhea in daycare facilities (25). The child should be excluded from the daycare center if there is diarrhea not contained by diaper or toilet use, if stools contain mucus or blood, or if there is associated fever.

CRITICAL INTERVENTIONS

- Recognition and correction of dehydration, acidosis, electrolyte disturbances, hypoglycemia, shock, or associated sepsis
- ORT should be administered over a period of 3 to 4 hours.
- Additional ORS should be administered for ongoing losses.
- Prompt return to an age-appropriate diet once rehydration is achieved
- Selective utilization of antibiotics based on exclusion of *E. Coli* 0157:H7 and *Salmonella* by culture as well as by the criteria listed in Table 224.6
- Avoidance of antisecretory or antiperistaltic medications
- Instruction of parents on hygienic precautions.

DISPOSITION

If more than 5% dehydration is present, a pediatrician should be consulted for probable admission, with rehydration efforts beginning in the ED. With chronic diarrhea, consultation with a pediatrician or pediatric gastroenterologist is in order. Diarrhea may paradoxically complicate surgical conditions (e.g., Hirschsprung disease), in which case a pediatric surgeon should be consulted.

Indications for hospitalization are listed in Table 224.7. Sepsis and serious illness in infants younger than 1 month old may be clinically subtle or occult. Even mild dehydration in young infants deserves careful consideration for admission.

TABLE 224.7
Indications for Admission

Dehydration >5%
Significant electrolyte disturbances
Suspected sepsis
Intractable vomiting
Bilious vomiting
Complicated chronic diarrhea with failure to thrive
Poor social situation
Parental noncompliance or inability to follow prescribed therapy
Suspected deprivation or neglect
Neonate with dehydration

Simple diarrhea with dehydration requires only judicious oral or intravenous rehydration and rarely requires transfer unless there are no inpatient pediatric services. Complicated cases of dehydration (e.g., those associated with hypernatremia) or those of chronic duration usually require specific pediatric expertise.

Common Pitfalls

- Failure to appreciate that the young infant with diarrhea may initially appear well but develop serious dehydration over a short period
- Use of restrictive or progressive diets
- Failure to rely on the caregiver's history of decreased or absent urine output, lethargy, or inability to tolerate fluids may lead to inappropriate management and disposition.
- Underestimation of the degree of hypovolemia and failing to identify subtle signs of shock
- Failure to follow strict hand hygiene

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Lowell Clark and Ghazala Sharieff to the content of this chapter.

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CHAPTER 225 Dehydration

Todd Wylie and Mark S. McIntosh

The diagnosis and management of dehydration in children and infants requires an understanding of fluid and electrolyte balance. Total body water varies with age, ranging from approximately 75% in the term newborn to 65% in the 1-year-old, and decreasing to 55% to 60% in adolescents and adults. Although infants have a greater percentage of total body water than adults, this does not provide extra protection from dehydration. Children, and infants in particular, have larger surface area to body weight ratios, greater resting metabolic rates, and a higher rate of fluid turnover. In fact, fluid turnover in infants is roughly double that of adults. The increased rate of fluid turnover makes infants susceptible to dehydration stemming from excessive losses or lack of fluid intake.

Multiple organ systems and a variety of mechanisms are involved in maintaining electrolyte and fluid balance. Volume status is linked primarily to the concentration of sodium in the extracellular space. Antidiuretic hormone, aldosterone, the renin–angiotensin system, and kidneys work in concert to maintain sodium equilibrium and hence volume status.

CLINICAL PRESENTATION

The clinical presentation of dehydration consists of a spectrum ranging from mild with few or no obvious signs or symptoms, to severe in which signs and symptoms include tachycardia, anuria, lethargy, skin tenting, parched mucous membranes, and hypotension (Table 225.1). The degree of dehydration can be expressed as a proportional deficit of the pre-illness body weight, with deficits of

3% to 5%, 6% to 9%, and ≥10% corresponding to "mild," "moderate," and "severe" dehydration respectively (1).

The clinical presentation is not only influenced by the degree of dehydration as a proportion of weight, but also by the serum sodium concentration. Isonatremic dehydration (Table 225.2), the most common form, is characterized by a proportional loss of both water and electrolytes, as occurs, for example, in children with short bouts of diarrhea. In hyponatremic dehydration, the intravascular volume is compromised as fluid translocates into the intracellular compartment in an effort to maintain osmotic equilibrium. Hyponatremic dehydration may occur as a result of gastroenteritis, renal losses (e.g., proximal renal tubular acidosis, diuretic use, salt-wasting nephropathy), syndrome of inappropriate secretion of antidiuretic hormone (SIADH), or in patients with cystic fibrosis exposed to high environmental temperatures. Infants with hyponatremic dehydration may be prone to exhibiting signs of shock with only moderate dehydration. Hypernatremic dehydration results from a greater loss of water relative to sodium. Causes of hypernatremia include diarrhea in conjunction with a persistent fever, diabetes insipidus, excessive exogenous sodium (e.g., sodium bicarbonate, hypertonic saline, improperly diluted infant formula), and inability to regulate fluid intake. Redistribution of fluid out of the intracellular compartment into the extracellular compartment, as occurs with hypernatremic dehydration, may mask some signs of dehydration, even in the face of significant fluid deficits.

TABLE 225.2
Type of Dehydration Based on Serum Sodium Concentration

Dehydration Type	Serum Sodium Concentration (mEq/L)
Hyponatremic	<130
Isonatremic	130–150
Hypernatremic	>150

DIFFERENTIAL DIAGNOSIS

Dehydration in children usually results from either increased fluid output (gastrointestinal losses, renal loses, insensible losses), decreased fluid intake, or a combination of both. Translocation of fluids, as occurs with significant burns or ascites, may also cause dehydration, though these conditions are less commonly encountered. Increased gastrointestinal losses in the form of diarrhea and vomiting are the most common source of dehydration in children. Estimates of mortality due to diarrheal disease for young children in the developing world range from approximately 1.6 to 2.2 million deaths annually (2). In developed nations, dehydration accounts for significant morbidity in the pediatric population, although the mortality rate is relatively low given the prevalence of disease. In the United States, acute gastroenteritis in children accounts for more than 1.5 million outpatient visits annually, 200,000 hospitalizations, and approximately 300 deaths (3). Increased fluid losses may also occur from renal losses, insensible losses due to fever, increased respiratory rate, and environmental conditions. Renal losses may result from hyperglycemia, diabetic ketoacidosis, congenital adrenal hyperplasia, proximal renal tubular acidosis, diuretic use, and diabetes insipidus. Fever in an infant can increase insensible water losses by approximately 0.42 mL/kg/°C for each degree >37°C. Decreased fluid intake may be secondary to pharyngitis, stomatitis, vomiting, or respiratory distress (particularly in infants). For this reason, any infant presenting with decreased oral intake, fever, vomiting, diarrhea, and especially respiratory distress, regardless of etiology, must be carefully assessed for potential dehydration.

ED EVALUATION

Multiple disease states contribute to dehydration in children. Identification of the source is simplified by focusing on factors that affect intake, loss, or translocation of fluids (e.g., burns, ascites). The frequency and amount of urine, output must be elicited from the history as well as an accurate sense of the volume and composition of oral intake. Losses, in terms of emesis and or diarrhea, must also be characterized and carefully quantified whenever possible. Baseline

body weight, if known, should be compared with the current weight in conjunction with physical examination findings to estimate the degree of dehydration. Dehydration is a clinical diagnosis and the degree of dehydration is best determined by measurement of acute weight loss which directly reflects total body water deficit. However, since an accurate pre-illness weight often is not known in the acute setting, clinical assessment is used to inform estimates of overall fluid deficits. Signs and symptoms used for clinically assessing the degree of dehydration are listed in Table 225.1. The degree of dehydration is generally expressed as a proportion of the pre-illness body weight. As mentioned above, body fluid deficits of 3% to 5%, 6% to 9%, and $\leq$10% correspond to "mild," "moderate," and "severe" dehydration respectively for infants and small children (1). The reliability of clinical parameters for evaluation of dehydration has been evaluated in multiple studies (4–7). One study found the median number of clinical findings varied with degree of dehydration; specifically patients with mild, moderate, or severe dehydration displayed 1, 5, and 8, associated findings, respectively (4). Four specific findings were found to be independently associated with dehydration, including general appearance, capillary refill $>$2 seconds, dry mucous membranes, and reduced tears (4). A meta-analysis reviewing the utility of symptoms and signs for evaluating dehydration in children found abnormal capillary refill time, abnormal skin turgor, and abnormal respiratory pattern to be the most useful signs for predicting 5% dehydration (5). The same study found that a combination of clinical signs predicted dehydration better than any single sign (5). As a general rule, the majority of pediatric emergency department (ED) patients will fall into the mild dehydration category. Patients with fluid losses significant enough to be categorized as moderate dehydration will subjectively appear far more ill than patients with only 3% to 5% weight loss, independent of formal quantification of signs or symptoms.

TABLE 225.1
Clinical Assessment of Hydration Status and Percentage Dehydration

Extent of Dehydration	Mild (3–5%)	Moderate (6–9%)	Severe (≥10%)
Eyes	Normal	Sunken	Markedly sunken
Skin turgor	Normal	Decreased	Tenting
Heart rate	Normal	Slightly increased	Significantly increased
Blood pressure	Normal	Normal to orthostatic	Shock
Mental status	Normal for age	Normal to listless	Depressed/lethargic
Thirst	Slight increase	Moderate increase	Marked increase
Mucous membranes	Normal	Dry	Parched
Tears	Normal	Decreased	Absent
Anterior fontanelle	Normal	Sunken	Markedly sunken
Skin/capillary refill	Normal	Delayed capillary refill	Cool/mottled/poor
Urine output	Unchanged	Decreased	Anuric

Adapted from King CK, Glass R, Bresee JS, et al. Managing acute gastroenteritis among children: Oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep.* 2003;52(RR-16):1–16; Gorelick MH, Shaw KN, Murphy KO. Validity and reliability of clinical signs in the diagnosis of dehydration in children. *Pediatrics*. 1997;99:E6; Steiner MJ, DeWalt DA, Byerley JS. Is this child dehydrated? *JAMA*. 2004;291:2746–2754.

The diagnosis of dehydration does not require the use of laboratory studies, and no single laboratory test reliably identifies the degree of dehydration. However, abnormalities in the serum electrolytes, glucose, blood urea nitrogen (BUN), and other laboratory studies may occur, particularly in children with moderate to severe dehydration (8–11). Serum glucose may be reduced in up to 10% of dehydrated children (8). In one study of children with mild, moderate, or severe dehydration, 48% were found to have one or more serum electrolyte abnormalities, which led to a change in management for 10% of patients (8). In that study, an inappropriately low serum bicarbonate (<16 mmol/L) was the most common abnormality (8). A low serum bicarbonate level has been found to occur in association with dehydration, although it does not always appear to reliably reflect the degree of dehydration (9–11). One study demonstrated that a serum bicarbonate concentration <17 mEq/L was 77% sensitive for predicting moderate dehydration and 94% sensitive for predicting severe dehydration (10). A very low serum bicarbonate (≤ 13 mEq/L) has been associated with a higher clinical degree of dehydration in several studies (8–10). Other laboratory abnormalities either occur less frequently or are unreliable as predictors of dehydration. An elevated BUN level was found to have an association with moderate to severe dehydration if

it was >100 mg/dL, but was not helpful if between 40 mg/dL and 100 mg/dL (11). Another study found that the BUN level did not accurately reflect dehydration (12). The concentrating ability of the kidneys is immature in neonates and young infants; renal blood flow and glomerular filtration do not reach adult values until approximately 1 year of age. This may result in a poor correlation between urine-specific gravity and urine ketones with the degree of dehydration in young children and infants presenting to the ED (13).

Despite the limited utility of laboratory studies in pediatric patients with dehydration, serum electrolytes, BUN, creatinine, and serum glucose should be measured in all patients with moderate to severe dehydration requiring prolonged observation or admission. This is especially true in very young infants and neonates, where metabolic perturbations may present more subtly and be markers of underlying illness. It is vital, however, to appreciate that laboratory studies serve as markers of dehydration severity and not as tools to establish the diagnosis of dehydration. Thoughtful testing in the dehydrated patient in the age of oral rehydration is important as one considers resource utilization from both the point of view of cost containment and ED flow. Venipunctures divert nursing resources away from other patient needs in the ED, since more than one nurse is frequently required to obtain the sample. Realizing that the majority of pediatric ED patients are only mildly dehydrated, a fingerstick glucose measurement may be the best initial test to stratify patients and guide early therapy.

ED MANAGEMENT

Intravenous rehydration is not necessary in all cases of dehydration. There is a strong support for the use of oral rehydration therapy (ORT) in children with mild dehydration secondary to acute gastroenteritis (2,3,14–16). *In most children, ORT is the recommended initial approach to therapy* (2,3). At least two meta-analyses have concluded that ORT is as effective as IV therapy for mild to moderate dehydration associated with gastroenteritis (17,18). Moreover, the time required to initiate therapy with oral rehydration may be less

than that with IV fluid therapy (16), which often exceeds the recommended 4-hour time period (19).

The physiologic basis of ORT is the sodium-glucose cotransport mechanism linking the reabsorption of salt and glucose at the intestinal brush border. Clinical studies, initially in cholera patients and subsequently in patients with viral or bacterial diarrhea, have shown that sodium- and glucose-containing oral solutions are effective in treating dehydration secondary to diarrheal disease.

There are a variety of commercially available oral rehydration solutions (ORSs) (Table 225.3). Most of these solutions have lower concentrations of sodium (45–50 mmol/L) than the solutions originally studied. Although these products were previously thought to be appropriate only for use as maintenance solutions, it is now felt that they can be satisfactorily used to rehydrate children with mild or moderate dehydration (3). In 2002, the World Health Organization recommended the use of a lower osmolality ORS with 75 mmol/L sodium, 75 mmol/L glucose, and total osmolality of 245 mOsm/L (2). Use of this solution has demonstrated fewer unscheduled intravenous infusions, less vomiting, and decreased stool output when compared to the standard formula (20). Parents, as well as health care providers, must be informed that commonly consumed beverages such as colas, sport drinks, and juices are nonphysiologic and should not be used to treat dehydration.

TABLE 225.3
Contents of Oral Rehydration Solutions

Solution	Carbohydrate (g/L)	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	Base (mmol/L)	Osmolarity (mOsm/L)
WHO ORS (1975)	20	90	20	80	30	311
WHO ORS (2002)	13.5	75	20	65	30	245
Pedialyte	25	45	20	35	30	250
Rehydralyte	25	75	20	65	30	305

Adapted from King CK, Glass R, Bresee JS, et al. Managing acute gastroenteritis among children: Oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep.* 2003;52(RR-16):1–16.

Oral rehydration is accomplished by providing frequent small volumes of an appropriate solution over 2 to 4 hours (Table 225.4). For children with gastroenteritis and minimal or no dehydration, fluid intake in the form of an appropriate ORS compensates for increased losses; one recommended regimen is 10 mL of fluid per

kilogram of body weight for each diarrheal stool and 2 mL of fluid per kilogram of body weight for each emesis (2). With mild to moderate dehydration, the goal is to provide 50 mL/kg over 2 to 4 hours in mildly dehydrated children and 100 mL/kg over 2 to 4 hours in moderately dehydrated children (2,3,14). Therapy is initiated with 5 mL (1 tsp) every 1 to 2 minutes (2,3). The amount can be increased gradually as tolerated. Frozen rehydration solutions can be tried in patients who initially refuse oral fluids or have difficulty tolerating oral fluids. Ongoing losses from diarrhea or emesis should be continually replaced as described.

TABLE 225.4
Guide to Oral Rehydration Therapy

Degree of Dehydration	Rehydration Phase	Replacement of Ongoing Losses	Diet
Mild dehydration	1. Replace fluid deficit over 2–4 hrs using appropriate oral rehydration solution (ORS) 2. Administer ORS in frequent, small amounts: 5 mL every 1–2 min using syringe, spoon, or cup 3. Goal: 50 mL/kg of ORS over 2–4 hrs	Replace ongoing losses from diarrhea (10 mL/kg/watery stool) and vomiting (2 mL/kg/episode of emesis) with ORS.	Return to age-appropriate diet as soon as rehydration phase is complete.
Moderate dehydration	1. Replace fluid deficit over 2–4 hrs using appropriate ORS 2. Administer ORS in frequent, small amounts: 5 mL every 1–2 min using syringe, spoon, or cup 3. Goal: 100 mL/kg of ORS over 2–4 hrs	Replace ongoing losses from diarrhea (10 mL/kg/watery stool) and vomiting (2 mL/kg/episode of emesis) with ORS	Return to age-appropriate diet as soon as rehydration phase complete.

Adapted from King CK, Glass R, Bresee JS, et al. Managing acute gastroenteritis among children: Oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep.* 2003;52(RR-16):1–16.

Patients should have an age-appropriate diet restarted as soon as they have been rehydrated (2,3). Foods that are high in simple sugars (e.g., soft drinks, juices, gelatin desserts) should be avoided because they may worsen diarrhea (2,3). Caretakers should be instructed to have the patient return if losses continue. Refusal of oral fluids or failure to tolerate oral fluids should prompt initiation of intravenous rehydration. Severely dehydrated children and those who do not improve with oral rehydration require intravenous rehydration as well.

Patients who refuse to drink, continue to vomit, or consume inadequate amounts of fluid can present a clinical problem. In this situation, administration of an ORS by nasogastric tube may be an alternative to intravenous rehydration. One prospective study demonstrated that this was as safe and effective as using the IV route (21). Patients who received nasogastric hydration (50 mL/kg over 3

hours) had faster resolution of acidosis, decreased ketonuria, and lower urine-specific gravity than those who received the same amount of IV hydration.

Certain antiemetics remain controversial, primarily because of the adverse effects associated with these medications. However, several studies have shown ondansetron to be relatively safe and effective in the management of acute gastroenteritis in the ED setting (22–24). Oral ondansetron reduces the vomiting associated with acute gastroenteritis, in addition to facilitating oral rehydration and reducing the rate of hospital admission (22,23). Clinicians must keep in mind that ondansetron treats nausea and vomiting, but not the underlying cause(s). Clinicians must assure the effects of ondansetron are not masking important acute causes of vomiting, such as subtle signs of increased intracranial pressure or diabetic ketoacidosis.

Subcutaneous fluid administration is another potential alternative to intravenous rehydration in children with mild to moderate dehydration. Potential benefits of this approach include reported ease of use, safety, efficacy, and parental acceptance (25). Obstacles to the use of subcutaneous fluid administration include a lack of familiarity with the process, and the potential need for hyaluronidase to facilitate success of the procedure. In addition, subcutaneous fluid administration is not indicated for the management of severe dehydration. As the data supporting this technique in children is limited, future studies are necessary to evaluate and determine appropriate settings for implementation.

In moderate and especially in severe dehydration, the immediate goal is to treat shock by rapidly expanding the intravascular volume with intravenous fluids. In the presence of decompensated shock, if intravenous access is not rapidly obtainable, intraosseous access is an alternative (see Chapter 219). Once access is obtained, successive fluid boluses of 20 mL/kg of an isotonic solution are given until clinical improvement is noted. An isotonic crystalloid solution is the only solution recommended for volume resuscitation in these circumstances. Blood should be drawn for laboratory studies, which should include electrolyte levels, BUN, creatinine, and a bedside serum glucose screening to rule out hypoglycemia. Before initiating

fluid therapy, it is important to palpate the liver for size. Cardiogenic shock, although rare, may be misdiagnosed as hypovolemia in the infant or neonate with undiagnosed congenital heart disease, and a few hundred mL of excess fluid, in this instance, could contribute to heart failure.

It is reasonable to administer up to 60 cc/kg of isotonic solution in the initial fluid resuscitation phase. Subsequent boluses may be given as needed with reevaluation after each bolus. Close attention to cardiopulmonary status must be maintained to avoid iatrogenic pulmonary edema. This is particularly true for children with underlying pulmonary or cardiac conditions. If the child is not in shock, the 20-mL/kg fluid bolus may be given more slowly (i.e., over a period of 30 minutes to 1 hour).

Patients with hyponatremic dehydration may present with nausea, vomiting, or seizures. The classic case is the infant who has received improperly prepared overdiluted powdered formula resulting in administration of excess free water. These symptoms typically resolve when the serum sodium is restored to above 125 mEq/L. In the presence of seizures, however, the serum sodium must be rapidly corrected for seizures to resolve. Subtracting the current serum sodium level from the desired level and multiplying by 0.6 and the patient's weight in kilograms provides the amount of 3% saline required for acute correction. An alternative approach is to administer 3 to 5 cc/kg of 3% saline intravenously until seizures terminate.

Subsequent management after rapid repletion of the intravascular space consists of calculating the deficit of fluids and evaluating the acid–base and electrolyte disturbances, but this kind of management is not necessarily the responsibility of the emergency physician. In the consolidation phase, calculating deficit fluids, maintenance fluids, and ongoing losses determines the total volume of fluid required to complete treatment. Sample calculations are illustrated below.

Calculation of Fluid Deficits

1. If the normal baseline weight of the patient is known, the fluid deficit (in liters) is easily calculated with the formula:

Fluid (free water) deficit (liters) = normal wt (kg) − present wt (kg)

2. If the normal weight is not known, it may be calculated by using the patient's estimated percent dehydration and the present weight, using the following formula: Normal wt = present wt × (100/[100 – % dehydration]).
3. Determine whether the dehydration is hypotonic, isotonic, or hypertonic, based on the criteria in Table 225.2 and calculate the sodium and potassium deficits.
4. Calculate the rate of deficit replacement. For isotonic dehydration, half of the deficit is replaced in the first 8 hours, and the second half is replaced over the next 16 hours. This should be given in addition to (and in conjunction with) the maintenance fluids required for the 24-hour period.

Calculation of Maintenance Fluids

1. Free water needs for a 24-hour period are 100 mL/kg/24 hr for the first 10 kg of body weight; 50 mL/kg/24 hr for the second 10 kg; and 20 mL/kg/24 hr for every kg of body weight >20 kg. Alternatively, to calculate per hour needs use 4 mL/kg/hr for the first 10 kg; 2 mL/kg/hr for the next 10 kg; and 1 mL/kg/hr for every kg >20 kg. For example, maintenance fluids for a 25-kg child will be (1,000 mL + 500 mL + 100 mL)/24 hr = 67 mL/hr.
2. Sodium requirements are 2 to 3 mEq/kg/d.
3. Potassium requirements are 1 to 2 mEq/kg/d.

An alternative method for managing fluid needs during the consolidation phase is to replace the remaining calculated fluid deficit over the first 8 hours with $D_5$0.45NS + 20 mEq/L of K^+. Then, the calculated maintenance fluid needs for a 24-hour period are given over the next 16 hours. As 24 hours' worth of maintenance fluid is given over 16 hours, the rate of fluid administration is 1.5 times the usual hourly maintenance rate. To accommodate for

ongoing losses, fluid losses from vomiting and diarrhea can be replaced mL for mL with normal saline every 4 to 6 hours, unless the losses are severe, in which case more frequent replacement may be required. This approach should apply to the majority of dehydrated patients requiring intravenous rehydration.

It is important to note that hypertonic dehydration is not approached in the same manner as above. Overly rapid fluid administration in the setting of hypertonic dehydration may result in fluid shifts with catastrophic repercussions, including cerebral edema and intracranial bleeding. If in shock, the patient should be treated accordingly; but once hemodynamically stabilized, fluids should be given over an extended period of time. The rate of decline in serum sodium should not exceed 10 mEq/L/24 hr.

CRITICAL INTERVENTIONS

- Maintain a low threshold to obtain a bedside glucose measurement in patients with altered mental status or signs of dehydration.
- Use isotonic solutions for bolus intravenous therapy. Never use hypotonic fluids for bolus therapy.
- Reevaluate the patient after every intravenous bolus of fluids before giving another.
- Treat severely dehydrated patients aggressively with adequate volumes of intravenous isotonic fluids.
- In the setting of hypernatremia, reduce the serum sodium concentration slowly.

DISPOSITION

In many centers, the clinical diagnosis of dehydration mandates intravenous therapy and, therefore, admission. This is the more classic and accepted management, but some centers advocate intravenous rehydration over a period of 3 to 4 hours for selected patients in the ED. The physician then determines the need for admission. Infants with severe dehydration by clinical criteria,

acidosis, ongoing losses, electrolyte abnormalities, intolerance to oral fluids, or social needs should be admitted.

Common Pitfalls

- Failure to appreciate the acuity of the ongoing process.
- Failure to recognize and treat shock secondary to dehydration. This includes failing to give boluses of 20 mL/kg until end-organ perfusion is improved, or the use of nonisotonic fluids to accomplish this task.
- Failure to monitor ongoing therapy, which may result in overhydration or underhydration.
- Failure to address associated abnormalities of electrolyte and acid–base balance.
- Failure to address the underlying cause of dehydration (e.g., pyloric stenosis, diabetic ketoacidosis, child abuse or neglect).

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CHAPTER 226 Failure to Thrive

Jeffrey Hom

Failure to thrive (FTT) is a common term in pediatrics but lacks a clear definition (1–4). Historically, it refers to a "failure to gain weight" (weight less than the third percentile for age or weight for height below the fifth percentile). In addition, etiologies for FTT were organized into organic versus nonorganic causes. Regardless of cause, the final common pathway is failure to consume adequate nutrition for optimal growth and development. The causes are often complex and multifactorial. FTT has been reported as the seventh most common reason for hospitalization in children's hospitals. Terms such as undernutrition, malnutrition, or weight faltering have evolved as more contemporary descriptors (1,4,5).

CLINICAL PRESENTATION

Infants with FTT may present in extremis secondary to acid–base imbalances, severe anemia, malnourishment, or dehydration. More commonly, however, growth failure may simply be an incidental finding of an observant clinician.

Measuring growth parameters of weight, length, and head circumference determine whether growth failure or undernourishment exists. These parameters should be plotted on growth charts downloadable from the Centers for Disease Control and the National Center for Health Statistics Web site (http://www.cdc.gov/growthcharts/) (6). When possible, comparing them to prior measurements, either from the medical record or at a minimum reported weight from the caregiver, will allow a rough

determination of growth trends. Growth patterns will differentiate between undernourishment (poor weight gain) and poor growth (low weight, short stature, and small head circumference).

DIFFERENTIAL DIAGNOSIS

The etiology of FTT is malnutrition, expect in cases of familial short stature and constitutional growth delay. FTT can be classified into three groups: (1) normal head circumference with weight reduced out of proportion to height (e.g., caloric insufficiency), (2) normal (or enlarged) head circumference with weight moderately reduced in proportion to height (e.g., endocrinopathies), and (3) weight, length, and head circumference all reduced (e.g., fetal alcohol syndrome) (Table 226.1). The most common form is the first, frequently attributed to *caloric insufficiency*. This can be due to inadequate caloric intake, caloric wasting, increase caloric needs, or abnormal regulation. Decreased caloric intake is commonly caused by psychosocial impairment in the child's environment such as poverty, behavioral feeding difficulties, maternal depression, infant–parent bonding, interpersonal violence in the home, Münchausen syndrome by proxy, neglect, or nonaccidental trauma (7–16). The child presents with a markedly decreased weight compared with length and head circumference. Social history and environmental circumstances are vital to this assessment. Caloric intake can also be impaired by organic disease causing regurgitation (e.g., severe gastroesophageal reflux, pyloric stenosis, rumination syndrome), mechanical problems (e.g., sucking/swallowing abnormalities, neurologic disease, perinatal asphyxia), or malabsorption (e.g., cystic fibrosis, lactase deficiency, renal tubular acidosis). An underlying history of chronic disease may also explain the malnutrition.

TABLE 226.1
Classification of Failure to Thrive

Group I

Most common type. Normal head circumference; weight reduced out of proportion to height. In most cases of failure to thrive, malnutrition is present as a result of either deficient caloric intake or malabsorption.

Group II

Normal or enlarged head circumference for age; weight only moderately reduced, usually in proportion to height; structural dystrophies, constitutional dwarfism, endocrinopathies

Group III

Subnormal head circumference; weight reduced in proportion to height; primary central nervous system deficit; intrauterine growth retardation

From Kempe CH, Silver HK, O'Brien D, eds. *Current Pediatric Diagnosis and Treatment*, 6th ed. Los Altos, CA: Lange, 1980:624.

The second group presents with normal or enlarged head circumference with *weight and length equally affected.* Most of these patients have underlying metabolic disorders such as hypothyroidism, growth hormone deficiency, galactosemia, or renal tubular acidosis.

The third group consists of children whose *weight, length, and head circumference* are all reduced. This category includes patients with genetic disorders (e.g., Turner syndrome, structural dystrophies) or congenital problems (e.g., fetal alcohol syndrome, small for gestational age) (1,2,5,17–19).

ED EVALUATION

FTT is multifactorial and patients frequently do not fit cleanly into any one particular group, making the differential diagnosis difficult to manage. The emergency physician's primary role is recognition of growth deficiency. This is more difficult to do when caretakers use the emergency department (ED) as their primary care outlet where growth records are not routinely maintained. When a child is brought to the ED with an acute illness, physicians can easily fail to recognize the insidious and more serious problem of growth failure. Weight measurements should be part of the initial evaluation of *all* children seen in the ED, and be routinely charted, ideally on a growth chart. When the diagnosis of FTT is suspected, a thorough

history (with in-depth social history), physical examination, and growth pattern evaluation must be performed.

Laboratory tests are of limited value in most cases, but they can help diagnose serious conditions that require immediate attention. Tests commonly performed in the ED are a complete blood count with differential, urinalysis with culture, serum electrolytes, calcium, phosphorous, albumin, and total protein (2). More specific tests should be individualized, such as thyroid function tests and human immunodeficiency virus. Imaging studies should be directed to specific concerns (suspected congenital heart disease, nonaccidental trauma, malnutrition). If nonaccidental trauma or neglect is suspected, proper referral to child protective services and law enforcement should be made.

KEY TESTING

- Confirm that weight loss is persistent and substantial, that is, supportive weight, length, and head circumference from different times are needed for confirmation.
- Isolated laboratory testing does not confirm the diagnosis, rather it rules in or rules out specific diagnosis, related to the patient's growth retardation.
- CBC, electrolytes, calcium, phosphorous, albumin and total protein, urinalysis and culture
- Thyroid function, HIV testing as indicated
- CXR for congenital heart disease if suspected. Extremity images, skeletal survey, and/or head CT in cases of suspected child abuse
- History and physical examination are central for assessment. Assessment for the three causes of FTT: (1) inadequate intake of nutrient or appropriate nutritional content, (2) improper absorption of nutrition, and (3) increased metabolic demands due to chronic disease or genetic or metabolic disorders.

ED MANAGEMENT

The emergency physician's primary responsibility is to recognize FTT and not necessarily determine its cause. As with any patient in

the ED, assessing for medical stability is first and foremost. Airway, breathing, and circulation may all be affected in severe cases of FTT as a consequence of acid–base status from dehydration or an underlying metabolic abnormality. Most commonly, infants with FTT present to the ED in a stable condition. The growth failure may be associated with chief complaints such as vomiting or poor feeding or may be an incidental finding by an astute physician.

CRITICAL INTERVENTIONS

- Address the ABCs, which may be compromised in children who are medically unstable from severe dehydration, acidosis, trauma (nonaccidental trauma), or underlying metabolic disorder.
- Recognition of malnutrition.
- Recognition of possible nonaccidental trauma and/or neglect.
- Recognition of the indications for hospitalization:
  - Medical instability
  - Nonaccidental trauma/neglect with no options for safe placement
  - Severe undernourishment
  - Laboratory abnormalities indicating medical instability

DISPOSITION

To facilitate evaluation and promote feeding, patients with FTT were traditionally admitted. Hospitalizations promoted prolonged inpatient stays that were disruptive to the child and family; therefore hospitalizations are currently reserved for patients exposed to frank neglect, unstable home or social situations, and/or with definitive medical problems (1,2).

Outpatient management is encouraged if the FTT is: (1) mild or has no obvious organic cause, (2) the medical provider is comfortable with the social environment to which the infant will be discharged, and (3) follow-up with the primary physician is established. Ensuring the child has a medical home is imperative. A multidisciplinary team approach, involving a social worker, psychiatrist, and nutritionist, enhances success in both inpatient and

outpatient management. Healthcare provider home visitation has demonstrated significantly improved growth rates of affected children, compared with conventional management (4,20). In all cases of FTT, communication between the emergency physician and the primary physician is critical to effective decision making.

Common Pitfalls

- Failing to recognize FTT by addressing only the acute illness of presentation.
- Failing to look for signs and symptoms of nonaccidental trauma and/or neglect.
- Failing to consider social, environmental and physiologic factors as they impact growth failure.
- Failing to provide adequate follow-up.

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CHAPTER 227

Crying, Fussy Infant

Naghma S. Khan

Mammals and birds use vocal signals to get attention. In humans the cry of the newborn promotes the release of oxytocin in the mother, which is essential not only for infant nutrition, but also for the development of attachment between mothers and their infants (1,2). Excessive crying usually signals an unmet need or distress and evokes significant apprehension and stress in both caregivers and healthcare providers. Persistent crying has been shown to contribute to family stress and plays a significant role in child abuse (3). Normal infant crying lasts less than 3 hours per day and peaks between 3 PM and 11 PM (1,4). Emergency physicians must be able to distinguish prevalent "normal" crying from crying indicative of acute or life-threatening illness that requires immediate intervention.

CLINICAL PRESENTATION

Parental temperament and experience greatly determine the crying threshold where medical help is sought. A visit to the emergency department (ED) is most likely to be precipitated by prolonged, inconsolable, and recurrent episodes of crying or a single act of crying that is abnormally high-pitched or perceived to be associated with pain (4). Most commonly, the presentation is in the late evening or the middle of the night and caregivers are anxious, frustrated, and sleep deprived. A febrile infant with extreme irritability and fussiness does not pose as much of a diagnostic challenge as does an afebrile child with the same symptoms (5).

DIFFERENTIAL DIAGNOSIS

It is important to differentiate recurrent benign crying syndromes (such as colic) from those that may be the harbinger of a limb or life-threatening disease. The differential diagnosis is broad and involves virtually every organ system (6,7).

Traumatic injuries are a frequent cause of crying and range from a strangulated digit, penis, or clitoris (usually by an encircling hair or a sock fiber) to insect bites and anal fissures, to more serious instances of head trauma, rib or extremity fractures. Signs of child abuse and neglect must be carefully sought; potentially life-threatening injuries can be easily missed. A bulging fontanel may suggest increased intracranial pressure, which may be related to either meningitis or intracranial bleeding. Milk bottles heated in the microwave can cause scald burns on the buccal mucosa or tongue. Open diaper pins in cloth diapers and pain at vaccination sites after the diphtheria–pertussis–tetanus vaccination can also lead to unexplained crying (8). Corneal abrasions are fairly easy to rule out with fluorescein staining and should be a strong consideration when other more serious or obvious causes have been ruled out (9).

Nontraumatic or infectious causes are also important to consider. An acute suppurative otitis media is easy to miss since the tympanic membrane in infants is horizontal, rather than vertically oriented, and the external canal is narrow. Septic arthritis and osteomyelitis should be considered, in addition to other forms of invasive bacterial illness; these may present more subtly and can be difficult to diagnose. A high degree of suspicion and a careful physical examination are required to evaluate for intussusception, testicular torsion, and incarcerated hernias; thresholds for imaging if any of these are suspected should be low. Cardiac causes include a tetralogy of Fallot spell, congestive heart failure, or supraventricular tachycardia. Many of these patients will have a well-established history of congenital heart disease, but a few will not. A history of difficulty feeding is often a telltale sign. Cocaine exposure (including passive inhalation) and drug withdrawal are also an important part of the differential diagnosis (6,7,10).

It is vital to note *infantile colic is a diagnosis of exclusion in an ED setting*. It is arbitrarily defined by the rule of threes: an otherwise healthy, thriving infant crying for more than 3 hours a day, more than 3 days in a week, for more than 3 weeks. The cry is paroxysmal, develops into a piercing scream, with legs drawn up, abdominal distention, and passage of flatus. The infant appears to be in severe abdominal pain (11,12). Cow's milk allergy, infant temperament, overstimulation, and gastroesophageal reflux have been implicated in the cause of "colic," but others regard it as the extreme end of the normal crying spectrum (5,11,13). Regardless of cause, there is spontaneous resolution by 3 to 4 months of age.

Table 227.1 lists conditions associated with the abrupt onset of inconsolable crying in young infants.

TABLE 227.1
Causes of Excessive Crying in Afebrile Infants

Head and Neck

Head
- Head trauma (intracranial hemorrhage, shaken baby syndrome)
- Meningitis/encephalitis

Eye
- Corneal abrasions
- Ocular foreign body

Ear
- Otitis media

Throat
- Oral mucosal burns
- Teething
- Herpangina/herpes stomatitis/oral thrush
- Foreign body in oropharynx

Chest

Cardiac
- Supraventricular tachycardia
- Congestive heart failure
- Coarctation of the aorta
- Anomalous left coronary artery

Respiratory
- Pneumonia
- Rib fractures

Abdomen

Intussusception, volvulus
Appendicitis
Gastroenteritis
Constipation
Gastroesophageal reflux

Genitourinary

Urinary tract infection
Incarcerated hernia
Strangulated penis, clitoris (hair tourniquet syndrome)
Torsion testis

Extremities

Fractures
Strangulated digit (hair tourniquet syndrome)
Osteomyelitis/Septic arthritis
Open pin in diaper
Pain at vaccination site (especially after diphtheria–pertussis–tetanus vaccine)
Insect bites (brown recluse spider)

Metabolic

Inborn errors of metabolism
Metabolic acidosis
Aspirin overdose

Miscellaneous

Colic
Night terrors
Overstimulation
Maternal depression
Environmental deprivation (starvation, neglect)

DIAGNOSTIC APPROACH

A thorough history and physical examination remains the cornerstone of making the diagnosis. Review the vital signs. The infant should be undressed fully, including removal of the diaper. Carefully inspect the skin for bruises, inflammation, injury, or rash. Palpate the long bones, ribs and clavicles, and check the joints for mobility. Examine the corneas after fluorescein staining and evert the eyelids to check for a foreign body. Carefully examine for hernias, and check for anal fissures. The presence of fever and excessive crying in an infant less than 8 weeks of age mandates a sepsis workup. In one study, only 5% of afebrile infants were noted to have a serious underlying cause for crying, with urinary tract infections being the most common cause. The diagnosis of serious infection was made by the history and physical examination alone in 66% of the infants and by a single diagnostic test (urinalysis and urine culture) in 1.5% of cases. Thus screening for urinary tract infection is mandatory in afebrile crying infant in the first few months of life. Other investigations should be performed on the basis of clinical findings (6,7).

The head should be examined for any signs of trauma or a bulging fontanel. An abdominal examination is difficult to perform in a crying infant. It is important to examine the abdomen and chest, listening to the heart before attempting any invasive or painful procedures; if possible, this examination should be done while the infant is in the mother's lap and sucking on a bottle or pacifier. Flexing the legs at the hip may help relax the abdominal muscles enough to allow for a good abdominal examination. Before attempting a rectal examination, the physician should check the anal area for signs of trauma or anal fissures.

If a careful history and physical examination do not reveal or suggest a cause for crying, further studies are indicated. At a minimum, a catheterized or suprapubic urine sample must be obtained to rule out a urinary infection. A skeletal survey, cranial computed tomography (CT), and an alanine and aspartate

aminotransferase (ALT/AST) are indicated in suspected child abuse to look for healing fractures, intracranial bleeding, or a liver injury, respectively. If an abnormal cardiac rhythm is auscultated, a 12-lead electrocardiogram and a chest radiograph may lead to a diagnosis. Suspected gastrointestinal (GI) emergencies like intussusception and small bowel obstruction should be confirmed with appropriate studies, such as an abdominal ultrasound or an air contrast enema or upper GI series. A sepsis workup is indicated if there is any suspicion of an infectious etiology, especially in a febrile neonate.

CRITICAL INTERVENTIONS

- An in-depth history and physical examination of a fully undressed infant is essential.
- Colic should be a diagnosis of exclusion.
- If the diagnosis is not obvious, consider obtaining a urinalysis to rule out urinary tract infection.
- Fluorescein staining is simple, noninvasive, and diagnostic for corneal abrasion.
- In febrile infants, perform a full sepsis workup to rule out sepsis or meningitis
- Have a high index of suspicion for abuse. A good funduscopic examination to rule out retinal hemorrhages may require dilation of the pupils.

DISPOSITION

Disposition, including subspecialty consultation and treatment, is based on the clinical findings and diagnosis. Parents who present to the ED with a crying infant may not readily accept the physician's judgment that the crying is not a sign of a serious condition and may insist on medication, or another solution. These parents are typically stressed, sleep-deprived, and genuinely afraid for the welfare of their child; they may require a great deal of time to carefully discuss their child's evaluation and assessment.

Only 4% of infants benefit from formula change to a protein hydrolysate formula, because of an underlying cow's milk allergy

(14). Probiotics may or may not be of benefit, but have not been shown to be harmful (15,16). There is no evidence to support gastroesophageal reflux as a cause of excessive crying, and proton pump inhibitors are not recommended (13). Multiple studies have shown the danger of using alcohol-based preparations and Dramamine–Donnatal combinations for colic (17). If no treatable cause for the infant's crying is identified, it is important to empathize with the parents and take time to counsel them on methods to console the child early; possible interventions include rocking slowly in a quiet room, warm compresses to the abdomen, frequent feeding, and burping. Parents should be counseled never to shake the infant, even gently, because of the risk of shaken baby syndrome.

All children who present to the ED with crying need appropriate follow-up, especially if the diagnosis is "colic." Consultation with subspecialists and admission are determined by the diagnosis.

Common Pitfalls

- Taking a hurried and superficial history and not listening to the parents.
- Failure to completely expose the infant for a comprehensive physical examination.
- Ignoring abnormal vital signs.
- Failure to rule out a urinary tract infection.
- Failure to consider child abuse or neglect.
- Failure to sit and *carefully* listen to parents' concerns.

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CHAPTER 228
Abdominal Pain

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CLINICAL PRESENTATION

Abdominal pain is a common complaint in children presenting to the emergency department (ED), with an extensive differential diagnosis and variable age-dependent clinical presentations. The emergency physician must be able to identify those patients with serious causes (Table 228.1). There are broad principles that may guide the emergency physician in navigating the wide range of possible diagnoses related to pediatric abdominal pain. Ischemic pain typically has a sudden onset, as is seen with torsion or volvulus. Obstruction is most commonly associated with the entities in the mnemonic "double-AIM" (A-A-I-I-M-M): *a*ppendicitis, *a*dhesions, *i*ncarcerated inguinal hernia, *i*ntussusception, *m*alrotation/midgut volvulus, and *M*eckel diverticulum. If the evaluation suggests peritonitis, the most frequent etiology is appendicitis, but other acute surgical conditions are possible as well. Nonbowel conditions such as pyelonephritis or sickle cell disease should also be considered.

TABLE 228.1
Differential Diagnosis of Abdominal Pain in Children

Infants	Toddlers	School-Aged	Teenager
Colic	Acute gastroenteritis	Idiopathic	Appendicitis
Intussusception	Urinary tract infection	Appendicitis	Pelvic Inflammatory Disease
Malrotation	Constipation	Acute gastroenteritis	Peptic ulcer disease
Volvulus	Referred pain	Constipation	Ectopic pregnancy
Hirschsprung disease	Appendicitis	Urinary tract infection	Mittelschmerz
Necrotizing enterocolitis		Peptic ulcer disease	Ovarian/testicular torsion
Incarcerated hernia			

DIFFERENTIAL DIAGNOSIS

In infancy, *colic* is a common cause of abdominal pain (1). The predominant symptom is excessive crying. The infant may have mild abdominal distention and may pull the knees up as if in pain. This typically occurs in the evening and is associated with facial flushing and passing flatus (1). The physical examination, except for the crying, is often unremarkable. Management options are limited to encouraging breast-feeding or trying bottle feeds of a protein hydrolysate formula. It is prudent for breast-feeding mothers to avoid stimulants and spicy foods. It may be difficult to confidently rule out a more serious condition, and laboratory or imaging studies may be required if a serious diagnosis cannot be excluded (see Chapter 227). A prolonged ED observation period may be useful to rule out a serious cause.

Vomiting is abnormal in a neonate and suggests obstruction or a potentially serious infection. Necrotizing enterocolitis occurs in premature infants, but it is known to occur in term infants as well (2). Bilous vomiting in a neonate and in infants up to 12 months of age should be considered a midgut volvulus until proven otherwise (2). In older infants and children, vomiting due to gastroenteritis is common, but vomiting due to gastroenteritis is usually not accompanied by abdominal pain. When vomiting occurs in conjunction with observational evidence of abdominal pain, a more serious diagnosis should be considered. Abdominal distention (with or without bilious vomiting) is suggestive of a more serious disorder. Nonsurgical causes of bilious vomiting may include sepsis, urinary tract infection, and inborn errors of metabolism. Surgical causes may

include intussusception, malrotation complicated by midgut volvulus, and appendicitis.

Intussusception can be defined as a telescoping of a proximal section of bowel (the lead point is called the *intussusceptum*) into a more distal segment (the *intussuscipiens*). This results in a bowel obstruction with consequent ischemia. This most commonly occurs in children less than 2 years of age, but it can occur in older children and should remain part of the differential diagnosis at least through the age of 4. There is typically a dramatic, acute onset of pain (manifested by crying and/or curling up) that is associated with vomiting which often comes in cycles every 3 to 20 minutes, with the child relatively normal or drowsy between episodes (2). The classic triad of intussusception (colicky abdominal pain, emesis, and bloody stools) is not present in the vast majority of patients (3,4). The term "currant jelly" stool is often used to refer to bloody, mucousy stool, which is typically a late finding and is rarely seen. Intussusception should be considered when there is hematemesis or any blood in the stool (dysentery, maroon stool, etc.). Younger infants may present with profound lethargy, *without vomiting* or *abdominal pain* (2,3). A right-sided sausage-shaped abdominal mass is sometimes palpable when the child is relaxed or drowsy. Intussusception usually starts in the cecum, with the ileum intussuscepting into the ascending colon. Thus, clinical and radiographic investigations should focus on the right side.

Malrotation complicated by midgut volvulus is a surgical emergency (2,4). Normally the mesentery attaches broadly to the entire posterior abdominal wall. In malrotation, the mesentery and the vessels responsible for perfusing the bowel are instead attached to a more focal location forming "guts on a stalk", which can twist, resulting in a catastrophic midgut volvulus (2). These infants often present with an acute onset of pain followed by distention and bilious vomiting. Severe ischemia of the entire small bowel develops rapidly, and necrosis can occur in 1 to 2 hours. Although most patients with malrotation present with acute midgut volvulus during infancy, the malrotation can be silent and present later in childhood with an acute midgut volvulus. Some patients may experience a

volvulus that spontaneously reduces while others may have intermittent symptoms to suggest an “intermittent volvulus”; this is best identified by an upper gastrointestinal (GI) series. The upper GI series is the study of choice; a lower GI study may miss some cases (2,4).

Appendicitis in infants often presents with peritonitis; perforation occurs in approximately 85% of infants (5). The infant may have irritability, crying, refusal of feedings, and vomiting, in conjunction with fever, distention, shallow, grunting respirations, and shock (2,5). An indurated and erythematous abdominal wall may be present in these delayed presentations. Older children present with more classic symptoms of appendicitis, such as low-grade fever, anorexia, and periumbilical pain that localizes to the right lower quadrant. On physical examination, tenderness in the right lower quadrant and peritoneal signs may be noted (5,6). Appendicitis is very common and it commonly presents in an atypical fashion (6,7). In comparisons of clinical scoring methods, the Alvarado score (8) and the Pediatric Appendicitis score (PAS) (9) performed the best but neither were sufficiently diagnostic to be used alone (6,7). Since it is difficult to confirm appendicitis clinically (especially early on), advanced imaging studies are often employed.

Meckel diverticulum, located in the jejunum or ileum, can cause a diverse set of serious acute surgical conditions (2,10). The diverticulum contains acid-secreting gastric mucosa that may cause a bleeding ulcer and present with painless rectal bleeding. Also, being a tubular pouch, it may become inflamed (similarly to the appendix), resulting in Meckel diverticulitis (similar to appendicitis, but with pain in an atypical location). Meckel diverticulum may occasionally ulcerate, and perforate, and present as a bowel perforation without the preceding symptoms of diverticulitis. Meckel diverticulum may be attached to the abdominal wall (near the umbilicus) by a stalk-like connection around which a volvulus can occur (similar to malrotation). A Meckel can also form a lead point for intussusception (often ileo-ileal intussusception). Meckel diverticulum is said to follow the rule of 2s: present in 2% of the population, only 2% of these patients manifest clinical problems, symptoms commonly occur

at 2 years of age, the diverticulum is usually 2 in long, and its typical location is 2 ft proximal to the terminal ileum (2,10).

Hirschsprung disease (congenital aganglionosis of the distal colon) usually presents insidiously with constipation, episodes of recurrent crampy abdominal pain, and/or poor weight gain; alternatively, it may present acutely with peritonitis, acute abdominal pain, or bowel obstruction. The diagnosis is made on rectal biopsy or by barium enema that demonstrates a "transition zone" between the dilated proximal colon (normal ganglionic colon) and the nondilated (abnormal aganglionic) distal colon. Patients who have had a surgical resection of the distal aganglionic colon are at risk for "enterocolitis," a condition of severe gastroenteritis functionally resulting in bowel obstruction and requiring hospitalization for IV fluids and rectal dilation.

Gastroesophageal reflux may present with only a vague suggestion of abdominal or esophageal pain and manifested only as irritability. Other symptoms include failure to thrive, respiratory disturbances (wheezing, recurrent cough, pneumonia), or ALTE (apparent life-threatening event) (11). Peptic ulcer disease is uncommon in infants but should be considered in adolescents.

Recurrent abdominal pain is a common somatic complaint of children and is most often found to have no organic cause. Red flags for organic disease include fever, vomiting, weight loss, poor growth, delayed puberty, night awakening, anemia, bloody stools, localized pain or tenderness, and family history of inflammatory bowel disease or peptic ulcer disease (12,13).

Cholecystitis and *cholelithiasis* are generally considered to be uncommon, yet studies show an increasing incidence, partially due to the increasing use of ultrasound. Risk factors for cholelithiasis include parenteral nutrition, hemolytic disease, Kawasaki disease, cystic fibrosis, and obesity. As the teen years approach, cholelithiasis and cholecystitis become more common, and are often associated with female gender, obesity, and positive family history (14,15).

Abdominal pain may be the chief and only complaint after *trauma.* Signs of hemodynamic instability suggest spleen or liver injury. Peritoneal signs suggest a hollow viscous injury or free peritoneal

blood. Delayed presentation with recurrent emesis may indicate a duodenal hematoma or traumatic pancreatitis (not an uncommon sequelae of handlebar injuries).

In postpubertal females with abdominal pain, a source in the reproductive tract, such as ectopic pregnancy, pelvic inflammatory disease, tuboovarian abscess, ovarian torsion, or corpus luteal cyst, must be carefully considered. Secondary sexual maturity characteristics (Tanner stage) suggesting puberty in a female who has not had her first menstrual period (premenarche) raises the possibility of an imperforate hymen and subsequent hematocolpos.

Abdominal pain and fever in the child with immunodeficiency, nephrotic syndrome, or ascites suggests primary peritonitis. Sexual abuse may manifest as a vague abdominal complaint in some children. A high degree of suspicion is required for the emergency physician to include this possibility in the differential diagnosis.

The most common ED cause of pediatric abdominal pain is abdominal cramping due to the failure of stool to move forward with peristalsis. As stool moves distally through the colon, it may fail to move forward (e.g., at the splenic flexure). The colon then contracts more forcefully, resulting in crampy abdominal pain that suddenly remits once the stool moves forward and normal peristalsis resumes. This is sometimes called *constipation,* but the term is often used loosely to refer to painful defecation, difficulty with defecation, the passage of hard stools, or the failure to have a bowel movement every day (see Chapter 230).

DIAGNOSTIC APPROACH

A detailed history is useful but can be misleading as well. In particular, some children with appendicitis are fairly stoic, ambulatory, and complain of only mild abdominal pain, demonstrating few if any of the classic historical elements of appendicitis. Assessing the quality and severity of pain is difficult and unreliable.

Approach the physical examination in a friendly manner; younger children may remain on the parent's lap. Ask parents to bounce a young child gently while being held; most children are comforted by

this, but crying or signs of discomfort may suggest peritonitis. Inspection for distention, asymmetry, or abdominal wall erythema is followed by auscultation with a warm stethoscope. If the parent is carrying the child, the examiner can palpate the abdomen from behind, by bringing his or her hands around the child's abdomen. Palpation in the supine position should then proceed, palpating very slowly for tenderness or masses, initially in the area of the abdomen away from the suspected pathology. The groin and genitals should always be examined for inguinal hernias, scrotal or testicular abnormalities, or vaginal abnormalities. A rectal examination should be performed only if there is a specific indication (e.g., checking for stool impaction or for occult blood) (16). A pelvic examination may be indicated in sexually active or pubertal females.

Ill-appearing patients require IV fluid resuscitation and other indicated treatments. Surgical and radiologic consultation, if needed, should be promptly obtained. In some instances, a constellation of signs and symptoms may suggest a particular diagnosis. For example, painless rectal bleeding suggests a Meckel diverticulum; vomiting, bloody stools, and colicky abdominal pain suggest intussusception. Obtain an imaging study that can help to establish an early diagnosis of a serious condition.

Plain radiographic criteria for identifying a bowel obstruction in children are different from those in adults. These include bowel gas maldistribution, a paucity or excess of bowel gas, dilated bowel (smooth bowel walls with loss of haustra and plications), and large air–fluid levels with J-turns (also known as *hairpin loops* or *candy cane loops*). Plain-film radiographic signs of intussusception include the target sign, the crescent sign, absence of the subhepatic angle, and bowel obstruction (2). Pneumonia causes abdominal pain and is frequently missed on abdominal films because the lung, visible at the upper margin of the film, is easily overlooked. Many children have abdominal films that reveal a large amount of stool. If pain and other symptoms resolve completely after an enema, the child can be discharged home, but if symptoms persist further evaluation is necessary.

The preferred advanced imaging study of choice is evolving. CT scanning was used frequently in the recent past because of its high definition, rapid scan time, and wide availability. As part of the informed consent process, patients and parents should be counseled about the risk of radiation exposure. Ultrasound is less diagnostic, but involves no radiation exposure and can frequently be completed without sedation. The limited availability of trained pediatric ultrasound technicians is a potential disadvantage, but many emergency physicians have, or are acquiring, bedside ultrasound skills in this area. Magnetic resonance imaging (MRI) has an expanding role due to its increasing availability, expanding indications, focused scanning sequence strategies, lack of ionizing radiation, and more widespread availability of pediatric sedation. Study selection depends on facility expertise, resource availability, clinical application, and the availability of sedation, if needed. However, when a clear surgical diagnosis is established clinically, no imaging studies are required and prompt surgical intervention is warranted.

For appendicitis, the diagnostic accuracy of CT is slightly superior to that of ultrasound (17). Since the radiation exposure from CT is of concern, ultrasound is most often chosen as the initial advanced imaging study in a staged approach (18,19). The presence of pelvic free fluid increases the likelihood of appendicitis, while its absence decreases the likelihood (20). However, ultrasound is frequently nondiagnostic (the appendix cannot be visualized). Many studies report that CT is used more frequently at night due to lack of ultrasound services during late evening and night shifts (6). CT is often performed after a nondiagnostic ultrasound; however, its use may be declining (18,6,19) as experience with ultrasound accumulates. Some studies support the use of MRI after an inconclusive ultrasound examination (21). The use of MRI may increase in the future due to its increasing availability and known safety profile.

Intussusception can be reliably diagnosed by ultrasound, making it the study of choice when this diagnosis is suspected (3,4). Plain film x-rays can sometimes confirm the diagnosis, but ultrasound is clearly

superior (3). Once intussusception is confirmed, a contrast enema (air, barium, or water-soluble contrast under fluoroscopy) should be performed in a timely fashion to reduce the intussusception and obviate the need for surgery. The type of contrast should be at the discretion of the radiologist performing the procedure.

If the clinical presentation and plain film radiographs suggest a midgut volvulus, an upper GI series may demonstrate the corkscrew shape of twisted bowel or a halt in the progress of barium at the ligament of Treitz (2). If the clinical presentation suggests intermittent volvulus, an upper GI series remains the best test to identify the malrotation (2,4).

Barium enema and upper GI series often fail to identify Meckel diverticulum, and a "Meckel scan" (nuclear medicine scintigraphy) can then be performed to make the diagnosis. The radioisotope is taken up by gastric mucosa, so it typically images the stomach, but it can also identify ectopic acid-secreting gastric mucosa (2).

DISPOSITION

For seriously ill patients with a surgical abdomen, a surgeon should be consulted immediately while resuscitation measures are instituted. For patients who are less acutely ill, surgical consultation can be initiated after the diagnosis condition has been made or when the diagnosis is still in doubt after initial testing. Surgical emergencies in infants require a surgeon with specific pediatric expertise.

In most cases, advanced imaging studies permit the diagnosis of disorders requiring hospitalization to be made during the ED encounter. In unclear cases, patients should be admitted for observation until an abdominal emergency can be excluded. Given the variability in presentations, it is vital for emergency physicians to appreciate the value of observation as a diagnostic test in children with abdominal pain.

Patients with intussusception whose history suggests a short duration of symptoms and who are doing well following contrast enema reduction, can be discharged following a period of ED observation (2,4,22). While appendicitis is generally considered to be

a condition requiring surgery, a nonsurgical antibiotic option can be considered (23). Both options should be included in the informed consent process.

Low-risk cases can be discharged to home without an advanced imaging study. Regardless of the diagnostic impression at discharge, patients should be discharged with a standardized set of "abdominal pain" instructions stating that the diagnosis is never certain and that the specific cause of abdominal pain can often be difficult to determine. It should list signs and symptoms of serious causes of abdominal pain (appendicitis, intussusception, bowel obstruction, GI bleeding, etc.) that require an immediate return to the ED.

Common Pitfalls

- Approximately 50% of patients with acute appendicitis present with atypical features.
- Midgut volvulus is a true surgical emergency that should be considered in all infants with bilious vomiting.
- Intussusception is easily missed. Abdominal pain or blood in the stool should raise suspicion of this entity.
- Bloody diarrhea, though often due to bacterial dysentery such as shigellosis, may be due to intussusception. Currant jelly stools occur in the minority of cases. Any type of blood in the stool may be due to intussusception

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of Lowell Clark, Javier I. Escobar II, and Steven A. Godwin to the content of this chapter.

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***For additional X-Ray images resources, please access the bundled eBook chapter for this text.

CHAPTER 229

Gastrointestinal Bleeding

Michael Gayle and Niranjan Kissoon

Gastrointestinal (GI) bleeding in children is uncommon with reported incidence available for critically ill children only (1). While the common causes of GI bleeding vary with the child's age, the site of bleeding and character of the blood is age independent, and provides important clues in diagnosis and therapy. For instance, hematemesis (vomiting of blood) implies a source proximal to the ligament of Treitz. Vomited blood may have the appearance of coffee grounds or may be bright red, implying ongoing bleeding. Blood from the upper GI tract or proximal small bowel, when passed per rectum, is typically black or tarry, is sticky, has a characteristic aroma and is termed *melena.* Bright red blood per rectum or maroon stools (hematochezia) implies a more distal GI source (2). Upper GI bleeding, however, if blood loss is considerable and transit time is short, may present as hematochezia.

GI bleeding is an alarming problem in children, with many causes that are common to both children and adults. However, lesions such as necrotizing enterocolitis (NEC) or allergic colitis are unique to pediatrics (3). **Tables 229.1** and **229.2** outline the causes of GI bleeding in children and illustrate the wide, age-related differential diagnosis (2,4,5).

TABLE 229.1
Differential Diagnosis of Upper GI Bleeding

Newborn (0–1 mo)	Preschool (2–5 yrs)
Idiopathic	Esophagitis
Swallowed maternal blood	Gastritis
Esophagitis	Peptic ulcer
Gastritis	Varices (esophageal, gastric)
Stress ulcer	Mallory–Weiss tear
Vitamin K deficiency	Foreign body
Bleeding disorders	Bleeding disorders
Vascular anomalies	Vascular anomalies
Infant (1 mo–2 yrs)	**School Age (>5 yrs)**
Esophagitis	Esophagitis
Gastritis	Gastritis
Stress ulcer	Peptic ulcer
Mallory–Weiss tear	Varices (esophageal, gastric)
Vascular anomalies	Mallory–Weiss tear
Foreign body	Inflammatory bowel disease
Duplication	

TABLE 229.2
Differential Diagnosis of Lower GI Bleeding

Newborn (0–1 mo)	Preschool (2–5 yrs)
Anal fissure	Anal fissure
Local trauma	Polyps
Swallowed maternal blood	Infectious colitis
Upper GI bleeding	Meckel diverticulum
Necrotizing enterocolitis	Hemolytic–uremic syndrome
Malrotation with volvulus	Henoch–Schönlein purpura
Infectious colitis	Inflammatory bowel disease
Hirschsprung disease	Intussusception
Allergic colitis	Pseudomembranous colitis
Coagulopathy	Lymphonodular hyperplasia
Infant (1 mo–2 yrs)	**School Age (>5 yrs)**
Anal fissure	Anal fissure
Hirschsprung disease	Polyps
Allergic colitis	Infectious colitis
Intussusception	Hemorrhoids
Infectious colitis	Inflammatory bowel disease
Meckel diverticulum	Pseudomembranous colitis
Intestinal duplication	Lymphonodular hyperplasia
Lymphonodular hyperplasia	Hemolytic–uremic syndrome
Pseudomembranous colitis	Meckel diverticulum
Polyps	

CLINICAL PRESENTATION

Bleeding from anal fissures or from the upper GI tract is the most common reason children with GI bleeding visit the emergency department (ED). Life-threatening hemorrhage is rare and more likely to present as hemorrhagic shock. The GI tract as the source of bleeding is usually obvious although GI bleeding in a child may present as microcytic anemia from chronic upper GI bleeding or occult bleeding in the stool (e.g., cow's milk protein hypersensitivity) (2,6). The increased use of NSAIDs such as ibuprofen and naproxen for pain and fever in children, especially when combined with salicylate, appears to have resulted in a greater rate of gastric ulceration and erosions (7).

Acute bleeding can be classified as occult, overt, or massive. Massive bleeding (e.g., variceal bleeding) is the most dramatic

presentation and is usually accompanied by some degree of hemodynamic compromise.

DIFFERENTIAL DIAGNOSIS

A thorough history and clinical examination can usually lead to the diagnosis. Most patients presenting to the ED are stable yet, the differential diagnosis GI bleeding is large (**Tables 229.1** and **229.2**). The most important initial step is to determine whether the bleeding is of upper or the lower GI tract origin. The easiest method is to atraumatically insert a small, soft, nasogastric tube and perform a gastric lavage with tap water or normal saline at room temperature. Normal saline at room temperature (not chilled or "iced") should be used as the lavage fluid to avoid hypothermia, especially in infants or young children who are more prone to heat loss (8). If blood is not evident in lavage, it is unlikely the bleeding originates from above the ligament of Treitz.

The differential diagnosis of suspected GI bleeding in children is generally divided by age: (1) neonates to 1 month of age, (2) infants 1 month to 2 years, (3) preschool children 2 years to 5 years, and (4) school-aged children over 5 years. While some items in the age-specific differentials may overlap, there are unique causes of GI bleeding in each of these groups.

Newborn (0 to 1 Month)

Most causes of bleeding in neonates are never identified, since most bleeding is mild and stops spontaneously between 24 and 48 hours of life. Significant upper GI bleeding is more likely in neonates with sepsis, an intracranial lesion, or other major illness, in the form of stress ulcers or hemorrhagic gastritis. Hematemesis may also result from hemorrhagic disease of the newborn (vitamin K deficiency) or congenital bleeding disorders such as hemophilia, congenital thrombocytopenia, or the swallowing of a mixture of amniotic fluid and maternal blood (swallowed blood, however, may also manifest as lower GI bleeding). Swallowed maternal blood in breast-fed infants may come from a cracked nipple. The adult hemoglobin in

these cases can be easily differentiated from upper GI bleeding of patient origin (which will be fetal hemoglobin) using the Apt–Downey test (adding sodium hydroxide to a blood sample). Fetal hemoglobin resists alkaline degradation remaining pink whereas adult hemoglobin turns a brownish color (12).

Anal fissures and local trauma are the most common causes of rectal bleeding in the first month of life. However, both NEC and enterocolitis due to Hirschsprung disease (see Chapters 228 and 230) may present with occult or overt rectal bleeding. NEC is more common in preterm infants but may also be seen in the stressed term infant. Bilious vomiting, abdominal distention, and rectal bleeding are the most common clinical features and may also be due to surgical emergencies such as midgut volvulus. The finding of air in the bowel wall (pneumatosis intestinalis) on an abdominal radiograph is pathognomonic for NEC. While NEC is extremely rare relative to anal fissures clinicians should document pertinent negatives favoring a more benign anal fissure over more serious etiologies such as NEC.

Infant (1 Month to 2 Years)

In the infant upper GI bleeding is frequently caused by esophagitis, gastritis, or stress ulcers. Congenital malformations, such as duodenal web, while more likely to present in the newborn period, can present after the first month of life.

Lower GI bleeding is most commonly due to anal fissure and allergic colitis. Considerations should also include anorectal lesions, such as juvenile polyps (5). Intussusception, which may occasionally present with currant jelly stools, is most common in infants 7 to 12 months old (see Chapters 228 and 270). Infectious colitis is usually secondary to species of *Salmonella, Shigella, Campylobacter jejuni, Yersinia enterocolitica,* and *E coli* 0157:H7 (4) (see Chapter 224). *Clostridium difficile* infections are not always associated with recent antibiotic use and should therefore also be considered (4). In very limited circumstances other organisms that could be considered include *Aeromonas hydrophila* and *Entamoeba histolytica* (4). In

children with the acquired immunodeficiency syndrome (see Chapter 279), GI bleeding due to opportunistic infections such as cytomegalovirus should also be considered in the differential diagnosis (13).

Preschool (2 to 5 Years)

Anal fissures, infectious enteritis, and juvenile polyps are the most frequent causes of lower GI bleeding in the preschool age group. These polyps are usually solitary and benign and can often be felt on rectal examination (5). Massive GI bleeding from Meckel diverticulum is sometimes seen in preschool children. Infectious enterocolitis from agents similar to those described for the infant may also present with bloody stools. Multisystem diseases such as hemolytic–uremic syndrome and Henoch–Schönlein purpura are less common causes of bloody stools (see Chapter 287).

Varices in both the upper and the lower GI tracts can lead to massive, life-threatening hemorrhage in the appropriate patient population. Two-thirds of patients with portal hypertension sustain bleeds before 5 years of age, and 85% do so by age 10 years. On physical examination, other signs of portal hypertension or liver disease, such as splenomegaly, hepatomegaly, and dilated abdominal veins are present (14). Foreign body ingestion, although uncommon, should also be considered as a cause of upper GI bleeding (see Chapter 273).

School Age (Over 5 Years)

Anal fissures and juvenile polyps account for the majority of cases of lower GI bleeding. Intestinal lymphonodular hyperplasia of childhood has a peak incidence between 6 and 10 years; inflammatory bowel diseases (e.g., Crohn disease and ulcerative colitis) have a peak incidence in children over 5 years (15).

Esophagitis, gastritis, and peptic ulcer disease account for most cases of upper GI bleeding in school age children. Acute erosions of the gastric mucosa may occur after any major physiologic stress, such as trauma, shock, burns, or sepsis. Peptic ulcer disease may be

either primary or secondary to medications such as those used in patients with cystic fibrosis (e.g., corticosteroids and nonsteroidal anti-inflammatory agents). The possibility of occult oral ingestion of illicit drugs (e.g., cocaine) or iron tablets should be considered in cases of unexplained shock and hemorrhagic diarrhea (15).

ED EVALUATION

If the patient presents with signs and symptoms of cardiovascular compromise, immediate attention to restoring intravascular volume is necessary (see Chapters 217 and 219). Usually, however, the evaluation can be done in less urgent manner, beginning with a thorough history and physical examination. Under these circumstances, the emergency physician's initial step is to determine the site and magnitude of bleeding and whether it is ongoing.

Important elements of the history and physical examination are outlined in Table 229.3. A nasogastric tube should be inserted and fluid aspirated, unless a distal source is obvious. A positive aspirate for blood almost certainly indicates that the site of bleeding is proximal to the ligament of Treitz. However, a negative aspirate does not exclude an upper GI bleeding site beyond the pylorus.

TABLE 229.3
History and Physical Examination for GI Bleeding

History

Bleeding (duration, quantity, color, rectal vs. oral)
Associated abdominal pain
Vomiting/diarrhea
Medication history (e.g., aspirin, NSAIDs, steroid, alcohol)
Illicit drugs (e.g., cocaine)
Systemic diseases
Family history (e.g., bleeding disorder)
Social history

Physical Examination

Vital signs
Site of bleeding (nose, mouth, outside GI tract)
Acuity or chronicity
Anthropometric data
Cutaneous signs (e.g., spider nevi)
Abdominal tenderness/mass
Hepatomegaly
Splenomegaly
Anorectal examination

In most cases, the cause of bleeding is evident, but before beginning an expensive and possibly invasive workup, clinicians should confirm whether the patient is actually passing blood. Many foods and medications (e.g., tomato or cranberry juice, flavored gelatin, Kool-Aid, red licorice, ampicillin, rifampin, iron, and bismuth preparations [Pepto-Bismol]) can give stools a bloody appearance or a positive test for blood (2). In most hospitals, guaiac benzidine or benzidine derivative test pads (Hemoccult or Hematest) are used to detect blood. These tests use a hydrogen peroxide developer and are based on the peroxidase activity of hemoglobin and its derivatives. In the presence of hydrogen peroxide, these substances catalytically oxidize substrates such as guaiac or benzidine. The oxidation produces a color change in the substrate, indicating a positive test. However, false-negative results can be obtained if the patient has ingested large doses of ascorbic acid or if intestinal bacteria have degraded the hemoglobin to porphyrin. False-positive results can be seen if the patient has eaten

rare red meat or peroxidase-containing fruits and vegetables such as broccoli, radishes, cauliflower, cantaloupe, or turnips. The HemoQuant test, appears to be more sensitive and less prone to erroneous results (16).

Radiographic and nuclear imaging studies are rarely necessary in the ED. A plain abdominal x-ray may be useful if a foreign body ingestion, bowel perforation, or a bowel obstruction is suspected. Ultrasonography is indicated when intussusception, liver disease, portal hypertension, or vascular anomalies are suspected (10,11).

Laboratory studies (Table 229.4) should include a complete blood count with platelet and reticulocyte counts and a coagulation profile. An elevated eosinophil count signifies milk allergy or parasitic infestation. If bleeding is severe, blood should also be sent for a crossmatch. The BUN/Cr ratio is often used as an indicator of a source of bleeding in the upper GI tract and may provide an estimate of the severity of blood loss. An elevated BUN level is more likely to be associated with an upper than a lower GI bleed (9,17). Hepatic and renal function tests should be obtained. If an infective cause is suspected, stool should be examined promptly for fecal leukocytes, aerobic, and anaerobic cultures, and microscopy for ova and parasites (4,18).

TABLE 229.4
Laboratory Studies

Blood count: CBC with reticulocyte count
Coagulation profile: platelet count, prothrombin time, partial thromboplastin time, fibrinogen
Hepatic profile: bilirubin, SGPT, SGOT, albumin, alkaline phosphatase
Renal profile: Blood urea (BUN), creatinine (Cr), BUN/Cr ratio
Blood bank: type and crossmatch
Stools: Guaiac test, leukocytes, aerobic and anaerobic stool cultures, *C difficile* antigens, microscopy for ova and parasites

Plain radiography and sonography are noninvasive and minimally distressing and may give definitive information, such as a classic appearance of multiple short fluid levels in the abdomen in a

neonate with volvulus, or the appearance of an intraluminal mass on sonography with intussusception. If intussusception is suspected but the ultrasound is equivocal or inconclusive, an abdominal computed tomographic (CT) should be performed to evaluate for a rare form of intussusception known as small bowel intussusceptions disease which is usually ileal (19).

If the source of bleeding is not obvious after initial testing, more detailed evaluation, including endoscopy and complex radiographic procedures, may be necessary. However, most of these will not be conducted as part of the ED workup. In children with a positive nasogastric aspirate, endoscopy within the first 24 hours can determine the source of upper GI bleeding in 90% of cases. Emergency endoscopy in children has shown that the most common causes of bleeding are esophagitis, esophageal varices, gastritis, and duodenal ulcers (20, 21). Endoscopy is especially necessary in children with a history of esophageal varices, because the source of bleeding may be from other lesions. Upper GI barium studies are less accurate than endoscopy and may interfere with subsequent endoscopic examination.

Both endoscopy and barium studies may fail to determine the source of bleeding in patients with massive bleeding (bleeding greater than 0.5 mL/min, renders endoscopic examination of limited use). In these patients, arteriographic examination or nuclear scans (preferred by some clinicians due to lower complication rates (22)) of the superior and mesenteric arteries and the celiac axis may reveal a common cause of bleeding or, some less frequent causes such as hepatic artery aneurysm, traumatic hematobilia, arteriovenous malformation or hemangioma.

If the nasogastric aspirate does not contain blood, a rectal examination and colonoscopy can identify the source of rectal bleeding in 80% of cases. Additional studies are needed to identify the other 20%. Dark blood mixed with stool, in the absence of abdominal pain or diarrhea, may indicate Meckel diverticulum, intestinal duplication, or right-sided colonic polyps. A bleeding Meckel diverticulum is the cause in 80% of cases and can often be diagnosed by a nuclear medicine scan. Colonoscopy and, ultimately,

an air-contrast barium enema should be performed if the scan is inconclusive.

KEY TESTING

- Nasogastric aspiration to determine if source of bleeding is proximal to the ligament of Treitz
- Apt test in neonates or infants who may have swallowed maternal blood from cracked nipples
- CBC, PT, INR, and type and screen in appropriate patients with moderate to severe bleeding
- BUN and creatinine, liver function tests
- Plain x-ray of the abdomen for evidence of foreign body, bowel perforation, or pneumatosis
- Ultrasound for intussusception, or evaluation of portal hypertension
- Stool studies for infectious bloody diarrheas

ED MANAGEMENT

Assessment of Cardiovascular Status

Management depends on the child's clinical status and the severity and site of bleeding (Fig. 229.1).

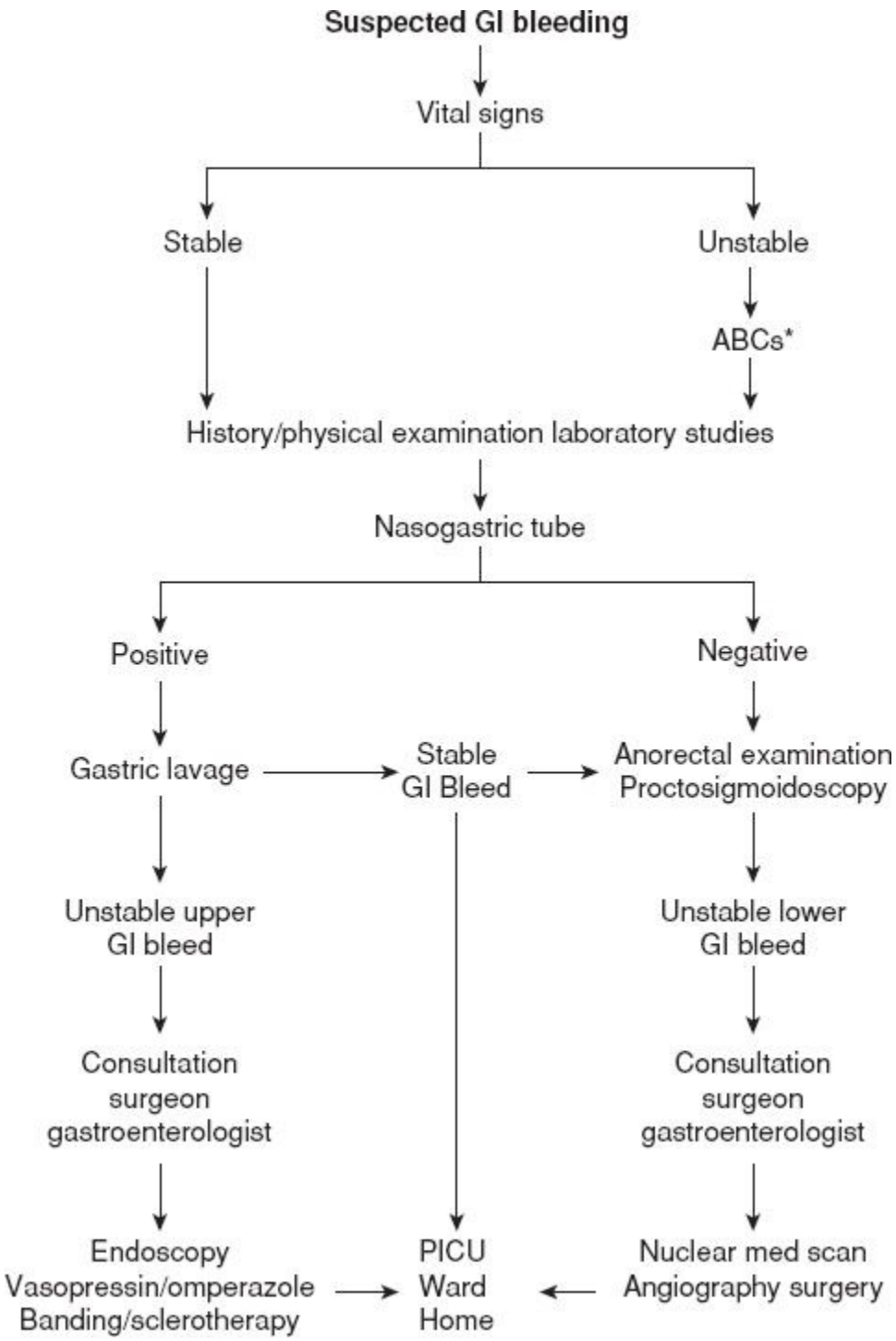

FIGURE 229.1 Flow diagram of suggested Management of GI bleeding in the ED ABCs (Airway Breathing Circulation) include attention to respiratory status (may include endotracheal intubation) and cardiovascular support (include vascular access, crystalloid, FFP, platelets, and blood infusions).

Initial management is based on the child's condition, including factors such as age, source, rate, and amount of bleeding, and associated medical illnesses. Assessment of cardiopulmonary status and prompt attention to any derangements should be a priority (see Chapters 217 and 219). Oxygen administration and venous access, followed by fluid boluses of crystalloids (20 mL/kg lactated Ringer or normal saline), are mandatory, particularly if the patient has signs of volume compromise (anxiety, tachycardia, weak pulses, delayed capillary refill, hypotension, tachypnea). Additional fluid boluses should be given as determined by frequent reevaluations. A nasogastric tube is then placed in the stomach, and lavage with tap water or room temperature saline should be started.

Occult Bleeding

In the stable child with occult bleeding, management is geared toward establishing a diagnosis and excluding serious conditions. Investigations are dictated by the history and physical examination, but most tests, including cultures, radiologic or nuclear medicine scans, and endoscopy, can be performed on an outpatient basis. The cause of occult upper GI bleeding in children is often not from the GI tract. Although anal fissures account for most cases of occult blood in stools, physicians should always consider less benign causes (e.g., NEC or intussusception) in the ill appearing neonate or infant. Occult bleeding may also presage other serious events, such as Meckel diverticulum.

Overt Bleeding

Administration of crystalloids (normal saline or Ringer lactate) to restore intravascular volume is the management priority. Samples for urgent type and crossmatch should be sent or O-negative blood made immediately available. The child who has lost 10% to 20% of his or her blood volume does not necessarily require blood replacement, provided the bleeding has stopped. If, after 20% of the blood volume has been replaced by crystalloid and bleeding continues then transfusion will likely be necessary. The child's age

and physical condition may also dictate the need for blood; for example, children with heart and chronic lung disease may require transfusion earlier. Platelets, fresh frozen plasma, or vitamin K (1 mg per year of age, up to 10 mg) is given to correct an identified coagulopathy. Consideration should be given to the use of recombinant factor VII therapy (60 to 90 μgm/kg per dose, intravenously) in cases of bleeding due to severe coagulopathy from DIC or an unknown cause (23). In the neonate suspected of vitamin K deficiency, vitamin K (1 mg) is given intramuscularly. H_2 blockers are best given intravenously by continuous infusion. Ranitidine is the recommended agent at a dosage of 1.5 to 6 mg/kg/d intravenously, depending on the patient's age. High-dose antisecretory therapy with an intravenous pump inhibitor such as omeprazole, has been shown to be relatively safe in the treatment of children with GI hemorrhage (24). Acid suppression therapy with antacids, H_2 blockers, sucralfate, and a proton pump inhibitor, may be administered although there are no studies demonstrating clear benefits in children.

Massive Bleeding

Aggressive fluid resuscitation and administration of blood components is the usual management, however, in some cases, endotracheal intubation, to secure the airway and decrease the work of breathing, is needed in a patient with low cardiac output. Endotracheal intubation allows adequate sedation without the risk of hypoventilation or aspiration, and also facilitates endoscopy (see Chapter 218). Continuous monitoring of vital signs, urine output, and oxygen saturation are essential. Central venous catheter placement, although not mandatory, may be helpful for vascular access and for monitoring intravascular volume status.

Management of children with massive variceal bleeding from portal hypertension includes NG tube placement, correction of coagulopathy with platelets, vitamin K and FFP, intravenous vasopressin (0.33 U/kg bolus and infusion of 0.2 U/1.73 m^2/min infusion), octreotide infusion (1 to 5 μg/kg/hr), and variceal

injection, or ligation via endoscopy (14). In life-threatening GI bleeding, consideration should also be given to the use of recombinant activated factor VII (23).

Massive bleeding can also occur in children with Meckel diverticulum; these patients also require aggressive resuscitation. Following cardiovascular stabilization, the site of bleeding can be confirmed by a nuclear scan or by arteriography. If massive bleeding precludes stabilization, immediate laparotomy may become necessary.

CRITICAL INTERVENTIONS

- Assessment of cardiorespiratory status—determine if shock or respiratory distress is present and resuscitate appropriately
- If the patient has a massive GI bleed, start two large bore IVs. Send blood for type and crossmatch, and coagulation factors
- Quick history and physical examination—determine source of bleeding
- Pass a NG tube and perform gastric lavage if the source is not obvious or is suspected to be from the upper GI tract
- Check stools to see if blood is present

DISPOSITION

Conditions requiring urgent surgical evaluation include volvulus, vascular malformations, and NEC in the neonate. Some cases of GI bleeding from stress ulcers, variceal bleeding, or intussusception may also require urgent surgical evaluation. Consultation with a pediatric gastroenterologist, pediatric surgeon, and/or pediatric intensivist may be necessary early in management. Panendoscopy to establish a specific diagnosis and to assess the rapidity of bleeding, the risk of rebleeding, and, the administration of definitive therapy may be required (20,21).

During interhospital transfer, the child with GI bleeding is prone to compromise the cardiorespiratory system. Oxygenation and vascular access with the administration of crystalloid are priorities if there is evidence of vascular compromise. Continuous monitoring to

ensure an adequate airway and stable vital signs is mandatory. Although personnel skilled in advanced pediatric life support should accompany the child, attention to stabilization before transport should minimize the need for interventions during transport.

Common Pitfalls

- Assuming the colored material is blood. Many foods and medicines can give secretions or stools a bloody appearance.
- Failing to perform an Apt test on a neonate's gastric contents or stool to rule out swallowed maternal blood.
- Using the wrong-sized nasogastric tube. Smaller bore tubes may be adequate for assessing bleeding, but not for removing clots.
- If the nasogastric aspirate does not sample duodenal contents, or if bleeding is intermittent, a false-negative aspirate may result.
- A traumatically placed nasogastric tube may yield a false-positive aspirate and cause distress to the patient. Iodine, supplemental iron, and ingestion of red meat may cause false-positive results.
- A normal hemoglobin level does not exclude significant, rapid GI bleeding.
- A normal or increased blood pressure in children does not exclude hypovolemia.
- Performing a barium study before endoscopy.
- Not considering sexual abuse as a cause of anal fissures.
- Failing to consider nonorganic causes (e.g., Munchausen syndrome by proxy) of GI bleeding.

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CHAPTER 230 Constipation

Le N. Lu and Dewesh Agrawal

Although there are relatively few situations in which disorders of bowel control are truly emergent in children, parental concerns about constipation frequently result in emergency department (ED) visits. Emergency physicians should be able to distinguish abnormal from normal bowel habits and advise concerned parents about the developmental process of bowel control, including normal stooling patterns.

In the pediatric population, a single definition of constipation has not been agreed upon. Although many parents focus on the length of time between bowel movements, a determination of normal should encompass stool consistency and the ease with which the stool is passed. The North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) defines constipation as a delay or difficulty in defecation present for 2 or more weeks sufficient to cause significant distress to the patient (1). The epidemiology and clinical scenarios commonly associated with constipation vary with age. In infants and toddlers, constipation occurs equally in boys and girls. In older, prepubertal children, constipation is more common in boys, with a male-to-female ratio of 3:1. During adolescence, this ratio reverses, with constipation being three times more common in girls (2).

There is a wide variation of “normal” stool patterns. The normal newborn passes a meconium stool within the first 48 hours of life and a mean of four stools per day during the first week of life. Some breast-fed newborns may pass a small, loose stool after each feeding, whereas others may not produce stools for several days.

The frequency of stooling gradually declines to a mean average of 1.7 stools per day by age 2, approaching the adult mean of 1.2 stools per day by age 4. In children beyond infancy, the normal frequency ranges from one stool every other day to three per day (1,2). The color of stool changes from thick tarry meconium in the first few days of life to yellow mustard-colored stools ("milk stools") a few days after the mother's milk comes in. Formula-fed babies may have tan, green, or yellow stools.

CLINICAL PRESENTATION

A newborn infant discharged from the hospital before reaching 48 hours of age is brought to the ED with a history of constipation, progressive abdominal distention, and vomiting. This disorder may be caused by imperforate anus, anal stenosis, meconium plug syndrome, meconium ileus, or Hirschsprung disease.

Many healthy infants cry, strain, grunt, and turn red or purple in the face for 5 to 10 minutes during normal bowel movements. Distraught parents, erroneously interpreting this behavior as a sign of constipation, may present to the ED seeking relief for the infant's perceived abdominal pain. This behavior is caused by the infant's immature coordination between abdominal muscle contraction and relaxation of the pelvic floor (2,3). As long as the stools are soft in consistency and normal in appearance, parents should be reassured that this condition generally resolves spontaneously (4). Rectal stimulation may be counterproductive, and routine laxatives and enemas are unnecessary and should be avoided.

Constipation in children older than 24 months is far less likely to be serious or life-threatening, yet is a source of great anxiety and frustration for some parents. These children usually present with periumbilical abdominal pain, distension, anorexia, and irritability. Upon questioning, a history of similar episodes of abdominal pain and marked symptomatic improvement after a large bowel movement may be elicited. Occasionally, parents describe actions such as squirming, standing on toes, rolling into fetal position, or other ritualistic behaviors, which are often misinterpreted as

straining to defecate, but are actually attempts to withhold stool and relieve the urge to defecate. The association of pain with defecation leads to the cycle of retention and subsequent avoidance of defecation, and increasing fecal mass with further degrees of retention (4). This situation may be caused or complicated by the development of anal fissures, which cause pain with the passage of each large stool. Eventually, the fecal mass may become impacted, and unformed liquid stool may leak around the impaction, resulting in overflow incontinence and soiling of undergarments. A lower abdominal mass may be found on palpation, and a rectal examination may reveal fecal impaction (2). In addition, there is an association between stool retention behavior and dysfunctional urinary voiding which may lead to renal tract dilation and urinary tract infection (5–7).

DIFFERENTIAL DIAGNOSIS

The major causes of constipation in children can be divided into two broad categories: functional and organic (Table 230.1). Functional constipation is defined as constipation without objective evidence of a pathologic condition (1). Although organic causes are responsible for fewer than 5% of cases, failing to diagnose these may have serious consequences. Findings associated with an organic etiology for constipation include delayed growth, delayed passage of meconium, urinary incontinence or bladder disease, hematochezia, melena, constipation from birth, fever, vomiting, or an empty rectum on physical examination. In the newborn, failure or delay in passing meconium is of organic etiology until proven otherwise. Anatomic malformations and congenital intestinal disorders are more likely to present in infancy than at a later age, but nonorganic causes of constipation predominate at all ages (2,8). Findings supporting a functional etiology include stool withholding behavior, good response to conventional laxatives, or onset of symptoms coinciding with dietary changes, toilet training, or painful defecation. Beyond the immediate newborn period, constipation tends to be less emergent in nature, and most cases have either a

functional or dietary cause (8,9). In a child presenting with a chief complaint of abdominal pain, functional constipation should be a diagnosis of exclusion after all pathologic causes of abdominal pain have been ruled out.

TABLE 230.1
Differential Diagnosis of Constipation

Functional
Developmental: cognitive handicaps, attention deficit disorders
Situational: coercive toilet training, school bathroom avoidance, sexual abuse
Reduced stool volume and dryness: low-fiber diet, dehydration, malnutrition
Organic
Anatomical: imperforate anus, anal stenosis, anal stricture, anteriorly displaced anus, pelvic mass, rectal abscess
Metabolic/endocrine: hypothyroidism, hypercalcemia, hypokalemia, cystic fibrosis, diabetes mellitus, gluten enteropathy
Neurologic: Hirschsprung disease, spinal cord abnormalities, neuronal dysgenesis, tethered cord, neurofibromatosis, cerebral palsy
Muscular: prune belly, gastroschisis, myopathy, infant botulism
Connective tissue disorders: scleroderma, lupus, Ehlers–Danlos syndrome
Drugs: opiates, phenobarbital, sucralfate, antacids, anticholinergics, antidepressants
Other: cow's milk intolerance, botulism, lead toxicity, vitamin D intoxication

Adapted from Baker SS, Liptak GS, Colletti RB, et al. Evaluation and treatment of constipation in infants and children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2006;43(3):e1–e13.

Imperforate anus is usually diagnosed by inspection, which reveals no anal opening. In anal stenosis, the anus appears small with a central black dot of meconium.

Meconium plug syndrome is strongly related to Hirschsprung disease and presents with little or no meconium in the newborn period and with progressive signs of intestinal obstruction. Hirschsprung disease is the cause of up to 25% of neonatal intestinal obstructions. Gentle digital examination may produce passage of a dry, hard plug of meconium. Hirschsprung disease typically presents with an empty rectal vault and a long, sleeve-like anal canal around the examining finger. It is more common in boys and is occasionally

associated with Down syndrome. More advanced cases may present in early infancy with enterocolitis, sepsis, fever, vomiting, and diarrhea that can progress to toxic megacolon. Newborns who are not diagnosed may present later in childhood with chronic constipation, abdominal distention, and failure to thrive. In addition to a failure to pass meconium within the first 48 hours of life, these patients experience ongoing constipation and small-diameter (ribbon-like) stools.

Meconium ileus occurs when meconium becomes inspissated and obstructs the distal ileum. It is virtually pathognomonic of cystic fibrosis and precedes the respiratory symptoms of the disease, which are usually absent in the newborn. The clinical picture is usually dominated by the bowel obstruction and its associated complications including perforation, peritonitis, or volvulus.

Botulism is a rare but potentially life-threatening neuroparalytic syndrome from the action of the neurotoxin produced by *Clostridium botulinum*. Although the disease presentation and severity varies, the initial presentation may simply involve constipation, followed shortly by weakness, feeding difficulties, respiratory difficulties, descending paralysis, drooling, anorexia, and a weak cry.

The clinical manifestations of lead poisoning vary with lead level, the age of the exposed individual, and the acuity of poisoning. Lead colic includes sporadic vomiting and intermittent abdominal pain. Constipation may occur with blood lead levels >60 μg/dL (2.9 μmol/L).

ED EVALUATION AND MANAGEMENT

The Constipation Subcommittee of NASPGHAN has developed a clinical practice guideline for the evaluation and management of constipation (1). A history and physical examination often provide the diagnosis without requiring further studies in the ED (8). Information regarding the time after birth of the first bowel movement, length of time the condition has been present, frequency of bowel movements, consistency and size of stools, presence of pain and blood, and toilet use habits (if applicable) should be obtained.

Dietary habits, medications, associated fever, abdominal distention, anorexia, vomiting, weight loss, and poor weight gain should be assessed. Physical examination should include abdominal palpation for masses, especially fecal masses in the left lower quadrant; inspection of the perineum and perianal area for fissure, anterior displacement, or stenosis; and inspection of the sacrum and lower extremity neurologic examination for signs of myelodysplasia. Gentle rectal examination with a well-lubricated fifth digit should be attempted, but not forced on an unwilling child, to assess perianal sensation, anal tone, rectal size, presence of an anal wink, and the amount and consistency of stool within the rectum.

Exhaustive laboratory and radiographic investigation is not usually required in the ED (8). It is recommended that a test for occult blood in the stool be considered in all infants with constipation and in any child who also has severe abdominal pain, failure to thrive, intermittent diarrhea, or a family history of colon cancer or colonic polyps. If the history is chronic, a urine culture should be obtained to avoid missing an occult urinary tract infection. If the rectal examination reveals the presence of large amounts of stool in the rectal vault an abdominal radiograph is not necessary to diagnose fecal impaction and is in fact a redundant test. Occasionally, a plain abdominal radiograph may be helpful in confirming the diagnosis when the history or physical examination are confusing or inconclusive, or other causes of acute abdominal pain have been ruled out.

The first step in managing constipation is education of the child and family. Disimpaction may be necessary prior to initiation of maintenance therapy. Disimpaction can be accomplished by using oral medications (Table 230.2), rectal medications, or a combination of the two. All approaches have been determined to be effective in clinical trials (1,10–13) and the individual approach should be discussed with the child and family. Rectal disimpaction may be performed in older children using sodium phosphate soda enemas, saline enemas, mineral oil enemas, milk and molasses enemas, or polyethylene glycol (PEG, MiraLAX) oral solution (10–13). Although an enema may provide more immediate relief of symptoms than

polyethylene glycol, they are equally effective (10,12). Cathartics, suppositories (other than small glycerin suppositories), and enemas should generally be avoided in infants (1). The use of soap suds, tap water, and magnesium enemas is not recommended because of potential toxicity; tap water enemas have been associated with acute hyponatremia, seizures, and death (14).

TABLE 230.2
Oral Disimpaction Therapy

Mineral oil[a]: 1–4 mL/kg/d divided daily or bid
Milk of magnesia: 1–3 mL/kg/d divided daily or bid
Lactulose: 1–3 mL/kg/d divided daily or bid
Polyethylene glycol (MiraLAX):
Disimpaction: 1.5 g/kg/d × 3–6 d (maximum 100 g/d)
Maintenance: 1 g/kg/d divided bid (maximum 17 g/d; prepared by mixing 1 capful of powder in 8 oz of liquid)
Sorbitol: 1–3 mL/kg/d divided BID (70% solution)
Senna: 2–6 yrs old, 2.5 to 7.5 mL daily; 6–12 years old, 5–15 mL daily (syrup)
Bisacodyl: 5–10 mg daily

[a]Contraindicated in infants and children at risk for aspiration.
bid, twice daily.

Maintenance therapy of constipation, best managed by the child's primary care clinician, consists of dietary changes, behavioral modification, and laxatives (1,8). Dietary management includes increasing fluid intake and adding bulk and fruits, such as prunes or plums, to the diet. Barley malt extract (Maltsupex) or corn syrup (Karo) can be safely recommended for infants in a dosage of 5 to 10 mL two to four times daily, added to formula, juice, or food. Behavioral modification for the older child with stool withholding includes regular toilet sitting (especially immediately after meals to harness the gastrocolic reflex), stool diaries, and reward systems. Parents and children should be educated about stool-withholding behaviors and rituals. Although there is some evidence that increased fiber may be more effective than placebo for chronic childhood constipation, there is insufficient evidence for other

nonpharmacologic interventions such as prebiotics, probiotics, increased fluid intake, behavioral therapy, and other forms of alternative medicine (15,16). In older infants and toddlers, maintenance therapy may include milk of magnesia, mineral oil, lactulose, or polyethylene glycol (MiraLAX). A systematic review failed to find sufficient evidence to recommend any one laxative or dietary treatment over another (15). Polyethylene glycol and milk of magnesia are equally effective in the long-term treatment of children with constipation and fecal incontinence (8,17,18). Docusate or senna extract can also be safely used daily in older children.

Management of anal fissure includes frequent, gentle, thorough cleansing of the anus and liberal lubrication with petroleum jelly. A stool softener must be used, and a topical anesthetic ointment such as dibucaine may be necessary (19). Aggressive care of the simple fissure is necessary to prevent a pain-retention cycle from becoming established.

KEY TESTING

- Careful complete history and physical examination.
- Abdominal radiograph may be indicated in patients with no stool in the rectal vault and when the history and physical are inconclusive.
- Urinalysis and culture in patients with history of chronic constipation to evaluate for occult UTI

CRITICAL INTERVENTIONS

- History and physical examination are essential to evaluating a child with constipation.
- All newborns presenting with constipation should be evaluated for serious or life-threatening etiologies.
- Aggressively treat anal fissures to break the pain-retention cycle.
- Provide parent education regarding behavior modification and the importance of regular follow-up with a primary care provider.

DISPOSITION

Consultation for routine constipation is unnecessary. Infants with suspected Hirschsprung enterocolitis or bowel obstruction should be expeditiously referred to a pediatric surgeon. Older children with suspected Hirschsprung disease should be referred to a pediatric gastroenterologist or pediatric surgeon. Children with chronic constipation with or without encopresis should be referred to a pediatrician for long-term management.

The following are indications for admission: (1) failure to pass meconium within the first 48 hours of life, (2) acute bowel obstruction, or (3) evidence of toxic megacolon complicating Hirschsprung disease. Occasionally, complicated disimpaction and the initiation of a therapeutic regimen for chronic constipation with encopresis may require admission, but this is rare.

Common Pitfalls

- In the newborn or young infant, failing to entertain a broad differential diagnosis which should include Hirschsprung disease, necrotizing enterocolitis, congenital gastrointestinal malformations, and infant botulism.
- In older children with marked stool retention, misinterpreting withholding behaviors as straining to defecate.

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CHAPTER 231
Cough

George Waterman

CLINICAL PRESENTATION

Cough is a frequent complaint for children who present to the emergency department (ED). Coughing is a vital reflex for clearing secretions from the airway and for protection from inhalation of foreign matter. Although in many cases cough is caused by a self-limited viral illness, it is a nonspecific symptom requiring a systematic approach to exclude serious pathology (1).

DIFFERENTIAL DIAGNOSIS

There are multiple possible etiologies for coughing in a child. Selected causes will be discussed in more detail. A more comprehensive list can be found in Table 231.1.

TABLE 231.1
Causes of Cough in Children (2)

Congenital Abnormalities	Inflammatory/Environmental
Vascular Ring	Allergic rhinitis
Laryngomalacia	Asthma
Tracheomalacia	Smoke exposure
Tracheoesophageal fistula	Foreign body aspiration
Infectious	**Other**
Viral upper respiratory illness	Tourette syndrome
Sinusitis	Foreign body in ear canal
Bronchitis	Gastroesophageal reflux
Croup	Medications
Pertussis	Cardiac
Bronchiolitis	
Pneumonia	

The most common cause of childhood cough is viral upper respiratory infection (3). These children are typically well appearing and often exhibit rhinorrhea on examination. Coughing associated with these illnesses is expected to resolve within 3 weeks (4).

Upper airway cough syndrome is a common cause of cough due to irritation of the upper airway from postnasal drip due to viruses or allergens. This is a frequent cause of acute cough in children with common colds (5).

Asthma may sometimes present with coughing as the predominant symptom (6). Supportive evidence of a diagnosis of asthma includes a personal or family history of atopic symptoms such as eczema or allergic rhinitis (7).

Coughing has been cited as a common symptom in many cases of foreign body aspiration (8). A foreign body must be ruled out if a persistent cough follows a choking episode.

Cough associated with fever, tachypnea, and rales on auscultation is a concern for pneumonia. These children are often ill appearing with increased work of breathing. *Streptococcus pneumoniae* is the most common bacterial pathogen, but other likely possibilities include viruses, *Mycoplasma pneumoniae,* and *Chlamydia pneumoniae* (see Chapter 265) (9).

Bordetella pertussis should be considered if cough is prolonged (>3 weeks) in duration, if it is paroxysmal, and if associated with

posttussive emesis (10). Despite widespread vaccination, the incidence of pertussis has been on the rise for the past 15 years (see Chapter 262) (11).

Chronic cough in infants and children is often caused by asthma or recurring viral upper respiratory infections. Anatomic abnormalities, such as anomalies causing compression of the airway, can lead to persistent or recurrent symptoms. These include vascular rings, coarctation of the aorta, hemangiomas, pulmonary sequestrations, and masses in the mediastinum. Tracheoesophageal fistula should also be suspected in infants with repeated episodes of aspiration or in those with features of VACTERL association (a group of abnormalities that may include *V*ertebral defects, *A*nal atresia, *C*ardiac defects, *T*racheo-*E*sophageal fistula, *R*enal anomalies, and *L*imb abnormalities) (12).

Tuberculosis is a consideration in children who have a history of traveling to endemic areas, particularly if there are associated symptoms of weight loss, hemoptysis, and night sweats (13).

DIAGNOSTIC APPROACH

The examination of any patient with a cough will begin with evaluation of the airway and of the effectiveness of breathing and circulation. The airway should be evaluated for patency, and breathing for accessory muscle use and abnormal sounds. A complete set of vital signs including pulse oximetry should be obtained on arrival. If there is concern for increased work of breathing or hypoxemia, oxygen should be administered and the child should be kept in a position of comfort. Advanced airway equipment should be readily available for the child who does not respond to basic interventions. Children with severe croup or those with foreign bodies in the trachea may require intubation if they show signs of respiratory failure. Although rare in Western countries nowadays, if epiglottitis is suspected, intubation is ideally performed in the operating room. After initial stabilization as needed, a more detailed history and physical examination should be

initiated. In the majority of cases, this will be sufficient to arrive at a diagnosis. Important historical elements are listed in Table 231.2.

TABLE 231.2
Historical Elements

Age of onset of cough
Duration of cough
Characteristics and associated symptoms
Factors that improve/worsen cough
Past medical history including surgical procedures
Medications/allergies
Environmental exposure including travel history, trauma
History of choking prior to cough

The physical examination should begin with the overall appearance of the child while at rest. If possible, it may be useful to have a child sit in the caregiver's lap initially to assess for work of breathing while the patient is calm. Important findings to note on physical examination are listed in Table 231.3.

TABLE 231.3
Physical Examination

Overall appearance including body habitus
Work of breathing (retractions, grunting, nasal flaring)
Nasal discharge/swollen nasal turbinates
Allergic shiners/nasal creasing
Foreign material in ears/nose
Tonsillar hypertrophy
Heart murmurs
Breath sounds (wheezes, rales, stridor)
Organomegaly
Clubbing/cyanosis

A chest x-ray should be obtained if there is suspicion of a foreign body, significant respiratory distress, or concern for a bacterial etiology. If concern for foreign body persists despite

nonvisualization on x-rays, bronchoscopy should be arranged. Other testing to consider in selected cases of cough include viral assays, sputum culture, pulmonary function testing, and swallowing studies.

Treatment for cough is targeted to the underlying cause. If the etiology is viral, there is no evidence that over-the-counter medications are useful and they may in fact have harmful side effects (14,15). Bronchodilators or racemic epinephrine may be used in conjunction with steroids if indicated for bronchospastic symptoms or croup. Antibiotics should be reserved for children with a likely bacterial source and follow-up should be arranged to ensure that symptoms are resolving as expected.

CRITICAL INTERVENTIONS

Evaluation of the ABC's is the first priority in any patient with a cough, and is followed immediately by interventions needed for stabilization (e.g., nebulized medications, steroids). If signs of respiratory distress are present, cardiac and respiratory monitoring are indicated. Supplemental oxygen should be provided in patients who display increased work of breathing or hypoxia. If there is concern for aspiration of a nonradioopaque foreign body, bronchoscopy should be arranged.

DISPOSITION

Most children with cough may be discharged home if they do not have an oxygen requirement, are tolerating oral intake, and are not experiencing increased work of breathing. Other reasons to consider admission include the need for inpatient workup, outpatient antibiotic treatment failure, and concern for the parent's ability to care for the child. It is important to stress to families that coughing associated with routine viral illnesses can last up to several weeks and that the utility of over-the-counter cough suppressants is modest at best and may be harmful.

Common Pitfalls

- Failing to optimize the conditions for physical examination. Auscultation for breath sounds should take place with the child in a position of comfort prior to uncomfortable aspects of the examination.
- A child with continued symptoms of foreign body aspiration should not be discharged even if the chest x-ray is negative.
- Failing to establish close follow-up in children with pneumonia and in those going home with bronchodilators.
- Prescribing empiric antibiotics when there is not a likely bacterial source and use of over-the-counter antitussives.

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CHAPTER 232 Shortness of Breath

Denis Pauze

Respiratory distress represents a compensatory response to impaired oxygen delivery to tissues, with or without decreased carbon dioxide elimination. The respiratory tract can be divided into two anatomic categories: (1) the lungs, or gas-exchange portion; and (2) the "respiratory pump," consisting of the thoracic cage, respiratory muscles, and neural pathways governing the system, Pathology involving any of these areas can present with signs and symptoms of respiratory distress. Other factors, outside the respiratory system, can also lead to shortness of breath, including myocarditis, supraventricular tachycardia (SVT), sepsis, and metabolic abnormalities such as diabetic ketoacidosis (DKA). Depending on the etiology of the respiratory compromise and the time until presentation to the emergency department (ED), these signs and symptoms may be obvious or subtle.

There are a number of differences between the pediatric and the adult patient that place children at greater risk for respiratory compromise. Infants and young children have a subglottic airway that is smaller and has less cartilaginous support, making it easier for obstruction to occur secondary to edema, secretions, constriction, or compression. Dynamic collapse of a partially obstructed airway, as seen in croup during inspiration, is an example of the consequences of a high-compliance airway (1). Children younger than 1 to 2 years of age may not have the anatomic pathways or "collateral ventilation" that allows aeration distal to an obstruction, thereby increasing the risk of atelectasis and ventilation–perfusion mismatching.

Because of the increased chest-wall compliance of the pediatric patient, compensatory diaphragmatic breathing may result only in distorting the rib cage as opposed to creating the necessary negative pressure to expand the lungs. The younger the child, the greater the pliability of the chest wall. This places the neonate at greatest risk for fatigue and respiratory failure.

In addition to anatomic differences, there are important physiologic differences. Hypoxemia and acidosis occur more rapidly in children with respiratory compromise because of their higher metabolic rate, which causes an increase in oxygen demand (1). Furthermore, tachypneic infants experience increased insensible losses in the form of exhaled water vapor. These losses become clinically significant as patients experience feeding difficulties in the face of progressive respiratory compromise.

CLINICAL PRESENTATION

The presentation of a child in respiratory distress varies, depending on the specific etiology, duration of illness, age, underlying medical conditions, and interventions prior to arrival in the ED.

Signs of respiratory distress can be separated into those that are visible and those that are audible (Table 232.1). Initially, simply observing a child and listening from afar (avoiding prolonged eye contact or use of a stethoscope) can provide critical information without creating anxiety or agitation, which may serve to worsen the patient's condition.

TABLE 232.1
Indicators of Actual or Possible Respiratory Compromise

Visual	Audible
Chest retractions	Cough
Abnormal behavior	Stridor
Altered mental status	Wheezing
Tachypnea/bradypnea	Grunting
Shallow/deep respirations	Abnormal voice or cry
Nasal flaring	
Head bobbing	
"See-saw" respirations	
Cyanosis	

Visual inspection begins with the child's subjective behavior. Normal behavior does not rule out pathology, but does indicate that the child is comfortable and needs no urgent intervention. When possible, children should be allowed to find their "position of comfort" to optimize oxygenation and ventilation; the demeanor and position assumed can be diagnostic. For example a quiet, serious child who prefers sitting upright in a sniffing position is a cause for concern and requires immediate assessment. Restlessness and irritability can be subtle clues to hypoxemia. Drooling or changes in phonation should also be considered an emergency until proven otherwise. Altered mental status can represent either generalized central nervous system (CNS) disease or hypercarbia, with or without hypoxemia.

The presence of either tachypnea or bradypnea is taken as evidence of respiratory compromise. It is important for clinicians to be familiar with the range of normal pediatric respiratory rates and to appreciate the wide range of "normal." In addition, fever, pain, and anxiety may result in an increased respiratory rate in the absence of primary pulmonary disease. Patients younger than 1 year of age have a median respiratory rate of 37–43, with a range from 22–66. Patients 2 to 3 years of age have a median range of 28, with ranges from 18–38. Respiratory rates in children 8 and above start falling in the adult range (2).

The best markers of respiratory distress are changes in the respiratory rate, character, and depth, rather than the number of breaths per minute measured at a fixed point in time. Shallow respirations are often seen in lower airway obstruction, and deep

respirations often represent central compensatory mechanisms in response to metabolic acidosis. Retractions may be seen in the supraclavicular, subcostal, and intercostal areas. Chest retractions begin subcostally with mild disease and progress upward as patient's condition becomes worse. Nasal flaring is sometimes a subtle sign that is more commonly present in infants and younger children and is associated with lower tract disease. Head bobbing with each breath and "see-saw" or "rocky" respirations, where the chest pulls in as the abdomen thrusts out, are signs of severe distress; the latter is an inefficient means of ventilation that can quickly lead to respiratory failure (1). Cyanosis usually correlates with a $PO_2 < 40$ and an arterial oxyhemoglobin saturation of $\leq 85\%$. Anemic patients can be acyanotic and profoundly hypoxic, making cyanosis an unreliable indicator of hypoxemia (1).

Certain indicators of respiratory distress can be heard without the use of a stethoscope. Persistent, forceful, nonproductive coughing may indicate a foreign body lodged in the upper airway, with the potential for complete obstruction. Stridor is a harsh, crowing sound occurring during inspiration (3) and commonly seen in the pediatric population. Stridor, produced by rapid, turbulent air flow through a narrowed area, signifies upper airway pathology. Wheezing represents expiratory obstruction of the lower airways. If heard without chest auscultation, wheezing indicates serious disease and the need for urgent intervention. Grunting, an end-expiratory sound, is produced by glottic closure during exhalation in an attempt to provide physiologic positive end-expiratory pressure (PEEP). Grunting indicates a disease process causing increased alveolar and/or interstitial fluid. An abnormal voice or cry, particularly if muffled in quality, should alert the clinician to possible upper airway disease and the need for prompt, nonthreatening evaluation. In the absence of visual and audible signs of respiratory distress, the likelihood of an infant or child having serious respiratory pathology requiring emergent intervention is small.

Neonates deserve special mention. Normally, neonates have respiratory rates of approximately 40 to 50 breaths/min. A

respiratory rate of 60 or more should usually be considered abnormal. Neonates with tachypnea may also exhibit grunting, stridor, accessory muscle use, and central cyanosis. On the other hand, neonates may present with irregular, but nonetheless normal, breathing patterns because of immature respiratory centers. Additionally, the neonate with shortness of breath may also have intermittent episodes of apnea, as seen with advanced RSV.

DIFFERENTIAL DIAGNOSIS

Determining the precise etiology of respiratory distress in the pediatric patient can be challenging; the differential diagnosis is substantial (Table 232.2). Clinicians must recognize the signs and symptoms of respiratory distress in a child and must be able to judge the degree of severity. In moderate to severe degrees of distress, a rapid assessment of the likely etiology is necessary so that appropriate therapy can be initiated. The most common etiologies include asthma, bronchiolitis, croup, and pneumonia, which are described in other chapters.

TABLE 232.2
Etiologies of Respiratory Distress

INFECTIOUS

Respiratory Tract

Upper

Croup
Epiglottitis
Upper respiratory infection
Bacterial tracheitis
Peritonsillar abscess
Retropharyngeal abscess

Lower

Pneumonia
Bronchiolitis

Central Nervous System

Meningitis
Encephalitis
Brain abscess

HYPERACTIVE AIRWAY

Asthma
Anaphylaxis

TRAUMA/MECHANICAL

Hemothorax
Pneumothorax
Pulmonary contusion
Flail chest
Spinal cord injury
Intracranial hemorrhage
Abdominal distension

ENVIRONMENTAL

Foreign body
Smoke inhalation
Near drowning
Ingestions

OTHER

Seizures
Cardiac failure
Cystic fibrosis
Metabolic acidosis
Vocal cord dysfunction
Congenital anomalies
Hypocalcemia

Age is an important factor in differentiating etiologies of dyspnea. Neonates are more prone to congenital diaphragmatic hernia, congenital lobar emphysema, bronchogenic cysts, and tracheomalacia, which may present within the first days or weeks of life. Other congenital anomalies, such as vascular rings or laryngeal webs, though uncommon, are additional potential etiologies of dyspnea in the neonatal period.

Stridor indicates some form of upper airway obstruction, and when it is associated with fever, one should suspect an infectious etiology. Croup classically presents between 6 months and 3 years of age with a history of a low-grade fever and upper respiratory infection (URI) symptoms for a few days, followed by the gradual onset of a barking cough, hoarseness, and stridor, with or without chest retractions (4).

In any child thought to have croup, the diagnosis of epiglottitis must also be considered. Epiglottitis may also be a life threatening cause of stridor, and can occur at any age. While epiglottitis was once common in the 3–8 year age range, the post vaccination era has shifted epiglottitis towards older patients. Today viruses, other

bacteria and different Hib serotypes make up the etiologic factors behind acute epiglottitis (5). On physical examination, the most common signs of epiglottitis have been reported to be stridor (88%), retractions (81%), and temperature $\geq 38^{\circ}C$ (85%); drooling (66%) and a preference for sitting (58%) are less common. The time course from the first clinical sign of epiglottitis to respiratory failure can be short, often less than 12 hours (6). Other early signs and symptoms of epiglottitis include “pain out of proportion to examination” and a child that is “not getting better with antibiotics.” In distinguishing between epiglottitis and croup in a child presenting with fever, stridor, and retractions, the importance of the history cannot be overemphasized. Drooling in the absence of spontaneous cough is the most specific indicator of acute epiglottitis.

Recurrent croup should be noted as a red flag. Approximately one-third of these children may have some type of anatomical airway abnormality and should be referred to a specialist for evaluation of the airway anatomy (7).

Other etiologies to consider in a child with fever and stridor include bacterial tracheitis and peritonsillar or retropharyngeal abscesses (RPAs). Patients with bacterial tracheitis typically have initial symptoms suggestive of croup but with progressive development of high fever, toxicity, and purulent tracheal secretions, resulting in airway compromise (8). Peritonsillar abscesses are most common in older adolescents and young adults (9). There is sudden elevation of temperature, ill appearance, and unilateral throat pain following a preceding tonsillitis. The patient complains of trismus, drooling, and a muffled voice (10). Examination may reveal bilateral tonsillar hypertrophy or unilateral tonsillar enlargement with uvular deviation contralaterally (11). Unlike peritonsillar abscesses, RPAs usually present in young children, from infancy to 3 years of age (12). The clinical picture may be similar to epiglottitis but with a less sudden onset (12). Children with RPA present with limitation of neck movement, especially when looking upward. Patients with RPA rarely present with respiratory distress or stridor but do tend to be febrile and ill-appearing. Computed tomography (CT) scan is useful to distinguish

RPA from retropharyngeal cellulitis. Most patients with retropharyngeal cellulitis and a few with RPA can be treated without surgery.

Not infrequently, a URI alone can cause signs of mild-to-moderate respiratory distress in the very young infant. Suctioning the nares with a bulb syringe after placing a few drops of saline can be very useful and may be all that is required in these patients. This is an opportune moment to educate parents on proper suctioning technique so as to optimize home care after discharge from the ED.

Infectious etiologies of the lower respiratory tract that may cause respiratory distress include bronchiolitis and pneumonia. Bronchiolitis presents as any wheezing-associated illness in the first year of life that is preceded by a URI (13). Differentiation from acute attacks of asthma, often triggered by viral infections, may be difficult. As a general rule, patients presenting with wheezing in the first year of life are assumed to have bronchiolitis and not asthma, which therefore precludes treatment with steroids.

In patients presenting in respiratory distress that is not clearly associated with infection, the history and physical examination should quickly provide an answer. Most commonly, a diagnosis of reactive airway disease will be made. An important etiology to include in the differential diagnosis is anaphylaxis, a multisystem syndrome involving the cutaneous, respiratory, cardiovascular, and gastrointestinal systems; involvement of at least two systems is required to make the diagnosis (8). Both the upper and lower airways can be involved, leading to hoarseness, stridor, wheezing, and cough. Early diagnosis and differentiation of anaphylaxis from more benign conditions is essential, as these patients can progress rapidly to anaphylactic shock (8).

Foreign-body aspiration (FBA) can be difficult to diagnose and is a leading cause of death in children under the age of four. Commonly aspirated food products include nuts, seeds, grapes, corn, and beans; peanuts account for nearly 25% of food-based aspirations. Aspiration of hot dogs, candy, and grapes causes the highest mortality. Marbles, coins, toys, and pills are also responsible for many cases (14). The presenting signs and symptoms depend upon

the location of the foreign body in the respiratory tract. A partially obstructing foreign body in the upper airway may cause stridor and shortness of breath and requires immediate intervention to prevent progression to complete obstructions. Children with prolonged cough, unilateral wheezing, or recurrent pneumonias should also be evaluated for FBA. Stridor or wheezing that is not responsive to therapy requires further evaluation, beginning with lateral and anteroposterior radiographs of the neck and chest, preferably during both inspiration and expiration (15).

Not all shortness of breath has an airway, lung, or respiratory cause. Children with myocarditis or cardiomyopathy may present with wheezing and dyspnea. Unfortunately, these entities may easily be confused with RSV, bronchiolitis, bronchitis, or pneumonia. Arrhythmias such as SVT are also common, and may lead to dyspnea and heart failure. Other important causes of respiratory compromise in the child include seizures, cystic fibrosis, and metabolic acidosis caused by sepsis, DKA, renal disease, and certain ingestions (e.g., salicylate, methanol, ethylene glycol).

Neuromuscular diseases, including Guillain–Barré, botulism, and myasthenia gravis, also should be considered. Vocal cord dysfunction, believed to represent a conversion disorder, results in either inspiratory or expiratory stridor that may be confused with wheezing. Congenital anomalies should be considered in infants younger than 6 months who present with stridor; such anomalies include vascular rings, laryngeal webs, vocal cord paralysis, and laryngomalacia. Hypocalcemia, in addition to having neurologic, cardiovascular, and psychiatric manifestations, can also result in apnea, laryngeal spasm, bronchospasm, or biphasic respiratory noises and should be included in the differential diagnosis of any patient with respiratory distress (16).

ED EVALUATION

The pediatric assessment triangle (PAT), comprised of work of breathing, general appearance, and circulatory status, is a widely used evaluation tool for the assessment of the pediatric patient. It is

simple and allows for a rapid global assessment of the potentially ill child. The initial evaluation begins when the physician enters the room, noting any visual and audible indicators of actual or possible respiratory compromise. The child in respiratory distress must be approached in a gentle, reassuring manner and allowed to find the most comfortable position, whether it be on the examining table or on a parent's lap. Initial priorities (concurrent with the PAT triangle) include assessing the relationship between work of breathing and hydration status. Clinicians must establish baselines in these two areas from which clinical changes can be measured. Patients with increased work of breathing, especially infants, are likely to have had greater difficulties feeding and greater insensible water losses from exhaled water vapor. Bringing these two factors together in pediatric patients is vital and goes beyond merely quantifying the respiratory rate. The hydration status is a foundational component of disposition decisions in young infants and children with respiratory illnesses and should not be overlooked. Patients with moderate degrees of tachypnea who otherwise look well must prove that they can maintain their hydration status as outpatients before being discharged.

In the child who is alert and attentive, the evaluation can proceed with the history and physical examination. However, any child with altered mental status, irritability, or restless with other evidence of distress must have an immediate assessment of the ABCs of resuscitation – airway, breathing, and circulatory status.

Important historic points include underlying medical problems (e.g., asthma, cystic fibrosis, or seizure disorder), the onset and type of current symptoms, and the possibility of FBA or ingestion. If epiglottitis is suspected, forced visualization of the pharynx should be avoided in the ED. Forced visualization may result in a vasovagal response, causing cardiopulmonary collapse, respiratory obstruction, and death (17). We recommend the traditional approach where the child with suspected epiglottitis goes to the operating room for direct visualization of the airway under optimal conditions and in the presence of personnel skilled in establishing the airway.

Following the history and physical examination, the etiology of the respiratory distress is usually clear. Noninvasive monitoring can be used to help with clinical assessment. Pulse oximetry provides a continuous and generally valid measure of the arterial hemoglobin oxygenation saturation and arterial pulse. Blood gas measurements stress an already distressed child, add little or no useful information to the evaluation, and should be avoided.

In situations in which FBA is suspected, lateral and anteroposterior neck and/or chest radiographs should be obtained; if normal, either an assisted expiratory film, bilateral decubitus radiographs, or fluoroscopy should be done (18). One should have a low threshold for specialty consultation despite negative imaging results, if FBA is seriously suspected. Direct visualization with bronchoscopy is the test of choice when clinical suspicion is high but the initial evaluation is negative. If the distinction between croup and epiglottitis is not obvious, and the child is stable and only mildly ill, a lateral neck radiograph has been traditionally viewed as appropriate. However, Ragosta et al. (19) found lateral neck films to be of limited value in the initial evaluation of suspected epiglottitis and recommend against their use.

Repeated evaluations at regular intervals, as well as noninvasive monitoring, are essential in any child presenting in respiratory distress. Once appropriate therapy is instituted, the child's response to treatment must be periodically assessed. Often, the best way to determine whether an adult or older child is improving is simply to ask, "Are you feeling better?" In the nonverbal or frightened child, changes in clinical parameters that have been observed early in the evaluation (e.g., activity level, eye contact, and ability to take fluids) are appropriate to gauge improvement.

The plain chest X-ray (CXR) remains the diagnostic tool of choice for the evaluation of dyspnea in pediatric patients. The CXR may reveal pneumothorax, pneumonia, foreign body, pleural effusion, or cardiomegaly, and offers the advantage of being fast and readily accessible.

Ultrasound may gain favor as a diagnostic tool for assessing pulmonary pathology. Ultrasound can be fast and informative,

minimizes radiation exposure, and can be performed at the bedside. Ultrasound also offers the opportunity to repeat examinations serially to monitor for progression of illness or response to treatment. For the diagnosis of pneumonia, ultrasound has been compared to conventional chest radiography and has been judged to be as reliable as CXR in experienced hands (20). However, the use of ultrasound for this indication is still somewhat preliminary; and as with all ultrasound studies the utility of the test is operator dependent.

KEY TESTING

- Pulse oximetry
- Chest radiographs as indicated depending on differential diagnosis
- Thorough history and physical examination

ED MANAGEMENT

The importance of a gentle, nonthreatening approach cannot be overemphasized. Interventions of any sort are usually poorly tolerated by young children and, at least temporarily, may result in a worsening of their condition. The benefit of any intervention must always be weighed against its potential for adversely affecting the child.

Management of the child in respiratory distress generally involves two goals: Keeping the patient calm and comfortable and providing appropriate therapy. Treatment typically begins with humidified oxygen. Infants and some children often do not tolerate masks well and, depending on their oxygen requirement, may best be served with blow-by oxygen administered by the parent. In addition to the physical examination, pulse oximetry is useful in determining oxygenation status. Normal pulse oximetry readings have been reported as 91.5% to 100% in infants 6 months and younger who are awake, and 96% to 100% (median, 99.5%) in children 2 to 16 years of age who are asleep. If the anxiety produced by the administration of oxygen to children in mild distress worsens their

condition, the oxygen is clearly doing more harm than good and should be avoided. However, the anxiety elicited by the administration of oxygen is usually transient. For severely distressed or cyanotic patients, 100% humidified oxygen must be provided quickly, irrespective of their acceptance.

Common diagnoses that respond to specific medical therapy include croup, asthma, and bronchiolitis. Steroids, given orally, parenterally, or via nebulizer, have been shown to be effective in the management of croup, however (10,21–23). For severe croup, nebulized epinephrine can rapidly relieve distress, but its effect lasts only 1 to 3 hours (24). Although nebulized epinephrine's activity is short lived, studies indicate that when it is used with steroids (e.g., dexamethasone, 0.15 to 0.6 mg/kg, intramuscularly or orally), patients can be safely discharged home after 2 to 4 hours if clinically well (e.g., without retractions and stridor at rest) (24–26). Caution should be used when employing nebulized epinephrine if epiglottitis is suspected, as it may precipitate airway obstruction.

CRITICAL INTERVENTIONS

- Keep patients in their position of comfort for as long as possible.
- Consider a foreign body in the patient who presents with paroxysmal cough or new-onset wheezing.
- Give steroids when administering epinephrine for croup.
- Assessing hydration status in conjunction with respiratory status.

DISPOSITION

For the stable child in moderate distress, admission to an inpatient pediatric floor is appropriate. When there is a concern that the patient may deteriorate because of the particular disease process (e.g., anaphylaxis) or medical history (e.g., an asthmatic previously requiring intubation), admission to a PICU should be considered. If necessary, transfer to the nearest hospital having a PICU should be arranged, in accordance with federal guidelines. The transfer should be done by personnel skilled in airway management (i.e., an advanced cardiac life-support unit or the pediatric transfer team of

the receiving hospital). Ground transport is adequate for the stable child in only moderate distress.

Children in severe distress should be admitted to a PICU. If transfer is necessary, consideration should be given to intubating and stabilizing the airway before departure, rather than risking deterioration and the need for a potentially difficult intubation en route. Transfer by ground units with personnel skilled in airway management is adequate for most patients in severe distress. However, the need for ground versus air transport must always be individualized.

Common Pitfalls

- Starting an intravenous line that is not needed for initial therapy (24).
- Forcing oxygen on the child in mild distress who will not tolerate it.
- Obtaining blood for blood gas analysis in a severely distressed patient before providing therapy.
- Doing a detailed history and physical examination before intervening in the severely distressed child.
- Misinterpreting decompensation for improvement.
- During pulse oximetry monitoring, determining a sleeping infant to be hypoxic without further evaluating him or her in an awake state.
- Failing to consider the addition of intravenous fluid therapy in a child with increased insensible losses and decreased oral intake due to tachypnea.

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of Richard Cantor to the content of this chapter.

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outpatient therapy? *Am J Emerg Med.* 1994;12:613–616.

CHAPTER 233

Apnea and Apparent Life-Threatening Events

Raymond Pitetti

An apparent life-threatening event (ALTE) is an incident in a child younger than 2 years characterized by some combination of apnea, color change, abnormal muscle tone, and choking that is frightening to an observer. If a cause for the episode is identified, the course of management is clear. However, most ALTE cases presenting to the emergency department (ED) offer no clues regarding cause. In addition, there are conflicting recommendations regarding how to evaluate and manage children presenting with a first-time ALTE. In 1987, the Consensus Statement of the National Institutes of Health Consensus Development Conference on Infantile Apnea and Home Monitoring was published in an effort to serve as a guide for future research (1). The definitions published in the consensus statement are used in this chapter (Table 233.1). This chapter focuses on the evaluation, differential diagnosis, and management of the neonate and young infant with apnea or an ALTE.

TABLE 233.1
Definitions of Apnea

Apnea: Cessation of respiratory airflow. The respiratory pause may be central or diaphragmatic (i.e., no respiratory effort), obstructive (usually due to upper airway obstruction), or mixed. Short (<15 sec) central apnea can be normal at all ages.

Pathologic apnea: A respiratory pause is abnormal if it is prolonged (>20 sec) or associated with cyanosis, abrupt, marked pallor or hypotonia, or bradycardia.

Periodic breathing: A breathing pattern in which there are three or more respiratory pauses of >3-sec duration with <20 sec of respiration between pauses. Periodic breathing can be normal.

Apnea of prematurity: Periodic breathing with pathologic apnea in a premature infant. Apnea of prematurity usually ceases by 37 wks' gestation (menstrual dating) but occasionally persists for several weeks past term.

Apparent life-threatening event: An episode that is frightening to the observer and that is characterized by some combination of apnea (central or occasionally obstructive), color change (usually cyanotic or pallid but occasionally erythematous or plethoric), marked change in muscle tone (usually marked limpness), choking, or gagging. In some cases, the observer fears the infant has died.

Apnea of infancy: An unexplained episode of cessation of breathing for 20 sec or longer, or a shorter respiratory pause associated with bradycardia, cyanosis, pallor, or marked hypotonia. The term *apnea of infancy* generally refers to infants who are more than 37 wks' gestational age at onset of pathologic apnea. Apnea of infancy should be reserved for those infants for whom no specific cause of an ALTE can be identified. In other words, these are infants whose events are considered idiopathic and believed to be related to apnea.

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Apnea, one of many types of breathing problems seen predominantly in infants and is defined as the cessation of breathing for 20 seconds or longer, or for a shorter period when accompanied with bradycardia, cyanosis, pallor, or hypotonia. Apnea may or may not occur in an infant who has had an ALTE.

The incidence of ALTE in infants is reported to be between 0.5% and 6% of all children, and mortality rates to range from 2% to 6% (2). Infants presenting with apnea during sleep may have a mortality of up to 10%, with the risk of death tripling with two or more recurrences. In more than 50% of ALTEs, no definitive cause can be found (2).

ALTE should be differentiated from sudden infant death syndrome (SIDS). SIDS occurs in about 2 per 1,000 live births in the United States and has been defined as "the sudden death of an infant less

than 1 year of age that remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene and review of clinical history" (3). The National Institute of Child Health and Development Cooperative Epidemiological Study of SIDS found that only 2% to 4% of cases had a hospital record of apnea of prematurity and only <7% had a history of an acute life-threatening event (1). Therefore, ALTEs, though historically termed "near SIDS," are not thought to be a precursor or risk factor for SIDS. The American Academy of Pediatrics has made several new recommendations regarding SIDS prevention; these are listed in Table 233.2.

TABLE 233.2
AAP Recommendations on SIDS Prevention

Neonate/Infant	Both	Toddler/Young Child
Stridor		
Vascular ring	Vocal cord paralysis	
	Foreign body	
	Croup/epiglottitis	
Prematurity	Positional	Laryngeal web
	Laryngomalacia	Tracheostomy plug
	Tracheomalacia	Subglottic stenosis
		Bronchopulmonary dysplasia
Abnormal Airway		
Choanal atresia/ stenosis	Craniofacial abnormalities	Large tonsils/adenoids
Tracheoesophageal fistula		
Other	Gastroesophageal reflux	
	Hemangioma/ lymphangioma	
	Pharyngeal/retro-pharyngeal mass	

CLINICAL PRESENTATION

In the neonate and young infant, apnea is the final common pathway of many pathophysiologic processes. Respiratory function is a complex system that is regulated in the pons and medulla, which receive afferent stimuli from chemoreceptors, as well as stretch receptors in the bronchioalveolar tree. Efferent impulses from respiratory centers are mainly found in the vagus, phrenic, and intercostal nerves. The neonate has a greater concentration of nerve endings and smooth muscle in and around the walls of the smaller airways and a thinner pulmonary arterial wall that contributes to decreased vascular resistance.

These features, coupled with the overall immaturity of the cardiorespiratory system, translate into wide swings in both pulmonary vascular and distal airway resistance, resulting in acute ventilatory-perfusion disturbances, intrapulmonary shunting, and hypoxemia. In addition, gastroesophageal reflux has been associated with central, obstructive, or mixed apnea secondary to reflex hypoxemic episodes.

There is no typical clinical setting or presentation of a child with apnea. Most children are brought to the ED in stable condition by the parents, who say the child "stopped breathing." The child may present, however, in cardiopulmonary arrest or in respiratory distress with an unstable airway (see Chapter 217 for management). Infants who present with an ALTE may or may not have had a reported episode of apnea.

It is vital to determine the child's position and activity, and the exact sequence of events before and during an episode of apnea or ALTE (4). The child may have spontaneous inspiratory effort or may require stimulation after an apneic episode. The child may also be noted to have a change in color, usually cyanosis, but the color may vary from pallid to erythematous. Changes in muscle tone can be seen before or during the apneic event. Changes in tone may vary from arching or extension of the extremities to marked hypotonia and limpness (5). An understanding of the specific event sequence may help guide the diagnosis; for instance, arching with apnea after feeding, with or without formula in the oronasal passages, can be attributed to gastroesophageal reflux (6).

In general, there are two types of apnea: (1) obstructive and (2) central. An absence of respiratory airflow in the presence of respiratory effort and chest wall movement suggests obstructive apnea. The absence of all three elements—respiratory effort, chest wall movement, and respiratory airflow—is consistent with central apnea.

Parents are usually extremely frightened by what they have seen and frequently believe their child is dying. In most cases, parents administer some form of cardiopulmonary resuscitation (CPR) or stimulation. A thorough history is vital to determine whether CPR was actually necessary.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of apnea and ALTE in neonates, infants, and older children are shown in **Tables 233.3** to **233.5** (7). Davies and Gupta (8) found the most common discharge diagnoses in patients admitted with an ALTE to be gastroesophageal reflux (26%) (9), seizures (9%), pertussis (9%), and urinary tract infection (5%). Apnea may be the only manifestation of a seizure, or a seizure may be precipitated by a hypoxic event. In the toddler and young child, foreign body ingestion and poisoning should also be considered.

TABLE 233.3
Differential Diagnosis of Obstructive Apnea

Neonate/Infant	Both	Toddler/Young Child
Stridor		
Vascular ring	Vocal cord paralysis	
	Foreign body	
	Croup/epiglottitis	
Prematurity	Positional	Laryngeal web
	Laryngomalacia	Tracheostomy plug
	Tracheomalacia	Subglottic stenosis
		Bronchopulmonary dysplasia
Abnormal Airway		
Choanal atresia/ stenosis	Craniofacial abnormalities	Large tonsils/adenoids
Tracheoesophageal fistula		
Other	Gastroesophageal reflux	
	Hemangioma/ lymphangioma	
	Pharyngeal/retro-pharyngeal mass	

TABLE 233.4
Differential Diagnosis of Central Apnea

Neonate/Infant	Both	Toddler/Young Child
Central nervous system	Seizures	Apneustic breathing (achondroplasia)
	Brainstem tumor	
CNS immaturity	Chiari type 1 malformation	
Aberrant thermo regulation	Increased intracranial pressure	
	Vascular malformation/ hemorrhage	
	Congenital central hypoventilation syndrome	

CNS, central nervous system.

TABLE 233.5
Other Causes of Apnea

Neonate/Infant	Neonate/Infant and Toddler/Young Child
Cardiovascular	Shock
	Dysrhythmias
	Congenital heart disease
	Prolonged QT syndrome
Infectious Diseases	
Infant botulism	Sepsis
Respiratory syncytial	Pertussis
Virus	Meningitis
	Encephalitis
	Pneumonia
Miscellaneous	Child abuse
	Anemia
	Trauma
	Poisoning
	Neuromuscular disorders
	Munchausen syndrome by proxy
	Metabolic disorders

Often, the clinician must differentiate between a breath-holding spell and an ALTE. A breath-holding spell is an involuntary event occurring during expiration while a healthy toddler or young child is awake (10). The most common type is the cyanotic or classic spell, which begins with crying, usually after an obvious precipitating event. The child then stops breathing at end expiration, which results in cyanosis and loss of consciousness. The spell usually resolves spontaneously, with resumption of breathing and the patient's gradual recovery to a baseline state. There may be associated body jerks and urinary incontinence (6). This sequence and description of a breath-holding spell does not apply to spells occurring during sleep. A cyanotic spell differs from a pallid breath-holding spell which involves a sudden painful incident, with resulting vagally mediated bradycardia or asystole. The patient turns pale and limp and may have tonic–clonic seizure activity, but ultimately resumes normal behavior.

Child abuse has been detected in 2.3% of patients presenting with an ALTE and, therefore, should be considered in all infants

presenting in this manner (11,12). Infants should be examined for retinal hemorrhages or signs of increased intracranial pressure. Patients suffering from Munchausen syndrome by proxy (MSBP) may present with recurrent episodes of apnea or cyanosis as a consequence of repeated intentional suffocation by a parent or caregiver. Apnea is the chief presenting complaint in about 20% of cases of MSBP (13).

Cyanotic congenital heart disease usually presents in the first few weeks of life and is due to varying degrees of right-to-left shunt; lower pulmonary blood flow (due to greater degrees of shunting) results in more severe cyanosis. These children tend to have feeding difficulties and poor weight gain. The administration of 100% oxygen can differentiate pulmonary from cardiac causes of cyanosis. The oxygen saturation measurement and PaO_2 increase when cyanosis is secondary to a pulmonary cause and typically fail to increase in an infant with cyanotic congenital heart disease.

Infants with *Bordetella pertussis* typically do not present with the classic history of a "whooping" cough. However, they can present with apnea, prolonged coughing, and post-tussive episodes of vomiting. Similarly, infants early in the course of respiratory syncytial virus (RSV) infection may present solely with apnea and no other symptoms. Many infants who are on home monitors because of a history of apnea are brought to the ED for "frequent alarms." False alarms account for more than 90% of monitor alarm events (14) and typically are due to shallow breathing or loose lead placement (5). A thorough history usually helps to differentiate between a true apneic event and a false alarm.

ED EVALUATION AND MANAGEMENT

Most infants who present to the ED with a history of an ALTE appear well and have a normal physical examination. However, a complete and thorough history and physical examination should nonetheless be performed.

A detailed history can help to determine an underlying cause of an event or determine which patients are at a higher risk for subsequent morbidity and mortality. The following information is helpful in risk-

stratification and determining the likelihood of a serious underlying disorder.

The Event

- Who was present during the event?
- Was there any preceding history?
- How was the caretaker alerted to the event?
- How was the infant found, including position of the baby?
- Was there vomitus or blood in the mouth or nose?
- Was the baby's color different (e.g., blue, red, pale) from normal?
- What was the baby's tone like?
- What was the baby's conscious state like?
- Was the baby moving?
- Was the baby breathing?
- What did the caretakers do?
  - Did they perform back blows?
  - Did they perform mouth-to-mouth breathing and chest compressions?
- How long did it take for the baby to recover?

It is important to remember that apnea lasting less than 15 seconds is likely to be benign in nature and does not require further medical evaluation or treatment. However, any period of apnea that is associated with a color change should be taken seriously. When talking with caregivers about color changes, ask exactly what color the baby was, where the color change occurred on the child's body, the duration of color change, and the room lighting. As a general rule, cyanotic changes are of more concern than episodes in which the infant was noted to "turn red." Perioral cyanosis is evidence of central hypoxia and must be further evaluated.

One historical element that helps to distinguish an ALTE due to organic disease from one due to nonaccidental trauma (NAT) is inconsistently explained ALTEs witnessed by the same caregiver. This pattern is of particular concern if the events decrease in frequency or cease upon admission to the hospital or if the events suffered in the hospital occur only in the presence of the same caregiver. When

initially interviewing the caregiver of an ALTE patient with suspected NAT, it should be assumed that the observer's account is accurate and reliable, even if the events do not seem credible at the time.

Past medical history: This should include that of the baby's birth, feeding practices, growth history, immunization status, developmental history, and history of previous similar episodes. In addition, a recent history of illness and medication use should also be obtained. Caregivers should be questioned as to use of prescription medications, over-the-counter medications, and homeopathic or herbal remedies. Breastfeeding mothers should be asked what medications, both prescribed and otherwise, they are taking that could be transmitted to the infant via breast milk.

Family history: Caregivers should be questioned about a family history of ALTE, SIDS, congenital heart disease, epilepsy, or other unusual illnesses that may present in young children. Interestingly, a family history of SIDS may be found in as many as 15% of patients presenting with an ALTE (8).

Social history: A detailed social history may identify social and environmental precipitants of the event. In particular, the presence of smokers in the home, the type of heating in the dwelling (risk of carbon monoxide poisoning), and factors that may indicate possible child abuse may help guide the clinical decision-making and disposition decisions.

Children who present with an ALTE should have a complete physical examination, including a thorough neurologic examination and developmental assessment. In addition, a dilated fundoscopic examination should be performed, if possible. However, it is likely that the child's examination will be normal. Specific physical examination findings that may help in identifying the underlying cause of the events could include the presence of retinal hemorrhages (child abuse), unusual bruising (child abuse), neurocutaneous findings (tuberous sclerosis), or a full anterior fontanelle (increased intracranial pressure). The oropharynx must be carefully examined for evidence of abnormal bruising beneath the tongue, the gums, and on the inner aspect of the buccal mucosa or

the frenulum. Such evidence may be indicative of a smothering attempt.

After the history and physical examination, the physician should be able to conclude whether the child has had an ALTE and whether any apneic event was obstructive, central, or mixed (see **Tables 233.3–233.5**). If there was a significant event consistent with ALTE, a consultant should be contacted for further inpatient evaluation and management (Fig. 233.1).

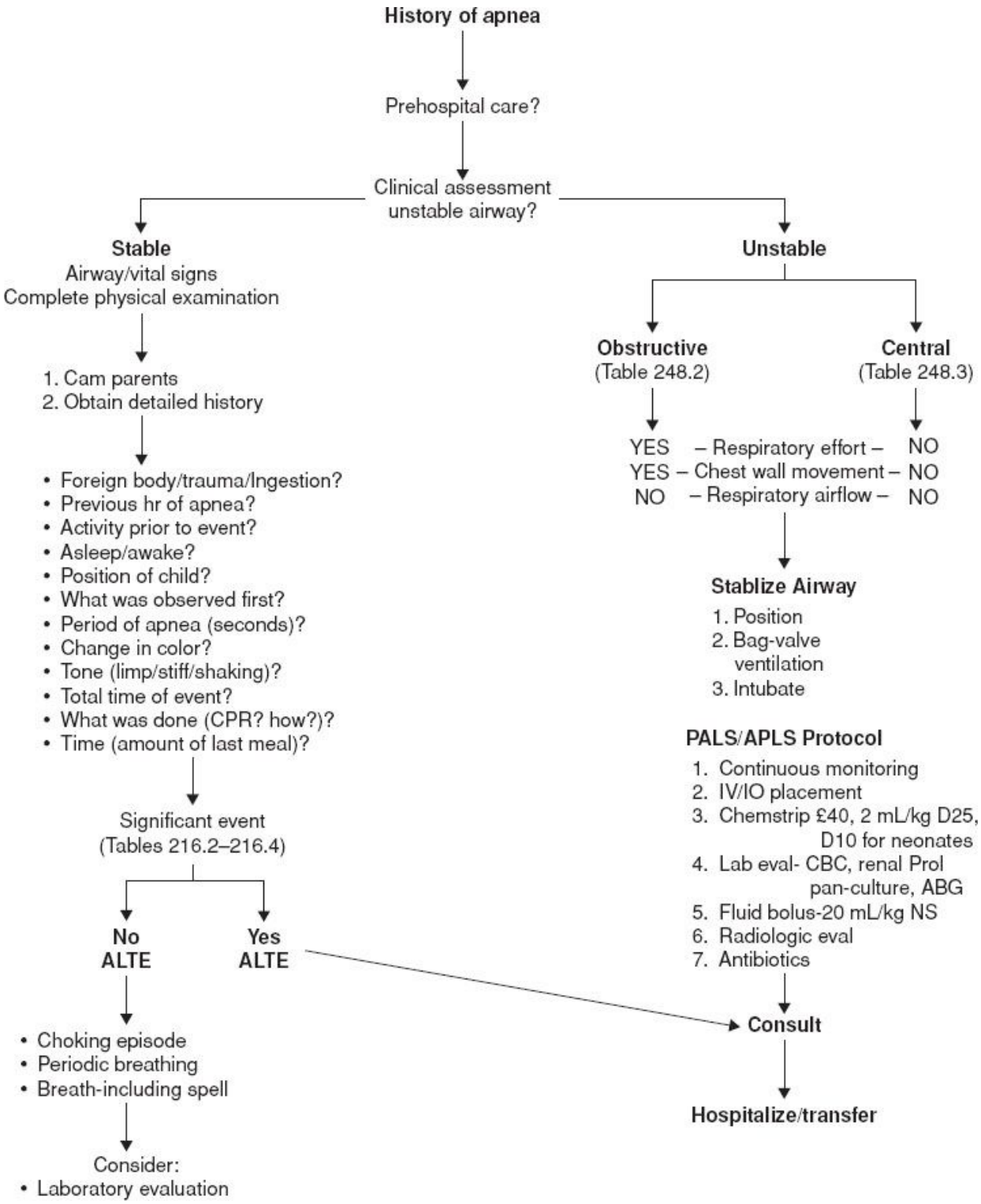

FIGURE 233.1 Algorithm for ED management and evaluation of apnea in an infant/young child.

Laboratory evaluation must be guided by the history and physical examination and may include a complete blood count, renal profile, urinalysis, blood and urine cultures, and possibly pertussis, chlamydia, and RSV studies. RSV testing should be performed in infants who were premature and in those with congenital heart disease; as noted above, infection with RSV is associated with an increased risk of apnea (14).

The radiographic evaluation consists of a chest radiograph and, if upper airway obstruction is suspected, anteroposterior and lateral soft-tissue radiographs of the neck. Occasionally, patients with apnea have ingested caffeine or aminophylline; therefore, a theophylline level may be checked (4).

An electrocardiogram may be obtained to rule out arrhythmias; supraventricular tachycardia, ventricular tachycardia, and prolonged QT syndrome, in particular. In addition, a computed tomography scan of the head or cranial ultrasound may be obtained in patients with an altered level of consciousness, abnormal muscle tone, focal neurologic findings, or retinal hemorrhages. Further inpatient evaluation may include an EEG, swallowing studies, esophageal pH probe, and polysomnography (2).

Diagnostic evaluations must be tailored to the history and physical examination findings. While some patients may require extensive evaluations, many others may not mandate such extensive testing. An ECG, chest x-ray, urinanalysis, and finger-stick glucose may help to rule out a number of important causes of ALTE.

One systematic review pertaining to ALTEs sought to determine what historical and physical examination findings placed an infant at risk for a future adverse event or serious underlying diagnosis and to determine what testing is indicated (15). A history of prematurity, multiple ALTEs, or suspected child maltreatment were identified as significant risk factors. It was also concluded that routine screening tests were of low yield in infants without historical risk factors or suggestive physical examination findings.

A recent study by Willwerth et al. reported factors that were associated with an increased risk of apnea. These included (1) full-term infants younger than 1 month; (2) premature infants younger

than 48 weeks postconception age; and (3) infants with witnessed apneic episodes prior to presentation to a physician (16). Another smaller study evaluated 59 infants with ALTE and recommended outpatient management for infants older than 1 month with only one episode of apnea (17). This was a relatively small study, however, and it is thus still prudent to admit all patients with ALTE until larger studies can confirm these recommendations.

CRITICAL INTERVENTIONS

- Obtain bedside glucose.
- Check electrocardiogram for dysrhythmias and prolonged QT syndrome.
- Consider a full septic workup, especially in infants younger than 2 months.
- Consider pertussis and RSV studies.
- Perform neuroimaging in patients with altered mental status or abnormal neurologic findings.

DISPOSITION

Any child who meets criteria for an ALTE, should be admitted for further evaluation, observation, and parental education, despite a normal initial evaluation. Most children can be admitted to a general pediatric ward with an apnea-bradycardia monitor to detect apneic episodes and to determine their frequency and duration and any associated bradydysrhythmias.

Common Pitfalls

- Failing to believe the caretaker about the event, particularly when the child is happy and alert on presentation.
- Failing to obtain an immediate bedside glucose level. It should be repeated within 5 minutes after giving the dextrose bolus. Sepsis can present with respiratory instability, and hypoglycemia must be treated.
- Failing to hospitalize patients with ALTEs.

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CHAPTER 234

Chest Pain and Palpitations

Steven M. Selbst

CLINICAL PRESENTATION

Children frequently present to the emergency department (ED) with the complaint of chest pain. While not as common as abdominal pain or headache, chest pain is a frequent complaint in children. Between 0.3% and 0.6% of visits to a pediatric ED are for chest pain (1,2). The symptom occurs equally in boys and girls, and it is found in children of all ages and races. Approximately one-third of children with this complaint are awakened from sleep by the pain, and one-third miss school because of the pain (2). The mean age of children with this complaint is about 12 years (2).

Unlike adults, children with chest pain *rarely* have serious organic pathology (2–7). Most children with chest pain are not in extremis and the pain is not acute in nature. Understandably, patients and their families associate chest pain with heart disease, and are frightened by media reports of sudden death in young athletes. Infrequently, pediatric chest pain will present with significant distress and require immediate resuscitation in the ED, and while, regardless of the presentation, the complaint should be taken seriously, *fatal heart disease is extremely rare in the pediatric population.* In general, a thorough history and careful physical examination can guide the emergency physician to order appropriate laboratory studies and to refer a child with chest pain to a specialist for further evaluation, if indicated (1,2,7).

DIFFERENTIAL DIAGNOSIS

Age is a helpful tool for stratifying potential etiologies of pediatric chest pain. Young children are more likely to have a cardiorespiratory cause for their pain, such as cough, asthma, pneumonia, or cardiac pathology (including myocarditis, pericarditis, arrhythmia, or ischemia), while adolescents are more likely to have pain associated with stress or a psychogenic disturbance (1,2). Because there are occasional children with serious pathology related to chest pain, the ED physician must carefully contemplate an extensive differential diagnosis when evaluating a child with chest pain (see **Tables 234.1** and **234.2**).

TABLE 234.1
Cardiac Disorders Leading to Chest Pain in Children

Coronary Artery Disease—Ischemia/Infarction
Anomalous coronary arteries
Kawasaki disease (coronary arteritis)
Diabetes mellitus (long standing)
Arrhythmia
Supraventricular tachycardia
Ventricular tachycardia
Structural Abnormalities of the Heart
Hypertrophic cardiomyopathy
Infection
Pericarditis
Myocarditis

TABLE 234.2
Noncardiac Causes of Pediatric Chest Pain

Musculoskeletal Disorders
Chest wall strain
Direct trauma/contusion
Rib fracture
Costochondritis

Respiratory Disorders
Severe cough
Asthma
Pneumonia
Pneumothorax/pneumomediastinum
Pulmonary embolism

Psychological Disorders
Stress-related pain

Gastrointestinal Disorders
Reflux esophagitis
Pill-induced esophagitis
Esophageal foreign body

Miscellaneous Disorders
Sickle cell crises
Abdominal aortic aneurysm (Marfan syndrome)
Pleural effusion (collagen vascular disease)
Shingles
Pleurodynia (Coxsackievirus)
Breast tenderness (pregnancy, physiologic)

Idiopathic

Cardiac Pathology

Previously undiagnosed cardiac pathology is a rare cause of chest pain in children but should be considered. A recent study showed that <1% of children with chest pain presenting to a pediatric ED had previously unrecognized heart disease as the etiology for their pain (4). Myocardial ischemia or infarction should be considered in any child who has pain with exertion or syncope (8,9). Myocardial infarction (MI), particularly in young infants, can result from an anomalous coronary artery, often with no warning of this underlying condition. Some children, however, will have a pansystolic, continuous, mitral regurgitation murmur or gallop

rhythm suggesting myocardial dysfunction. In many cases, exercise (e.g., feeding for infants) induces chest pain secondary to increased myocardial oxygen demand in the face of limited coronary blood flow. Electrocardiograms (ECGs) in these patients may demonstrate a classic ST elevation MI pattern typically seen in adult patients.

Some children may have medical and social histories that predispose them to a higher likelihood of angina or infarction. For instance, children with long-standing diabetes mellitus may develop coronary artery disease leading to angina or MI. Patients with a past history of Kawasaki disease may have coronary artery aneurysms, which may produce problems long after the original illness (10). Pediatric patients with chronic anemia, such as sickle cell disease, are also at risk for angina or other cardiac pathology as are teenagers who abuse cocaine. Cocaine causes tachycardia and vasoconstriction, which can lead to increased oxygen demand, hypertension, and chest pain (4,11). Arrhythmias can cause palpitations, pain, or an abnormal cardiac examination. Supraventricular tachycardia is the most common of these arrhythmias in childhood, but premature ventricular tachycardia can also lead to episodes of brief, sharp chest pain (4,12).

Some children with structural abnormalities of the heart may develop ischemia and chest pain. One structural abnormality deserving special mention is hypertrophic obstructive cardiomyopathy, which is the leading cause of sudden cardiac death in children and adolescents. This disorder has an autosomal dominant pattern of inheritance, so there is often a family history. Children with this disorder have a murmur best heard when the patient is standing or performing a Valsalva maneuver. The ECG may reveal left ventricular hypertrophy, ST segment depression, and T-wave inversion. The risk for ischemic chest pain increases with exertion (7–9,13).

Cardiac infections such as pericarditis and myocarditis, although uncommon, should be considered as potential causes of pediatric chest pain (4,13). Children with pericarditis may present with sharp, stabbing, midsternal chest pain that improves when the patient sits up and leans forward. The child with this infection is usually febrile

and may be in respiratory distress. A friction rub is pathognomonic for pericarditis but is present in only 25% of cases (14). Distant heart sounds are more likely with a large accompanying pericardial effusion; neck vein distention and *pulsus paradoxus* suggest pericardial tamponade (13). Myocarditis is more common and may present more subtly (15–17). The condition is often misdiagnosed because the signs and symptoms mimic other conditions such as influenza infection. Children with myocarditis have mild, nondisruptive chest pain for several days (13,16,17). After 2 to 4 days of fever and other systemic symptoms such as vomiting and lightheadedness, the patient may develop chest pain with exertion and shortness of breath (15–16). Examination may reveal muffled heart sounds, a low-grade fever, tachypnea, a gallop rhythm, or tachycardia that is out of proportion to the degree of fever present. The patient may also have orthostatic changes in pulse or blood pressure (pulse increase >30 beats/min, blood pressure decrease by >20 mm Hg when moving from supine to standing position). These changes are often misinterpreted as volume depletion because children with myocarditis may not drink well and may indeed be mildly dehydrated. However, cardiogenic causes such as myocarditis should be suspected when orthostatic changes do not improve with fluid resuscitation. In both myocarditis and pericarditis, a chest x-ray usually shows cardiomegaly and the ECG is abnormal, prompting further evaluation with an echocardiogram (13,16,17).

Musculoskeletal Pain

Musculoskeletal pain is one of the most common diagnoses in children with chest discomfort (2,4,18). Active children frequently strain chest wall muscles while wrestling, carrying heavy books, or exercising. Some children suffer a mild contusion of the chest wall from direct trauma. With more significant force, a rib fracture, hemothorax, or pneumothorax is possible. In most cases, there is a straightforward history of trauma and the diagnosis is clear. Generally, a careful physical examination will reveal chest wall

tenderness, bruising or pain with movement of the torso or upper extremities.

Costochondritis is a related musculoskeletal disorder that is common in children. This disorder is characterized by mild to moderate anterior chest wall pain that may radiate to the chest, back, or abdomen. Exercise or an upper respiratory infection may precede the pain. The pain may be bilateral, and is generally sharp and exaggerated by physical activity or breathing. Eliciting tenderness over the costochondral junctions with palpation makes the diagnosis. Such pain may persist for several months (7,18).

Respiratory Conditions

Many children have a respiratory condition as the etiology for their chest pain (2–4). For instance, children with severe, persistent cough or asthma may complain of chest pain caused by overuse of chest wall muscles. Diagnosis is made by history or the findings of rales, wheezes, tachypnea, or decreased breath sounds. Some children who complain of chest pain with exercise may have exercise-induced asthma, a diagnosis readily established by a treadmill test (3). In addition, an occasional teenager will develop a spontaneous pneumothorax or pneumomediastinum and complain of pain associated with respiratory distress (19,20). Children at high risk for these conditions are those with asthma, cystic fibrosis, or Marfan syndrome (18,19). However, previously healthy children may rupture an unrecognized subpleural bleb with minimal precipitating factors such as coughing, sneezing, stretching. If the pneumothorax is significant, the patient can have respiratory distress, and possibly decreased breath sounds on the affected side or palpable subcutaneous air (19). Adolescents who snort cocaine are at risk for similar barotrauma and may complain of severe, sudden chest pain with associated anxiety, hypertension, and tachycardia (11,13).

Chest pain associated with fever should prompt concern for an infectious etiology such as pneumonia (1,2,4). Most such patients have a history of cough and may also be tachypneic. In addition,

children with underlying systemic lupus erythematosus may develop a pleural effusion causing chest pain worsened by deep inspiration. Auscultation of decreased breath sounds should raise suspicion for this condition, and radiographs should confirm the presence of an effusion.

Finally, pulmonary embolism is extremely rare in pediatric patients but may be considered in an adolescent girl with dyspnea, fever, pleuritic pain, cough, and hemoptysis. The likelihood of this diagnosis is increased if the patient has a central venous catheter, had recent surgery, had recent trauma, is taking birth control pills, or recently had an abortion (18,21).

Psychogenic Disturbances

Psychogenic disturbances can precipitate chest pain in both boys and girls at equal rates. Stress-related pain accounts for about 10% of children with chest pain who present to the ED (1,2,18). Often the anxiety and stress that results in somatic complaints is not easily apparent. Not all such children present with hyperventilation or an anxious appearance. A careful history is essential. If the child has had a recent major stressful event such as separation from friends, death or divorce in the family, or school failure that correlates temporally with the onset of the chest pain, it is reasonable to suspect that the symptoms are related to underlying stress (7,18).

Gastrointestinal Disorders

Gastrointestinal disorders such as reflux esophagitis often cause chest pain in young children and adolescents. The pain is classically described as burning, substernal, and worsened by reclining or eating spicy foods. The diagnosis can be made clinically or with a therapeutic trial of antacids (7).

Some young children complain of acute chest pain following the ingestion of a coin, button battery, or other foreign body that lodges in the esophagus (18).

Likewise, some adolescent patients may present to the ED with pill-induced esophagitis. Teenagers who take pill medications,

especially tetracycline or doxycycline, can develop esophagitis, particularly when the medication is taken with minimal water and the teen lies down (22). Doxycycline produces an acidic solution or gel as it dissolves, and it is caustic when it remains in the esophagus. Symptoms may be noted several days after beginning the medication, but frequently pain occurs after taking the first dose. A careful history makes the diagnosis; physical examination is likely to be unremarkable (22).

Miscellaneous

Miscellaneous causes of chest pain include pain related to underlying diseases. For instance, a child with sickle cell disease may have a vasoocclusive crisis, which localizes in the chest or produces acute chest syndrome (4). Marfan syndrome may result in chest pain and fatal dissection of an abdominal aortic aneurysm (18). Herpes zoster infection, or shingles, may produce severe chest pain that precedes the classic vesicular rash by several days or occurs simultaneously. Coxsackievirus may rarely lead to pleurodynia with paroxysms of sharp pain in the chest or abdomen ("devil's grip"). Teenagers or preteens may complain of chest pain when there is breast tenderness from physiologic changes of puberty or from early changes of pregnancy. A child with a thoracic tumor (Hodgkin disease or non-Hodgkin lymphoma) may present with chest pain but undoubtedly would have other signs and symptoms of disease as well (7). The pain may also be part of an underlying systemic disorder such as a collagen vascular disease (if there is also joint pain, rash, or fever).

Precordial catch syndrome (Texidor twinge or "stitch in the side") may explain unilateral chest pain that lasts a few seconds or minutes and is associated with bending or a slouched posture. It is believed that this pain arises from the parietal pleura, but the etiology is unclear. Straightening up and taking shallow breaths relieves the pain. The pain may recur often or remain absent for months (23). Finally, some children may complain of pain under the ribs, and sometimes hear a clicking or popping sound when they lift objects,

flex the trunk, or walk; these patients have a rare disorder called "slipping rib syndrome" (24).

Similar to abdominal pain, in 20% to 45% of cases of pediatric chest pain, no diagnosis can be determined with certainty. Therefore, the child's pain is often labeled as idiopathic and it is incumbent upon the emergency physician to have thoughtfully eliminated the most life-threatening entities from the differential diagnosis and provide families with appropriate return instructions or follow-up as needed (7).

DIAGNOSTIC APPROACH

A complete history is vital and reveals the etiology of chest pain in most cases. Family history may also be helpful with disorders such as hypertrophic obstructive cardiomyopathy where previous familial sudden deaths may yield vital clues (8,13). Past medical histories of previous ischemic heart disease or conditions such as asthma, diabetes mellitus (hyperlipidemia), or Kawasaki disease potentially place patients at greater risk for serious causes of their pain (10,18).

Keeping in mind that young children are often vague in their descriptions, it is important to determine the location, onset, frequency, and severity of the pain and most importantly if it interrupts the child's daily activities. Children with acute onset or who are awakened from sleep because of pain are more likely to have an organic etiology, although not necessarily serious disease (1,2). Those with chronic pain who have gone for extended periods without a diagnosis are more likely to have idiopathic or psychogenic pain (2). Burning pain in the sternal area suggests esophagitis, and sharp stabbing pain relieved by sitting up and leaning forward suggests pericarditis in a febrile child (13).

Precipitating factors associated with the pain should also be carefully investigated; a history of trauma, rough play, or choking on a foreign body may be quite relevant. Exertional chest pain should always be taken seriously, as it may be related to either cardiac disease or, more commonly, exercise-induced asthma. Associated complaints such as syncope or palpitations are also

significant and may be indicative of undiagnosed cardiac disease. Chest pain associated with fever makes an infectious process such as pneumonia or myocarditis more concerning.

A careful physical examination, beginning with vital signs as a first priority, will likely point to the cause of the pain. A quick general assessment often differentiates the child in severe distress such as a patient with a pneumothorax, from those with more benign causes of chest pain. This subjective assessment may also yield other subtle clues to the diagnosis. For example hyperventilation may be distinguished from respiratory distress by the absence of cyanosis or nasal flaring. Signs of chronic disease such as pallor or poor growth suggest a more complex problem like a neoplastic process (e.g., mediastinal mass) or collagen vascular disease. Consider the possibility of Marfan syndrome if the patient is tall and thin with an upper extremity span that exceeds his or her height. Examine the skin for rashes or other lesions. Bruises distant from the chest may indicate unrecognized chest trauma. Carefully examine the abdomen for sources of referred pain to the chest. Note any signs of anxiety that could indicate the presence of emotional stress. The origins of psychogenic pain should be carefully evaluated and not be treated as a diagnosis of exclusion; it is imperative to enquire about stressful conditions at home or school (see Chapter 289). For some adolescents with chest pain, substance abuse (cocaine, in particular), use of birth control pills (pulmonary embolism), and oral medications (pill-induced esophagitis) (22) should be considered. Table 234.3 summarizes important history in a child with chest pain.

TABLE 234.3
History Questions for Children with Chest Pain

When did the pain begin?
How severe is the pain?
How often does the pain occur?
How long does the pain last?
What is the pain like?
What seems to bring on the pain?
Are there associated symptoms?
What is the child's past medical history?
Is there a family history of heart disease or chest pain?
What treatments for the pain have been tried?
What is the patient or guardian concerned about?

A complete cardiopulmonary examination may reveal important findings such as rales, wheezes, decreased breath sounds, murmurs, rubs, muffled heart sounds, clicks, or arrhythmias that may indicate the need for an ECG and/or chest x-ray. A murmur that intensifies with Valsalva and the standing position is the hallmark of hypertrophic cardiomyopathy. The chest wall should also be evaluated for external signs of trauma, tenderness (suggesting musculoskeletal pain), or subcutaneous air (suggesting a pneumothorax or pneumomediastinum) (19,20).

Chest radiographs and ECG should not be routinely ordered unless indicated by the history and/or physical examination (18; see Table 234.4). A chest x-ray and/or ECG are more often indicated if the history reveals acute onset of pain (beginning in the prior 2 or 3 days) or is otherwise concerning for pulmonary problems or cardiac pathology (e.g., tachypnea, or tachycardia, or exercise induced) (18). Exertional pain should prompt consideration of cardiac ischemia or asthma, and warrants an ECG and chest x-ray and potentially a referral for exercise stress testing, although the value of this is controversial (1–7,18). Fever with chest pain is highly correlated with pneumonia, but pericarditis or myocarditis should also be considered if cardiomegaly is noted on the chest radiograph.

TABLE 234.4
Indications for Laboratory Studies in Children with Chest Pain

Worrisome History

Acute onset of pain

Pain on exertion

History of heart disease

Serious associated medical problems (diabetes mellitus, asthma, Marfan syndrome, Kawasaki disease, anemia, lupus erythematosus)

Use of drugs (cocaine, oral contraceptives)

Associated complaints (syncope, dizziness, palpitations)

Significant trauma

Foreign body ingestion/aspiration

Fever

Abnormal Physical Examination

Respiratory distress

Palpation of subcutaneous air

Decreased breath sounds

Cardiac findings (murmurs, rubs, arrhythmias)

Fever

Trauma

Laboratory studies usually only confirm previously known disorders or abnormal findings already suspected clinically. If the history and physical examination do not lead to a specific diagnosis for chest pain, laboratory tests are unlikely to be helpful. This is especially true in the child with chronic pain, a normal physical examination, and no history to indicate cardiac or pulmonary disease. Reassure the family the child is unlikely to have a serious etiology for the pain and that studies will not be helpful. Blood counts and sedimentation rates are of limited value unless sickle cell disease, collagen vascular disease, infection, or malignancy are suspected. A drug screen for cocaine may be indicated in the older child with acute pain and associated anxiety, tachycardia, hypertension, or shortness of breath. Cardiac enzymes are rarely of value unless there are specific concerns for ischemic disease from the history or examination.

CRITICAL INTERVENTIONS

- Enquiring about the presence of exertional pain, syncope, or fever.
- Obtaining an ECG and oxygen saturation.
- Ascertaining whether the patient has an underlying disease process such as diabetes, Marfan syndrome, or systemic lupus.
- Enquiring about drug use and obtaining a toxicology screen if necessary.

DISPOSITION

The child in severe distress or with abnormal vital signs should be admitted to the hospital for monitoring, further diagnostic studies, and treatment. Patients who have exertional pain, dizziness, palpitations or syncope should be urgently referred to a cardiologist for further evaluation which may include a Holter monitor or echocardiogram to evaluate for an arrhythmia or structural heart disease (7,8,25). Similarly, a child with known or suspected heart disease may be best served by a visit to a cardiologist even if the pain proves to be unrelated. A specialist should also be consulted for patients with suspected esophageal foreign body for rapid removal of the object. If the patient has a serious emotional problem that cannot be managed by the ED staff, referral to a psychiatrist is warranted.

In all cases, appropriate follow-up should be arranged; many children with ill-defined chest pain have persistent symptoms for many months. Although serious organic pathology is unlikely to be found in the future, some patients are kept from participating in their usual activities because of the pain, and some patients manifest significant psychoemotional problems or exercise-induced asthma that was not recognized at the initial ED visit (26,27).

Common Pitfalls

- Failure to consider serious pathology (e.g., myocarditis) in the child with chest pain.
- Failure to consider pneumonia or viral myocarditis in febrile patients with chest pain.

- Failure to consider cardiac disease if pain is associated with exertion, syncope, or dizziness.
- Failure to consider esophageal foreign body (e.g., coin ingestion) in a toddler with sudden onset of chest pain.

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CHAPTER 235
Syncope

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Syncope is the sudden transient loss of consciousness (LOC) accompanied by an inability to maintain postural tone, with spontaneous resolution. The sensation or feeling of being about to pass out is near-syncope or presyncope. The causes and management are analogous to that for syncope. Syncope is a common complaint in patients of all ages, accounting for 1% to 1.5% of emergency department (ED) visits and up to 6% of hospital admissions (1,2). In children and adolescents, syncope accounts for 2% of pediatric ED visits (3) and 5% of pediatric hospital admissions (4,5). In the pediatric population, syncope occurs more often in females than males, and most often in adolescents, with the highest incidence in the 15- to 19-year-old age group (6). About 25% of all adolescents will have had at least one syncopal episode (7), although higher incidences of nearly 50% have been reported (8,9).

The etiology of syncope is established in only about half of adult patients following an initial ED visit and in only 70% of patients who have been admitted to the hospital (10). The findings in pediatric patients are similar where nearly one in five patients have “syncope of unknown origin” (11).

Syncope of unknown origin is less common in children under 5 years of age, in whom primary cardiac dysrhythmias, seizures, and breath-holding spells are the main considerations. Although the general categories of disorders resulting in syncope are similar in adults and children, the specific causes and evaluations differ between adults and children/infants.

The pathophysiology of syncope involves dysfunction of cerebral hemispheres or the reticular activating system in the brainstem, typically from an acute decrease in cerebral blood flow. Syncope occurs when cerebral blood flow decreases to less than 30% to 50% of baseline (12). This is most often the result of systemic hypotension, but may also be due to cerebral vasoconstriction or regional hypoperfusion of the central nervous system (CNS). Decreased cerebral perfusion impairs delivery of substrate (e.g., oxygen and glucose) to the brain. Less commonly, cerebral blood flow is adequate, but there is deficient substrate, as in hypoglycemia, carbon monoxide poisoning, severe anemia, or asphyxia.

CLINICAL PRESENTATION

Vasovagal syncope, also known as *neurocardiogenic, neurally mediated, vasodepressor,* and *reflex* syncope, is the most common cause of pediatric and adult syncope. It is responsible for about half of cases of pediatric syncope (11,13). Typical cases are individuals who faint while experiencing pain, anger, or fear (e.g., at the sight of blood), or while standing erect for a prolonged time in a warm environment (as in the military, a parade, or a religious service).

The mechanism of vasovagal syncope has been thought to be a vagally mediated reflex that causes bradycardia, and a decreased peripheral vascular resistance with venous pooling in the periphery resulting in hypotension from a loss of sympathetic tone. Decreased venous return leads to a relatively empty ventricle. Strong myocardial contractions against an empty ventricle stimulate the vagal reflex causing bradycardia, and sympathetic withdrawal results in decreased peripheral vascular resistance and a drop in arterial blood pressure. However, the occurrence of “vasovagal” syncope in patients with a heart transplant indicates that other mechanisms may also be responsible. Possibilities include neurohumorally mediated sympathetic inhibition, impaired responses in the peripheral vessels (affecting peripheral vascular

resistance), and abnormal CNS control mechanisms, or a combination of such factors.

Cardiovascular causes of syncope can be categorized into several groups: dysrhythmia, obstruction to flow, myocardial dysfunction, or vascular. The common pathophysiology is a decrease in cardiac output (CO) resulting in decreased cerebral perfusion. Cardiac syncope occurs when CO is decreased from inadequate stroke volume (SV) or an abnormal heart rate (HR), leading to inadequate filling of the ventricles.

Although *dysrhythmias* are a less frequent cause of syncope in pediatric patients than adults, this possibility should be in the differential because of the association with sudden death. Patients with heart disease, whether congenital or acquired, are at high risk for dysrhythmias and sudden cardiac death. Congenital heart disease is the number one cause of dysrhythmias resulting in syncope in pediatric patients. Most sudden cardiac deaths associated with dysrhythmias occur in pediatric patients who are status after corrective cardiac surgery, especially repair of tetralogy of Fallot, or a baffle (Mustard or Senning procedure) for transposition of the great vessels. Estimates of the incidence of sudden cardiac death with congenital heart disease are as follows:

Tetralogy of Fallot 2.5% to 10%

Eisenmenger syndrome = 10% to 47%

Ebstein anomaly = 2.5% to 20% (14).

Other cardiac disorders associated with dysrhythmias include Ebstein anomaly, arrhythmogenic right ventricular dysplasia, and cardiac tumors.

In patients with a structurally “normal” heart, syncope and sudden death can occur with Wolff–Parkinson–White syndrome (WPW), long QT syndrome, short QT syndrome, ventricular tachycardia, complete heart block, and the Brugada syndrome.

The diagnostic hallmark of WPW is a short PR interval and a delta wave. Supraventricular tachycardia results from reentrant conduction down the atrioventricular node and up the accessory pathway (Kent bundle). Rapid conduction over the Kent bundle can proceed to ventricular fibrillation and sudden death. An

electrophysiologic study with radio-frequency ablation is the recommended treatment.

The long QT syndrome is due to abnormal ventricular depolarization resulting in a prolongation of the refractory period. This can cause torsades de pointes with the potential to degenerate into ventricular fibrillation and sudden death. The long QT syndrome is characterized by QT interval prolongation. There are several forms of the long QT syndrome. The congenital types of long QT syndrome include the Romano–Ward syndrome and the Jervell and Lange-Nielsen syndrome. The Romano–Ward syndrome has an autosomal dominant inheritance, whereas the Jervell and Lange–Nielsen syndrome has an autosomal recessive inheritance and deafness. Acquired prolongation of the QT interval can be due to electrolyte abnormalities (hypocalcemia, hypokalemia), drugs/overdose, and increased intracranial pressure. Medications associated with prolongation of the QT interval include psychotropics (tricyclic antidepressants, phenothiazines), antihistamines, and promotility drugs (such as cisapride), especially in combinations with other medications (e.g., erythromycin and ketoconazole). The short QT interval is also associated with dysrhythmias and sudden death.

Bradyarrhythmias, which can cause syncope and sudden death, include complete heart block and sick sinus syndrome. Atrioventricular block may be congenital or acquired. Acquired causes are most common after cardiac surgery; but rheumatologic diseases, infections, and neuromuscular diseases (e.g., Lyme disease, acute rheumatic fever, endocarditis, diphtheria, myotonic dystrophy, certain forms of muscular dystrophy, and Kearns–Sayre disease) are other etiologies for complete heart block. Congenital heart block can occur as an isolated condition or with structural heart disease, especially defects of the atrioventricular septum, L-transposition of the great vessels, or ventricular inversion. Infants born to mothers with systemic lupus erythematosus may have complete heart block secondary to transplacental antibodies cross-reacting with fetal cardiac tissue.

Sinus node dysfunction most commonly occurs in patients who have undergone cardiac surgery, especially atrial surgery. These patients are also at risk for atrial arrhythmias (e.g., atrial flutter and atrial fibrillation). The combination of atrial flutter/fibrillation with a rapid ventricular response plus sinus node dysfunction can lead to syncope from hemodynamic compromise and is a harbinger for dysrhythmias and sudden death.

Ventricular tachycardia/fibrillation leading to syncope and sudden death can occur in patients with myocardial disease (such as myocarditis, cardiomyopathy, and myocardial ischemia) and with ventricular damage or scarring post cardiac surgery (even years after surgical repair).

The second category of cardiac syncope involves *obstruction to blood flow*. The classic example is hypertrophic obstructive cardiomyopathy. Aortic stenosis with outflow obstruction may cause syncope, anginal chest pain, and dyspnea on exertion. Severe coarctation of the aorta or severe mitral valvular disease can also present with syncope. Similarly, patients with primary pulmonary hypertension or severe pulmonic stenosis may develop syncope. Sudden death in Eisenmenger syndrome is probably due to a drop in blood flow from a sudden increase in pulmonary vascular resistance. Tumors such as an atrial myxoma causing decreased CO are a rare cause of cardiac syncope.

Myocardial disease is the third category of cardiac syncope and includes cardiomyopathies, myocarditis, myocardial ischemia (congenital from anomalous coronary arteries or acquired as in Kawasaki disease), and diseases infiltrating/destroying the myocardium such as amyloidosis or Chagas disease.

Vascular causes of syncope include aortic dissection, subclavian steal, thoracic outlet syndrome, and very rarely pericarditis leading to tamponade.

Respiratory diseases ranging from status asthmaticus to severe pneumonia or any cause of respiratory failure resulting in hypoxemia can cause syncope from decreased oxygen delivery to the brain. Posttussive or cough syncope, occurring after severe coughing, is due to decreased venous return (and, thus, decreased

CO) caused by the Valsalva maneuver. Cough syncope is a type of vasodepressor syncope. Pulmonary emboli (PE) while in the respiratory system exert their effect by obstruction of blood flow.

Other respiratory causes of syncope include breath-holding spells, which are unique to pediatrics, and hyperventilation. Hyperventilation syncope generally occurs when there is an emotional upset, pain, or anxiety, and is often associated with light-headedness, tachypnea, dyspnea, chest pain, and paresthesias. The pathophysiology is thought to be from decreased oxygen/glucose delivery to the brain caused by vasoconstriction of the cerebral arteries from the hypocapnia caused by hyperventilation.

Breath-holding spells are common, occurring in about 4.6% of children (15). Breath-holding spells usually begin between 6 to 18 months of age (with a range from the first week of life to 3 years) and end by 6 years of age in 90% of children. There are two types of breath-holding spells: cyanotic and pallid. Cyanotic spells are more common. Both spells are due to transient cerebral anoxia.

Typically, the cyanotic breath-holding spell is precipitated by the child's or infant's crying after being angered. The vigorous crying results in transient cerebral ischemia caused by (a) cerebral arterial vasoconstriction from hypocapnia, (b) hypoxemia from apnea, and (c) decreased CO from a prolonged Valsalva effect. The pallid breath-holding spell generally occurs after a painful or anxiety-producing incidence such as a minor fall. The transient cerebral ischemia occurring with the pallid breath-holding spell is due to an exaggerated vagal response to pain causing prolonged asystole or bradycardia. Breath-holding spells are a benign entity with no sequelae although they are commonly misdiagnosed as seizures.

Neurologic syncope can occur as a result of cerebral hypoperfusion from cerebral vasoconstriction (as with hyperventilation syncope) or from focal hypoperfusion of CNS structures. Cerebrovascular disease (more common in adults) could cause syncope, but usually there are other neurologic signs and symptoms. Other causes of syncope from focal hypoperfusion of CNS structures include subarachnoid hemorrhage, vasculitis (affecting cerebral vessels), CNS tumors, CNS trauma, and basilar artery migraine.

Psychiatric "disorders" are in the differential diagnosis of syncope. "Hysterical syncope" usually occurs before an audience, with no injuries occurring to the patient, and often is accompanied by dramatic moaning, gestures, and attention-seeking behavior with secondary gain.

The most common final diagnoses, according to a pediatric ED study of syncope in children and adolescents, were vasovagal (50%), orthostatic hypotension (20%) due to dehydration (15%) or anemia (5%), atypical seizure (7.5%), migraine (5%), and minor head trauma (5%) (13). A multicenter inpatient study of pediatric syncope from China reported the following causes of syncope; autonomic mediated reflex syncope (73%) consisting of vasovagal 43%, postural orthostatic tachycardia syndrome (POTS) 27%, situational 1.7%, and orthostatic hypotension 1.3%; followed by cardiac syncope 2.9%, neurologic syncope 2.1% consisting of seizure 1.9% and migraine 0.2%; psychiatric syncope 2.3%, metabolic syncope 0.8% comprised of hypoglycemia 0.4%, severe anemia 0.2% and hyperventilation syndrome 0.2%, and unknown origin 18.9% (11). Although it is likely that the ED and inpatient populations are different in these two studies, the most common cause of pediatric syncope in all age groups, whether ED or inpatient, is vasovagal with cardiac and neurologic syncope generally both $<5\%$.

DIFFERENTIAL DIAGNOSIS

Not all patients with a "transient loss of consciousness" are diagnosed with syncope (Table 235.1). In one study of adults presenting to an ED with an LOC, 12.3% of patients had a diagnosis other than syncope (1). The nonsyncope patients were categorized as either a disorder with LOC or a disorder mimicking an LOC. For the group with a disorder with LOC, hypoglycemia accounted for the majority of patients, with other diagnoses including transient ischemic attack, seizure, migraine, and other metabolic (hypoxia, hyperventilation) causes. Somatization disorders and drop attacks comprised the category of disorders mimicking an LOC (1). Another

ED study diagnosed seizures in 29% of patients who presented with a transient LOC (16). Comparable results were noted in a study of pediatric syncope patients with a neurologic condition diagnosed in 17.5% (atypical seizure 7.5%, migraine 5%, minor head trauma 5%) 13).

TABLE 235.1
Causes of Syncope in the Pediatric Patient

Vasodepressor (vasovagal, neurocardiogenic, neurally medicated, reflex)

- Triggers: pain, fear, prolonged standing, heat exposure
- Situational syncope: cough (posttussive), deglutition, micturition, defecation, hair grooming
- Carotid sinus sensitivity

Orthostatic (postural)

- Decreased intravascular volume: vomiting, diarrhea, hemorrhage; or relative hypovolemia: sepsis, extended bed-rest; drugs/toxins: diuretics, medications causing vasodilatation
- Postural orthostatic tachycardia syndrome

Dysautonomic syndromes: primary or secondary autonomic failure

- Primary autonomic failure

Multiple system atrophy: cerebellar/pyramidal, Parkinsonian

- Secondary autonomic failure

Central (CNS): multiple sclerosis, syringobulbia, CNS malignancies

Spinal: transverse myelitis, syringomyelia, spinal tumors

Peripheral nerve: rheumatologic/autoimmune diseases, AIDS, paraneoplastic syndrome, renal failure, familial dysautonomia, dopamine β-hydroxylase deficiency

Cardiovascular

1. Dysrhythmias: congenital or acquired
   - Bradyarrhythmias: sinus node disease, atrioventricular block (Stokes Adams syndrome)
   - Tachyarrhythmias: long QT syndromes, Wolf–Parkinson White syndrome, ventricular tachycardia, supraventricular tachycardia, torsades de pointes, ventricular fibrillation, arrhythmogenic right ventricular dysplasia
   - Postoperative congenital heart disease patients, certain congenital heart defects (tetralogy of Fallot, Ebstein anomaly, others) are especially high risk for dysrhythmias and sudden death
   - Pacemaker malfunction, AICD malfunction
2. Outflow obstruction
   - Hypertrophic obstructive cardiomyopathy, pericarditis with tamponade, severe aortic stenosis, pulmonary hypertension, prosthetic valve dysfunction, pulmonary emboli, some cyanotic congenital heart defects, severe coarctation, severe mitral stenosis, Eisenmenger syndrome, right ventricular dysplasia, cardiac tumor mass (atrial myxoma)
3. Myocardial disease/dysfunction
   - Cardiomyopathy, myocarditis, coronary artery abnormalities (congenital—anomalous coronary artery; or acquired—Kawasaki disease); rheumatologic/immunologic/vasculitis disorder: Lyme disease, amyloidosis, sarcoidosis; neuromuscular disorders: muscular dystrophy, others
4. Vascular
   - Aortic dissection, connective tissue disorders: Marfan disease, Ehlers–Danlos syndrome
   - Subclavian steal
   - Thoracic outlet syndrome

Neurologic

- Subarachnoid/epidural/subdural/intracerebral hemorrhage
- Transient ischemic attack/stroke
- Migraines: caused by spasm of vertebrobasilar arteries
- Neuropathies (see also dysautonomic syndromes)
- Seizures

Metabolic/endocrine

- Hypoglycemia

Respiratory/pulmonary

- Pulmonary emboli (see also cardiac)
- Cough (posttussive)
- Hyperventilation
- Breath-holding: cyanotic, pallid, mixed (autonomic dysregulation is presumed)
- Hypoxia
- Pulmonary disease or respiratory failure causing hypoxia
- Carbon monoxide poisoning, other toxins
- Severe anemia

Drugs

- Poisons, toxins
- Substance abuse, alcohol, opiates
- Prescription drugs: antidepressants (tricyclics, phenothiazines) antihypertensives (α- and β-blockers, hydralazine, ACE inhibitors, ganglionic blockers), vasodilators (calcium channel blockers, nitrates)

Psychiatric

- Hysteria

Thus, the main considerations for other "nonsyncopal" causes of a transient LOC are either a neurologic disease or a metabolic disorder. Neurologic disorders range from an acute neurologic event from a transient ischemic attack/cerebrovascular accident or hemorrhage/emboli to a migraine or seizures. Neuropathies can precipitate orthostatic (postural) hypotension and syncope. The differential illustrates the importance of the neurologic examination in any patient with syncope.

Hypoglycemia is the most common diagnosis in the metabolic/endocrine category of patients who may present with a transient LOC. Hyperventilation, drugs (alcohol/illicit drugs/prescription drugs), toxins, liver failure, renal failure, various congenital metabolic disorders, and carbon monoxide poisoning are also in the differential.

Seizures are often mistaken for syncopal events and vice versa. Brief tonic–clonic movements may occur with vasodepressor syncope. Akinetic seizures may be present like a syncopal episode. The history may help distinguish between syncope and a seizure. The following suggest a seizure, not syncope: focal neurologic signs, bowel/bladder incontinence, prolonged LOC or confusion, tongue biting, and a prodromal aura. With a syncopal episode, the period of unconsciousness is brief (only seconds) and has a rapid recovery to a normal mental status.

ED EVALUATION AND MANAGEMENT

The history and physical examination are the key components of the evaluation of the pediatric patient with syncope. After ruling out mimickers of pediatric syncope, such as seizures and breath-holding spells, the first consideration is to determine whether the etiology of the syncope is benign or life-threatening. With near syncope or presyncope, the syncopal symptoms resolve before LOC occurs. The evaluation of the near syncope patient, however, is similar to that of the syncope patient.

The history and physical examination should guide the ordering of laboratory and ancillary tests. If the history is pathognomonic, such as vasodepressor syncope (e.g., teenager who passed out while getting a routine immunization) or an infant with a breath-holding spell, further testing may not be necessary. If the history suggests orthostatic syncope due to dehydration from vomiting or diarrhea, checking electrolytes and providing intravenous fluids may be all that is needed.

The physical examination may provide clues to the diagnosis. Cardiac findings, such as a murmur, loud S2, the presence of a click, S3, or S4, suggest cardiac syncope. The presence of neurologic symptoms and signs may indicate CNS disease or a seizure. If there are differences in pulses and/or blood pressures between the extremities, consider the possibility of a dissecting aneurysm, a coarctation of the aorta, or subclavian steal. Focused testing in selected patients based on the history and physical examination is probably the most useful and cost-effective approach (17,18). Simple cost-effective tests may be helpful, such as abnormal orthostatic vital signs, supine tachycardia, or severe dizziness upon standing (3,13), suggesting orthostatic syncope; or hemoccult of the stool with melena, indicating gastrointestinal bleeding. A pregnancy test should be considered in female adolescents with syncope, as bleeding during pregnancy (as with ectopic pregnancy) can cause syncope. Patients with hypoglycemic symptoms can present with syncope, and thus a serum glucose or dextrostix might be useful, especially in a diabetic. When pallor is present or bleeding is suspected, a hematocrit is appropriate.

If cardiac syncope is being considered, an electrocardiogram (ECG) and chest roentgenogram are indicated. Additional evaluation such as an echocardiogram, Holter monitoring, pediatric cardiology consultation, or hospital admission may be warranted if cardiovascular syncope is strongly suspected and supported by the evaluation (3).

Many clinicians recommend an ECG in any pediatric or adult patients with syncope no matter the history to detect occult cases of cardiovascular syncope (4,7,17,18).

Routine computed tomography (CT) scans are usually not helpful, but a head CT scan may be indicated if neurologic signs/symptoms are present or new onset of seizures is a likely diagnosis. A chest CT scan or ventilation perfusion scan can be done if PE is a consideration. However, in the adolescent population a D-dimer may be useful to rule out PE and avoid unnecessary CT scanning. If orthostatic syncope from a dysautonomic syndrome is being considered, referral for tilt testing may be appropriate. The tilt test has been useful in selected pediatric patients, including those with "unexplained" syncope (19).

Several rules have been developed including the San Francisco Syncope Rule and the OESIL (Osservatorio Epidemiologico sulla Sincope nel Lazio) in order to predict which patients with syncope are likely to have an adverse outcome (2,20). However, these rules apply only to adults and prospective studies indicate clinical judgment performs as well as these rules (21,22).

CRITICAL INTERVENTIONS

- Obtain a clear history of the events prior to, during, and immediately after the syncopal event.
- Perform a thorough physical examination (particularly cardiac and neurologic), in addition to orthostatic vital signs.
- Perform a blood glucose in patients with altered level of consciousness and a urine pregnancy test in adolescent females.
- Obtain an ECG on patients with syncope, especially those with possible cardiac syncope to check for long QT syndrome, WPW syndrome, and other causes of cardiac syncope. A chest radiograph may be indicated in selected patients with ECG findings indicative of cardiomyopathy.
- Consider all patients with a history of cardiac disease (congenital or acquired, especially those who have had heart surgery) to have a potentially life-threatening dysrhythmia as the cause of their syncope.

DISPOSITION

Testing, referral, and the decision to admit to the hospital are generally guided by the findings on the history, physical examination, and ECG. Although most causes of syncope are benign, some are life-threatening, and syncope may be a warning sign of later sudden death. Thus, patients with cardiac syncope typically require referral and admission. Patients experiencing vasopressor syncope or breath-holding spells may be discharged home without additional testing. Patients with orthostatic syncope from dehydration can usually be treated with intravenous fluids in the ED and then discharged home. Patients with a dysautonomic syndrome generally need to be referred.

Common Pitfalls

- Failure to differentiate syncope from seizures and breath-holding spells.
- Failure to recognize potentially life-threatening causes of syncope.
- Failure to identify the high-risk patient (e.g., the patient with congenital heart disease or a history of cardiac surgery) and refer or admit to the hospital.
- Failure to perform a pregnancy test on sexually active adolescent females.

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CHAPTER 236

Seizures

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A seizure in a child can be a dramatic event, provoking fear and panic in parents and caregivers, and not surprisingly frequently presents to the emergency department (ED). A seizure is a series of excessive, abnormal electrical discharges of cerebral neurons producing transient involuntary alterations in consciousness, motor activity, behavior, and/or autonomic regulation. Seizures affect 4% to 6% of children by age 16, and are the most common childhood neurologic disorder (1).

During seizure activity, consumption of oxygen and glucose is increased in cerebral tissues. Early physiologic changes include hypertension, hyperglycemia, and hypoxemia. With subsequent or prolonged seizure activity, progressive lactic acidosis, rhabdomyolysis, hyperkalemia, hyperthermia, and hypoglycemia may develop, possibly leading to permanent neurologic damage.

Most childhood seizures are brief and isolated and have a good outcome in both the short and long terms. At the other extreme, status epilepticus (SE), as historically defined, is recurrent or continuous seizure activity lasting longer than 30 minutes without recovery of baseline mental functioning. However, many experts have argued that continuous or recurrent seizure activity lasting longer than 5 minutes should be considered SE. Current evidence suggests that seizures that do not resolve spontaneously over this brief period are unlikely to do so and that more aggressive antiepileptic drug therapy is indicated at that point (2). SE is one of the most common neurologic emergencies encountered in children, and up to 10% of children with new onset seizures will present in SE

(3). Given their frequency, the ED physician should be familiar with all aspects of seizure management, including initial stabilization, primary investigation of cause, acute management, and disposition.

CLINICAL PRESENTATION

Broadly, seizures are classified as either generalized or partial. Generalized seizures may be convulsive or nonconvulsive and are almost always attended by an altered level of consciousness. If the seizure has a motor component it is bilateral, as both cerebral hemispheres are involved. Partial seizures, which originate in one cerebral hemisphere, may be simple (without affecting consciousness) or complex (associated with impaired mental status), and may manifest in a variety of ways. These include tonic, clonic, tonic–clonic, or myoclonic motor activity; sensory distortions or hallucinations; autonomic symptoms such as sweating and piloerection; repetitive, stereotyped movements; or isolated behavioral changes, such as continuous crying or bicycling movements seen in infants (4). See Table 156.1 in Chapter 156.

By the time the patient is in the ED, many seizures have spontaneously ceased. At this stage, the most important task of the ED physician, after a brief primary survey, is to obtain a thorough history and physical. At this time the physician can determine whether a postictal phase is present, whether loss of bowel and/or bladder control occurred, or whether a focal neurologic deficit remains. This will help differentiate true seizures from alternative diagnoses presenting similarly. Furthermore, such information can help determine when further workup is warranted. For example, a hemiparesis (Todd paralysis) or other focal neurologic deficit is an important localizing sign suggesting that the seizure had a focal component. However if the focal deficit is new and persists, neuroimaging is indicated to identify a potential CNS lesion.

When a child presents with concern for seizure, the most important initial task is to determine whether there is ongoing seizure activity. If seizure activity is continuing, managing the ABCs and terminating the seizure are the first priorities.

DIFFERENTIAL DIAGNOSIS

Seizures have many potential causes, which vary with age (Table 236.1). Rather than a litany of laboratory tests, a detailed history of the event from a witness is the single most important element to accurately determine etiology. This history can then guide further diagnostic testing. A detailed history can also be the key to determining whether the child has actually had a seizure, as other childhood conditions can be mistaken for epileptic events. These disorders can be classified into one of three categories based on presentation: (1) sudden loss of consciousness (LOC), (2) paroxysmal movements, or (3) sudden change in behavior.

TABLE 236.1
Acute Causes of Seizures by Age

Neonatal

Congenital CNS abnormalities

Hypoxic–ischemic CNS insult

Intracranial hemorrhage

Intrauterine drug exposure/drug withdrawal

Metabolic disorders (e.g., hypoglycemia, hyponatremia, hypernatremia, hypomagnesemia, hyperphosphatemia, hypocalcemia)

Inborn errors of metabolism

Hypertension

Infections/sepsis

Epilepsy (e.g., infantile spasms)

Pyridoxine deficiency

Benign familial neonatal seizures/benign idiopathic neonatal seizures ("fifth day fits")

Early Childhood

Past birth-related injury

Febrile seizures (6 mos to 5 yrs)

Meningitis/encephalitis

Metabolic disorders

Neurocutaneous syndromes

Cerebral degenerative disorders

Tumors

Head trauma (shaking or direct injury)

Epilepsy (± medication noncompliance)

Children and Adolescents

Head trauma

Meningitis/encephalitis

Epilepsy (± medication noncompliance)

Cerebral degenerative disorders

Tumors

Idiopathic

Any Age Group

Ventriculoperitoneal shunt malfunction or infection

Toxins (PLASTIC)

- *P*esticides, phenothiazines, phencyclidine
- *L*idocaine, lindane, lithium
- *A*lcohol, amphetamines, antihistamines, antidepressants, anticholinergics
- *S*alicylates
- *T*heophylline
- *I*nsulin, isoniazid, Inderal
- *C*amphor, caffeine, carbon monoxide, cocaine

CNS, central nervous system.

Disorders with sudden LOC include breath-holding spells, syncope, cardiac dysrhythmias, and complicated migraine. In contrast to true seizures, in these conditions a postictal state is rare. The LOC in vasovagal syncope is brief and recovery is rapid, though these episodes may occasionally be accompanied by a brief generalized seizure. With complicated migraine, LOC may be associated with or preceded by blurred vision, blindness, dizziness, or loss of postural tone. Breath-holding spells, typically seen in young children between 6 months and 6 years, are associated with emotional upset or minor trauma and result in LOC. They are differentiated from seizures by the characteristic precipitating stimulus and color change preceding LOC. Disorders involving paroxysmal movements include tics, shuddering attacks, benign sleep myoclonus, and pseudoseizures. Shuddering attacks typically begin in infancy and are characterized by rapid tremors of the entire body, which may occur up to 100 times a day. They are thought to be benign but EEG is indicated to help differentiate them from true seizures (5). Psychogenic nonepileptic seizures (formerly pseudoseizures) are episodes of motor, sensory, or cognitive disturbance that are not due to central nervous system (CNS) dysfunction but mimic epileptic seizures. They can be difficult to distinguish from true seizures, particularly as they often occur in patients with true epilepsy. However, clues that an episode is nonepileptic include asynchronous motor movements, lack of self-injury or incontinence, and forced eye closure. Ultimately, video EEG monitoring may be required for definitive diagnosis. Lastly, disorders with sudden behavioral changes may mimic seizures. One such example is night terrors, wherein the school-age child wakes from sleep with intense fear and autonomic arousal; the child typically does not remember the event (4).

ED EVALUATION

The history and physical examination are the most useful tools in the ED evaluation. The history should focus on a detailed description of the seizure including seizure duration, type of seizure (focal or generalized), associated LOC, presence of incontinence or cyanosis, length of postictal period, any postictal neurologic abnormalities,

and, for patients with a known seizure disorder, whether the current seizure is different or the frequency has increased. Further history should focus on potential causes: trauma, infection, recent immunization, presence of a cerebrospinal fluid (CSF) shunt, intoxication, a history of seizures, anticonvulsant use and compliance, or use of the ketogenic diet. The history should include any prehospital observations and treatment by either caretakers or emergency medical service (EMS) providers. The administration of benzodiazepines by caretakers or EMS providers may explain a prolonged postictal phase (7).

The physical examination should focus on signs of trauma (including retinal hemorrhages), increased intracranial pressure (ICP), focal neurologic abnormalities, and meningeal irritation. In addition, one should assess for hepatosplenomegaly for possible metabolic or glycogen storage disease and the skin for café-au-lait spots (neurofibromatosis), vitiliginous lesions (tuberous sclerosis), or port-wine stains (Sturge–Weber syndrome).

Laboratory testing should be guided by the history and examination. A rapid bedside glucose should be done on all seizure patients; however, serum electrolytes, calcium, magnesium, ammonia, complete blood count, and urine toxicology have been shown in several studies to have a low yield in patients without identifiable risk factors (1). They should therefore be reserved for patients with a significant pretest probability of an acute electrolyte disturbance. In patients on chronic anticonvulsants, appropriate serum drug levels should be obtained.

With the exception of the neonate, a lumbar puncture is not indicated for the child with a seizure who has no other clinical findings supportive of meningitis. Emergent head CT is also not routinely warranted in patients presenting with a first afebrile seizure (1). However, emergent neuroimaging should be strongly considered in the patient who demonstrates persistent focal deficits on neurologic examination, has signs of increased ICP, is younger than 6 months, has a ventriculoperitoneal shunt, presents in SE, is immunocompromised, has traveled to an area endemic for cysticercosis, has suspected cerebrovascular disease, has a bleeding

disorder or hypercoagulable state (including sickle cell disease), or in whom head trauma is suspected (8,9). If emergent neuroimaging is not required, brain magnetic resonance imaging is the preferred modality for new-onset seizure in children and can be arranged on an outpatient basis. EEG is rarely required emergently, with the notable exceptions of refractory SE or when a diagnosis of nonconvulsive SE is being considered (10).

ED MANAGEMENT

Seizure activity upon arrival in the ED should be considered SE until further history can be obtained, and the main priorities should be maintenance of airway, breathing, and circulation, followed by interventions to stop the seizure. A brief history should focus on finding an acute cause of the seizure, such as trauma, infection, or intoxication, along with a previous history of seizures and known anticonvulsant use. A rapid physical examination should search for signs of trauma, increased ICP, and meningeal irritation. If meningitis is a concern, appropriate antibiotics should be given expeditiously.

Benzodiazepines are the drugs of choice for initial management of all seizures in children older than 28 days. Lorazepam may be preferred because of its long half-life, though diazepam and midazolam are also effective choices. Midazolam has become more frequently utilized in prehospital and ED settings since it may be delivered intranasally, buccally, or intramuscularly, which is a distinct advantage in critically ill pediatric patients in whom intravenous access may be challenging (8). Diazepam can be given rectally, and a viscous solution for rectal administration called Diastat is available for use at home. Important side-effects of benzodiazepines are respiratory depression and, in higher doses, hypotension.

Fosphenytoin or phenytoin has traditionally been used as a second-line agent if seizure activity continues after benzodiazepine administration. Fosphenytoin (a prodrug of phenytoin) is often preferred for use in children because it is less likely to cause hypotension with IV infusion or tissue necrosis after accidental

infiltration. Fosphenytoin (like midazolam) can be given intramuscularly if vascular access has not been established.

In the recent years, levetiracetam has been increasingly employed in the management of SE, most frequently as a second-line agent. It has a favorable side-effect profile and has been demonstrated to be safe in children as young as 6 months of age (25). Valproate has also demonstrated utility as a second-line drug in pediatric patients, with the advantage that it lacks adverse effects on cardiorespiratory function (12). Phenobarbital continues to be used as a second- or third-line agent in pediatric SE, though caution should be exercised as there is a significant risk of respiratory depression with phenobarbital, particularly when given after benzodiazepines.

In 25% of patients with SE, seizures will continue despite initial therapies. In these cases, SE is considered refractory and induction of general anesthesia is often indicated. Commonly utilized agents include midazolam, pentobarbital, and propofol, and limited evidence suggests that none of these agents is clearly superior to the others (13). See Table 236.2 for dosing information of available medications.

TABLE 236.2
Medications Used in the ED for Seizures and Status Epilepticus

Use	Drug	Route/Dosage/Max Dose	Adverse Effects
First-line agents	Midazolam	IV: 0.1 mg/kg, up to 10 mg	Loss of airway control, hypoventilation
		IM: 0.2 mg/kg, up to 10 mg	Hypotension: rare
		IN: 0.2–0.4 mg/kg, up to 10 mg	
		Buccal: 0.2–0.5 mg/kg, up to 10 mg	
	Diazepam	IV, IM: 0.2–0.3 mg/kg, up to 10 mg	Loss of airway control, hypoventilation
		PR: 0.5 mg/kg, up to 20 mg	Hypotension: rare
			PR: erratic absorption
			IM: sterile abscess
	Lorazepam	IV: 0.1 mg/kg, up to 4 mg	IM: erratic absorption, accumulation of drug with multiple doses
		IM: 0.2 mg/kg	
Second-line	Phenytoin	IV: 20 mg/kg over 30–45 min, up to 1,000 mg	Hypotension and arrhythmias with rapid infusion
	Fosphenytoin	IV: 20 mg PE/kg over 15 min, up to 1,000 mg	Expensive
		IM: same, several sites needed	Less effective for seizures due to toxins/drugs
	Levetiracetam	IV: 20–30 mg/kg over 15 min, up to 2,500 mg	Few side effects, limited evidence for use
	Valproic acid	IV: 20–40 mg/kg over 10 min	Hepatotoxicity, pancreatitis, thrombocytopenia
Third-line	Phenobarbital	IV: 20 mg/kg over 30 min	Loss of airway control, hypoventilation, hypotension, prolonged obtundation
Fourth-line	Pentobarbital	IV: 5–15 mg/kg slow bolus then 1–3 mg/kg/hr	Loss of airway control, hypoventilation, hypotension, prolonged obtundation
	Midazolam	IV: 0.1–0.2 mg/kg slow bolus then 0.06–0.12 mg/kg/hr (1–2 µg/kg/min) titrate by 0.06 mg/kg/hr (1 µg/kg/min) every 10 min as needed	Loss of airway control, hypoventilation, hypotension, prolonged obtundation
	Propofol	IV: 2.5–3.5 mg/kg over 30 sec, then 0.2–0.3 mg/kg/min	Hypotension; contraindicated in ketogenic diet; not recommended in patients <3 yrs of age

PE, phenytoin equivalents; IV, intravenous; IM, intramuscular; PR, per rectum.

CRITICAL INTERVENTIONS

- The following protocol is suggested to manage SE (7,11–16):

At 0 to 5 minutes

- Maintain airway, give oxygen, support ventilation, and consider cervical spine immobilization for trauma patients.
- Obtain IV access, check bedside glucose, and send blood samples for electrolytes, complete blood count, glucose, and anticonvulsant levels, as appropriate.
- Monitor vital signs, pulse oximetry, end-tidal CO_2, and electrocardiography.
- Administer first dose of benzodiazepine (see **Table 236.2**) IV. If delay in obtaining IV access, administer midazolam or lorazepam IM, diazepam PR, or midazolam IN/buccal.
- Consider intravenous glucose 2 mL/kg of D_{25} (use D_{10} solution in newborns) for documented hypoglycemia only, and pyridoxine (50–100 mg IV) for neonates (or for isoniazid overdose).

At 5 to 15 minutes, if seizure continues

- Administer second dose of benzodiazepine (see **Table 236.2**).
- Start loading dose of phenytoin/fosphenytoin versus levetiracetam versus valproate, consider phenobarbital for neonates (see **Table**

236.2).
- Search for reversible causes of seizures (trauma, toxins, shunt malfunction, and electrolyte abnormalities) and initiate appropriate management.
- Continue monitoring of VS, including pulse oximetry and now core temperature for hyperthermia.

At 15 to 30 minutes, if seizure continues
- Start loading dose of phenobarbital versus levetiracetam versus valproate, if not already used (see **Table 236.2**).
- Reevaluate airway and strongly consider need for intubation.
- Initiate contact with referral pediatric intensive care unit (PICU) and transfer patient if necessary.
- Continue search for reversible causes of seizure and initiate appropriate management.
- Check electrolyte results; consider need for intravenous hypertonic saline for symptomatic hyponatremia.

At >30 minutes, if seizure continues
- Consider additional phenobarbital/levetiracetam/valproate.
- Consider consultation with pediatric neurologist. Continuous EEG monitoring needed.
- Consider continuous pentobarbital, midazolam, or propofol infusions, in consultation with neurology/anesthesiology.
- Intubate now if not previously done.
- Consider central venous access for multiple infusions including possible vasopressors and central venous pressure monitoring. Consider continuous arterial pressure monitoring.

At beyond 60 minutes, if seizure continues
- Begin additional continuous infusion regimen with pentobarbital, midazolam or propofol, or general anesthesia while awaiting transfer or admission to PICU.

DISPOSITION

Children with first-time seizures without SE can be followed up as outpatients if they appear well, the parents are comfortable with outpatient management, and follow-up can be assured. These children frequently do not require maintenance anticonvulsant

therapy, but the decision to start therapy, and which agent to use, should be done in consultation with a pediatric neurologist and the primary care physician (1). Hospital admission is reserved for children with a prolonged seizure or SE, even if successfully treated in the ED. Additional high-risk factors for early recurrence of seizures that may justify admission are age younger than 1 year, multiple seizures within 24 hours, and children requiring treatment in the ED (17). Children requiring intubation and ventilatory support or those with refractory SE should be transported to a tertiary care facility with a PICU and pediatric subspecialists.

SPECIAL CONSIDERATIONS

Febrile Seizures

Febrile convulsions are the most common form of seizures in childhood, occurring in 2% to 5% of children. Febrile seizures are defined as a seizure in association with a febrile illness, without CNS infection, previous afebrile seizures, known brain disorder, or electrolyte imbalance. They usually occur between the ages of 6 months and 5 years; the peak incidence is at approximately 18 months of age. Febrile seizures are classified as simple or complex. A febrile seizure is complex if it is focal, lasts longer than 15 minutes, or multiple (more than one seizure in 24 hours). The majority of febrile seizures are simple, and by definition are brief, isolated, and generalized (18). The pathophysiology of febrile seizures remains unclear, though viral infections, immunizations, and genetic predisposition have been implicated (19). Mortality is extremely rare, and there are no differences in cognitive abilities after a febrile seizure, even when it is prolonged (20).

To diagnose a febrile seizure, meningitis, encephalitis, electrolyte abnormality, and other acute neurologic disease must be ruled out. However, most of these can be eliminated by a careful history and physical examination. There has been much debate over whether lumbar puncture is a necessary diagnostic test in children with simple febrile seizures. In 2011, the American Academy of Pediatrics revised its guidelines for the evaluation of children with simple

febrile seizures who are between the ages of 6 months and 5 years (18). According to these guidelines, a lumbar puncture should be considered in all infants aged 6 to 12 months who have not received recommended vaccinations for *Streptococcus pneumoniae* or *Haemophilus influenza* type b or when immunization status cannot be determined. It should also be considered in all children aged 6 months to 5 years who have been pretreated with antibiotic therapy. Children who present with simple febrile seizures who satisfy neither of these conditions do not require lumbar puncture; indeed, patients with simple febrile seizures have the same risk of serious bacterial illness, including meningitis, as matched febrile patients without seizures (18). Further, neuroimaging of any kind is not routinely required, and additional routine laboratory studies are of limited value. Other than evaluation and treatment of the underlying cause of the fever, the majority of cases require only reassurance and education of parents about febrile seizures.

The evaluation of a child with complex febrile seizures (CFS) is less straightforward and definitive guidelines do not exist. Therefore, evaluation must be tailored to the clinical situation. Generally, acute bacterial meningitis does not present with CFS as its sole manifestation. A study in 2011 included 340 patients with CFS who underwent lumbar puncture; of these patients, 3 met criteria for acute bacterial meningitis. One patient was unresponsive at presentation, a second had a bulging fontanel and apnea, and the third was a 7-month old with recurrent seizures. Two of the three patients presented before introduction of the conjugated pneumococcal vaccine. Acute bacterial meningitis, then, is very rare in patients with CFS in the absence of other suggestive features (21). Lumbar puncture should be considered in patients who present with prolonged seizures or focal features. Routine neuroimaging is not warranted, though may be indicated in the child who presents with an abnormal physical examination or SE (22).

Neonatal Seizures

Due to an immature nervous system and insufficient myelination, neonatal seizures are often clinically subtle. They may manifest as

apnea, eye deviations, abnormal chewing movements, or abnormal extremity movement such as “bicycling.” Less frequently, in contrast with the coordinated tonic–clonic movements often seen in older children, seizures may present as asynchronous clonic movements involving one or more extremities, tonic movements, or brief myoclonic jerks (23). Occasionally, an excessively “jittery” baby may be thought to be having seizures, but these movements can often be suppressed with gentle restraint. Crucially, in contrast to older patients, most neonatal seizures are provoked by an underlying abnormality, and a vigorous search for an etiology is appropriate. The most common etiology of neonatal seizures is hypoxic–ischemic encephalopathy from a perinatal anoxic insult, which usually presents within the first 48 hours of life. Intracranial hemorrhage accounts for a sizable number of cases, while inborn errors of metabolism, sepsis, metabolic derangements, CNS malformations, and toxins are less frequent etiologies (24). Pyridoxine deficiency is an autosomal recessive disorder that is a rare cause of neonatal seizures but does not readily respond to the usual treatment of SE; it is eminently treatable with supplemental pyridoxine and should be thought of when seizures are resistant to initial therapy. There are two benign neonatal seizure disorders that are diagnoses of exclusions: *Benign familial neonatal convulsions,* which present in the first 3 days of life in patients with a strong family history of epilepsy or neonatal seizures, and *benign idiopathic neonatal convulsions* (“fifth day fits”) that peak on the fifth day of life and consist of multifocal clonic seizures and apnea. Both may require therapy but overall have a favorable prognosis (25).

The workup of neonatal seizures should always include an imaging study (magnetic resonance imaging, cranial ultrasound, or CT). Laboratory workup should include electrolytes (including magnesium, calcium, and phosphate), bedside glucose determination, and toxicology studies when indicated. If an inborn error of metabolism is suspected, blood studies for amino acids, lactate, pyruvate, and ammonia, and urine for organic acids are indicated. Sepsis is always high on the differential in any sick neonate, and the workup generally includes a complete blood count with differential,

blood culture, urinalysis and urine culture, and CSF testing (including consideration of tests for herpes simplex).

The management of neonatal seizures is initially the same as for older infants and children, with attention to the ABCs and to terminating the seizure. Historically, first-line therapy for neonatal seizures has been phenobarbital, though fosphenytoin has also been frequently utilized. There is little evidence for the use of benzodiazepines in neonates and concerns exist regarding their long half-life and associated respiratory depression; however, midazolam has shown promise in the treatment of neonatal SE. Levetiracetam has seen more frequent use as an off-label therapy for neonatal seizures, given its favorable side-effect profile and the limited efficacy of other agents (24,25). Pyridoxine should be considered if seizures are refractory to first-line agents. Perhaps the most effective therapy for neonatal seizures is identifying the underlying etiology and correcting the derangement. Therefore, electrolyte and glucose abnormalities should be aggressively sought and treated appropriately. Most neonates with seizures are initially treated with antibiotics for potential sepsis, and all are admitted to an appropriate monitored bed.

Common Pitfalls

- Failure to address airway, breathing, and circulation as the first priority in SE.
- Failure to expeditiously treat ongoing SE with loading doses of anticonvulsants if benzodiazepines have not been effective.
- Performing diagnostic tests on febrile seizures when not indicated.
- Failure to consider child abuse in young children.

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CHAPTER 237
Altered Mental Status

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Altered mental status (AMS) is a commonly used term for any change in the level of consciousness (LOC). *Lethargy, obtundation, delirium, stupor,* and *coma* are often used interchangeably but are not synonymous. These conditions occur along a continuum, with lethargy indicating the least amount of dysfunction and coma indicating the most (Table 237.1) (1).

TABLE 237.1
Terms Used to Describe Altered Mental Status

Term	Description
Lethargy	Difficulty maintaining a state of wakefulness but arouses to vocal stimuli
Obtundation	Blunted state of alertness when responding to stimulation other than pain
Delirium	Decompensation in mental status characterized by one or more of the following: disorientation, trepidation, misinterpretation of sensory stimuli, or hallucinations
Stupor	Responsive only to painful stimuli that is forceful and continuous
Coma	Unresponsive to painful stimuli

CLINICAL PRESENTATION

Coma occurs if there is either bilateral cerebral dysfunction, injury to the ascending reticular activating system (ARAS), or both. The ARAS within the brainstem activates the cerebral cortex, resulting in wakefulness, attention, and a normal LOC (2).

Encephalopathy is a state of global brain dysfunction with at least two of the following symptoms: altered LOC, altered behavior, or seizures. Acute mental status changes and cerebrospinal fluid pleocytosis are most often seen in individuals with acute encephalitis.

Structural abnormalities, as seen with trauma or tumors, can lead to compression of the ARAS and produce focal deficits. Supratentorial lesions can cause compression of underlying structures with shifting of the intracranial contents and herniation (3). In uncal herniation, an expanding lesion in the temporal fossa or temporal lobe displaces the uncus and hippocampal gyrus toward the midline and the edge of the tentorium. The initial complaint may be of headache with subsequent progression to AMS. A unilateral dilated pupil is most often noted on the ipsilateral side of the lesion. Further expansion of the lesion results in increased intracranial pressure (ICP), decerebrate posturing, and transtentorial or central herniation. Central or transtentorial herniation occurs with caudal displacement of the thalamus and hypothalamus through the foramen magnum, into the posterior fossa. Compression of the brainstem results in abnormal posturing, abnormal breathing patterns, and abnormal pupils, ranging from small and reactive to midposition and fixed (4,5). Abrupt onset of coma coupled with a rapidly deteriorating clinical course suggests an acute subtentorial lesion such as cerebellar tonsillar herniation.

In pediatric patients, the majority of cases of coma are due to nonstructural causes (infection, toxic ingestion, metabolic abnormalities) and result in bilateral cerebral hemisphere dysfunction with global but symmetric deficits. In general, confusion, stupor, and obtundation precede any motor deficits. Pupillary responses remain preserved, but the respiratory rate and pattern may be altered (3).

DIFFERENTIAL DIAGNOSIS

Several different schemas have been used in the evaluation of a patient with AMS. The AEIOU-TIPS coma mnemonic (see Table

237.2) (4) is often used for adult patients with AMS. Although clinically useful as a starting point, several diagnoses specific to the pediatric patient must be highlighted. The most notable are child abuse, infection, intussusception, metabolic disorders, accidental ingestions, and seizures.

TABLE 237.2
Pediatric Altered Mental Status: The "AEIOU–TIPS" Mnemonic

A	Alcohol
	Abuse (nonaccidental trauma)
E	Encephalopathy (infectious, metabolic, toxic, Reye syndrome)
	Electrolyte abnormalities (hypoglycemia, hypo- or hypernatremia, hypocalcemia)
	Endocrinopathy (inborn error of metabolism, congenital adrenal hyperplasia)
I	Infection (meningitis; encephalitis; sepsis; focal, such as brain abscess)
	Intussusception
	Inborn errors of metabolism (fatty acid oxidation disorder, urea cycle defect)
O	Overdose (carbon monoxide, opiates, sedatives)
U	Uremia (hemolytic uremic syndrome, renal failure, Reye syndrome)
T	Trauma (intracranial hemorrhage)
	Tumor
	Toxins (lead)
I	Insulin (diabetic ketoacidosis, ketotic and nonketotic hypoglycemia)
P	Psychogenic (pseudoseizure, conversion disorder)
S	Seizure (neonatal, atypical, complex)
	Shock
	Shunt malfunction (increased intracranial pressure, infection)
	Stroke (arteriovenous malformations, hemoglobinopathies)

Abuse or Trauma

Child physical abuse (nonaccidental trauma) is the primary cause of serious head injury in infants (see Chapter 290). Findings consistent with the diagnosis of "shaken-baby syndrome" or "shaken-impact syndrome" include subdural hematoma, subarachnoid hemorrhage, retinal hemorrhage, as well as rib and long bone fractures.

Discrepancies between the history and the findings on the physical examination should alert the physician to the possibility of physical abuse. Children may present with AMS and a paucity of external physical findings on the initial evaluation. Retinal hemorrhages seen on the fundoscopic examination are suspicious for physical abuse. Previously, it was postulated that retinal hemorrhages could be a result of vigorous resuscitative efforts, but studies do not support this theory (6). Evidence of papilledema is suggestive of increased ICP and should alert the physician to the possibility of child abuse (6,7).

Infection

Infection must always be considered as a potential cause of AMS. This is especially true in younger patients with limited communications skills. It is also vital to consider infection in immunocompromised patients with abnormal behavior or altered alertness. Clues such as fever, ill contacts, or associated symptoms such as headache, photophobia, or meningismus may be helpful. Nevertheless, even in their absence it is important to rule out occult infection when alternative diagnoses do not present themselves.

Intussusception

Intussusception occurs most often in children between the ages of 3 and 12 months, with a male to female ratio of 4:1 (see Chapter 270). Although patients typically present with complaints of abdominal pain and vomiting, up to 10% of infants present solely with a depressed LOC. It is postulated that endogenous opioids are released from the bowel wall. The “classic triad” of colicky abdominal pain, vomiting, and currant jelly stools is seen infrequently (<25% in some reports) (8,9).

Metabolic Disorders

Inborn errors of metabolism should be considered in a young infant with a history of vomiting, poor feeding, failure to thrive, and AMS.

These are divided into two groups: (1) those with metabolic acidosis and (2) those with hyperammonemia. Seizures, especially in the neonatal period, may be associated with the initial presentation of a metabolic disorder. While these disorders most frequently manifest during the neonatal period, later childhood presentations are possible, sometimes triggered by a mild viral illness. Specific laboratory studies including serum pyruvate, lactate, and ammonia may be helpful in distinguishing between disorders causing acidosis versus hyperammonemia. There have been improvements in the recognition and diagnosis of fatty acid oxidation disorders, particularly medium-chain acyl-coenzyme-A–dehydrogenase deficiency (MCAD), which many believe mimic most of the symptoms associated with Reye syndrome. Early identification and treatment of these children can prevent long-term neurologic sequela (4,10).

Accidental Ingestions

AMS caused by lead encephalopathy is still seen in children, especially those living in older buildings or those who live near construction sites. Lead encephalopathy can present with a prodrome of vomiting, abdominal pain, and fatigue. Ingestion of paint chips or dust coating the surface of objects put into a child's mouth can cause a rapid and acute rise in the serum lead level resulting in AMS. Symptoms include seizures, cranial nerve palsy, lethargy, and coma (11).

Other ingested substances associated with AMS are listed in Table 237.3 (1). Many substances can cause AMS in small amounts, and some of these can be truly toxic or deadly. All exposures should be reported to the regional poison control center.

TABLE 237.3
Substances Associated with Altered Mental Status

Substances Associated with Altered Mental Status	
Alcohols	Heavy metals
Anticholinergics	Insulin
Amphetamines	Lithium
Anticonvulsants	Lysergic acid diethylamide (LSD)
Barbiturates	Narcotics
Carbon monoxide	Nonsteroidal anti-inflammatory drugs
Clonidine	Nicotine
Cocaine	Organophosphates
Cyclic antidepressants	Phencyclidine (PCP)
γ-Hydroxybutyrate (GHB)	Theophylline

Seizures

Neonatal seizure patterns vary greatly between older infants and children (see Chapter 236). The incompletely myelinated neural pathways of neonates are incapable of propagating true tonic–clonic seizures. In addition, many newborns thought to be having generalized tonic–clonic movements are actually exhibiting tremulousness. More typical of neonatal seizure are apnea with tonic stiffening, focal clonic movement, myoclonic jerks, lateral or upward tonic deviation of the eyes, or patterned stereotypical behavior such as paroxysmal laughing or chewing (3).

DIAGNOSTIC APPROACH

The initial evaluation of a child with AMS begins with attention to the ABCs: ensuring the protection and patency of the airway, adequacy of breathing, and maintenance of a normal circulatory status. During the subsequent secondary evaluation are a number of important clues in the history and physical examination. An effort should be made to obtain at least an AMPLE history: *A*llergies, *m*edications, *p*ast medical history, *l*ast meal, and *e*vents of recent occurrence. Specifically note if the history includes any possible ingestions or exposures, vomiting, trauma, fever, or unusual behavior.

The infant's open anterior fontanelle can be palpated to gain a rough sense of ICP and hydration. It is helpful to smell the patient's

clothes and breath to discover clues to possible ingestions or exposures. The child should be completely undressed, viewed, rolled, and palpated from head to toe and from front to back to evaluate for any signs of trauma, with specific attention to nonaccidental trauma to the head, abdomen, or extremities. The abdomen should be assessed for any evidence of hepatosplenomegaly, mass, or overall tenderness. The skin should be examined for rashes or bruising, and the extremities should be examined for tone and capillary refill (1,3,4).

The child's LOC can be assessed by using either the AVPU (alert, responds to verbal stimuli, responds to painful stimuli, unresponsive) or the Glasgow coma scale (GCS). A modified scoring system has been developed for use in nonverbal pediatric patients (Table 237.4) (12,13).

TABLE 237.4
Pediatric Glasgow Coma Score and Glasgow Coma Score

Best Response	Score	Pediatric GCS	GCS
Eye	1	No eye opening	No eye opening
	2	Eye opening to pain	Eye opening to pain
	3	Eye opening to speech	Eye opening to verbal command
	4	Eyes open spontaneously	Eyes open spontaneously
Verbal	1	No verbal response	No vocal response
	2	Inconsolable, agitated	Incomprehensible sounds
	3	Persistent crying or screaming	Inappropriate words
	4	Cries but consolable	Confused conversation
	5	Smiles, interactive	Orientated
Motor	1	No motor response	No motor response
	2	Extension to pain	Extension to pain
	3	Flexion to pain	Flexion to pain
	4	Withdraws from pain	Withdraws from pain
	5	Localizing pain	Localizing pain
	6	Obeys commands	Obeys commands

GCS, Glasgow coma score.

Abnormal respiratory patterns can imply either a metabolic insult or a structural lesion. In Cheyne–Stokes respiration, periods of hyperpnea alternate with apnea, with the hyperpneic phase lasting longer than the apneic phase. This may indicate either a lesion deep inside both cerebral hemispheres (bilateral cerebral infarction) or a metabolic encephalopathy (e.g., due to hypoglycemia) (1).

Abnormal pupillary responses may help to localize the level of the lesion. Small but reactive pupils imply either a metabolic or diencephalic lesion. A fixed, dilated pupil can be seen with expanding supratentorial lesions involving the uncus and the ipsilateral third nerve. Midsize unresponsive pupils imply a midbrain lesion, whereas widely dilated, completely unresponsive pupils suggest brainstem pathology.

Induced eye movements such as the doll's eye (oculocephalic) reflex and cold water caloric testing (oculovestibular, responses) may be useful. A normal response to the doll's eye maneuver is conjugate deviation of the eyes opposite to the direction in which the head is turned. This test is strictly prohibited in any patient with possible cervical spine injury. When testing the oculovestibular reflex in an unconscious individual with an intact brainstem, the fast component is absent, and the eyes move toward the side irrigated with cold water and then remain tonically deviated for 1 minute or longer. The response to the doll's eye maneuver and caloric testing are initially brisk for most causes of metabolic coma but become more difficult to elicit as coma deepens.

Two types of reflex posturing may be elicited by painful stimuli. Decorticate posturing (arm flexion and lower leg extension) occurs with injury to the cerebral hemispheres but intact brainstem function. Decerebrate posturing (internal rotation and extension of the arms with lower leg extension) occurs with damage to the midbrain and pons at the level of the brainstem, implying brainstem dysfunction and therefore a worse prognosis. Flaccidity (no response) is seen with generalized central nervous system (CNS) depression or with compression of the medulla, which indicates a grave prognosis (1,5).

CRITICAL INTERVENTIONS

Initial management of a patient begins with assessment, stabilization, and control of the ABCs, providing supplemental oxygen and ventilation support as needed. Obtain bedside glucose determination with intravenous (IV) access. Focused laboratory testing may include additional studies, including a complete blood count, electrolytes, calcium, renal, liver function tests, blood gas, and a serum ammonia level. Blood and urine cultures of the blood and urine should be sent if there is concern for infection. The child should have continuous cardiopulmonary and oximetry monitoring. An electrocardiogram (ECG) is recommended in cases of dysrhythmia and selected poisonings. A trial dose of naloxone (0.1 mg/kg) should be administered, particularly if the pupils are miotic.

Signs and symptoms of herniation or increased ICP warrant immediate intubation and mild hyperventilation, IV mannitol (0.25 to 0.5 g/kg), and potentially 3% saline may be helpful, but the overriding concern must be the perfusion status and avoiding hypotension (see Chapter 246). Children with focal deficits, evidence of herniation, or increased ICP, and suspected head injury require imaging with head computed tomography (CT). Lumbar puncture is indicated in patients suspected of meningitis if patient is clinically stable enough for the procedure. Consider the use of IV hypertonic saline for patients with AMS and diabetic ketoacidosis with cerebral edema (14,15) (see Chapter 274).

Further management and treatment options are based on the history, signs, symptoms, and physical findings. Therapeutic options include administration of broad-spectrum antibiotics for patients with suspected infection, antidote therapy for suspected poisonings, antiepileptic medications for seizures, and correction of fluid, electrolyte, or acid–base abnormalities. Young children can quickly become hypothermic when exposed to the ambient temperatures in the ED. External or overhead warming devices are strongly recommended to prevent hypothermia (1,4,16).

DISPOSITION

Final disposition is dependent on the suspected diagnosis and the child's condition. Generally, a child with AMS warrants further inpatient evaluation in an intensive care unit. Ongoing reevaluation, reassessment, and modification of therapy are essential until transfer can be accomplished.

Common Pitfalls

- Failure to adequately assess and aggressively manage the ABCs.
- Failure to obtain a rapid bedside glucose or to consider an electrolyte disturbance.
- Failure to consider diagnoses that may present as AMS in children: Atypical or subtle seizures (no tonic–clonic activity), intussusception, ingestions, and child abuse (17).
- Failure to reassess and modify therapy as needed.

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CHAPTER 238

Ataxia

Peter S. Auerbach and Jennifer C. Huffman

Acute ataxia is an uncommon and distressing emergency department (ED) complain, but in a previously healthy child is generally due to a benign process and carries an excellent prognosis for full recovery. Emergency physicians must nevertheless remain aware of the rare life-threatening causes of ataxia.

Ataxia refers to any disturbance in the coordination of movement and can be the result of dysfunction at virtually any level of the nervous system. Moreover any general metabolic disturbance of the central nervous system (CNS), such as hypoglycemia or drug or toxin exposure, can also cause ataxia (1).

Ataxia can be divided into categories based on the neurologic structure involved: (1) cerebellar (the most common), (2) sensory, (3) vestibular, and (4) motor. Cerebellar ataxia typically manifests as a wide-based staggering gait, abnormal gross motor movements, or swaying of the trunk or head while at rest. In contrast, sensory ataxia is associated with a cautious high-stepping gait (exaggerated elevation of the feet, which are then brought down suddenly in a flopping manner), an abnormal Romberg sign (loss of balance with the eyes closed), problems with fine motor movements, and loss of position and vibratory sensation. Vestibular ataxia presents with vertigo, nausea, and nystagmus. Motor ataxia (sometimes called *pseudoataxia*) results from muscle weakness rather than a loss of coordination, and may be associated with loss of reflexes and tone, as in Guillain–Barre Syndrome (GBS).

Ataxia can also be classified into acute, episodic or recurrent, and chronic causes. *Acute* ataxia, defined as ataxia present for <72

hours in a previously healthy child, is of primary concern to the emergency physician. Episodic and chronic ataxias are usually associated with other CNS abnormalities, or with genetic or metabolic disorders. *Acute ataxia is generally benign, and requires no treatment once serious conditions such as posterior fossa tumor, encephalitis, or demyelinating diseases, including GBS, have been ruled out.*

CLINICAL PRESENTATION

Most previously well children with acute ataxia are brought to the ED for an unsteady gait or refusal to walk. Other less common complaints include difficulty in reaching for toys, abnormal eye movements, or a change in speech. The two most common causes of acute ataxia in children are acute postinfectious cerebellar ataxia (APCA; also known as acute cerebellar ataxia) and drug ingestions. Features indicating a more serious cause of ataxia, such as encephalitis or a mass lesion, include acute changes in mental status, behavior or personality change, headache, vomiting, fever or meningismus, and diplopia. Other important historical features include recent head injury, seizures, a loss of developmental milestones, or a family history of neurologic disorders.

Physical examination should focus on ruling out potentially life-threatening causes of ataxia such as mass lesion, infection, or trauma. Patients must be carefully examined for subtle focal neurologic deficits, as well as papilledema, which may indicate a mass lesion. Changes in mental status, signs of trauma, fever, and meningismus are clues to either trauma or acute infection. A toxicologic cause of ataxia may be suggested by manifestations of a specific toxidrome (e.g., anticholinergic), an altered level of consciousness, or nystagmus. Children with APCA should have a normal mental status and general physical examination aside from their ataxia, including normal vital signs (2).

The neurologic examination may be very challenging in a young child. Coordination testing must focus on a careful observation of gait, truncal position and stability, ability to reach for toys and

manipulate objects, and eye movements. Assessment of speech is important in older children, specifically to detect the scanning type of dysarthria which can occur with cerebellar dysfunction (characterized by abnormal variation in volume and separation of syllables) (Table 238.1).

TABLE 238.1
Important Aspects of the Physical Examination

Mental status
Eye movements (e.g., nystagmus)
Gait
Reflexes
Finger-to-nose testing
Quality of speech
Papilledema
Signs of head/neck trauma

DIFFERENTIAL DIAGNOSIS

Acute ataxia in a previously healthy child is almost always caused by a limited number of etiologies (Table 238.2). More than 60% of children with acute ataxia have either APCA or a drug ingestion (3). GBS and acute disseminated encephalomyelitis (ADEM) account for a smaller proportion of cases. Table 238.3 lists a number of rare but serious causes of acute ataxia that should not be missed in the ED, but these conditions almost never present with isolated ataxia in an otherwise well child.

TABLE 238.2
Common Causes of Acute Ataxia in Children

Acute postinfectious cerebellar ataxia
Drug ingestion
Demyelinating disease (e.g., Guillain–Barré syndrome, ADEM)

TABLE 238.3
Life-Threatening Causes of Acute Ataxia in Children

Hypoglycemia
Drug overdose
Cerebellitis/encephalitis
Meningitis
Intracranial mass lesion
Hydrocephalus
Intracranial bleed
Vertebrobasilar dissection
Stroke
Vasculitis
Paraneoplastic syndrome (e.g., opsoclonus–myoclonus syndrome from neuroblastoma)

APCA, accounting for more than one-third of cases of acute ataxia cases in children, is thought to result from cerebellar demyelination following an antecedent illness, either as an autoimmune phenomenon or from direct infection (3). It is seen most commonly in children younger than 6 years and is most often been linked to varicella infection (4,5). It has also been reported in association with Epstein–Barr virus, enterovirus, herpes viruses, influenza A and B, hepatitis A, as well as with viral upper respiratory tract infection and some bacterial infections. The symptoms appear suddenly 1 to 3 weeks after an illness, are maximal at onset, and include dramatic truncal ataxia and gait instability. Most children recover completely within 3 months without treatment (6). APCA is not associated with fever, seizures, altered mental status, or focal neurologic deficits, and *the presence of any of these factors makes the diagnosis highly unlikely.*

Drug ingestion and toxin exposure should figure prominently in the differential diagnosis, even if not initially reported (3). Young children often present with ataxia caused by ingestion of anticonvulsants (e.g., phenytoin, phenobarbital, carbamazepine, valproic acid, topiramate), antihistamines, benzodiazepines, dextromethorphan, or alcohol (7). Older children often present after

recreational drug or alcohol use. In both age groups, the ataxia is often accompanied by mental status changes. Because the history may not be readily forthcoming and because drug ingestions are not uncommon in children, the physician should have a low threshold for ordering a toxicology screen.

Guillain–Barré syndrome, an acute ascending inflammatory demyelinating polyneuropathy, presents with ataxia in up to 15% of pediatric cases (8). Because this syndrome affects the peripheral nerves and typically spreads from distal to proximal, the extremities are generally more affected than the trunk. As with APCA, Guillain–Barré syndrome is usually a postinfectious, autoimmune phenomenon; the key to diagnosis is extremity ataxia combined with areflexia or hyporeflexia early in the course of the disease. The Miller–Fisher variant of Guillain–Barré syndrome is characterized by the triad of ataxia, areflexia, ophthalmoplegia, and other cranial nerve abnormalities. In contrast to APCA, Guillain–Barré syndrome requires hospitalization since it may progress to respiratory failure. Treatment options include intravenous immunoglobulin (IVIG) and plasmapheresis, although most patients recover completely without treatment (9). Other less common postinfectious neurologic syndromes may also present with ataxia, including ADEM and transverse myelitis, both of which are often treated with high-dose steroids (10).

Acute cerebellitis is a localized form of acute encephalitis that is potentially life-threatening and often associated with a poor outcome (11). Although both APCA and cerebellitis are infectious or postinfectious in etiology, cerebellitis presents with variable degrees of altered mental status (ranging from mild somnolence to coma), headache, irritability, and vomiting; neuroimaging is abnormal, with findings ranging from localized cerebellar edema to compression of the fourth ventricle, acute hydrocephalus, and tonsillar herniation (12).

Another serious cause of acute ataxia is intracranial mass lesion. More than half of primary brain tumors in children are located in the brainstem or cerebellum, and can produce ataxia by a direct mass effect or as a result of hydrocephalus. A history of progressive

ataxia is usually elicited, along with headache, visual changes, morning vomiting, and personality changes. The physical examination may reveal papilledema or focal neurologic deficits. Metastatic lesions can affect the cerebellum as well, and occult distant malignancies can present with ataxia in association with opsoclonus (rapid, chaotic eye movements) and myoclonus (rapid, chaotic contractions of individual muscles or muscle groups). Opsoclonus–myoclonus syndrome occurs most commonly in children between the ages of 6 months and 3 years and is the result of a cerebellar paraneoplastic autoimmune response; it is seen in more than half of cases of neuroblastoma (13).

Head injuries can lead to ataxia because of intracranial hemorrhage, mass effect, or cerebellar contusion. Postconcussive syndrome may also cause ataxia, but this is a diagnosis of exclusion. Neck injuries can cause vertebrobasilar artery dissection, with cerebellar and brainstem ischemia or infarction. Cerebellar strokes, though rare in children, can result from bleeding disorders, arteriovenous malformations, or CNS vasculitis (e.g., Kawasaki disease).

Less serious causes of ataxia include childhood migraine variants, epilepsy, conversion disorder, labyrinthitis, and myositis. Basilar migraine and benign paroxysmal vertigo (BPV) may explain most forms of episodic or recurrent ataxia in children or adolescents (14). Epilepsy infrequently manifests as ataxia, usually in association with some degree of altered consciousness (e.g., complex partial seizures). More commonly, patients with known epilepsy are ataxic as a side effect of their seizure medications. Conversion disorder is a diagnosis of exclusion but can usually be identified by characteristic features (e.g., complex lurching movements that require a high degree of coordination; absence of a wide-based stance; or variable and inconsistent physical examination findings, especially when the patient is unaware of being observed) in the face of an otherwise normal neurologic examination.

ED EVALUATION

Keeping in mind that most cases of acute ataxia in otherwise healthy children are caused by either APCA or drug ingestion, the primary goal of the ED evaluation is to eliminate the possibility of a more serious etiology. The first and most important step is a thorough history and physical examination, which together can help eliminate the vast majority of life-threatening causes.

In the absence of other findings, a comprehensive toxicology screen may be a useful laboratory test, even when an ingestion is unsuspected by history. A limited “drugs of abuse” screen will miss the majority of ingestions in younger children. Routine laboratory studies, such as electrolytes and a complete blood count, are of very low yield (3). But in children taking antiepileptic drugs, as well as in those with family members taking such medications, drug levels should be checked.

Lumbar puncture is of low utility in cases consistent with APCA or drug ingestion, and in well-appearing, mildly symptomatic patients. However, it is particularly important in patients with altered mental status or fever. If performed due to altered mental status, an opening pressure should be measured because initial cerebrospinal fluid (CSF) analysis may be normal in cases of cerebellitis and with other serious CNS infections. An elevated CSF cell count suggests meningitis or encephalitis, and an elevated protein in combination with a normal cell count (cytoalbuminologic dissociation) is supportive of Guillain–Barré syndrome or other demyelinating diseases.

Neuroimaging should be performed if a mass lesion, hydrocephalus, elevated ICP, or trauma is suspected. Although CT is more readily available than MRI, it is of limited value in visualizing the posterior fossa and brainstem. If a mass lesion is strongly suspected, an MRI must be obtained (though not necessarily on an emergent basis) despite a normal CT. MRI may show other abnormalities missed by CT, such as findings indicative of acute cerebellitis, stroke, or demyelinating disease.

Electroencephalography (EEG) may be helpful if epilepsy is suspected by history, and consultation with a neurologist should be considered.

KEY TESTING

- Comprehensive toxicology screen
- Lumbar puncture if patient has altered mental status
- MRI or CT of the head, depending on availability

ED MANAGEMENT

Treatment is typically focused initially on identifiable causes of ataxia such as hypoglycemia, encephalitis, meningitis, elevated ICP, and drug overdose. Most children with APCA recover completely within 3 months, there is no specific treatment, and hospitalization is often unnecessary (2). Children with drug ingestions are managed according to the specific drug(s) involved, but a social service or Children's Protective Services (CPS) referral should be made depending upon the circumstances.

Guillain–Barré and other demyelinating neurologic syndromes (e.g., ADEM) may require emergent airway management if severe and require admission in all cases. Early consultation with a neurologist is essential. Other causes of ataxia, such as tumors and CNS infection, generally require admission.

CRITICAL INTERVENTIONS

- Rule out life-threatening etiologies of ataxia.
- Reassure parents of the benign and self-limited nature of most causes of acute ataxia in childhood.

DISPOSITION

Children who are mildly symptomatic, appear well, and have a history and physical examination consistent with APCA may require no further ED evaluation and can be discharged home if close follow-up can be assured. Parents should be counseled on injury prevention, as children with APCA are at increased risk of injury until recovery is complete. If the diagnosis is in doubt, further testing should be done to rule out other diagnostic possibilities.

Most other causes of acute ataxia require admission for treatment or further evaluation, including consultation with appropriate specialty services. In the case of minor ingestions, discharge from the ED should be considered if the home environment and social situation are judged to be safe.

Common Pitfalls

- Failure to do a thorough history and physical examination before ordering extensive laboratory tests or neuroimaging.
- Failure to obtain a comprehensive toxicology screen, even in the absence of a history of ingestion.
- Failure to admit an ataxic patient when the diagnosis is in doubt or when prompt outpatient follow-up cannot be assured.
- Failure to counsel on injury prevention if the patient is being discharged.

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CHAPTER 239 Pediatric Headache

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Headache is a common emergency department (ED) complaint among children. The majority are found to have headache secondary to minor infectious illnesses or primary headaches such as tension-type or migraine. The complaint of headache in a child or adolescent can be worrisome for patients and caretakers fearing the child has a serious or life-threatening medical condition. There exists a misperception among laypeople that "kids do not get headaches"; however, epidemiologic studies report an incidence of pediatric headache ranging from 3% during the preschool years to over 75% by late adolescence (1–3). Chronic or recurrent headaches in children and adolescents may cause significant school, family, and social disruption. While serious neurologic conditions are rare in pediatric patients, medical providers must remain vigilant and not assign a benign etiology to all pediatric headaches. A careful history and physical examination alone often leads to the correct diagnosis; neuroimaging and laboratory studies are indicated in only a small minority of patients.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Headaches are classified as either primary or secondary. Primary headaches include predominantly tension-type or migraine headache. Secondary headaches are the result of a variety of conditions ranging from benign, self-limited viral illnesses to life-threatening infections or mass lesions. The emergency physician should endeavor to distinguish primary from secondary headache to ensure appropriate

treatment, evaluation and follow-up for secondary headache, and provide a plan for acute symptom relief in the case of primary headache. Providers must also provide reassurance and guidance for patients and families on types of headaches, management of symptoms, and recognition of changing patterns of pain or other worrisome symptoms that should prompt further evaluation.

As in adult patients (see Chapter 12), headache may be further categorized by pattern as acute, acute recurrent, chronic progressive, or chronic recurrent. The differential diagnosis of pediatric headache is quite broad, Table 239.1 lists some common causes, but is by no means an all-inclusive list; a careful history and physical examination are crucial for every patient. Establishing this pattern helps guide an appropriate differential diagnosis (Table 239.1) (4,5). Acute onset headache may be the initial presentation of primary headache disorders, but is more often secondary to an underlying medical condition. The differential diagnosis for this group is broad, including everything from mild viral illnesses to life-threatening infections or other central nervous system etiologies. A careful history and physical examination can generally differentiate between minor and major illness; worrisome features of serious pathology include severe or incapacitating pain, altered mental status, and focal neurologic deficits, such as a new onset cranial nerve dysfunction. Patients with a history of shunted hydrocephalus require special mention, as headache is a common presenting symptom of shunt malfunction and usually requires further investigation in this population.

TABLE 239.1
Common Differential Diagnosis of Headache in the Pediatric Patient

Acute Headache	Recurrent Headache	Chronic Progressive Headache	Chronic Recurrent Headache
Viral respiratory infection	Tension headache	Intracranial tumor	Tension headache
Group A streptococcal pharyngitis	Migraine headache	Idiopathic intracranial hypertension	Migraine headache
Viral meningitis		Intracranial abscess	Analgesic rebound
Bacterial meningitis			
Acute trauma			
Dental caries or abscess			
Toxic exposure			
Ventricular shunt dysfunction			

Acute, recurrent headache describes a pattern of headaches that recur periodically with the same intensity and characteristics. This pattern is most suggestive of a primary headache disorder. The diagnosis of migraine in children rests primarily upon the modified clinical criteria set forth by the International Headache Society in 2004 (6). Migraine may affect even young children, although their inability to completely describe symptoms makes it more difficult to diagnose. Migraine may be frontal or bilateral in children, as opposed to the classic unilateral presentation often described in adults. The pain is described as throbbing, pulsatile, and often incapacitating, in contrast to the dull, annoying nature of tension-type headache pain. The pain of migraine is typically located in the region of the eyes, forehead, and temple and may last from <1 hour to several days. There is often associated nausea or vomiting, and pain is preceded by an aura in some patients. Light, noise, and movement usually aggravate the pain, and a period of sleep frequently results in resolution of symptoms (1,3,4).

Chronic progressive headaches, those increasing in frequency or severity over time, are more concerning for serious intracranial pathology. Associated symptoms such as visual disturbances, weight loss, early morning vomiting, headaches that awaken the child from sleep, and changes in personality, behavior, or school performance should prompt heightened concern for intracranial lesions. However, idiopathic intracranial hypertension (IIH) is another important cause of chronic, progressive headache that deserves consideration. Risk factors for IIH include obesity, female gender, use of certain

antibiotics (e.g., tetracyclines), hypervitaminosis, and oral contraceptive use. Patients may report worsening of headache with Valsalva maneuver, changes in visual acuity, transient visual obscurations, or pulsatile tinnitus. Early recognition is vital given that untreated IIH, can result in optic nerve damage and potentially permanent visual loss (4,7).

Chronic, recurrent headaches are most suspicious for tension-type headache and may be associated with poor sleep habits, obstructive sleep apnea, lack of adequate exercise, poor nutritional habits, or depression. A careful history can often accurately demonstrate these contributing elements. These headaches are typically dull and annoying in character, occur toward the end of the day, and are often relieved with a period of rest. Unfortunately, tension-type headaches are often treated with regular use of analgesic medications, instead of addressing underlying sources of tension or stress. As a result, many patients risk developing analgesic rebound headache.

Analgesic rebound headache has been well described in adults and is widely recognized in children of all ages, especially those who use analgesics more than three times per week. This entity generally presents as frequent, uniform headache, often occurring in the afternoon or evening, and lacking association with other worrisome symptoms (1,4,5,8). These headaches often respond temporarily to analgesics, but the pain will typically return as the medication wears off. Limiting analgesic use is the first step in treatment. Patients also should be counseled on the importance of regular dietary and sleep habits in preventing headache recurrence. Poor sleep habits are a common cause of recurrent headache in children and adolescents. Families should be counseled on the importance of good sleep hygiene, including removal of television, video games, and portable electronic devices from the sleeping area. Enforcing regular mealtimes, encouraging physical activity, and normalizing school attendance and other routines are other lifestyle interventions that may improve these headaches (Table 239.1) (1,4,5,8).

ED EVALUATION

Patients presenting to the ED with headache are frequently seeking pain relief as well as an explanation for concerning symptoms. A complete history and physical examination is of utmost importance and often informs the diagnosis as well as suggesting a management plan.

All patients seen in the ED with a complaint of headache should have a complete set of vital signs, including temperature and blood pressure. Blood pressure in pediatric patients must be interpreted using age-based normal values. While elevated blood pressure itself rarely causes headache, with the exception of hypertensive encephalopathy, persistently elevated blood pressure is concerning for increased intracranial pressure or other pathologic process.

The best assessment of central nervous system "well-being," reflecting cerebral perfusion, oxygenation and overall function, is the patient's level of consciousness. In the pediatric patient, mental status must be judged with regard for the patient's age, developmental level, and usual baseline functioning. Young children may be frightened and uncooperative with an unknown examiner, but should be consolable and interactive with parents or other known caregivers. Older children and adolescents should be appropriately interactive with the treatment team. A full neurologic examination is fundamental and should include evaluation of cranial nerves, motor function, gait, sensation, and deep tendon reflexes. Special care must be taken when approaching the sleeping child, especially during nap or nighttime sleep. While children may be sound sleepers and difficult to awaken, it is imperative that examiners awaken the child enough to obtain an accurate assessment of the child's mental status, including appropriate ambulation.

The head, ears, eyes, nose, and throat should be carefully examined for any signs of trauma or for minor infections such as pharyngitis, otitis media, or upper respiratory infection, all of which are common causes of acute headache. The teeth and gums should be checked carefully for caries or abscess. Fundoscopic examination should be attempted on every patient with headache of unclear etiology. In cases of suspected increased intracranial pressure, pharmacologic dilation and ophthalmology consultation may be

necessary to visualize the fundus adequately and evaluate for papilledema. The patient presenting with fever and headache should be routinely examined for neck stiffness indicative of meningeal inflammation. Finally, the skin and musculoskeletal examination should include inspection for petechiae or purpura, especially in the febrile or ill-appearing patient.

Laboratory evaluation is not routinely indicated in pediatric headache patients, but should be guided by the clinical history and physical examination. Potentially useful tests include rapid streptococcal throat screen or culture, toxicology assay in patients with altered consciousness, co-oximetry in cases of suspected carbon monoxide exposure, and pregnancy testing in adolescent females. Lumbar puncture (LP) should be performed in any patient with fever and neck stiffness or altered mental status, suspicion of subarachnoid hemorrhage, or in patients with persistent headaches and ophthalmologic findings suggestive of IIH. When LP is performed, cerebrospinal fluid (CSF) should be sent for culture, cell count, protein, and glucose. Other studies (cytology, viral testing) may be pursued as clinically indicated. In cases of suspected IIH it is important to obtain a CSF opening pressure. Patients with immunocompromise secondary to malignancy, sickle cell disease, transplant, or HIV infection are at elevated risk of meningitis and specialized laboratory testing should be considered when these patients present with fever and headache.

Neuroimaging, as with laboratory studies, must be guided by historical features and clinical findings. Most children with acute or recurrent headache and a normal neurologic examination do not require emergent neuroimaging. Computed tomography (CT) scan should be considered in patients with altered mental status or focal neurologic deficits, head trauma with severe or worsening headache, or paroxysmal onset of excruciating headache (worrisome for subarachnoid hemorrhage, a relatively rare cause of pediatric headache), and in those with known or potential coagulation abnormalities or with shunted hydrocephalus. Controversy exists as to the necessity of performing CT scanning before undertaking LP because of the theoretical risk of causing cerebral herniation in

patients with space-occupying intracranial lesions. In cases of suspected subarachnoid hemorrhage or IIH, it is probably prudent to obtain imaging prior to LP. In cases of suspected meningitis, if the patient is alert and has a nonfocal neurologic examination, LP may be safe to perform, but should be delayed (without delaying the administration of empiric antibiotics, however) in patients with altered mental status, hemodynamic instability or focal neurologic findings (9,10).

Magnetic resonance imaging (MRI) should be considered in patients with recurrent morning headaches, chronic progressive headache, focal neurologic findings such as cranial nerve deficits, balance or gait abnormalities, persistent head tilt in a young child, and headache associated with personality changes or a decline in school function. MRI allows for better imaging of the posterior cranial fossa, a common site of mass lesions in children (1,3,9). MRI also avoids the radiation exposure associated with CT imaging.

KEY TESTING

- All testing should be guided by history and physical examination
- Emergent neuroimaging should be obtained in patients with altered mental status, concern for intracranial hemorrhage or mass lesion, patients with coagulopathy or bleeding disorders, patients with shunted hydrocephalus, or when concern exists for increased intracranial pressure
- laboratory testing might include pregnancy testing, toxicology screening (including co-oximetry measurement), and evaluation of cerebrospinal fluid for infection
- MRI is preferred over CT imaging for evaluation of the posterior cranial fossa

ED MANAGEMENT

Treatment of the pediatric headache patient is based on presumptive diagnosis. Many acute headaches are caused by minor viral or bacterial infections such as streptococcal pharyngitis. Once more serious causes are excluded, these headaches are often adequately

treated with short courses of over-the-counter analgesics such as ibuprofen or acetaminophen. Tension-type or migraine headaches may also respond to acetaminophen or ibuprofen in appropriate weight-based doses, especially if given early in the headache attack.

For migraine headaches, an abundance of treatment regimens have been proposed and investigated yet none have proven completely efficacious, making firm recommendations difficult. Among these are ketorolac, magnesium, antihistamines, valproic acid, and centrally acting dopamine agonists such as metoclopromide. In addition, intravenous hydration and supplemental oxygen are used by some providers. The 5HT1 agonists or “triptans” are another group of medications used to treat migraine, but their use has not been proven to be superior to other regimens in studies of adult or pediatric migraine. Antiemetics are also an important consideration, as the nausea and emesis associated with migraine can be debilitating for many patients. Narcotics should be used sparingly, if ever, in cases of migraine as they may lead to rebound pain, have the potential to be habit-forming, and may have an unfavorable side-effect profile. Important adjuncts to pharmacologic treatment include providing a dark, quiet room to minimize stimulation and promote sleep, which may abort or shorten the migraine attack (1,4,5,11–14).

A migraine lasting more than 72 hours may be considered status migrainosus and often requires consultation with a pediatric neurologist. Proposed treatment protocols include combinations of antiemetics, sedatives, steroids, ergotamines, or analgesics, but there are no rigorous studies to support the use of any particular treatment regimen (11–14).

In cases of suspected IIH, LP may be both diagnostic and therapeutic. It is important that opening pressure be measured in all cases of suspected IIH. Consideration should be given to draining a larger than normal volume of CSF during the procedure and obtaining a closing pressure measurement at the end of the procedure to demonstrate a decrease in CSF pressure.

Patients discharged from the ED should be encouraged to seek medical attention if the headache worsens, changes in character, or

persists for more than 2 to 3 days. They should be encouraged to see their primary care provider to ensure proper follow-up.

CRITICAL INTERVENTIONS

- A thorough history, full set of vital signs (including blood pressure), and physical examination should be performed on all patients presenting with headache.
- Emergent neuroimaging and laboratory analysis should be considered for patients presenting with headache accompanied by altered mental status or an abnormal neurologic examination.
- In cases of suspected meningitis, empiric antibiotic coverage should be provided if LP is delayed for the purpose of obtaining imaging or stabilizing an ill-appearing patient.
- LP may be both diagnostic and therapeutic in cases of suspected IIH. Imaging before LP should be considered on a case-by-case basis.

DISPOSITION

ED disposition of pediatric patients with headache is dependent on the presumed underlying cause of the headache. Patients with life-threatening causes such as meningitis, intracranial hemorrhage or mass lesion, or ventricular shunt malfunction should have appropriate subspecialty consultation and admission to the hospital for further evaluation and treatment. Patients with IIH can potentially be discharged if headache improves after LP and if close neurology and ophthalmology follow-up can be ensured, but they may require admission for medical management, repeat therapeutic LP, or consideration of surgical procedures to decrease intracranial pressure and preserve vision. Patients with minor infections may be discharged with appropriate follow-up instructions and treatment, if indicated, for the underlying infection as well as instructions for safe use of over-the-counter analgesic medications.

Patients with migraine or tension-type headache may be discharged after treatment if they have experienced sufficient relief of pain, are able to tolerate oral intake without vomiting, and

maintain normal vital signs and mental status. These patients should be counseled on early use of analgesics with headache attacks, but warned of the danger of rebound headache in cases of analgesic overuse. Patients with severe migraine refractory to standard ED management may require hospitalization for subspecialty consultation and pain management.

Patients with chronic or recurrent headaches resistant to common analgesics may benefit from referral to a neurologist for evaluation and consideration of prophylactic treatment. Patients with chronic or recurrent headaches interfering with school or social functioning may also benefit from a multidisciplinary pain management service where they may receive not only medication but counseling and support services, as these headaches are often associated with social or behavioral comorbidities.

Common Pitfalls

- Inappropriately assuming a child is just sleepy because it is nap time or late at night. Subtle signs of altered mental status can be easy to miss during the overnight hours.
- Pursuing CT scanning or extensive laboratory analysis on a pediatric headache patient because of the misperception that "kids do not get headaches."
- Failure to recognize that recurrent headaches awakening a child from sleep, occurring upon morning awakening, or associated with personality changes, gait disturbance or head tilt may be signs of increased intracranial pressure or an intracranial mass lesion, especially in young children.

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CHAPTER 240
Oral Lesions

Therese L. Canares and Dale Steele

Pediatric oral lesions are primarily the result of infectious etiologies including herpes, Coxsackie and group A *Streptococcus* (GAS), among others. Complaints of oral bleeding may arise from post-tonsillectomy eschar. Autoimmune causes of oral lesions in children include Kawasaki disease (KD) and Stevens–Johnson syndrome (SJS).

CLINICAL PRESENTATION

Herpes simplex virus (HSV) causes primary herpetic gingivostomatitis and is characterized by fever, gingivitis, and a vesicular rash that leaves shallow, painful ulcers (Fig. 240.1).

FIGURE 240.1 Infant with herpetic gingivostomatitis. An infant with a healing vesicle on the upper lip and a shallow ulcer in the buccal mucosa. Vesicles are seen in the anterior oral mucosa, periorally or, particularly in a thumb-sucking child in the periungual area (i.e., herpetic whitlow).

Coxsackievirus causes herpangina, a summertime condition characterized by small, tender vesicles with an erythematous halo that may be similar to herpes gingivostomatitis, however appear primarily in the posterior pharynx. Coxsackievirus is also the infectious etiology associated with hand-foot-and-mouth disease (Fig. 240.2).

FIGURE 240.2 Hand, foot and mouth disease: This is caused by coxsackie virus, and manifests as herpangina, with fever, and a

papulovesicular rash in the palms, soles or buttocks.

Infectious mononucleosis and GAS pharyngitis both present with exudative pharyngitis, palatal petechiae, cervical lymphadenopathy, and fever. GAS pharyngitis patients commonly complain of fever and sore throat without a cough. Mononucleosis is distinguished by profound fatigue and posterior cervical lymphadenopathy. Oral candidiasis causes a white, friable pseudomembrane, frequently seen in infants or immunosuppressed patients. The clinician should evaluate for erythematous satellite papules of candidal diaper dermatitis. Measles is a clinical diagnosis based on whitish-blue papules on an erythematous base in the buccal mucosa (Koplik spots), and associated cough, coryza, conjunctivitis, and rash. As declining vaccination rates threaten herd immunity, measles outbreaks in the United States are reaching their highest rates since 1996 and are increasingly relevant for the emergency clinician (1).

Surgical consultation is occasionally needed for intraoral emergencies. Delayed post-tonsillectomy hemorrhage is uncommon (1% to 5%) but potentially life-threatening and should be thoroughly evaluated (Fig. 240.3) (2).

Many autoimmune conditions have associated oral findings, however the clinician must be diligent to identify high-acuity conditions such as KD and SJS. Oral lesions of KD may include cracked red lips, strawberry tongue, crusting of the lips and mouth, or a nonexudative pharyngitis. Similarly to KD, SJS causes severe mucositis with painful erosions, crusting, and sloughing of mucous membranes (Fig. 240.4).

FIGURE 240.3 Post-operative tonsillectomy eschar and hemorrhage: During healing, a whitish-yellow fibrin clot or eschar (left) develops in the tonsillar fossae, which may be confused as exudate or thrush. The eschar sloughs from underlying granulomatous tissue 7-10 days post-operatively, which may cause bloody sputum, hematemesis, or hemodynamic instability. Clot is visible in the right tonsillar pillar.

FIGURE 240.4 Oral findings in Stevens–Johnson syndrome. A 9-year-old with ulcerated, crusted, macerated lips.

DIFFERENTIAL DIAGNOSIS

Beyond the aforementioned pathologic conditions, a number of benign oral lesions may be seen in the ED. These include aphthous ulcers, geographic tongue, angular cheilitis, gum boil, ranula, Bohn nodules, Epstein pearls, mucocele, papillomas, fibromas, hemangiomas, pyogenic granulomas, lichen planus, and dental eruption cysts.

ED EVALUATION

Oral lesions can often be diagnosed clinically. Confirmation of HSV is made by viral culture, polymerase chain reaction, or immunofluorescence staining (DFA) on cells scraped from the base of unroofed vesicles (3). GAS pharyngitis is diagnosed by rapid antigen testing and confirmatory culture (4). Mononucleosis frequently causes an atypical lymphocytosis on complete blood count (CBC). To better characterize the diagnosis of mononucleosis EBV serology should be performed, since the heterophile antibody (Monospot) test

has poor sensitivity in children. Heterophile antibodies are positive in only 25% to 50% of children under 12 years of age (5). A CBC and type and screen should be obtained on those with post-tonsillectomy hemorrhage. Autoimmune disorders show nonspecific elevation of acute-phase reactants. Patients with concern for KD should have CBC, chemistry, urinalysis, and liver function tests to evaluate for anemia, sterile pyuria, and transaminitis (6).

KEY TESTING

- CBC with type and cross for post-tonsillectomy hemorrhage
- Serum electrolytes in dehydrated children with oral lesions and limited PO intake

ED MANAGEMENT

Management of oral lesions consists of supportive care and treatment of the underlying disease (Table 240.1). Assessment of dehydration and pain control are absolutely essential and may justify inpatient admission. Painful oral lesions are initially approached with analgesics such as ibuprofen or acetaminophen. “Magic mouthwash” is often used for painful lesions, with care not to overdose diphenhydramine. Avoid toxicity from topical lidocaine by using cotton-tipped applicator in infants, or have the child swish and spit (7). Narcotics are indicated for failure of over-the-counter analgesics or in severe cases. Tolerance of oral fluids must be demonstrated prior to discharge. Inability to tolerate liquids or severely dehydrated patients with tachycardia, dry mucous membranes and decreased urination may require intravenous hydration and perhaps admission. Patients with mononucleosis should be advised to avoid contact sports for at least 3 weeks to reduce the risk of splenic rupture (5). Subspecialty consultation should be made for post-tonsillectomy hemorrhage and potential intraoperative cauterization or for autoimmune conditions that require systemic treatment.

TABLE 240.1
Suggested Therapy for Pediatric Oral Lesions (8)

Condition	Medication	Dose	Route	Freq	Duration	Note
Painful oral lesion or mucositis	"Magic mouthwash" (diphenhydramine + Maalox, +/– viscous lidocaine 2%)	Limit by diphenhydramine 5 mg/kg/d	PO	q6h	As needed	Mix as a 1:1:0.5 ratio If using lidocaine, patient should swish and spit
HSV primary	Acyclovir	40–80 mg/kg/d (max 1 g/24 hr)	PO	q6–8h	5–10 d	For age <12 yrs; start within 3–4 d onset
HSV recurrent	Acyclovir	1 g/d	PO	q4–6h	5 d	In recurrent HSV, may opt for 2.4 g/d, q8h, × 2 d. May use valacyclovir for less frequent dosing
GAS pharyngitis	Benzathine penicillin G	600,000 units (<27 kg) or 1.2 million units (>27 kg)	IM	Once		Medication selection is based on compliance, palatability, and parental preference
	Amoxicillin	25–50 mg/kg/d	PO	q8–12h	10 d	
Oral candidiasis	Nystatin	1 mL to each side of mouth (infants); 4–6 mL (children)	PO	q6h	Until 48–72 hrs postsymptom resolution	Children should swish and swallow. Parent should clean all nipples and pacifiers. May opt for fluconazole
KD	IVIG	2 g/kg	IV		Institution protocol	Initiate within 10 d of symptom onset

CRITICAL INTERVENTIONS

- Assess for dehydration in infants and toddlers with poor oral intake or decreased urine output
- Use topical lidocaine with caution for systemic toxicity (arrhythmias or seizures) (7)
- In post-tonsillectomy bleeds ensure a patent airway, obtain a CBC, T&S, and consult the surgeon
- Treat KD with IVIG within the first 10 days of illness to prevent coronary artery aneurysms (6)

DISPOSITION

Disposition is case dependent. Patients may be discharged home with over-the-counter, or rarely narcotic pain medication. Patients are admitted if unable to tolerate oral intake, there is evidence of sepsis or systemic disease warrants admission.

Common Pitfalls

- Ensure adequate pain control and tolerance of oral liquids prior to discharge.
- Consider child abuse if oral HSV coincides with genitourinary lesions in a prepubertal child.
- Maintain an index of suspicion for KD in children with prolonged fever.
- Consider mononucleosis with splenic rupture in fever, fatigue, tonsillar lesions, and left upper quadrant abdominal pain.

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CHAPTER 241
Neck Masses

Bonnie Mackenzie and Siraj Amanullah

Neck masses present frequently in pediatric practice and constitute a wide range of diagnostic possibilities. The ED is often the frontline for diagnosis of congenital cysts and malignancies. A basic understanding of anatomy and embryology can simplify the approach to evaluating nontraumatic neck masses of infectious, inflammatory, or malignant origin. While the vast majority of patients have benign diagnoses related to lymphadenitis, clinicians must always ensure that potential airway problems are addressed in a timely fashion.

CLINICAL PRESENTATION

The head and neck develop from a branchial apparatus which, at the mesodermal level, is comprised of the first through fourth and sixth branchial arches (the fifth arch regresses and is not clinically relevant). The branchial arches, derived structures, and associated congenital cyst types (congenital neck masses) are summarized in Table 241.1.

TABLE 241.1
Branchial Arches, Derived Structures, and Associated Congenital Neck Masses

Arch	Important Nerve	Important Muscles	Important Bones/ Cartilages	Important Soft Tissues	Location of Associated Congenital Cyst Type (Frequency)
First (mandibular)	CN V (trigeminal)	Muscles of mastication	Malleus, incus, mandible	External ear canal	Duplication anomaly of external auditory canal or cyst below angle of mandible (rare)
Second (hyoid)	CN VII (facial)	Muscles of facial expression	Stapes, styloid process, lesser horn of the hyoid	Palatine tonsils	Inferior to angle of the mandible and anterior to sternocleidomastoid (**most common;** 10% bilateral)
Third	CN IX (glossopharyngeal)	Superior constrictor muscles	Greater horn of the hyoid	Internal carotid artery	Deep to the lower third of sternocleidomastoid, often lateral to carotid artery (uncommon)
Fourth and Sixth	CN X branches (vagus): superior laryngeal, recurrent laryngeal	Inferior constrictors, esophageal striated muscles	Thyroid cartilage, cricoid cartilage, arytenoid cartilage, corniculate cartilage, cuneiform cartilage	Aortic arch, right subclavian artery, aorta, thyroid gland, parathyroid glands	Deep to the internal carotid artery, can extend into the thyroid gland (very rare)
Fifth regresses	N/A	N/A	N/A	N/A	N/A

Anatomically, the neck can be divided into an anterior and posterior triangle separated by the sternocleidomastoid muscle. The boundaries of these triangles, and the important contents of each, are outlined in Table 241.2 and Figure 241.1 (2).

TABLE 241.2
Boundaries and Contents of the Anterior and Posterior Triangles of the Neck

Triangle	Boundaries	Contents
Anterior	Midline of the neck, inferior edge of mandible, sternocleidomastoid muscle	Suprahyoid and infrahyoid muscles, mylohyoid, and facial nerve
Posterior	Sternocleidomastoid muscle, anterior border of trapezius muscle, middle third of clavicle	Cutaneous branches of the cervical plexus, CN X (accessory), arterial branches of the thyrocervical branch, lymph nodes, veins

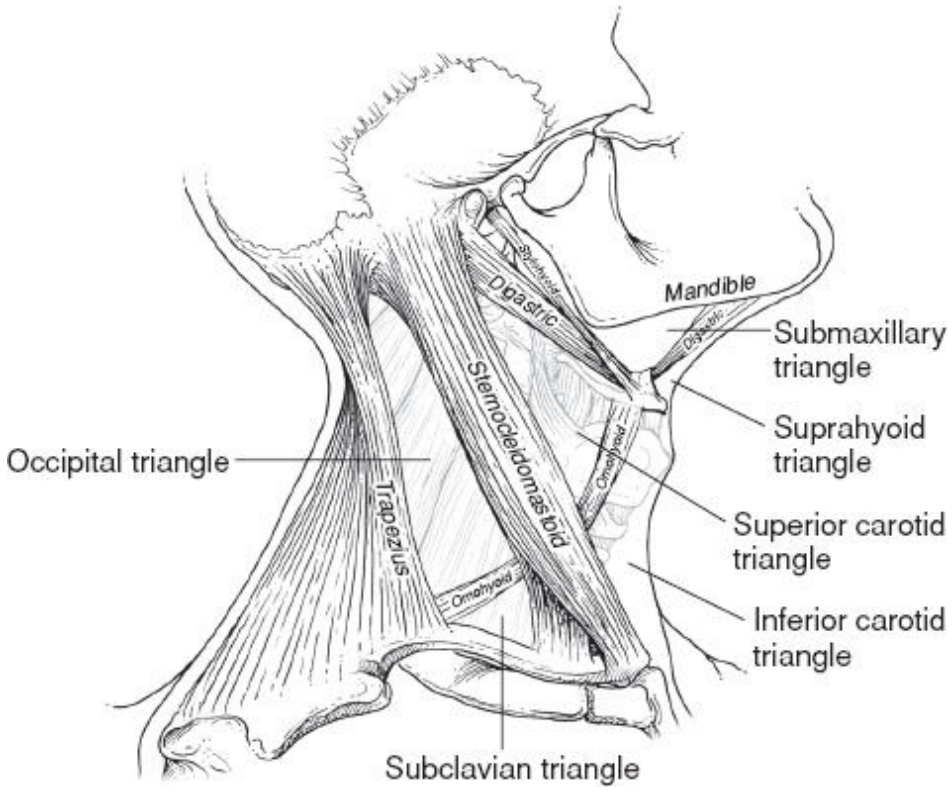

FIGURE 241.1 The anterior and posterior triangles of the neck, lithograph plate from Gray's Anatomy.

The clinical presentation of a neck mass can include diffuse or localized swelling, fever, poor oral intake, neck stiffness, torticollis, drooling, and various other symptoms; see Table 241.3 (3).

TABLE 241.3
Common Presenting Symptoms Associated with Neck Masses

Neck swelling (localized, diffuse)	Globus phenomena (sensations of lump in throat)	Stridor
Fever	Odynophagia	Speech disorders Hoarseness
Erythema	Otalgia	Head tilt/torticollis
Ecchymosis	Muffled, hot potato voice	Respiratory difficulty
Dysphagia	Trismus	Weight loss
Drooling		CN IX–XII palsies

Table 241.4 lists common presentations of neck masses by anatomic location, with likely etiologies and distinguishing clinical features.

TABLE 241.4
Anatomic Neck Mass Presentations

Location	Etiologies	Distinguishing Features
Midline	Thyroid mass/goiter	Tachycardia, weight loss
	Thyroglossal duct cyst	Moves with tongue protrusion
Anterior triangle	Lymphadenopathy	Enlarged, mobile nodes
	Lymphadenitis	Erythema, tender, fever
	Branchial cleft cysts	Often secondarily infected
	Sialadenitis	Parotitis obscures jaw angle
	Laryngocele	Lateral air-filled sac
	AV fistula	Pulsatile, bruit
Posterior triangle	Cystic hygroma	Diffuse edematous swelling
	Lymphadenopathy Lymphadenitis	Consider malignancy if persistent, fever, weight loss
Diffuse swelling or head tilt/ torticollis	Deep neck infections	Fever, sore throat, neck pain
	Fibromatosis colli	Firm mass on sternocleidomastoid in infant

Ill-Appearing Child with Fever

Fever and localized neck swelling that is tender and warm to the touch (with or without skin changes) suggests a superficial or deep neck infection. This may originate from local structures including tonsils, middle ear, lymph or salivary glands, a congenital cyst or, rarely, from a malignancy.

Deep neck infections include peritonsillar abscesses (with possible extension in neck planes), retropharyngeal abscesses (primarily seen in children $\leq$5 years old due to regression of involved lymph nodes with age), parapharyngeal abscesses, sialadenitis, supramylohyoid infections, and superinfected congenital malformations. Congenital malformations can become clinically evident at any point in life, and often present as a result of super-infection (1).

Diagnosing potentially life-threatening infections can be challenging due to the anatomic complexity and the subtle or overlapping presentations of more benign conditions such as cervical lymphadenitis. In addition, relative to adults, pediatric patients have the potential for retropharyngeal or parapharyngeal infections of lymphoid tissue in spaces that generally atrophy by adulthood. Such infections present with neck pain, swelling, or stiffness, associated with sore throat, poor oral intake, drooling, stridor, or lymphadenopathy. Drooling is an especially worrisome marker for airway compromise. In very young infants (<9 months), the most common presenting symptoms of deep neck infections include neck swelling, lymphadenopathy, fever, rhinorrhea, poor oral intake, and cough (3).

Potentially life-threatening complications of deep neck infections include mediastinitis, Ludwig angina, and Lemierre syndrome. Ludwig angina is a rapidly progressive, firm cellulitis of the floor of the mouth usually originating from a diseased tooth, but it may also originate from a peritonsillar or parapharyngeal abscess, epiglottitis, or a penetrating injury to the floor of the mouth. Lemierre syndrome, usually seen in older children, is an infected thrombosis of the internal jugular vein that is associated with parapharyngeal infections such as pharyngitis, tonsillitis, cervical lymphadenitis, and parotitis. Lemierre syndrome should be considered in a sick-appearing child with significant neck pain (3,4).

Neoplasm should be considered in a child with a firm, nonmobile, enlarging neck mass, and a history of fevers, weight loss, bone pain, or night sweats. Other concerning features include a persistently enlarged lymph node that has been present for several weeks, enlarged nodes in the posterior triangle or supraclavicular space, or lymphadenopathy that is associated with recurrent epistaxis, hoarseness, cranial nerve palsies, or otorrhea, which may indicate local tissue invasion by a mass (5,6). A list of benign and malignant head and neck neoplasms is included in the differential diagnosis in Table 241.4.

Well-Appearing Child with Fever

The most likely diagnoses include reactive lymphadenopathy, lymphadenitis due to viral or bacterial pathogens, and salivary gland infections. If fever and adenopathy are persistent (i.e., for more than a few weeks), etiologies to be considered should include mycobacterial infections, granulomatous processes, and *Bartonella henselae* infection (catscratch fever) (6).

Salivary gland infections should be considered as a cause of neck swelling because the majority of the parotid gland tissue is below the angle of the mandible. Parotitis often presents as an acute neck swelling that obscures the angle of the jaw Figure 241.2. In pediatric patients, acute tender enlargement of the parotid gland is usually infectious, or due to salivary duct stones (7). The differential diagnosis of parotitis includes viral infections, including mumps due to paramyxovirus, rarely seen in immunized patients, Coxsackieviruses, CMV, HIV-related EBV infection, *Staphylococcus aureus* infection, *mycobacterium* tuberculosis, juvenile recurrent parotitis (a chronic condition without a well-defined etiology that develops between age 3 and 6 years), and bulimia nervosa sialadenosis (8).

FIGURE 241.2 Parotitis in a toddler. Note how the enlarged parotid gland obscures the angle of the mandible.

Well-Appearing, Afebrile Child

This category includes mostly noninfected congenital lesions and vascular anomalies. Congenital malformations are common in the pediatric population, but may not become evident until adolescence or adulthood; they should therefore be considered in the differential of any patient presenting with a neck mass (1,9,10). The most common include branchial cleft anomalies (cysts being most common), thyroglossal duct cysts, cystic hygromas, laryngoceles, and epidermoid and dermoid cysts (see Chapter 261).

While patients with vascular malformations may not appear toxic, these lesions can potentially cause life-threatening complications due to airway compromise, bleeding, or high-output cardiac failure. Hemangioma, a very common pediatric vascular tumor, may present as a neck mass and cause subglottic obstruction or high-output cardiac failure. Hemangiomas are generally enlarging red or blue masses that typically proliferate before involuting. Cutaneous lesions may indicate the presence of hemangiomas in other organs, and one-half of infants with subglottic hemangiomas also have a cutaneous hemangioma. Any hemangioma found in the "beard distribution" (the preauricular areas, chin, anterior neck, and lower lip) should trigger further evaluation for associated airway hemangiomas (1,11). For children without stridor or drooling, this evaluation may take place as an outpatient. Cavernous hemangiomas are venous malformations due to thin-walled, dilated veins that grow with the child, are usually soft with a blue hue, and carry a risk of thrombosis or bleeding. Arteriovenous malformations can be distinguished by their palpable thrill, audible bruit, warmth, and redness. Most importantly, these lesions carry a risk of high-output cardiac failure (12).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of neck mass can be organized according to suspected etiologies (Table 241.5).

TABLE 241.5
Etiologies of Pediatric Neck Masses

Etiology	Typical Presentation
Inflammatory	
Reactive lymphadenopathy (secondary to systemic infection)	Superficial, mobile, tender nodes, fever, other systemic symptoms of illness, i.e., sore throat, vomiting, etc.
Typical causes: EBV, CMV, toxoplasmosis	
Lymphadenitis secondary to local head/neck infection	Erythematous, tender node, fever, may drain
Typical causes: Streptococcal, staphylococcal, mycobacterial, *Bartonella henselae* (catscratch disease), fungal, tularemia	
Sarcoidosis	Firm, enlarged node, +/– fatigue, cough
Sialadenitis	Enlarged, tender gland, parotid often obscures angle of jaw
Retropharyngeal abscess	Neck fullness, torticollis, adenopathy, sore throat, difficulty swallowing/handling secretions
Congenital	
Cystic hygroma (lymphangioma)	Soft swelling, often posterior triangle
Hemangioma	Red or blue soft mass
Thyroglossal duct cyst	Midline, moves with tongue protrusion
Branchial cleft cyst	Most commonly from second arch, mass inferior to mandible and anterior to sternocleidomastoid muscle
Dermoid cyst	Thin walled, may contain fatty or horny masses or hairs
Laryngocele	Generally lateral, compressible neck bulge from anomalous air sac communicating with larynx; can be acquired; cough, hoarseness
Thymic cyst	Generally unilateral and left sided, rare
Neoplasms	
Keloid scars	Hypertrophied tissue overlying area of trauma or surgical site
Benign	
Fibroma, lipoma	Can present in any location, fibromas may be firm/rubbery or soft loose connective tissue, lipomas are comprised of soft, fatty tissues
Thyroid nodule	Generally midline or anterior neck triangle, may or may not have abnormal TFTs
Malignant	Lymphadenopathy, firm, nonmobile, matted, or enlarged >2–3 cm nodes, fevers, weight loss, night sweats, fatigue, bone pain, failure to thrive
Lymphoma	
Leukemia	
Rhabdomyosarcoma	
Neuroblastoma	
Nasopharyngeal squamous cell carcinoma	Respiratory compromise, voice change, epistaxis
Salivary gland tumor	Swelling overlying salivary gland
Thyroid tumor	Anterior neck, +/– abnormal TFTs, weight loss, generalized lymphadenopathy
Metastasis	

ED EVALUATION

Diagnostic evaluation begins with a thorough history and physical examination. The child's overall appearance, the location of the neck mass, the appearance of the pharynx, and the patency of the airway all help guide the clinician's next steps. In most well-appearing children, infectious and inflammatory causes predominate and little further diagnostic testing is required. When reactive lymphadenopathy or lymphadenitis is suspected, a thorough investigation of the head and neck, including the tympanic membranes, pharynx, and skin, should be performed. In patients with fever, tonsillar erythema, and exudate, a rapid streptococcal antigen test may be diagnostic. In young children with suspected infectious mononucleosis (lymphadenopathy, fever, pharyngeal erythema, enlarged spleen), a CBC may reveal atypical lymphocytes, which support the diagnosis. In adolescents, heterophile antibody testing (monospot) can be helpful, but in younger children, EBV-specific serologies must be obtained because heterophile antibodies are often falsely negative in children less than 12 years of age (up to 50% false-negative rate) (13). Erythrocyte sedimentation rate and C-reactive protein measurements can be helpful in tracking infections, but are not necessary in well-appearing children. If there is a draining mass, a Gram stain and culture may guide therapy. Well neonates with a firm mass overlying the lower third of the sternocleidomastoid muscle (with or without torticollis) are likely to have fibromatosis colli, a clinical diagnosis confirmed with ultrasound (US). Treatment is physical therapy.

In the ill-appearing child without airway compromise a complete blood count, blood cultures, CRP, ESR, and x-rays of the neck and chest may help to initially guide diagnosis. Further testing should be based on history (exposures, duration of illness, and review of systems) and physical examination findings. In the ill-appearing child with evidence of airway compromise, x-rays of the neck (AP and lateral soft tissue) and chest can help assess the patency of the airway and lung fields (14). If there is respiratory failure, the airway should be secured by the most experienced operator, with equipment available for an emergent surgical airway (15).

In children with suspected malignancy, a complete and differential blood count is indicated, as well as a screening chest x-ray for the presence of a mediastinal mass. For suspected thyroid masses, thyroid function testing is recommended.

In addition to plain films (particularly the lateral neck film, which can quickly assess for potential airway compromise), US is the initial imaging modality of choice in children (14,16). US is readily available, can be interpreted quickly, does not involve radiation exposure, and is noninvasive. US is particularly useful in children, given their smaller neck size and less prominent subcutaneous fat, allowing for improved sonographic penetration and resolution compared to adults (14). When additional imaging is needed, magnetic resonance imaging and computed tomography (CT) are both useful for defining anatomy. CT is usually readily available, has a short study time that may obviate the need for sedation in younger children, and allows for excellent assessment of bone involvement. However, these benefits must be balanced against the risks of ionizing radiation. MRI is excellent for assessment of soft tissues and carries no radiation risks, but may have limited availability and usually requires sedation.

CRITICAL INTERVENTIONS

- Most well-appearing children with neck masses have lymphadenopathy or lymphadenitis that requires little intervention beyond consideration of antibiotic therapy if a bacterial origin is suspected.
- Antibiotics providing coverage of common head and neck pathogens should be instituted for neck masses that appear infected or for children who appear systemically ill.
- Cultures of neck drainage or blood cultures in systemically ill patients should be obtained prior to antibiotic therapy to tailor the antibiotic choice.
- Incision and drainage of neck masses is not recommended without a definitive diagnosis having been made; this may lead to fistula formation in the case of congenital malformation, or may seed the incision tract in the case of tumor.

- Lymphadenopathy that has persisted beyond several weeks or that is unresponsive to treatment should be considered a potential malignancy or atypical infection, and warrants imaging and consultation.

DISPOSITION

Well-appearing children without airway compromise may be managed as outpatients with appropriate follow-up. Most children with lymphadenitis can be prescribed outpatient antibiotics with primary care follow-up. In the stable child with evidence of a congenital malformation, referral to a pediatric surgeon or otolaryngologist is recommended. Ill-appearing children should be admitted to the hospital with airway support and antibiotics as indicated.

Common Pitfalls

- Failure to recognize impending respiratory failure from airway obstruction due to a neck mass.
- Ordering a CT scan of a neck mass when US or MRI is available and appropriate.
- Incision and drainage of a neck mass in the absence of a definitive diagnosis.
- Failure to recognize possible superinfected congenital malformations.

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CHAPTER 242
Limp

Margaret S. Wolff

Limp represents any alteration in gait and is a common reason for presentation to the emergency department (ED) for children (1). The majority of cases are the result of trauma, but a lesion of the central nervous system, spine, peripheral nervous system, intra-abdominal contents, hip, knee, ankle joints, feet, or any of the weight-bearing long bones can lead to an alteration in gait (2,3). This chapter discusses the approach and evaluation of the child with limp in the ED.

CLINICAL PRESENTATION

A detailed history and physical examination are essential in making the correct diagnosis. The caregiver and child should be questioned regarding any temporal relationships, patterns related to physical activity, posture during sleep, and the location of pain. In the nonverbal child, the parents may be able to localize the source of the child's limp. A history of an acute traumatic event, such as a fall, twisting injury, direct blow, or penetration by a foreign body, should be obtained. A history of recent fever, current or recent antibiotic use, antecedent infectious process, or other ill exposures may help to determine an inflammatory or infectious etiology. Historical features which may suggest an etiology of the limp are listed in Table 242.1.

TABLE 242.1
Historical Features of Pediatric Limp

History	Possible Diagnosis
Abdominal pain	Acute surgical abdomen
	Inflammatory bowel disease
	Pelvic inflammatory disease
Back pain	Diskitis
	Pathologic fracture
	Psoas abscess
	Vertebral osteomyelitis
Bleeding disorder	Hemarthrosis
Fever	Infection
	Malignancy
	Rheumatologic disorder
Morning stiffness	Rheumatologic disorder
Pain at night	Malignancy
Preceding sore throat	Acute rheumatic fever
Radicular pain	Nerve involvement
Recent diarrheal illness	Reactive arthritis
Recent intramuscular injection	Inflammation
	Infection
Sickle cell disease	Avascular necrosis of femoral head
Testicular pain	Inguinal hernia
	Testicular torsion
Tick bite or erythema migrans	Lyme disease

In the preschool-aged child, the initial examination can be conducted with the child on a parent's lap. Begin with inspection and evaluate the position of the patient at rest. Examine the skin for evidence of hemorrhagic diathesis, occult trauma, penetrating wounds, rash, or infection. Soft tissue swelling and skin changes may suggest pyoderma, cellulitis, or a deeper plane infection. Evaluate for asymmetry of gluteal, thigh, and popliteal creases. Effusion or distension of the joint capsules of the hip, knee, or ankle may also aid in the diagnosis.

Only after inspection should the physician palpate for localized induration, warmth, or tenderness near the bones, particularly metaphyseal regions of long bones. Assess the degree of restriction of flexion, extension, abduction, and rotation. Palpate the spine in the midline, looking for paraspinal muscle spasm or scoliosis. Examine

the feet thoroughly for embedded foreign bodies. If a thorough musculoskeletal examination has not revealed any abnormalities, perform a thorough neurologic examination including deep tendon reflexes, motor strength, cranial nerve function, and sensory deficits or nuchal rigidity. The patient should also be asked to stand and to attempt to walk.

DIFFERENTIAL DIAGNOSIS

Normal gait requires coordinated action of the entire lower extremity; therefore pain, weakness, or dysfunction at any level can lead to gait disturbances. Traumatic and infectious etiologies account for the majority of patients seen in the ED with limp (Table 242.2). Because of their frequency, overt or occult trauma and infectious diseases should be part of the differential diagnosis for any child with an acute gait disturbance (3).

TABLE 242.2
Causes of Limp in Children

Trauma (most common)
- Contusion
- Fracture
- Sprain
- Overuse injury

Infectious
- Diskitis
- Osteomyelitis
- Pyomyositis
- Septic Arthritis

Postinfectious
- Acute rheumatic fever
- Reactive arthritis

Orthopedic
- Legg–Calvé–Perthes Disease (LCP)
- Slipped capital femoral epiphysis (SCFE)

Intra-abdominal pathology

Neuromuscular disorders

Oncologic conditions

Rheumatologic disorders

Conversion disorders

Traumatic Etiologies

In early childhood, a spiral fracture of the tibia or fibula (toddler's fracture) should be considered the probable diagnosis in an afebrile child less than 5 years old who suddenly refuses to walk or place any weight on a single lower extremity. The absence of direct trauma should not cause the physician to rule out the diagnosis, because these fractures may occur as the result of trivial, indirect injury associated with the child's daily activity (4). Older children may limp from stress fractures of the femoral head, tibial tubercle, and tibial or fibular shaft. They also may limp from avulsion of the ischial apophysis, lesser trochanter, or navicular tuberosity, or from lacerations and compression of cartilage plates, fracture of the epiphyseal ossification centers, shaft fractures, and infractions at various levels of the long-bone metaphyses. These traumatic lesions may present singly or in various combinations and may be acute or more chronic (5). Trauma and repeated stress may be important

factors in the genesis of slipped capital femoral epiphysis, transient synovitis, and Legg–Calvé–Perthes disease, three of the most common hip afflictions associated with antalgic gait (6).

Nontraumatic Etiologies

An early presumptive diagnosis for the cause of gait disturbance must be established for a few conditions (Table 242.3). Failing to consider these conditions at the initial encounter may lead to deformity, functional disability, or ultimate patient demise (7). Serious infectious diseases predominate among the nontraumatic conditions that can cause altered gait with serious late complications if not detected early (8). A history of fever should heighten concern for a focal cellulitis of the lower extremity, unifocal septic arthritis of a weight-bearing joint, and osteomyelitis of the femoral or tibial metaphyses (8).

TABLE 242.3
Disease States Associated with Limp that Require Prompt Recognition

Osteomyelitis
Long bone, spine, pelvis
Pyarthrosis
Hip, knee, ankle
Sacroiliac infection
Psoas abscess
Deep-plane infection
Epidural abscess
Intramedullary abscess of the spinal cord
Slipped capital femoral epiphysis
Cord tumor
Guillain–Barré syndrome
Tick paralysis
Meningitis
Encephalitis
Cerebral abscess
Appendicitis

Modified and reproduced with permission from Singer J. Evaluation of acute and insidious gait disturbance in children less than 5 years of age. In: Barness LA, et al., eds. *Advances in Pediatrics*. Vol. 26. Chicago, IL: Year Book; 1979:210.

Pain associated with osteomyelitis of the long bones is primarily located at the affected metaphysis. Direct pressure at the affected metaphysis produces extreme discomfort. Swelling is limited to the immediate metaphyseal area initially, but it can spread rapidly to involve an entire extremity or adjacent periarticular tissue. Joints adjacent to the infected metaphysis may have some limitation of motion caused by voluntary guarding or sympathetic effusion. Neck pain, back pain, and refusal to walk may signal the presence of osteomyelitis of the spine. Fever associated with back, buttock, or hip pain with gait disturbance may be the initial expression of osteomyelitis of the pelvis (9). Children are prone to nontraumatic osteomyelitis, so the diagnosis should receive consideration.

Patients with pyogenic arthritis are usually readily diagnosed because of the protective posturing imposed by joint capsule distention. When there is hip involvement, children assume a characteristic position of comfort (Fig. 242.1). If the knee or ankle is involved, it is erythematous, warm, swollen, and painful to palpate, with limited range of motion. Minimal active motion, extreme

muscle spasm, and pain with passive movement are distinguishing features of pyarthrosis in weight-bearing regions. Rarely, children with pyogenic arthritis can present with more subtle symptoms mimicking transient synovitis (10,11).

FIGURE 242.1 Child with septic hip. He is holding his left lower extremity flexed and externally rotated at the hip, as is characteristic with bacterial infection of the joint. (From Fleisher GR, Ludwig W, Baskin MN. Atlas of Pediatric Emergency Medicine. Philadelphia, PA: Lippincott Williams & Wilkins; 2004).

Children with transient synovitis have a unilateral inflammatory reaction in the hip. These patients usually present with either acute or progressive discomfort in the hip, anteromedial thigh, or ipsilateral knee that eventually leads to an antalgic gait. There may be antecedent minor trauma, recent upper respiratory tract

symptoms, or low-grade fever. A fever of ≤38.5°C should raise the suspicion of septic arthritis. Clinically, this condition may be indistinguishable from Legg–Calvé–Perthes disease. In both cases, children do not appear systemically ill. They choose a position with the thigh flexed, abducted, and externally rotated. They guard the hip during examination and have pain with internal rotation of the hip and, to a lesser extent, with hip extension (6). The peak incidence of Legg–Calvé–Perthes disease is between 5 and 7 years of age (12).

Hip, groin, abdomen, lower back, buttock, or upper thigh pain associated with fever and limping may occur with a psoas abscess. Like patients with septic arthritis of the hip, those with psoas abscess may assume the position of hip flexion, abduction, and external rotation. Rotation of the fully flexed hip is typically pain free. Several findings may differentiate psoas abscess from septic arthritis or osteomyelitis: the presence of abdominal guarding with tenderness in lower quadrants or a palpable mass in the iliac fossa or pelvic floor detectable by rectal examination. Patients also may have bulging of the flank with or without cutaneous edema, scoliosis, immobility of the spine with spasm of the paravertebral muscles, or decreased excursions of the diaphragm (13).

Deep-plane infection refers to suppuration that extends to the depth of fascia or muscle. In necrotizing fasciitis, fat and fascia are destroyed. Muscle is typically uninvolved, and skin, on occasion, may be spared (14). In bacterial myositis, the striated muscle is involved, and there may be localized abscess formation within the muscle (pyomyositis). Clinical features of fasciitis and myositis overlap. Neither disease is common in immunologically intact children. Predisposing conditions include diabetes mellitus, chronic cardiac or pulmonary disease, collagen vascular disease, varicella complicated by pyoderma, and antecedent blunt trauma. Symptoms are often insidious, starting with poorly localized extremity pain that impairs gait. Fever may be absent or only of low grade. Pain out of proportion to the degree of physical findings may be the only clue to the correct diagnosis at the initial encounter (14). Rapidly developing skin changes suggest the diagnosis. These changes

include a localized soft tissue swelling, erythema, and either darker discoloration of the skin (pyomyositis) or bullae formation, and spontaneous sloughing (necrotizing fasciitis). If misdiagnosed at the time of initial presentation, children may return in extremis within 24 to 48 hours in septic shock (14).

In cases of acute or chronic slipped capital femoral epiphysis, deep groin pain and hip, distal medial thigh, or knee pain may be of sudden onset or progressive over weeks. Classically, pain is vague, dull at rest, and exacerbated by ambulation. Children seek comfort by externally rotating the leg when walking. They limp, is often accompanied by a truncal shift with ambulation to accommodate hip abductor weakness. Examination demonstrates a partially flexed, irritable hip maintained in external rotation. Maximal hip flexion is restricted, and complete internal rotation is not possible. Delay in recognition of an acute slip may result in further displacement or may increase the risk for avascular necrosis.

Pathology outside the musculoskeletal system may also present as limp. Patients with uncomplicated appendicitis, or a perforated or abscessed appendix may present with a slow cautious, gait accompanied by flexion of the trunk (15). Hip pain and limp may be the presenting complaints with epidural abscess, but most patients in this instance seek medical attention because of unremitting back pain. At the onset, most patients exhibit fever, headache, malaise, and aching midline back pain. Patients may have tenderness on palpation of the spinous processes at the level of their back pain. Overt cord involvement may be heralded by weakness of voluntary muscles and bowel and bladder sphincters or by sensory abnormalities, most often characterized as ascending anesthesia (16). Limp may be the initial presentation of systemic illness such as acute lymphoblastic leukemia or lymphoma (17). Systemic symptoms such as fever, weight loss, and night time pain may suggest these diagnoses.

ED EVALUATION

ED evaluation should be guided by history and physical examination (Fig. 242.2). When there is a history of trauma or the area of pain

has been localized, radiographs limited to the area of interest have proven diagnostic efficacy. Plain radiographs are specific for fractures, destructive lesions, and avascular necrosis (18–21). Radiographs are often insensitive and unreliable, especially in the early course of patients with toddler's (tibial) fractures, septic hip, osteomyelitis of the long bone or pelvis, sacroiliac joint infection, and intervertebral disk infection.

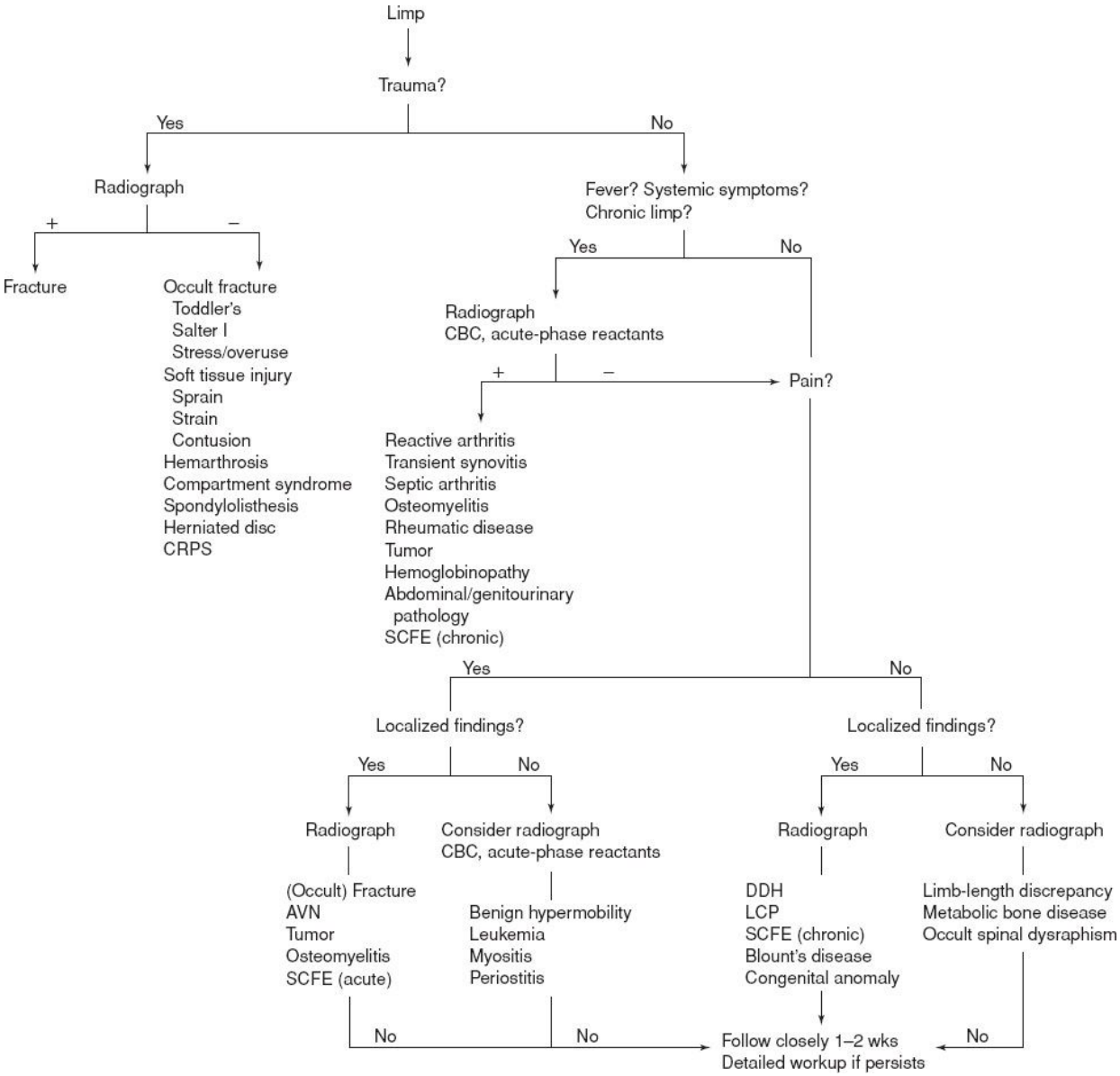

FIGURE 242.2 Algorithmic approach to the child with a limp. CRPS, complex regional pain syndrome; CBC, complete blood count; SCFE, slipped capital femoral epiphysis; AVN, avascular necrosis; DDH,

developmental dysplasia of the hip; LCP, Legg–Calvé–Perthes disease. (From Gary RF, Stephen L, Fred MH, et al. *Textbook of Pediatric Emergency Medicine.* 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.)

Patients with fever or systemic symptoms require a more extensive evaluation. Laboratory evaluation should include a complete blood, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and blood culture (if febrile). A CRP level >2 mg/dL is consistent with a septic joint or osteomyelitis when the clinical picture is suggestive (11,22–24). It is important to note that fever, leukocytosis, and elevated acute phase reactants may not uniformly accompany infectious diseases associated with gait disturbance (11).

In patients with fever or other systemic symptoms, further imaging is indicated if initial radiographs are negative and the suspicion is high for bacterial infection of the bone, joint, or soft tissue (24). Patients with hip irritability should undergo ultrasonography to assess for presence of an intra-articular effusion (25). Magnetic resonance imaging (MRI) is superior to both plain films and CT scans for soft tissue detail. MRI may be the most sensitive means of establishing an early diagnosis of Legg–Calvé–Perthes disease, differentiating bone infarction from osteomyelitis in the sickle cell patient and benign from malignant bone tumors. MRI may be useful in certain anatomic regions that are difficult to evaluate with plain films (e.g., region of the sacroiliac joint, vertebral bodies, and intervertebral disks) (18).

KEY TESTING

- Plain radiographs of affected extremities
- Blood cultures if febrile
- CBC
- ESR
- CRP
- Ultrasound of hips if indicated
- CT MRI for equivocal cases

ED MANAGEMENT

Rarely, a patient with limp, pseudoparalysis, or paresis requires establishment of an airway or ventilatory support or hemodynamic instability. If present, initiate prompt resuscitation prior to proceeding with evaluation of limp. Neurologic deficits may be rapidly progressive in a few conditions associated with gait disturbance. Continuous monitoring of neurologic status is warranted for patients suspected of having Guillain–Barré syndrome, poliomyelitis, acute transverse myelitis, tick paralysis, brain abscess, meningitis, or cerebral vascular accident.

For all patients with limp, ensure that any associated pain is well controlled. Additional management will vary depending on the history, physical and evaluation. Patients with traumatic injuries may require splinting, reduction of fractures, or operative repair, and consultation with orthopedics can be beneficial. Patients with fever should receive antibiotics if a source is located or if the patient is hemodynamically unstable. Septic joints require urgent arthrocentesis and consultation with orthopedics. Patients with suspected osteomyelitis or deep soft tissue infections not identified in the ED require admission for further evaluation such as MRI. In patients with presumed transient synovitis, a dose of ibuprofen can markedly improve symptoms and aid in diagnosis.

CRITICAL INTERVENTIONS

- Obtain plain radiographs in children with traumatic limp.
- Perform a thorough physical examination, including neurologic examination, in patients with nontraumatic limp.
- Order CBC, acute phase reactants, and blood culture for children with fever and limp.
- Patients with hip irritability and fever require prompt ultrasonography, and arthrocentesis if hip effusion present.

DISPOSITION

Admission is warranted for children with gait disturbance in certain circumstances. All patients who appear to have a serious bacterial

infection require admission. Admission is warranted for all patients with neurologic abnormalities, such as altered consciousness, cranial nerve involvement, subjective or objective sensory disturbance, ataxia, alteration of sphincter tone, urinary retention, altered deep tendon reflexes, or loss of voluntary movement. Admit patients with gait disturbance who may have injuries due to nonaccidental trauma in consultation with child protective services.

Common Pitfalls

- Think of trauma when there is an abrupt onset of gait disturbance without prodromal events in a previously healthy child.
- De-emphasize the history of trauma, even if witnessed, when fever or systemic symptoms are present; this scenario suggests serious bacterial infection.
- Fever, leukocytosis, and acute phase reactants may not uniformly accompany infectious diseases associated with gait disturbance.

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CHAPTER 243 Hematuria and Dysuria

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HEMATURIA

Hematuria is the presence of blood in the urine, which can be gross (visible to the naked eye) or microscopic. Microscopic hematuria is defined as the presence of 3 to 5 RBCs/HPF on at least two of three examinations over a 2- to 3-week period, and is a common finding in the pediatric population, with a prevalence of 0.5% to 2%, although less common than in adults, where the prevalence is up to 21%. Gross hematuria presents as a discoloration of the urine that is either red/pink or cola or tea colored. It is important to note that a small amount of blood (1 mL in 1,000 mL of urine) can cause discoloration of the urine (1). Gross hematuria is noted in about 0.1% of children, as compared to 2.5% in adults (2). Distinguishing emergent reasons for evaluation in the pediatric patient is essential for the emergency practitioner.

CLINICAL PRESENTATION

Microscopic hematuria is often an incidental finding in children during evaluation for genitourinary (GU) symptoms. The primary tool for screening is a urine dipstick; a result of blood 1+ and greater is considered positive. The dipsticks used for detection of blood in the urine are very sensitive in detecting red blood cells (RBCs) and minute amounts of free hemoglobin and myoglobin. Dipstick screens should be confirmed with microscopic examination of the urine to exclude false-positive and false-negative results.

DIFFERENTIAL DIAGNOSIS

The causes of hematuria are numerous, and in the pediatric population are more often medical than surgical in nature (3). In developing a differential diagnosis, in addition to classifying hematuria as gross or microscopic, clinicians must be able to differentiate the origin of the hematuria. In children gross hematuria is often glomerular in origin. Glomerular bleeding tends to be associated with cola- or tea-colored urine (30% of patients), whereas bleeding from the lower tract and bladder presents with red- or pink-colored urine. Furthermore, with glomerular hematuria there are often findings of proteinuria, red cell casts, and red cell dysmorphology, coupled with systemic findings such as hypertension and edema (1,4). The passage of blood clots usually points to the bladder or urethra as the source of bleeding (3,5).

Acute glomerulonephritis (AGN) results from immunologic effects on the glomerular tissue and is divided into three broad categories: postinfectious, due to intrinsic renal disease, and due to systemic disease (Table 243.1). Postinfectious acute glomerulonephritis (PIAGN) is a common cause of pediatric glomerulonephritis and the most common cause of glomerular gross hematuria in the pediatric patient. It has a peak incidence between the ages of 2 and 6 years and frequently follows streptococcal infections of the skin or pharyngitis with certain nephrogenic strains of group A β-*hemolytic streptococci.* Characteristically, there is a latent period between the streptococcal infection and the onset of nephritis, which can be 8 to 14 days for pharyngitis and 14 to 21 days for skin infections (4,6).

TABLE 243.1
Causes of Glomerulonephritis

Postinfectious	Renal	Systemic
Bacteria: Streptococcus (PSAGN), Staphylococcus, mycobacteria, Salmonella	Membranoproliferative glomerulonephritis	Wegener granulomatosis
Viral: CMV, Coxsackie, EBV, hepatitis, rubella, mumps	IgA nephropathy (Berger disease)	Hypersensitivity vasculitis
Fungal: Coccidioides immitis	Idiopathic rapidly progressive glomerulonephritis	Cryoglobulinemia
Parasite: Plasmodium spp, Schistosoma mansoni, Toxoplasma gondii, filariasis, trichinosis, trypanosomes		Systemic lupus erythematosus Polyarteritis nodosa Henoch–Schönlein purpura Goodpasture syndrome

PSAGN, Post-streptococcal acute glomerulonephritis; CMV, cytomegalovirus; EBV, Epstein–Barr virus.

Urinary tract infection (UTI) represents the most common cause of gross hematuria and is often associated with dysuria, frequency, or abdominal pain (7). A history of recent trauma, including catheterization, masturbation, urethral foreign bodies, or recent strenuous exercise (running, bicycle riding) can explain transient hematuria (8). Any past history of renal colic or a family history of nephrolithiasis or hypercalciuria should be elicited. Specific pulmonary symptoms, such as hemoptysis (Goodpasture syndrome), or the triad of sinusitis, AGN, and pulmonary infiltrates (Wegener granulomatosis) may provide important clues to a diagnosis.

Pseudohematuria is caused by substances other than blood that discolor the urine (Table 243.2). This may include oxidizing contaminants, such as bacterial peroxidases from a UTI, or a delay in reading the dipstick. Newborns often present with the parents' concern for a red or pink discoloration in the front of the diaper, often referred to as "brickdust urine," which is caused by urate crystals deposited in the diaper. Certain foods (e.g., beets, blackberries, rhubarb), and medications (e.g., rifampin, cefdinir) can also cause urine discoloration that is mistaken for hematuria (4,7). A positive dipstick reaction in the absence of RBCs on microscopy can be caused by myoglobinuria (rhabdomyolysis) or hemoglobinuria (seen in conditions causing hemolysis). In the menstruating girl, vaginal bleeding can be confused with urinary

blood. A catheterized urine specimen may be necessary to determine the source of the bleeding. It should also be noted that a false-negative dipstick reading can occur when the urine has a high specific gravity or contains large amounts of reducing substances, such as ascorbic acid.

TABLE 243.2
Cause of Pseudohematuria

Myoglobinuria (seen in rhabdomyolysis)
Hemoglobinuria (seen in conditions causing hemolysis)
Oxidizing contaminants (e.g., bacterial peroxidase from UTI)
Delay in reading dipstick
Foods (e.g., beets, blackberries, rhubarb)
Medications (e.g., rifampin, cefdinir)
Brickdust urine (caused by urate crystals in the diaper)
Vaginal bleeding

The differential diagnosis for childhood hematuria is listed in Table 243.3, and can be remembered by using the alphabetic sequence A through I (9).

TABLE 243.3
Differential Diagnosis for Childhood Hematuria

Anatomy/vascular (renal cysts, arteriovenous malformations, obstruction with hydronephrosis)
Boulders (renal stones, hypercalciuria and hyperuricosuria)
Cancer (Wilms tumor or adenocarcinoma and infiltration of the kidney by leukemia or solid tumors)
Drugs/Dehydration (over-the-counter or illicit drugs, methicillin, cyclophosphamide, anticoagulants)
Exercise-induced hematuria
Foreign body, familial (Alport) or factitious
Glomerulonephritis (GN):
Primary GN: poststreptococcal, IgA nephropathy (Berger Disease), membranoproliferative
Secondary GN: Henoch–Schönlein Purpura, hemolytic–uremic syndrome, systemic lupus erythematosus
Hematology (hemoglobinopathy, coagulopathy)
Infectious (cystitis caused by adenovirus, tuberculosis, schistosomiasis in patients with recent travel to the Middle East or Africa)

ED EVALUATION

The diagnostic approach to the pediatric patient with hematuria should incorporate specific elements of both the past and family history. The workup differs from that in adults since renal and urologic malignancies are far less common (10,11). The history should identify antibiotics use, chemotherapy, radiation for malignancies, exposure to tuberculosis, or the use of over-the-counter medications, some of which can cause interstitial nephritis. Rash or arthritis can be found in systemic vasculitides such as systemic lupus erythematosus (SLE) or Henoch–Schönlein purpura (HSP). Umbilical catheterization in the neonatal period, often in premature infants, can cause renal vein or artery thrombosis, which may result in hematuria (12). Inquiry into family history can uncover other potential etiologies. For example, a family history of hearing deficits and renal failure may suggest Alport syndrome. Other diseases that have a familial association include SLE, sickle cell anemia, hemophilia, IgA nephropathy, and other coagulation factor deficiencies.

The physical examination is often nonspecific, but several elements deserve attention and are useful in diagnosis and management. An elevated blood pressure should alert the physician to the possibility of a more severe underlying condition, such as aortic interruption or intrinsic renal disease. The child's height and weight should be plotted and past values should be carefully reviewed to detect failure to thrive associated with long-standing acidosis or chronic renal insufficiency. Evaluation for periorbital and genital edema is important.

Pulmonary findings on auscultation, in addition to exercise intolerance or dyspnea, may provide clues to fluid overload. Costovertebral angle tenderness may indicate a UTI. Recent trauma maybe suggest by findings of flank bruising and pain. Examination of the abdomen for masses is critical for the identification of renal and urologic malignancies (Wilms tumor being the most common in pediatrics), polycystic kidneys, or hydronephrosis (11). The examination of the skin and joints may provide evidence of arthralgias and pallor or rashes, which may be significant in diseases such as hemoglobinopathies, leukemia, HSP (petechial or

purpuric lesions on the lower extremities), or SLE (malar rash) (7). The genital examination should be included to identify abuse or trauma, discharge, or meatal stenosis, all of which can cause hematuria.

The child with a history of flank, back, or abdominal trauma and gross hematuria should undergo renal imaging to identify renal injury. Ultrasound is useful for detecting free fluid in the abdomen in the case of trauma, but computed tomography (CT) provides more specific information for diagnosing and grading renal injuries. Gross hematuria is not the only presentation for significant high-grade renal injuries. In fact, significant injuries may present with microscopic hematuria or an entirely normal urinalysis. Therefore, the decision to pursue imaging for renal injuries should not be based on urinalysis alone, but on a combination of clinical status, physical examination findings, and mechanism of injury (13). A high index of suspicion must be maintained for lesions of the urinary tract in patients with gross hematuria after minimal-force blunt abdominal trauma. Some authors recommend a CT scan of the abdomen and pelvis for patients with 50 or more RBCs on urinalysis, hypotension at the time of emergency department (ED) presentation, or a serious mechanism of injury such as high-speed motor vehicle accident deceleration injuries (5). If blood is noted at the urethral meatus, a retrograde urethrogram must be done prior to catheterization to verify urethral integrity.

Dysuria and urinary frequency, or the presence of systemic signs (fever, vomiting, and abdominal pain), should suggest the possibility of a UTI, including pyelonephritis, and a screening urinalysis and urine culture must be sent. The child with gross hematuria and severe episodic flank or abdominal pain should be evaluated for urolithiasis. The literature on using radiography to diagnose urolithiasis in pediatrics describes varying sensitivities and predictive values for different radiologic modalities. Plain radiography is insufficient to detect stones and ultrasound can detect intrarenal stones, especially those more than 5 mm in diameter (14). Noncontrast CT is the gold standard, but concerns about the long-term effects of radiation exposure have led many

clinicians to reserve CT for patients with persistent or refractory symptoms, or a nondiagnostic US. Urologic consultation is appropriate if a stone is detected. Since a metabolic abnormality can be identified in 40% to 50% of cases of urolithiasis in children, a basic metabolic panel and urine calcium determination are an appropriate part of the initial workup (15,16).

Gross hematuria combined with the presence of proteinuria suggests glomerulonephritis. Proteinuria should not exceed 2+ if the only source of protein is from the blood. Postinfectious glomerulonephritis is the most common cause of acute nephritis in the pediatric population. Pertinent laboratory evaluation includes a complete blood count (hemolytic–uremic syndrome), and culture from the throat and skin should be sent in an effort to isolate a nephrogenic strain of streptococcus, although these cultures are usually negative at the time of diagnosis. Elevated anti-streptolysin O (ASO) titers suggest recent infection (2 to 6 weeks); however, the ASO titer may not rise after streptococcal pyoderma. Anti-DNase B can be elevated for up to 6 months after infection, and is the best single test to detect recent streptococcal infection. The complement C3 level is low in acute poststreptococcal glomerulonephritis, membranoproliferative glomerulonephritis, and SLE, but returns to normal in 6 to 8 weeks (4,6). Further immunologic workup, including antinuclear antibody tests, may be helpful if a diagnosis of underlying systemic disease is being entertained (7).

Less common causes of gross hematuria include hypercalciuria, nephrocalcinosis, sickle cell trait, and glomerular basement membrane defects. Diagnosis begins with a urine Cr/Ca ratio or a 24-hour urinary calcium excretion, serum creatinine, and renal sonography. Consultation with a pediatric nephrologist is recommended if the underlying etiology in unclear on the initial evaluation.

KEY TESTING

- Urinalysis with verification of hematuria by microscopic evaluation

- For potential renal trauma: CT or ultrasonography, CT is preferred for more accurate grading of injury
- For nephrolithiasis: ultrasonography or CT, metabolic panel, and serum calcium
- For glomerulonephritis: skin culture, throat culture, ASO titre, anti-DNase B and C3 complement levels; CBC for possible HUS

ED MANAGEMENT

Management of hematuria depends on the specific etiology involved. Pain management must be addressed in the uncomfortable child. Ketorolac and morphine are the mainstays of analgesia for renal colic. Medical expulsive therapy with agents such as tamsulosin has not been well studied in the pediatric population (17). Asymptomatic hematuria does not require acute ED management, with the exception of UTI, in which appropriate antibiotic therapy is needed (see Chapter 288).

In PSAGN, no specific therapy has been found to influence healing of the glomerular lesions, and much of the treatment is supportive. Antibiotics do not alter the ultimate course of the initial streptococcal disease (with the exception of prevention of rheumatic fever) but may decrease the spread of nephrogenic strains of streptococcus in patients with positive cultures. Thus, penicillin should be administered to the nonallergic patient. For the child with acute renal failure, hypertension, or hyperkalemia, appropriate treatment should be initiated promptly, in consultation with a nephrologist (18).

Up to 85% of patients with postinfectious glomerulonephritis have edema and hypertension, in addition to hematuria, and up to 10% to 30% may have hypertensive encephalopathy presenting with headache, nausea, vomiting, seizures, or transient cortical blindness (6). For hypertensive emergencies in children with PSAGN, therapy should be gradual and controlled. Drugs such as diazoxide, hydralazine, labetalol, loop diuretics, and calcium channel blockers are increasingly chosen because of their quick onset of action. However, decreasing blood pressure by more than 20% to 25% can

cause decreased cerebral perfusion and has the potential to cause stroke. In patients with glomerulonephritis that is nonstreptococcal, corticosteroids or cytotoxic agents may be prescribed in consultation with a nephrologist.

Less common causes of hematuria in children include coagulation abnormalities and some anatomic or vascular problems (7). These, and other conditions requiring advanced workup (Table 243.4), should be referred to a pediatric nephrologist or urologist.

TABLE 243.4
Evaluation of the Child with Hematuria

Initial Evaluation of child with hematuria
History/family history
Physical examination
Urinalysis with microscopy, protein measurement
Red blood cell morphology
Urine culture
Calcium–creatinine ratio
Sickle cell screen, if applicable
Complete blood count, creatinine, and blood urea nitrogen levels
Renal ultrasound
Advanced evaluation of child with hematuria
Urine of first-degree relatives
Complement level (membranoproliferative, SLE, postinfectious glomerulonephritis)
Anti-streptolysin O and anti-DNAse B (Acute poststreptococcal glomerulonephritis)
Antinuclear antibody (SLE)
Audiogram (Alport syndrome)
Antiglomerular basement membrane antibodies
Antineutrophil cytoplasmic antibodies (Active crescentic glomerulonephritis)
Tuberculosis testing
Renal biopsy

SLE, systemic lupus erythematosus.

CRITICAL INTERVENTIONS

- The decision to order renal imaging after blunt trauma should be based on clinical status, history, and mechanism of injury and not on the urinalysis alone.
- Acute management of pediatric hypertensive emergencies should be gentle and controlled, often in consultation with a pediatric

nephrologist.

DISPOSITION

Referral to a pediatric nephrologist should occur for children with gross hematuria, coexisting significant proteinuria, hypertension, abnormal kidney function tests, persistent hypocomplementemia, findings suggestive of a systemic disease, or a family history of glomerulonephritis, nerve deafness, chronic renal failure, end-stage renal disease, or familial hematuria. If parental anxiety is high, referral to a pediatric nephrologist may help alleviate fears and serve as additional reassurance to the family that dangerous and treatable conditions have been ruled out by the emergency physician. Parents are often concerned that their child is losing large amounts of blood due to the color of the urine, and they should be reassured and reminded that as little as 1 mL of blood in 1,000 mL of urine can make the urine red (3,7,19).

Patients with newly diagnosed renal disease should be admitted with pediatric nephrologist consultation, given the possible complications, including hypertension, hyperkalemia, and acute renal failure.

It is important to remember the most common causes of microscopic hematuria without casts or proteinuria are benign and do not require immediate treatment. The overall prognosis for these children is very good. A poor prognosis is, however, associated with proteinuria at presentation, persistent hematuria, and hypertension.

Common Pitfalls

- Failure to perform a urine dipstick followed by formal urinalysis to confirm the presence of blood in the patient with “red urine” can lead to unnecessary further laboratory testing.
- Failure to obtain relevant information such as a history of recent pharyngitis, trauma, or renal stones
- Failure to detect proteinuria, hypertension, or subtle signs of fluid overload

- Failure to recognize that the presence of polymorphonuclear leukocytes and renal epithelial cells may be the only abnormalities in early AGN
- Failure to include AGN in the differential diagnosis of hematuria, particularly when there are other signs such as edema
- Failure to send a urine culture when there are signs and symptoms of UTI

DYSURIA

Many GU conditions can present with dysuria, the most common being UTI, sexually transmitted infection (STI), and vaginitis. Rarely, dysuria may be a presenting complaint associated with systemic disease.

CLINICAL PRESENTATION

Dysuria is defined as pain with urination and may be the chief complaint of a verbal child ($\geq$2 years), or the perceived complaint reported by the parent of a preverbal child who cries with urination or diaper changes. The clinical presentation of dysuria varies depending on the underlying cause.

DIFFERENTIAL DIAGNOSIS

Table 243.5 outlines common causes of dysuria.

TABLE 243.5
Causes of Pediatric Dysuria

- Disorders of the Genitourinary Tract
  - Urinary Tract Infections: pyelonephritis, cystitis (bacterial and viral)
  - Sexually Transmitted Infections: Neisseria gonorrhea, Chlamydia spp, herpes simplex virus, syphilis
  - Vulvovaginitis: bacterial (Candida, Trichomonas, Gardnerella), atopic or chemical irritant (bubble bath, detergent, fabric softener)
  - Trauma: masturbation, sexual activity, minor injury
  - Foreign body
- Systemic Causes
  - Stevens–Johnson Syndrome
  - Behçet disease
  - Reactive arthritis
- Rare Causes
  - Urinary stones
  - Idiopathic hypercalciuria/hyperuricosuria
  - Dysfunctional voiding
  - Urethral stricture

UTI is defined as infection of the bladder (cystitis), kidney (pyelonephritis), or both. UTIs account for 5% to 14% of pediatric ED visits in the United States (20). The clinical presentation varies depending on the age of the child. Preverbal children are more likely to present with fever and nonspecific symptoms such as vomiting or fussiness, while older children are more likely to present with specific urinary symptoms such as dysuria, frequency, urgency, and suprapubic abdominal pain. Findings most useful for identification of a UTI include history of a previous UTI, fever, suprapubic tenderness, and lack of circumcision in males. In verbal children, abdominal pain, back pain, dysuria, frequency, and new-onset incontinence may be findings associated with UTI (21). Pyelonephritis is typically associated with a fever $\geq$38.5°C, while children with cystitis are less likely to have fever.

STIs are a common cause of dysuria; the reported ED prevalence of STIs in symptomatic adolescent patients has been as high as 26% (22). *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are the most common causes in adolescents while *Trichomonas vaginalis* occurs less commonly. Urethritis is a localized inflammation of the urethra, usually caused by infection. When left untreated, up to 40% of STIs will lead to more serious conditions including pelvic inflammatory disease (PID), chronic pelvic pain, and even infertility (22). In

addition to urethritis and PID, ulcerative STIs, such as herpes or syphilis, may present with dysuria.

Vulvovaginitis presents with vaginal discharge and vulvar irritation, typically with redness, burning, itching, and soreness. Dysuria is usually due to the pruritus and excoriation. Recurrent vulvovaginitis can also be bacterial, and occurs most commonly in prepubertal girls aged 2 to 7 years, due to low estrogen levels (23). Infections from *Candida, Trichomonas,* and *Gardnerella* are uncommon in prepubertal girls. Young girls can have vulvar irritation without virginal discharge, usually due to atopic or irritant dermatitis. Common local irritants include fragranced soaps, bubble bath, laundry detergents, and fabric softeners. Physical examination is often unremarkable, or may reveal mild genital erythema without discharge. In some cases, excoriations caused by vulvar irritation may lead to labial adhesions as the skin heals.

Pruritus due to pinworm infection may also be reported as dysuria. Symptoms tend to be worse at night, when worms emerge from the anus and lay eggs around the anus and vaginal area. Nausea, vomiting, and abdominal pain may develop if there is a large worm burden.

Additional causes of dysuria in the pediatric population worthy of consideration based on the history and physical examination include minor trauma from self-exploratory behavior, masturbation, or sexually activity. A foreign body may cause pain or pruritus that may be reported or misinterpreted as dysuria. Examples include retained toilet paper from poor hygiene, or small objects, such as a bead or toy, in a younger child. Rarer causes include urinary stones, idiopathic hypercalciuria or hyperuricosuria, dysfunctional voiding, and urethral structure.

Systemic conditions as a cause of dysuria are uncommon, but may be potentially serious. The mucocutaneous lesions of Stevens–Johnson syndrome can involve the genitalia. Reactive arthritis presents with arthritis, conjunctivitis, and urethritis, and occurs more commonly in sexually active males. Behçet disease is a multisystem vasculitis that can present with oral and genital ulcers,

as well as ocular, joint, gastrointestinal, skin, and neurologic involvement.

ED EVALUATION

The history is critical in guiding the approach to a child with dysuria. Important points to note include associated GU symptoms such as hematuria, frequency, urgency, hesitancy, incontinence, burning with urination, or vaginal or penile discharge. Systemic symptoms, including the duration and height of fever, joint pain, ocular complaints, or rash, are important to identify. Vomiting, abdominal pain, suprapubic pain, and back pain should also be noted. All adolescents should have a sexual history obtained with the parents outside the room. However, the sexual history may be unreliable in this population, so history alone should not guide management decisions. A previous history of UTI and STI should also be documented. The physician should inquire about any exposures to chemical irritants that may cause dysuria (e.g., perfumes, soaps, bubble bath, laundry detergents, or fabric softeners).

In younger children, consider beginning with auscultation of the heart and lungs before beginning any potentially uncomfortable portions of the examination. Care should be taken to note any oral lesions, which can be seen with systemic illness such as Stevens–Johnson syndrome or Behçet disease. Examine the abdomen for tenderness over the suprapubic region and right, and left lower quadrants, which may suggest cystitis. Tenderness on palpation at the costovertebral angle suggests pyelonephritis. The skin should be examined for rashes.

A GU and perianal examination should be performed to evaluate for discharge, lesions, vesicles, ulcerations, gross anatomical abnormalities (e.g., labial adhesions), or the presence of a foreign body. In males, the scrotum should be examined for swelling, redness, or tenderness to palpation. If the patient is uncircumcised, the foreskin should be examined for signs of inflammation. The female GU examination should be performed in the frog-leg position

on the examination table, or in a less cooperative child, on the parent's lap. The child should lie on her back, bend the knees, place the feet together, and open the legs like a frog with the lateral aspect of knees touching the examination table if possible. Inspection should be performed using labial traction by gently grasping the labia majora and pulling laterally and downward to improve visualization. If better visualization of the vaginal vault is needed, consider the knee-chest position by having the child lie on her face and chest with the buttocks in the air and with the knees bent and 6 to 12 in apart. The underwear should also be inspected for signs of discharge.

In addition to the external GU examination, a bimanual examination should be performed in all sexually active adolescent females to assess for cervical motion tenderness or uterine or adnexal tenderness. In the setting of advanced diagnostic testing for STIs, invasive speculum examinations are not always routinely indicated for dysuria. The speculum examination should be performed in adolescent females with accompanying vaginal bleeding, suspected foreign body, pregnancy, or persistent symptomatic vaginal discharge.

The physician must be able to interpret the results of the urinalysis, initiate antibiotic treatment when appropriate, and ensure follow-up of urine culture results. The need for further diagnostic studies should be guided by the history and physical examination, coupled with the physician's index of suspicion for other entities.

UTI is diagnosed based on the presence of significant bacteriuria and pyuria on an appropriately collected urine specimen. Significant bacteriuria is characterized by any organisms on a suprapubic specimen, at least 50,000 colony-forming units per milliliter (CFUs/mL) in a catheterized specimen, or at least 100,000 CFU/mL in a clean-catch specimen. *Escherichia coli* is the most common pathogen causing UTI. Other common organisms include *Klebsiella, Proteus, Enterobacter, Citrobacter, Staphylococcus saprophyticus, Enterococcus,* and adenovirus. Pending culture confirmation, urinalysis results can aid in making a presumptive diagnosis and

determining the need to begin antibiotic therapy. Significant pyuria is characterized by at least 10 white blood cells (WBCs) per microliter on an enhanced unspun urinalysis, or 5 WBC per high power field on a centrifuged specimen. Dipstick urinalysis has a specificity of 93%. When it is negative for both nitrite and leukocyte esterase, the negative likelihood ratio (LR) for UTI is 0.2; if either is positive, there is a positive LR of 6, and the LR is 28 if both are positive (24).

Distinguishing between an STI and a UTI based on history, physical examination, and urinalysis can occasionally be challenging, given that there is often an overlap in symptoms (25,26). All adolescent patients presenting with dysuria should have a urine pregnancy test and also be tested for STIs by obtaining cervical swabs for culture. Alternatively, the emergency physician can send nucleic acid amplification testing (NAAT) for *N. gonorrhoeae* and *C. trachomatis* from a self- or physician-obtained cervical swab, vaginal swab, or urine specimen. The sensitivity of NAAT testing depends on the collection method; a urine specimen is more sensitive when obtained at the initiation of urination without cleaning the perineum. Testing and treatment for *Trichomonas vaginalis* in both males and females should be strongly considered based on the community prevalence of disease. Patients with ulcerative lesions on examination should have HSV testing and syphilis serology. Counseling and testing for HIV should also be performed, or a referral made, depending on available resources. If discharge is present, vaginal smears should be sent for yeast and bacterial testing, as well as wet mount preparation if available.

The diagnosis of pinworms can be confirmed with the “scotch tape” test, applying tape to the perianal skin and placing the tape on a glass slide where eggs may be visualized on microscopy.

Routine blood work such as a complete blood count, metabolic panel, or blood culture, is rarely indicated.

KEY TESTING

- Urinalysis and urine culture

- STI testing

ED MANAGEMENT

It is important for the emergency physician to address analgesia for children in pain. The family should be instructed to increase fluid intake to help dilute the urine. Consider prescribing pyridium, a bladder analgesic, for children older than 6 years. Management of dysuria is otherwise guided by the suspected etiology. For children being treated for infection, the first antibiotic dose should be administered in the ED to ensure that oral therapy will be tolerated.

If the urinalysis is positive, children should be empirically started on antibiotic therapy and confirmatory cultures sent to further guide management decisions. Hospitalization with IV antibiotics should be considered for young infants and children with clinical signs of dehydration, vomiting (especially if unable to tolerate fluids and medications orally), ill-appearing children with signs of urosepsis, or concerns about patient compliance or follow-up. Community microbial resistance patterns must be considered when making empiric antibiotic choices (see Chapter 288 for antibiotic recommendations).

The physician must establish ways to ensure follow-up of positive STI tests. Patients must also be informed that their sexual partners need to be tested and treated if needed, and that they should abstain from sexual activity until at least 1 week after they and their partners have completed treatment. Expedited partner therapy, which involves providing prescriptions for patients to give to their sexual partners without first examining them, is an option to consider. Inpatient management with intravenous antibiotics should be considered for patients who have already failed outpatient treatment, children with immunodeficiency, those with a tuboovarian abscess identified on ED evaluation, those unable to tolerate oral fluids or medications, or if there is concern for compliance or the ability to follow-up (see Chapter 184 for details on recommended management).

No specific treatment is indicated for vulvovaginitis. Anticipatory guidance is key for parents, which should include instructions on wiping from front to back, wearing cotton underwear, avoiding tight clothing, and avoiding potential irritants. Barrier emollient creams can be used to reduce irritation. Antibiotics should generally be limited to those with bacteria isolated on culture. A presumptive diagnosis of candida vaginitis can be made based on the presence of a "cottage cheese" like discharge on examination, and treated with a single dose of fluconazole 150 mg. Treatment of symptomatic labial adhesions is with topical estrogen cream twice daily until separation occurs, usually within 1 month.

Pinworms can be treated with a single dose of 100 mg of mebendazole or 400 mg of albendazole. A second dose should be repeated in 2 weeks. All household members over 2 years old should be treated. Anticipatory guidance should be given on washing, bedding, and frequent hand washing to prevent reinfection.

CRITICAL INTERVENTIONS

- All pediatric patients with a suspected infectious cause of their dysuria should be assessed for signs of dehydration or sepsis.

DISPOSITION

All neonates with UTI should be admitted to the hospital for IV antibiotics as per febrile neonate guidelines. Admission should also be considered for children who are ill appearing, have signs of dehydration, or cannot tolerate fluids or medications by mouth. Most other patients can be safely discharged home with appropriate instructions that address supportive care at home, recommendations for follow-up, and indications to return urgently for further care.

Common Pitfalls

- Failure to perform a GU examination in child presenting to the ED with dysuria.
- Making testing and treatment decisions for STI based on sexual history alone, which can be unreliable in the adolescent

population.
- Failure to recognize STI in the adolescent presenting with a complaint of dysuria.
- Failure to recommend treatment for partners when treating patients for STI.
- Failure to diagnose UTI.
- Failure to recognize rare but serious systemic illnesses that may present with dysuria.

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CHAPTER 244

Vaginal Bleeding and Discharge in Childhood

Frances Turcotte Benedict, Susan Duffy, and Jonathan H. Valente

CLINICAL PRESENTATION

Vaginal bleeding can present in a wide variety of ways, from scant to copious. Profuse vaginal bleeding in an infant or prepubertal child should raise concern for trauma or abuse, while infants in the first month of life and postpubertal females can have a normal physiologic vaginal discharge called leukorrhea, which is usually clear, odorless, mucous-like, and whitish-yellow. In general, however, any visible vaginal discharge in infants older than 1 month or in prepubertal girls should be considered abnormal.

DIFFERENTIAL DIAGNOSIS

The causes of vaginal bleeding and discharge in children vary depending on patient age (Table 244.1). The withdrawal of maternal estrogen within the first few weeks of life is a common cause of vaginal bleeding or mucus-like bloody spotting in young infants.

TABLE 244.1
Differential Diagnosis for Vaginal Bleeding and Discharge in Infancy and Childhood

Dermatology	Hemangioma
	Lichen sclerosis
	Irritant vulvovaginitis
Endocrine	Neonatal withdrawal bleeding
	Precocious puberty
	Hypothyroidism
	Hyperthyroidism
	Hyperprolactinemia
Infections	Urinary tract infection
	Gonorrhea
	Chlamydia
	Trichomonas
	Group A *Streptococcus*
	Shigella vaginitis
	Candida
Medications	Birth control pills
	Estrogen creams
Neoplasm	Vaginal neoplasm
	Cervical polyp
Trauma	Straddle injury
	Sexual abuse
Other	Urethral prolapse
	Foreign body
	Urate crystals "pink diaper syndrome"

Precocious puberty, the appearance of pubertal development prior to age 8, may present with vaginal bleeding or discharge. Population-based studies have shown that, 27% of African American girls and 7% of White girls showed evidence of secondary sexual characteristics at age 7 (1). In girls less than 3 years of age, rare vaginal tumors such as rhabdomyosarcoma, germ cell tumors, and clear cell adenocarcinoma usually present as vaginal bleeding or spotting (2,3). Urethral prolapse, most commonly found among prepubertal African American females, should also be considered in the differential diagnosis of vaginal bleeding or spotting (4). Exogenous estrogen exposure from birth control pills, creams, and food are other potential cause of vaginal bleeding.

Trauma to the vaginal area or perineum can cause vaginal bleeding, most commonly as a result of straddle injury from falls, bicycle riding, and playing on jungle gyms (5–7). Sexual assault is another potential explanation of vaginal trauma and should be carefully considered if the child is less than 9 months of age and there is evidence of urogenital injury without a history of penetrating trauma, or if there are abnormal genital secretions, and the physical examination findings do not correspond with the history provided (8).

ED EVALUATION

The evaluation should begin with a history that includes questions about urogenital hygiene, trauma, previous history of urinary tract infections, irritation or rashes in the genital region, the presence of estrogen-containing medications in the home, signs of puberty, and any concerns for potential child abuse.

Examination of a prepubertal patient can be performed using two techniques, the frog-leg position or the knee-chest position. Gentle labial traction may need to be used to fully visualize the hymen. In prepubertal children the unestrogenized hymen is delicate and sensitive. To avoid causing pain and bleeding, do not use dry swabs to obtain cultures or specimens. The use of a small feeding tube, medicine dropper, or angiocatheter may be used to irrigate with a few milliliters of saline and then collect specimens at the vaginal introitus. A rectal examination may need to be performed if there is no evidence of blood on inspection of the external genitalia. Most prepubertal and postpubertal nonsexually active females, do not require visualization of the upper vagina and cervix. If there is concern for foreign body or if there is extensive trauma the examination should be completed under general anesthesia. The skin should also be examined for bruising, especially when considering a bleeding disorder or physical abuse.

KEY TESTING

- All menstruating females should have a urine pregnancy test.

ED MANAGEMENT

Reassurance and expectant management is needed for maternal hormonal withdrawal bleeding. For atypical or persistent bleeding with an unclear etiology, examination under anesthesia is recommended (9). If the initial discharge is greenish, bloody, or foul smelling, cultures should be obtained. If cultures are negative, consider Chlamydia testing or formal evaluation for a foreign body (10).

CRITICAL INTERVENTIONS

- Rule out pregnancy in all adolescents who have reached menarche.
- Notify state child protection authorities when there are concerns of child abuse.

DISPOSITION

The majority of patients can be sent home and followed up with their pediatrician. If the cause of their vaginal bleeding or discharge requires them to see a specialist, this follow-up should be arranged prior to discharge. Patients with a large amount of blood loss should be admitted. If there is concern for sexual abuse, the appropriate state child protection authorities should be notified along with a child protection consultant, if available.

Common Pitfalls

- Failure to perform a pregnancy test on children who have reached menarche.
- Failure to consider sexual assault in children with vaginal bleeding and discharge.
- Not arranging follow-up and/or further evaluation since most causes of vaginal bleeding/discharge in children will not be solved in the ED setting.
- Failure to perform a complete genitourinary examination in a child-specific manner.

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PART 4 • PEDIATRIC TRAUMA

CHAPTER 245

General Approach to Pediatric Trauma

Rick C. Place and Thom A. Mayer

Unintentional injury is the leading cause of death in the United States for children aged 1 to 19 years of age. Accidents, homicide, and suicide combined are responsible for over 12,000 deaths a year and are, respectively, the three leading causes of death. In children over the age of 10, motor vehicle crashes (MVCs) are by far the leading cause of death, while under 10, drowning and burns or smoke inhalation figure prominently (1). These figures contrast with the first year of life, during which only 4.4% of deaths are related to unintentional injury. During this same time period, there were over 9 million nonfatal injuries in children under 20 years of age (1).

CLINICAL PRESENTATION

Physiologic and Anatomic Differences

Just as the octogenarian is treated differently than the athletic university student, the approach to an injured infant differs greatly from that of the adolescent. While the transition is gradual, the changes are extraordinary. *Pediatric physiology evolves into more adult physiology during the school-age years, between 7 and 9 years of age.* This chapter focuses on the unique issues of the pediatric patient under the age of 7 and assumes an understanding of adult trauma care (Fig. 245.1) (see Chapter 18).

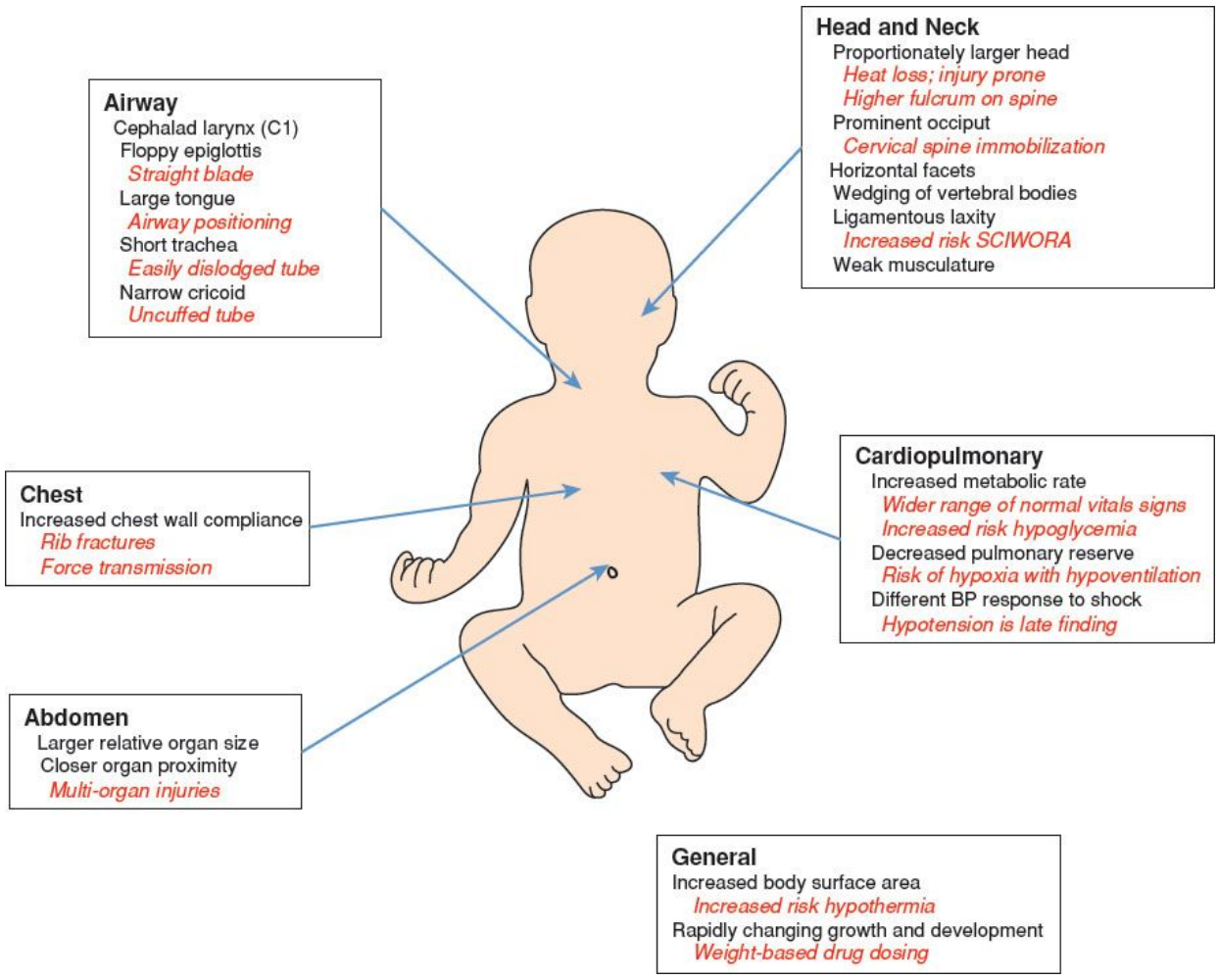

FIGURE 245.1 Pediatric anatomic differences.

One of the most important differences in children is the size of the head relative to the rest of the body. The infant's prominent occiput is comparatively heavy relative to the adult's, comprising 25% of body weight versus 10% in adults. This increased mass, coupled with weaker cervical musculature and hence less overall head control, makes infants and children highly vulnerable to injury. The cranial sutures, open at birth, gradually fuse by 12 to 18 months of age; open bulging fontanels may indicate increased intracranial pressure, but whether this results in meaningful decompression of the injured brain is debatable.

A thin and fragile skull, particularly in the first several months of life, is more liable to fracture with even a minor mechanism. In younger children, particularly those under the age of 2, a boggy

lesion over the site of impact may indicate a cephalohematoma from an underlying skull fracture.

The infant's brain has higher water content, incomplete myelinization, and greater biomechanical vulnerability to impact and shearing injuries relative to adults. This results in a higher rate of diffuse brain injury in children.

Physiologic and anatomic characteristics of the cervical spine, as well as differences in age-related activities, predispose children to different injury patterns. A relatively larger and heavier head results in a fulcrum of flexion at C2/C3, instead of C5/C6 in the fully grown adult. Weaker neck musculature, lax ligaments, anterior wedging of the vertebral bodies, and more-horizontal facets predispose to upper spinal cord injury (SCI). A predominance of upper cervical spine injuries and a greater incidence of SCI without radiographic abnormality (SCIWORA) have been noted in younger children (2,3).

The rate of cervical spine injury in children (approximately 0.7% to 1.6%) is substantially lower than in adults (2.4%). The risk of injury, however, approximately doubles (3.2%) for children involved in MVCs.

The cardiopulmonary response to stress in infants differs from older children and adults. The myocardium is stiffer, less contractile, and less able to generate ventricular wall tension. *The infant heart is therefore more rate dependent, without as much ability to increase stroke volume.* Similar to the heart, pulmonary reserve is more restricted by anatomic structure; minute volume is thus more dependent on rate rather than tidal volume. Children also have reduced functional residual capacity (i.e., oxygen storage) coupled with metabolic demands that are twice those of adults; consequently, desaturation may occur more rapidly and precipitously. *All told, differences in baseline cardiac and respiratory rates, as well as differences in age-related norms, make recognizing compensated shock challenging for providers.*

Certain structural and anatomic differences also place young children at risk for increased morbidity. Their relatively increased body surface area (BSA) increases the risk of hypothermia and leads to necessary modifications of the Rule of Nines chart used for burn

care resuscitation. The less mineralized pediatric rib cage is more likely to bend rather than break, transmitting forces internally without concomitant rib fracture, resulting in higher rates of pulmonary contusion. The pediatric liver and spleen are relatively larger, in closer proximity to one another without surrounding fat and connective tissue, and exist within a less developed, weaker abdominal musculature. This makes these organs, like the lung within the pediatric rib cage, more vulnerable to transmitted blunt forces.

Children's bones are softer and more porous, have increased ligamentous laxity and a greater percentage of unossified cartilage, which improves their ability to absorb blunt metaphyseal impact. However, this leads to a higher rate of epiphyseal injuries in children. While increased laxity serves to protect children from bony cervical spine injury, these same characteristics increase the vulnerability to *cord* injury, demonstrated in its purest form as SCIWORA.

General Approach to the Pediatric Trauma Patient

The fundamental primary survey–secondary survey format of the Advanced Trauma Life Support (ATLS) course remains the most effective and efficient manner of evaluating injured children of all ages.

This structured approach to major trauma is no different from that used in the evaluation of the adult trauma patient, but there are some critical differences. These include (1) the requirement for all team members to agree upon the patient's body weight in order to facilitate error-free weight-based administration of fluids and medications; (2) the need to maintain core body temperature; (3) the need to be especially concerned about the recognition of cervical spine injuries; (4) the need to establish an airway and use appropriate noninvasive ventilation techniques; (5) the need to recognize circulatory stability and shock; (6) the importance of promptly establishing adequate vascular access; and (7) the importance of proper management of pediatric head injury.

PRIMARY SURVEY

Airway and Breathing

The pediatric airway is anatomically immature and different from the airway of older children and adults, particularly in the first 2 years (see Chapter 218). Infants are "belly" breathers, meaning they require full diaphragmatic excursion to produce normal respirations. More-horizontal ribs and a flatter diaphragmatic insertions provide less mechanical advantage. Having said this, most respiratory issues in trauma are related to reduce respiratory effort because of CNS injury rather than respiratory distress from pulmonary pathology.

The highest priority in caring for either adult or pediatric patients with multiple traumatic injuries is ensuring or providing a patent airway with adequate ventilation and oxygenation while protecting the cervical spine. In the severely injured child with an altered level of consciousness and impaired respiratory effort, *the most frequent error is failure to position the airway properly*. In the trauma patient, the jaw thrust is the single most important airway maneuver, pulling the mandible and tongue away from the posterior pharynx. Placing a flattened towel under the shoulders will raise the torso and may help facilitate maneuvers to maintain patency by straightening the airway (Fig. 245.2).

FIGURE 245.2 Pediatric airway. Placing a towel under the shoulders helps better align the airway by raising the torso, optimizing breathing and visualization of the airway.

In pediatric patients with compromised respiratory effort, there is a natural tendency to rush toward endotracheal (ET) intubation, even in the face of suboptimal intubating conditions. This is a common but potentially fatal mistake.

Almost all children can be effectively ventilated by bag-mask ventilation (BMV). As noted above, proper airway positioning is the key to effective BMV. BMV in children is much easier than in adults because of the child's smaller size and more compliant physiology; it is also much easier to generate appropriate tidal volumes and airway pressures. However, it is also easier to produce compromising gastric distention, ventilatory compromise, and unwanted aspiration.

The ubiquitous tendency to overventilate the young child in an emergency situation, both in terms of volume and rate, should be resisted. In the absence of direct pulmonary injury, slow, steady breaths (saying “squeeze . . . release, release”) are all that is required. Furthermore, hyperventilation may be detrimental to the child with traumatic brain injury (TBI), inducing cerebral vasoconstriction and worsening focal or global ischemia.

Indications for emergent intubation of pediatric patients are the same as those for adults: airway obstruction, ineffective respiratory effort or hypoventilation, respiratory distress or hypoxemia, profound neurologic injury (Glasgow Coma Scale [GCS] <8), or altered mental status with combativeness (GCS >8).

A length-based system should be used to select the appropriately sized ETT and intubation equipment. An age-based formula is also commonly used. Choices of induction and paralytic agents are addressed more fully in Chapter 218.

Intubating children in the prehospital environment has been shown to be largely unnecessary and may produce worse outcomes than appropriately performed BMV. The unique anatomy of young children, combined with the rarity of pediatric procedures, results in a situation in which skill development and retention is suboptimal. The rate of unsuccessful intubation and complications is significantly higher than intubation in the emergency department (ED), whereas the benefits remain unproven. The vast majority of pediatric patients can be transported to the ED safely, using BMV or supraglottic devices where BMV is problematic.

In the exceedingly rare instance in which severe orofacial or direct laryngeal injury precludes performing ET intubation, needle cricothyrotomy can be considered. Cricothyrotomy is nearly impossible in infants and young children because the cricothyroid membrane is virtually nonexistent prior to age 4. Because the child can almost always be ventilated by bag-mask techniques, even with severe laryngeal injury, needle cricothyrotomy should be a procedure of last resort. Use of supraglottic airway devices, such as the laryngeal mask airway, may be a viable temporizing measure prior to attempting a surgical airway.

Circulation

Pediatric patients demonstrate more physiologic reserve than adults, and manifestations of hemorrhagic shock may not be obvious for the same degree of blood loss. In addition, persistent hypotension is as likely to be from head injury as uncontrolled hemorrhage, and this should be kept in mind before proceeding with aggressive fluid resuscitation.

As in adults, tachycardia is an early and important response to inadequate tissue perfusion. Infants in particular have a limited ability to increase contractility and must therefore maintain perfusion by increasing heart rate. Unfortunately, as reflected by the wide variation in normal heart rates in Table 245.1, tachycardia is not as specific a sign of blood loss as in adults. Children can greatly accelerate their heart rate from recognized or unrecognized pain, fear, and anxiety, as well as volume loss.

TABLE 245.1
Pediatric Vital Signs

		Infant	1 yr	2 yrs	7 yrs	10 yrs	Adolescent
HR	Upper limit	190	180	160	140	120	100
SBP	Lower limit	70	70 + twice age				90

Shock in children is more likely to present in a compensated fashion, with a normal blood pressure until profound blood loss occurs. A drop in blood pressure is considered more ominous and more likely to represent an advanced state of shock. Once blood pressure has been compromised, meticulous attention and urgent intervention must occur to prevent circulatory collapse.

Clinicians may be at risk of underestimating the presence of shock or the risk of imminent cardiovascular collapse because of a poor sense of what constitutes normal pediatric vital signs. Age-appropriate ranges for pediatric vitals sign should be posted in clear view for *easy* reference in critical circumstances. The formula [70 + (2 times age in years) = systolic blood pressure] for children over the age of 1 is a good

marker to gauge the lower limit of acceptable blood pressure in the trauma setting, where pain and anxiety may increase baseline blood pressures. Any child below this level should be considered hypotensive and in decompensated shock until proven otherwise.

A rapid bolus infusion of 20 cc/kg of crystalloid (normal saline or lactated Ringer solution) should be administered in any child in whom significant blood loss and hemorrhagic shock, compensated or decompensated, are suspected.

The principles of blood replacement in children are similar to those in adults. Once two crystalloid boluses have been administered, blood products should be considered for patients still in hemorrhagic shock or actively bleeding. A single "unit" equivalent of packed red blood cells in the pediatric patient is generally considered to be 10 cc/kg and is expected to raise the hemoglobin 3 gm/dL in the absence of ongoing hemorrhage. In the hemodynamically *stable* pediatric patient who has sustained significant blood loss, no clear consensus exists on what level of blood loss or hemoglobin level mandates transfusion.

There are limits to the reserves of pediatric victims of blunt trauma. Those presenting with severe hypotension (SBP <50) or cardiac arrest have an almost universally dismal outcome, rarely surviving without devastating neurologic disability. The vast majority of these patients die from associated head or SCI, not exsanguinating hemorrhage. The only survivors are likely to be patients without head injury who have a witnessed ED arrest and resuscitation.

Emergency venous access in the young pediatric patient outside specialized pediatric centers is one of the most challenging issues facing the emergency physician. The introduction of intraosseous needles with mechanical insertion devices (e.g., EZ IO™) has dramatically altered the landscape of pediatric venous access. Traditional teaching has been that advanced access methods should be instituted if peripheral access cannot be obtained in three attempts or 90 seconds. However, practically speaking, in the unstable, critically injured child, the patient should be simultaneously prepped for intraosseous insertion as peripheral lines

are attempted. Cannulation of the proximal tibia, distal femur, or humeral head with an intraosseous needle can often be accomplished in seconds. Essentially any pharmacologic agent can be injected through an intraosseous line, including epinephrine, bicarbonate, antibiotics, blood products, phenytoin, and even iodinated computerized tomography (CT) contrast agent (4). Aggressive fluid resuscitation can be optimized by using higher-pressure infusion devices such as pressure bags to maximize flow rates if necessary. In awake and semiconscious patients, pain with infusion can be an issue; after line placement, 0.5 mg/kg of preservative-free lidocaine can be infused to anesthetize the marrow cavity. Pediatric venous access is discussed in detail in Chapter 219.

Neurologic Injury

Providing the "ABCs" is critical not only to the survival but to the functional outcome of the head-injured child. The presence of a significant head injury does not alter the focus on the airway and circulation, but early awareness should heighten the clinician's concern for even brief drops in blood pressure and oxygenation. Hypotension and hypoxia are both critical determinants of neurologic outcome in children with severe TBI.

During the primary survey, the goal is simply to provide an *initial, general* assessment, and the best way to *rapidly* assess overall CNS injury is the patient's level of consciousness. At this stage, the AVPU (Alert, Voice, Pain, Unresponsive) mnemonic is preferred to the Pediatric GCS until there is time for a more in-depth evaluation. By using this brief, simple assessment, the emergency staff can gain a sense of whether significant CNS injury is present.

SECONDARY SURVEY

After the initial survey of the patient's respiratory and circulatory status, the child must be fully undressed for an adequate secondary survey. Although it is important to ensure that the child is undressed rapidly and completely, infants and small children are especially vulnerable to hypothermia, an issue that is easily overlooked in a

busy resuscitation. Temperature is the forgotten vital sign in a critical resuscitation and it should be monitored closely.

Although the purpose is to identify additional injuries that are not immediately life-threatening, one must not neglect closer reassessment of the cardiorespiratory system during the secondary survey. The systematic examination is essentially the same as one would perform in an adult trauma patient, except that some findings may be more subtle in young or frightened children. Two factors may result in deviation from a systematic approach to the secondary survey: (1) a dramatic injury or (2) a frightened, difficult to calm child. Awareness of these issues will prevent injuries from being missed in an otherwise disciplined, systematic, head-to-toe examination.

Head and Brain

The relatively low mortality rate for pediatric blunt trauma rises exponentially in the presence of TBI. TBI is one of the leading causes of traumatic deaths in children, with more than 5,500 deaths per year in the United States. Almost 500,000 ED pediatric visits for head trauma take place every year.

The principles of diagnosis and management of severe TBI (defined as GCS ≤ 8) are similar in children and adults. Diagnosis can usually be made on clinical grounds and management dictated by findings on diagnostic imaging (i.e., CT). The primary injury occurs at the time of impact and is unalterable. However, secondary injury takes place over the ensuing hours to days and is amenable to therapy. Prehospital, ED, and intensive care management of secondary injury may have a profound effect on outcome.

Initially, the major focus should center on prevention of secondary injury from concurrent hypoxia, hypercarbia, and hypotension. Even a relatively brief decrease in cerebral perfusion pressure results in cerebral ischemia and worsened outcomes (5). Ischemic injury is the primary insult in the first 6 to 12 hours, *after which* a second phase of hyperemia and increase in intracranial pressure become increasingly critical. Meticulous attention to blood pressure and oxygenation status is critical in optimizing the outcome in patients with serious

neurologic injury. Hypoxia (oxygen saturation $<90\%$), either from hypoventilation or concomitant pulmonary injury, is associated with increased mortality and must be corrected immediately. Blood pressure should be maintained with normal saline if possible and with vasopressors if necessary. Both the number and duration of hypotensive episodes prior to stabilization have been linked to significant increases in mortality.

Hyperosmolar agents and hyperventilation are the two mainstays of the management of acute brain herniation. Mannitol (0.25 to 1 mg/kg) has been the traditional hyperosmolar agent of choice and has long been used for the management of severe increased intracranial pressure with surprisingly little evidentiary support (5). More recent pediatric studies and the current recommendations of the Brain Trauma Foundation suggest that *the use of hypertonic 3% saline may be superior to mannitol* (5). Acute dosing recommendations for hypertonic 3% saline range from 6.5 to10 cc/kg.

Hyperventilation, which is very common albeit inadvertent in the pediatric resuscitation, reduces $PaCO_2$, inducing vasoconstriction, decreased cerebral blood flow, and decreased intracranial pressure, at the price of decreased brain oxygenation and induced ischemia. Hyperventilation in the setting of severe TBI continues to be used despite a lack of evidence supporting this practice (6). If used acutely as a temporizing measure to control severe increases in ICP and to prevent or limit acute herniation, the $PaCO_2$ should not be driven down below 30 mm Hg and should ideally be kept in the range of 32 to 35 mm Hg. Even a single episode of severe hypocarbia has been shown to produce an increase in mortality (6).

Cervical Spine and Cerebrovascular Injury

A bimodal distribution of cervical spine injury has been noted, with peaks between the ages of 2 to 4 years and 13 to 15 years. Motor vehicle–related injuries (automobile crashes and pedestrian-struck) are responsible for about half of pediatric cervical spine injuries (2). Athletic misadventures cause between one-quarter and one-half of cervical spine injuries and predominantly affect adolescent boys. Not

surprisingly, American football followed by diving are the highest risk activities.

The majority of cervical spine injuries in children under age 8 occur between the occiput and C3 (2). Injury patterns in older children tend to resemble those of adults, with a more equal distribution across all levels. However, even in younger children, fractures of the lower cervical spine (C4 to C7) are possible, and care must be taken to visualize the entire cervical spine when imaging is done. As many as 7% of children with spine injuries are found to have noncontiguous lesions (i.e., at more than one level), reinforcing the recommendation to image the entire spine when a fracture is identified. In addition to fractures, other injuries relatively unique to young children include atlanto-occipital dissociation, atlanto-axial rotary subluxation, and vertebral endplate fractures.

Even in young children with injury to the osseous structures of the cervical spine, traumatic myelopathy (spinal cord injury), is uncommon. Beyond early childhood, thoracic and lumbar SCI is nearly as frequent as traumatic cervical myelopathy. When SCI is diagnosed, the administration of methylprednisolone is expressly discouraged in the most recent guidelines of the American Association of Neurological Surgeons (7). A solid scientific foundation for this practice has never been established in children and recent data strongly suggests that harm outweighs any theoretical benefits of this practice.

SCIWORA, originally described by Pang in 1982, refers to the presence of SCI in the absence of fracture noted on conventional radiography (plain radiography and CT imaging). Ligamentous laxity of the pediatric spine allows for excessive movement and recoil of the spinal column without fracture. SCIWORA can occur at any level but is more common in the thoracic and cervical spine. Most studies report that younger children are more likely to manifest SCIWORA than older children, and when they do, it is likely to be more rostral and more severe. SCIWORA is a well-recognized phenomenon, but it is quite rare, found in less than 15% of pediatric patients with traumatic myelopathy. Neurologic signs or symptoms without a clear

explanation on conventional imaging should be further investigated with magnetic resonance neuroimaging (MRI).

Blunt carotid and vertebral cerebrovascular injuries do occur in children, and risk factors mimic those in adults (8). Vertebral artery injuries occur almost exclusively with cervical spine injuries, particularly C1 through C3. Carotid injuries, resulting from severe cervical hyperextension or rotation, are more strongly associated with major thoracic trauma. Other, lesser risk factors include basilar skull fracture and unexplained neurologic deficit or unexplained GCS <8 (i.e., normal head CT) (8).

When cerebrovascular injury is present, subsequent stroke risk is high and the window of opportunity that exists *before* neurologic signs and symptoms ensue should not be ignored. While the incidence in pediatric blunt trauma may be under 1%, the use of recognized risk factors may produce a yield above 20% (8). Any patient undergoing a thoracic CT scan or found to have a cervical spine fracture should be strongly considered for cerebrovascular CT angiography.

Thoracic Trauma

Severe chest trauma is second only to TBI as a cause of death in pediatric trauma patients. About 10% of children with blunt torso trauma are ultimately diagnosed with a thoracic injury, about half of whom have more than one finding (9). Major chest trauma is a marker for severe blunt force impact, and the presence of chest trauma in the setting of polytrauma is associated with a 20-fold increase in mortality. Severe thoracic trauma is also associated with other major injuries such as cerebrovascular, head, and cervical spine injury.

Abnormalities on the chest examination are reasonably sensitive for thoracic injury. However, increased chest wall compliance means that significant internal injury may exist in the absence of visible external injury (9). The majority of internal thoracic injuries in children are not accompanied by rib fracture. When present, fractures of more than one rib is associated with a significantly greater mortality rate (42% vs. 18%).

Predictors that have been associated with intrathoracic injury include (1) hypotension, (2) abnormal chest examination or chest auscultation, (3) altered mental status, and (4) femur fracture (9).

Hemothorax, pneumothorax, pulmonary contusion, and rib fractures are the most commonly encountered pediatric chest injuries (9). Fortunately, other more life-threatening tracheobronchial, esophageal, cardiac, and thoracic vascular injuries are extremely uncommon (10).

Pneumothorax is more common with major chest trauma in children than in adults and is associated with a significant increase in mortality. Other concurrent intra- or extrathoracic injuries are frequently present and should be sought after. While the presence of pneumomediastinum heightens concern for other major intrathoracic injuries, it generally has little clinical significance. Both simple pneumothorax and hemothorax can generally be managed with an appropriately sized tube thoracostomy.

Vascular injuries are the most lethal thoracic injuries but fortunately are exceedingly rare in children (10). Traumatic aortic injury is less common in children than adults and is more often discovered in ambulatory or bicycling children who are struck by a moving vehicle.

Cardiac contusion in blunt pediatric trauma is diagnosed by a combination of elevated cardiac enzymes, the presence of arrhythmias (usually noted in the ED) and depressed cardiac output on echocardiogram. As in adults, blunt cardiac injury occurs in the context of multisystem trauma, and isolated cardiac injury is rare.

Abdomen

After the head, the abdomen is the most commonly injured body area from MVCs. Of those who are restrained by seatbelts, children in the age range of 4 to 8 years who transition too early from child to adult belts are the most likely to be injured. The proper restraint is a booster seat, which provides optimal placement of the seat belt and allows the belt to sit on the pelvis. The pelvis is able to withstand greater force without injury than the viscera of the mid-abdomen.

The most valuable part of the pediatric abdominal examination is palpation. Verbal children should be asked if and where they hurt and the examination is then begun away from that site. Younger children are frequently frightened, and verbal responses to leading questions regarding either the presence or absence of pain should be interpreted cautiously; unsolicited complaints of pain should be taken very seriously. Serial examination of the abdomen may be necessary for accurate assessment and may reveal significant findings that were missed on the initial examination.

The significance of a seat belt sign or other visible evidence of abdominal trauma has been questioned. A recent study of 1,963 children with blunt torso trauma and visible evidence of abdominal trauma highlights the importance of this finding: 112 (5.7%) required active medical or surgical intervention (11). In the context of a seat belt sign, the presence of free fluid on abdominal CT predicts operative intervention (12). Chance fractures of the lumbar spine, less commonly seen with the near-universal use of three-point seat belts, can still occasionally be seen in inappropriately restrained children and may be associated with hollow viscous injury.

Each intra-abdominal organ has a unique anatomy and physiology that necessitates a particular approach. Solid organ injuries of the liver, spleen, or kidney in children have been managed nonoperatively since the 1980s with a success rate of over 90%, regardless of age (see Chapter 251).

Pelvic Fractures

Pediatric pelvic fractures are uncommon and are the result of high impact injuries, most notably pedestrians struck by vehicle and MVCs. Skeletal immaturity (prior to age 14 in boys and age 12 in girls) is protective and leads to less severe fracture patterns that are amenable to more conservative management. Severe pelvic hemorrhage and the need for blood transfusion is less common in children than adults, and any increase in mortality is almost exclusively related to concomitant injuries.

Torode and Zieg grade 4 injuries (unstable ring fractures usually involving the posterior elements) are very rare, but recent work

suggests that more aggressive surgical management results in improved outcomes. While bony injuries are often very forgiving in children, the pelvis does not undergo significant remodeling once union occurs, emphasizing the importance of establishing anatomic reduction and joint congruity. Pelvic asymmetry and leg-length discrepancy (from premature sacroiliac epiphyseal closure), scoliosis, chronic low back and sacroiliac pain, and hip dysplasia are all long-term complications of suboptimal management.

Injuries with Delayed Diagnosis

The rate of missed injuries in pediatric trauma patients has been reported to range from 1% to 19% but probably lies at the lower end of this range. Children with a delayed diagnosis are more likely to initially present with altered mental status, require emergent intubation, and have higher severity scores and more identified injuries. However, as many as 50% of delayed diagnoses do occur in patients with a low ISS score (<4) and an initial diagnosis of a single injury.

Fractures comprise the majority of delayed diagnoses, and most missed injuries are of relatively low consequence. However, delayed diagnosis of intra-abdominal injuries can result in significant morbidity. Gastrointestinal injuries are, not surprisingly, the most commonly missed intra-abdominal injury; thus, vigilance for these injuries must be maintained (11,13).

Pain Management

Effective pain management is a particular problem in young patients. This is probably due to a combination of inadequate experience in managing significant pain in pediatric patients, fear of overdosing young infants and children, and failure to fully appreciate the extent of anxiety and discomfort in younger patients. Nonverbal children are especially difficult to assess, both in terms of their degree of pain and in their response to analgesia. The inability to fully recognize pain in young children offers a subconscious excuse to undertreat these patients.

One additional barrier to effective pain management is the difficulty or discomfort of placing an intravenous line, particularly if it is solely for narcotic administration. A recent and effective solution to this problem is the administration of intranasal fentanyl. Typical doses are 1.5 to 2 μg/kg, with a maximum of 100 μg due to volume constraints. Nitrous oxide can also provide relief and can be used early on, prior to placement of an intravenous line.

Parental Presence and Family-Centered Care

Many medical providers, particularly those who provide pediatric care on a less regular basis, would prefer that parents *not* be present during a major resuscitation, either because of concerns regarding family interference, perceived psychological distress to the family, or increased stress on providers. Parents, however, would clearly like the option to choose whether to be present or not, and this choice is supported by American Academy of Pediatrics policy. Recent evidence supporting this policy demonstrates that family presence does not negatively affect the efficiency of pediatric trauma or medical resuscitation (see Chapter 293).

ED EVALUATION

Laboratory Studies

Laboratory studies should be ordered on patients in shock, with an altered level of consciousness, or with evidence of multisystem injury. At a minimum, these should include immediate bedside glucose testing, hemoglobin, electrolyte panel, and type and screen or crossmatch. This can be achieved with a single iSTAT analysis and type and hold.

Additional studies may be indicated depending on the clinical scenario and local institutional approach. Aspartate transaminase (AST) and/or alanine transaminase (ALT) are incorporated into diagnostic imaging protocols at some institutions (13,14). Although liver enzymes may not be a routine part of the trauma evaluation in all centers, they are felt to be useful in identifying the presence of occult intra-abdominal injury when the abdominal examination is

equivocal, for example, in patients with altered mental status or head injury, in toddlers and young children, and in infants in whom nonaccidental trauma is suspected (11). Coagulation studies should be ordered in patients with severe TBI, where the incidence of coagulopathy may be as high as 40%. Urine pregnancy testing should be routinely performed in adolescent girls over the age of 12.

Urinalysis should be examined for gross hematuria when available (13). Many pediatric studies suggest using a low threshold of microscopic hematuria as a driver for further imaging. However, isolated microscopic hematuria in the absence of another indication for abdominal imaging is not strongly associated with abnormal findings on CT (13). Interestingly, the presence of hematuria is less suggestive of genitourinary injury than to other intra-abdominal organs.

DIAGNOSTIC IMAGING

CT and Radiation Risk

The value of CT to diagnose traumatic injury in adults is well established. However, growing children are more susceptible to the effects of ionizing radiation than adults and have a longer period of time to develop a malignancy after exposure. It is estimated that the lifetime risk of developing cancer from an abdominal or head CT performed before the age of 10 is between 1 in 1,000 and 1 in 1,500. Therefore, thoughtful risk assessment should be employed to decide which children, if any, need CT imaging.

A cranial CT results in an average exposure of about 2 mSv, more than 100 times that of a plain chest x-ray (0.02 mSv) (Fig. 245.3). For comparison, a neck CT exposes the patient to 2 to 3 mSv, a chest CT 3 to 7 mSv, a CT of the abdomen and pelvis up to 14 mSv, and a “pan-scan” 21 mSv. In one study, the mean radiation exposure for admitted pediatric trauma patients was 17.9 mSv and 18.4 mSv for those who were discharged (15). These doses fall well within the range associated with an increased risk for leukemia, thyroid, and solid cancers.

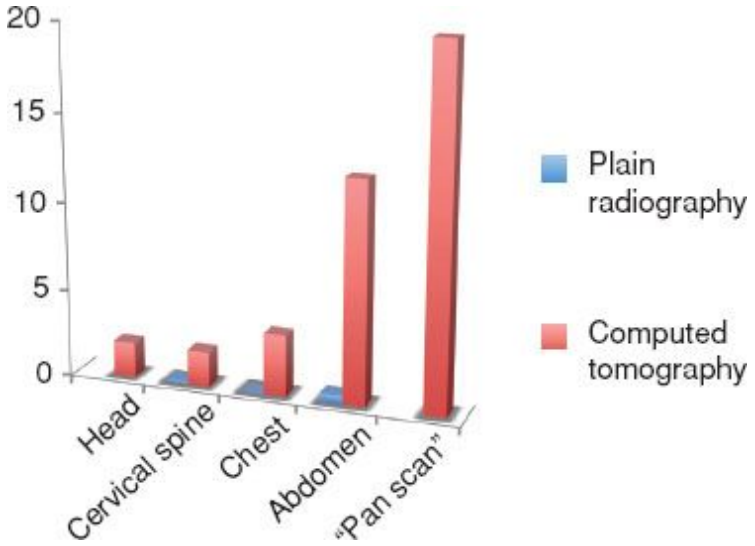

FIGURE 245.3 Ionizing radiation exposure by diagnostic study (mSv).

In adults, CT is routinely obtained to look for blunt aortic injury and cervical spine fracture, and its utility is well documented. The diagnostic yield for CT scanning is lower in children and its utility relative to plain radiography has not been convincingly demonstrated (15–18). Yet radiation exposure in pediatric trauma has become more indiscriminate, with a high percentage of scans being done in patients with relatively low acuity (ISS 6) and few positive findings (19%) (11,16). A composite of pediatric decision rules to determine the need for imaging is shown in Table 245.2.

TABLE 245.2
Risk Factors for Identifying Injury

Head

Altered mental status (*determined by parent*)

GCS ≤ 14 (*determined by MD*)

Palpable skull fracture

Vomiting

Loss of consciousness (*not transient*)

Severe headache

Cervical Spine

Altered mental status

Focal neurologic findings

Neck pain

Restricted range of motion

Major thoracic trauma

Cerebrovascular

Cervical spine fracture (vertebral)

Basilar skull fracture

Major thoracic trauma (carotid)

Neurologic deficit: Unexplained or GCS <8

Chest

Abnormal auscultation

Low blood pressure

Tachypnea

Altered mental status

Visible external injury

Abdominal

Seat belt sign

Abdominal pain/tenderness

Significant thoracic trauma

Femur fracture

Unexplained hypotension

Altered mental status

Head Injury

That children with obvious neurologic findings or unequivocally altered mental status after head trauma need an immediate head CT is not controversial. A major dilemma in pediatric emergency medicine, however, is the approach to diagnostic imaging of the child with minor head trauma and normal or near-normal mental status (i.e., GCS 13–15) (Table 245.2). This issue is particularly challenging in preverbal children (see Chapter 246, Major Head Injury; and Chapter 247, Minor Head Injury).

It should be remembered that head injury decision rules generally do not identify which children *require* CT imaging. Rather, they identify a low-risk population that *does not require* neuroimaging. The PECARN rule splits the non-low-risk population into those who require a CT and those who can be managed alternatively with clinical observation. Clinical judgment is still necessary to prevent unnecessary imaging.

Cervical Spine Injury

Cervical spine injury in children is distinctly uncommon and is noted in less than 1% of blunt trauma patients, compared with 2.4% of adult blunt trauma patients. Because the numbers of young children in major validation studies are low, guidelines such as NEXUS, and the Canadian Cervical Spine rules cannot be comfortably applied to young children. Most pediatric decision rules are derived from case series.

There are no clear pediatric guidelines for clinical clearance of the pediatric cervical spine. For this reason, imaging of pediatric trauma patients tends to be quite liberal, particularly in nonpediatric centers (16). In a study of radiation exposure in pediatric trauma, of patients getting at least one CT scan, 97% of patients had a head CT (of which 24% were positive) and 62% had a neck CT (of which only 3% were positive) (16). The extent of imaging found in many studies probably reflects the widespread belief, especially outside of pediatric trauma centers, that young children are difficult if not impossible to clear clinically (17). Recent work has begun to firmly establish that cervical spine imaging is not necessary in all patients, and that physicians can identify low-risk pediatric populations that can be cleared clinically (19).

Findings associated with a risk of intracranial injury include (1) altered mental status, (2) focal neurologic findings, (3) neck pain, (4) restricted range of motion, (5) thoracic trauma, and (6) mechanism predisposing to cervical spine injury such as diving or high-risk MVC (19).

The results of these studies *do not* imply that all children who fail to fall into the “low-risk” group require diagnostic imaging. Patients who do not fall into these low-risk parameters require heightened diagnostic judgment, not an automatic default to the radiology department.

Even though adult practice has steadily moved toward CT as the imaging study of choice, such a consensus does not exist in the pediatric literature. Evidence of equal benefit is lacking, and plain radiography appears to be more sensitive in children. The Canadian

Consensus and other guidelines suggest that there is still a primary role for plain radiography as the initial assessment tool in children (3,17). CT should be reserved for situations in which there is diagnostic uncertainty for clinical or radiographic reasons. Pediatric patients with an "unreliable" clinical examination should be treated cautiously and conservatively, but the simple fact that young children are preverbal does not automatically categorize their examination as "unreliable" (17) (see Chapter 249).

Thoracic Trauma

Chest radiography is a sensitive screening test for significant intrathoracic injury in children, particularly for those that require immediate surgical intervention (20). Other studies have noted that as many as one-third of thoracic injuries identified on CT are missed on plain chest film, the vast majority being pulmonary contusions, small pneumothoraces, and nondisplaced rib fractures (9,10,18). With the increase in "pan-scanning," the use of routine chest CT in children, with or without preceding chest x-ray, has greatly increased, without an apparent increase in detection of significant pathology. One study of 353 pediatric patients who had chest CT as part of their evaluation found no life-threatening injuries that were not suggested by plain chest x-ray, even as the use of chest CT doubled during the study period (20).

While CT has clearly been shown to be more sensitive than supine chest x-ray in identifying thoracic injuries, the clinical significance of those additional discoveries is questionable and management is rarely altered (10,18,20). Furthermore, evidence suggests that the great majority of significant intrathoracic injuries are located in the lower thoracic cavity and can actually be identified on abdominopelvic CT (9,10).

Plain chest films therefore remain the imaging study of first choice in pediatric chest trauma. CT should be reserved for patients with an abnormal chest x-ray or in whom major or potential life-threatening injuries (e.g., vascular, esophageal, or bronchopleural) are suspected, or for further assessment of major bony injury such as vertebral or sternal fractures (10).

Abdominal Trauma

Abdominal CT has become the near-gold standard for the identification of intra-abdominal injury. However, identifying which child needs intra-abdominal imaging remains a challenge. As few as 10% of CT scans performed for blunt abdominal trauma are diagnostic of injury (13). In an attempt to limit the number of unnecessary CT scans of the abdomen and pelvis, a number of decision rules (as opposed to guidelines) have been created over the past decade (13,14). These rules rely on combinations of physical examination findings and laboratory studies. While published pediatric algorithms provide some guidance as to what constitutes a low-risk group, the specificity and positive predictive value of these prediction rules is poor and if strictly applied, they would result in overimaging. In contrast to the application of cervical spine guidelines, there is a much greater need to combine clinical judgment with currently available evidence (13).

A recursive partitioning analysis of 1,095 pediatric trauma patients with blunt torso trauma, with a 10% rate of intra-abdominal injury, found three physical findings that were associated with intra-abdominal injury—hypotension, abdominal tenderness, and femur fracture. There were three laboratory findings as well—
elevated liver transaminases, microscopic hematuria (>5 RBC/hpf), and low hematocrit. More recently, a larger multi-center study of more than 12,000 pediatric victims of blunt torso trauma which looked only at historical and physical examination variables found that the most important predictors of intra-abdominal injury were, in decreasing order of importance, physical evidence of trauma to the abdomen, altered mental status (GCS ≤ 13), abdominal tenderness, physical evidence of trauma to the thoracic wall, complaint of abdominal pain, decreased breath sounds, and vomiting (11).

For clinicians relying primarily on clinical findings for decision making, the presence of visible abdominal trauma, abdominal tenderness, the presence of unexplained hypotension, and a low GCS (i.e., unreliable examination) are most highly associated with the need for intervention (11,13,14). Thoracic trauma and femur fracture

both serve as markers for major impact force and should prompt strong consideration of abdominal imaging.

The abdominal CT occasionally demonstrates the presence of free fluid in the absence of identifiable organ injury. A*ny* free fluid is suspicious for injury, but its mere presence does not mandate laparotomy and should be addressed with serial abdominal examinations (12). The amount of free fluid is clearly associated with the risk of intestinal injury; a significant probability of intestinal injury is found with large amounts of free fluid, whereas smaller amounts are more likely secondary to mesenteric and other injuries.

The decision to take a child to the operating room is largely a clinical one, based on physiologic parameters, either at presentation or over the ensuing period of observation. Patients taken to the operating room based solely on CT findings have a significantly lower rate of therapeutic laparotomy than patients taken for clinical reasons.

Pelvic and Extremity Trauma

The need for routine conventional pelvic radiographs is limited. Pediatric patients experience less than half the proportion of pelvic fractures of adults with similar mechanisms of injury. However, children with pelvic fractures have the same incidence of intra-abdominal injury as adults (around 15%), and thus serious consideration of abdominal CT imaging is warranted. Fortunately, the incidence of life-threatening bleeding from these fractures appears to be low in the pediatric population. It should be noted that, compared with CT imaging, conventional radiography is less sensitive than in adults, only 54% sensitive in one study.

Ultrasound FAST Examination

In experienced hands, the Focused Assessment of Sonography in Trauma (FAST) examination can be very helpful in identifying unstable trauma patients who need immediate operative intervention. It can be performed rapidly and without delay in the

resuscitation bay while other life-saving interventions are simultaneously taking place.

An important limitation of the FAST examination in pediatric patients with blunt abdominal trauma is that, compared with CT scanning, it may not be sensitive enough to identify all clinically significant hemoperitoneum (21). FAST examination is even less sensitive for identifying intra-abdominal organ injury when there is little or no associated free fluid (21). Therefore, unless unstable, patients in whom there is clinical concern for intra-abdominal injury should advance to CT imaging regardless of FAST scan results. Furthermore, while the presence of free fluid on FAST examination is very suspicious for injury, it is not an unequivocal indication for operative intervention; most pediatric patients with intra-abdominal injury will be managed medically (21).

In summary, the FAST examination is most useful in identifying which *unstable* pediatric trauma patient should receive immediate operative intervention. A negative FAST examination should not be relied upon for decision making in stable patients and CT remains the imaging modality of choice.

Disposition

In many areas of the country, pediatric victims of serious traumatic injury are preferentially directed toward established trauma centers with expertise in pediatric patients or to pediatric trauma centers. These centers provide evidenced-based care based on the latest protocols and guidelines. Trauma care is a team effort and in most centers it is a collaborative effort between emergency medicine (or pediatric emergency medicine) and trauma surgery.

Activation of the trauma team is dependent upon triage protocols that are designed to provide timely, optimal care to seriously injured patients without delivering expensive, inefficient care to those who do not need it.

The use of anatomic and physiologic criteria seems to be significantly more effective than traditional consideration of mechanism of injury for identifying the need for high resource utilization (22). Such an approach maintains similar sensitivity for

identifying traumatic injuries while reducing overactivation of strained resources.

The American College of Surgeons has mandated six triage criteria (ACS-6) for the highest level of activation for both adult and pediatric trauma centers:

- age-specific hypotension
- respiratory compromise
- provision of blood prior to transfer from another hospital
- gunshot wound to chest, abdomen, or neck
- GCS <8 or reduction of GCS by two or more from initial assessment

While these are adult criteria, they have been shown to be reasonably effective in triaging pediatric trauma patients. The addition of age-defined tachycardia and findings that indicate poor perfusion, and the need for prehospital fluid resuscitation with greater than 40 cc/kg crystalloid, improves the sensitivity of these criteria in children, with only a modest decrease in specificity.

Dedicated pediatric trauma centers, and adult trauma centers with added qualifications in pediatric trauma care, have increasingly been recognized to provide care that is superior to that available at adult level 1 or level 2 trauma centers or at general EDs. Mortality differences are difficult to demonstrate because of the low rate of traumatic death in children, but a focus on morbidity as revealed through "processes of care" have revealed stark differences (23). Adult surgeons managing trauma in the community setting are significantly more likely to intervene operatively than pediatric surgeons at a pediatric specialty center. These concerns go beyond just the potentially limited pediatric skills of the immediate providers but address the breadth of the support services for the critically injured pediatric patient: surgery, anesthesia, orthopedics, and especially pediatric intensive care services (23).

Ideally, this would mean that pediatric trauma patients are guided toward centers with the greatest pediatric expertise, balanced by the extent and threat of the injury, risk, inconvenience, distance from the specialized center, and resource expenditure. That having been said, access to trauma centers is not universal, particularly in the first

hours. The great majority of pediatric patients continue to be evaluated and treated, at least in the initial phase of their illness, at nonspecialized, general EDs. Children with major traumatic injuries should be transferred to a designated pediatric trauma center, or adult trauma center with pediatric expertise, where such designated regional referral centers exist. Ideally, established written protocols for interfacility should exist prior to transfer. Such an agreement would define reciprocal responsibilities, process for selecting the most appropriate transport service, and clinical indications for transfer.

Common Pitfalls

- Failure to appreciate age-related norms and the recognition of compensated shock in children.
- Failure to avoid even brief periods of hypotension or hypoxia in children with severe TBI.
- Failure to provide appropriate analgesia to the distressed child.
- Lack of familiarity with pediatric-specific criteria for the management of pediatric trauma patients.
- Overreliance on CT imaging in the assessment of pediatric trauma patients.

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CHAPTER 246

Severe Head Trauma and Traumatic Brain Injury in Children

Josh Easter and Rick Place

Traumatic brain injury (TBI) is a leading cause of death and disability in the pediatric population. Roughly 60,000 children aged 0 to 19 years are hospitalized every year for TBI. Of these, about 10%, or 6,000, die of their injuries; well over half of them are older teenagers (11).

In very young children, injury is primarily due to falls. In adolescents TBI is the result of falls, motor vehicle accidents, and impact by an object such as a motor vehicle (11). Such age-related differences have significant implications in terms of specific injury patterns and prognosis.

Rapid identification and aggressive management of children with severe TBI (sTBI) improves outcomes (3). A retrospective review of pediatric deaths following TBI classified nearly one-third as potentially preventable with early intervention (32).

CLINICAL PRESENTATION

The infant's brain differs from its mature counterpart in that the higher water content and incomplete myelinization make the young child more vulnerable to diffuse brain injury. The child's head is relatively larger and heavier in proportion to the body, creating a higher fulcrum of rotation in the neck, which explains the greater propensity for high cervical spine injuries. The calvarium is more

fragile in very young infants and more likely to fracture with minor impacts. While sutures may remain open until about 18 months of age, it is unclear whether they are effective in dissipating the force of an impact or in providing room for expansion in case of increased intracranial pressure.

The possibility of intracranial bleeding should be considered in any child with a significant head injury. The skull in young children is relatively flexible, and intracranial hemorrhage may be present in the absence of skull fracture (18,20).

Epidural Hemorrhage

Epidural hematomas are uncommon in infancy, as the dura is still firmly attached to the skull. In toddlers and older children, skull fractures arising from direct blows may lacerate meningeal arteries, the great majority of which are temporal/temporoparietal in location (20). Epidural hematoma may be venous in origin, however, arising from rotational injuries that damage sinus emissary veins. The mechanism may frequently be relatively minor; falls from less than 5 ft are the most common cause of epidural bleeds in young children and infants (34).

The classic presentation is a brief loss of consciousness followed by a lucid interval and then rapid deterioration as arterial blood accumulates to create a mass effect. The presentation varies and some children may have a relatively normal neurologic examination at the time of presentation (20). However, most exhibit headache, vomiting, or lethargy.

Epidural hematomas appear as lentiform (biconvex) hyperdensities on CT imaging, displacing the brain away from the skull (Fig. 246.1). As the dura usually remains firmly attached to the sutures, the hematoma generally does not cross suture lines (18). Areas of mixed hyperdensity and hypodensity, known as the “swirl sign,” suggest active bleeding at the time of the scan and typically requires immediate neurosurgical evacuation.

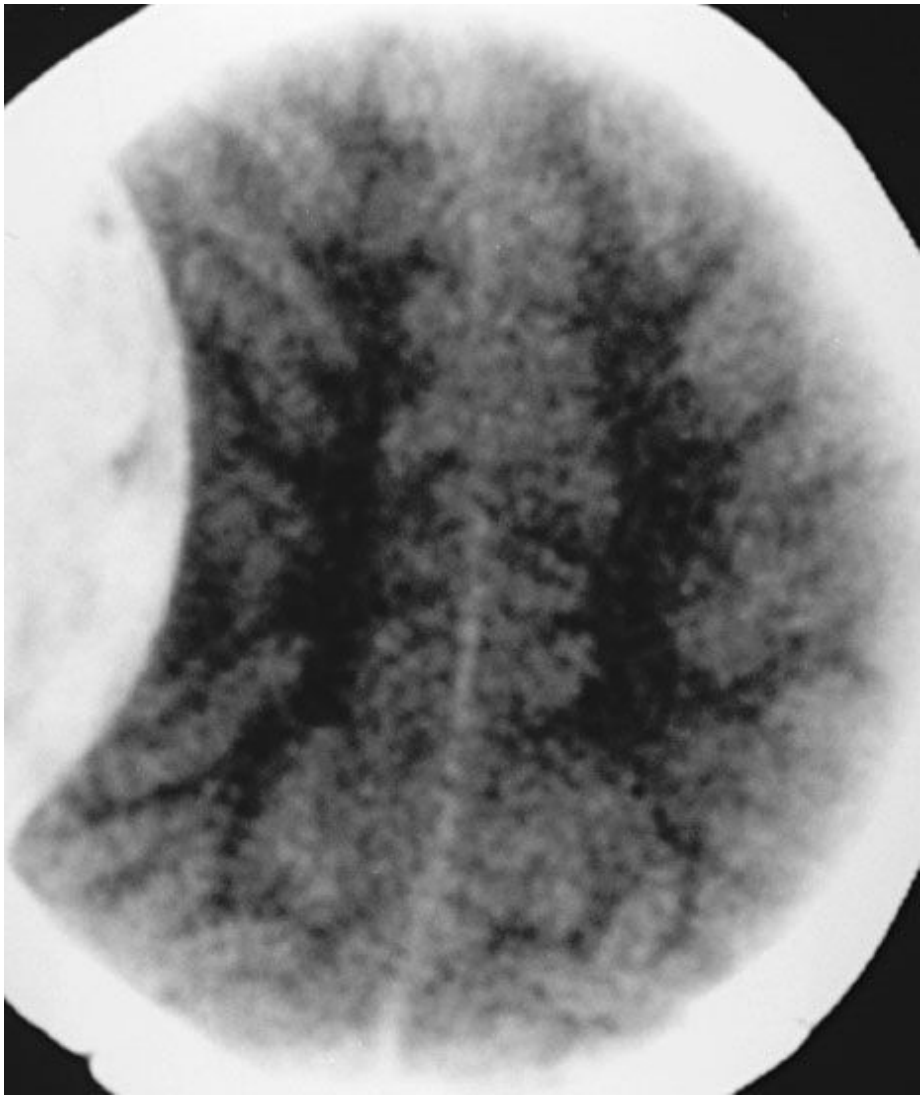

FIGURE 246.1 Epidural hematoma. This 8-year-old boy presented after a sledding accident. He had no loss of consciousness but complained of headache and vomiting. A head computed tomography scan shows the classic biconvex hyperdensity of an epidural hematoma. He proceeded to the operating room, where a large mass of clotted blood was removed.

The vast majority of children with epidural hematomas require operative intervention; neurosurgical consultation should be obtained emergently, regardless of the current mental status (20,34). Although conservative management has been advocated for patients with a small epidural hematoma (e.g., <1 cm) and a GCS of 15, the

majority of these patients ultimately proceed to surgery (20). Delay of neurosurgical intervention is the only factor that has been associated with increased mortality; even patients with a dilated ("blown") pupil are likely to survive and do well if operated on within 90 minutes. Outcomes are generally good and are largely dependent upon condition at presentation; children who have an initial normal neurologic examination uniformly do well (20).

Subdural Hemorrhage

Subdural hemorrhage is generally caused by an impact that produces severe acceleration/deceleration or rotational forces. Blood accumulates because of tearing of the bridging veins between the dura and the arachnoid membrane (Table 246.1). Injuries to cerebral cortical arterioles can also lead to arterial hemorrhage into the subdural space. Acute subdural hemorrhages (less than 72 hours old) commonly appear as homogenous, hyperdense, concave or crescent-shaped lesions on CT imaging. Unlike epidural bleeds, subdural hematomas are not limited by dural suture attachments and may cross sutures lines.

TABLE 246.1
Intracranial Lesions in Children

	Epidural Hemorrhage	Subdural Hemorrhage
Pathophysiology	middle meningeal artery injury	Bridging vein injury
Mechanism	Falls, MVCs	Nonaccidental trauma, MVCs
Presentation	Early	Late
Diagnosis (CT)	Biconvex hyperdensity, does not cross suture lines	Concave hyperdensity, crosses suture lines
Management	Medical > Surgery	Medical > Surgery
Associated Injury	80% skull fracture	60% concomitant brain injury
Mortality	5%	15%
Morbidity	15%	5%

MVC, motor vehicle collision.

Subdural hemorrhages are most common in infants and are usually the result of nonaccidental trauma (31). Bleeding that appears chronic (hypodense on CT imaging), is seen in the interhemispheric space or posterior fossa, or is noted at multiple sites, is highly suggestive of nonaccidental trauma. Beyond infancy, subdural hematomas are usually frontal and parietotemporal and are associated with a significant direct blow to the head (18). Association with other brain injuries is significantly more common than with epidural hematomas and the prognosis tends to be worse.

Children with a midline shift or mass effect require urgent operative management. Those with severe alteration in neurologic status often have concomitant brain injuries (e.g., diffuse axonal injury, cerebral contusions) and are sometimes managed nonoperatively.

Severe TBI results in both primary and secondary injuries. Primary brain injury, such as hematoma and shear injury, is a direct result of the precipitating event. Secondary injuries arise minutes to hours to days following the initial insult and are modifiable by therapeutic intervention. Secondary brain injury is exacerbated by hypoxemia, hypotension, elevated intracranial pressure (ICP), and seizure activity. Even brief episodes of hypotension or hypoxia after TBI are associated with worse outcomes (33). The primary goal of emergency management is to minimize secondary injury with timely intervention to optimize blood pressure, oxygenation, ICP, and cerebral blood flow.

Acutely *elevated* ICP, resulting from focal mass effect (e.g., epidural hematoma) or more global injury (e.g., diffuse axonal injury) may have deleterious effects on cerebral perfusion and the delivery of critical metabolic substrates, including oxygen and glucose, to the CNS (12). Cerebral blood flow is directly related to cerebral perfusion pressure (CPP), which is calculated as the mean arterial pressure *minus* the intracranial pressure (CPP = MAP − ICP). The ICP is measured most accurately by an intracranial pressure monitor.

In adults, the critical threshold for CPP lies in the range of 50 to 70 mm Hg, but in young children, it may be as low as 40 mm Hg, with a 100% mortality rate below this threshold reported in one

retrospective study (2,10,12,27). Above this level, however, a threshold beyond which active maintenance of CPP contributes to improved outcomes has not been well defined (2,3). It is likely that there are different CPP thresholds at different ages (25,27).

Hypotension (variously defined as a MAP or systolic pressure below the fifth percentile) can reduce CPP, leading to cerebral hypoxia and exacerbating secondary injury (1,33). Even a single episode of hypotension harbors a risk for poor functional outcome after sTBI in children, particularly in the first 6 hours post injury. Attention to this critical parameter has been suboptimal. In a recent study of children with sTBI presenting to a level 1 trauma center, 39% of children had documented hypotension, but it was addressed in less than half and the outcome was worse in those patients.

Increases in ICP can also be associated with cerebral hypoperfusion, regardless of the blood pressure. Extra-axial blood collections, vasogenic edema secondary to neuronal cell death, and loss of vascular autoregulation can lead to increased ICP. Pediatric studies have consistently demonstrated that elevations of ICP >20 mm Hg are associated with significantly increased adverse neurologic outcomes.

Severe TBI is defined as a Glasgow Coma Scale (GCS) of ≤ 8, moderate TBI as a GCS of 9 to 13, and mild TBI as a GCS of 14 to 15. The Pediatric GCS should be used for young children. Providers must reassess children frequently to promptly detect increased ICP; a child who arrives with a GCS suggestive of mild TBI may rapidly deteriorate and require emergent intervention.

Herniation occurs when brain parenchyma is displaced due to intracranial mass effect from intracranial hematoma or malignant cerebral edema. The four common cerebral herniation syndromes transtentorial, tonsillar, central, and subfalcine, are described in Table 246.2. Acute signs of herniation include anisocoria (pupillary asymmetry greater than 1 mm), pupillary dilatation, nonreactive pupils (less than 1 mm reactivity), unilateral weakness, extensor posturing, Cheyne–Stokes breathing (rapid, deep breathing alternating with apnea), and Cushing's triad (hypertension, bradycardia, and irregular respirations). Since few children manifest

the stereotyped *sequence* of events as classically described, any signs of herniation are ominous and must be addressed emergently. Progressive herniation results in neurologic devastation or ultimately death.

TABLE 246.2
Common Cerebral Herniation Syndromes

	Transtentorial	Tonsillar	Central	Subfalcine
Location	Temporal lobe through tentorium	Cerebellum through foramen magnum	Thalamus and hypothalamus through tentorium	Frontal lobe beneath falx cerebri
Etiology	Ipsilateral mass lesion; diffuse brain swelling	Posterior mass lesion	Diffuse brain swelling	Ipsilateral mass lesion
Pathophysiology	Compression CNIII, later midbrain	Compression ventricular outflow, medulla	Compression midbrain	Compression anterior cerebral artery
Presentation	• Decreased consciousness • Ipsilateral dilated pupil → ptosis and lateral deviation • Contralateral hemiparesis	• Neck pain • Vomiting • Decreased consciousness • Cushing's triad	• Decreased consciousness • Small sluggish pupils • Cheyne–Stokes respirations • Posturing	• Contralateral weakness

CN, cranial nerve.

ED EVALUATION

Cranial computed tomography (CT) is the cornerstone of the initial diagnostic evaluation of the severely head injured child. Its purpose is to identify lesions amenable to surgical intervention or identify severe cerebral edema. Important findings include evidence of brain contusion, subdural or epidural hematoma, intracerebral hematoma, diffuse axonal injury, acute brain swelling, pneumocephalus, subarachnoid hemorrhage, midline shift, or cerebral herniation.

Standard Advanced Trauma Life Support (ATLS) protocols apply to all patients with TBI, and attention should be paid to possible associated injuries, given that these patients are unable to communicate effectively (32,22). As many as 60% of patients with sTBI present with serious concomitant injuries (23). The potential for associated cervical spine injury is of particular concern, and patients with major TBI should be presumed to have cervical spine injury. Cervical spine immobilization should be maintained throughout the ED stay, regardless of initial results of cervical spine imaging.

As noted, scrupulous attention must be paid to the presence of hypotension and hypoxia (33). This means identifying visible or occult hemorrhage and aggressively managing hemorrhagic shock. Ongoing hemorrhage clearly complicates attempts at maintaining

CPP in patients with marginal blood pressure. Similarly, respiratory compromise, either from TBI-related hypoventilation or from pulmonary injury must be rapidly addressed. Such concerns are not restricted to the initial resuscitation; secondary insults from hypotension, hyperglycemia, hypocarbia, and hypoxia must be prevented if at all possible (22).

A standard laboratory panel including complete blood count and electrolyte panel is often obtained in multiply injured patients, regardless of the presence of associated injuries. Elevated liver transaminases may alert the clinician to an unrecognized intra-abdominal injury. A full coagulation panel also should be obtained, given that coagulation abnormalities are common and of prognostic importance in patients with sTBI (21).

KEY TESTING

- CT of head
- CBC, electrolytes, coagulation studies
- Imaging for associated injuries (e.g., cervical spine, abdominal trauma)

ED MANAGEMENT

Airway and Breathing: Patients with severe TBI typically require intubation for of loss of airway protective reflexes or due to hypoventilation (Fig. 246.2). A GCS of less than 8 has traditionally been used as an indication for intubation; this is typically performed as rapid sequence orotracheal intubation with in-line cervical spine immobilization.

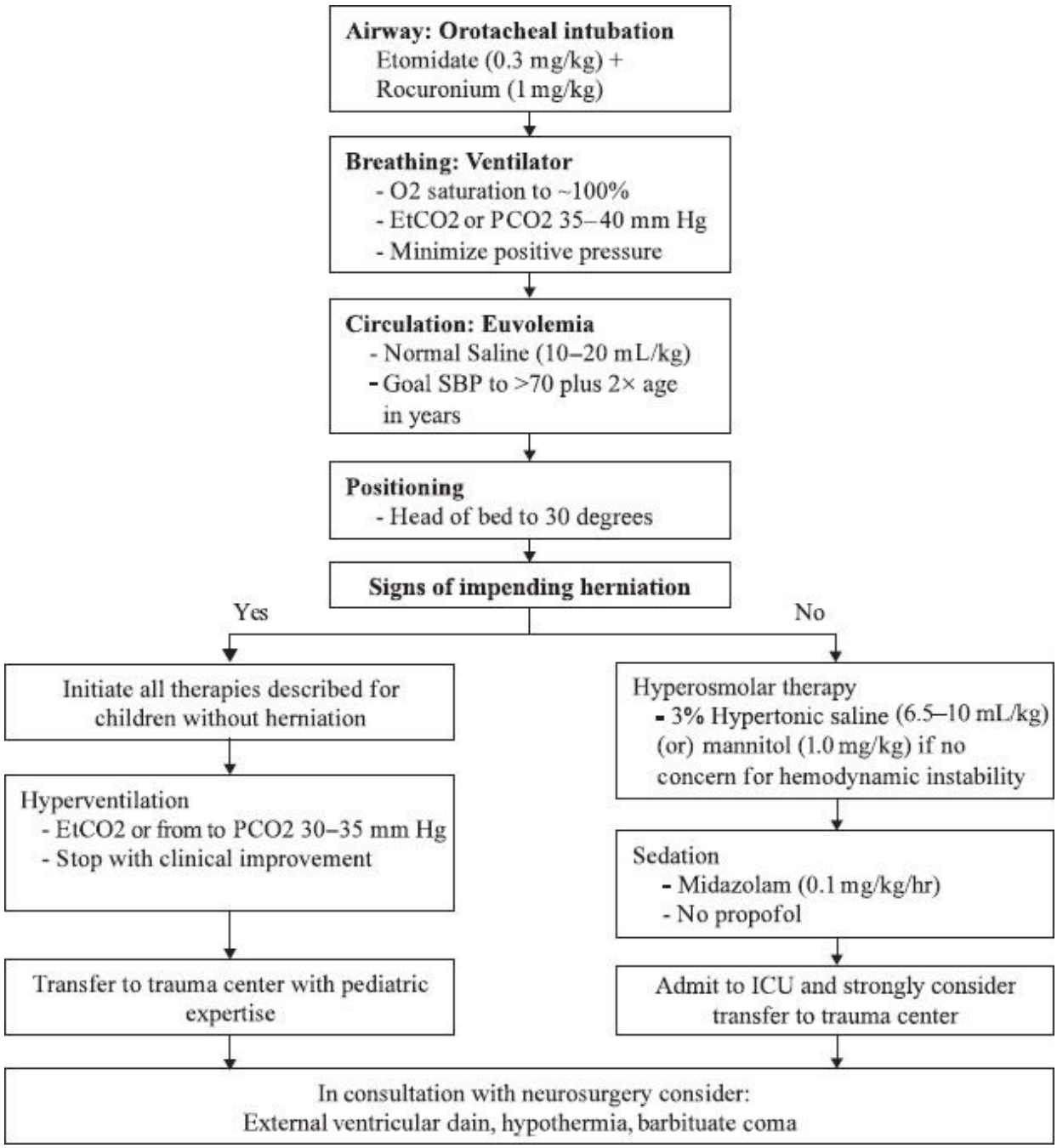

FIGURE 246.2 Emergency management of children with severe traumatic brain injury.

Several adjuncts have traditionally been used to blunt procedurally induced elevations in intracranial pressure in patients with head injury. More recent literature, however, has concluded that their effects in children are not clinically significant. Thus, defasciculation

prior to the use of succinylcholine is no longer considered to be necessary (5,28). Similarly, pretreatment with intravenous lidocaine is no longer recommended (5,28).

Etomidate is an ideal sedative agent, as it has minimal effects on blood pressure and lowers ICP following sTBI (6,28). However, because of concern about adrenal suppression, its use should be limited to a single dose in the ED (6). Thiopental and midazolam have potential neuroprotective effects but can lead to hemodynamic instability. Recent practice guidelines have removed head injury as a relative contraindication to the use of ketamine, which may actually be beneficial in terms of intracranial pressure and cerebral perfusion (8). Recent data suggests the use of ketamine for refractory elevations of ICP or prior to procedural interventions actually *improves* ICP in sedated ICU patients (17).

Ventilator settings should be adjusted to maintain oxygen saturations between 93% and 99%, while minimizing application of positive pressure, which impairs cerebral venous drainage (24). End-tidal carbon dioxide ($EtCO_{2)}$ should be monitored closely. Unless needed for the emergent treatment of acute herniation, hyperventilation should be avoided and $PaCO_2$ maintained between 35 and 40 mm Hg (7,24).

Circulation: Isotonic fluid (normal saline or lactated Ringer's solution) should be administered as necessary to achieve euvolemia. If hypotension persists despite aggressive resuscitation with crystalloid or blood products, vasopressors may be considered.

Positioning: The effect of position on intracranial pressure appears to exhibit interpatient variability and the optimal position may be patient-specific (19). Placement of the head in the midline and elevation of the head of the bed to approximately 30 degrees appear to promote venous drainage and reduce ICP, though with an equivocal effect on CPP (19). Elevation beyond 30 degrees is likely to reduce CPP and should be avoided.

Sedation: Analgesia and sedation can improve ICP by reducing pain and stress. Administration of analgesics and sedatives in small, frequent doses can help to reduce ICP while minimizing hypotension. While there are theoretical benefits to particular agents, none have

been compared empirically. However, reports of increased mortality from metabolic acidosis associated with propofol infusions in critically ill children have led to recommendations against its use in children with TBI (6). Similarly, multiple doses of etomidate are not recommended due to the possibility of adrenal suppression (6). Midazolam (0.1 mg/kg/hr) may be a more appropriate choice in the absence of overt hypotension.

Neuromuscular Blockade: Neuromuscular agents reduce ICP by decreasing airway and intrathoracic pressure, thereby promoting increased cerebral drainage. They also reduce metabolic demand and spikes in ICP by preventing muscle contraction. However, they mask neurologic findings and seizure activity and (except for use in RSI) should only be employed when sedatives do not correct elevations in ICP.

Anticonvulsants: The incidence of early posttraumatic seizures, defined as within 7 days of injury, is approximately 10% in children. Recommendations for prophylactic anticonvulsants are weaker than those in adults, but they may be considered when significant risk factors for posttraumatic seizures, such as depressed skull fracture, penetrating injury, cerebral contusion, or retained fragments, are present.

Hypothermia: Prophylactic hypothermia in the setting of severe pediatric TBI has not been shown to improve outcomes (14,15).

Management of herniation and severely elevated ICP: Aggressive intervention to address severely elevated ICP have been demonstrated to improve outcomes (9).

Interventions such as sedation, paralysis, judicious hyperventilation, hyperosmolar therapy, cerebrospinal fluid drainage, and surgical decompression improve mortality (7). Hypocapnia causes cerebral vasoconstriction, reducing cerebral blood flow, volume, and ICP. This may effectively reverse cerebral herniation as part of an emergent life-saving salvage strategy. However, children with sTBI should not be hyperventilated to a $PaCO_2$ below 30 mm Hg (7).

In children with sTBI, a single episode of $PaCO_2 < 30$ mm Hg in the first 48 hours has been associated with increased mortality (odds

ratio ~ 1.5). Two or more episodes of severe hypocarbia increase the odds ratio to 4 (16). Emergency providers should utilize $EtCO_2$ monitors to ensure that $PaCO_2$ is maintained in an appropriate range of 35 to 40 mm Hg, or 30 to 35 mm Hg during hyperventilation, for impending herniation.

Patients with increased ICP or herniation should receive intravenous mannitol (usual dose 1 gm/kg; recommended administration time 30 minutes). Mannitol, an osmotic diuretic, reduces ICP partly through the immediate reduction of cerebral blood volume (with maintained cerebral blood flow) and intracranial pressure, an effect that lasts less than 75 minutes (30). Mannitol also osmotically draws water from the brain parenchyma into the systemic circulation, reducing intraparenchymal volume and ICP; an effect which lasts up to 6 hours. Mannitol should not be used prophylactically but rather should be reserved for patients manifesting signs of imminent herniation.

Hypertonic saline is an alternative hyperosmolar agent. It appears to reduce ICP through mechanisms similar to those of mannitol, with production of an osmotic gradient across an intact blood–brain barrier (30). It causes less osmotic diuresis and hypotension than mannitol and is preferable for patients with multisystem trauma. While severe hypernatremia (>160 mEq/L) has been associated with poor outcomes in pediatric sTBI, this is unlikely to occur with therapeutic hyperosmolar treatment (26). There is currently insufficient evidence to support the use of saline concentrations greater than 3%, although this issue remains unsettled (26,27). While mannitol has long been the traditional hyperosmolar agent of choice used in the treatment of increased ICP, current recommendations favor the use of hypertonic (3%) saline (30).

CRITICAL INTERVENTIONS

- Early aggressive treatment of hypotension or hypoxia
- Recognition of concomitant traumatic injuries
- Adequate sedation during and after intubation

- Hyperosmolar therapy and mild hyperventilation (PCO_2 30 to 35 mm Hg) for herniation
- Early consultation with neurosurgery or transfer to pediatric trauma center

DISPOSITION

Management of pediatric patients with severe multi-system trauma is clearly associated with improved outcome; this is no different for children who have suffered severe head trauma (4). Admission to a specialized pediatric intensive care unit allows for the early aggressive management that has been demonstrated to improve outcome of sTBI in children.

Common Pitfalls

- Failure to recognize and promptly treat even brief episodes of hypoxemia or hypotension.
- Failure to reassess the neurologic examination frequently to identify signs of increased ICP.
- Failure to consider nonaccidental trauma in infants with TBI, particularly those with subdural hematoma.
- Excessive hyperventilation to $PaCO_2$ <30 mm Hg.
- Failure to consider concomitant injuries, including cervical spine injuries.

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CHAPTER 247
Minor Head Trauma

Lois K. Lee and Nathan Kuppermann

CLINICAL PRESENTATION

Blunt head trauma occurs commonly in children 0 to 18 years old, with more than 600,000 children evaluated in US emergency departments (EDs) annually for this complaint. Most children present with minor head trauma, and approximately 90% of children are treated and then discharged home (1). Falls, sports, and motor vehicle crash–related mechanisms are the leading causes of head trauma (1); however, injury mechanism alone is not strongly predictive of traumatic brain injury (TBI). Although severe mechanisms can lead to severe injuries, an isolated severe mechanism of injury ("Key Testing" table), without signs or symptoms of TBI, is not a substantial predictor of clinically important TBI (2). This is defined as TBI resulting in death, neurosurgery, intubation for greater than 24 hours, or hospitalization for two or more nights in association with TBI on CT (3).

The definition of minor head trauma varies in the research literature, but for the purposes of this chapter minor head trauma will be defined as Glasgow Coma Scale (GCS) scores of 14 to 15 after blunt head trauma (Table 247.1) (3,4). Children with minor head trauma can present variably and with a spectrum of symptoms and signs. For example, an infant who falls off a table onto a hard surface can present with a normal mental status and a large scalp hematoma. A school-aged child with head trauma sustained in a motor vehicle crash may present with vomiting and complaints of a headache. An adolescent with head trauma from playing football can present with a history of loss of consciousness (LOC) and may be slow to respond

to questioning. All of these children could meet the definition of minor head trauma on the basis of their GCS scores. The challenge in assessing a child with seemingly minor head trauma in the ED is weighing the immediate risk of clinically important TBI against the long-term risk of exposure to ionizing radiation from emergent cranial CT neuroimaging (5–7). Most earlier studies regarding the evaluation of children with blunt head trauma were characterized by their small sample sizes, retrospective nature, and varied definitions of predictors and outcomes. Recently, however, there have been several large prospective multicenter studies to guide clinicians in the evaluation of these patients.

TABLE 247.1
Pediatric Glasgow Coma Scale (GCS) Score Modified for the Preverbal Child (8)

Eye Opening	
Spontaneous	4
To voice	3
To pain	2
None	1
Verbal Response	
Coos, babbles	5
Irritable cries	4
Cries to pain	3
Moans to pain	2
None	1
Motor Response	
Spontaneous movements	6
Withdraws to touch	5
Withdraws to pain	4
Abnormal flexion	3
Extensor response	2
None	1

Pediatric GCS score: Eye opening + Verbal response + Motor response = 3 to 15

DIFFERENTIAL DIAGNOSIS

Minor head trauma uncommonly results in clinically important TBI. In a large prospective multicenter study of children 0 through 17 years with GCS scores of 14 to 15 after blunt head trauma, only 0.9% had clinically important TBIs (3). Another large population-based study of children with minor head trauma reported that a delayed diagnosis of intracranial hemorrhage occurred rarely after ED evaluation and discharge home (9). Nevertheless, children with seemingly minor head trauma may rarely have a serious intracranial hemorrhage. Such children may initially present with headache and a GCS of 15 and then progress to altered mental status, ultimately requiring emergent neurosurgical intervention (e.g., for an epidural hematoma). Although most children with minor head trauma have no intracranial injury, some may have skull fractures or concussions. The clinician must also remain vigilant for nonaccidental trauma in young, preverbal children (<2 years old) with blunt head trauma (10), as clinical prediction rules for the evaluation of blunt head trauma are not predictive if the history provided by the guardians is not accurate (3,4).

ED EVALUATION

The use of CT in the evaluation of children with blunt head trauma has greatly increased over the past two decades, but appears to have leveled off in recent years (6,11). Although cranial CT is the reference standard for emergently diagnosing TBI, there is a dose- and age-dependent increased lifetime risk of cancer attributable to the ionizing radiation associated with cranial CT scans (5,7). The estimated risks for leukemia range from 1 case per 5,250 scans for children younger than 5 years old to 1 case per 21,160 scans for children 11 to 14 years old; and for solid tumors the risk ranges from 1 tumor per 570 scans for girls younger than 5 years old to 1 solid tumor per 4,660 scans for boys 10 to 14 years old (6). As a result, the decision to evaluate a child with cranial CT imaging after minor head trauma should be considered carefully in the context of the history and physical examination.

The clinician should elicit a thorough history, (3,4) while the physical examination should begin with an overall assessment of the

child's mental status, including the GCS score. For children with moderate to severe head trauma (defined as GCS scores 3–13) emergent neuroimaging should be obtained, as the risk of intracranial injury is substantial (please refer to Chapter 246, Severe Head Trauma) (4,12). A detailed physical examination of the head should be conducted to explore for any scalp hematoma, ecchymosis, lacerations, evidence of skull fracture, hemotympanum, and other signs of basilar skull fractures. A complete neurologic examination including level of consciousness, as well as motor and sensory deficits, should be documented.

There have been several large, prospective observational studies in the past decade that have greatly helped clinicians evaluate children with blunt head trauma for the risk of TBI. One study developed two age-based rules, with a goal of identifying children at very low risk for clinically important TBIs who do not require emergent neuroimaging (3). These prediction rules were derived and validated in a prospective multicenter study of more than 42,000 US children with head trauma and GCS scores of 14 to 15, seen in the EDs in the Pediatric Emergency Care Applied Research Network (PECARN). The factors for these two age-based prediction rules are presented below under "Key Testing." The sensitivities of the age-based rules, one for children 2 through 17 years, and the other for children younger than 2 years, were between 97% and 99%, and the negative predictive values (NPV) were nearly 100%, with narrow confidence intervals (CI). Most importantly, in both age groups, in the absence of any of the PECARN prediction rule factors, the risk of clinically important TBI was on the order of 1:2,000 to 1:5,000; therefore, cranial CT imaging is not routinely recommended for children with no PECARN risk factors (Fig. 247.1) (3).

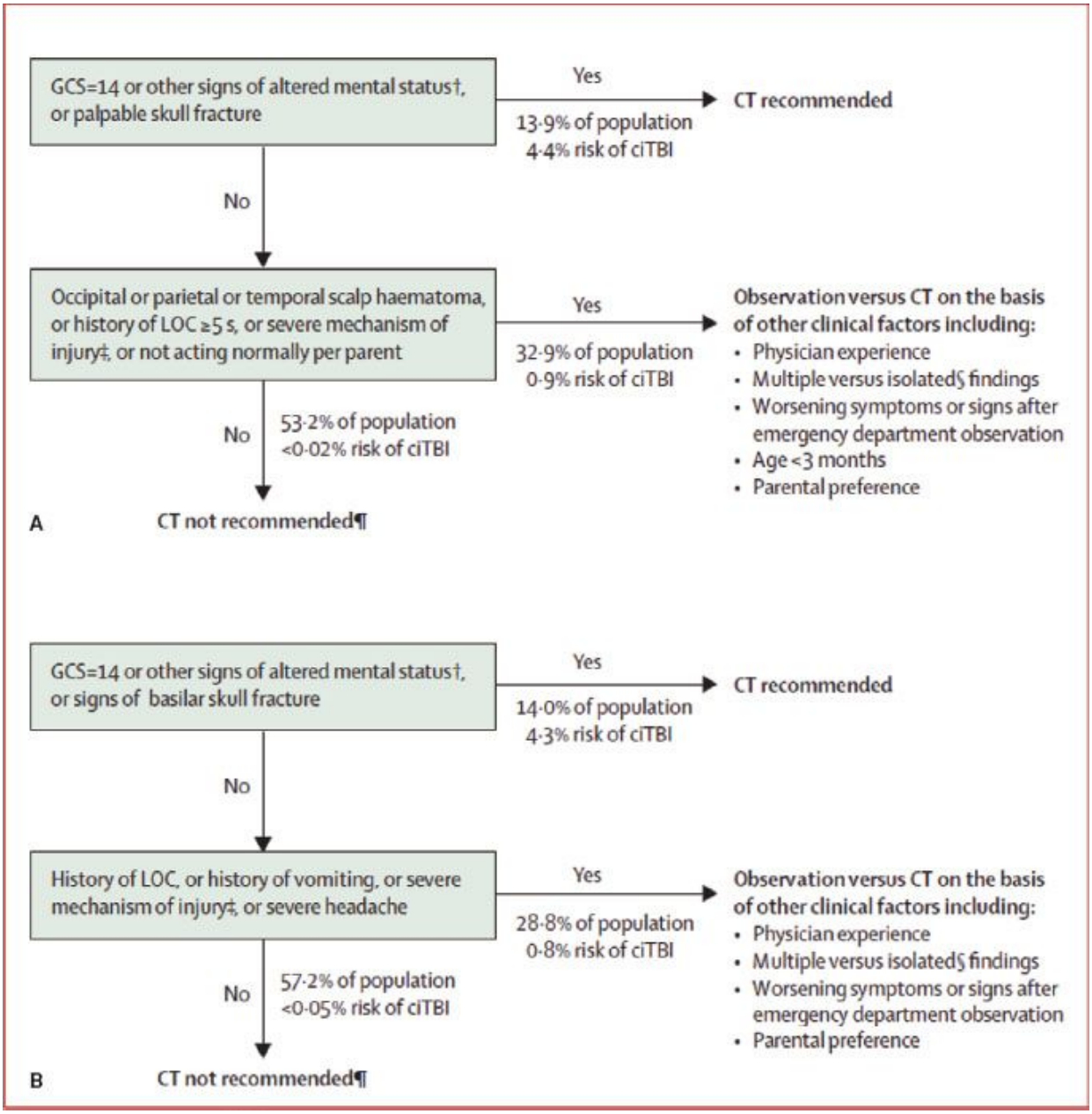

FIGURE 247.1 Suggested CT Algorithm for Children Younger than 2 Years **(A)** and for Those Aged 2 Years and Older **(B)** With GCS Scores of 14–15 After Blunt Head Trauma[3] Reprinted from The Lancet, Vol. number 374, Kuppermann N., Holmes JF, Dayan PS, et al., Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study, Pages 1160–1170, Copyright 2009, with permission from Elsevier.

In contrast to the PECARN prediction rules, which focus on identifying children at very low risk of clinically important TBI not requiring CT, two other rules focus on identifying children with significant intracranial pathology. The Children's Head Injury Algorithm for the Prediction of Important Clinical Events (CHALICE) was derived from a multicenter cohort of English children <16 years with a history or signs of head trauma (13); however, the complexity of the rule makes clinical implementation challenging. Another rule, the Canadian Assessment of Tomography for Childhood Head injury (CATCH) rule, was derived from a prospective multicenter cohort of Canadian children with blunt head trauma presenting with GCS scores of 13 to 15 and a history of LOC, amnesia, disorientation, persistent vomiting, or irritability (4). In this rule, the main outcome was need for neurosurgical intervention, and the variables associated with this outcome and for which a cranial CT is recommended include: a GCS score <15 2 hours after injury; suspected open/depressed skull fracture; history of worsening headache; or irritability on examination. This rule had a sensitivity of 100% (95% CI 86.2 to 100) (4). Although these last two rules have a high sensitivity for identifying children with significant TBI, only the PECARN prediction rules focus on children with minor head trauma, defined by GCS scores of 14 to 15, to identify children who *do not* require cranial CT evaluation (14,15). The American Academy of Pediatrics has identified the PECARN prediction rules in the "Choosing Wisely" campaign (16) and recommends the use of clinical observation prior to CT decision making for those children determined to be at low risk for clinically important TBI (17).

Although plain skull radiographs have limited utility in the evaluation of head trauma, for children younger than 2 years old who are asymptomatic and have only a scalp hematoma on physical examination, the use of skull x-rays (18) or point-of-care ultrasound to evaluate for a possible underlying skull fracture may be considered. Some recent studies have found point-of-care ultrasound to be an excellent test to rule out skull fractures in children (19,20). Most (>90%) linear skull fractures in children younger than 2 years of age have overlying soft tissue swelling or scalp hematomas, and

15% to 30% of skull fractures are associated with TBIs (18). Therefore, if a skull fracture is identified by either x-ray or ultrasound, a cranial CT should be obtained to assess for TBI (18). If there is no skull fracture on x-ray in an asymptomatic child with only a scalp hematoma, no further imaging is routinely required, and the patient may be discharged home, as the risk of intracranial injury is very low (21).

KEY TESTING

- Consider PECARN prediction rule factors in the decision to avoid emergent neuroimaging. Children with none of the PECARN factors are at very low risk for clinically important TBI and typically do not warrant immediate CT imaging.

PECARN Prediction Rule Factors (3)

Younger than 2 years old (pneumonic "SCALPS") (22)	Two years and older (pneumonic "BASILaR") (22)
Scalp hematoma (except frontal)	Basilar skull fracture, signs of
Caregiver concern for change in behavior	Altered mental status[a]
Altered mental status[a]	Severe headache
Loss of consciousness > 5 sec	Injury mechanism, severe[b]
Palpable skull fracture	Loss of consciousness
Severe mechanism of injury[b]	Regurgitation (vomiting)

[a]GCS <15 or other signs of altered mental status: agitation, somnolence, repetitive questioning, or slow response to verbal communication.
[b]Severe mechanism of injury: rollover/ejection/other passenger death in motor vehicle crash (MVC), fall >3 ft (for < 2 years) or fall >5 ft (for ≥2 years), nonhelmeted pedestrian/bicyclist struck by a motor vehicle, or patient struck by high impact projectile (3).

ED MANAGEMENT

In the PECARN head trauma cohort, observation of selected children was associated with decreased CT use. There was no difference in the rate of clinically important TBI between those who were observed before a decision was made on the use of CT and those who were not observed before CT decision making (17). For children who are observed and either do not improve or develop a worsening clinical picture (change in mental status, worsening headache, persistent

vomiting, or more ill appearance), cranial CT should be seriously considered.

CRITICAL INTERVENTIONS

- Cranial CT is recommended for children with persistent GCS scores <15 or altered mental status, or if there are signs of skull fracture (or if there are worsening signs or symptoms of TBI).
- Consider observation before CT decision making for children with isolated PECARN risk factors, other than those mentioned above.

Cranial CT is not recommended for children with no PECARN risk factors for clinically important TBI. These children should be discharged home, with instructions on when to return immediately (for developing signs of TBI).

DISPOSITION

Most children with minor head trauma can be discharged home (3,8). If a child with minor head trauma has a cranial CT performed with normal results, the risk of subsequent worsening is very low and the risk of requiring neurosurgical intervention is extremely low (23). Assuming a normal mental status, these children may be safely discharged home, unless they have persistent symptoms (e.g., vomiting) or develop new symptoms that require reevaluation.

Common Pitfalls

- Failure to recognize clinical deterioration, which can occur with an expanding intracranial hemorrhage, when a child presents with an initial GCS score of 15, but then deteriorates.
- Failure to recognize nonaccidental trauma, based on the history (vague or inconsistent with developmental stage or physical findings) or examination findings suggestive of inflicted trauma.

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CHAPTER 248 Sports-Related Concussion

Ryan Petering and Robert Cloutier

It is estimated that 3.8 million concussion injuries occur in the United States annually, though many of these go unreported and medical care is not sought (1). Between 2001 and 2009 an average of 173,285 persons aged 19 years or younger presented to emergency departments (EDs) annually for nonfatal traumatic brain injuries (TBIs) related to sports and recreational activities (2). Annual TBI ED visit rates increased 62% during this period. American football, playground activities, basketball, and soccer have the greatest number of TBI-related ED presentations (2). The most common ages for sports-related concussion ED presentation are 14 to 18 years. Males (77%) present more frequently than females (3). However, it appears that in sports with similar rules (e.g., soccer) females have a higher number of concussions and report increased severity compared with males (4). The majority of patients with sports-related concussion (95%) are discharged home following ED evaluation (3).

This chapter discusses concussion specifically in the setting of a sports-related event. See also Chapters 246 and 247.

CLINICAL PRESENTATION

Concussion, mild TBI, and TBI refer to similar events. TBI includes all head injuries and often refers to more serious and life-threatening presentations. Mild TBI typically refers to an injury to the head, with or without loss of consciousness, and a Glasgow Coma Scale (GCS) of 13 to 15 (5). Concussion is defined as a

traumatically induced transient disturbance of brain function (4,6). It is important to note that while concussion most often occurs following a direct blow to the head, other mechanisms such as whiplash may transmit force to the head and cause concussion as well. Symptoms are typically immediate and consist largely of functional disturbances; associated structural abnormalities on imaging studies are rare (7).

Consensus concussion panels have recommended avoiding previously associated adjectives such as “mild,” “moderate,” or “severe,” as these terms have little to no prognostic value for individual patients. Unfortunately, concussions judged as “mild” may cause persistent symptoms that can last for months to years.

The symptoms of concussion are diverse and variable. It is helpful to think of symptoms in the categories of (1) physical, (2) cognitive, (3) emotional, and (4) sleep-related. Physical symptoms include headache, nausea, vomiting, balance problems, dizziness, visual problems, fatigue, sensitivity to light and/or noise, or numb or tingling sensations. Loss of consciousness can occur with concussion injuries, but is not required for the diagnosis; only about 10% of concussions are associated with a loss of consciousness (4). Cognitive symptoms include feeling mentally “foggy” or dazed, difficulty concentrating, forgetfulness, confusion about recent events, slowness in responding to questions, and repetitive questioning. Emotional symptoms include irritability, sadness, emotional lability, and nervousness. Sleep changes include drowsiness, sleeping more or less than usual, and difficulty initiating sleep.

DIFFERENTIAL DIAGNOSIS

A comprehensive primary and secondary survey should be performed to identify coexisting injuries. Among the most important to consider are fracture, intracranial hemorrhage, and structural brain damage. The past medical history should identify preexisting medical conditions that may contribute to or complicate a concussion.

ED EVALUATION

Initial ED evaluation should determine whether imaging is required. Clinical evaluation should include a thorough history to determine the specifics of the injury mechanism and the symptoms reported. Physical exam should include a comprehensive neurologic examination.

Skull radiographs are not recommended (5). A level A recommendation is given for noncontrast computed tomography (CT) for patients with loss of consciousness or posttraumatic amnesia if one or more of the following are also present: headache, vomiting, drug or alcohol intoxication, deficits in short-term memory, physical evidence of trauma above the clavicles, posttraumatic seizure, GCS score less than 15, focal neurologic deficit, or coagulopathy. The guideline gives a level B recommendation for noncontrast head CT for patients without loss of consciousness or posttraumatic amnesia if focal neurologic deficit, vomiting, severe headache, physical signs of basilar skull fracture, GCS score less than 15, coagulopathy, or a dangerous mechanism of injury (ejected from motor vehicle, a pedestrian struck, and a fall from a height of more than 3 ft or five stairs) (5).

Up to 15% of patients presenting to the ED following TBI who have a GCS score of 15 are found to have an acute intracranial lesion on head CT (8–13). However, less than 1% of these patients require neurosurgical intervention (9,10,14).

KEY TESTING

- Noncontrast head CT scan MAY BE ordered in patients WITHOUT loss of consciousness OR posttraumatic amnesia with ONE of the following: (1) focal neurologic deficit, (2) vomiting, (3) severe headache, (4) physical signs of a basilar skull fracture, (5) GCS score less than 15, (6) coagulopathy, (7) dangerous mechanism of injury.
- Noncontrast head CT scan SHOULD be ordered for patients WITH loss of consciousness OR posttraumatic amnesia and any of the above criteria or any of the following: (1) drug or alcohol

intoxication, (2) physical evidence of trauma above the clavicles, (3) short-term memory deficits, (4) posttraumatic seizure.

ED MANAGEMENT

Headache and nausea or vomiting require symptomatic treatment. It is advisable for concussed patients to be kept in quite, low-light environments to avoid exacerbating their symptoms. Suspected fracture, intracranial bleeding or other injury, or focal neurologic deficits should prompt immediate neurosurgical consultation.

CRITICAL INTERVENTIONS

- Determine the need for imaging to identify fracture or intracranial injury.
- Arrange for close follow-up and inform the patient and caregivers about the natural course of concussive symptoms and the need for full cognitive rest.

DISPOSITION

Patients with isolated concussion may be discharged from the ED since they are at minimal risk for developing an intracranial lesion. However, it is important that discharge instructions note the possibility of worsening symptoms or signs consistent with an intracranial process. Repeated vomiting, worsening headache, loss of consciousness, increasing confusion or agitation, seizure activity, vision changes, weakness or numbness, and difficulty walking are symptoms that warrant further evaluation. The CDC has published downloadable documents ideal for use in the ED discharge setting; these can be found at http://www.cdc.gov/concussion/pdf/TBI_Patient_Instructions-a.pdf.

Consensus treatment guidelines recommend initial mental, physical, and emotional rest. Patients should be advised to rest as much as possible, avoid activities that worsen their symptoms, avoid physical activity, and avoid excessive screen time (television, phones, and electronic devices). Consideration should be given to

advising patients to miss school or work as needed while symptoms are present, as often these activities may exacerbate symptoms.

Discharged patients should be advised to follow-up within a week of injury with a provider familiar with the management of concussion. Athletes should be advised not to return to participation in sports until they are cleared by a medical provider. Patients are advised to rest until their symptoms resolve completely without the use of medications. A graded approach to physical activity is then recommended, with activities increased in intensity and duration each day. If symptoms increase during the return to play protocol, patients should return to the previous day's activity level. Return to play *must* be guided by symptoms and not by fixed time spans such as "1 week after injury."

It is estimated that 90% of concussion victims recover within 7 days of their injury (15–17). Concussion symptoms that persist 4 to 6 weeks following the concussive event are characterized as postconcussion syndrome. This syndrome may persist for months to years and can have a profound impact on patients' lives, school, or work schedules. Risk factors at initial presentation have yet to be identified to predict the risk of developing postconcussive syndrome. These patients should be referred to a concussion rehabilitation team, which typically includes medical providers, physical therapist, speech therapists, and occupational therapists trained specifically in concussion management.

Common Pitfalls

- Failing to diagnose a concussion when a patient has a distracting additional injury (e.g., fracture or other injury).
- Dismissing a concussion as "mild" because there are no severe findings on presentation.
- Recommending that an athlete can return to play at a predetermined amount of time (e.g., 1 week after injury) without undergoing further evaluation on follow-up.

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CHAPTER 249

Evaluation of the Pediatric Cervical Spine

Jeffrey R. Avner

The developing pediatric cervical spine has numerous features that make it challenging to evaluate. These include unfused synchondroses, incomplete ossification centers, and epiphyseal growth plates. In addition, due to the dynamic changes occurring during bone and ligament development the distribution patterns of fractures and dislocations differ from those of the adult spine. Furthermore, a significant percentage of pediatric spinal cord injuries may occur in the absence of any radiographically identifiable abnormality.

DEVELOPMENTAL ANATOMY

The first cervical vertebra (atlas) develops from three primary ossification centers: the body and two neural arches (Fig. 249.1). The neural arches ossify in utero and fuse posteriorly at approximately the third year of life. The body of C1 is not ossified at birth and does not become visible until approximately 1 year of age. The synchondroses between the body and neural arches (neurocentral synchondroses) fuse at approximately the seventh year of life (1).

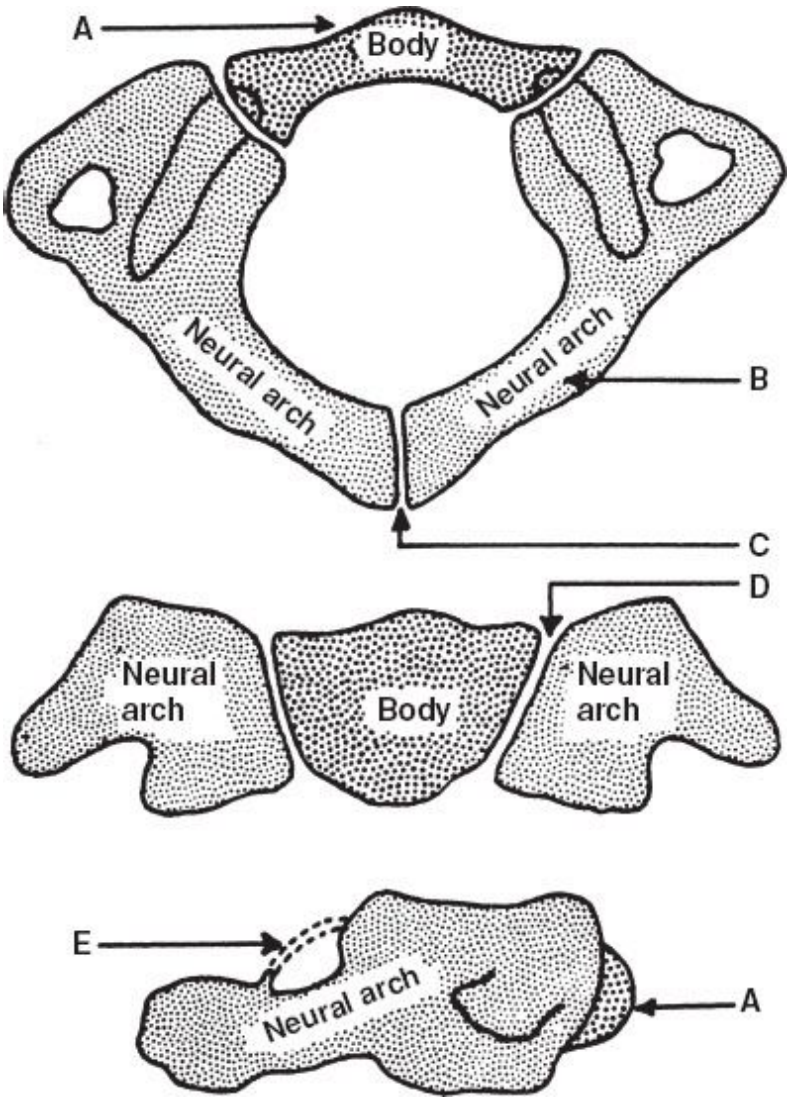

FIGURE 249.1 The first cervical vertebra (atlas). **A:** Body: ossification center becomes visible during first year of life. **B:** Neural arches: ossification center appears in utero at approximately the seventh fetal week. **C:** Synchondrosis of spinal process: fuses at approximately the third year of life. **D:** Synchondrosis about the body (neurocentral synchondrosis: fuses at approximately the seventh year of life). **E:** Ligament surrounding the superior vertebral notch: may ossify later in life. (Reproduced with permission from Fielding JW. Cervical spine injuries in children. In: The Cervical Spine Research Society, eds. *The Cervical Spine*. Philadelphia, PA: JB Lippincott Co.; 1983:268–281.)

The second cervical vertebra (axis) is the most difficult to interpret radiographically because of its four primary ossification centers: the odontoid, body, and the two neural arches (Fig. 249.2). All four ossification centers are visible at birth. A secondary ossification center appears at the apex of the odontoid (summit ossification center) at approximately 3 to 6 years and fuses with the odontoid by the 12th year of life. The synchondroses of the posterior neural arches fuse at approximately the third year. The synchondrosis between the odontoid or body of C2 and the neural arches fuse at approximately the third to sixth year. Before fusion, these synchondroses may be confused with fracture lines. The fusion line of the synchondrosis between the odontoid and the body of C2 commonly remains visible until age 11, and one-third of individuals have a visible fusion line throughout life.

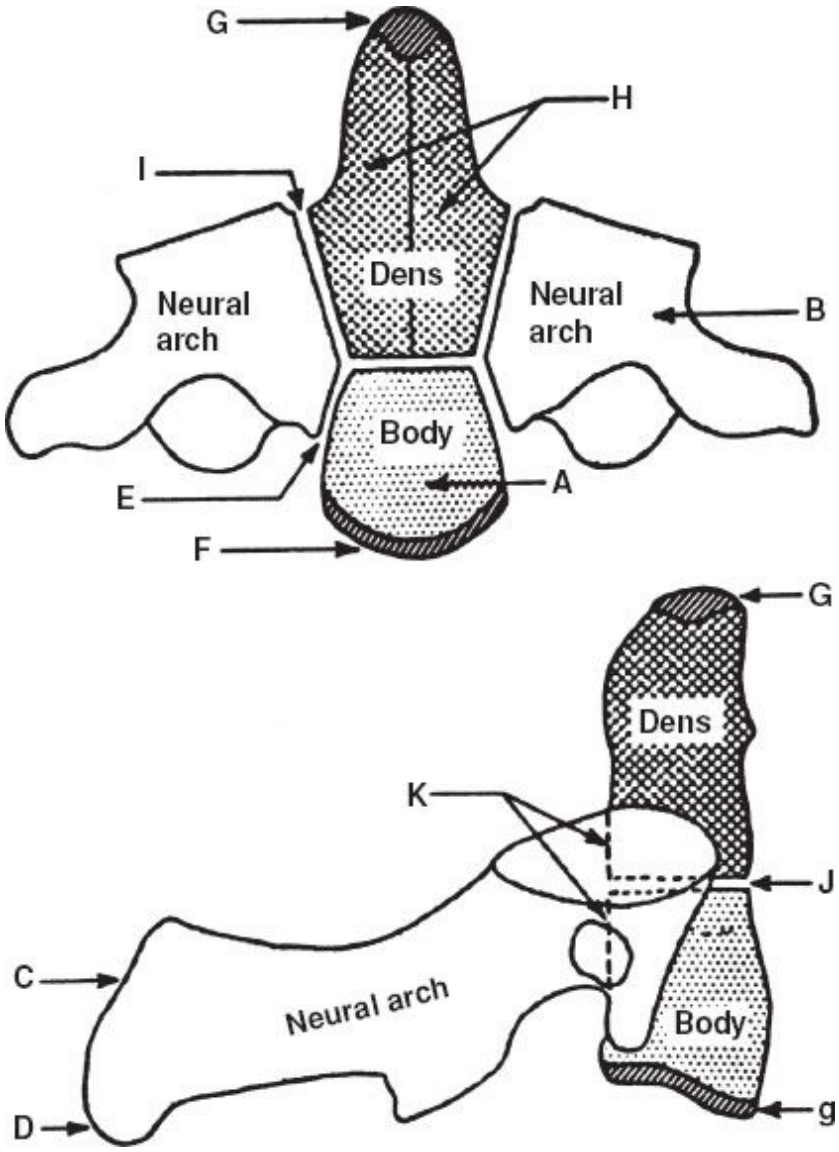

FIGURE 249.2 The second cervical vertebra (axis). **A:** Body: ossification center appears by the fifth fetal month. **B:** Neural arches: appear by the seventh fetal month. **C:** Synchondrosis of spinous process: fuses by the third to sixth year of life. **D,E:** Neurocentral synchondrosis: fuses by the third to sixth year. **F,g:** Inferior epiphyseal ring: appears at puberty and fuses to body at approximately 25 years of life. **G:** Summit ossification center for odontoid: appears at approximately the third to the sixth year and fuses with the odontoid by the twelfth year of life. **H:** Odontoid: develops from two ossification centers that fuse by the seventh fetal month. **J:** Synchondrosis between the odontoid and body: fuses at approximately the third to sixth year of life. (Reproduced with

permission from Fielding JW. Cervical spine injuries in children. In: The Cervical Spine Research Society, eds. *The Cervical Spine*. Philadelphia, PA: JB Lippincott Co; 1983:268–281.)

In the remaining C3 to C7 cervical vertebrae, there are three major ossification centers—the body and two neural arches—all of which are visible at birth (Fig. 249.3). The posterior synchondroses of the neural arches fuse at approximately the third year of life. The neurocentral synchondroses fuse at approximately the third to sixth year of life. Secondary ossification centers appear at puberty along the superior and inferior aspects of the cervical bodies (superior and inferior epiphyseal rings) and at the tips of the spinous processes. Before fusion, these ossification centers may be mistaken for chip fractures of the cervical bodies and clay shoveler's fractures of the spinous processes, respectively. These secondary ossification centers fuse with the main body by age 25. Development of the contiguous ring apophysis encircling the vertebral body surfaces, which occurs up to adolescence, gives the appearance of slight anterior vertebral wedging that must be differentiated from a fracture.

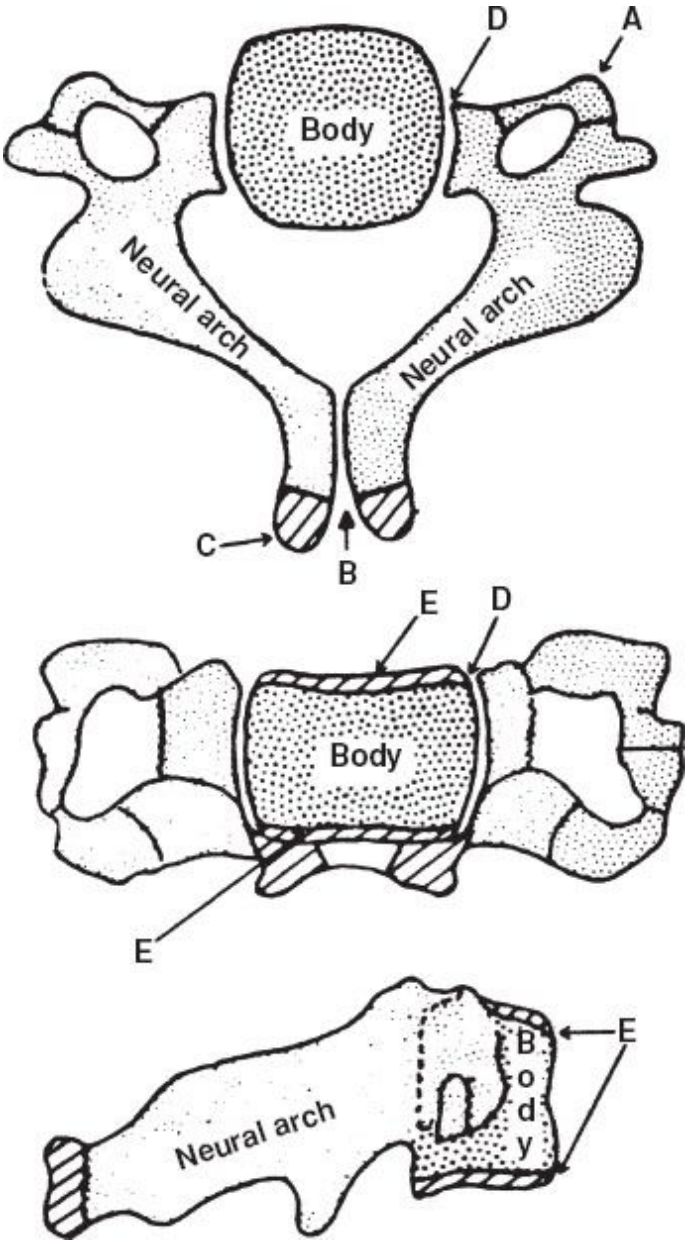

FIGURE 249.3 Typical cervical vertebrae (C3–C7). **A:** Anterior portion of transverse process: may develop from a separate ossification center that fuses by the sixth year. **B:** Synchondrosis between the spinous processes: fuse by third year. **C:** Secondary centers for bifid spinous processes: appear at puberty and fuse by 25 years of life. **D:** Neurocentral synchondrosis: fuses at approximately third to sixth year of life. **E:** Superior and inferior epiphyseal rings: appear at puberty and fuse with body by 25 years of life. (Reproduced with permission from Fielding JW. Cervical spine

injuries in children. In: The Cervical Spine Research Society, eds. *The Cervical Spine. Philadelphia*, PA: JB Lippincott Co.; 1983:268–281.)

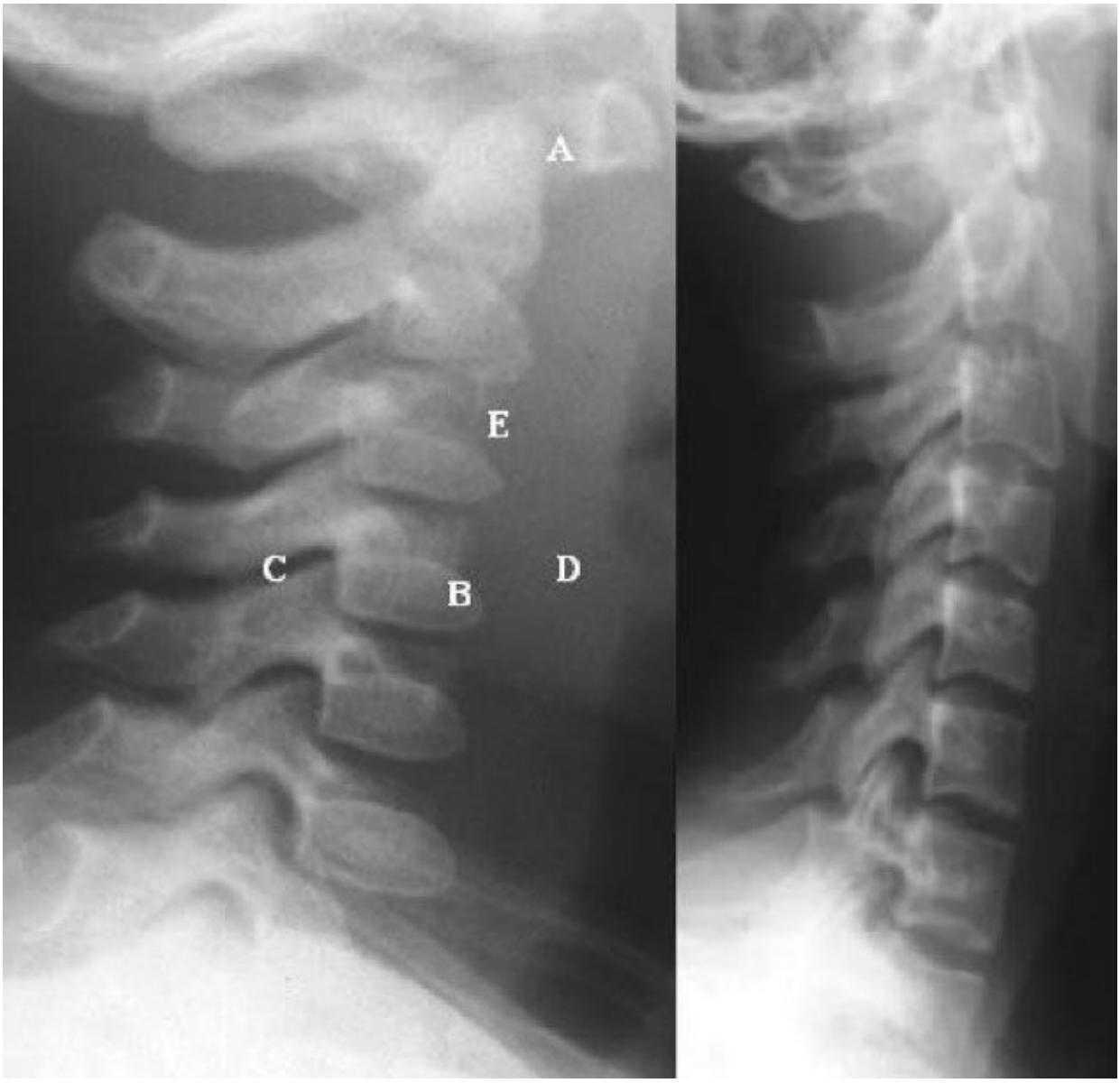

FIGURE 249.4 Comparison of a normal lateral cervical spine x-ray of a child (**left**) and adult (**right**). Normal anatomic differences notable in the pediatric spinal x-ray include **(A)** nonpathologic, widened predental space of 4.5 mm; **(B)** anterior wedging of the vertebral bodies; **(C)** flat interfacet joints; **(D)** increased soft tissue space anterior to the cervical spine; and (**E)** an anterior pseudosubluxation

of C2 on C3. (Reproduced with permission from Yamamoto LG. http://www.hawaii.edu/medicine/pediatrics/pemxray/v5c02.html.)

NORMAL VARIANTS AND CONGENITAL ANOMALIES

The development of the cervical vertebrae during childhood results in a range of normal anatomic and radiologic variants (Fig. 249.4). In particular, the weak support provided by relatively immature neck muscles, elastic interspinous ligaments, and flat interfacet joints create laxity of the vertebrae. In addition, during the ossification process of the immature cervical bodies, an appearance of anterior wedging is produced. Thus, there is more mobility of the vertebral structures in a child compared with an adult whose vertebral alignment is relatively fixed. Owing to this ligamentous laxity, absent lordosis is often a finding on the lateral radiograph in a child with a normal cervical spine, whereas in adults this finding may signify ligamentous injury.

The extreme laxity of ligaments can also exaggerate the vertebral override (pseudosubluxation) of adjacent vertebrae of children younger than 8 years. This finding is most pronounced at the level of C2 to C3 (see Fig. 249.4) but may be also present at C3 to C4. To distinguish pseudosubluxation from true subluxation, Swischuk (2) developed the concept of the posterior cervical line (Fig. 249.5). This line is drawn by connecting the anterior aspects of the spinous processes of C1 and C3. If the anterior aspect of the spinous process of C2 misses this line by 2 mm or more (1.5 mm is borderline), this finding is suggestive of a true subluxation or a hangman's fracture of the neural arches of C2. This posterior cervical line can be applied only in children demonstrating subluxation or pseudosubluxation of C2 on C3. If no subluxation or pseudosubluxation exists, the anterior aspect of the spinous process of C2 commonly misses the posterior cervical line by more than 2 mm.

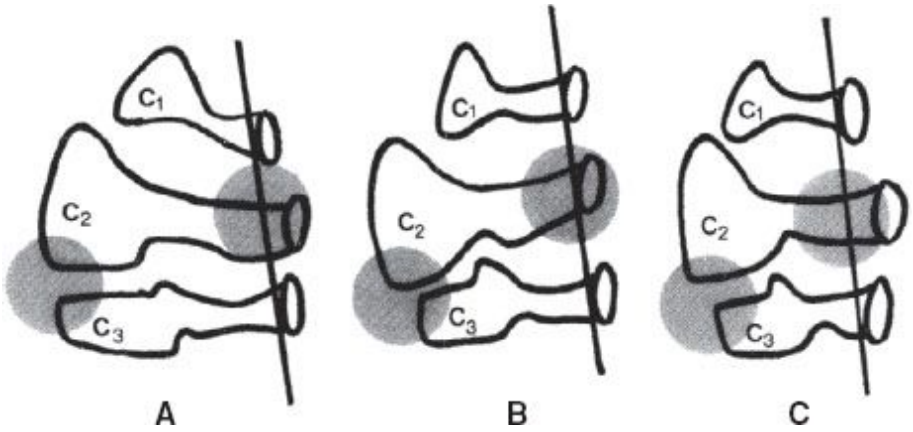

FIGURE 249.5 The posterior cervical line (PCL) is drawn by connecting the anterior aspect of the spinous processes of C1 and C3. The concept of the PCL can be applied only if subluxation or pseudosubluxation is present. **A:** Pseudosubluxation is absent: The anterior aspect of the spinous process of C2 will commonly miss the PCL by 2 mm—*normal* or *abnormal* (PCL cannot be applied). **B:** Pseudosubluxation is present: The anterior aspect of the spinous process of C2 lies on the PCL—*normal.* **C:** Subluxation is present: The anterior aspect of the spinous process of C2 misses the PCL by 2 mm. This finding is suggestive of a hangman's fracture of the neural arches of C2—*abnormal.* (Reproduced with permission from Fesmire FM, Luten RC. The pediatric cervical spine: Developmental anatomy and clinical aspects. *J Emerg Med.* 1989;7:133–142.)

In adults, widening of the predental space (>2.5 to 3 mm) frequently signifies rupture of the transverse ligament resulting in subluxation of C1 on C2. However, in children younger than 8 years, distances of 3 to 4 mm are common. Furthermore, distances up to 5 mm may be seen in nonpathologic instances (2); however, in these cases they should be considered abnormal until proven otherwise.

Widening of the prevertebral soft tissue owing to hemorrhage and edema is an important adult radiographic finding. In children, suggested norms have included soft tissue space <7 mm anterior to C2 or less than three-fourths of the adjacent vertebral body's width. The younger the child, the more unreliable these norms are due to dramatic increases in soft tissue density during expiration or when

the neck is held in mild flexion at the moment any given radiograph is taken.

CLINICAL PRESENTATION

Less than 1% of all spinal cord injuries occur in children younger than 12 years old, about 5% occur in children 12 to 16 years, and nearly 25% occur in 17 to 22 year olds (3). Furthermore, the incidence of pediatric cervical spinal injuries is only 1% to 3%, and only approximately 1% of all pediatric cervical spine radiographs reveal an abnormality (4–6).

The incidence of cervical spine fractures and dislocations increases with age. Radiographically apparent cervical spine injury, excluding birth trauma, is virtually nonexistent in children younger than 16 months (5–7). The cause of cervical spine fractures and dislocations is broad, and the epidemiology of injury may reflect regional differences. In general, motor vehicle accidents and falls account for the majority of injuries in children younger than 8 years old, whereas sports injuries are more common in older children (3,5,7).

Pediatric cervical injuries related to the use of front-passenger airbags have been increasingly described in the literature. Airbag deployment has produced a pattern of cervical injuries in older children traveling in front seats, and crush injuries to the skulls of infants in rear-facing safety seats (8). Thus, a child who is unrestrained or is inappropriately close to an airbag may be at risk of injury. Currently, the American Academy of Pediatrics recommends placing infants and toddlers in a rear-facing car safety seat (CSS) until they are 2 years of age. Children 2 years or older generally should use a forward-facing CSS with a harness for as long as possible, and all children whose weight or height is above the forward-facing limit for their CSS should use a belt-positioning booster seat until the vehicle lap-and-shoulder seat belt fits properly, typically when they have reached 4 feet 9 in in height and are between 8 and 12 years of age. Children younger than 13 years should be restrained in the rear seats of vehicles for optimal protection (9). Unfortunately, critical misuses of car safety restraints have been reported to be as high as 73% (10).

Types of pediatric cervical spine injuries can be divided into those of the upper cervical spine (C1 to C3) and those of the lower cervical spine (C4 to C7). Injuries most commonly seen in the upper cervical spine are fractures or synchondral separations of the odontoid with atlantoaxial dislocations, and hangman's fractures of the neural arches of C2. Abnormalities most frequently encountered in the lower cervical spine are anterior subluxations or dislocations, compression fractures, teardrop fractures, and spinous process fractures. The distribution of the level of cervical spine injury varies with age, reflecting the effect of the relatively large head of the child, coupled with the laxity of ligaments and the nearly horizontal facet joints. Young children have a larger head-to-body ratio that results in higher torques and shear forces being applied to the C1 to C3 regions, increasing their risk for upper cervical spine injuries (5,7,11). As a general rule, children younger than 8 years old have more upper cervical spine injuries, whereas children older than 14 years have more adult-like injury patterns with more low cervical spine lesions. Children between the ages of 8 and 14 are in a transition state between the two. The incidence of neurologic deficits with cervical spine fractures and dislocations also increases with age, with neurologic deficits occurring in 20% of children younger than 8 years of age but in approximately 40% of children aged 8 to 16 years (5).

In addition to vertebral injuries seen on plain x-rays, the pediatric patient may also suffer spinal cord injury without radiographic abnormality (SCIWORA), a term introduced before widespread use of magnetic resonance imaging (MRI). In the child, the flexibility and elasticity of the vertebral column are more than that of the spinal cord. Thus, a distraction injury may cause cord traction or ischemia without noticeable skeletal defects. The pathophysiology of SCIWORA is thought to involve a combination of a diverse multitude of mechanisms, all resulting in a disruption of microvascular blood supply. Proposed mechanisms include spinal cord traction, concussion, hyperextension with inward bulging of the interlaminar ligaments, reversible disc prolapse, flexion compression of the cord, and vertebral artery spasm.

There is wide variability in the reported incidence of SCIWORA, ranging between 18% and 38% of all pediatric spinal injuries (5,12,13). Because of the age-related anatomic differences, it is not surprising that SCIWORA injuries usually occur in younger children (mean age between 9 and 11 years) and involve the upper cervical spine in up to 80% of cases (5,12,13). Interestingly, in one series (12), sports-related activities were associated with 54% of cases of SCIWORA and involved older children and adolescents. Most cases of SCIWORA present with motor or sensory neurologic deficits, most commonly paresthesias, and have partial cord syndromes (5,12,13). However, delayed onset of neurologic deficits and complete cord transection can occur.

The increased mobility of the child's cervical spine also results in specific patterns of injury. For example, the energy of a blunt force tends to be dispersed over more vertebral segments, thereby increasing the incidence of contiguous and even noncontiguous fractures (11,14). Furthermore, the presence of a significant spinal injury implies that a high-energy event occurred; thus, approximately 60% of children with spinal fractures have associated injuries, most commonly thoracic, including pulmonary contusions, pneumothoraces, and rib fractures (11).

ED EVALUATION AND MANAGEMENT

It is often difficult to find appropriately sized cervical collars for infants and young children. Furthermore, improper spinal immobilization may cause neurologic injury, airway obstruction, pain, and increased intracranial pressure. Thus, extreme care must be used when immobilizing a pediatric trauma patient.

It should be noted there are no randomized controlled trials assessing the utility of cervical spine immobilization in trauma patients (15). As a general rule, children who are alert will not move a significantly injured part of the body. When an alert child vigorously resists immobilization, an injury may worsen. Thus, it is acceptable not to immobilize the cervical spine of a young alert child with no obvious injuries who is vigorously resisting medical

personnel. Children with potential cervical spine injury who are not actively resisting treatment however should be immobilized.

Prehospital cervical spine immobilization is best accomplished using a rigid plastic cervical collar and a backboard, combined with tape, sandbags, or a commercially available head-immobilization device. However, neutral position is difficult to achieve and may be present in as few as 11% to 20% of immobilized children presenting to the emergency department (ED) (3,16). The disproportionate head size of young children tends to cause cervical flexion in patients younger than 7 years when immobilized on a standard flat backboard. Flexion can be prevented either by placing padding beneath the back to raise the level of the thoracic spine or by using a spinal backboard with a recess for the occiput. The cervical spine is properly positioned when a line drawn through the external auditory meatus and the anterior aspect of the shoulder is parallel to the backboard.

In the recent past, it was recommended that all children who arrive at the ED with a new neurologic deficit consistent with a spinal cord injury and a history of trauma or concern for suspected trauma should be treated with high-dose methylprednisolone as soon as possible (17). This intervention remains controversial, however. Convincing data to support its use are lacking and there is evidence that high-dose steroids are associated with harmful side effects (18). Therefore, current guidelines do not recommend administration of methylprednisolone for acute spinal cord injury as a standard of care (18,19).

The management of the threatened airway in a child can be an urgent dilemma. Ventilation can frequently be accomplished with a chin-lift alone (which elevates the tongue off the hypopharynx) or in combination with bag-valve-mask ventilation. The jaw thrust maneuver is indicated when there is suspicion of cervical injury. Oral intubation, which is preferred in younger children, is best performed using manual inline stabilization *without* traction so as not to aggravate a distraction injury. Young children require little, if any, extension to visualize the glottis. Nasotracheal intubation should be attempted only in older children with spontaneous respirations.

Cervical spine injuries, although potentially devastating, remain rare. This has led to the development of clinical algorithms that identify children at high risk for cervical spine injury while avoiding unnecessary x-rays (and hence radiation exposure) in low-risk children. A prospective, multicenter study by the National Emergency X-Radiography Utilization Study (NEXUS) group (6) applied the following set of five predictors for low risk of cervical spine injury: (1) no midline cervical tenderness, (2) no focal neurologic deficit, (3) normal level of alertness, (4) absence of intoxication, and (5) no painful distracting injury. Thirty (0.98%) of the 3,065 patients who were younger than 18 years had a cervical spine injury. These clinical criteria correctly identified all cervical spine injury victims (sensitivity of 100%) and correctly designated 603 patients at low risk for cervical spine injury (negative predictive value of 100%). However, the positive predictive value was only 1.2%, and there were only a small number of infants and toddlers included, thus limiting the applicability of NEXUS to this age group.

Several other studies involving children are in broad agreement in supporting a low threshold for radiographic examination of the cervical spine in young children (20). A recent study validated the use of the NEXUS criteria to detect cervical spine injuries in children after trauma and safely allow clearance of the cervical spine by neurosurgical personnel (4). Finally, in a large multicenter study by PECARN of 540 children with cervical spine injury after blunt trauma, 8 clinical predictors of injury were identified: (1) altered mental status, (2) focal neurologic deficits, (3) complaint of neck pain, (4) torticollis, (5) substantial torso injury, (6) predisposing condition, (7) diving, and (8) high-risk motor vehicle crash. Having at least one of these criteria had a sensitivity of 98% and specificity of 26% for cervical spine injury (21).

In light of the existing data, a conservative approach to clearing the cervical spine with clinical criteria in children seems reasonable. If a child is brought to the ED with the neck immobilized but no history of a high-risk mechanism nor direct neck trauma and is awake, alert, cooperative with no distracting injury, has no complaint of neck pain and no neurologic deficit (or history of

transient paralysis or sensory change), the cervical collar can be removed for further neck examination. The child should try to maintain the neck in neutral position (with help from a clinician, if necessary) while the neck is inspected and the spine palpated. If there is no neck tenderness, gentle active range of motion of the neck is allowed. Children with a spinal injury typically limit their neck motion secondary to pain in order to protect the area of injury; therefore, never forcibly extend or flex the child's neck. If there is neck tenderness or limitation of movement due to pain, the cervical collar should be reapplied and appropriate radiographic examination performed. Otherwise, immobilization devices can be removed and the cervical spine cleared clinically.

For patients who cannot be cleared clinically, radiographic examination begins with a lateral cervical spine x-ray with the collar in place. This view, however, may miss 5% to 20% of injuries (2). Therefore, the standard three-view series (lateral, anteroposterior, and odontoid x-rays) should be obtained, recognizing that the open-mouth odontoid view is frequently impossible to obtain in young children. A cervical spine injury may be nevertheless missed because of altered mental status, distracting injury, inadequate examination, or SCIWORA. In addition, a limited appreciation of normal variants seen during growth and development, as well as suboptimal radiographic technique, may also lead to misdiagnosis. In a recent study of 206 children with blunt trauma-related bony or ligamentous cervical spine injury, adequate cervical spine radiographs had a sensitivity of 90% (95% CI: 85% to 94%); among the children with missed injuries, half had either altered mental status or focal neurologic findings (22).

There has been an increase in the use of high-speed computed tomography (CT) scanning to screen test for cervical spine injuries. It has a higher sensitivity (about 98%) for detecting fractures, as well as other injuries potentially missed on plain radiography (4,23,24). Cervical spine CT, however, results in significant exposure to ionizing radiation, which is concerning in children. Also, although CT scanning is preferred for identifying bony injuries, it is less sensitive in detecting ligamentous injuries, which are often seen in

children. In a study of 84 pediatric patients who underwent both CT and MRI studies of the cervical spine after trauma, MRI had a sensitivity of 100% and a specificity of 97% in detecting bony injury (25). Thus, MRI is preferred if there are symptoms of myelopathy or if the patient's mental status makes serial clinical evaluations problematic (24).

In children and young adolescents, the majority of cervical spine injuries occur in the upper cervical spine and are likely to be identified on three-view radiography. Three-view radiography should thus continue to be used for the initial evaluation of the cervical spine in children younger than 14 years, regardless of the child's mental status, given concerns regarding the greater radiation exposure from CT (24). CT scanning should be considered if: (1) adequate plain films cannot be obtained and there is suspicion for injury; (2) there is a fracture, displacement, or other suspicious finding on plain radiograph; or (3) there is high suspicion of injury based on clinical or physical exam findings. As SCIWORA is a real concern in some patients, all children with potential spinal injury should be questioned specifically concerning transient paresthesias at the time of the injury. If the history is positive, a spinal injury should be assumed to be present and immobilization should be maintained until neurosurgical consultation can take place.

KEY TESTING

- Use NEXUS or PECARN criteria, if appropriate, to clinically clear the cervical spine without unnecessary imaging.
- If radiographic clearance is needed, order two- to three-view plain radiographs of the cervical spine (add CT of C1/C2 if intubated).
  - If normal and child is asymptomatic: clear cervical spine.
  - If normal and child is symptomatic: order MRI.
  - If plain radiographs are abnormal or suspicious: order CT and MRI (if bone abnormality); MRI (if no bone abnormality).
- If child is symptomatic, has a neurologic deficit, evidence of SCIWORA, or there is high suspicion of injury based on clinical and physical examination findings: order MRI.

CRITICAL INTERVENTIONS

- Use a properly fitted hard cervical collar to maintain the neck in neutral position.
- If emergent airway management is needed, continue in-line immobilization without traction to avoid creating or exacerbating neurologic injury.
- Order imaging, beginning with a lateral neck x-ray, if the child has any of the following: cervical tenderness or pain, focal neurologic deficit, altered consciousness, intoxication, painful distracting injury, or high-risk mechanism of injury.
- If there is limitation of neck movement, persistent cervical pain, or neurologic symptoms even in the face of unremarkable three-view cervical spine x-rays, maintain immobilization and proceed with additional radiographic studies (e.g., fluoroscopy, CT, or MRI) and neurosurgical consultation.

DISPOSITION

All children suspected of having a cervical spine injury on the basis of clinical findings or radiographic studies should have neurosurgical consultation to assess the severity of injury and need for further evaluation and treatment. Pending further studies, it is prudent to admit all children with suspected cervical spine injury to the hospital. Adolescents with clinically insignificant vertebral injury (e.g., type 1 odontoid fracture, spinous process fracture) and a normal neurologic examination may be considered for outpatient management. Any child with a potentially unstable vertebral fracture or with a spinal column injury without cord damage should be admitted to an inpatient unit. All children with proven spinal cord injury should be admitted or transferred to a pediatric intensive care unit.

Common Pitfalls

- Open synchondroses and secondary ossification centers may be confused with fractures.

- Anterior wedging of cervical bodies, pseudosubluxation of C2/C3 or C3/C4, increased prevertebral soft tissue density, absence of normal lordosis, and widening of the predental space may be normal in pediatric patients.
- A normal radiograph does not definitely rule out spinal cord injury. All children with suspected cervical spine injury should be questioned specifically for transient paresthesias at the time of the injury; approximately half of patients with delayed onset of SCIWORA have this finding.
- A young alert child with no obvious injuries who is vigorously resisting all attempts at immobilization should not be forced into a restraining device, as this may result in secondary injuries.

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CHAPTER 250 Thoracic Trauma

Brent R. King

As is the case with adult patients, in children and adolescents trauma to the chest can either be blunt or penetrating, and injures can be restricted to the chest wall or may involve deeper structures.

Blunt trauma causes most injuries in all age groups, although adolescents may be victims of penetrating (1) chest trauma.

Because infants and young children have more compliant rib cages and less well developed thoracic musculature, blunt force to the chest wall is more easily transferred to deeper structures (2). Likewise, given the patient's smaller body mass, missile injuries can be more devastating than might be the case in older patients.

CLINICAL PRESENTATION

Children who have sustained thoracic trauma may present along a spectrum of illness. At one end are those children who appear to have no or very minor injuries and on the other end are those who are critically ill or in extremis. However, because pediatric patients have immature cognitive and verbal skills, emergency physicians must use extra care and rely more heavily upon the results of the physical examination, laboratory, and imaging studies. Additionally, as in the evaluation of any trauma patient, frequent reassessment is required in order to identify evidence of clinical deterioration or occult injuries.

The emergency physician should be alert for signs of intrathoracic injuries, including tachypnea, tachycardia, abnormal movement of the chest wall, and diminished or abnormal breath sounds. Less

specific signs such as hypotension and tachycardia are associated with significant injuries, including vascular injuries within the thoracic cavity (3). External signs of trauma like “seat-belt marks” and other bruises may indicate trauma to internal organs and should prompt further investigation. As is the case with adult patients, older children and adolescents who are conscious should be directly questioned and examined for the presence of chest wall pain or tenderness.

DIFFERENTIAL DIAGNOSIS

Blunt Chest Trauma

Blunt trauma, the most common mechanism of chest injury in the pediatric age group may cause injury to the chest wall musculature and ribs, as well as injury to the lungs, heart, great vessels, or diaphragm. Trauma involving both the chest and abdomen is more common than isolated thoracic trauma, making evaluation for the presence of associated intra-abdominal injuries mandatory.

Significant bruising of the chest wall, complaints of pleuritic chest pain, local tenderness to palpation, an unusual respiratory pattern, or abnormal excursion of the chest wall, all suggest rib fracture. Traditional wisdom has long held rib fractures uncommon in pediatric patients, but recent studies suggest that they are more common than was previously suspected (3,4). Rib fractures in very young children carry two important implications. First, rib fractures, especially lateral rib fractures in babies, are often associated with child abuse (fractures occur when the child’s chest wall is squeezed or compressed by an adult) (5); and second, due to the more compliant pediatric chest wall, rib fractures may indicate that there has been a significant blunt force and the patient may have sustained pulmonary, cardiac, or intrathoracic vascular injuries.

Abnormal or absent breath sounds suggest a pulmonary contusion, pneumothorax, or a hemothorax caused by intrathoracic vascular injury (3). Tachycardia and hypotension in the presence of unilaterally decreased breath sounds suggest tension pneumothorax. This injury can also be associated with other signs of elevated

intrathoracic pressure (e.g., distended neck veins). Tension pneumothorax is a life-threatening emergency requiring prompt treatment with a needle or tube thoracostomy.

On the other hand, tachycardia and hypotension in the presence of normal breath sounds imply injury to the heart or to vascular structures within the mediastinum; pericardial tamponade is the most common injury associated with these symptoms. In rare cases, direct blunt trauma to the heart can cause cardiac contusion, with potential subsequent cardiac dysrrhythmias. Commodio cordis represents a specific direct blunt injury to the heart itself that causes immediate ventricular fibrillation and cardiac arrest. It occurs most commonly among young males after a direct blow to the precordial chest region (e.g., a thrown baseball or elbow to the chest) (6).

Finally, it must be remembered that the esophagus travels through the mediastinum, so injures to mediastinal structures can also injure the esophagus. The esophagus can also be directly injured by forceful emesis, as a result of an attempted Heimlich maneuver, or when certain objects or substances are swallowed.

Penetrating Trauma

The differential diagnosis of penetrating chest injury is necessarily broad and depends on the mechanism of injury and its location. Projectile weapons, especially firearms, deliver significant force at the point of impact and beyond and can injure organs that are remote from the point where the projectile entered the body. Projectiles can be deflected by bones or other structures, and knives or other devices can lacerate tissues deeper than originally suspected upon examination of the blade. Therefore, it is safest to assume a patient with penetrating trauma has sustained injuries to multiple intrathoracic structures until evaluation proves otherwise. All of the injuries described in the section on blunt trauma can also occur as a result of penetrating trauma. Some injuries, however, like pericardial tamponade or injuries to mediastinal structures are more common after penetrating trauma (7).

ED EVALUATION

The evaluation of the child with blunt or penetrating chest trauma begins with a process familiar to most emergency physicians (8). After a patent airway is assured, the patient's chest is auscultated to note respiratory effort and the presence or absence of normal breath sounds in both hemithoraces. While normal bilateral breath sounds do not mean that no significant injury has occurred, they do suggest that the patient can tolerate a brief period of evaluation to determine the nature and location of specific injuries. Children who do not have adequate respiratory effort require immediate assisted ventilation, followed by placement of an artificial airway. Those who are hypoxemic but have a reasonably normal respiratory effort can be managed with supplemental oxygen, pending further investigation.

The patient's circulatory status is then addressed and life threats identified and treated. Hypotension in the presence of unilaterally decreased breath sounds implies the presence of a tension pneumothorax or a massive hemothorax. Tension pneumothorax can be associated with air hunger and decreased oxygen saturation. Hypotension is an inconsistent finding, and distended neck veins, while frequently discussed, may be present but are uncommonly found (9). Resonance with percussion of the chest wall might also be noted. On the other hand, because hemothorax is associated with significant blood loss, hypotension tends to dominate the clinical picture, but signs of respiratory distress are typically also present (9). The neck veins may not be distended and the large amount of blood in the chest cavity can result in dullness to percussion. Both findings require urgent intervention. Tension pneumothorax can be managed by immediate placement of a thoracostomy tube or can be temporarily converted to an open pneumothorax by needle thoracostomy. In younger, smaller patients, this procedure can be performed by placement of an over-the-needle plastic catheter in the second intercostal space in the mid-clavicular line or in the fourth interspace in the mid-axillary line. In larger adolescents, the mid-

axillary line is preferred as it avoids the musculature of the chest wall. Longer catheters may be required in obese children.

Massive hemothorax should be managed by tube thoracostomy and by transfusion to maintain circulatory function. In the past, emphasis was placed on autotransfusion of the blood evacuated from the thoracic cavity, but recent research has called this practice into question and it is currently considered controversial (10). Patients who have significant blood draining from the thoracostomy tube are candidates for urgent operative intervention.

Open pneumothorax is another potentially life-threatening injury. Also known as a “sucking chest wound,” this injury prevents the establishment of negative intrathoracic pressure during inspiration and renders effective respiration impossible. It can be definitively treated with placement of a tube thoracostomy and closure of the chest wall defect. In the emergency department (ED), however, it is sometimes treated by placement of an occlusive dressing over the wound which is left open on one side, creating a “flutter valve” that allows air to exit the thoracic cavity during expiration but prevents air from entering during inspiration.

Victims of trauma who have signs of life during transport but become moribund within minutes of arrival at a trauma center are potential candidates for ED thoracostomy. The indications for performing ED thoracostomy in children are identical to those in adult patients. Trauma centers that care for children should have available appropriate equipment to perform this procedure.

After the primary survey is complete and the patient is stabilized, a secondary survey should be performed. The secondary survey of the chest includes a careful external examination of the anterior, posterior, and lateral aspects of the chest to identify signs of injury, auscultation of the chest in several areas, and palpation of the soft tissues and bony structures of the chest wall. Any positive findings can then be used to guide further diagnostic testing.

Pneumothorax may be suspected on the basis of decreased breath sounds or the presence of air in subcutaneous tissues. Often, however, it is identified on routine chest imaging. Since pneumothorax can be difficult to detect by clinical examination,

most victims of significant blunt chest trauma and all victims of penetrating trauma must undergo routine chest radiography unless a near-immediate chest CT is being performed (1). Recently, the FAST examination (focused abdominal sonography in trauma) has become the E-FAST examination (extended FAST) with the addition of ultrasound evaluation of the upper lung fields. The absence of the normal finding of the pleural linings moving against one another (so-called lung slide or lung sliding) is indicative of pneumothorax (11). Computed tomography (CT) of the head, chest, abdomen, and pelvis in victims of major trauma has made it possible to identify virtually every significant injury, and many insignificant injuries, in a matter of minutes. CT allows the detection of even the smallest pneumothorax. However, this enhanced imaging capability comes at the price of a substantial dose of radiation. A small percentage of patients who undergo comprehensive CT scanning will later develop one of a variety of cancers as a result of this radiation exposure (see Chapter 245). As children have longer life expectancies than older patients and therefore a longer period after exposure to radiation, they are thought to be at greater risk. Consequently, many authorities recommend more judicious use of CT scanning in the pediatric population (12).

Pulmonary contusion is a common injury that is caused by a direct blow transmitted to the lung, resulting in hemorrhage, interstitial edema, alveolar collapse, and consolidation (3,13). Although evidence of chest wall injury may be minimal or absent, a pulmonary contusion should be suspected when there is history of a likely mechanism and the presence of hypoxemia or rib fracture (1,3). Pulmonary contusion may not be visualized on the initial chest x-ray, but may be visible on subsequent films, usually within 6 hours of the injury. The radiographic appearance is that of an opacified lung segment (13). If a patient has unexplained respiratory distress after blunt trauma, a CT may be indicated since it is more sensitive than plain films for identification of pulmonary contusion (13).

Hemothorax is usually the result of injury to an intrathoracic blood vessel or to the lung tissue itself. Hemothorax is suspected

when the patient has deceased breath sounds, evidence of hypovolemia, respiratory compromise, or dullness to percussion on the affected side (8,9). External evidence of injury to the chest wall should also raise clinical suspicion. In many cases, however, hemothorax will be identified on routine chest radiograph or will be seen when the diaphragm is visualized on E-FAST scanning. Most hemothoraces require evacuation with a thoracostomy tube. In the past, authorities have advocated the use of large-bore tubes to insure adequate drainage, but more recent literature suggests that this is not as important as was once thought (14). Persistent drainage of blood from the chest tube ($>$100 mL/hr or $>$20% of the child's blood volume) is an indication for surgical intervention.

Direct injury to the heart and mediastinal structures can occur with either blunt or penetrating trauma. Missile injuries or stab wounds in any part of the thorax can involve the heart and much of the chest and abdomen as well. Blunt trauma to the anterior chest can also involve the heart and the great vessels. Bruising and tenderness of the anterior chest wall, distant or muffled heart sounds, especially when accompanied by unexplained hypotension, or diminished pulses should all raise suspicion for an injury to the heart (8). Although some cardiac injuries (e.g., pericardial effusion) might be suspected based upon the findings of a routine chest x-ray, the test of choice for the urgent evaluation of the heart is bedside ultrasonography. The four-chamber subxyphoid (sometimes called "subcostal") view of the heart is a routine part of the E-FAST examination. This study can quickly identify the presence of a pericardial effusion with or without tamponade physiology and also allows for the rapid assessment of cardiac activity and the adequacy of ventricular function. Pericardial tamponade, which can be identified by the presence of right ventricular diastolic collapse on ultrasound, is a life-threatening emergency that requires urgent operative intervention or the performance of bedside emergency pericardiocentesis (15).

Cardiac contusion is a much rarer condition that can occur as a result of a forceful, direct blow to the anterior chest. Patients with myocardial contusion may present with dysrhythmias, unexplained

hypotension, or elevation of cardiac-specific enzymes (8,16). Two-dimensional echocardiography is essential for inspection of the valves, the pericardial space, and ventricular wall motion (1,16). Treatment of children with serious myocardial contusion should follow the same guidelines as for acute myocardial infarction in adults (16). In most cases, injuries are not serious and management is usually supportive, including continuous monitoring for rhythm disturbance and hypotension (1,16).

Injury to other mediastinal structures, most notably the aorta and the esophagus, are uncommon in children and adolescents but can occur as a result of significant blunt trauma or penetrating injuries. Signs of aortic injury include paraplegia, upper extremity hypertension, diminished pulses in the lower extremities, or hypotension. A widened mediastinum, sternal fracture, or first-rib fracture may be noted on plain chest x-ray (1). Victims of significant blunt and penetrating trauma will, however, very often undergo CT scanning of their chests. Contrast-enhanced CT identifies almost all significant aortic injuries.

KEY TESTING

- Plain chest radiography for most patients
- Bedside ultrasound to identify the presence of pneumothorax or pericardial tamponade in patients with hypotension, decreased or abnormal breath sounds, muffled heart sounds, or cardiac arrhythmias
- Electrocardiogram performed and cardiac enzymes measured in patients with arrhythmias after blunt chest trauma
- CT should be considered in patients suspected of having significant intrathoracic injuries and should be considered the test of choice for suspected thoracic aortic injury
- Patients with significant blood loss and those requiring large-volume transfusion should have a prompt type and cross match for blood products and should have their coagulation parameters measured

ED MANAGEMENT

The ED management of children and adolescents who are victims of chest trauma largely depends upon the findings identified during the initial clinical evaluation and testing. Some patients will be found to have sustained only minor injuries and can be treated with analgesia and local wound care. Other patients will require near-immediate transfer to the operating room for life-saving interventions. However, many patients will require some intervention or observation by the emergency physician. Patients with life-threatening injuries resulting in respiratory compromise, tension pneumothorax, massive hemothorax, or pericardial tamponade require urgent management as previously described. Hypoxemic patients should receive supplemental oxygen but the routine administration of oxygen to all patients has recently been discouraged (17). Likewise, patients with hypotension should receive fluid resuscitation and, if needed, blood and blood products (8,18). Fluid administration is not a substitute for identification and treatment of injuries, however, nor is it appropriate for hemodynamically stable children.

Rarely, patients with blunt chest trauma may have potentially dangerous dysrhythmias which require antidysrhythmic agents or electrical cardioversion.

As previously noted, ED thoracostomy is only likely to be effective if it is performed in a setting where appropriate resources are available for definitive management of the patient's injuries, and then only in selected patients.

Patients with isolated penetrating injuries, such as stab wounds, will require initial evaluation by chest x-ray, ultrasound, or CT. In the absence of pneumothorax or other significant injury, older patients can be observed for a period of 4 to 6 hours. If they remain clinically stable during observation and repeat chest imaging fails to identify the presence of a pneumothorax or other injury, they can often be discharged from the ED with precautions or transferred to an observation setting for continued monitoring (19). Younger children should most often be placed in an observation setting or

admitted to the hospital after such injuries, and especially so if the mechanism is unclear or if abuse is suspected.

Patients with pneumothorax require one of three types of treatment. Those with minor pneumothorax may be initially managed with inspiration of 100% oxygen and observation, without placement of a thoracostomy tube. In some cases no other treatment is needed. Those with larger pneumothorax who are clinically stable may be good candidates for the placement of a small-bore thoracostomy tube attached to a Heimlich valve. The Heimlich valve allows gas from the chest cavity to exit but does not allow gas from the external environment to re-enter the chest. These devices offer several advantages. They are smaller and can be placed over a guide wire with less discomfort than might be experienced during the placement of a thoracostomy tube. They leave a much smaller scar, which may be important for cosmetic purposes. Stable patients can ambulate with the device in place. Finally, if suction is deemed to be necessary for complete evacuation of the pneumothorax, these catheters can accommodate standard thoracostomy suction devices (20). Many patients will not be appropriate candidates for either observation or placement of a Heimlich valve, and should be treated with an appropriate thoracostomy tube.

Pulmonary contusions should be addressed with great caution. Hypoxemic patients should receive supplemental oxygen in the ED. More importantly, however, the emergency physician should recognize that although a pulmonary contusion might appear relatively minor on initial presentation, these injuries can evolve over time and eventuate in respiratory compromise. Thus, most, if not all, of these patients should be admitted to a monitoring setting (1,4,13).

CRITICAL INTERVENTIONS

- Prompt recognition of the physiologically stable versus physiologically unstable patient.
- In patients with inadequate respiratory effort or who are hypoxemic despite the administration of supplemental oxygen,

establish an artificial airway and insure adequate ventilation and oxygenation.
- Immediately treat tension pneumothorax with a needle or tube thoracostomy.
- In patients suspected of having a pneumothorax or pericardial tamponade perform a bedside ultrasound to evaluate the pleura and the pericardium.
- For patients with massive hemothorax and other causes of intrathoracic hemorrhage, employ balanced resuscitation using blood component therapy after one or two initial boluses of crystalloids.

DISPOSITION

Just as the nature and extent of the patient's injuries dictate her or his ED management, these factors also determine the appropriate disposition. Children who have been found to have not been injured or to have sustained only minor injuries can be safely discharged with the usual caveat that they must remain under the care of reliable adults who can bring them back for further attention should they have an unexpected change in their condition.

Many injured children not require operative or other intervention but have findings that warrant admission to an inpatient unit or an observation setting. Examples include children with minor pneumothorax or pulmonary contusion. Adolescents with fractures of one or two ribs (except those with fractures of the first, second, or third rib) may be safely discharged in the absence of other findings, but patients with multiple rib fractures warrant observation. Rib fractures in younger children suggest that significant blunt trauma was delivered to the chest wall. Such patients should usually be placed in an observation setting or admitted to the hospital. Patients with a flail chest should be admitted to an intensive care unit for close monitoring. Likewise, all children whose injuries are more serious or whose condition has the potential to become worse should be admitted to a monitored setting.

Children with ongoing hemorrhage and those with serious pulmonary, cardiac, diaphragmatic, or mediastinal injuries may require operative intervention and if so, should be taken directly to the operating room or admitted to an intensive care unit pending surgery.

In many cases, an injured child requires resources that are not available at the treating facility. Such children should be transferred to a pediatric trauma center. Ideally, such transfers should occur once the patient has been stabilized, but even if it is not possible to completely stabilize the patient, the benefits of transfer often outweigh the risks. Once the referring center has reached the limits of its capability, transfer is in the patient's best interest (8). When available, a dedicated pediatric transport team should be deployed to effect the transfer in a timely fashion. Referring physicians should also consider consultation with specialists at the trauma center (via telephone or telemedicine link) prior to transfer.

One special population of children bears mention. When the emergency physician suspects that a child's injuries have been intentionally inflicted or are the result of caretaker neglect, he or she has a duty to report these suspicions to the appropriate authorities and should not discharge the patient until cleared to do so.

Common Pitfalls

- Failure to recognize that chest injury in children may occur with little or no external findings.
- Failure to understand that seemingly minor pulmonary contusions can worsen over time, leading to significant respiratory compromise.
- Failure to promptly recognize hemodynamic instability in children.
- Failure to recognize evidence of child abuse.

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CHAPTER 251

Abdominal Trauma

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Abdominal trauma is a leading cause of morbidity and mortality in children (1–5). The poorly developed abdominal musculature of young children, as well as their more compliant thoracic cage, places them at risk for abdominal injuries (3,4,6). The majority of these injuries are caused by blunt trauma (80% to 90%) (2,5–7), with motor vehicle accidents (as passenger, pedestrian, or bicyclist) and falls as leading causes (1,4–7). Penetrating injuries are rare (10% to 20%) in infants and young children (2,6) but appear to be more prominent among adolescents (6,8).

CLINICAL PRESENTATION

Children who have sustained abdominal trauma may have clinical findings on a spectrum from little or no evidence of serious injury to obvious life-threatening injuries. In most cases, however, patients can be divided into two broad categories, those with evidence of physiologic compromise and those with no evidence of physiologic compromise (5,6). This distinction is important because those patients in the former category will require resuscitation prior to or concurrent with their diagnostic evaluation, whereas those in the latter group require diagnostic evaluation only (5,6). It is important, however, to recognize that patients can move up and down the spectrum of illness during their emergency department (ED) evaluation and that frequent reassessment is mandatory to avoid missing clinical deterioration (1,6).

Attention to the physical examination can provide clues to potential injuries. Initially, vital signs should be obtained, as a child with tachycardia, tachypnea, and hypotension may have significant intra-abdominal injuries (3). Patients who have incurred abdominal trauma may have external injuries such as bruises, tenderness, and distension (1,3,6,7). Abdominal distension may be a sign of hemoperitoneum, but it is also a common nonspecific later finding in the crying child with aerophagia (5). Some injuries such as concomitant femur fractures, as well as those patients with a Glasgow coma scale less than 13, are associated with intra-abdominal injury (4,9), However, abdominal injury may not always be immediately apparent. This is typically the case for children with altered sensorium, neurologic impairment, or painful distracting injuries (4).

DIFFERENTIAL DIAGNOSIS

Given that many vital organs are located in the abdomen, trauma, whether blunt or penetrating, often injures more than one organ (1,2,5,6,8). This fact necessarily makes the differential diagnosis broad. However, in many cases, the patient's clinical presentation allows the practitioner to focus on a few key diagnoses (5). For example the child who presents with hypotension after a blunt abdominal injury has, in all probability, an injury of the liver or spleen (1,5). It is also important to recognize injury patterns that suggest the diagnosis of "seat belt syndrome" (see below) (6,10,11) as these patients have a threefold risk of intra-abdominal trauma as well as a 13-fold increase in the risk of gastrointestinal injury (11). In addition, abdominal trauma secondary to child abuse (6) should always be suspected in cases where the history is inconsistent with the mechanism of injury (6).

Though it is appropriate to use initial clinical findings to narrow the differential diagnosis and focus the patient's evaluation, care must be taken not to prematurely exclude certain diagnoses (6). In many cases, early symptoms of injury may be subtle and only

diagnosed after a thorough initial assessment followed by continual reassessments (6,9,12).

ED EVALUATION

Early ED evaluation follows a pathway familiar to most emergency practitioners (5–7). The evaluation begins with an assessment of the airway, followed if necessary by definitive airway management. The second step is the evaluation of the adequacy and effectiveness of respiratory efforts. The patient with hypoxemia should receive supplemental oxygen, whereas respiratory failure should be treated with mechanical ventilation.

Once the patient is assured of a stable airway and adequate respirations, attention is directed to the evaluation of the circulatory system (5,6). Victims of blunt trauma with hemodynamic compromise are evaluated differently from those without physiologic abnormalities (1,5,13–15). Though both groups undergo an initial physical examination intended to identify areas of tenderness, guarding, and signs of peritoneal irritation, patients in the former group require urgent resuscitation and an urgent evaluation to identify intra-abdominal pathology as soon as possible (5,6).

Currently, the preferred first imaging study is the Focused Assessment with Sonography for Trauma (FAST) examination. The FAST examination is an ultrasound scan performed at the bedside, often during the resuscitation phase of care. The FAST examination is intended to identify fluid (blood) in the peritoneal cavity. A minimum of four sonographic views are used. The right and left upper quadrant scans are used to identify fluid in Morison pouch and the splenorenal recess. A suprapubic view is used to find fluid collected behind the bladder. Finally, the subxiphoid view helps to exclude nonabdominal causes of hypotension by evaluating the heart and the pericardium. If the FAST examination reveals intra-abdominal fluid in an unstable child, immediate surgery is usually indicated (5,7,16). If the FAST examination is unavailable or is negative in a patient with hemodynamic compromise who has no

other source for his or her symptoms, then a diagnostic peritoneal lavage (DPL) should be considered (6). If a DPL is necessary it should be performed by the surgeon caring for the child, as DPL may interfere with subsequent abdominal examinations or imaging on which the decision to operate may be based (1). However, neither DPL nor FAST can identify the source of bleeding, and the decision for surgical intervention in the unstable patient should not depend on these studies (5,6). Although the FAST examination has modest sensitivity when used alone to identify hemoperitoneum or intra-abdominal injury in children with blunt abdominal trauma, it is most useful in combination with both the physical examination and laboratory tests (16,17).

Further evaluation of the hemodynamically unstable patient should include laboratory values for hemoglobin and blood type and crossmatch (5). Other laboratory studies such as amylase for diagnosing pancreatic and small-bowel injury and transaminase levels as markers for hepatic injury (5–7) are more controversial. In females of childbearing age, a blood or urine specimen should be sent for a pregnancy test. Urine should also be sent for urinalysis and a drug screen, if indicated (1,6).

The child with blunt abdominal trauma who is hemodynamically normal may be evaluated somewhat less aggressively. In recent years, contrast-enhanced computed tomography (CT) has become the study of choice in the evaluation of victims of blunt trauma with abnormal abdominal examinations and in those whose examinations are unreliable because of an altered sensorium, poorly developed verbal skills, or the presence of distracting injuries (1,4–6). The identification of intra-abdominal injuries by CT in the hemodynamically stable child permits for nonoperative management by the surgeon (1).

However, CT is not without risks, as fatal cancers are predicted to occur in the future in approximately 1 in 1,000 children who have undergone CT (6). Therefore, CT should only be performed when medically necessary and when the results will change management. Criteria such as the Blunt Abdominal Trauma in Children (BATiC) score (negative predictive value of 97%) are available to predict

patient's at low risk for abdominal trauma. The BATiC score predicts the absence of abdominal organ injury from blunt abdominal trauma utilizing abdominal Doppler ultrasound, physical findings, (abdominal pain, hemodynamic instability, peritoneal irritation) and blood tests. If the score is ≤ 7, intra-abdominal lesions are not probable and a CT scan or hospital admission may be preventable (18).

The utility of baseline laboratory values in the hemodynamically stable patient is also controversial. Capraro et al. retrospectively reviewed the use of routine laboratory studies (complete blood count, chemistry, coagulation studies, liver function tests, and pancreas enzymes) as a screening tool in trauma and found that none had sufficient sensitivity (range 5% to 75%) or negative predictive value (range 63% to 75%) to rule out intra-abdominal injury (11). If the abdominal examination is normal but the history is still worrisome, a reasonable diagnostic approach includes obtaining a hemoglobin, alanine aminotransferase (AST), aspirate aminotransferase (ALT), and urinalysis; laboratory tests are most helpful when combined with other physical examination and diagnostic test studies rather than in isolation (4,7,8). It is, however, recommended that children suspected of being physically abused be screened more liberally with transaminases to identify occult abdominal injury (8).

Penetrating abdominal injuries are rare, and their precise incidence is unknown. These injuries always necessitate evaluation by a surgeon (6). It is important to note that thoracic gunshot wounds and any penetrating injury below the nipples anteriorly and the scapula posteriorly may also involve the diaphragm and the abdominal cavity (2,4,8). Hemodynamically stable patients with penetrating trauma and suspected thoracoabdominal injury should receive an upright chest roentgenogram to exclude an associated hemothorax or pneumothorax and to document the presence of peritoneal air (6). Using clips to mark all entrance and exit wounds, the stable patient with a gunshot wound should also undergo a supine abdominal x-ray to assist in identification of the missile track and the presence of retroperitoneal air (6). However, the

hypotensive unstable child with penetrating abdominal trauma requires prompt operative treatment, and there should be no screening radiographs in the ED if a surgeon is available (6,8). Likewise, if the patient is hemodynamically stable with penetrating injury and has microscopic or gross hematuria, further evaluation for urologic injury is indicated.

KEY TESTING

- CBC
- Blood type and crossmatch
- Transaminases in appropriate circumstances
- Urinalysis
- Urine pregnancy test in females of childbearing age

ED MANAGEMENT

All patients with abdominal injury should undergo resuscitation according to established guidelines (1,5,6). Prompt consultation of a surgeon is indicated if intra-abdominal injury is suspected (6). After a functional airway is established, one should assess breathing.

Patients with hemodynamic instability should receive a 20-mL/kg bolus of normal saline or Ringer lactate, administered rapidly via intravenous or intraosseous access (1,5,6). Nasogastric tubes (NGTs) and urinary drainage catheters (Foley) may be placed, while blood is obtained for hemoglobin and hematocrit and type and crossmatch (3,5). An NGT should not be placed if there is visible blood or cerebrospinal fluid in the nose, significant facial injury, or a basilar skull fracture (6). Foley catheters should be avoided when blood is seen at the urethral meatus, there is a perineal or scrotal hematoma, or there is a high-riding prostate (6).

If a child remains hemodynamically unstable after 40 mL/kg of crystalloid fluid, then 10 to 20 mL/kg or more of blood should be transfused and continued efforts made to identify the source of bleeding (5,6). After intrathoracic or central nervous system causes for the hemodynamic instability are excluded, abdominal sources of bleeding should be sought. A FAST examination or DPL is performed

to determine the presence of intraperitoneal blood and, if positive, necessitates a laparotomy (5,6). Other indications for surgical exploration in the hemodynamically unstable child include abnormal vital signs, transfusion needs exceeding 40 mL/kg, peritoneal signs, abdominal distension, hypovolemia, and base deficit. It is important to note that abdominal distension secondary to aerophagia can mimic an acute abdomen, and insertion of a NGT can decompress the stomach (5). Intravenous antibiotics, analgesics, and tetanus toxoid should be administered as indicated (6).

In contrast, management of patients who present with abdominal trauma but are hemodynamically stable depends on the injuries identified and investigations planned. Children who are hemodynamically stable with suspected abdominal injury should have a hemoglobin, transaminases, (AST, ALT) and urinalysis (3). Females of childbearing age should undergo a pregnancy test (6). Other laboratory values and radiographic studies are performed for specific indications (6). Although an IV hep-lock may be placed, NGTs and Foley catheters are not routinely placed.

CT is the diagnostic study of choice for evaluating stable patients with suspected blunt abdominal trauma, as most blunt solid organ (liver, kidney, spleen, and pancreas) injury in children can be successfully managed nonoperatively (4–6,11). Observation should be carried out in hospitals equipped and staffed to care for children with these injuries (4,6). Therefore, once the workup is complete, the patient should be admitted to the hospital or transferred to a facility capable of the required monitoring and of managing his or her injuries. In most cases, a surgeon should be involved in the patient's care (6). Patients should receive serial abdominal examination and hemoglobin levels (5,6). Children with hemoglobin that remains >7 mg/dL can be treated conservatively without blood transfusion. Indications for surgical exploration based on CT imaging are evidence of bowel injury, renovascular injury, bladder rupture, ureteral transection, pancreatic injury, and contrast extravasations (4,6).

Children with penetrating wounds of the abdomen require surgical consultation, as children are more likely to require surgical

intervention for these injuries than adults (2,6).

Penetrating wounds of the abdomen and associated hypotension, peritonitis, evisceration, or ongoing hemorrhage require operative intervention (6). Pneumoperitoneum, unexplained fever, or leukocytoses are additional indications for laparotomy. Children with abdominal gunshot wounds require mandatory surgical exploration (6), and hemodynamically unstable children with stab wounds also require surgery (2,6,8). However, children with anterior stab wounds who are asymptomatic may be managed expectantly by pediatric and trauma surgeons (2,6).

SPECIFIC INJURIES

Diaphragm

Diaphragmatic injuries caused by blunt or penetrating thoracoabdominal trauma are rare in children (13), and there is no gold standard for early diagnosis. Chest x-rays in patients with diaphragmatic injury may show an irregular contour of the hemidiaphragm, but this finding is present in $<50\%$ of patients (6). Diagnostic tools such as ultrasound and CT scan are not always accurate (13), and the diagnosis may be missed initially (13). Surgical repair remains the standard of care for these patients (13).

Spleen and Liver

The spleen and liver are the most commonly injured abdominal organs in children (5,11). A history of left-sided trauma and physical findings of left upper quadrant tenderness, left shoulder pain (Kehr sign), and anemia may accompany splenic injury, but in some cases physical findings are initially subtle (5). Stable children with hepatic injuries usually complain of right upper quadrant pain and/or right shoulder pain. In addition, elevated transaminases are often noted (4,5). Liver injuries in children are generally more severe than splenic injuries and are associated with a higher morbidity and mortality.

The CT can accurately identify and grade both splenic and hepatic injury (5,7), and a surgeon can manage many of these injuries

nonoperatively if the patient remains hemodynamically stable. Splenic injuries that require <40 mL/kg of blood (one-half blood volume) in the first 24 hours (5,6) typically do not require operative intervention. Liver injuries tend to rebleed, and a lower transfusion cutoff of ≤ 30 mL/kg in the first 24 hours is more indicative of the need for surgery.

Intestinal Perforation

Intestinal perforations are atypical in children unless associated with seat belt syndrome (5,10,12). The diagnosis is often not made until peritonitis occurs, and surgical intervention is always required. Complications occur often with duodenal injuries (20% overall), and mortality increases from 11% to 40% with operative delay of greater than 24 hours. Twenty percent of cases of duodenal injury are associated with pancreatic damage (10). If there is no clear mechanism of injury for the intestinal perforation, then child abuse should be suspected (5).

Kidney

Renal injuries are commonly seen in children after blunt abdominal trauma, but the majority can be managed nonoperatively (6,14). Hemodynamically stable children with gross hematuria, microscopic hematuria (≤ 50 RBCs/HPF), or a history of rapid deceleration injury should be evaluated with CT (1,14,19). Stable patients with isolated microscopic hematuria (<50 RBCs/HPF) and suspected renal contusion may be observed without initial radiographic imaging but should be followed with serial urinalyses and bed rest.

Pancreas

Pancreatic injuries are uncommon (5,20) and there is no consensus regarding the management of patients with blunt pancreatic injuries (15). Serum amylase levels, lipase levels, and abdominal CT can be useful in making the diagnosis, although an early normal serum amylase does not rule out major pancreatic injury (5). Likewise, the

CT scan may not be accurate in determining the location and type of injury (5,20). Patients with distal transection of the pancreas require operative management (5,15), and patients with pancreatic contusion but no major ductal injury can be managed nonoperatively (5). When there is uncertainty regarding the status of the main pancreatic duct, patients should undergo further testing with endoscopic retrograde cholangiopancreatography (ERCP), or magnetic resonance cholangiopancreatography (MRCP) (15).

Pelvis

Pelvic fractures are uncommon in children (21,22), and they are more likely to be present in patients with multiple injuries and high injury severity scores (5,21). Contrary to adult findings, pelvic fractures in children usually do not cause massive bleeding, and only a small number of patients have associated genitourinary tract injuries (5). In the past, the pelvic x-ray was routinely used to establish the diagnosis (5,6,21,22), although in most cases the physical examination alone is reliable. (5,21,22). Clinical predictors of pelvic fracture in children include the presence of pelvic contusions or abrasions, hip or pelvic pain, abdominal pain or distension, and femoral deformity or pain. These predictors can help to determine the need for a pelvic x-ray in children with Glasgow Coma scale 13 to 14 and a history of blunt abdominal trauma (21,22). The majority of pelvic fractures in children are stable ring fractures, and treatment tends to be nonoperative, with most being treated with bed rest.

Seat Belt Syndrome

Also called the *lap belt complex,* the seat belt syndrome consists of characteristic patterns of visible abdominal wall or hip ecchymosis, intra-abdominal injury, and lumbar spine injuries that result from compression, burst, or shearing which are associated with wearing a lap-type seat belt. The seat belt sign (contusion) may be found on the abdomen and hips (3,10,16), and small-bowel perforation may be present even when the abdominal CT scan is negative (5,6,10).

Thus, patients with a seat belt sign should be admitted for serial abdominal examinations (5,10).

Lumbosacral injuries (i.e., compression) and Chance fractures may also occur in patients with a seat belt sign and small-bowel perforation. Chance fractures are caused by hyperflexion over the fulcrum of the seatbelt (1,5,6,10,16), which results in bony and ligamentous injuries (3). Plain radiographs are the diagnostic study of choice (5), and treatment includes hyperextension in cast or brace for bony injuries and spinal fusion for ligamentous injuries. Such injuries should be considered in children with other signs of the seat belt syndrome.

Likewise, solid organ laceration or contusion may also occur (kidney, spleen, liver, pancreas, or bladder) in restrained children, and a high level of suspicion is needed (10).

CRITICAL INTERVENTIONS

- Management of the physiologically stable versus physiologically unstable patient (Table 251.1).

TABLE 251.1
Management of the Physiologically Unstable Versus Physiologically Stable Patient

Physiologically Unstable Patient with Abdominal Trauma	Physiologically Stable Patient with Abdominal Trauma
Airway	**Airway**
100% oxygen; evaluate the necessity for an ET tube or needle thoracostomy	100% oxygen initially
Fluids	**Fluids**
20 mL/kg NS or Ringer lactate via bolus	IV hep-lock may be placed
Repeat bolus one or two times if needed	
Transfuse 10–20 mL/kg of blood for ↓ BP	
If vital signs are unstable, repeat the blood transfusion and proceed to laparotomy	
Laboratory Studies	**Laboratory Studies**
Hb, HCT, type and cross, pregnancy test in childbearing females	Hb, HCT, transaminases (AST, ALT), urinalysis, pregnancy test in childbearing females
Place nasogastric tube and Foley catheter	
Diagnostic Studies	**Diagnostic Studies**
FAST to check for intra-abdominal bleeding	Chest radiograph to rule out chest injury; CT scan of the abdomen for blunt abdominal trauma
Laparotomy	**Laparotomy**
Stab wounds and gunshot wounds	GI perforation, bladder rupture, pelvic fractures
Disposition	**Disposition**
Operating room or the ICU	Solid organ injuries; abdominal pain; and a small subset of anterior stab wounds in asymptomatic patients
Operating room or the ICU	Admit solid organ injuries; abdominal pain; and a small subset of anterior stab wounds in asymptomatic patients

Hb, hemoglobin; HCT, hematocrit.

- Administer 20 mL/kg NS or Ringer lactate by bolus and repeat one or two times if needed in the unstable patient with

abdominal trauma.
- Transfuse 10 to 20 mL/kg of blood for unstable patients who have received two or three boluses of NS or Ringer lactate and continue to have low blood pressure.
- Perform a FAST examination to check for intra-abdominal bleeding in the unstable patient with abdominal trauma.
- Early consultation of pediatric trauma specialists for children with suspected intra-abdominal injury

DISPOSITION

The patient's clinical assessment, the injury severity, and diagnostic results must be considered (1,4,16) when deciding on the necessity of surgical consultation. However, a surgeon familiar with pediatric trauma should be contacted as early as possible if intra-abdominal injury is suspected (2,3,6–8). All children with penetrating injury should be evaluated by a surgeon because of the likelihood of exploratory surgery (1). Depending on the type of injury, other specialists may also be needed for consultation (1).

The majority of children with abdominal trauma are admitted to the hospital for observation. The determination of which hospital unit is most appropriate for the care of these children depends on the severity of the injury and the type of monitoring required. For example, most children with splenic and hepatic injuries are admitted to the ICU for observation, serial examination, and management. All patients with seat belt sign, even with a negative CT scan, should be admitted for observation (12).

When considering the disposition of patients with abdominal trauma, one should keep in mind that there are no laboratory tests that reliably diagnose solid or visceral injury. Intestinal injuries can be especially difficult to diagnose (22). Thus, all children with persistent abdominal tenderness on examination, a seat belt sign, laboratory abnormalities, or radiographic evidence of intra-abdominal organ injury must be admitted for monitoring. Patients with a major solid organ injury should be admitted to an area

capable of providing intensive monitoring or transferred to an appropriate facility.

A small group of children with minimal abdominal pain and a history of abdominal trauma may be discharged home if they appear well and no significant injuries have been detected after a complete ED evaluation. In most cases, these patients should be observed in the ED for a few hours and then reexamined. After discharge, they should have follow-up with their primary care physician.

In a multicenter study of children evaluated in EDs after blunt abdominal trauma Kerry et al. (23) concluded that intra-abdominal injuries were rarely diagnosed after a normal abdominal CT scan result. The authors concluded that a normal physical examination and a normal abdominal CT may not require routine hospitalization for children after blunt abdominal injury. Safe discharge home is possible when there is no other reason for admission (16,23).

All patients admitted for observation of abdominal injuries should be managed in concert with pediatric or trauma surgical specialists (6). If a patient with abdominal injuries arrives at a hospital not equipped to care for children or the type of injury the patient has, then the patient should be rapidly stabilized and transferred to a regional pediatric or general trauma center (6). Patients with a pediatric trauma score of ≤ 8, or a revised trauma score < 12, should be transferred to a designated trauma facility (15). Similarly, children with multiple rib fractures at risk for splenic and liver injury may require transfer to a specialized center, as these injuries should be managed by surgeons familiar with nonoperative solid organ injury in facilities equipped to handle sequelae promptly (6).

Common Pitfalls

- Failure to promptly recognize hemodynamic instability in children.
- Failure to identify rupture of the small-bowel in seat belt syndrome.
- Failure to recognize evidence of child abuse.
- Failure to recognize that crying may cause abdominal distention.

• Failure to consult a pediatric surgeon or trauma specialist early.

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CHAPTER 252 Pediatric Fractures

Robert L. Cloutier

Fractures account for 15% of all pediatric ED visits. It has been reported that 42% of boys and 27% of girls will have at least one fracture by age 16. Fractures result from recreation, falls, sports, motor vehicle accidents, abuse, or other causes. It is important for ED physicians to recognize pediatric fracture patterns, be able to properly describe fractures, understand which fractures need orthopedic consultation in the ED, and provide proper disposition.

Children's fractures, in the context of a growing skeleton, differ from those in adults for a number of anatomic and physiologic reasons. The most obvious is the presence of the physis, or "growth plate," by which longitudinal bone growth occurs. The physis divides the young bone into four distinct zones: Epiphysis ("upon the physis"), physis (growth plate), metaphysis ("next to the physis"), and diaphysis ("between the physes"). The growing skeleton is more porous, which allows for greater flexibility and deformation before a fracture occurs. Pediatric bone is also contains more radiolucent cartilage than in adults, which is an important consideration when interpreting radiographs. Attachments such as ligaments and tendons are often stronger than the bone itself, making fractures about the physis more common than sprains or dislocations. The thick, active periosteum in children allows fractures to remodel and heal quickly, so proper alignment and reduction are essential to prevent progressive deformity.

DIFFERENTIAL DIAGNOSIS

The pattern of a fracture may reveal the mechanism of injury, which is important when determining whether a fracture pattern is consistent with the history. *Spiral* fractures are produced by a twisting mechanism. *Oblique* fractures occur with overloading in a longitudinal plane. *Transverse* fractures occur as a result of linear forces applied across the longitudinal axis of a bone, resulting in angulation. *Butterfly* fractures occur when both a longitudinal and linear force are applied to the same bone; these fractures are intrinsically unstable.

Torus or *buckle* fractures are a common type of pediatric fracture, particularly of the radius. These fractures occur when the cortex buckles secondary to an applied compression force. These fractures are stable and there are any complications. *Bowing* fractures, or *plastic deformations,* occur when longitudinal forces cause persistent bowing or deformation of a bone without any radiographically visible change to the cortex or periosteum. This injury requires reduction, and most commonly appears in the ulna or fibula. *Greenstick* fractures occur near the metaphyseal–diaphyseal junction when, because of the plasticity of children's bones, there is just enough force to start a fracture but not enough to cause it to extend across both cortices. Greenstick deformities are the most common fracture pattern seen in children. *Avulsion* fractures usually occur in adolescents around the pelvis, tibial tubercle, or phalanges after a strong muscular contraction when the ligaments and tendons are stronger than the adjacent bone.

The Salter and Harris (SH) classification scheme for physeal fractures is widely used. In an SH type I fracture, the fracture extends only through the physis. This type of injury may not be evident on radiographs because of minimal displacement, but the diagnosis can be made clinically when there is tenderness over the physis and adjacent soft tissue swelling. The SH type II fracture is one that extends from the physis into the metaphysis and is the most common physeal fracture seen in children (Fig. 252.1). In type III, the fracture extends from the physis into the epiphysis and the joint. This fracture tends to occur when the physes begin to partially close in mid- to late adolescence. SH type IV fractures cross the epiphysis

and the physis, exit through the metaphysis. The type IV is also intra-articular and most commonly appears in the lateral condyle of the humerus or in the tibia. The SH type V fracture describes a physeal injury that results from a crushing and compressive force and can often result in growth arrest. Initial radiographs may be normal, and the diagnosis is usually made in follow-up after the onset of growth arrest.

FIGURE 252.1 A Salter–Harris II fracture of the ring finger proximal phalange. The fracture extends along the physis and exits across the metaphysis. Closed reduction and splinting are appropriate for this fracture.

Understanding how to describe fractures when communicating with orthopedic colleagues is an important skill and can help to ensure optimal patient care. The radiographs should be described

using anatomic terms such as proximal, distal, diaphysis, metaphysis, and physis. Specific details should include the fracture pattern (e.g., spiral, oblique, greenstick), amount of displacement, degree of angulation, and description of any shortening or malrotation. Displacement is measured by using a percentage relative to the width of the bony shaft. Hairline fractures are described as nondisplaced, and anything less than 10% is considered minimally displaced. Angulation is described by using the direction of the apex and the degree of angulation (e.g., the Colles fracture has a dorsally displaced hand but is best described as having a certain degree of volar angulation). Physeal fractures should be described using the SH I to IV classification. Importantly, the presence of neurovascular compromise or of an open wound or a puncture wound must be communicated to the consultant.

ED EVALUATION

The diagnosis and initial management of pediatric fractures are very important because callous formation starts within a week. It is important to establish the circumstances and the mechanism surrounding the injury. Developing rapport while taking the history also allows the physician to gain the trust of the child and hopefully obtain a better examination.

The physical examination cannot be overemphasized, and it can be improved with adequate pain control. The examination should always start with an assessment of the neurologic and vascular status distal to the injury. Most children will cooperate with a light-touch sensory and limited motor examination. Next, the injured limb should be completely exposed by removing any splints or clothing and then exposing the uninjured limb for comparison. The injured extremity should be inspected closely for point tenderness, soft tissue swelling, or breaks in the skin. Radiographs are necessary for areas of significant swelling or tenderness, and breaks in the skin suggest the possibility of an open fracture. Surrounding joints should be examined through a gentle range of motion, looking for pain or possible dislocation.

High-quality radiographs are imperative; accepting poor radiographs can result in misdiagnosis or a missed fracture. Radiographs should include at least two views (anteroposterior and lateral) made at a 90-degree angle to one another. Injuries near a joint (e.g., wrist, elbow, knee, and ankle) frequently require an oblique, or third, view. Additional radiographs of the joint above and below the injury should be considered. To get the highest-quality films with the least amount of patient discomfort, it is important to address pain control before sending the patient to radiology.

Unique aspects of the interpretation of pediatric radiographs are the various stages of bone development and physeal closure. When there is a question regarding a fracture versus normal developmental anatomy, resources such as oblique views, a radiology textbook of normals, or comparison views of the uninjured extremity can be extremely helpful. Computed tomography (CT) scans can occasionally be useful when evaluating complex fractures and are often used to evaluate spinal injuries. Overall, stress-view radiographs have fallen out of favor. Finally, there are very few indications in the ED for modalities such as magnetic resonance imaging, arthrography, arteriography, or bone scanning.

Compartment syndrome is rare, but may occur following forearm and lower leg injuries (Fig. 252.2). The typical history is of a fracture or crush injury followed by bleeding and swelling within the inelastic adjacent fascial compartments. The earliest signs are pain out of proportion to the injury and extreme pain with passive range of motion. Findings such as pallor, paresthesias, and pulselessness are all late manifestations. Compartment syndrome is a true limb-threatening orthopedic emergency. Immediate consultation with an orthopedist is warranted to measure compartment syndromes and to consider emergency fasciotomy.

FIGURE 252.2 A tibia and fibula fracture resulting from high-energy trauma. This fracture is at an increased risk for compartment syndrome and should be followed up closely.

KEY TESTING

- Proper radiographs including two views (anteroposterior and lateral) made at a 90-degree angle to one another. Strongly consider x-rays of a joint above and below the injury.

ED MANAGEMENT

Once a fracture has been diagnosed, the emergency physician has three options: Immobilization with outpatient referral to a specialist; orthopedic consultation in the ED; or provision of definitive fracture care. The first option is the most common choice and should be considered for nondisplaced or minimally displaced fractures with a

low risk of short-term complications. In contrast, ED consultation by an orthopedist is necessary if there is any suggestion of compartment syndrome or neurovascular compromise, and urgent consultation should also be strongly considered for any open, moderately displaced, intra-articular, or unsuccessfully reduced fracture. Detailed follow-up care instructions should also be provided to every fracture patient.

The goal of immobilization is to maintain the fracture in a reduced position, prevent further injury, and improve patient comfort. Splinting is the most common form of immobilization utilized in the ED, and splints are available in plaster, in padded fiberglass, and in premade form. The benefit of plaster is the ease of molding, but plaster requires padding and special attention to the bony prominences. The benefit of fiberglass with prepadding is the ease of application, but these are more difficult to mold. Premade commercial splints are quick, but improper fits may result in poor immobilization. Proper splints should immobilize the fractured bone completely, which may require extending the splint to joints above and below the fracture. It is important to document neurovascular status *both* before and after splint application. The keys to splinting are adequate padding, a proper mold, and over-wrapping.

Casts are less commonly used in the ED because of concerns about progressive swelling inside a rigid cast. This concern may be alleviated to some degree by splitting the cast. Proper cast application requires skill and the right balance between being tight enough for immobilization and loose enough to allow for swelling. In most emergency settings, a properly applied splint is more appropriate, is safer, and is easier to apply.

Operative management should be considered for any unstable fracture. Operative management is the mainstay for SH III and IV fractures, malaligned intra-articular fractures, fractures with high risk for neurovascular compromise, and open fractures.

TREATMENT OF SPECIFIC FRACTURES

Shoulder

Fractures of the clavicle are common; 80% involve the middle third. They can be managed effectively with either a sling or a figure-of-eight brace for 3 to 4 weeks. Slings appear to be more commonly used. When pain allows, gentle range of motion exercises should be encouraged, but activity restrictions continue for at least 6 weeks following the injury. The rare indication for orthopedic intervention in the ED is when there is skin tenting or posterior displacement of the medial portion of the bone. Skin tenting can lead to local necrosis and the delayed creation of an open fracture. Medial clavicle fractures with posterior displacement pose a risk to mediastinal structures and should be imaged with CT scanning before attempts at reduction.

Fractures of the proximal humerus respond well to immobilization using a sling or shoulder immobilizer for 4 weeks. Most proximal humerus fractures are SH I or II fractures and, given the tremendous remodeling capabilities of the proximal humerus, heal well even with moderate displacement and angulation.

The scapula is rarely fractured, but it can be expected to heal with a sling or shoulder immobilizer. Exceptions are scapular fractures associated with clavicle fractures or with extension into the glenoid. These two situations require orthopedic consultation. A scapular fracture represents a high-energy injury and should trigger a careful history and evaluation for associated injuries.

Elbow

Pediatric elbow injuries are challenging. Proper radiographs must include both a true lateral and an AP view because these fractures may be subtle. Lateral radiographs should be carefully inspected for three specific findings that help in the diagnosis of occult elbow fractures. The first is the “sail sign,” which is seen when either the anterior or posterior fat pads is elevated because of hemarthrosis after a fracture. The second is the anterior humeral line, which should bisect the middle third of the capitellum when there is no fracture. The third is the alignment of the radial head and the capitellum, which should form a straight line extending along the

axis of the radius and passing through the center of the capitellum. Oblique or comparison views should be considered if clinical suspicion persists.

Occult fractures and nondisplaced supracondylar fractures can be managed with a posterior splint and close follow-up with orthopedics. Displaced supracondylar fractures are usually managed with operative pinning. The majority of lateral condyle fractures, medial condyle fractures, and radial neck fractures with more than 30 degrees of angulation are also managed operatively because of the need to maintain anatomic reduction. Fractures around the elbow are at high risk for neurovascular injury.

Forearm

Fractures of the radius and ulna are very common in pediatrics. The majority do very well with closed reduction and immobilization. It is important to also examine the elbow and wrist because associated injuries can be overlooked (e.g., Monteggia fractures are proximal ulna fractures with radial head dislocation, and distal torus fractures of the ulna are associated with physeal radial fractures). Torus or "buckle" fractures of the radius are managed with immobilization in a splint or cast for 3 to 4 weeks. Most reductions of single- or two-bone forearm fractures can be successfully performed with procedural sedation, but close follow-up is mandatory since reductions can drift into progressive deformities.

Hand and Wrist

Fractures of the pediatric hand remodel much better than those in adults. The vast majority of phalangeal fractures can be managed nonoperatively with splinting. The preferred position for immobilizing interphalangeal joints is in extension. Before splinting, closely inspect each digit for malrotation by looking at the alignment of the nail bed in extension and its orientation toward the scaphoid in flexion. Malrotation deformities will not remodel well and require reduction or operative attention. Metacarpal fractures, such as the "boxer's fracture" of the fifth metacarpal, are much more

common in adolescents and athletes who take part in contact sports. Metacarpal fractures tolerate significant angulation and are usually managed nonoperatively with immobilization (flexion of the metacarpophalangeal joint is preferred). Thumb fractures are managed by closed reduction and immobilization with a thumb spica. Tenderness in the snuffbox region suggests a scaphoid fracture and requires special scaphoid views in addition to the routine AP and lateral radiographs. Scaphoid fractures are difficult to diagnose in the ED, so when this is suspected, the patient should be placed in a thumb spica splint and have close follow-up arranged. Special attention should be paid to crush injuries of the hand and nailbed injuries with underlying phalangeal fractures.

Hip and Pelvis

Hip and pelvis fractures are relatively rare in children and usually occur as part of high-energy trauma or in sports-related avulsions. High-energy trauma is associated with pelvic fractures, acetabular fractures, and fractures of the proximal femur. These require orthopedic intervention as well as management of associated nonorthopedic injuries. It is important to determine whether the fracture is stable or unstable. Pelvic fractures can be accompanied by hemodynamic instability, gastrointestinal injury, or genitourinary injury. Slipped capital femoral epiphysis (SCFE) can mimic proximal femur fracture on radiographs, but a good history differentiates SCFE from high-energy trauma. Avulsion fractures of the hip and pelvis occur in adolescents when one of the hip muscles suddenly contracts, causing avulsion of the connected bone. Avulsions usually heal with pain control and protected weight bearing for 3 to 4 weeks. All pelvic and hip injuries need an AP radiograph of the pelvis. The standard lateral view is a frog-leg, but a cross-table lateral is preferred when there is concern about displacing a fracture with external rotation of the hip.

Knee

Fractures of the young knee commonly involve the distal femoral physis. The proximal tibia and the patella are less commonly fractured in children. Sports injuries in adolescents can result in avulsion fractures of the tibial plateau or the tibial tubercle. Standard radiographs of the knee include an AP, lateral, and patellar view (Merchant or sunrise view). The hip needs to be closely evaluated with any apparent knee injury because of the frequent occurrence of referred pain from hip pathology. Most physeal fractures of the knee do well with closed reduction and long-leg immobilization, but intra-articular fractures require surgical reduction and fixation. Patellar fractures and avulsion fractures can be managed with straight-leg immobilization and nonweight bearing until follow-up.

Leg

Fractures along the shaft of the femur and tibia require orthopedic consultation. Femoral fractures are managed on the basis of age and fracture characteristics, but either traction, spica casting, external fixation, or internal fixation can be expected. Tibial fractures with angulation or displacement require closed or open reduction, depending on the severity. Nondisplaced tibial and fibular fractures can be managed with long-leg immobilization, nonweight bearing, and close orthopedic follow-up. Importantly, tibial fractures are at increased risk for compartment syndrome and for progressive deformities.

A *toddler's fracture* is an oblique, nondisplaced, distal tibia fracture occurring in children up to 4 to 6 years of age. Toddler's fractures often present to the ED with limping after rather minor trauma or an unwitnessed event. Physical examination signs are subtle, and oblique views may be helpful. Patients with suspected toddler's fracture should receive long-leg immobilization and orthopedic follow-up because radiographs and the physical examination may be unremarkable in the ED.

Ankle

Younger children are more likely to experience physeal fractures than sprains after ankle injuries. SH I fractures of the distal fibula may occur after inversion injuries; radiographs are often negative except for soft tissue swelling, yet the clinical examination reveals tenderness over the physis. SH I and II fractures of the fibula are treated with short-leg immobilization, and reduction if necessary. SH II fractures of the tibia result from much greater forces and require reduction with long-leg immobilization. Fracture patterns in the ankle begin to change once the growth plates start to close in adolescence. SH III fractures of the tibia are known as Tillaux fractures (Fig. 252.3). They occur when the medial tibial physis closes before the lateral portion, and the strong tibiofibular ligament avulses the lateral epiphysis with a strong external rotational force. The triplane fracture is classified as a SH IV fracture that occurs during adolescence. It is unique because the fracture exists in three planes: Sagittal, transverse, and coronal. Triplane fractures require a CT scan to determine the degree of bony displacement. Triplane and Tillaux fractures both require orthopedic consultation, and most eventually undergo surgical fixation.

FIGURE 252.3 A classic Salter–Harris III fracture of the distal tibia called the "Tillaux." The fracture extends along the physis, across the epiphysis, and into the intra-articular space. This is an intra-articular fracture and requires orthopedic consultation and surgical fixation.

Foot

Most fractures of the foot involve the phalanges or the metatarsals and can be managed with short-leg immobilization or a hard-sole shoe (insert or postop shoe). Fractures of the fifth metatarsal, first metatarsal, and great toe need special attention to ensure maintenance of the foot borders. If one of these requires reduction, short-leg immobilization without weight bearing should follow. Pain at the base of the second metatarsal should alert the clinician to the possibility of a tarsometatarsal dislocation known as a *Lisfranc injury*. Calcaneal fractures are often the result of a fall from a

significant height and should prompt radiographs of the spine to look for associated compression fractures. Complex foot fractures require CT in addition to AP, lateral, and oblique radiographs.

Child Abuse and Nonaccidental Trauma

Child abuse is a major pediatric concern and should be considered with any fracture (see Chapter 290). Twenty-five to 50% of abused children have a fracture, and 10% of all injuries in children younger than 2 years are nonaccidental. Specific fractures such as transphyseal distal humerus fractures, spiral fractures, and "corner" or "bucket-handle" fractures are frequently mentioned as classic for child abuse, but the most common nonaccidental fracture is the routine transverse fracture. Suspicious histories inconsistent with the fracture pattern, or any fracture in a child younger than 2 years, should raise concerns about abuse. It is important to inquire about the mechanism and history of the injury. A suspicion of nonaccidental trauma demands a skeletal survey, and physicians are required by law to notify social services. Suspected cases of abuse must be admitted to the hospital to ensure patient safety and to allow for further investigation.

Open Fractures

Open fractures are treated in the ED with intravenous antibiotics, wound irrigation, and tetanus prophylaxis as needed. Most open fractures are taken to the operating room for irrigation, debridement, and fixation within 6 to 8 hours of injury. Lawnmower injuries are responsible for a large number of open hand and foot injuries in children.

CRITICAL INTERVENTIONS

- Obtain emergent consultation for signs of compartment syndrome or neurovascular compromise.
- Inspect injuries closely for evidence of a puncture or open wound.

- Recognize high-risk fractures—callous formation is rapid and a missed fracture may result in later deformity.
- Immobilize all fractures securely for protection and healing.

DISPOSITION

Discharge instructions can be referred to by the family long after they have left the ED, and thus should not be overlooked. Many fracture care discharge instructions can be incorporated into a standardized form that can be modified as necessary. Routine information about cast and splint care should be included, along with emphasis on the importance of ice and elevation. Specific instructions about follow-up care within 5 to 7 days, and a detailed list of problems warranting return to the ED (e.g., increased pain, discoloration, or sensory changes), is absolutely necessary. It is important to remember that young patients need analgesic medications, and specific instructions on their use should be provided.

When a child is being transferred or referred for definitive care, it is crucial to avoid immobilizing the injury in a position that tents the skin. Tenting can progress to necrosis or an open fracture in just a few hours. Inflatable splints should also be avoided because they can put external pressure on tissue that is already traumatized.

Common Pitfalls

- Failure to obtain high-quality radiographs; at least two to three radiographic views are required.
- Failure to provide early and adequate analgesia; pain control is crucial before radiographs and physical examination and upon discharge.
- Failure to consider child abuse when there is a suspicious history.

ACKNOWLEDGMENT

The author gratefully acknowledges the contributions of Greg Canty to the content of this chapter.

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CHAPTER 253 Pediatric Sports Injuries

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Despite our nation's obesity epidemic, the number of children participating in sports has continued to climb, and pediatric athletes frequently present to the emergency department (ED) after an injury. More than 20% of pediatric injury-related visits involve a sports-related injury. More than 30 million, or half, of all children and adolescents participate in organized sports, and many others participate in unorganized sports such as skateboarding and bicycling. The most common sports injuries evaluated in the ED are fractures, dislocations, sprains, strains, head injuries, contusions, and lacerations. ED physicians also need to be familiar with sports-specific injuries such as avulsion fractures, overuse syndromes, and brachial plexus injuries. The presentations are rarely life-threatening, but the conditions can result in chronic morbidity if not recognized and treated properly.

Overall the most common sports injuries are fractures and dislocations. Fractures may involve the diaphysis, metaphysis, or physis. Fractures surrounding the physis are common since the adjacent physis itself, not its surrounding ligamentous structure, is the weakest component. As a result, physeal fractures occur when forces are transmitted across the joint from the stronger ligaments to the weaker areas of physeal bone. This is in contrast to similar injuries in adults where sprains occur because weaker ligaments tear while pulling on stronger, mature bone. Most physeal fractures seen in sports are classified as Salter–Harris I or II. However, once the physis begins to close during adolescence, unique patterns such as the Salter–Harris III and IV fractures emerge. The adolescent suffers

more ligamentous sprains, similar to adults, because of the maturing skeleton. It is helpful to remember the adage that "the younger the child, the more likely a sports injury will result in a fracture."

Dislocations are common in adolescent athletes, but are very rare in athletes younger than 10 to 12 years. The most frequent dislocations associated with sports involve the proximal interphalangeal (PIP) joints of the hand. PIP dislocations occur when the fingertip is hyperextended during contact sports or when catching a ball. Other common dislocations involve the patella and the glenohumeral joint of the shoulder. Patella dislocations occur with a twisting mechanism on a partially flexed knee, and they are almost always lateral dislocations. Glenohumeral shoulder dislocations occur with contact sports such as wrestling and football when forces are applied to an abducted, externally rotated arm. Ninety percent of glenohumeral dislocations are anterior.

Avulsion injuries occur when stronger muscle tendons adhere to weaker areas of bone called *secondary ossification centers* or *apophyses.* When a strong muscular contraction occurs, the tendon may pull the bony apophysis away from the larger bone. As the force of muscular contraction increases in adolescence, these injuries increase in number. The most common site for avulsion injuries is the pelvis, where the iliac crest, anterior inferior iliac spine, anterior superior iliac spine, or the ischium can be avulsed. Another example is the tibial spine (or eminence) avulsion resulting from hyperextension of the knee. The tibial tubercle, greater trochanter, lesser trochanter, and phalanges may also be avulsed.

Overuse injuries are increasing in children with the advent of year-round training and overtraining. Overuse injuries come in many varieties and often present to the ED because of an acute exacerbation of chronic pain, such as in a stress fracture. The most common stress fractures involve the proximal to middle third of the tibia, but the metatarsals, femur, and humerus may also be affected. Spondylolysis is a stress fracture through the pars interarticularis of the vertebrae, and is common in young athletes with lumbar back pain. Little League shoulder is a Salter–Harris I injury of the proximal humerus in overhand-throwing athletes such as baseball

pitchers; Little League elbow is a constellation of elbow pain, medial condyle tenderness, and a subtle flexion contracture from the repetitive valgus stress of throwing. Overuse conditions in the lower extremities include Osgood–Schlatter disease and Sinding–Larsen–Johansson syndrome ("jumper knee"), which present as tenderness of the tibial tubercle and tenderness at the distal pole of the patella, respectively. Sever disease is an inflammation of the calcaneal physis where it joins the Achilles tendon. Severs tends to develop and flare during growth spurts; while painful, it is a temporary condition that will resolve with rest and symptomatic treatment. Medial tibial stress syndrome (MTSS or "shin splints"), which appear frequently with running sports, is a diffuse area of tenderness over the middle to distal third of the posterior-medial tibia. The diffuse tenderness of MTSS can be contrasted with the point tenderness of tibial stress fractures.

Ligamentous injuries are the topic of some debate because of the adage that "kids don't get sprains." However, the incidence of ligamentous injury (sprain) increases as patients approach adolescence. Sprains are becoming more apparent in young athletes, but they must still be carefully distinguished from the more common physeal fracture. Sprains are classified as mild (grade I), moderate (grade II), or severe (grade III). Ankle sprain is the most common joint injury in all of sports. The ankle is typically injured laterally owing to an inversion mechanism, and this mechanism may result in injury to the lateral ankle ligaments or the physis of the distal fibula.

Anterior cruciate ligament (ACL) knee injuries appear to be increasing, most likely because of improved recognition in addition to higher participation rates in sports. The usual mechanism of ACL injury is hyperextension, and this mechanism may result in either an ACL sprain or the previously mentioned tibial spine avulsion.

Sports injuries involving muscle are either contusions or strains. Contusions result from direct blows to the muscle, most of which are mild. However, complications can arise with hematomas in large muscle groups such as the quadriceps. A rare complication of contusions with intramuscular hematomas is myositis ossificans, a

benign proliferation of bone and cartilage that appears weeks after a large contusion. Muscle strains occur when a sudden contraction of a muscle results in stretching or tearing of muscle fibers. Strains usually occur at the point where muscle and tendon fibers join. The classic muscle strain is that of the hamstrings, where the individual cannot bear weight after experiencing a "pop."

Brachial plexus injuries ("stingers" or "burners") result from trauma to the neck and shoulder region. The nicknames for brachial plexus injuries come from the burning or stinging sensation that tends to radiate down one arm in a nondermatomal pattern. The differential diagnosis includes spinal cord injury, which must be excluded in any patient with bilateral upper extremity symptoms or radicular symptoms into the legs.

ED EVALUATION

Most sports injuries involve an injured extremity, and a standardized approach to evaluation is recommended. Adequate pain control prior to physical examination or radiographs cannot be overemphasized. The injured extremity should be fully exposed to reveal any erythema, ecchymoses, or swelling, and the region should be palpated closely for any point tenderness. Exposing the injured extremity for comparison is often helpful. Adjacent joints should be assessed for both active and passive range of motion. The Ottawa knee and ankle rules have been found to be highly sensitive in school-age children and should be applied when deciding whether radiographs are indicated. Adequate visualization requires at least two views, and often three.

Patients with brachial plexus injuries may have unilateral weakness of the deltoid, biceps, or rotator cuff. A positive Tinel sign at the supraclavicular fossa also suggests a plexus injury. Close inspection of the cervical spine is necessary to rule out a cervical spine injury.

KEY TESTING

- Radiographs are necessary to evaluate for fractures in children or adolescents

ED MANAGEMENT

The keys to ED management of sports injuries are pain control, injury recognition, proper immobilization, and appropriate consultation. Pain control is best provided prior to any detailed examination or imaging and permits a better physical examination, better radiographs, and less patient discomfort. The majority of sports injuries can be immobilized and seen by an orthopedist or sports medicine physician within 5 days. The exceptions to this rule are limb-threatening injuries, intra-articular fractures (Salter–Harris III and IV), markedly displaced fractures, and dislocated joints that cannot be successfully reduced. Proper immobilization does not differ from that employed with other musculoskeletal injuries. Ideally, the joints proximal and distal to an injury are immobilized. If this cannot practically be done, immobilization techniques should provide for stabilization and protection from further injury.

Dislocations require prompt recognition and pain control. After appropriate radiographs, procedural sedation is recommended for reduction. Numerous techniques exist for reducing dislocations, and ED physicians need to be familiar with the different approaches. After successful reduction, postreduction radiographs and immobilization are indicated.

Avulsion injuries of the lower extremities and pelvis are managed with crutches and non-weight bearing until follow-up. The management of ligamentous and tendinous injuries depends upon their severity. More severe injuries require immobilization until follow-up. Stress fractures also require immobilization, but most other overuse injuries merely require a cessation of the related activities. If there is any doubt, the best plan is to immobilize the affected area and arrange for close follow-up in 3 to 5 days.

Brachial plexus injuries without progressive symptoms require minimal ED management once the diagnosis is made, but any focal findings suggestive of intracranial bleeding or cervical spine injury

require emergent imaging. Chronic symptoms or persistent neurologic deficits are best evaluated with MRI.

CRITICAL INTERVENTIONS

- Emergent consultation for any injury with suspected neurovascular compromise or compartment syndrome
- Prompt reduction of any dislocated joint using analgesia and procedural sedation
- Emergent imaging for suspected cervical spine injury

DISPOSITION

Disposition and discharge instructions need to be emphasized in sports injuries. All of these patients need the classic "PRICE" discharge instructions covering the basics of *p*rotection, *r*est, *i*ce, *c*ompression, *c*ast/splint care, and *e*levation. Modifying this to "PRICE-FM" emphasizes *f*ollow-up, *m*edications, and *m*obility for ideal management. Follow-up should be scheduled for 3 to 5 days with an orthopedist, sports medicine physician, or primary physician. Opioids should be provided if necessary, although this should be rare. More commonly, nonsteroidal anti-inflammatory drugs suffice. Mobility and range of motion are emphasized for ligamentous and muscle injuries. Return-to-play decisions are best left to the physician who will be monitoring the patient's condition on follow-up.

Common Pitfalls

- Assuming that the young athlete with a sports injury has a sprain. The younger the athlete, the more likely an injury will result in a fracture.
- Forgetting to emphasize the importance of proper follow-up and rehabilitation.

ACKNOWLEDGMENT

The author gratefully acknowledges the contributions of Greg Canty to the content of this chapter.

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PART 5 • SPECIFIC DISEASES

CHAPTER 254 Newborn Problems

Esther Yue

The evaluation of newborns can be challenging to emergency providers who are less familiar with complaints typically managed in the general pediatric ambulatory setting. It may be difficult to differentiate a well and thriving infant who requires no intervention and can be safely discharged home from the subtly ill infant who requires interventions and hospitalization. The goal of this chapter is to provide emergency medicine physicians with a review of benign, nonlife-threatening complaints that present in the newborn period.

During the first few months of life, an infant's job is to "eat, sleep, pee, poop, and breathe." As described in Chapter 215, a detailed history demonstrating the baby's normal performance of these basic functions can often exclude many serious pathologic conditions and reassure both parents and clinicians.

NEURO

Crying/Colic

All babies cry, but the intent behind the cry can be difficult for caregivers to interpret. Crying can be a sign of hunger, pain, distress, or fatigue. Crying for prolonged periods can be distressing for parents and prompt a visit to the clinic or emergency department (ED). It is helpful for clinicians to understand normal crying behavior. Between 2 and 6 weeks of life, the duration of crying *increases* from an average of 2 hours a day to an average of 3 hours a day. Crying then tapers down to an average of 1 hour a day by 12 weeks of life (1). "Excessive crying" or colic has been described as

crying for longer than 3 hours a day. (A more traditional definition is crying for longer than 3 hours a day, for more than 3 days per week, for more than 3 weeks). Colic has no identifiable etiology and may be the extreme of normal infant crying (2,3). Less than 5% of infants evaluated for excessive crying are found to have an organic etiology. Nonetheless, these infants should have a thorough physical examination to identify sources of pain, including skin lesions, corneal abrasions, hair tourniquets, or signs of abuse such as fractures or bruises. A more detailed investigation of the **crying infant** is described in Chapter 227. Although for most babies colic resolves by 12 weeks of life, 15% of infants with colic continue to have excessive crying beyond this time. Clinicians can help families to develop good techniques for soothing their infants such as swaddling, singing, white noise, gentle rocking, or gentle vibration. Equally important to emphasize are dangerous techniques to avoid, such as shaking a baby or placing a baby on a vibrating clothes dryer, which can result in falls. Babies with excessive crying are at risk of abuse; it is important for parents to find ways to manage their own stress, such as taking short breaks from caregiving (4).

Myoclonic Jerks

Newborns spend the majority of their time sleeping, up to 16 hours per day. In babies, sleep is categorized as active sleep and quiet sleep. Active sleep matures into random eye movement sleep (REM) in older children and adults, whereas quiet sleep becomes nonrandom eye movement sleep (NREM). It is typical for newborns to start their sleep cycle in active sleep, in contrast to children and adults who begin their sleep in NREM sleep. Each sleep cycle is approximately 60 minutes in length, as compared to 90 minutes in children and adults. There is significant motor activity during active sleep which some parents may mistake for seizure activity (1,5,6). Periodic breathing, rapid eye movements, and myoclonic leg jerking accompany active sleep (7). These normal movements, however, should be differentiated from signs of neonatal seizures such as rhythmic lip smacking, tongue thrusting, eye blinking, eye rolling, apnea, or bicycling or rowing movements. **Neonatal seizures** are

reviewed in Chapter 236. If there is any doubt, parents should be encouraged to keep a record of these movements and their timing so as to provide a more detailed history for the physician.

RESPIRATORY

Periodic Breathing

Newborns have a characteristic pattern of periodic breathing consisting of rapid breathing for 10 to 15 seconds followed by a pause for 5 to 10 seconds, with *no* cyanosis or significant hypoxemia. Periodic breathing has been attributed to an immature central nervous system. Pathologic apnea is typically defined as lasting longer than 20 seconds or being associated with cyanosis or significant hypoxemia. If parents describe episodes of cyanosis, or apnea longer than 20 seconds, those babies should have a more thorough evaluation for **Apparent Life-Threatening Event,** described in Chapter 233.

GASTROINTESTINAL

Newborns who are exclusively breastfed can lose up to 10% of their birth weight in the first few days of life, but should regain this weight by 7 to 14 days of life when maternal milk patterns are more regular. Formula-fed infants will lose some birth weight during the first few days of life but often regain the weight more quickly than breast-fed infants. Once birth weight is reestablished, babies gain approximately 30 g (1 oz) per day. Full-term infants require 100 kcal/kg/d to achieve adequate weight gain. A typical newborn drinks 15 to 30 mL (0.5 to 1 oz) of breast milk or formula per feed for the first few days, which is sufficient because of in utero nutritional storage. By the end of the first week, infants drink 2 oz approximately every 2 to 3 hours, and by the end of the first month of life, infants drink 3 to 4 oz approximately every 3 to 4 hours (3). Overfeeding of babies may result in postprandial emesis (see below).

Choice of Formula

Emergency providers may be unfamiliar with the various types of infant formula and with the indications for some babies to require specific types (Table 254.1). In most cases, infants should be on a cow's milk-based formula that is fortified with iron and provides 20 kcal/oz. Soy milk-based formula, also providing 20 kcal/oz, is indicated for infants who have temporary or chronic lactose intolerance or galactosemia. Changing to soy milk-based formula for a suspected milk protein allergy is *not* recommended because there is a 30% antigenic crossover between milk protein and soy protein. Instead, babies with milk protein allergy should be on hypoallergenic formulas such as extensively hydrolyzed protein or amino acid formulas (8,9). In general, changes to formula should not be made in the ED setting as these infants will require close follow-up, preferably by their general pediatrician or family doctor.

TABLE 254.1
Composition of Pediatric Formulas (per Liter) (10)

	kcal/oz	Protein Source	Protein gram	Fat Source	Fat gram	Carbohydrate Source	Carbohydrate gram	Suggested Use
Human Milk								
Term human milk	20	Human milk protein	11	Human milk fat	39	Lactose	72	Infants
Preterm human milk	20	Human milk protein	14	Human milk fat	39	Lactose	66	Preterm infants
Preterm Infant Formulas								
Enfamil Enfacare LIPIL (Mead Johnson)	22	Nonfat milk Whey protein concentrate	21	HO Vegetable oil Soy oil MCT oil Coconut oil DHA and ARA	39	Maltodextrin Lactose	77	Preterm infant after discharge from NICU
Similac NeoSure Advance (Abbott Ross)	22	Nonfat milk Whey protein concentrate	21	Soy oil Coconut oil MCT oil DHA and ARA	41	Corn syrup solids Lactose	75	Preterm infant after discharge from NICU
Cow's Milk-Based Infant Formulas								
Enfamil Premium (Mead Johnson)	20	Nonfat milk Whey protein concentrate	14	Palm olein oil Soy oil Coconut oil HO sunflower oil DHA and ARA	36	Lactose	74	Infants with normal GI tract
Enfamil A.R. (Mead Johnson)	20	Nonfat milk	17	Palm olein oil Soy oil Coconut oil HO sunflower oil DHA and ARA	34	Lactose Rich Starch Maltodextrin	74	Thickened feeding for infants who spit-up frequently
Good Start Supreme DHA and ARA (Nestle)	20	Enzymatically hydrolyzed reduced minerals Whey	14.7	Palm olein oil Soy oil Coconut oil HO safflower oil or HO sunflower oil DHA and ARA	34	Lactose Maltodextrin	75	Infants with normal GI tract
Similac Advance (Abbott Ross)	20	Nonfat milk Whey protein concentrate	14	HO safflower oil Soy oil Coconut oil DHA and ARA	37	Lactose	76	Infants with normal GI tract
Similac for Spit-Up (Abbott Ross)	20	Nonfat milk Whey protein concentrate	14	HO safflower oil Soy oil Coconut oil DHA and ARA	37	Lactose Rice Starch	76	Thickened feeding for infants who spit-up frequently
Soy-Based Infant Formulas								
Enfamil Prosobee LIPIL (Mead Johnson)	20	Soy protein isolate L-Methionine	17	Palm olein oil Soy oil Coconut oil HO sunflower oil DHA and ARA	36	Corn syrup solids	71	Infants with galactosemia or lactose malabsorption

	kcal/oz	Protein Source	Protein gram	Fat Source	Fat gram	Carbohydrate Source	Carbohydrate gram	Suggested Use
Soy-Based Infant Formulas								
Good Start Soy PLUS (Nestle)	20	Partially hydrolyzed soy protein isolate	17	Palm olein oil Soy oil Coconut oil HO safflower oil or HO sunflower oil DHA and ARA	34	Corn maltodextrin Sucrose	75	Infants with galactosemia or lactose malabsorption
Isomil Advance (Abbott Ross)	20	Soy protein isolate L-Methionine	17	HO safflower oil Soy oil Coconut oil DHA and ARA	37	Corn syrup Sucrose	70	Infants with galactosemia or lactose malabsorption
Casein, Extensively Hydrolyzed Infant Formulas								
Nutramigen (Mead Johnson)	20	Casein hydrolysate L-Cysteine L-Tyrosine L-Tryptophan	19	Palm olein oil Soy oil Coconut oil HO sunflower oil DHA and ARA	36	Corn syrup solids Modified corn starch	69	Infants with food allergies or protein malabsorption
Pregestimil (Mead Johnson)	20	Casein hydrolysate L-Cysteine L-Tyrosine L-Tryptophan	19	MCT oil Soy oil Corn oil HO sunflower oil	38	Corn syrup solids Dextrose Modified corn starch	69	Infants with food allergies, protein or fat malabsorption
Alimentum (Abbott Ross)	20	Casein hydrolysate L-Cysteine L-Tyrosine L-Tryptophan	19	Safflower oil MCT oil Soy oil DHA and ARA	37	Sucrose Modified tapioca starch	69	Infants with food allergies, protein or fat malabsorption
Amino Acid-Based Infant Formulas								
EleCare (Abbott Ross)	20	Free L-amino acids	20	HO Safflower oil MCT oil Soy oil	32	Corn syrup solids	72	Infants with severe food allergies, fat malabsorption
Neocate	20	Free L-amino acids	21	HO Safflower oil Coconut oil Soy oil	30	Corn syrup solids	78	Infants with severe food allergies

Physiologic Gastroesophageal Reflux

Many newborns regurgitate after meals. They have low tone in the lower esophageal sphincter, allowing stomach contents to move up into the esophagus with minimal pressure on the intra-abdominal region. As the lower esophageal sphincter becomes more competent, this benign condition typically resolves around age 3 to 6 months of age. The usual presentation of gastroesophageal reflux (GER) in infants is the production of frequent small mouthfuls of breast milk or formula in an *effortless* manner. There is no active emesis. See Chapter 223 for a comprehensive review of **vomiting** in children.

Common descriptions of GER by parents include “spitting up” or “wet burps.” These babies have adequate numbers of wet diapers,

and they have appropriate weight gain (about 30 g/d). This is to be differentiated from pathologic cases of gastroesophageal reflux disease (GERD), which are associated with more severe symptoms such as crying with regurgitation, back-arching, and recurrent coughing or wheezing. Babies with pathologic GERD may have poor weight gain, recurrent pneumonia from aspiration, or concomitant esophagitis (3,11,12).

Techniques to minimize benign GER include thickening feeds with rice or oatmeal cereal (1 tablespoon of cereal per 2 oz of formula), avoiding overfeeding, frequent burping while feeding, and holding the infant upright for 15 to 20 minutes after eating. A common mistake by caregivers is to place a baby in a semi-upright position (also known as semi-reclined) such as in a bouncy chair, car seat, or swing, immediately after feeding. The semi-reclined position increases intra-abdominal pressure, allowing stomach contents to regurgitate into the esophagus.

Constipation

While parents are often concerned about their babies spitting up, they are equally concerned about their stooling habits. Stool patterns vary. Breast-fed newborns generally stool more frequently than formula-fed babies. Babies who have not passed meconium in the first 48 hours of life require a more thorough evaluation for imperforate anus, intestinal obstruction (e.g., Hirschsprung disease), or hypotonia (see Chapter 230). In general, infants have 3 to 4 stools per day on days 3 to 4 of life, then 4 to 6 stools per day on days 4 to 6 of life, and 8 to 10 stools per day in weeks 2 to 4 of life. Normal stool patterns can range from once every 2 to 3 days to 8 to 10 times a day (9,13). After the passage of meconium in the first few days of life, the stool's appearance can vary in color and consistency, from loose watery yellow or green to more solid brown.

Constipation is defined as a difficulty passing stool or passage of hard, dry, pellet-like stools for 2 weeks (1). It is very rare for exclusively breast-fed babies to have constipation. The absence of bowel movements for up to 7 days can be normal in newborns and does not necessarily signify constipation. Clinicians can be reassured

if the baby continues to eat and void, and has a soft abdomen. Rectal stimulation in the ED with a rectal thermometer probe or lubricated cotton swab often results in a bowel movement by the end of the encounter.

Rice cereal can sometimes cause constipation, especially if more than the recommended 1 tablespoon per 2 oz of formula is added to thicken feeds for babies with GER (discussed above). In these cases, oatmeal cereal is an adequate substitution for rice cereal. Another treatment for constipation is to give infants fruit juice (prune, apple, or pear juice), starting with ½ oz of juice per day and not exceeding 2 oz of juice per day. Juice introduces an osmotic load into the intestinal lumen, causing more water to enter the gastrointestinal tract. If fruit juice does not produce regular soft stools, clinicians may advise glycerin suppositories as the next step. Mineral oil, molasses, and karo syrup are *not* recommended for the treatment of infant constipation.

Infantile Dyschezia

Infants may experience symptoms of straining for prolonged periods and crying, followed by a passage of *soft stool.* This pattern of difficult defecation is called infantile dyschezia, which is different from constipation, and is present typically in the first 6 months of life. In order to have successful passage of stool, babies need to coordinate intra-abdominal pressure increase and pelvic floor relaxation. Babies with infantile dyschezia have not developed effective coordination of these two events. Eventually, after a period of crying and straining, which increase intra-abdominal pressure, infants relax their anal sphincter and pass soft stools effortlessly. In time, babies learn to bear down (Valsalva maneuver) to increase their intra-abdominal pressure and have less difficulty with bowel movements (9,13). There is no treatment for this and in fact, routine treatments for constipation are not recommended for infantile dyschezia. Suppositories and rectal stimulation are not appropriate and can be counter-productive. Infantile dyschezia resolves spontaneously and rarely lasts more than 1 to 2 weeks.

GENITOURINARY

Voiding patterns vary among infants, but in general, they should produce 6 to 10 wet diapers per day. Most newborns should void at least once in the first 24 hours and pass meconium within the first 48 hours of life. Newborns generally void one time for each day of life: At least two voids per day on day of life 2, three voids on day of life 3, up to 10 voids by day of life 10.

Urate Crystals

Families may present to the ED with a diaper containing a pink crystalline substance or salmon-pink residue. This is the result of urate crystals being deposited in the diaper. Urate crystals are typically easily distinguishable from blood, but clinicians can perform occult blood testing if they are not sure. Urate crystals are usually found when there is concentrated urine, typically in the setting of dehydration. This should prompt the clinical to carefully assess hydration, including asking about the frequency of wet diapers, and checking for a sunken fontanelle or dry mucous membranes on physical examination. If there are concerns about the baby's hydration, parents should be advised to increase either the frequency or volume of feeds (3).

Vaginal Discharge

Because of transplacental passage of maternal hormones, normal newborn girls have well-estrogenized vaginal mucosa. The estrogenized mucosa produces a milky-white vaginal discharge which is a normal finding in newborn girls. Within the first week of life, newborn girls often have slight vaginal bleeding due to the withdrawal of maternal estrogen. Both of these are normal findings and parents can be reassured (3). If there is frank vaginal bleeding beyond a week of life, other diagnoses such as congenital endocrine disorders or sexual abuse need to be considered.

DERMATOLOGY AND OTHER CONSIDERATIONS

Oral Cavity

Primary teeth typically erupt at about 6 months of age, although this can range between 3 months and 16 months of age. **Natal teeth,** present at approximately the time of birth, are usually primary teeth that have erupted early. Natal teeth are typically poorly formed, with a thin layer of enamel, and are poorly attached to a mucosal stalk. In general, it is not recommended to remove these, since this may affect the spacing of secondary teeth. The only indications for removal of natal teeth are if they are causing significant irritation to the tongue or if they are an aspiration risk, given the poor attachment to the mucosal surface (14). Sometimes mistaken as natal teeth are **dental lumina cysts,** which are clear fluid-filled sacs located on the surfaces of gums. These cysts can be located bilaterally or quadrilaterally, are typically not painful, do not interfere with feeding, and disappear within a few weeks. Yellow-white collections of epithelial cells are called **Bohn nodules** when they are located on the alveolar ridge and **Epstein pearls** when they are found at the junction of the hard and soft palate. These cysts also require no treatment and disappear within a few weeks (15). These benign cysts should be differentiated from **oral thrush** caused by *Candida albicans,* which requires treatment. Thrush produces thick, white, adherent patches with surrounding erythema, located on the oral mucosa. Unlike residual breast milk or formula on the baby's tongue and buccal mucosa, thrush is quite adherent to the mucosal surface and difficult to scrape off with a tongue depressor. Babies typically have decreased feeding secondary to thrush, and they should be treated with a topical antifungal (usually nystatin solution). It should be emphasized to the family to avoid reinfection from pacifiers and nipples, so mothers will need topical antifungal therapy as well.

Benign Neonatal Rashes

Healthy newborns often present with benign rashes which can worry their caregivers. **Erythema toxicum neonatorum** is the most common newborn rash and develops *within 3 to 4 days after birth.* It is characterized by an eruption of 2-mm erythematous macules, papules, and pustules anywhere on the body. These lesions are not vesicular, not pruritic, and are typically not located on the palms and

soles. Erythema toxicum is transient, often erupting in crops and disappearing spontaneously. There is no treatment, but it often resolves by 2 weeks of age.

Another benign neonatal rash is **transient neonatal pustular melanosis,** more commonly seen in darker pigmented babies. This is characterized by pustules and vesicles without underlying erythema that are present *at birth.* The pustules then rupture and leave behind collarettes of scale and hyperpigmented macules that fade and resolve spontaneously after a few weeks.

Maternal hormonal stimulation may be the cause for **infantile seborrhea dermatitis,** but the cause is largely unknown. Babies present during the first few months of life with greasy yellow scales and sometimes underlying erythema, fissuring, and oozing. When localized to the scalp, these patches are sometimes called "cradle cap," but they can appear on the ears, face, trunk, and flexural areas as well. The lesions are not pruritic, which distinguishes it from atopic dermatitis. Parents can gently loosen the scales with a soft brush while shampooing the area. Application of an emollient or oil before shampooing the area may help to soften the scales. More severe cases can be treated with an antifungal shampoo or mild topical corticosteroid (16,17).

Mastitis

Most term infants, both boys and girls, will have breast buds. Sometimes there is hypertrophy of these breast buds as a result of maternal hormones passing through the placenta in utero. In up to 6% of normal infants, maternal estrogen or neonatal prolactin actually causes **galactorrhea,** which is a thin milky discharge from the hypertrophied breast buds. Both galactorrhea and breast hypertrophy resolve within several weeks, although sometimes breast hypertrophy may persist slightly longer in baby girls. Families should be counseled on the potential for **mastitis,** an infection in hypertrophied breast buds, typically caused by *Staphylococcus aureus.* While most commonly caused by gram-positive bacteria, this infection can also be the result of gram-negative organisms. The breast bud is red, warm, swollen, tender, and sometimes has purulent

drainage or fluctuance suggestive of a breast abscess. Babies with mastitis typically have no systemic signs and symptoms such as fever, vomiting, lethargy, or irritability. If there are *no* associated systemic symptoms, mastitis can be treated first with intravenous, and then oral, antibiotics with good *S. aureus* coverage. Appropriate cultures, including culture of nipple drainage if present, should be obtained before starting treatment (18,19).

Diaper Rash

Diaper rash occurs frequently during the newborn period. Moisture from wet diapers promotes both skin irritation and the growth of *C. albicans*. Contact dermatitis appears as simple redness in the diaper area, with distinct borders at the diaper edges and sparing of the skin folds. Infants have sensitive skin and some babies have a reaction to the coloring dye used in some diapers. For contact dermatitis, using dye-free diapers, changing diapers more frequently, and applying a protective agent such as zinc oxide ointment are usually sufficient. For severe cases, a brief course of a mild topical corticosteroid may be indicated.

Candida diaper rash has a well-defined erythematous appearance, with satellite lesions and small pustules, and generally involves the skin folds. Application of nystatin or clotrimazole ointment to affected areas with each diaper change cures most cases (20). As yeast thrives in the moist environment of wet diapers, caregivers should be advised to apply the antifungal ointment for a few days beyond resolution of the rash. If diaper dermatitis is recalcitrant, other diagnoses such as zinc deficiency should be considered (21).

Common Pitfalls

- Babies with excessive crying are at risk of abuse; outline ways for caregivers to manage their own stress.
- A history of effortless gastroesophageal reflux in a thriving infant does not warrant blood work or imaging.
- Avoid making any infant formula changes in the ED; this should be left to the primary care provider to ensure close monitoring.

- Normal infant stooling patterns can vary widely and usually do not require any interventions.

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CHAPTER 255

Eye Disorders

Janet G. Alteveer and Dunisha G. Ranasuriya

Ophthalmologic disorders in children represent a wide variety of diseases, both congenital and acquired, the diagnosis of which hinges on a careful history and a thorough examination of the eye. The elements of the examination change with patient age and developmental stage. Most children with ophthalmologic emergencies present to the ED with eye redness, eye swelling, or abnormal vision.

THE PEDIATRIC EYE EXAMINATION

A complete pediatric eye examination includes inspection of the eyelids, conjunctivae, pupil, and iris; evaluation of the extraocular muscles; fundoscopy; and testing of visual acuity. This examination is an essential part of the evaluation in any child presenting primarily with ophthalmologic conditions such as conjunctivitis, periorbital edema, visual change or loss, and trauma or neurologic complaints.

Inspection of the eyelids and conjunctivae should document the presence of erythema, ecchymosis, edema, proptosis, or masses. The cornea should be evaluated for normal contour and clarity. A bulging or hazy cornea in a neonate may indicate congenital glaucoma. The cornea should be stained using topical anesthetic drops and fluorescein test strips after rest of the examination is completed so as not to interfere with visual acuity testing. Shining a Wood light on the cornea in a darkened room will reveal stain adherent to corneal defects caused by an abrasion, herpetic infection, or ulcer. The pupil should be assessed for contour, bilateral symmetry, and reactivity to light. An abnormally shaped or reactive pupil may indicate defects in

the iris or disruption of the afferent or efferent nerve pathways to the eye.

Extraocular muscle testing can be accomplished by 4 months of age. By this age, a normal, full-term infant should be able to fixate on and follow a small, brightly colored toy held 6 to 12 in from the baby's face. By 5 to 6 months, the infant should fixate and follow an object through the full range of motion. By 2 to 3 years of age, most children, with gentle encouragement, will follow a light or finger.

Evaluation of the posterior chamber via direct ophthalmoscopy is dependent on the child's age and cognitive development, becoming easier as cooperation increases. The use of a short-acting topical parasympatholytic such as tropicamide (Mydriacyl 0.5%) will facilitate the examination of the retina. To encourage the child to look beyond the examiner and away from the direct light, use a brightly colored toy or have the parent wave at the child from directly behind the examiner. The minimum examination in an infant is the documentation of a normal red reflex. The presence of an abnormal red reflex (leukocoria or white reflex), which could indicate a cataract or intraocular tumor, mandates formal consultation with a pediatric ophthalmologist.

The corneal light reflex, or Hirschberg test, is useful in detecting strabismus or an ocular muscle palsy. It is conducted by shining a penlight, held 3 ft (1 m) away, centrally onto the child's face. In a normal child, the light will reflect centrally on both pupils when the child is fixated on the light or a small toy held in front of the face. If the light reflex is eccentric on one eye, a strabismus or palsy is present.

Visual acuity testing is an extremely important aspect of the complete eye examination. The manner of testing is dependent on the age and cognitive ability of the child. Visual acuity also varies by age (Table 255.1). To assess an infant, have the baby fixate (on a bright toy or light) and cover one eye gently with your thumb. If the uncovered eye has normal vision, the child will continue to fixate on the object. If the uncovered eye has poor vision, the child may lose interest, push the covering thumb away or protest.

TABLE 255.1
Visual Acuity by Age

Age	Visual Acuity
6 mos	20/60–20/100
3 yrs	20/25–20/30
5–7 yrs	20/20–20/25
By 8 yrs	20/20

By 3 years of age, depending on developmental and cognitive ability, more objective visual testing can be achieved. The Allen chart, HOTV matching test, or "Tumbling E" game can be used. By 5 years of age, most cognitively normal children can use the Snellen chart. Testing with the Snellen, Tumbling E, or HOTV chart should be performed at a distance of 20 ft (6 m). The Allen test can be performed at 10 ft (3 m).

In all of these charts, letters or objects are presented as a group. Children with poor vision have increased difficulty identifying objects when presented as a group (the crowding phenomenon) and will perform better when objects are presented singly.

CONJUNCTIVITIS AND THE RED EYE

CLINICAL PRESENTATION

Conjunctivitis results in 5 million outpatient visits per year (1) or 1% to 4% of all pediatric ambulatory complaints (2). The causative agent may be either bacterial, viral, allergic or chemical. Bacterial conjunctivitis predominates in infants and young children: 55% to 78% in recent studies (3). Common pathogens in young children are nontypable *Haemophilus influenzae, Streptococcus pneumoniae,* and *Moraxella catarrhalis. Staphylococcus Aureus* may be the causative agent in any age group and the incidence of methicillin-resistant *S. aureus* (MRSA) approaches 30% in some urban areas (4).

Neisseria meningitides and *Neisseria gonorrhoeae* are uncommon pathogens. Gonococcal conjunctivitis may occur occasionally outside of the neonatal period and in the prepubescent child who is not sexually active. Sexual abuse must be ruled out in these cases;

however, transmission from infected caregivers not abusing the child has been reported (5).

Infectious neonatal conjunctivitis is most commonly caused by *Chlamydia trachomatis,* followed by *N. gonorrhoeae* (ophthalmia neonatorum), and herpes simplex virus (HSV). The infant is infected at birth during passage through the vaginal canal. Women are routinely screened during pregnancy and prior to delivery so that risk factors would be absence of prenatal care, substance use, or history of a sexually transmitted infection. Neonatal prophylaxis for ophthalmia neonatorum is recommended universally in the United States. Currently only 0.5% erythromycin ophthalmic ointment is available in the United States, however, only silver nitrate solution is effective in prevention of infection by a penicillinase-producing gonococcus. The incubation period for gonococcal conjunctivitis is 2 to 7 days. Neonatal chlamydial conjunctivitis develops a few days to several weeks after birth. Fifty percent of infants born to infected women acquire *C. trachomatis,* and, of those, 25% to 50% develop conjunctivitis. Neonatal ophthalmic prophylaxis is not effective in the prevention of chlamydial conjunctivitis. Neonatal HSV infection occurs in 1 per 3,000 to 1 per 20,000 live births. The infant is mostly at risk if the mother has a primary infection at the time of delivery. The risk to an infant born to a mother with a recurrent infection is much lower. Neonatal HSV infections are of three types: generalized infection (25%), localized central nervous system (CNS) infection (30%), or disease of the skin, eye, and mouth (45%) (5). In addition, the above neonates may develop conjunctivitis due to gram-negative bacteria such as *Klebsiella* or *Pseudomonas* while in the NICU.

Bacterial conjunctivitis is most often bilateral and occurs predominantly in infants and preschool-aged children. It tends to come on abruptly and not be associated with fever or sore throat. In a recent study the history of “gluey” or “sticky” eyelids in the morning and physical findings of mucoid or purulent discharge demonstrated the highest likelihood for bacterial disease, whereas watery discharge and burning were more likely indicative of viral etiologies. Other low-risk predictors for bacterial disease include age greater than 6 years, onset between April and November, watery

discharge, and the absence of adherent eyelids upon awakening. The presence of three factors predicted a negative conjunctival culture 76% of the time, while the presence of all four factors was predictive of a negative culture 92% of the time (1). *N. gonorrhoeae* typically causes copious purulent exudates in all age groups referred to as a waterfall discharge. A neonate with ophthalmia neonatorum may appear toxic, with a copious purulent discharge. *C. trachomatis* infection causes a beefy red conjunctiva (5).

Viral conjunctivitis is often bilateral, occurs in school-aged children, often has a copious and clear discharge (however, a mucopurulent discharge may be present) and the presence of a conjunctival inflammatory membrane is diagnostic. Marked periorbital edema can be present, and should not be mistaken for periorbital cellulitis (POC). Significant eye pain suggests the likelihood of an etiology other than simple conjunctivitis, such as corneal abrasion, herpetic infection, or anterior uveitis.

In the summer, adenoviruses may predominate, particularly among children older than 6 years. Adenoviral conjunctivitis may be associated with two distinct clinical syndromes: pharyngoconjunctival fever and epidemic keratoconjunctivitis. Pharyngoconjunctival fever is caused by adenovirus types 3 and 7. It is most commonly spread by person-to-person contact but has also been reported to be spread through swimming; thus, the infection may be referred to as “swimming pool” conjunctivitis. Adenovirus types 8, 19, and 37 cause epidemic keratoconjunctivitis. This entity is transmitted by direct contact with infected people or contaminated instruments and is often iatrogenic. Attention to frequent hand washing prevents transmission (6).

Contact lens use is increasing in children and adolescents who may not always adhere to proper hygiene and lens disinfection procedures, put themselves at increased risk of pseudomonas and acanthamoeba infection (7).

Nontypable *H. influenzae* commonly causes concomitant otitis and conjunctivitis, which may play a role in the etiologies of infection in children less than 6 years old, where 25% with bacterial conjunctivitis also have otitis media.

HSV infection of the eye may be bilateral and is frequently accompanied by involvement of the skin and mouth. Skin and mouth lesions may not be present at the time of presentation, however; furthermore, the characteristic dendrites (seen on fluorescein staining) may be observed in only 30% of patients (8). This may lead to significant delay in diagnosis in cases where HSV presents only as a nonspecific appearing recurrent blepharoconjunctivitis with no fluorescein findings. Failure to diagnose HSV stromal disease in a timely manner can lead to significant scarring and potential vision loss (8). Herpes zoster virus (HZV) infection of the first division of the trigeminal nerve may affect the eye. There may be characteristic vesicular lesions on the forehead and eyelid. The conjunctivae are usually injected and fluorescein staining may show pseudodendrites. HZV is a unilateral infection and often, periorbital pain precedes the appearance of the vesicles (5).

Rarely, the red eye may be due to keratitis from HSV or HZV infection. Herpesviruses can cause ocular involvement during primary or recurrent infections. HSV is ubiquitous and is transmitted from person to person during primary and recurrent infections that may or may not be symptomatic. Periocular inoculation can occur from the HSV-1 perioral infections. Herpes zoster represents a reactivation of latent varicella-zoster virus. When it occurs in the dermatomal distribution of the trigeminal nerve, it can cause keratitis with conjunctivitis (5).

The most common cause of allergic conjunctivitis in children is seasonal rhinoconjunctivitis. The symptoms are caused by a localized IgE-mediated hypersensitivity reaction to airborne allergens, with resultant release of histamine and other products from mast cells. Pollens and grasses are the most common allergens. In up to 25% of children, ocular findings may be the sole manifestation (6). The findings are caused by the release of products from mast cells, predominantly histamine. Allergic conjunctivitis is bilateral with variable conjunctival injection and watery eye discharge. Other allergic symptoms such as boggy nasal turbinates, watery nasal discharge, and allergic shiners (dark circles around the eye), may or may not be present.

Chemical conjunctivitis is most often caused by ocular medications. Neomycin has the greatest incidence of contact sensitivity. Silver nitrate was a common cause in the neonate. Accidental environmental exposure to a toxin, such as cleaning agents, is also common. Chemical conjunctivitis presents with conjunctival injection and often, a burning sensation.

A host of other entities may present as a red eye. Corneal abrasion may present with a unilateral red eye. In the preverbal child it may be difficult to obtain the history of trauma to the eye. There is generally tearing, pain, and photophobia. Anterior uveitis classically presents with eye pain, a constricted pupil, potentially decreased visual acuity, and perilimbic injection of the conjunctiva (injection that is limited to the area of the conjunctiva surrounding the cornea) (9). Five percent of uveitis in the United States presents in children younger than 16 years and 41% of cases are associated with juvenile rheumatoid arthritis. Toxoplasmosis accounts for approximately 10% of cases. HSV and HVZ may also cause uveitis. Uveitis in children is a chronic disease with a high incidence (up to 20%) of developing blindness in one eye (9).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the red eye is extensive and includes bacterial, viral, allergic, and chemical causes. More specific considerations should include Kawasaki disease, blepharitis, dacryocystitis, corneal abrasions, dry eye syndromes, and Parinaud oculoglandular syndrome (catscratch disease) involving the conjunctiva and an ipsilateral preauricular lymph node.

ED EVALUATION

The ED evaluation of the red eye begins with a detailed history and physical, including a complete age-appropriate eye examination. A slit-lamp examination in an older child who is cooperative is helpful. Outside of the neonatal period, conjunctival cultures are usually obtained only in recurrent cases or those unresponsive to initial treatment. An office-based, rapid adenovirus detector test is available with a sensitivity of 89% and a specificity of 94%; it may be useful in

the clinically unclear case (10). Fluorescein staining should be considered, especially with severe photophobia or corneal changes. Keratitis may appear as punctuate spots on the corneal surface. A Gram stain should be obtained if the discharge is copious, suggesting *N. gonorrhoeae* infection.

All young infants in whom the diagnosis of ophthalmia neonatorum or skin, eye, and mouth disease secondary to HSV is being considered must undergo a full evaluation for disseminated disease. This evaluation must include blood and cerebrospinal fluid (CSF) studies (complete blood count, chemistries, blood culture, CSF culture for bacteria and viruses, glucose, protein, Gram stain), conjunctival cultures for bacteria and viruses should also be obtained. In suspected gonococcal infection, a Gram stain of the eye drainage may be diagnostic and aid in early confirmation. A Tzanck preparation may be useful in herpetic infections. A conjunctival scraping for epithelial cells is more sensitive than swab cultures. When a chlamydial infection is suspected, cultures or specimens for rapid antigen testing of the conjunctiva and nasopharynx should be obtained using a Dacron swab (5). A chemical conjunctivitis is suggested when a history of ocular exposure to a toxin or ophthalmic medication is obtained in the presence of conjunctival injection.

Anterior uveitis is diagnosed with the slit lamp, showing cells (leucocytes) and flare (protein) in the anterior chamber. A corneal abrasion will also be evident on fluorescein staining with or without slit-lamp evaluation.

Fluorescein staining should identify the abrasion. Eversion and examination of the palpebral conjunctiva is necessary to ensure that there is no retained foreign body.

KEY TESTING

- Fluorescein examination
- Gram stain in suspected gonoccocal conjunctivitis
- Slit-lamp evaluation in the cooperative child

ED MANAGEMENT

The management of conjunctivitis is dependent on the suspected etiology and the age of the child. Treatment ranges from supportive care to hospital admission for parenteral antibiotics. Bacterial conjunctivitis, although a self-limited disease, is most frequently treated with topical ophthalmic antibiotics because this results in a bacterial cure and faster clinical improvement (11). This in turn allows children to return to day care or school and their parents to return to work. The ideal topical antibiotic should be broad spectrum, rapidly bactericidal, nontoxic to the eye, easy to use, inexpensive, and have low-resistance rates to the most common pathogens. Unfortunately bacterial resistance continues to rise: 29% of *H. influenzae* and 60% of *S. pneumoniae* exhibit resistance to penicillins and only 44% of the *S. pneumoniae* sp are included in the pneumococcal vaccine; *S. aureus* resistance to the older quinolones is increasing and while the newer quinolones (moxifloxacin and besifloxacin) have improved profiles against gram-positive organisms; they are expensive. Polymyxin B/trimethoprim has decreased efficacy against *H Influenzae* and *S pneumoniae* however trimethoprim is still effective against MRSA (4). Sulfonamides are no longer recommended because of increasing bacterial resistance and significant discomfort on instillation. Gentamicin and tobramycin are toxic to the corneal epithelium and should be reserved for gram-negative organisms (4). Choice of topical antibiotic should reflect the antibiogram of the community and also be somewhat case specific: is this a young child with presumed *H. influenzae* sp. or other common organism? Is there a risk of MRSA? Or is this a contact lens wearer with a high risk of *pseudomonas sp?*

In the instance of conjunctivitis–otitis syndrome, oral therapy with an appropriate antibiotic to treat *H. influenzae,* such as amoxicillin–clavulanate, will cure both the otitis and the conjunctivitis. Oral therapy for conjunctivitis without otitis has been shown to decrease the occurrence of otitis in the ensuing 2 weeks. Further data are needed to substantiate the efficacy of oral treatment of conjunctivitis. Meningococcal and gonococcal conjunctivitis is treated with systemic antibiotics.

Table 255.2 lists the etiologies of neonatal conjunctivitis with the indicated treatment.

TABLE 255.2
Etiology of Neonatal Conjunctivitis and Therapy

Organism	Medications	Other Therapy
N. gonorrhoeae	Ceftriaxone 25–50 mg/kg IV or IM, given once[a] Or Cefotaxime 100 mg/kg IV or IM	Frequent eye irrigation with saline
C. trachomatis	Erythromycin 50 mg/kg/d divided qid PO for 14 d	
Herpes simplex virus	Acyclovir 60 mg/kg/d IV divided q8h Duration: 14–21 d and 1–2% trifluridine, 1% iododeoxyuridine, or 3% vidarabine, applied topically	Ophthalmologic consultation

Data from American Academy of Pediatrics (Red Book).
[a]For prophylaxis of neonates, ceftriaxone 25–50 mg/kg single dose not to exceed 125 mg.

Localized HSV infections involving the eye should be treated with acyclovir 60 mg/kg/d in three divided doses for children younger than 1 year of age, and for older children, 1,500 mg/m^2/d in three divided doses for 7 to 10 days. Higher dosing and intravenous (IV) dosing (maximum 80 mg/kg/d) are used for disseminated or CNS disease (5,8). Some sources also advocate initiating topical antivirals (5). Acyclovir-resistant herpesvirus (an issue usually only with HIV-infected children previously exposed to acyclovir) is treated with foscarnet 80 to 120 mg/kg/d in two or three divided doses, although there is insufficient data for the appropriate dosage in children (5).

Adenoviral conjunctivitis is treated with supportive therapy. To prevent the spread of infection to other family members, the family should be counseled to wash hands frequently and to avoid sharing washcloths. The infected child should be kept away from immunocompromised persons and neonates, because this group is at increased risk for severe disease. The child should also be kept home from school or day care for 5 to 7 days.

The treatment of allergic conjunctivitis is avoidance of the allergen and topical therapy with vasoconstrictors and cool compresses. There are a number of topical H_1 blockers on the market as well as mast cell stabilizers such as lodoxamide or nedocromil. These latter may be more effective than topical nonsteroidal anti-inflammatory drugs (NSAIDs); however, they may require several days to a few weeks to effect symptom improvement (6).

Corticosteroid-containing eye drops have no place in the treatment of acute conjunctivitis. They may be necessary in the treatment of uveitis or severe keratitis but should be used only after consultation with an ophthalmologist. Long-term use of steroid drops can endanger vision by causing cataracts or glaucoma. Short-term use may inhibit the hosts' ability to limit infection and prolong viral shedding in contagious conjunctivitis. Corticosteroid/antibiotic combinations may also promote or increase the severity of fungal keratitis.

The cornerstone of treatment of chemical exposure is decontamination: copious flushing of eye exposure with water or normal saline. This is followed by visual acuity testing, fluorescein staining, and slit-lamp evaluation.

Corneal abrasions are treated symptomatically and often with antibiotic drops as well. Contact lens wearers should be prescribed a fluoroquinolone preparation because of the concern for pseudomonas. Eye patching has not been shown to be of benefit and may retard healing in abrasions <10 mm in length (12). Cycloplegics, thought to relieve pain from ciliary muscle spasm, also may not be effective. Ketorolac drops, although safe, are expensive (6).

DISPOSITION

Bacterial conjunctivitis, with the exception of gonococcal disease, outside of the neonatal period is an outpatient disease. Follow-up with a primary care provider should be recommended. School districts have policies with regard to when children with presumed bacterial conjunctivitis may return to school. Many will allow children who have been on 24 hours of antibiotic drops to return to

class. Viral conjunctivitis is much more infectious; if there is keratitis they should be referred to an ophthalmologist for follow-up.

If large corneal defects, especially those involving the visual axis are detected, emergent ophthalmologic evaluation is necessary. All cases of suspected ophthalmia neonatorum, HSV, and HZV ophthalmic infection as well as anterior uveitis should be referred to a pediatric ophthalmologist emergently. The risk for ocular damage and permanent visual loss is significant.

Neonatal, herpetic, meningococcal, and gonococcal conjunctivitis requires inpatient therapy at a facility well versed in pediatric care with pediatric ophthalmologic resources. When chlamydial infection is suspected, consultation with a pediatrician is helpful.

Significant chemical exposures should be referred to an ophthalmologist.

Common Pitfalls

- Failure to recognize herpetic infection of the eye. Delay in treatment can often lead to visual loss, CNS disease, or systemic disease.
- Inappropriate use of corticosteroid-containing eye drops, unless discussed with an ophthalmologist.
- Ignoring the presence of eye pain which may indicate corneal abrasion, herpetic infection or anterior uveitis

PERIORBITAL&NDASH;ORBITAL CELLULITIS AND THE SWOLLEN EYE

CLINICAL PRESENTATION

Children with a swollen, red eye are a relatively common problem in the ED. POC, also called preseptal, and orbital cellulitis (OC) are distinct clinical entities with different pathogenesis and treatment (13). *POC* is defined as an inflammatory or infectious process superficial to the orbital septum while *OC* is an inflammation or infection *deep* to the orbital septum. OC may involve the ocular structures, causing abscess formation, most commonly subperiosteal,

and vision loss. The veins draining the periorbital skin and soft tissues, orbital structures and ethmoid and maxillary sinuses are valveless and anastomosing, allowing easy spread of infection to the cavernous sinus and CNS (14).

POC may occur via two different routes. The skin barrier near the eye may be broken by local trauma, an insect sting, or an HZV lesion with local spread of infected material to the periorbital tissues. Alternatively, there may be seeding of periorbital tissues from bacteremia, often several days after onset of an upper respiratory infection (URI). OC develops from sinusitis, most often beginning with formation of a subperiosteal abscess that then spreads into the orbital tissues. The ethmoid sinus develops earliest, so younger children present with ethmoiditis and ethmoid sinusitis. In older children, the frontal sinuses can be the origin of infection. Uncommonly, OC results from extension of infection through natural bony dehiscences of the ethmoid bones, which form the medial wall of the orbit. In one recent study, OC occurred with a similar frequency in older and younger children and ethmoid sinusitis was present in 98% of the study population. Figure 255.1 shows the close proximity of the sinuses to the orbital cavity (13).

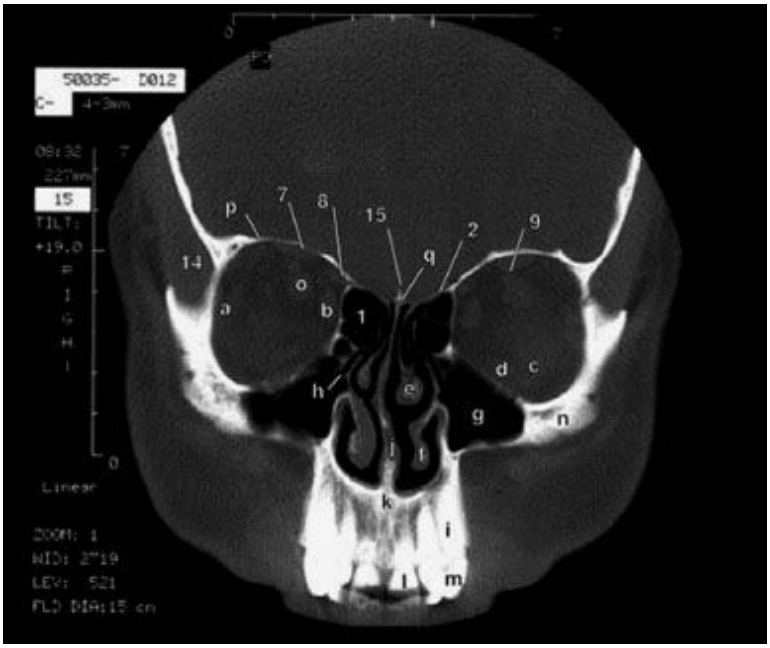

FIGURE 255.1 General anatomy imaging and technology CT and MRI.

The thin skin and loose connective tissue of the eyelid allow for easy and rapid accumulation of fluid. A child with POC/OC may often present within hours of onset with a red and swollen eyelid. Ninety-five percent of cases are unilateral, with the actual color of the lid described as violaceous or purple. Seventy-five percent of children are febrile. Two-thirds will have an upper respiratory infection; one-third, a history of minor trauma; one-fourth, an acute otitis media; and one-fifth, an associated conjunctivitis (15). In bacteremic or posttraumatic POC, palpation of the periorbital tissues will elicit tenderness, but the eye itself should move freely and painlessly. In inflammatory POC due to an underlying sinusitis, the periorbital tenderness is variable. The edema may initially present in the early morning and be intermittent with resolution of edema as the day progresses. In advanced OC, the eye may be proptotic and extremely painful to voluntary movement of the extraocular muscles and visual acuity may be reduced. There may be diplopia on upward gaze. The child may appear "toxic" or irritable, with early meningeal signs.

A bacterial pathogen in POC/OC is identified, mostly, by blood culture in only 30% of cases. Prior to the introduction of the *Haemophilus influenzae type b* (HiB) and *S. pnemoniae* vaccines, 80% of the cultures in bacteremic POC, were positive for *H. influenzae;* with the remaining cases due to *S. pneumoniae.* Widespread usage of vaccines has resulted in a significant decrease in the incidence of bacteremic POC (16). The agents causing OC or inflammatory POC are the same that cause acute sinusitis: *S. pneumoniae,* nontypable *H. influenzae,* and *M. catarrhalis* (14). Since 2000, however there has been a significant decrease in invasive pneumococcal disease, as well as a decrease in drug-resistant *S. pneumoniae.* Consequently there has been a concomitant increase in both disease and colonization by nonvaccine serotypes; fortunately these organisms are less likely to cause invasive disease.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the swollen eye beyond orbital and periorbital cellulitis includes local allergic reaction, trauma, sinusitis, bulbar or retrobulbar neoplasms, and dacryoadenitis (inflammation or infection of the lacrimal gland).

ED EVALUATION

The examination of the eye must include not only gentle palpation of the periorbital area but also an assessment of whether the globe is proptotic, the function of the extraocular muscles, and whether there is any pain with movement of the eye. Visual acuity, pupillary function, and confrontation visual fields must be assessed, if necessary, with the use of lid retractors. Specialists currently use a staging process of stage I to IV with stage I being POC and stage II through IV reflecting increasingly severe levels of OC (15).

Laboratory studies are of limited value, although a white blood cell count >15,000 may suggest bacteremia. Cultures of any wounds near the eye should be obtained; keeping in mind, conjunctival or nasopharyngeal swabs are generally not helpful. Blood cultures have been reported to be positive in up to 30% of children; however 70% to 80% of these were *H. influenzae* in the prevaccine era (13). It seems like blood cultures will identify fewer and fewer organisms. In the pre-HiB era, lumbar puncture (LP) was considered almost mandatory in the young child because of the invasive and virulent character of *H. influenzae* bacteremia. Currently, most authors reserve LP for children younger than 1 year of age with increased risk of *S. pneumoniae* bacteremia (13), those who are “toxic” or irritable, or those who have not yet received or completed the Hib and pneumococcal vaccination series.

Computed tomography (CT) of the orbit is useful in delineating sinusitis, subperiosteal and orbital abscesses, orbital involvement, or intracranial extension. It should be reserved for the child who presents with proptosis, pain on extraocular movement, limitation of eye movements, double vision, vision loss, ANC >10, 000 cell/μL or inability to conduct a full eye examination (12,13).

KEY TESTING

- Culture of any open wound(s) near the eye
- Blood cultures
- CT with IV contrast

ED MANAGEMENT

For OC: After appropriate cultures have been obtained, an IV line should be started and antimicrobial therapy initiated with an eye to covering the most likely organisms (Table 255.3). Subspecialty consultation with an ophthalmologist is mandatory.

TABLE 255.3
Antibiotic Treatment of Orbital Cellulitis

S. pneumoniae *M. catarrhalis* Nontypable *H. influenzae* Ceftriaxone 50–75 mg/kg IM or IV q24h or Cefotaxime 50 mg/kg per dose q6h plus Clindamycin 10 mg/kg per dose q8h or Nafcillin 100–200 mg/kg/d divided q6h or Augmentin/sulbactam 200 mg/kg/d divided q6h plus Vancomycin 60 mg/kg/d divided q6h[b]	High prevalence of community-acquired MRSA For moderate infections: Clindamycin 40 mg/kg/d divided q6–8 (max 2.7 g/d)[a] For severe infections: Vancomycin 60 mg/kg/d divided q6–8 (5) Fluoroquinolones not approved for use in young children

[a]There have been documented treatment failures due to inducible resistance in erythromycin-resistant strains (5).
[b]If suspicious for highly resistant *S. pneumoniae*.

For POC: The choice of outpatient antibiotics should reflect the level of antibiotic resistance within the community to *S. pneumoniae,* group A *Streptococcus,* and *S. aureus.* Blood cultures should be drawn prior to antibiotics. Treatment recommendations are presented in Table 255.4.

TABLE 255.4
Outpatient Treatment of POC

Condition	Gram + Organisms	High Prevalence of MRSA
Uncomplicated posttraumatic (no purulent draining wound)	Cephalexin, doxycycline (children >8 yrs) or clindamycin (1)	Clindamycin 30 mg/kg/d divided every 6–8 hrs or trimethroprim–sulfamethoxazole 6–10 mg/kg/d of TMP divided every 12 hrs
Nontraumatic	Ceftriaxone 50 mg/kg (not to exceed 1 g) followed by ampicillin–clavulanate 45 mg/kg/d in two divided doses for 7–10 d Penicillin allergic: Azithromycin 12 mg/kg (max 500 mg/d) once a day for 5 d	Same as above

DISPOSITION

All children with OC should be admitted to the hospital. Immediate consultation with an ophthalmologist and/or otolaryngologist should be undertaken if there are any physical findings suggestive of orbital involvement (proptosis, pain on eye movement, or decreased visual acuity), if there is difficulty obtaining an adequate eye examination, or if there has been failure to respond to parenteral antimicrobial therapy. Surgical evacuation is currently recommended for those patients who develop optic nerve findings such as decreasing visual acuity, afferent pupillary defects, visual field deficits, or who do not respond to 24 to 36 hours of medical management (13). The presence of sinusitis should prompt an otolaryngologic evaluation for possible endoscopic sinus surgery.

Recently, selected children with POC have been managed on an outpatient basis. There are several criteria that must be met before the child can be discharged: (1) There must be *no* orbital involvement (proptosis, ophthalmoplegia, or decreased visual acuity), (2) the child should be well-appearing, and (3) caregivers must demonstrate willingness to take the child home and to return the child immediately to the ED should the child's condition deteriorate. The child will need to have daily examinations to document resolution until blood cultures are negative (usually 48 hours) (15,17).

Common Pitfalls

- Failure to conduct a thorough eye examination, thus missing signs of orbital involvement.
- Failure to consult an ophthalmologist and or an otolaryngologist early in cases of orbital involvement, which could result in a poor outcome, possible visual impairment, or loss of the eye.

VISUAL DISTURBANCE

CLINICAL PRESENTATION

The clinical presentation of visual loss varies with age and developmental stage. An infant may be brought to the ED because parents have noted unilateral swelling of the globe or haziness of the cornea. Parents may complain that the 2- to 3-month-old infant does not seem able to fixate on and follow objects. There may be no complaints at all, and the physician may discover one of these findings incidentally or note an abnormal red reflex or the presence of nystagmus.

The parents of a preverbal child may bring them to the ED because of perceived strabismus or a persistent head tilt. Intraocular tumors may present with decreasing visual acuity, leukocoria (absent red reflex), strabismus, or gradually increasing proptosis and corneal edema. Rhabdomyosarcoma may present explosively, with rapid development of proptosis and decreased visual acuity (18). Craniopharyngiomas may present with advanced visual field defects, with or without headache, and sometimes with an unusual vertical "see-saw" nystagmus. By contrast, optic neuritis (ON) presents with sudden, severe unilateral or bilateral visual loss. There may be a history of an antecedent viral infection. On examination, there is reduced vision, nonreactive pupils, and swollen optic nerves. Hemorrhages and exudates may be seen on the optic disc.

Table 255.5 lists the differential diagnoses of abnormal vision.

TABLE 255.5
Differential Diagnosis of Abnormal Vision[a]

Physical Finding	Age	Differential Diagnosis
Leukocoria	Infant	Cataract
	Older child	Retinoblastoma
	Other tumor	
Tearing	Neonate	Congenital nasal lacrimal duct obstruction
		Glaucoma
Failure to fix or follow	2–3 mos	Abnormal visual development
		Any cause of decreased vision
		Strabismus
Nystagmus	Infant	Benign
	Older child	Any cause of decreased vision
		Tumor
		Amblyopia
		Drug induced
Decreased visual acuity (monocular)	Infant	Cataract
		Glaucoma
		Tumor
		Refractive errors
	Child	Amblyopia
		Refractive errors
		Tumor
		Orbital cellulitis
	Older child	Optic neuritis
	Adolescent	Tumor
		Trauma
		Refractive errors
Decreased visual acuity (binocular)	Variable ages	Glaucoma
		Retinoblastoma
		Optic neuritis
		Refractive errors
		Cortical visual loss
Proptosis	All ages	Rhabdomyosarcoma
		Other tumor
		Retrobulbar infiltrative process
Strabismus	All ages	Amblyopia
		Muscle palsy
		Large unilateral refractive error

[a]This table is intended as a guide to the more common diagnoses and is not comprehensive.

Children with complaints related to vision rarely present to the ED. When they do, the visit is prompted by their own complaints of abnormal vision or complaints from their parents, teachers, or school nurses. Occasionally, the ED physician, during the course of an examination, discovers a particular finding that necessitates urgent ophthalmologic referral. The complaints and etiologies for visual loss can vary greatly with the age of the child.

Nystagmus in childhood may be congenital or acquired. The etiologies of congenital nystagmus are essentially the same as those causing visual impairment in infancy. Nystagmus that develops in the older child is usually either drug-induced or associated with severe visual loss or intracranial neoplasm.

The most common complaint in the toddler and preschool-aged child seen in the primary care office (and, therefore, the pediatric ED as well) is strabismus or ocular malalignment. At birth, most babies display mild exotropia (outward deviation). This neonatal misalignment typically resolves by 3 months of age, and any strabismus after this age is abnormal. Large-angle esotropia (inward deviation) is also abnormal in infants (19).

Cataracts, glaucoma, intraocular tumors, optic nerve problems, and nystagmus may all present in infancy. The incidence of congenital cataracts is 1 to 4 of 10,000 live births in industrialized countries and 5 to 15 of 10,000 births in the developing world. Cataracts usually present in the newborn nursery (20). However, with home births and the easy movement of populations between developing countries and the industrialized world, it is conceivable that the first presentation may be in the ED. Cataracts are strongly associated with several chromosomal abnormalities (trisomy 13, 18, 21), perinatal infections (rubella, toxoplasmosis, or HSV), and inborn errors of metabolism (20).

Primary glaucoma has an incidence of <1 in 10,000 live births in Western countries; certain south Asian populations have up to a ninefold increased incidence related to increased rates of consanguinity in marriage. Most cases present before 6 months of age and 80% within the first year of life. Secondary glaucoma may occur as a result of prior eye surgery, uveitis, or in association with syndromes such as Sturge–Weber. Children with secondary glaucoma can present later than those with primary glaucoma.

Cortical visual impairment, defined as bilateral visual impairment in the presence of normal ocular structures and pupillary light reflex and absence of nystagmus, has increased in the United States in the past decade to become one of the most common causes of childhood blindness. The most common cause is perinatal hypoxia; however,

many other entities such as CNS infections, CNS malformations, epilepsy, malignancy, drugs, and head trauma may result in cortical visual impairment (21).

Retinoblastoma is the most common intraocular malignancy. The average age of presentation is 18 months, with 90% occurring prior to 5 years of age (22). One-third of tumors is bilateral and present earlier than unilateral tumors. The 10% of cases that present in older children are unilateral and not of the familial type (22).

Visual loss in childhood may result from compression of the optic nerve by tumor, inflammation of the optic nerve, and heredodegenerative conditions. Ten percent of rhabdomyosarcomas occur in the eye, arising from the intraocular muscles. The peak incidence is at age 8, with 75% occurring before age 10. Optic Neuritis (ON) in the child may be a postviral autoimmune phenomenon. The most common preceding infections are measles, mumps, varicella, pertussis, mononucleosis. Optic neuropathy has been reported in a few children with Lyme disease. Until recently, it was felt there was a weak association in children between ON and multiple sclerosis (MS). However, a recent small study showed that children with unilateral ON had a 36% progression rate within 2 years to MS. The presence of extraocular white matter lesions on MRI, bilateral ON, and extraocular clinical findings led to higher rates of MS diagnosis (11).

Optic gliomas and craniopharyngiomas are the two most common tumors that compress the optic nerve. Optic gliomas are intrinsic tumors of the optic nerve. They usually occur between 4 and 8 years of age. There is a strong association with neurofibromatosis. Craniopharyngiomas are the third most common brain tumor of childhood, representing 10% of all tumors in childhood. They arise from the embryonic rests of Rathke pouch near the sella turcica. Craniopharyngiomas affect visual acuity by compressing the optic chiasm or the optic nerve (22).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for visual disturbance includes, cataracts, glaucoma (either primary or secondary), intraocular tumors,

nystagmus, or ON (Table 255.5).

ED EVALUATION

When a tumor is suspected, neuroimaging, beginning with a CT scan, is imperative. Particularly, any finding of proptosis, with or without decreased vision, necessitates an urgent CT scan or MRI. The evaluation of ON includes magnetic resonance imaging and an LP. The LP usually reveals a monoclonal pleocytosis and mild protein elevation.

KEY TESTING

- CT scan if tumor is suspected
- MRI and LP if ON is suspected

ED MANAGEMENT

The emphasis in management, in the majority of these conditions, should be on recognition of the potential severity of the problem; timely neuroimaging, when applicable; and prompt, sometimes emergent, referral. Surgery is the mainstay of treatment for glaucoma, but medications such as pilocarpine or a β-blocker are often used initially to control intraocular pressure while awaiting surgery.

Therapy for ON is based on randomized clinical trials conducted in adults. The optic neuritis treatment trial (ONTT) demonstrated that IV steroids resulted in a more rapid improvement in vision, a benefit that waned at 12 months. There was, however, a significant reduction in progression in adults to multiple sclerosis at 2 years, but this effect was lost at 5 years. Oral steroids (prednisone) alone were conclusively shown to be detrimental. The decision to treat with IV steroids remains somewhat controversial but is frequently offered by ophthalmologists to children with bilateral disease because of a worse prognosis for visual recovery. The steroid therapy of choice is methylprednisolone 15 to 30 mg/kg/d for 10 to 14 days. This is followed by a slow prednisone taper over 1 to 2 months. Too rapid a taper has been associated with a recurrence of ON and compounded

visual loss. In spite of severe initial visual deficits, 80% of children had excellent visual recovery.

The treatment of cataracts, tumors, or glaucoma is largely surgical. Because infancy, particularly the first 2 months of life, represents a critical period in normal visual maturation, failure to remove the obstruction to clear vision could result in irreversible amblyopia, a functionally blind eye or difficulties with stereoscopic vision (19).

DISPOSITION

Tumors, glaucoma, cataracts, and ON often involve urgent admission to the hospital. The facility, as well as the consultant, should be experienced in pediatric eye disorders. Because the growth of some tumors, such as rhabdomyosarcoma, can be explosive, consultation with an experienced ophthalmologist is emergent.

The presence, in an infant, of leukocoria or a swollen anterior chamber requires urgent referral to an ophthalmologist comfortable with the treatment of pediatric cataracts, tumors, and glaucoma.

Because nystagmus can represent a structural lesion as well as amblyopia, there should be referral to an ophthalmologist on a semiurgent basis.

The finding of strabismus in the preverbal or preschool child mandates outpatient referral to an ophthalmologist.

Children with known risk factors for secondary glaucoma should undergo periodic routine ophthalmic evaluation.

Common Pitfalls

- Failure to perform an age-appropriate, complete eye examination.
- Failure to refer a time-dependent process urgently to an appropriate ophthalmologist.

NASOLACRIMAL DUCT OBSTRUCTION AND DACRYOCYSTITIS

CLINICAL PRESENTATION

Congenital nasolacrimal duct obstruction (CNLDO) is a common problem of infancy, with 20% of children exhibiting some symptoms within the first year of life. Canalization of the nasolacrimal duct may not be complete at birth. In most of these children, a membranous obstruction is the etiologic factor; however, a nasolacrimal duct cyst may also result in obstruction (23). Ninety-six percent of infants with CNLDO show spontaneous resolution of the obstruction by the first birthday. Refer to Figure 255.2 for anatomy of the nasolacrimal duct.

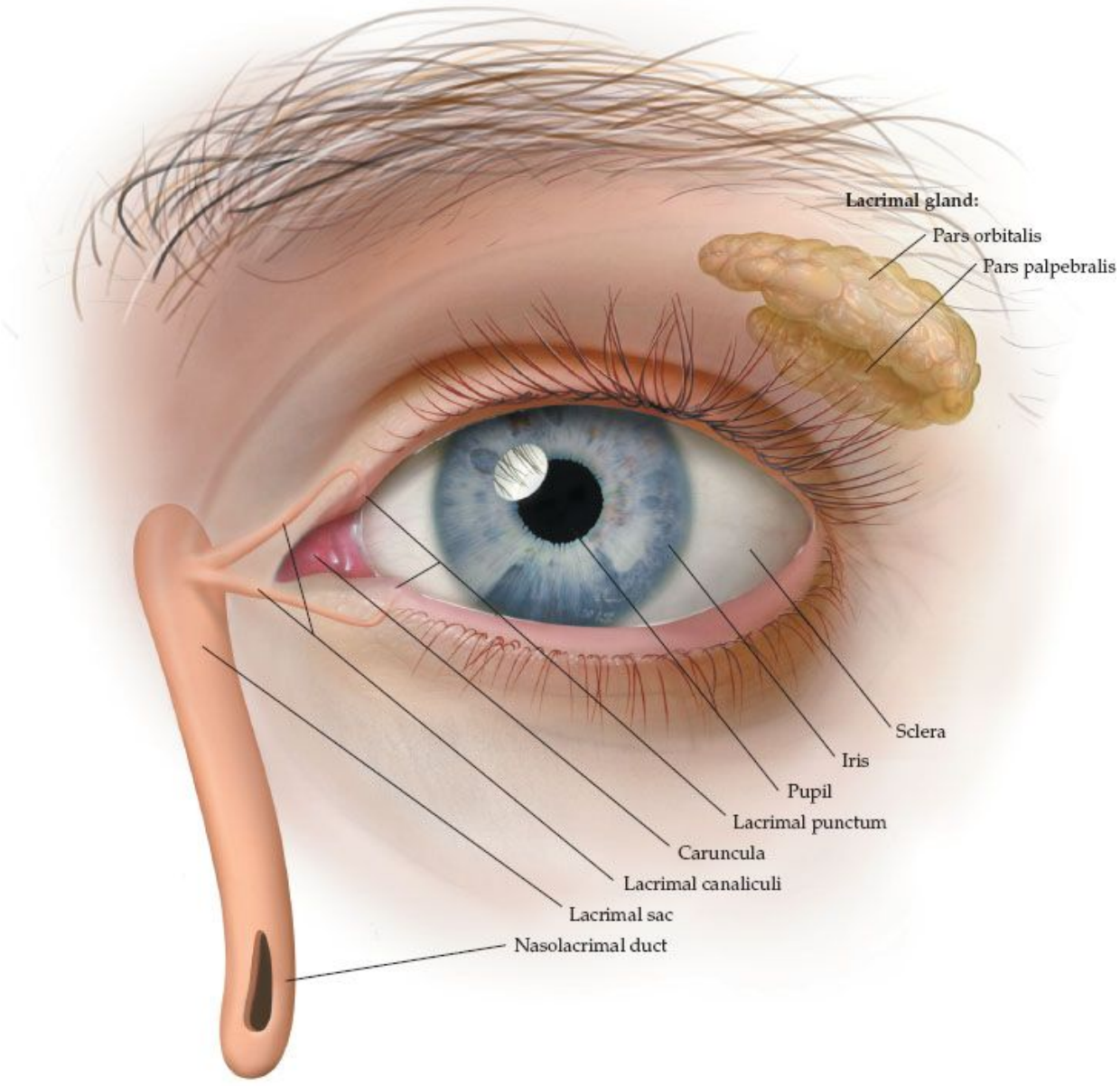

FIGURE 255.2 Eye anatomy; left eye outer labeled. (Asset courtesy of Anatomical Chart Company, ©2014.)

Dacryocystitis, or infection of the nasolacrimal duct, may be acute or chronic. It may occur as a complication of CNLDO or of acquired nasolacrimal duct obstruction (ANLDO). In the neonatal period, dacryocystitis is rare, occurring in <2% of infants with CNLDO. However, if a duct cyst is the etiology of the obstruction, the risk of dacryocystitis is greater, with earlier presentation, usually by 2 weeks of age (23). The causative organisms are most often *S. aureus, Staphylococcus epidermidis,* and α-hemolytic streptococci. *Corynebacterium diphtheriae* and Epstein–Barr virus have also been reported (24). The risk of bacteremia is higher in the neonatal period than in the older infant or child. ANLDO may occur as the result of ethmoidal sinusitis or maxillary fracture through the wall of the nasolacrimal duct (24).

Symptoms of CNLDO may be present at birth or may be delayed for several weeks, until normal tear production develops. Signs include excessive tear lake, tear overflow, or a mucoid discharge that is produced by the lacrimal sac. The tearing is often distressing to the parent. There may be crusting or stickiness of the eye; however, the conjunctivae are clear, the eye is neither red nor swollen and the patient should not be febrile.

Dacryocystitis is characterized by erythematous and swollen skin over the lacrimal sac and purulent drainage from the punctum. Fever may be present and POC or OC may develop as a complication of dacryocystitis (24).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for dacryocystitis includes corneal abrasion, local trauma with infection (i.e., insect bite), conjunctivitis, and in advanced cases OC or POC.

ED EVALUATION

A careful history and physical examination should differentiate CNLDO from dacryocystitis. In the latter case, cultures of any purulent drainage, as well as blood cultures, need to be obtained. A complete blood count may be helpful, with a high white blood cell count indicating a higher risk of bacteremia. In the infant who is 1-month old or younger, a full sepsis workup, including lumbar puncture, should be done.

KEY TESTING

- Culture of drainage and blood cultures
- Full sepsis workup in the infant less than 1 month of age

ED MANAGEMENT

In dacryocystitis, antibiotics to cover *Staphylococcus* and *Streptococcus* species should be started immediately after cultures are obtained. The choice of particular antibiotics should reflect *Staphylococcus* and *Streptococcus* resistance and the increase in MRSA within each community

Recommended agents include:

- Clindamycin 40 mg/kg/d IV in three or four divided doses
- Nafcillin 150 mg/kg/d IV doses
- Cefuroxime 150 mg/kg/d IV in three divided doses

In the penicillin-allergic infant or child, vancomycin can be used (5).

DISPOSITION

All patients with acute dacryocystitis should be admitted to the hospital due to the potential complications of sepsis and/or meningitis. Immediate consultation with an ophthalmologist is required, because early nasolacrimal duct probing is important for successful treatment of acute dacryocystitis. Because neonatal dacryocystitis is often associated with a nasolacrimal duct cyst, a complete intranasal examination at the time of surgery and marsupialization of any cyst is imperative to prevent recurrence (23).

The treatment of chronic or “low-grade” dacryocystitis is primarily surgical, with duct probing within several weeks of presentation. Systemic antibiotics are not necessary, although some consultants recommend a topical antibiotic ointment such as polymyxin B (23).

Dacryocystitis after facial fracture or sinusitis requires referral to the appropriate specialist: ophthalmology, otolaryngology, or plastic surgery (23).

Conservative management of CNLDO includes warm water compresses (to remove the mucoid discharge) and nasolacrimal duct massage; performed by occluding the common canaliculus with the index finger and then stroking firmly downward. This maneuver increases the hydrostatic pressure in the nasolacrimal sac, with the ultimate goal of overcoming the membranous obstruction. Massage the duct in repetitions of 5 to 10 passes, 4 to 6 times a day is recommended. Erythromycin ophthalmic ointment applied 4 times a day is also recommended; however, its efficacy in speeding recovery is not proven. Referral to an ophthalmologist is recommended for cases that do not resolve with conservative management. Probing will cure 90% of these infants (23). Newer, minimally invasive techniques such as balloon dacryocystoplasty, lacrimal stents, conjunctivoplasty, and endoscopic dacryocystorhinostomy are continually being refined and may be offered in individual cases.

Common Pitfalls

- Failure to consider bacteremia, sepsis, or meningitis in the neonate or young infant.
- Failure to consult an ophthalmologist early in cases of acute dacryocystitis.

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CHAPTER 256

Ear Infections

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Earache can be caused by infections or can result from referred pain from pharyngitis, odontogenic pain, external otitis, parotitis, or a foreign body in the ear canal. Infections of the ear can involve the middle ear (otitis media) and mastoid air cell system (mastoiditis), as well as the outer ear (otitis externa [OE]).

ACUTE OTITIS MEDIA

Acute otitis media (AOM) is the most common reason for antibiotic prescriptions in children, and a leading cause of acute care visits (1). Young children are prone to develop AOM secondary to their eustachian tube (ET) anatomy (short, narrow, horizontal, and floppy) and their frequent viral upper respiratory infections (URIs). URIs cause ET dysfunction via inflammation and consequent edema as well as decreased ciliary activity. This prevents physiologic drainage of middle ear secretions into the nasopharynx, and creates a negative pressure that draws bacteria from the nasopharynx into the middle ear. Accordingly, AOM is most commonly diagnosed in children less than 2 years of age, especially in those who attend daycare and experience frequent URIs. Other risk factors include smoke exposure, lack of breast-feeding in the first 6 months of life, pacifier use beyond the first 6 months of age, and craniofacial anomalies (e.g., Down syndrome, cleft palate).

The most common pathogens are *Streptococcus pneumoniae* and nontypeable *Haemophilus influenzae* followed by *Moraxella catarrhalis.* Since the introduction of the heptavalent pneumococcal conjugate vaccine (PCV-7), the microbiology of AOM has shifted toward a

predominance of *H. influenzae* and non-PCV-7 strains of *S. pneumoniae* (2,3). While the proportion of penicillin (PCN)-resistant *S. pneumoniae* and beta-lactamase–positive *H. influenzae* has remained stable in children with first-time AOM, there has been a notable increase in resistant strains in children with treatment failures or recurrent AOM (2). Several highly resistant serotypes of *S. pneumoniae* (19 A, 7 F, 6 C) that are not included in PCV-7 have emerged as major pathogens causing the incidence of *S. pneumoniae* to be comparable to pre-PCV-7 rates (2). In 2010, the 13-valent pneumococcal conjugate vaccine (PCV-13) was introduced. Preliminary studies of nasopharyngeal carriage rates in children less than 2 years of age with AOM who received PCV-13 showed a marked decrease in the prevalence of serotypes 19 A, 7 F, and 6 C (4). Viruses also cause AOM and may be clinically indistinguishable from bacterial AOM; common viral etiologies include picornavirus, respiratory syncytial virus, and enterovirus. Of note, infants under 8 weeks of age with AOM most often have the typical pathogens, but can also have Group B *streptococcus* and gram-negative bacilli (5). In children with tympanostomy tubes, *Staphylococcus aureus* and *Pseudomonas aeruginosa* are also common, with methicillin-resistant *S. aureus* becoming more prevalent (6).

CLINICAL PRESENTATION

The symptoms of AOM have an acute onset, usually within 48 hours of clinical presentation, and include otalgia, fever, excessive crying or fussiness, restless sleep, and decreased appetite. Otalgia has the highest likelihood ratio in predicting the presence of AOM (3). In nonverbal children, otalgia may be indicated by tugging or rubbing the ear. The absence of fever does not rule out AOM and in fact, studies have demonstrated that presence of fever cannot predict the diagnosis of AOM (7).

DIFFERENTIAL DIAGNOSIS

When AOM is not present, the most likely cause of otalgia is referred pain from infection or trauma in regions with shared innervation, namely the pharynx, nares, and teeth. ET dysfunction causing

negative pressure and temporal–mandibular joint pathology can also cause otalgia.

ED EVALUATION

In an attempt to increase the diagnostic accuracy of AOM as well as decrease the unnecessary use of antibiotics, guidelines have been published and most recently revised in 2013 (8). According to these guidelines, AOM is diagnosed if the tympanic membrane (TM) is bulging severely or moderately, indicating a middle ear effusion (MEE), *or* there is new onset of otorrhea not due to OE (8). AOM can also be diagnosed if there is mild bulging of the TM *and* onset of ear pain within the last 48 hours or intense erythema of the TM (8). In the absence of a MEE, AOM cannot be diagnosed.

Examination of the TM is facilitated by using the largest speculum that fits comfortably in the canal to allow proper visualization. Pneumatic otoscopy involves assessing TM mobility by insufflating air into the external ear canal. This technique can aid in confirming the presence of a MEE, in which case the TM is not mobile; however, this will not be successful as a diagnostic test unless the speculum forms a tight seal on the ear canal. If the TM cannot be visualized because of cerumen, the cerumen can be removed with a curette or by gentle irrigation with warm water. Cerumenolytics can be instilled before irrigation. MEE can signify either AOM or otitis media with effusion (OME); it is the presence of inflammatory changes that distinguishes AOM from OME. A red TM and the acute onset of otalgia that interferes with a child's normal activities are consistent with inflammation of the middle ear. It is important to note that although redness of the TM can represent inflammation, it can also be secondary to vascular engorgement caused by fever or crying. Relying on TM redness alone will result in the overdiagnosis of AOM. This finding, combined with the acute onset of symptoms and evidence of MEE on examination is more specific for AOM.

It is important to assess for complications of AOM on physical examination by including the mastoid process and cranial nerves (refer to Chapter 68). A cholesteatoma (a white cystic mass behind or involving the TM) can develop within the middle ear, leading to a

facial nerve palsy secondary to inflammation of the facial nerve as it traverses the inner and middle ear.

Adjunctive Diagnostics

Tympanocentesis, needle aspiration of MEE, is useful to establish a bacterial diagnosis. It should be considered in neonates and patients with immunosuppression, persistent treatment failure and/or suppurative complications (1). This is most commonly performed by an otolaryngologist.

KEY TESTING

- No specific diagnostic tests are generally indicated.

ED MANAGEMENT

The primary goals of treatment are to relieve symptoms and prevent complications. Appropriate management decisions are based upon the child's age, allergies, recent antibiotic exposure, and the severity of the infection. Refer to Table 256.1 for drug dosages. Febrile or irritable neonates require hospitalization for parenteral antibiotics. In the rare circumstance that a cranial nerve palsy is present, an emergent myringotomy should be performed by an otolaryngologist.

TABLE 256.1
Oral Antibiotic Treatment Options for AOM

Antibiotic	Dosage
High-dose amoxicillin[a]	90 mg/kg/d divided BID
High-dose amoxicillin–clavulanate[b]	90 mg/kg/d divided bid based on amoxicillin component, using ES preparation
Cefuroxime	30 mg/kg/d divided bid
Cefpodoxime	10 mg/kg/d divided qd or bid
Cefdinir	
Ceftriaxone[c]	14 mg/kg/d divided qd or bid
50 mg/kg /d IM or IV for 3 d	

Standard duration of therapy is 10 days. For those older than 6 years who have nonsevere illness, a 5–7-day course is acceptable (1).
[a]Recommended first-line treatment.
[b]Treatment after 48–72 hours of initial antibiotic if symptoms fail to improve.

Pain Management

Pain from AOM may be significant in the first few days of infection, and therefore it is important to manage in the emergency department (ED). Studies have shown that children less than 2 may have pain for longer periods than older children with AOM, even extending up to 3 to 7 days after initiating antibiotics (9). Oral analgesics such as ibuprofen and acetaminophen are effective in controlling pain from AOM and should be initiated even if antibiotics are not started (8). In rare cases, opioids may be needed. There is not sufficient evidence to support the routine use of topical analgesics (8). If used, they should only be utilized in the presence of an intact TM. Other adjunctive medications, namely decongestants, antihistamines, and systemic steroids, are not beneficial and are associated with increased side effects.

Decision for Antibiotics

The decision to treat a child with antibiotics is based on the child's age and severity of symptoms (Fig. 256.1). For children age 6 to 24 months, antibiotics should be initiated for AOM with otorrhea, bilateral AOM, or AOM with severe symptoms (defined as toxic appearance, otalgia for more than 48 hours, temperature of 39°C or above in the past 48 hours, or uncertain access to a follow-up visit) (8). For a certain diagnosis of unilateral AOM without severe

symptoms, antibiotics may be started, or watchful waiting may be used (see below). For children **older than 24 months,** antibiotics are recommended for AOM with otorrhea or AOM with severe symptoms (8). For unilateral or bilateral AOM without severe symptoms, either antibiotics or watchful waiting may be utilized. For children **less than 6 months,** antibiotics should be initiated for AOM. However, it is important to also evaluate for alternative sources of infection in the urine, blood, and potentially the CSF, if fever is present in this age group.

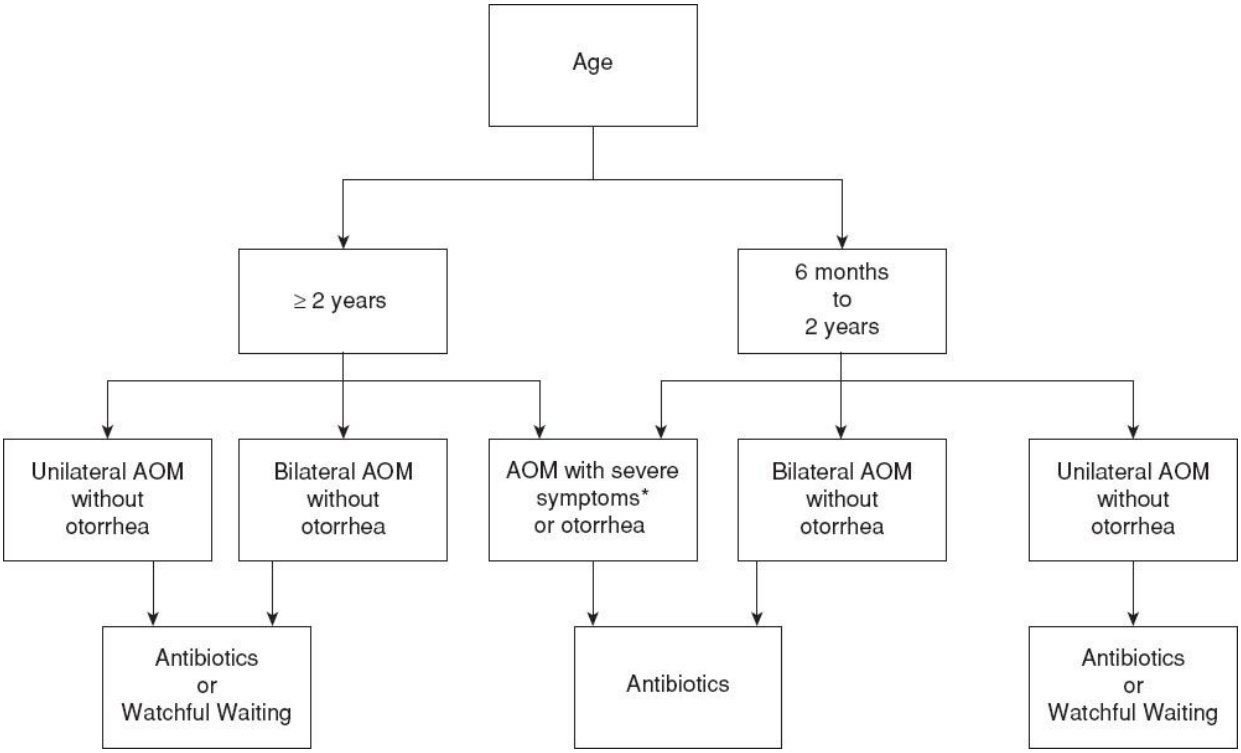

FIGURE 256.1 Algorithm for Management of Acute Otitis Media. *Severe symptoms are defined as toxic appearance, otalgia for more than 48 hours, temperature of 39°C or above in the past 48 hours, or uncertain access to a follow-up visit.

A management strategy of "watchful waiting" with the avoidance of antibiotics for certain patient populations initially gained support in the United States in the early 2000s. When compared to those who successfully avoided antibiotics with watchful waiting, patients treated with antibiotics had higher rates of multidrug-resistant

pathogens, and suffered more antibiotic sides effects, most notably diarrhea (10). In addition to decreasing bacterial resistance, proponents also sited the high rate of spontaneous resolution of bacterial AOM. If the "watchful waiting" strategy is chosen, follow-up must be assured and antibiotics must be able to be initiated if symptoms worsen or fail to improve within 48 to 72 hours. In the ED setting, this may be facilitated by giving the parents a prescription to hold for 2 to 3 days that is filled if symptoms are not improved over this time period. If follow-up cannot be assured, the "watchful waiting" strategy should not be utilized (8).

Antimicrobial Therapy

Because *S. pneumoniae* and *H. influenzae* remain the most common pathogens in first-time AOM, initial therapy is directed at these organisms. High-dose (HD) amoxicillin (90 mg/kg/d divided bid; Table 256.1) is the first-line agent in treating AOM (8). In addition, amoxicillin is relatively inexpensive, and tolerated well by children in regards to taste and side effects. For children that have had amoxicillin within the past 30 days, have purulent conjunctivitis on examination, or have a history of recurrent AOM that did not respond to amoxicillin, additional beta-lactamase coverage is needed and HD amoxicillin–clavulanate is the recommended initial agent (8). HD amoxicillin–clavulanate is an ES (extra strength) preparation which allows HD amoxicillin dosing (90 mg/kg/d based on the amoxicillin component, divided bid) while keeping the clavulanate portion in a range less likely to cause diarrhea and other side effects. HD amoxicillin–clavulanate is preferred for patients with concomitant conjunctivitis because of the association of nontypeable *H. influenzae* with conjunctivitis–otitis (11). For patients with a penicillin allergy, reasonable first-line choices include cephalosporins (Table 256.1).

Most children treated for AOM will not feel significantly better within the first 24 hours of treatment. However, if signs and symptoms fail to improve after 48 to 72 hours, second-line therapy should be started (8). Second-line therapy should take into consideration the spectrum of the "failed" antibiotic in order to

provide coverage against the most likely organism(s) untreated by this regimen. Treatment failure with HD amoxicillin suggests beta-lactamase producing organisms; thus, options include HD amoxicillin–clavulanate, select second-generation cephalosporins and ceftriaxone (Table 256.1) (8). Of these oral agents, HD amoxicillin–clavulanate is preferred because it is more biologically potent than the second-generation cephalosporins and proven highly effective against both beta-lactamase producing pathogens as well as penicillin nonsusceptible *S. pneumoniae* (12). Although a single injection of ceftriaxone (50 mg/kg IM) can be used for first-line therapy in patients who are vomiting or who cannot take oral antibiotics, a three-dose (3-day) regimen is recommended if the AOM was unresponsive to initial antibiotic therapy (8). For resistant AOM, some experts recommend a dose of 75 mg/kg of ceftriaxone followed in 48 hours by a second dose of 75 mg/kg. While no specific clinical trials have been conducted using tympanocentesis to document eradication, this regimen is supported by the pharmacokinetics and pharmacodynamics of ceftriaxone (13).

Children with AOM and otorrhea secondary to acute TM perforation are managed similarly to patients without a perforation. However, some clinicians advocate the concomitant use of ototopical agents to hasten the resolution of AOM and prevent the development of OE (14). Because the perforation may seal before sterilization of the middle ear, topical agents cannot be used as monotherapy.

There is no standard therapy for children with tympanostomy tubes and otorrhea from AOM. Monotherapy with topical agents, specifically ciprofloxacin–dexamethasone, is as effective as systemic agents for the typical pathogens and is also effective for *P. aeruginosa,* a common pathogen in this setting for which no oral systemic antibiotic is approved for children (15). Studies have shown that topical ciprofloxacin–dexamethasone compared to oral antibiotics results in more rapid resolution of symptoms (15). Moreover, topical agents do not lead to bacterial resistance, have fewer side effects, and are more convenient for the patient compared with systemic therapy. Ciprofloxacin–dexamethasone dosing for AOM with tympanostomy tubes is the same as for OE (Table 256.2),

four drops twice daily for 7 days. However, ofloxacin dosing for AOM with tympanostomy tubes differs and should be dosed as five drops instilled twice a day for 10 days. Pumping the tragus after the installation of ear drops can improve delivery through the tube. Concomitant treatment with systemic antibiotics is advocated by some clinicians for those children with systemic signs and symptoms or with copious exudate that may interfere with the administration of topical agents. In these cases, use of an agent with additional staphylococcal coverage, such as HD amoxicillin–clavulanate, is useful as *S. aureus* is common in those with chronic drainage. Although routine culture of otorrhea is unnecessary, careful culturing with appropriately sized swabs after cleaning the ear canal can be helpful in those with persistent infection.

TABLE 256.2
Ototopical Antibiotics for Treatment of Otitis Externa

Antibiotic	Product Name(s)	Antiseptic	Acid	Steroid	Dose	Duration
Polymyxin B/neomycin	Cortisporin suspension	+	–	+	3 gtts tid–qid	10 d
	Pediotic	+	–	+	3 gtts tid–qid	10 d
	Cortisporin solution	+	+	+	3 gtts tid–qid	10 d
Ofloxacin	Floxin otic	+	+	–	1–12 yrs: 5 gtts qd	7 d
					>12 yrs: 10 gtts qd	7 d
Ciprofloxacin and dexamethasone	Ciprodex	+	+	+	4 gtts bid	7 d

DISPOSITION

If no evidence of serious systemic infection is present, children may be managed as outpatients. A follow-up appointment with the primary care physician should occur in 2 to 3 weeks to monitor recovery of the MEE. Instruction should be given for patients to seek care sooner if symptoms, including fever, do not resolve in 48 to 72 hours or signs of worsening infection develop. Children with toxicity, other serious systemic infections, intracranial complications, or clinically significant immunodeficiencies and febrile neonates should be hospitalized and placed on parenteral antibiotics.

Common Pitfalls

- Overdiagnosis of AOM secondary to failure to remove cerumen from ear canal.
- Diagnosis based solely upon redness of the TM.
- Failure to distinguish OME from AOM.
- Failure to consider other more serious coexisting diagnosis, such as sepsis or meningitis.

MASTOIDITIS

Mastoiditis is a suppurative complication of AOM. It most commonly affects children less than 2 years of age, but can be seen in all age groups. The overall incidence of mastoiditis has decreased since the introduction of antibiotics for the treatment of AOM. Mastoiditis is a spectrum of disease ranging from infectious inflammation of mastoid air cells to abscess development and subsequent spread to contiguous areas. The most common bacterial pathogens are *S. pneumoniae* and *Streptococcus pyogenes,* followed by *S. aureus, P. aeruginosa, and* nontypeable *H. influenzae.* In the post-PCV-7 era, *S. pneumoniae* remains the predominant pathogen with serotype 19 A and other drug-resistant serotypes becoming increasingly common (16).

CLINICAL PRESENTATION

Acute mastoiditis (AM) represents a spectrum of disease**. AM without periostitis or osteitis** is the initial subclinical stage involving inflammation of the lining of the mastoid air cells. Because the mastoid is directly connected to the middle ear, almost all episodes of AOM are thought to be associated with some inflammation of the mastoid. Diagnosis of this stage is often made incidentally when cranial imaging, obtained for other reasons, reveals cloudy mastoids without evidence of bony erosion. There are no specific clinical signs or symptoms of mastoiditis in this stage, and no special treatment is required.

AM with periosteitis occurs when the infection spreads into the periosteum. Patients present clinically with postauricular edema, erythema, and tenderness. The postauricular crease may be absent. The auricle may be displaced downward and outward. Fever, ear

pain, and irritability are common, especially in younger children. Up to half of children presenting with mastoiditis may not have had AOM diagnosed within the preceding weeks (17). This may occur when a middle ear infection resolves but granulation tissue or edema obstruct the narrow tube connecting the middle ear to the mastoid thus preventing drainage and resolution of the mastoiditis. In addition, studies have demonstrated that up to half of patients with mastoiditis were treated prior with antibiotics for AOM (17,18), suggesting that appropriate treatment of AOM may not prevent the development of mastoiditis. Most importantly, since the introduction of AOM "watchful waiting" guidelines in 2004, no significant increase in the incidence of AM has been noted (18).

AM with osteitis occurs when the infection results in erosion of the bony septae that separate the mastoid air cells, resulting in an empyema; making some children appear toxic. Infection can spread laterally creating a postauricular subperiosteal abscess, anteriorly creating a preauricular abscess, inferiorly toward the sternocleidomastoid muscle, medially into the petrous air cells and inner ear labyrinth, or posteriorly into the calvarium.

Chronic mastoiditis is most commonly a manifestation of chronic suppurative otitis media (otitis with perforation and persistent otorrhea) that has failed outpatient therapy. However, it can occur in a child with ineffectively treated AM.

Differential Diagnosis

The differential diagnosis of AM includes OE with postauricular cellulitis, perichondritis of the pinna, and postauricular lymphadenitis. In each of these, middle ear disease is usually absent, and with perichondritis of the pinna and postauricular lymphadenitis, the posterior auricular crease usually remains intact. Postauricular lymphadenitis is usually seen in the presence of scalp infection or inflammation.

ED EVALUATION

If symptoms and signs of mastoiditis are present, a CT scan of the temporal bones should be performed. Key findings of mastoiditis are destruction and coalescence of the mastoid air cells. Historically, a head CT was not recommended unless signs and symptoms of intracranial complications were present. However more recently, a case series of 70 patients with AM showed that of 10 patients with intracranial complications (parasinus empyema, sigmoid sinus thrombosis, epidural abscess, and subdural abscess), none had neurologic signs or symptoms on presentation. This suggests that a head CT with contrast should strongly be considered in all patients presenting with suspected AM (19).

KEY TESTING

- CT scan of the mastoid bone
- CBC
- Palpation of the mastoids to check for tenderness.

ED MANAGEMENT

It is recommended that all patients with mastoiditis be admitted for treatment (20). However, some clinicians will advocate an attempt at outpatient treatment in mild cases when close follow-up can be assured. HD amoxicillin–clavulanate will treat the most common pathogens, with the exception of *P. aeruginosa.* Fluoroquinolones are relatively contraindicated in young children because of theoretic, but unproven, concerns about cartilage toxicity. When *P. aeruginosa* is suspected, tympanocentesis can be helpful in directing therapy. Any patient with AM presenting with fever, ill appearance or osteitis should be admitted for parenteral antibiotics and otolaryngology consultation (20). Traditional treatment involved intravenous antibiotics and mastoidectomy with the removal of necrotic bone. More recently, the use of myringotomy with or without the placement of tympanostomy tubes has obviated the need for mastoidectomy in many cases. Serial CT scans are used to document resolution of infection. Ampicillin–sulbactam or third-generation cephalosporins are acceptable for initial intravenous antibiotic

therapy. In the post-PCV7 era, the resistance of *S. pneumoniae* to both PCN and ceftriaxone is increasing and therefore some have suggested empiric treatment with both ceftriaxone and clindamycin (16). For patients who have proven ceftriaxone-resistant *S. pneumoniae* or in those for which there is a high index of suspicion, vancomycin can be added. If *P. aeruginosa* is suspected, initial, empiric antipseudomonal coverage with ceftazidime or piperacillin–tazobactam can be used. Subsequent therapy can be modified based upon culture results from tympanocentesis.

Chronic mastoiditis may be treated with a parenteral antipseudomonal antibiotic. Otolaryngology consultation is advised as mastoidectomy is necessary for patients that do not improve with medical management.

DISPOSITION

Patients with early, mild cases of AM with periosteitis may be managed as outpatients using antibiotic therapy combined with close follow-up. All other cases require hospital admission, parenteral antibiotics, and otolaryngology consultation.

Common Pitfalls

- Failure to recognize AM or distinguish AM from OE with cellulitis, perichondritis of the pinna or postauricular lymphadenitis.
- Failure to consider concurrent intracranial complications of AM such as meningitis and brain abscess.

OTITIS EXTERNA

OE is a diffuse inflammation or infection of the external ear canal which is most often acute in nature (refer to Chapter 68). Although swimming is the most common precipitant, a break in the epithelial lining from any cause (e.g., trauma, foreign body, and eczematous skin disorder) can result in OE. The lifetime incidence of OE is 10% and peaks between the ages of 7 and 12 years; it is rare in those less than 2 years (21). The most common bacterial pathogen is *P. aeruginosa* followed by *S. aureus*. Fungal OE (*Candida and Aspergillus*

species) is rare in the United States and occurs more often in cases of chronic OE and refractory infection (22).

CLINICAL PRESENTATION

The diagnosis of OE is consistent with a history of rapid onset of symptoms over 48 hours, including otalgia, otorrhea, pruritus, and sense of ear fullness. Additional but less common symptoms include hearing loss or jaw pain. The infection may spread to the surrounding soft tissue resulting in a periauricular cellulitis and perichondritis. Bone infections can occur with spread to the mastoid or cranium. Necrotizing (malignant) OE is a rare, but aggressive infection (usually caused by *Pseudomonas* species) may be potentiate systemic spread (refer to Chapter 68).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes middle ear infections, other external ear canal disorders (furunculosis, herpes zoster oticus) and mastoiditis. OE and AOM can often be distinguished clinically by the presence or absence of pain with manipulation of the outer ear. However, if an episode of AOM is complicated by TM perforation, the purulent drainage can cause a secondary OE. *Furunculosis* is caused by an infected hair follicle in the distal portion of the external canal causing a localized OE. This condition responds well to drainage and antistaphylococcal antibiotics. Ramsay Hunt syndrome is a *Herpes zoster* infection in the distribution of the facial nerve presents with vesicles in the external auditory canal or auricle, facial nerve paralysis, hearing loss, and vertigo. Finally, *mastoiditis* may be difficult to distinguish from OE with postauricular cellulitis, and may require diagnostic imaging to clarify the diagnosis. Loss of the postauricular fold and tenderness over the mastoid are more common in mastoiditis.

ED EVALUATION

The diagnosis of OE is based on history and physical examination. Key examination findings are tenderness elicited by manipulation of the tragus or pinna and diffuse ear canal edema or erythema (21).

Canal wall edema may progress to obstruction, trapping debris and secretions in the proximal canal and preventing visualization of the TM (refer to Chapter 68).

KEY TESTING

- Careful physical examination, looking for purulent discharge and manipulation of tragus or pinna to elicit pain

ED MANAGEMENT

Management of OE consists of controlling inflammation and infection; thus, it is important for the appropriate topical otic agents to reach the inflamed, edematous canal. In mild OE, secretions can be dry mopped with rolled tissue or swabs prior to antibiotic administration. In severe OE with near-obstruction of the canal, a wick made of compressed cellulose or gauze can be inserted. The topical antibiotic is then dripped onto the absorbent wick allowing delivery of the medication to the obstructed portion of the canal. If the wick does not fall out on its own as the canal edema decreases, it should be removed in 2 to 3 days. In the absence of an ear wick, the topical antibiotic should be instilled in the outer ear canal while the patient is lying with the affected side up. Medication delivery is enhanced by gently moving the pinna to and fro. The patient should remain on their side for 3 to 5 minutes. The canal may be then left open (21).

Topical antibiotics are recommended as first-line treatment for uncomplicated OE (21). Oral antibiotics are reserved for immunocompromised hosts and cases where infection extends beyond the external ear canal, including concomitant AOM. Classes of ototopicals currently used to treat OE include acidifying agents, antiseptics, antibiotics, and steroids. Topical acidic solutions inhibit bacterial growth, but are not commonly used because they cause local burning and irritation. Topical antimicrobials aimed at treating the leading causative organisms (*P. aeruginosa* and *Staphylococcus spp*) are the mainstay of therapy (Table 256.2). Polymyxin B–neomycin–hydrocortisone agents have been used extensively for

years with good results; however, they have been associated with hypersensitivity and ototoxicity and should be avoided if the TM is perforated. Topical fluoroquinolones (ofloxacin and ciprofloxacin) are now used more commonly due to a decreased risk of ototoxicity and hypersensitivity. Newer research also shows that quinolones may be superior to traditional agents regarding both bacterial eradication and cure of OE (23). The two fluoroquinolones differ in that the ciprofloxacin preparation contains dexamethasone whereas the ofloxacin preparation does not. Fluoroquinolones are the only topical agents approved in OE with TM perforation. Studies comparing topical antibiotics with and without a steroid have shown comparable clinical cure rates (24). Fungal OE treatment involves cleansing with acidifying agents (2% acetic acid or 90% alcohol solution); antifungal drops are reserved for severe infections (25). Eczematous OE treatment is the same as for the primary disorder.

DISPOSITION

In the absence of an accompanying cellulitis with systemic symptoms, children can be managed at home. Reevaluation should occur if symptoms do not improve in 48 to 72 hours. Follow-up is also recommended in severe cases when complete examination of the external canal and TM is not possible or when an ear wick is placed. Patients should be advised to abstain from swimming for 7 to 10 days during treatment; hearing aids should not be inserted until pain and otorrhea has resolved (21). Prophylaxis against recurrent swimmer's ear includes application of drops containing equal parts vinegar and alcohol (to alter pH and dry the canal, respectively) immediately after swimming. A hairdryer set on low and held one foot from the ear can also be used to dry the ear canal after swimming. The use of earplugs for prevention of OE is controversial. Earplugs will keep the canal dry only when properly fitted and may cause local irritation and impaction of debris/cerumen.

CRITICAL INTERVENTIONS

- Examination of the TM with pneumatic otoscopy, paying careful attention to patient positioning, comfort, and speculum size to

optimize visualization and seal.
- Careful follow-up for patients when the "watchful waiting" strategy is adopted.
- Otitis media is rare in patients less than 6 months old. Pay careful attention to alternative sources of infection such as meningitis in neonates and young infants.
- CT scanning of the temporal bone and mastoid air cells in cases of suspected mastoiditis.

Common Pitfalls

- Failure to diagnose concurrent AOM.
- Failure to use a wick in severe cases.
- Failure to recognize complicating conditions (periauricular cellulitis and necrotizing OE; immunocompromised status) that require systemic antibiotics.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Noel S. Zuckerbraun, Katalin I. Koranyi, and Robert W. Hickey, who wrote the previous versions of this chapter.

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CHAPTER 257
Sinusitis

Kelli A. Petronis

Acute sinusitis is defined as inflammation of the mucosal lining of the nasal passage and paranasal sinuses lasting less than 4 weeks. Predisposing factors include allergens, environmental irritants, and infection. The most frequent cause of sinusitis is an upper respiratory infection (URI) (1). It is estimated that children between the ages of 6 and 35 months of age have six episodes of URI per year, and acute bacterial sinusitis (ABS) complicates viral URI in 8% (2). Children in day care have a higher risk of developing sinusitis than those in home care (3). The second most common predisposing factor in the development of childhood acute sinusitis is allergic inflammation (4). Other predisposing conditions include cystic fibrosis, immune disorders, abnormal ciliary function, nasal polyps, nasal foreign bodies (including indwelling nasal tubes), cleft palate, adenoidal hypertrophy, septal deviation, and gastroesophageal reflux disease (5).

Streptococcus pneumoniae, Haemophilus influenzae, and *Moraxella catarrhalis* are the most common etiologic agents in ABS. Visit rates for acute sinusitis in children have not decreased after the introduction of the pneumococcal vaccine (6). Although some recent studies have suggested that *Staphylococcus aureus* is a major pathogen in ABS, they should be interpreted with caution. The majority of isolates in the pediatric studies were taken from cultures of the middle meatus, which has not been established as a reliable surrogate for maxillary sinus aspirates in children (7).

CLINICAL PRESENTATION

Children with ABS present with upper respiratory symptoms that are either persistent or severe. Most viral URIs last approximately 5 to 7 days, and almost all are resolved or improving by 10 days (2). Children who have symptoms beyond 10 days without improvement should be considered to have ABS. The most common symptoms include cough and nasal discharge. The cough may be either “wet” or “dry” and is usually present in the daytime but may worsen at night. Fever or history of fever is present in about half of patients (5). The nasal discharge may be of any quality, ranging from clear to purulent, thin to thick. Malodorous breath is commonly reported by parents of preschool-aged children (8). Headache and facial pain or swelling, common symptoms of sinusitis in adults, are uncommon in children younger than 5 years of age but may be present in older children and adolescents (9).

Children who present with severe upper respiratory symptoms and high fever should also be suspected of having ABS. In the usual course of a viral URI, fever may be present during the first 48 hours but usually disappears, and purulent nasal discharge does not usually develop until later in the illness. In contrast, children with the severe onset of ABS are ill appearing and present with concurrent high fever ($>39^{\circ}C/102^{\circ}F$) and purulent nasal discharge for 3 to 4 consecutive days. In addition, they may complain of intense headache above or behind the eye or present with periorbital swelling (8).

In children, the most common manifestations of bacterial sinusitis are cough (80%), nasal discharge (76%), and fever (63%). Some children also have malodorous breath. Symptoms of headache, facial pain, and swelling are uncommon (1).

Any of the following clinical presentations are recommended for identifying patients with ABS (1):

- Persistent symptoms
  - Nasal congestion/discharge and/or daytime cough (may be worse at night) (4)
  - Lasts ≤ 10 days without any evidence of clinical improvement (1)

- Presence of fever, headache, or facial pain is variable (1)
- Severe symptoms (1,4)
  - High fever (≤39°C/102°F)
  - AND purulent nasal discharge or facial pain
  - AND lasting at least 3 to 4 consecutive days at the BEGINNING of illness
- Worsening symptoms (1)
  - New onset of fever, headache, or increase in nasal discharge following typical viral URI that lasted 5 to 6 days and was initially improving
  - If nuchal rigidity is present, the patient should be evaluated for meningitis.

Complications of acute sinusitis include bony, orbital, and central nervous system extension (10). Osteomyelitis of the frontal bone is called Pott's puffy tumor. Orbital complications include subperiosteal abscess, orbital cellulitis, and orbital abscess. Central nervous system complications include cavernous or sinus venous thrombosis, meningitis, subdural empyema, and subdural, epidural, or brain abscesses.

DIFFERENTIAL DIAGNOSIS

- Viral URI (1,4)
  - If fever is present, it typically occurs in the first 24 to 48 hours and then resolves
  - Purulent nasal discharge is not generally present until the fourth or fifth day of illness
- Sequential viral URI
- Allergic rhinitis
- Nasal foreign body (often presents with unilateral nasal discharge)

ED EVALUATION

There are no physical examination findings that are specific for sinusitis. There may be mild erythema and edema of the nasal turbinates with mucopurulent discharge, but patients with

uncomplicated viral URIs may have similar findings. Facial tenderness is rare, although reproducible unilateral pain to percussion or direct pressure over the frontal or maxillary sinus may indicate sinusitis. In addition, periorbital swelling suggests ethmoid sinusitis (2), although one must be careful to rule out true orbital complications in these patients. Findings that suggest an orbital or intracranial complication include proptosis, abnormal extraocular movements, focal neurologic deficits, or signs of intracranial pressure. If nuchal rigidity is present, the patient should be evaluated for meningitis. Transillumination is unreliable in children younger than 10 years (2).

The most important part of the emergency department (ED) evaluation is the history, since the diagnosis is usually made clinically. The physical examination is most important for ruling out complications, rather than diagnosing sinusitis. No physical examination findings are specific for sinusitis; mild erythema and edema of the nasal turbinates with mucopurulent discharge may be present, but also occur with URI (4).

Facial tenderness is rare, but reproducible unilateral pain to percussion or direct pressure over maxillary or frontal sinus may indicate sinusitis (4). Periorbital swelling suggests ethmoid sinusitis, although one must be careful to rule out true orbital complications in patients with this finding (4).

Findings suggestive of orbital or intracranial complications (5) include proptosis, abnormal extraocular movements, focal neurologic deficits, signs of increased intracranial pressure, altered mental status, or nuchal rigidity.

Sinus aspiration is the gold standard for the diagnosis of bacterial sinusitis but should only be performed by specialists. Sinus aspiration is not recommended for the routine diagnosis of ABS in children (2). Cultures of the throat and nasopharynx have poor correlation with those of maxillary sinus aspirates and are not recommended (11).

Laboratory Studies

Sinus aspiration (4) is the gold standard, but should only be performed by specialists and is not recommended for routine diagnosis of ABS in children. *Nasal/nasopharyngeal cultures* are not useful in predicting the results of culture of the paranasal sinuses themselves (8).

Imaging

Plain films are not recommended for the diagnosis of acute uncomplicated bacterial sinusitis in children by the American Academy of Pediatrics, the American College of Radiology, and the Sinus and Allergy Health Partnership. It should be reserved for children who do not improve or worsen with therapy (4).

Computed tomography (CT) scanning is recommended for patients with suspected suppurative complications such as orbital or intracranial extension (1,12). It is also indicated in patients who do not respond to therapy (12).

Magnetic resonance imaging (MRI) should be considered in those with suspected intracranial complications (13). Obstacles include limited availability, length of test, and need sedation often required in children.

There are limited studies of *ultrasound,* but there may be a role in evaluating fluid collections in the maxillary sinus in pediatric patients (12).

Findings on plain film that may help confirm a diagnosis of sinusitis include air–fluid levels, complete sinus opacification, and mucosal thickening (≤ 4 mm). Studies have shown strong correlation (80% to 92.5%) between persistent symptoms and abnormal radiographs (10,12). In studies in which sinus aspirates were taken from children with persistent or severe symptoms and abnormal radiographs, bacteria were recovered in 70% to 75% of cases (2). Because there is such a high correlation among persistent symptoms, abnormal radiographs, and positive sinus aspirates, the American Academy of Pediatrics, the American College of Radiology, and the Sinus and Allergy Health Partnership do not recommend the routine use of radiography in the diagnosis of acute

uncomplicated sinusitis in children (2). Instead, radiography should be reserved for children who do not improve with therapy or who worsen during therapy.

CT scans are indicated for patients with suspected complications, with persistent or recurrent infections, who fail to respond to therapy, and who are being considered for surgical treatment (2). MRI is also recommended for patients with suspected intracranial complications, but MRI often has limited availability.

KEY TESTING

- History and physical examination are the most important elements of the evaluation.
- CT scan is reserved for selected patients who are at risk for infectious complications, including abscess or orbital cellulitis.

ED MANAGEMENT

The most current recommendations for the management of ABS in both adults and children were published in 2012 by the Infectious Disease Society of America (IDSA) using a multidisciplinary panel. Recent randomized controlled trials of antimicrobial therapy versus placebo for treatment of ABS show a modest benefit favoring the use of antimicrobials. Therefore, the IDSA guidelines do recommend antimicrobial therapy be initiated as soon as the clinical diagnosis of ABS is made (1).

Antibiotics are the mainstay of treatment for ABS (Table 257.1). Many children will improve spontaneously without the use of antibiotics, but improvement is more rapid when antibiotics are used. In a study comparing antimicrobial treatment to placebo, 83% of children receiving antimicrobials were cured or improved by day 3, in comparison to only 51% of those in the placebo group (12). The antibiotic chosen should have adequate coverage for the most common causative organisms of ABS (see introduction). Resistance of *S. pneumoniae* to penicillins has been increasing, and attention should be paid not only to local resistance patterns but also to factors that increase the risk that a child harbors a resistant strain.

These factors include day care attendance, age younger than 2 years, and antibiotic use within 90 days (2).

TABLE 257.1
Antibiotic Recommendations

- First-line: standard dose amoxicillin–clavulanate (45 mg/kg/d orally divided twice daily) for 10–14 d
- Second-line: high dose amoxicillin–clavulanate (90 mg/kg/d orally divided twice daily) for 10–14 d reserved for the following instances outlined below.
  - Geographic areas with high endemic rates (≥10%) of invasive penicillin nonsusceptible *S. pneumoniae*
  - Severe infection (T ≥39°C/102°F)
  - Risk factors for resistance: daycare, age >2 yrs, hospitalization within past 5 d, antibiotic use within last month, comorbidities, immunocompromise
  - Failed initial therapy (symptoms worsen after 48–72 hrs or no improvement after 3–5 d)
- Alternative second-line options:
  - Clindamycin (30–40 mg/kg/d orally divided three times daily) PLUS cefixime (8 mg/kg/day orally divided twice daily) or cefpodoxime (10 mg/kg/d orally divided twice daily)
  - Levofloxacin (10–20 mg/kg/d orally every 12–24 hrs)
- Vomiting not tolerating oral antibiotics: ceftriaxone (50 mg/kg intravenously or intramuscularly) as a single dose, followed by oral antibiotic 24 hrs later if vomiting resolved
- Penicillin-allergic:
  - Type I hypersensitivity: levofloxacin (10–20 mg/kg/d orally every 12–24 hrs)
  - Non-type I hypersensitivity: clindamycin PLUS cefixime or cefpodoxime (see dosing above)
- Severe infection requiring hospitalization:
  - Ampicillin/sulbactam (200–400 mg/kg/d intravenously divided every 6 hrs)
  - Ceftriaxone (50 mg/kg/d intravenously divided every 12 hrs)
  - Cefotaxime (100–200 mg/kg/d intravenously divided every 6 hrs)
  - Levofloxacin (10–20 mg/kg/d intravenously divided every 12–24 hrs)
- *Not recommended*
  - Amoxicillin, macrolides, TMP/SMX (due to increasing resistance)
  - Second- and third-generation oral cephalosporins as monotherapy
  - Coverage for *S. aureus* (including MRSA) during initial empiric therapy

Antihistamines, decongestants, sinus irrigation (9)

From Chow AW, Benninger MS, Brook I, et al. IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinutis in Children and Adults. *Clin Infect Dis*. 2012;54:e72–e112.

Amoxicillin in a usual dose (45 mg/kg/d divided bid) or high dose (90 mg/kg/d divided bid) can be used as first-line therapy in children who have mild to moderate uncomplicated ABS, do not attend day care, and have not been on antibiotics in the past 90 days. Although amoxicillin does not adequately cover β-lactamase producing organisms, approximately 80% of children without risk factors for resistance can be expected to respond to amoxicillin. This is because *S. pneumoniae* is the most common causative organism, and 50% to 75% of sinusitis caused by *H. influenzae* and *M. catarrhalis* will resolve spontaneously. In children who attend day care, have received antibiotics in the past 90 days, have moderate to severe illness, or do not improve on usual dose amoxicillin, therapy should be initiated with high-dose amoxicillin–clavulanate (80 to 90 mg/kg/d of amoxicillin component in two divided doses). In children who are allergic to penicillin, there are the following options: cefdinir (14 mg/kg/d in one or two doses), cefuroxime (30 mg/kg/d divided bid), or cefpodoxime (10 mg/kg/d once daily). In children who have had anaphylactic reactions to penicillins, many prefer instead to use clarithromycin (15 mg/kg/d divided bid) or azithromycin (10 mg/kg/d on day 1 and 5 mg/kg/d $\times$ 4 more days, given once daily). A final option in the allergic patient is clindamycin (30 to 40 mg/kg/d in three divided doses). A single dose of intramuscular (IM) or intravenous (IV) ceftriaxone (50 mg/kg) may be used for children who are vomiting, followed by completion of a treatment course with an oral antibiotic starting 24 hours later. Recent studies have shown significant resistance of *S. pneumoniae* to trimethoprim–sulfamethoxazole and erythromycin–sulfisoxazole; therefore, these antibiotics should not be used (2).

Current recommendations for length of treatment vary from 10 to 28 days. In most cases, treatment for 7 days beyond the time when the patient becomes symptom-free results in adequate treatment (2,8). Most patients become symptom-free by 3 days of treatment, so 10 days of treatment usually suffices. A good recommendation for ED treatment is treat for 10 days and have patients with longer symptomatic periods follow-up with their primary care physician for continuation of antibiotics.

Saline nasal irrigation, antihistamines, topical or systemic decongestants, mucolytic agents, and topical intranasal steroids have all been suggested as ancillary treatments, but few data exist on their efficacy, especially in children (2). In one study, intranasal budesonide spray was added to antibiotics, and a significant improvement in symptoms of cough and nasal discharge was noted in the treatment group compared to the placebo group, but only at the end of the second week of treatment (3). Another study compared the addition of topical decongestant and oral decongestant–antihistamine to placebo (in addition to amoxicillin in both groups) and found similar treatment response in both groups (6).

Any child suspected of having an orbital or central nervous system complication should be treated aggressively. This includes imaging, IV antibiotics, and emergent consultation with appropriate subspecialists. Antibiotic treatment for orbital complications should be with either ceftriaxone (100 mg/kg/d IV divided bid) or ampicillin–sulbactam (200 mg/kg/d IV in four divided doses) or an antibiotic with equivalent antimicrobial spectrum. Antibiotic treatment for intracranial complications should be with ceftriaxone (see previous dose) or cefotaxime (200 mg/kg/d divided q6h). Vancomycin (60 mg/kg/d in four divided doses) should be added if *S. pneumoniae* resistance is suspected (2).

CRITICAL INTERVENTIONS

- The diagnosis of sinusitis in children can be made based on clinical criteria: persistent upper respiratory symptoms without improvement (>10 days), severe upper respiratory symptoms (high fever AND purulent nasal discharge for 3 to 4 days), or worsening symptoms (new onset of fever, headache, or increased nasal discharge following URI that lasted 5 to 6 days and was initially improving).
- Careful examination to rule out potential orbital and central nervous system complications.

- Imaging should be reserved for toxic-appearing patients, those suspected of having complications, or those who have failed treatment.
- Antibiotic therapy should be initiated with amoxicillin–clavulanate (standard-dose or high-dose depending on risk factors) for 10 to 14 days. Options for penicillin-allergic children include levofloxacin for type I hypersensitivity reactions, and clindamycin PLUS cefixime or cefpodoxime for non-type I hypersensitivity reactions.
- Patients suspected of having orbital or central nervous system complications need aggressive treatment, including IV antibiotics, imaging, emergent consultation with the appropriate subspecialist, and hospital admission.

DISPOSITION

Uncomplicated ABS:

- Discharge from ED with appropriate antimicrobial treatment
- Follow-up with primary care physician if worsening, or if no improvement after 3 to 5 days
- Follow-up immediately if any signs or symptoms of a complication develop

Toxic-appearing, immunocompromised, or suspected orbital or intracranial complications:

- Admit
- Appropriate antimicrobials (typically parenteral)
- Appropriate imaging (typically CT)
- Subspecialty consultation (consider ENT, Ophthalmology, Neurosurgery)

Common Pitfalls

- Not performing a thorough neurologic examination and missing signs of an associated intracranial or suppurative complication of sinusitis.
- Relying on laboratories and/or imaging to make the diagnosis of sinusitis in children.

• Prescribing inappropriate antibiotics.

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CHAPTER 258 Lymphadenitis

Keri L. Carstairs

Lymph nodes are commonly palpated in children's necks. Cervical nodes >10 mm are considered abnormal and referred to as lymphadenopathy (1). Enlarged lymph nodes can arise in association with a wide variety of infectious, inflammatory, or neoplastic disease processes (2). The most common cause of a benign neck mass in children is cervical lymphadenopathy secondary to an upper respiratory tract infection, usually of viral origin.

Lymphadenitis is one type of lymphadenopathy and can be either acute or chronic. Although some define lymphadenitis broadly as an "inflammation of a lymph node," others restrict the definition to include only bacterial infections (1,3).

After invading regional tissues, microorganisms enter the lymphatic system, where they are trapped and destroyed by phagocytes. This activity, coupled with the lymphocytic proliferation and transformation results in swelling of the node. Infectious organisms able to survive intracellularly can represent a persistent stimulus leading to a chronic lymphatic cell hyperplasia. Lymph nodes may become infiltrated with neutrophils in response to bacteria, with histiocytes in histiocytosis (and certain storage diseases), and with malignant cells in leukemia, lymphoma, or metastatic solid tumors (2).

In the case of bacterial infection, abscess formation may ensue when neutrophils accumulate within lymph nodes. (1,4). Group A β-*hemolytic Streptococci* sp and *Staphylococcus aureus* are the most frequent pathogens of bacterial lymphadenitis, accounting for nearly 95% of acute bacterial lymphadenitis. Children with staphylococcal

infections generally have a longer history of symptoms and an increased incidence of fluctuance compared with those with streptococcal infections (1,4,5).

CLINICAL PRESENTATION

Cervical lymphadenitis presents most commonly in children between 1 and 4 years of age, and there is no significant difference in incidence between genders. It is helpful to determine whether the cervical lymphadenitis developed in an acute, subacute, or chronic manner. The acute bacterial nodal enlargement usually develops rather quickly and unilaterally. These nodes are typically very tender and sometimes feel fluctuant. Erythema of the overlying skin is occasionally noted. Affected children often experience malaise and irritability and may be febrile. Frequently, a concurrent pharyngitis, otitis media, upper respiratory tract infection, dental abscess, or adjacent skin infection can be detected, or a recent history of infection can be elicited. Subacute or chronic lymphadenitis develops in 2 to 3 weeks and tends to be relatively painless. Lymphadenitis may be caused by catscratch disease, atypical mycobacteria, or tuberculosis.

Acute bilateral lymphadenitis most often occurs in response to an acute upper respiratory infection such as pharyngitis caused by viral pathogens or *Streptococcus pyogenes* and *Mycoplasma pneumoniae.* These nodes are usually small, soft, can be either tender or nontender, and do not have associated erythema or warmth.

There are rarely significant sequelae when adenitis is managed appropriately. Of particular concern is the possibility of misdiagnosing and consequently mismanaging another more serious problem (6). It is sometimes difficult to distinguish lymphadenopathy or adenitis from a true neck mass. Neck masses may be congenital or acquired, infectious or neoplastic, benign or malignant. In children, the incidence of neoplastic lesions is low compared to adults. In neither group does the neck mass commonly present as an acutely emergent or life-threatening problem.

DIFFERENTIAL DIAGNOSIS

Obtaining a careful history and performing a complete examination can often differentiate the disorders most commonly confused with adenitis (Table 258.1) (6).

TABLE 258.1
Differential Diagnosis of Lymphadenitis

Differential Diagnoses	Causative Agents	Comments
		Viral
Lymphadenopathy	Adenovirus	Lymphadenopathy usually resolves within a few days to 2 wks
	EBV	Often bilateral
	CMV	Respiratory viruses commonly involved
	Human herpesvirus 6	
	Coxsackie	
	Rubella	
	Rubeola	
	Varicella (5,7)	
Bacterial lymphadenitis	Group A *β-hemolytic streptococcus*	Erythema, warmth, and tenderness overlying a node typically indicates bacterial lymphadenitis
	Staphylococcus aureus	Rubbery or firm in consistency and freely mobile
		Often unilateral
		Untreated nodes tend to suppurate and may rupture onto the skin or dissect into underlying soft tissues
Infectious mononucleosis	EBV	Often presents as acute or subacute cervical lymphadenopathy
		Nodes tend to be posterior cervical, bilateral, and moderately painful
		Associated findings include malaise, fever, tonsillopharyngitis, hepatosplenomegaly, and generalized node enlargement
		Positive heterophil (Monospot) confirms the diagnosis except in children younger than 4 yrs for whom EBV titers should be done
		Treatment is supportive; avoid contact sports for several months
Catscratch disease	*Bartonella henselae*	In approximately 50% of cases, primary lesion is at the site of a 7–14-d-old scratch or bite by a cat
		Begins as indurated erythematous papule and later may become vesicular or pustular; resolves in 10–20 d
		Days to weeks later, the nodes draining this area become enlarged
		Nodes are typically only moderately tender but occasionally suppurate
		Associated symptoms include fever, headache, myalgia or malaise
		Complications such as encephalitis, hepatosplenic abscess, and osteolytic lesions are uncommon
		Consider azithromycin to shorten the clinical course
Atypical mycobacterial lymph-adenitis	Nontuberculous mycobacteria	Subacute or chronic unilaterally enlarged lymph nodes.
		Does not respond to antibiotics
		Infected nodes tend to be relatively painless
		Systemic symptomatology is uncommon
		Tuberculin skin testing is unreliable
		Treatment of choice is excisional biopsy
Kawasaki disease	Unknown	Also known as mucocutaneous lymph node syndrome
		Diagnosed in the presence of fever plus four of the diagnostic criteria including cervical lymphadenopathy, rash, oral exanthem, conjunctival injection, and swelling and redness of palms and soles
		Exclusion of other illnesses is necessary
		Cervical lymphadenopathy is only found in 50% of cases
		Nodes are usually unilateral and confined to the anterior triangle
		Early diagnosis is critical because treatment can prevent coronary aneurysm
Tuberculous lymphadenitis	*Mycobacterium tuberculosis*	Rare
		Diseased nodes are similar to those of nontuberculous mycobacterial adenitis
		Workup includes history of TB exposure, a TB skin test, and chest x-ray
		Tuberculous lymph nodes should never be aspirated because this could lead to sinus development
		Antituberculous drugs are effective in treating this condition
		Infection should be reported to public health authorities
Group B streptococcal cellulitis–adenitis syndrome	Group B *Streptococcus* sp	This syndrome occurs in neonates;
		Abrupt onset of fever and facial or submandibular erythema and swelling
		Symptoms include irritability, poor feeding, and toxicity
		About 80% have ipsilateral otitis media
		Meningitis may accompany lymphadenitis
		Organism can be isolated from blood and lymph node or cellulitis aspirates
		Complete sepsis workup should be performed, admission and IV antibiotics
Toxoplasmosis	*Toxoplasma gondii*	May present as single, enlarged, posterior cervical node that may or may not be tender
		Nodes vary in size but do not suppurate
		The diagnosis can be made by performing serial toxoplasma titers
		Pharmacologic therapy should be withheld unless fever or a complication such as pneumonitis, myocarditis, meningitis, or encephalitis ensues

EBV, Epstein–Barr Virus; CMV, cytomegalovirus; TB, tuberculosis.

Viral Lymphadenopathy

Viral infections, especially those producing viremia, are the most common cause of lymphadenopathy in children and usually subside within a few days to 2 weeks. Often bilateral, causative agents include respiratory viruses such as herpes simplex gingivostomatitis, adenoviral syndromes, roseola, Enterovirus, human herpesvirus 6, Coxsackievirus, rubella, rubeola, varicella and infectious mononucleosis caused by Epstein–Barr virus (EBV), or cytomegalovirus (CMV) (1,2,4).

Bacterial Lymphadenitis

The presence of erythema, warmth, and tenderness overlying a node typically indicates the acute inflammatory response of pyogenic bacterial lymphadenitis. Most acutely infected nodes in children are rubbery or firm in consistency and are freely mobile. Left untreated, these nodes, often unilateral, tend to suppurate and may rupture onto the skin or, less commonly, dissect into the underlying soft tissues (1,4,5).

Infectious Mononucleosis

EBV causes infectious mononucleosis. It often presents as acute or subacute cervical lymphadenopathy. These nodes tend to be posterior cervical, bilateral, and moderately painful (4). They are present in 93% of infected children (2). Associated findings include malaise, fever, tonsillopharyngitis, hepatosplenomegaly, and generalized lymph node enlargement. A positive heterophil test (Monospot) confirms the diagnosis. In children younger than 4 years of age, the heterophil test is unreliable, and specific EBV titers should be done. Treatment is supportive. The patient should be instructed to avoid contact sports for several months after the illness because of the risk of splenic rupture. Rarely, cervical lymphadenopathy in infectious mononucleosis is associated with respiratory distress because of extremely enlarged (“kissing”) tonsils, and this condition may require hospitalization and steroid use.

Catscratch Disease

Most cases of catscratch disease are caused by *Bartonella henselae.* In approximately 50% of cases, there is a primary lesion at the site of a 7- to 14-day-old scratch or bite by a cat. This lesion begins as an indurated erythematous papule and later may become vesicular or pustular. The lesion resolves within 10 to 20 days. Catscratch disease usually presents subacutely. Several days to weeks later, the lymph nodes draining this area become progressively enlarged. The most common sites of lymphadenopathy are the axilla (52%) followed by the neck (28%) (2). These nodes are typically only moderately tender, but occasionally will suppurate. Sometimes, patients are febrile and may experience headache, myalgia, or malaise. Other complications, such as encephalitis, hepatosplenic abscesses, and osteolytic lesions, are uncommon. Although the diagnosis is usually made on clinical grounds, it can be confirmed serologically. The adenopathy generally resolves in 6 to 8 weeks with supportive treatment only. However, azithromycin is recommended for lymphadenopathy related to catscratch disease (5). Fluctuant nodes often need surgical intervention (1,8–10).

Methicillin-Resistant *Staphylococcus aureus*

With the changing epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in healthy individuals, this bacterium should be considered when patients present with soft tissue infections. MRSA should be considered in patients presenting with cervical lymph node swelling (11). MRSA infections can also occur in healthy newborns (11,12).

Mycobacterial Lymphadenitis

Atypical mycobacterial cervical lymphadenitis usually presents as subacute or chronic unilaterally enlarged lymph nodes that do not respond to antibiotics (1,13). Nontuberculous mycobacterial lymphadenitis generally occurs in early childhood. Infected nodes tend to be relatively painless but are sometimes tender and may even suppurate and drain. Systemic symptomatology is uncommon. Tuberculin skin testing is unreliable. Antituberculous drugs are not

recommended, and excisional biopsy is both diagnostic and therapeutic (14).

Tuberculous lymphadenitis is rarely seen in the United States (10,15,16). Diseased nodes are similar to those of nontuberculous mycobacterial adenitis. To exclude the diagnosis, the family should be questioned about their exposure to tuberculosis, a tuberculin skin test should be done, and a chest radiograph ordered. Tuberculous lymph nodes should never be aspirated, because aspiration may lead to sinus development. Antituberculous drugs are effective in treating this condition. Lastly, infection should be reported to public health authorities.

Kawasaki Disease

Also known as mucocutaneous lymph node syndrome, Kawasaki disease is diagnosed in the presence of fever, plus four of the five diagnostic criteria (cervical lymphadenopathy, rash, oral exanthem, conjunctival injection, and swelling and redness of palms and soles) and exclusion of other illnesses. Cervical lymphadenopathy is found in only 50% of cases. Nodes are usually unilateral and confined to the anterior triangle, moderately tender, nonfluctuant, and firm, with or without overlying erythema. The early diagnosis of Kawasaki disease is critical, because treatment with salicylates and intravenous immunoglobulin can prevent serious complications, namely, coronary aneurysm (10).

Group B Streptococcal Cellulitis–Adenitis Syndrome

The group B streptococcal cellulitis adenitis syndrome occurs in neonates (5). The neonate presents with the abrupt onset of fever, facial or submandibular erythema and swelling, irritability, poor feeding, and toxicity. About 80% have an ipsilateral otitis media. Meningitis may accompany lymphadenitis. The organism can be isolated from blood and from aspirates of the lymph node or the cellulitis. A complete sepsis workup should be performed, and the infant must be admitted to the hospital for intravenous antibiotic therapy (5,10,17).

Toxoplasmosis

Acquired toxoplasmosis sometimes presents as a single, enlarged, posterior cervical node that may or may not be tender (1,18,19). These nodes tend to vary in size but do not suppurate. The diagnosis can be made by performing serial toxoplasma titers. Pharmacologic therapy should be withheld unless fever or a complication such as pneumonitis, myocarditis, meningitis, or encephalitis ensues.

Other Infectious Etiologies

Other uncommon causes of cervical lymphadenopathy include *Pasteurella multocida, Yersinia pestis,* histoplasmosis, and CMV.

Rheumatologic Lymphadenopathy

A number of rheumatologic illnesses can cause cervical lymphadenopathy; chief among them is juvenile rheumatoid arthritis.

Neoplasms

Neoplasms are rare in children, occurring in 1.4% of patients younger than 17 years of age with a superficial lump on any part of the body. Careful follow-up of all lymphadenopathy is mandatory, especially if it is associated with fever or weight loss or if it fails to resolve (1,9,20).

Benign neoplasms in children that present as neck masses include hemangiomas, lymphangiomas, fibromas, neurofibromas, and lipomas. Malignant neck neoplasms in children tend to be single, nontender, *immobile,* and *fast growing* and are located in the posterior triangle of the neck. Age is a key element in the occurrence of the various malignant neck neoplasms. From ages 1 to 5, neuroblastoma, rhabdomyosarcoma, histiocytic lymphoma, and Hodgkin disease are the most common. In the older child, histiocytic lymphoma and Hodgkin disease occur equally often. The adolescent most commonly acquires Hodgkin disease. Rhabdomyosarcoma is the most common pediatric solid tumor of the head and neck and one of the most

common tumors in children younger than age 6; frequently presenting with rapid growth in the orbit, nasopharynx, ear, mastoid, face, or tongue. Neuroblastoma is the most common solid tumor in children overall, but presents as a neck mass only about 5% of the time.

ED EVALUATION AND MANAGEMENT

Many of the aforementioned diagnoses can be made simply by taking a complete history and performing a thorough examination. The following points should be addressed when questioning the family: duration of adenopathy or mass; history of an adjacent skin lesion, earache, upper respiratory tract infection, sore throat, or dental problem; presence of fever or weight loss; exposure to tuberculosis; contact with cats; and travel (1,4). When attempting to determine whether a neck mass may be a lymph node, it is important to recognize the location of the normal chain of cervical lymph nodes. The size, consistency, mobility, and tenderness of each affected node must be noted (1,10). Marking the dimensions with ink and recording them in the emergency department (ED) record can be helpful to the next physician who evaluates the patient. The head, ears, eyes, nose, oropharynx, and neck are examined, and the child is evaluated for hepatomegaly, splenomegaly, and other adenopathy (1).

Useful studies include a complete blood cell count, erythrocyte sedimentation rate, C reactive protein, a Monospot or EBV serology, a throat culture for group A *Streptococcus* sp, and a tuberculin skin test. It is unnecessary to order all of these tests on every patient. The tests prove most helpful when the cause of the adenopathy is unknown. A blood culture should be obtained if the patient appears toxic. Older children with cervical adenitis are rarely bacteremic, but neonates often are and must be evaluated for possible sepsis (17). Additional studies may be needed in the older child, depending on the history and physical examination (e.g., serology for catscratch disease or EBV). Sometimes, a definitive diagnosis is not made until a biopsy is performed.

Needle aspiration is useful both diagnostically and therapeutically, and any fluctuant node should be aspirated if tuberculous lymphadenitis cannot be excluded. An ultrasound can help determine whether a node or mass is cystic or solid, if necessary (22). The largest, most fluctuant node is selected, the overlying skin is cleansed, a 20-gauge needle attached to a 20-mL syringe is inserted into the fluctuant region, and aspiration is done. If pus is not obtained, 1 to 2 mL of sterile, nonbacteriostatic saline is injected into the node, which is reaspirated. The aspirate is sent for Gram stain and cultures for aerobic bacteria, anaerobic bacteria, mycobacteria, and fungi (1,2,4).

If bacterial cervical lymphadenitis is suspected, treatment with antibiotics effective against the principal bacterial pathogens, group A β-*hemolytic Streptococcus* sp and *S. aureus,* should be initiated. Analgesics and warm compresses may also be helpful (1). Most patients can be successfully managed as outpatients with follow-up arranged. Outpatient and inpatient therapy is outlined in Table 258.2 (1,18,23). Failure to respond to oral antibiotics does not necessarily mean the cause of adenitis is not bacterial; parenteral antibiotics may be required. If the lymphadenitis is associated with dental disease, anaerobic infection needs to be considered (1,23).

TABLE 258.2
Management of Bacterial Lymphadenitis

Outpatient Therapy (3,6,13)	Inpatient Therapy (3,6,13)
1. Cefadroxil 30 mg/kg/d divided q12h PO	1. Cefazolin 100 mg/kg/d divided q8h IV
2. Clindamycin 20 mg/kg/d divided q8h PO	2. Clindamycin 40 mg/kg/day divided q6h to q8 h IV
3. Cefuroxime 20 mg/kg/d divided q12h PO	3. Nafcillin 125 mg/kg/d divided q6h IV
Failure to respond to oral antibiotics does not necessarily mean that the cause of adenitis is not bacterial; parenteral antibiotics may be required	
If the lymphadenitis is associated with dental disease, anaerobic infection needs to be considered, and the following agent is recommended: amoxicillin–clavulanate (Augmentin) 45 mg/kg/d divided q12h PO (3,5)	
Treatment should last at least 10 d (5,12). After a good response to parenteral antibiotics is observed, oral agents can be substituted (5)	

PO, by mouth; IV, intravenous.

KEY TESTING

- History and physical examination should drive testing and treatment decisions
- Neonates and children who are septic-appearing should have CBC, CRP, ESR, and blood cultures obtained
- Ultrasound can be used to differentiate solid from cystic masses
- Aspiration of fluid for Gram stain and culture when indicated by history and physical examination.

CRITICAL INTERVENTIONS

- Take a detailed history, including travel and animal contact, to differentiate lymphadenitis from other disorders.
- Arrange follow-up for all case of lymphadenitis, especially for patients with large nodes, fever, weight loss, or other concerning systemic signs.

DISPOSITION

Most children can be managed successfully as outpatients. They should be reevaluated, to monitor their progress, within 2 to 3 days of the ED visit. Follow-up is very important and is done best by the patient's primary care physician, who should reexamine the child serially until the node regresses.

Admission for intravenous antibiotics is warranted if the child appears toxic, if the lymphadenitis is severe (e.g., node diameter >3 to 4 cm or high fever), if the lymphadenitis fails to respond to oral medications, or if the patient is a neonate or cannot tolerate oral antibiotics (18). Admission for further evaluation is recommended if there is mediastinal lymphadenopathy on the chest radiograph, weight loss, fever for more than 1 week, or a suspicion of Kawasaki disease or malignancy (9).

Biopsy is indicated if the node increases in size or does not decrease in 4 to 6 weeks or return to normal in 8 to 12 weeks (9). Particularly worrisome findings are weight loss, persistent fever, or fixation to adjacent tissues or overlying skin (1,4,7).

Common Pitfalls

- Treating patients with severe lymphadenitis orally and delaying an inevitable admission for intravenous antibiotics.
- Failure to consider atypical mycobacterial lymphadenitis, Kawasaki disease, and catscratch disease in the differential diagnosis.

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of Mobeen H. Rathore and Sabiha Hussain to the content of this chapter.

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CHAPTER 259 Torticollis

Robert L. Cloutier

Torticollis is derived from the Latin words *tortus,* meaning "twisted," and *collum,* meaning "neck." Medically, it is defined as "a contraction, often spasmodic, of the muscles of the neck; the head is drawn to one side and usually rotated so that the chin points to the other side." It is a manifestation of illness, not a disease itself, which means that one needs to determine the etiology. Depending on the etiology and time of onset, torticollis is classified as either congenital or acquired.

CLINICAL PRESENTATION

In the newborn, torticollis often presents as a firm, nontender, unilateral enlargement in the sternocleidomastoid muscle noticed shortly after birth (1). There may be associated findings such as plagiocephaly and facial asymmetry (2).

Older children present with the head rotated on the neck, tilted to the affected side, with the chin pointed to the opposite direction of the spasm. In addition, they may complain of intermittent, painful muscle spasms.

DIFFERENTIAL DIAGNOSIS

Congenital Torticollis

Congenital causes include both malformations (defect during morphogenesis) and deformations (secondary to intrauterine postures and crowding).

Malformations can occur in the cervical spine, the cervical musculature, or the central nervous system. A number of rare cervical spine anomalies can cause torticollis, including odontoid hypoplasia, cervical spine fusions (Klippel–Feil), spina bifida, hemivertebrae, and scoliosis (3,4). Torticollis can also result from deformations of the spine caused by intrauterine positioning secondary to uterine tumors, oligohydramnios, or multiple gestations. These cases are usually transient and resolve within a few months (4).

"Pseudotumor of infancy" and congenital muscular torticollis occur with an incidence of 0.4% and 1.3%, respectively (5). Intrauterine factors may cause muscle injury by an intramuscular compartment syndrome that results in localized ischemia and unilateral fibrous contracture of the sternocleidomastoid (3,6,7). There is a higher prevalence in breech births, in deliveries assisted by forceps, and in patients with cephalohematoma, clavicular fracture, or brachial plexus injury (2,3). It is typically diagnosed prior to 1 month of age and resolves by 6 months of age (6). On physical examination a firm, nontender, immobile mass is noted (1).

Congenital ocular disturbances, usually fourth nerve palsies with resultant strabismus, may be of the cause of torticollis presenting later in infancy, representing approximately 4% of cases (3,8).

Acquired Torticollis

The causes of acquired torticollis are varied. Trauma to the cervical spine from subluxation, fracture, or dislocation is among the most important causes to consider in the ED setting. The trauma can be relatively minor, as from the hyperflexion/hyperextension of a "whiplash" injury. In some cases the onset of symptoms may be delayed by several months (4). The most commonly areas affected are the atlantoaxial area and the junction of C-2 on C-3; ligamentous laxity in the atlantoaxial region can be a contributing factor in subluxation (4). These cases are often associated with underlying disorders such as trisomy 21 (Down syndrome), mucopolysaccharidosis, and invasive erosion from a surrounding

soft tissue infection (3,8). Cervical spine infections, such as osteomyelitis and discitis, and metastatic or primary osteomas can also present as torticollis (4,8).

Other causes of torticollis are not associated with cervical spine pathology. They include clavicle fracture, with splinting because of pain, nasopharyngeal or retropharyngeal abscess, cervical adenitis, tonsillitis, mastoiditis, and sinusitis (3,4,8,9). If the infection is extensive, there may be erosion of paraspinous ligaments, with rotatory subluxation in the atlantoaxial region (4). In one study, 37% of patients with computed tomography (CT)-confirmed retropharyngeal abscess had physical examination findings consistent with torticollis (10). Interestingly, pseudotumor cerebri can present as torticollis in older children (11).

Paroxysmal torticollis of infancy presents between the ages of 2 and 8 months and is due to vestibular dysfunction. It is often associated with vomiting, pallor, ataxia, or irritability and is usually self-limited, resolving by age 2 to 3 years (12–14).

Dystonic reactions to medication, most commonly phenothiazines, can present as torticollis but are usually also associated with other symptoms. The diagnosis is made by the presence of ocular symptoms (oculogyric crisis) and response to appropriate therapy.

The nuchal rigidity of bacterial meningitis can be confused with torticollis in younger patients, but torticollis will not typically be the only symptom. In rare instances torticollis can be an indication of severe underlying disease such as posterior fossa tumor, encephalomyelitis, or spinal epidural hematoma (15).

ED EVALUATION

In infants, especially those younger than 1 month of age, a careful birth history should include birth presentation and the use of forceps. Physical examination often shows a sternocleidomastoid mass, making the diagnosis of “pseudotumor of infancy.” Findings consistent with brachial plexus palsy or fractured clavicle are diagnostic of torticollis due to these etiologies.

Careful questioning is important to determine the onset, severity, location, and radiation of the pain and abnormal neck posture. In classic cases of torticollis, there is unilateral neck pain which may radiate to the ipsilateral shoulder. Historical data concerning fever and constitutional signs and symptoms help identify infectious or inflammatory causes. A careful medication history should be helpful in identifying recent phenothiazine ingestion.

In older children, acute torticollis often presents after trauma. Even with seemingly mild trauma, radiographic evaluation of the cervical spine (with plain films or CT) is often necessary to rule out fracture or subluxation. If no injury is found, a thorough examination of the head, eyes, ears, nose, and throat should be performed to search for inflammatory or infectious causes. Screening radiographs to search for underlying osseous abnormalities are not useful, given the low yield of plain films, and can lead to further unnecessary testing (16).

Physical examination findings should be able to clearly distinguish torticollis from the nuchal rigidity of meningitis. Bony pain or crepitus on palpation of the clavicle suggests fracture. Neurologic examination should reveal no motor or sensory deficit in congenital muscular torticollis or in torticollis due to muscle spasm. A finding of papilledema requires further workup (11).

The evaluation of chronic torticollis depends on whether it is episodic or constant. For episodic cases, neurologic examination and a careful history of drug and medication use are important. Torticollis that is constant requires a careful ophthalmologic examination for strabismus and neurologic examination for subtle neurologic signs (including cerebellar signs).

KEY TESTING

- Cervical spine imaging (plain film, CT, MRI) in cases of traumatic or acquired torticollis
- Funduscopic examination
- Neurologic examination

ED MANAGEMENT

Patients younger than 1 month of age who present with a physical examination consistent with "pseudotumor of infancy," brachial plexus injury, or clavicle fracture from birth injury should be referred to their pediatricians for follow-up. Similarly, those with a history and examination consistent with an intrauterine deformity due to multiple gestation, uterine tumor, or oligohydramnios should also be referred for follow-up.

Older children with a history of trauma but no radiographic abnormalities are given anti-inflammatories (ibuprofen 10 mg/kg body weight every 8 hours). Children with muscular spasm as the etiology of torticollis are managed similarly.

Those without a history of trauma are managed according to the presumed etiology. Abnormalities on neurologic examination are an indication for brain imaging with CT or MRI. Signs and symptoms of an infectious or inflammatory process should trigger appropriate diagnostic studies prior to institution of antibiotic treatment or other therapy. In torticollis related to phenothiazine use, diphenhydramine (2 mg/kg body weight IV [50 mg maximum]) will counteract the dystonic reaction.

Depending on the etiology, consultation with neurosurgery, neurology, ophthalmology, or radiology should be considered.

CRITICAL INTERVENTIONS

- Obtain neurosurgical consultation for patients with evidence of cervical spine injury or other abnormality.
- Consider phenothiazine ingestion as a cause of acute torticollis.

DISPOSITION

Follow-up by the primary care pediatrician is sufficient in infants with "pseudotumor of infancy" or congenital muscular torticollis. Most cases resolve spontaneously or with conservative physical therapy; only 10% to 20% progress and require other intervention (6,7).

Treatment for the underlying cause of the torticollis is the mainstay of management. Neurosurgical consultation should be obtained for all patients with evidence of cervical spine fracture, subluxation, or dislocation.

Common Pitfalls

- Failure to consider nonmuscular causes of torticollis.
- Failure to immobilize the neck and to rule out fracture or subluxation in patients with a history of trauma.
- Failure to consider phenothiazine side effects, even at therapeutic dosages.
- Failure to consider infectious causes (e.g., retropharyngeal abscesses or cellulitis).

ACKNOWLEDGMENT

The author gratefully acknowledges the contributions of Gregory G. Gaar to the content of this chapter.

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CHAPTER 260 Pharyngitis

Denis Pauze

Sore throat is a common chief complaint among pediatric emergency department (ED) patients, and accounts for more than 7 million ED visits annually (1). Many infectious agents cause acute inflammation of the tonsils and pharynx, including Epstein–Barr virus (EBV), adenovirus, parainfluenza virus, rhinoviruses, group A and other β-*hemolytic streptococci,* and *Mycoplasma pneumoniae* (2–5). Nonbacterial agents are the cause of pharyngitis in 70% to 85% of patients, especially in adolescents and in children younger than 2 years of age (3).

Group A β-*hemolytic Streptococcus* (GABHS) remains the most important cause of acute pharyngitis (2–4). Though other pharyngeal infections typically resolve without intervention, GABHS infection if inadequately treated may lead to suppurative complications, including peritonsillar and retropharyngeal abscesses, sinusitis, otitis media, mastoiditis, cervical adenitis, and the nonsuppurative complication of acute rheumatic fever (ARF). Given the breadth of illnesses and potential associated complications, for individual and public health reasons, GABHS infections should be diagnosed and effectively treated.

CLINICAL PRESENTATION

Generally, patients with pharyngitis complain of a sore throat. Additional symptoms may include fever, headache, nausea, vomiting, myalgias, dysphagia, cough, runny nose, and fatigue.

GABHS pharyngitis has an incubation period of 2 to 5 days and affects children between ages of 5 and 15, mostly during the winter and spring months (3). Transmission occurs via respiratory droplets and is associated with close contact (3). Most children with acute pharyngitis present with one or more complaints in addition to sore throat. Those with GABHS infection typically report the sudden onset of throat pain which may be associated with fever, headache, abdominal pain, nausea, or vomiting (2–4). On physical examination, patients with streptococcal pharyngitis usually have tonsillopharyngeal erythema with or without tonsillar exudates, palatal petechiae, and tender anterior cervical adenopathy (2–4). Other findings may include a beefy, red, swollen uvula, excoriated nares (especially in infants), and rarely a fine, diffusely papular erythroderma ("sandpaper" or scarlatiniform rash) in cases of toxin-producing strains of GABHS (4). Bacterial pharyngitis is uncommon in children younger than 3 years; patients in the 3- to 5-year age group are more likely to present atypically with copious purulent rhinorrhea, as opposed to pharyngeal exudates (1,2).

No findings are specific for GABHS pharyngitis, and patients frequently exhibit atypical combinations of signs and symptoms compared to those considered "classic" (4). For example, some children may present with abdominal pain as the chief complaint. A systematic review evaluating the predictive accuracy of signs and symptoms in GABHS identified no single diagnostic sign or symptom. However, five findings were noted to increase diagnostic accuracy by to more than 50%: scarlatiniform rash, palatal petechiae, pharyngeal exudates, vomiting, and tender cervical lymph nodes (6).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes a number of life-threatening conditions. Pertinent negatives related to these diseases should be noted as part of the evaluation. These conditions include Kawasaki disease, Stevens–Johnson syndrome, epiglottitis, Lemmiere syndrome, deep space abscesses (both retro- and peripharyngeal

abscesses), and Ludwig's angina. Other less threatening but nonetheless important agents include EBV, herpes simplex virus, adenovirus, parainfluenza viruses, rhinovirus, and human immunodeficiency virus. Important bacterial causes besides GABHS include *Fusobacterium necrophorum, Neisseria gonorrhoeae,* group C streptococcus, Mycoplasma, and Corynebacterium.

Fortunately, epiglottitis due to *Hemophilus influenzae* type B (Hib) is now rare in the developed world thanks to widespread use of the Hib vaccine. Presently, viruses, non-B Hemophilus serotypes, and other bacteria are the primary causes of acute epiglottitis. Changing trends in the post-Hib vaccination era note a shift towards older patients, with an increase in the mean age of disease from 5.8 to 14.6 years over the decade 1992 to 2002 (7). Conversely, national trends found an increase in cases of epiglottitis in infants less than 1 year of age from 1998 to 2006 (8). While the overall incidence has decreased, however, cases of pediatric epiglottitis occur and the diagnosis should be suspected in immunosuppressed or unvaccinated or partially vaccinated children.

Lemmiere syndrome is a life-threatening form of pharyngitis caused by normal oropharyngeal bacteria (including anaerobic gram-negative bacteria such *F. necrophorum*). It is characterized by sore throat or pharyngitis, bacteremia, and thrombosis of the internal jugular vein. Although rare, Lemmiere syndrome is rising in incidence (9). Patients are usually adolescents or young adults with fever and pharyngitis who often have failed outpatient antibiotic treatment for suspected GABHS. Patients are often ill-appearing, with swelling or tenderness over the sternocleidomastoid muscle, and may have respiratory complaints related to an associated pneumonia or septic pulmonary emboli. Demonstration of a jugular vein thrombosis by CT or ultrasound can make the diagnosis early.

Acute pharyngitis may be accompanied by peritonsillar, parapharyngeal, or retropharyngeal abscess. Patients with deep tissue abscess appear ill, are febrile, and have localized pain. A patient with a peritonsillar abscess often presents with trismus, a muffled ("hot potato") voice, and unilateral swelling of the soft palate with uvular deviation away from the affected side.

Parapharyngeal abscess is frequently associated with tender unilateral neck swelling on the affected side. Younger children with acute pharyngitis may develop retropharyngeal lymphadenitis that spreads into the retropharyngeal space. The diagnosis of retropharyngeal abscess should be considered, along with epiglottitis, in a toxic-appearing toddler with dysphagia, drooling, signs of airway obstruction, and pain with neck movement.

ED EVALUATION

The diagnosis of acute pharyngitis can be made from historical and physical examination findings, but differentiating GABHS from other causative organisms is challenging. Patients with GABHS may have more significant pharyngeal inflammation, prominent exudates, and tender anterior cervical lymphadenopathy than patients with viral etiologies, but these findings are not reliable. Numerous studies over the past 60 years document clinicians' inability to clinically differentiate GABHS from non-GABHS pharyngitis (6). Certain signs or symptoms may be more suggestive of nonstreptococcal causes, however. For example, *Mycoplasma* often presents with a history of prolonged cough or pneumonia or bronchitis (2,4). EBV may present with extreme fatigue, significant pharyngeal exudates, generalized lymphadenopathy, and/or hepatosplenomegaly. Adenoviral pharyngitis is typically accompanied by nonpurulent conjunctivitis and preauricular adenopathy. Coxsackie pharyngitis is associated with the discrete painful posterior pharyngeal ulcers of herpangina, whereas parainfluenza virus causes croup or laryngitis in older children.

While no sign or symptom is specific or sensitive enough to diagnose GABHS, a number of clinical decision rules (CDRs) have been developed to aid diagnosis. The Centor criteria are perhaps the best known and consist of four signs, with one point each given for fever, exudates, tender nodes, and absence of cough. Patients with a score of 0 or 1 are presumed to have viral pharyngitis and require no further testing, whereas higher scores are progressively more likely to reflect GABHS infection. The performance of CDRs for the

diagnosis of GABHS in the pediatric population however, is weak at best (4).

In spite of these diagnostic challenges, patients with pharyngitis must be evaluated for conditions that require acute intervention; these include airway compromise, pain, and dehydration. Edematous tonsils may obstruct the upper airway, resulting in respiratory distress or sleep apnea. Often, children refuse to drink because of pain and can become dehydrated, occasionally requiring admission. Secondly, patients should be evaluated for suppurative complications. A CT scan of the neck with intravenous contrast may be indicated if a deep space abscess is suspected.

Patients should be evaluated for GABHS using a rapid antigen detection test (RADT), if available. RADTs provide quick and highly specific identification of the GABHS antigen and have been shown to increase appropriate care of ED patients with GABHS pharyngitis (10). Recent data suggest that RADTs using newer technologies such as optical immunoassay or DNA probes may be more sensitive than other RADTs and perhaps sensitive enough for use without a confirmatory backup throat culture (3,6,11). However, in contrast to diagnostic recommendations for adults with pharyngitis, numerous advisory groups continue to recommend that confirmatory cultures be performed in children and adolescents with negative RADTs because of the relatively higher pediatric incidence of streptococcal infection and ARF (6,11). These advisory groups recommend that physicians who elect to use any RADT in children and adolescents without confirmation of negative results by blood agar plate (BAP) culture should do so only after adequately demonstrating in their own practice that their RADT is as sensitive as BAP culture, which remains the gold standard for diagnosis of GABHS pharyngitis (3,6,11). False-negative RADTs often result from obtaining inadequate amounts of tonsillar or pharyngeal secretions on the specimen swab. To minimize false-negative results, specimens should be obtained by vigorous swabbing of both tonsils and the posterior pharyngeal wall (1,4,6).

ED MANAGEMENT

For airway obstruction secondary to enlarged tonsils, a nasopharyngeal airway should restore airway patency and intravenous fluid resuscitation and analgesics may be used to treat acute dehydration and pain. Most often, analgesics such as acetaminophen or ibuprofen in association with cold fluids provide adequate pain relief. Steroid treatment for pain relief still remains controversial. The Infectious Disease Society of America does not currently recommend steroid therapy for pain relief, but the topic remains controversial and there is evidence to support their use (5,12).

If GABHS is identified by laboratory testing, antibiotic therapy is currently recommended in the United States. Although antimicrobial therapy for GABHS may shorten the clinical course of illness, the disease is usually self-limited, with resolution within 3 or 4 days, even without treatment (4). This is why some countries do not treat GABHS pharyngitis. Therapy can be postponed up to 9 days from initial to the onset of symptoms and still safely prevent rheumatic fever; empiric therapy is thus not recommended (1,2,4,7). Numerous antibiotics are effective for GABHS pharyngitis (4). However, penicillin—an inexpensive drug with a narrow spectrum of activity and well-proven efficacy and safety—remains the drug of choice (1–4). A 10-day course of oral penicillin V is recommended at 400,000 U (250 mg) two to three times daily for children weighing 27 kg (60 lb) or less, or 800,000 U (500 mg) twice daily for those weighing more than 27 kg (1). In patients who are felt to be unlikely to complete a 10-day course of therapy, benzathine penicillin G, 600,000 U intramuscularly, should be given to children weighing less than 27 kg (60 lb), and 1.2 million U to larger children (1,3). Amoxicillin for 10 days at the doses described is equivalent to penicillin and may improve compliance, given its better palatability in suspension.

From a compliance perspective, 10-day treatment regimens have become controversial. It is estimated that only about 10% of patients complete a full 10-day course of antibiotics, but with no

increased incidence of complications (13). Shorter courses have been studied, including the use of azithromycin or cephalosporins (10). A recent Cochrane review included over 13,000 cases of confirmed GABHS pharyngitis and compared short-course antibiotics to standard 10-day treatment with penicillin and found them to be equivalent (14). Preliminary data suggest that a 10-day course of oral amoxicillin given as a single-daily dose is as effective as 10 days of penicillin V given three times daily (1,4). If confirmed by additional studies, once-daily amoxicillin could eventually become an alternative treatment option given its low cost, acceptable taste, and relatively narrow antimicrobial spectrum (4). While once-daily amoxicillin is supported by the AAP, both the AAP and IDSA currently recommend a standard 10-day course of either penicillin or amoxicillin as first-line treatment.

Penicillin allergic patients should be treated with a cephalosporin. For those patients with a Type 1 hypersensitivity to penicillins, the provider should consider clindamycin (20 mg/kg/day in 3 divided dosages, max 1.8 g/day). Macrolides are also acceptable alternatives for treatment, although macrolide resistance has been reported (15). The AAP does not recommend tetracyclines, fluroquinolones or sulfonamides for the treatment of GABHS penicillin-allergic patients who do not have immediate hypersensitivity-type reactions to penicillin is a 10-day course of a first-generation cephalosporin such as cefadroxil or cephalexin (1). Due to the relatively higher cost and wider spectrum of antibacterial activity of cephalosporins when compared to penicillins, however, this class of agents is not recommended for routine use in patients with GABHS pharyngitis who are not penicillin-allergic (1,4). Numerous once-daily and short-course antibiotic regimens have been approved by the Food and Drug Administration for treatment of GABHS pharyngitis in recent years. However, these regimens generally use unnecessarily broad-spectrum antibiotics and are less cost-effective when compared to penicillin; therefore, they are not recommended as first-line therapy (4,11).

It is important to acknowledge antibiotic treatment for GABHS is controversial. Many Western European countries do not treat

confirmed GABHS and there is no evidence of increased rates of ARF or other suppurative complications (16,17). Antibiotic prescribing trends in England over a 10-year period support a similar conclusion, where a 50% reduction in antibiotic prescriptions was not associated with an increased incidence of rheumatic fever. The decision to treat or not to treat depends on careful communication with parents about the pros and cons of treatment relative to the needs of the individual patient.

DISPOSITION

Most children with pharyngitis can be evaluated and managed as outpatients. For patients with airway obstruction or deep tissue abscesses, admission to monitored settings is recommended. An otolaryngologist should evaluate patients with confirmed abscesses to assess the need for surgical drainage. Admission should also be considered for those children who continue to refuse oral intake and require intravenous rehydration.

CRITICAL INTERVENTIONS

Acute Pharyngitis

- Assess and manage airway patency, hydration status, and pain.
- Always look closely (even in the uncooperative child) for oropharyngeal abscess.
- Diagnose and treat GABHS pharyngitis with appropriate antibiotics.

Common Pitfalls

Acute Pharyngitis

- Failure to obtain an adequate throat swab for RADT or culture.
- Failure to send a confirmatory throat culture if RADT is negative in children and adolescents.
- Failure to evaluate and document the airway examination.

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CHAPTER 261

Croup and Other Upper Airway Disorders

Cristina M. Estrada and Timothy G. Givens

Infections of the upper airway are potentially life-threatening in that they may rapidly progress to obstruction, respiratory failure, and arrest. Inflammation of the supraglottic, glottic, or subglottic regions may produce laryngeal obstruction. Likewise, abscess formation may occur in the peritonsillar, retropharyngeal, or parapharyngeal spaces, leading to pharyngeal obstruction. Because of the confined spaces in which they occur, these entities share many clinical traits regardless of the offending organism.

Croup is a clinical syndrome characterized by a bark-like cough, hoarseness, inspiratory stridor, and respiratory distress of variable severity. The two most common forms are viral laryngotracheobronchitis (LTB) and spasmodic croup. The former is due to infection with parainfluenza viruses types 1, 2, and 3; respiratory syncytial virus; influenza virus type A; human coronavirus NL63 (HCoV-NL63); adenovirus; or rhinoviruses (1,2). The virus causes inflammation of the subglottic tissues and sometimes of the tracheal mucosa. The supraglottic structures are normal. Spasmodic croup is of uncertain etiology, is seen more commonly in patients with recurrent episodes of croup unaccompanied by infectious symptoms, and a family history of asthma, or allergies. Treatment of spasmodic croup ultimately does not differ from that of LTB.

The peak incidence of LTB is during late fall and early winter. It can occur in all age groups but is most prevalent during the second

year of life. There is a 2:1 male-to-female ratio, with a recurrence rate of 5%. Most cases of croup are mild to moderate and self-limited.

Epiglottitis, in contrast, is an acute life-threatening bacterial process. The epiglottis and the aryepiglottic folds become critically inflamed, while the glottis and subglottis remain unaffected. Epiglottitis is typically caused by *Haemophilus influenzae* type B (HIB); however, since the introduction of HIB vaccination the incidence of epiglottitis has declined precipitously among children (3). Epiglottitis occurs year round and can present in any age group, but it most often afflicts preschool children aged 2 to 6 years. Due to widespread HIB vaccination the burden of disease has shifted to older children, adolescents, and even adults. The onset is usually rapid, with a fulminant course leading to respiratory arrest from either airway obstruction or respiratory fatigue associated with a partial airway obstruction. When properly managed, the signs and symptoms of acute infection resolve within 24 to 72 hours. Epiglottitis does not recur following the first infection.

Bacterial tracheitis is a croup variant also known as *pseudomembranous croup.* This relatively uncommon illness occurs in children between 6 months and 8 years of age. Its distinguishing features are the presence of thick mucopurulent secretions. Although most commonly caused by *Staphylococcus aureus or* methicillin-resistant *Staphylococcus aureus* (MRSA), other pathogens such as *Streptococcus pneumoniae, Haemophilus influenzae,* α-hemolytic streptococcus, pneumococcus, and *Moraxella catarrhalis* have also been implicated (4). Owing to the evolution in treatment options including widespread immunization against *H. influenzae* type b and the use of corticosteroids for the treatment of viral croup, bacterial tracheitis has eclipsed croup and epiglottitis in terms of overall morbidity.

Infections of the retropharyngeal and peritonsillar spaces may range from cellulitis to frank abscess formation. Retropharyngeal abscess (RPA) typically afflicts patients younger than 6 years, probably because of the prominence of retropharyngeal lymph nodes in young children, which involute over time. RPA usually

develops by lymphatic spread, though extension from contiguous tissues, local trauma, or presence of a foreign body may be the inciting event. Peritonsillar abscesses represent extension of tonsillar infections and are more common in adolescents and adults rather than younger children. Both varieties of abscesses are polymicrobial in origin, with *S. aureus,* streptococcal species, and anaerobes the usual offenders (5).

CLINICAL PRESENTATION

LTB is characterized by a 1- to 2-day prodrome of coryza with a low-grade fever, followed by inspiratory stridor and the characteristic barking cough, with mild to moderate respiratory distress. Symptoms peak by 2 to 3 days, with respiratory distress worsening when the patient becomes agitated or cries; improvement and resolution is noted by 5 to 7 days (6). Patients presenting with wheezing, tachypnea, and stridor have a combined illness of bronchiolitis with overlying croup. Clinical scoring systems may assist physicians in assessing the degree and progression of respiratory distress (Table 261.1). In spasmodic croup, the same barking cough, stridor, and labored breathing are observed, but the patient is afebrile and does not have the upper respiratory symptoms preceding LTB. Patients with spasmodic croup are usually responsive to cool, humidified air and often improve by the time they reach the emergency department (ED).

TABLE 261.1
Comparison Between Epiglottitis and Laryngotracheobronchitis

Characteristics	LTB	Epiglottitis
Age	6 mos–3 yrs	2–6 yrs
Onset	Gradual	Rapid
Etiology	Viral	Bacterial
Swelling site	Subglottic	Supraglottic
Symptoms		
Cough voice	Hoarse cough	No cough Muffled voice
Posture	Any position	Sitting
Mouth	Closed; nasal flaring	Open-chin forward, drooling
Fever	Absent to high	High
Appearance	Often not acutely ill	Anxious, acutely ill
Radiograph	Narrow subglottic area	Swollen epiglottis and supraglottic structures
Palpation larynx	Nontender	Tender
Recurrence	May recur	Rarely recurs
Seasonal incidence	Winter	None

From Backofen JE, Rogers MC. Upper airway disease. In: Rogers MC, ed. *Textbook of Pediatric Intensive Care*, vol. 1. Baltimore, MD: Williams & Wilkins, 1987.

On the clinical disease spectrum, bacterial tracheitis lies between croup and epiglottitis. Similar to patients with LTB, bacterial tracheitis patients may have a viral prodrome; however, they may rapidly develop septic appearance with high fever and signs of upper airway obstruction. As opposed to epiglottitis, bacterial tracheitis patients often cough, are able to lie flat, and have no problems managing their secretions. Lastly, they often fail to respond to standard treatment for croup, including racemic epinephrine and systemic steroids (4).

Patients with epiglottitis typically have an abrupt onset of sore throat, high fever, and one or more of the “four D’s”: dysphagia, dysphonia, drooling, and distress. Inspiratory stridor may be audible, but there is usually no cough. Secretions, laryngospasm, and fatigue can further compromise breathing. Classically, patients assume a tripod sitting position, with the mandible extended forward in an effort to maintain airway patency. Patients appear very apprehensive and are often septic (3).

Both retropharyngeal and peritonsillar abscesses present with vague symptoms of fever and odynophagia which may evolve into a septic appearance. Patients with RPA may feed poorly, have stridor, exhibit difficulty handling secretions, and develop neck stiffness, pain or torticollis, all of which may combine to create a confounding picture consistent with meningitis. Those afflicted with peritonsillar abscesses may complain of unilateral ear or neck pain and speak with a "hot potato voice." Development of trismus is a clear clue to the presence of a peritonsillar abscess, and a unilateral erythematous bulge of the soft palate around the tonsil with uvular deviation away from the affected side is visible on inspection of the oropharynx (5). The absence of uvular deviation is an important pertinent negative in the evaluation of the adolescent patient with throat pain.

DIFFERENTIAL DIAGNOSIS

Atypical clinical features should prompt other considerations. Occasionally, a child with LTB caused by parainfluenza or influenza virus will present with stridor and wheezing and be diagnosed with bronchiolitis. Epiglottitis relative to croup is differentiated by its more acute and fulminant presentation (Table 261.1); in addition, a history of HIB vaccination does not entirely rule out epiglottitis. Ludwig angina, a rapidly spreading inflammation of the sublingual, submandibular, and submaxillary spaces (more common in adults) and retropharyngeal and peritonsillar abscesses are suspected based on careful inspection of the sublingual space and posterior pharynx. If membranes are noted in the oropharynx, diphtheria and infectious mononucleosis should be considered. Bacterial tracheitis is a primary consideration when a patient continues to deteriorate in spite of treatment or fails to respond to the standard management for LTB. Afebrile stridulous patients with a history of coughing or choking should be evaluated for possible foreign-body aspiration (see Foreign Body Chapter 273) (7). Patients with recurrent or persistent stridor or LTB during an atypical time of year should be considered at risk for the following diagnoses: congenital airway

anomalies, acquired tracheal stenosis secondary to previous intubations, congenital heart disease with associated vascular anomalies, tracheal hemangiomas, or recurrent angioneurotic edema.

ED EVALUATION

Croup is typically a clinical diagnosis; laboratory and radiographic studies are usually unnecessary (6). If the history and physical examination suggest LTB, the physician may apply a clinical scoring system to assess the patient's degree of compromise (Table 261.2). Sequential scoring is done after each intervention (8). An inspiratory soft tissue lateral neck radiograph and chest radiograph may be helpful in distinguishing LTB from other more ominous clinical entities (Fig. 261.1–Fig. 261.3). Classic radiographic signs of epiglottitis include the thumb sign (enlarged epiglottis), swelling of the aryepiglottic folds, blunting of the vallecula, and obliteration of the piriform sinuses. In LTB, the "steeple sign" (a gradual narrowing at the subglottic area) may be observed, however, all supraglottic structures should appear normal. The pseudomembranes of bacterial tracheitis, radiographically, may make the tracheal air column appear hazy. Radiographic widening of the soft tissue between the air column and cervical vertebrae is indicative of RPA or cellulitis. Since retropharyngeal cellulitis without abscess formation can be managed with antibiotics alone, a CT scan may prevent a surgical exploration for a stable patient in whom RPA was suspected.

TABLE 261.2
Clinical Croup Score

	0	1	2
Inspiratory breath sounds	Normal	Harsh with rhonchi	Delayed
Stridor	None	Inspiratory	Inspiratory and expiratory
Cough	None	Hoarse cry	Barking cough
Retractions/ flaring	None	Flaring, suprasternal retractions	As in 1 plus subcostal/ intercostal retractions
Cyanosis *or*	None	In room air	In 40% O_2
PaO_2 (mm Hg)	70–100	<70	<70
CNS function	Normal	Depressed/agitated	Coma

Modified with permission from Downes JJ, Raphaely RC. Pediatric intensive care. *Anesthesiology*. 1975;43:238–250.

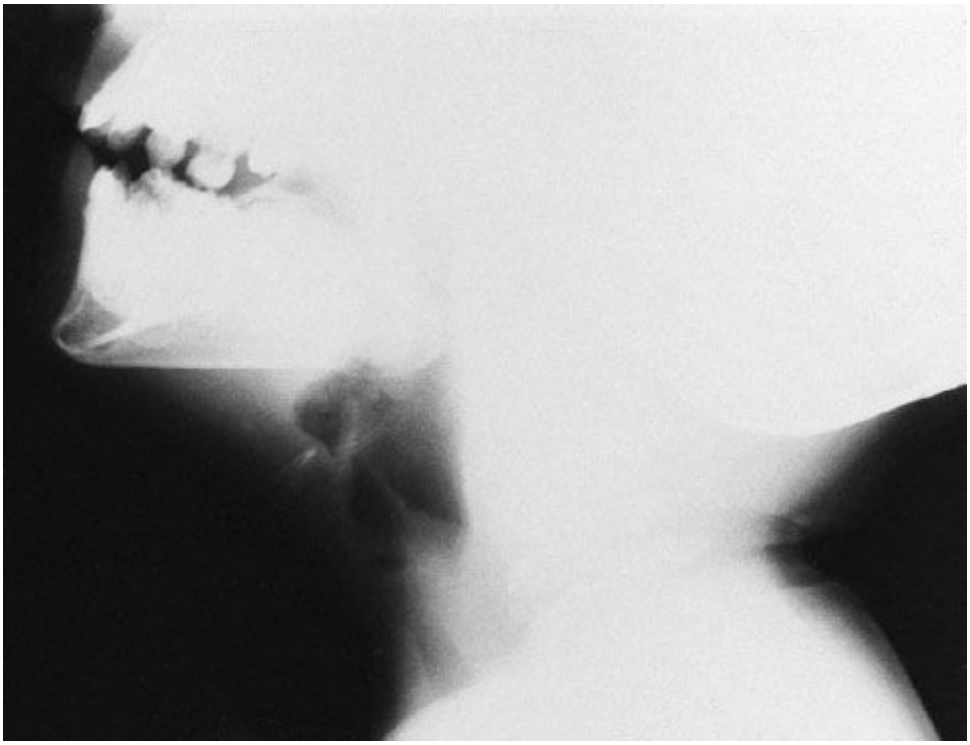

FIGURE 261.1 Normal inspiratory soft tissue lateral neck radiograph.

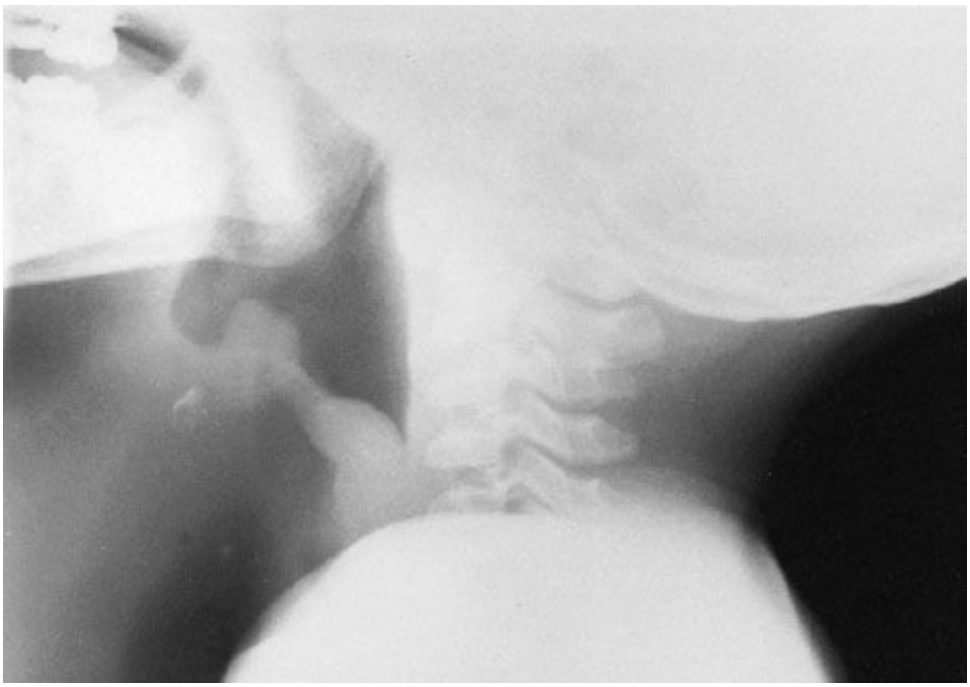

FIGURE 261.2 Epiglottitis on inspiratory soft tissue lateral neck radiograph. Supraglottitis.

FIGURE 261.3 Croup. Steeple sign on a soft tissue neck radiograph.

KEY TESTING

- Inspiratory soft tissue lateral neck radiographs may be performed when the diagnosis is in question.
- Chest radiographs can demonstrate the presence of a steeple sign in croup.
- CT scan with intravenous contrast may be helpful in delineating the extent of abscesses, in diagnosing complications, and in planning surgical intervention.
- Laboratory studies are of limited diagnostic utility in children with croup.

ED MANAGEMENT

Maintenance or provision of an adequate airway is the first priority in any illness in which airway obstruction is possible. A child in respiratory distress should not be separated from parental comfort unless respiratory arrest is imminent (6). Minimizing manipulation serves to reduce agitation and avoids increasing the child's work of breathing or worsening respiratory distress; for this reason venipuncture should be deferred if possible. The physical examination consists of inspection and observation at a comfortable distance from the patient. Oxygen should be delivered in a manner tolerable to the child. Strong subjective airway assessment skills are vital under these circumstances. When epiglottitis or critical tracheitis is established as the diagnosis, immediate arrangements should be made to transport the patient to an operating room for secure placement of an artificial airway. A physician experienced in airway management must accompany the child during transport to the operating room.

Each institution must establish an epiglottitis and critical tracheitis protocol that can be rapidly activated to mobilize personnel once these diagnoses are established (9). Patients with epiglottitis or critical tracheitis should be taken to the operating room immediately, where inhalational anesthesia is given with the patient in a sitting position (10). The hypopharynx is then visualized, and rapid intubation is performed with an endotracheal

tube 0.5 to 1 mm smaller in diameter than predicted for the patient's age and weight. A surgeon skilled in pediatric tracheostomy should be prepared to perform an emergency tracheostomy in the event attempts at intubation fail. Intravenous access and laboratory studies are usually obtained after induction of anesthesia.

For patients who present to the ED with impending or complete respiratory arrest, the airway must be addressed immediately in the ED. These patients may include those with more advanced cases of epiglottitis or tracheitis or LTB patients with croup scores >7. Bag-valve-mask (BVM) ventilation with 100% oxygen should be initiated. Higher positive pressures are sometimes necessary, requiring a two-handed technique to obtain an adequate chest rise. If these measures are unsuccessful within 15 to 30 seconds, a rapid oral intubation should be attempted. Ventilatory failure should be suspected in critical upper airway obstruction in patients who do not respond quickly to initial therapeutic maneuvers, who lose head control or become lethargic. Because of airway narrowing, an endotracheal tube size smaller in diameter than that predicted for the child's age and weight should be used if intubation becomes a necessity. Tips for intubating children with epiglottitis (or other types of critical upper airway narrowing) include using a smaller size endotracheal tube, using a stylet, and looking for an air bubble at the glottic opening while an assistant compresses the chest. If intubation is impossible, emergency cricothyrotomy or tracheostomy may need to be performed (see Chapter 218).

In milder cases of LTB, the treatment provided depends on the patient's level of respiratory distress. In mild cases (croup score <4), a trial of humidification therapy may be offered. However, no significant benefit of cool mist therapy has ever been proven, and a recent randomized, controlled trial of children with moderate croup failed to demonstrate the effectiveness of mist therapy in improving the clinical symptoms of croup (11).

There is ample evidence to suggest that corticosteroids are of benefit to patients with croup (12). Steroids promote resolution of laryngeal edema through their anti-inflammatory activity.

Dexamethasone (Decadron), 0.15 to 0.6 mg/kg, administered either orally or as a single intramuscular injection, has been shown to reduce the severity of symptoms, rate of hospital admissions, need for subsequent nebulized epinephrine treatments, and duration of hospital stay or observation in the ED (13,14). It reduces the number of return visits to the ED and speeds the resolution of symptoms in children with mild croup (13,14). Dexamethasone has a half-life of 54 hours, so one dose is usually sufficient. Inhaled budesonide has a rapid onset (within 2 to 4 hours) and has also been shown to be effective in mild to moderate croup (15).

Both oral and intramuscular routes of administration have been shown to be effective (12), and a randomized clinical trial comparing equivalent doses of intramuscular and oral dexamethasone showed no difference between the two in terms of clinical efficacy (16). The ease of administration of oral dexamethasone over nebulized or intramuscular agents makes the oral route preferable in most cases. The other routes become options in complicated croup requiring admission or associated with vomiting. As the effects of corticosteroid treatment may take up to 6 hours to appear, early administration is important. All patients who require epinephrine therapy should also receive steroids.

Patients with LTB and a clinical score ≤ 4 or inspiratory stridor at rest should receive oxygen and nebulized racemic epinephrine (0.05 mL/kg per dose [maximum dose, 0.5 mL] of a 2.25% solution diluted in 3 mL of saline and delivered with humidified oxygen, repeated as necessary) (8,17). Equivalent doses of either racemic epinephrine or (Levo) L-epinephrine have been shown to be equally effective (18). The L-epinephrine dose is 0.5 mL/kg of a 1:1,000 concentration to a maximum of 5 mL per dose. There should be almost immediate clinical improvement owing to reduction of edema and vasoconstriction of the inflamed mucosa through stimulation of the α-adrenergic receptors. Parents should be encouraged to deliver the nebulized treatment in a nonthreatening manner. Heart rate should be monitored during treatment with

nebulized sympathomimetics. The treatment should be stopped if the heart rate exceeds 200 beats/min or if dysrhythmias occur.

In the past, patients who received nebulized epinephrine were admitted to the hospital because of concern about a rebound effect, a clinical worsening thought to be due to vasodilatation and increased mucosal edema as the adrenergic effects abate. This phenomenon usually occurs within 2 to 4 hours after epinephrine treatment. Recently, the need for hospitalization has been reassessed; several studies suggest discharge from the ED is safe after 2 to 4 hours of observation, if the patient has no stridor at rest, normal air entry, normal color, and a normal level of consciousness (1).

Heliox, a combination of helium and oxygen gas, has a low viscosity and a low specific gravity and allows for greater laminar air flow through the respiratory tract (16). In clinical trials, heliox has *not* been shown to be more effective than humidified oxygen or racemic epinephrine in reducing croup scores (7,19).

Antibiotics are unnecessary for patients with LTB. Patients with epiglottitis or bacterial tracheitis should receive intravenous antibiotics as soon as IV access can be safely established. Epiglottitis can be treated with ceftriaxone (100 mg/kg/d at 12-hour intervals), cefuroxime (150 mg/kg/d at 8-hour intervals), cefotaxime (150 mg/kg/d at 8-hour intervals), or chloramphenicol (100 mg/kg/d at 6-hour intervals). Adequate coverage for *S. aureus* should be a consideration in cases of bacterial tracheitis. Bronchospasm and excessive secretions can be treated with β_2-agonist nebulization (e.g., albuterol) and suctioning. Additional supportive treatment includes antipyretics and intravenous fluids for patients with compromised oral intake.

Both retropharyngeal and peritonsillar abscesses are treated with intravenous antibiotics, with or without incision and drainage. Gram-positive and anaerobic coverage are standard. Antibiotic choices include clindamycin (30 mg/kg/d) or ampicillin–sulbactam (50 mg/kg per dose every 6 hours intravenously) (20).

CRITICAL INTERVENTIONS

- Have appropriate airway equipment available for the rare child with critical airway obstruction and respiratory distress.
- Administer oral or IM dexamethasone in a timely manner to all patients with LTB or spasmodic croup.
- Administer racemic epinepherine via nebulization to patients with stridor at rest, increased work of breathing, with a croup score >4.

DISPOSITION

LTB patients with a clinical score ≤ 4 (significant respiratory distress), those with persistent stridor at rest, and those with minimal or no response to treatment with nebulized adrenergic agents should be admitted, as should those with bacterial tracheitis and infections of the retropharyngeal space.

Instructions to parents whose children are sent home include monitoring the child's work of breathing (respiratory rate, retractions, and agitation), implementing a method of rapid and easy communication access between physician and family, and ensuring minimal physical exertion and stimulation during the convalescent phase of the illness.

Common Pitfalls

- Separating children from parents during initial assessment or during administration of nebulized medications or oxygen.
- Performing medical procedures (venipuncture, vital signs, laboratory, and x-ray studies) while patient is acutely symptomatic in lieu of administering steroids or nebulized epinephrine.
- Delaying the establishment of an artificial airway or not having the appropriate equipment readily available to manage the rare critical airway.
- Failure to consider bacterial tracheitis or RPA in a patient not responding appropriately to treatment.

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CHAPTER 262
Pertussis

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Pertussis is a highly contagious respiratory illness, occurring in all age groups, but is particularly symptomatic in unprotected infants and children. Mortality and hospitalization rates are greater in preterm and unimmunized infants younger than 12 months of age (1). Neonatal pertussis, with maternal peripartum pertussis as the usual source, is particularly severe. The incidence of pertussis has decreased since the institution of the pertussis vaccine. However, there has been an increasing incidence of pertussis across the population, especially among adolescents and adults (2,3). In 2012, 51% of cases occurred in patients over the age of 11; whereas 10.8% were in infants less than 1 year of age (4).

Bordetella pertussis, a gram-negative pleomorphic bacillus, is the causative agent. Less frequently, a similar disease can be caused by *Bordetella parapertussis.* Transmission is by respiratory droplets, with extremely high attack rates (70% to 100%) in susceptible hosts. The incubation period is 5 to 21 days, with a mean of 7 to 10 days (1,5).

Although immunization reduces the incidence and mortality of pertussis, it is neither complete nor permanent. Immunity to pertussis wanes 3 to 5 years after vaccination. After 10 to 12 years, protection from vaccination is minimal (6–8).

CLINICAL PRESENTATION

The clinical manifestations of pertussis depend on age and previous immunization or infection. The classic illness, which lasts for 6 to 10 weeks, is generally divided into three stages: catarrhal, paroxysmal,

and convalescent. The course of the disease may be atypical, especially among adolescents and adults (3). Adult manifestations are often limited to rhinorrhea, sore throat, and persistent cough.

The *catarrhal stage* is characterized by nonspecific upper respiratory symptoms that may include rhinorrhea, lacrimation, mild cough, and low grade or no fever. This stage lasts 1 to 2 weeks, and the diagnosis is often not suspected. Patients are most infectious during the catarrhal phase.

In the *paroxysmal stage,* which may last from 1 to 6 weeks and up to 10 weeks, episodes of coughing increase in severity and number. A characteristic repetitive series of 6 to 12 forceful coughs during a single expiration is followed by a sudden, massive inspiratory effort that produces the classic “whoop” as air is inhaled forcefully against a narrow glottis. Cyanosis, bulging eyes, protrusion of the tongue, salivation, lacrimation, and distention of the neck veins may occur during episodes of coughing. The paroxysms can be precipitated by feeding, crying, or even hearing another person cough.

Physical examination during this stage may reveal conjunctival hemorrhages and petechiae over the neck and head. Some patients have diffuse rhonchi and rales on auscultation. In very young infants, the paroxysms and whoop are often absent with typical chief complaints of choking spells, apnea, bradycardia, cyanosis, and unresponsiveness.

In the *convalescent stage,* usually lasting 1 to 2 weeks but in some cases persisting up to 6 to 10 weeks, symptoms gradually abate (1,3,5,9,10).

Complications of pertussis include otitis media, failure to thrive, pneumonia, seizures, encephalopathy, epistaxis and other hemorrhages, cerebral hypoxia, and death. Most deaths due to pertussis occur in patients 6 months of age or younger (3,5,10). Pneumonia complicates pertussis in 5% to 20% of cases and may be due to *B. pertussis* or secondary bacterial infection. Apnea is a serious complication and is most common in children younger than 6 months of age. Other pulmonary manifestations include aspiration pneumonitis, subcutaneous emphysema, and pneumothorax. Seizures occur in 1% to 2% of cases, whereas encephalopathy occurs

in about 1% of cases (10,11). Of 100 deaths due to pertussis between 2000 and 2004, 90 were infants younger than 4 months, and 76 were younger than 2 months (1). Premature infants are at especially high risk for severe disease.

DIFFERENTIAL DIAGNOSIS

In classic disease, the clinical diagnosis of pertussis can be made without difficulty. Other infectious agents causing similar illness include *Mycoplasma pneumoniae, Chlamydia trachomatis, Chlamydia pneumoniae,* adenoviruses, respiratory syncytial virus, and other respiratory viruses. *B. parapertussis* and *B. bronchiseptica* occasionally produce a pertussis-like syndrome (5).

Spasmodic attacks of coughing may be observed in infants and children with bronchiolitis, bacterial pneumonia, cystic fibrosis, tuberculosis, an airway foreign body, and other diseases that cause lymphadenopathy and extrinsic compression of the trachea and bronchi.

Difficulty in recognizing pertussis occurs in the catarrhal stage, in mild illness, and in adults or very young infants where symptom complexes may vary widely. Pertussis should be included in the differential diagnosis of infants presenting with choking or apneic episodes and in children who present with a history of severe, spasmodic coughing or posttussive emesis.

ED EVALUATION

A child or infant suspected of having pertussis should be observed with formal monitoring for signs and symptoms of respiratory distress. Paroxysmal coughing episodes should be documented and the patient's hydration status should be carefully assessed. Between attacks, patients may appear normal and are usually in no distress. It is vital to remember young infants require hospitalization and close observation, in spite of looking well between paroxysms.

Diagnostic testing for pertussis is imperfect. Evaluation of the white blood cell count may be helpful; a leukocytosis of 20,000 to 50,000 cells/mm^3, with an absolute *lymphocytosis* (i.e. right shift), is

characteristic of severe disease. Chest radiographs are nonspecific and may show a perihilar infiltrate, atelectasis, or a "shaggy" heart border (10).

Culture of nasopharyngeal secretions remains the diagnostic gold standard when performed within the first 2 weeks of illness; false-negative results increase after 2 weeks. The test's specificity is reported to be 100% (3).

PCR is being used more frequently and if performed within 0 to 3 weeks of symptom onset has a reported sensitivity and a specificity of 94% and 97%, respectively (3). To optimize PCR test characteristics, the CDC has suggested a set of testing best practices, which include (1) testing only symptomatic patients, (2) being aware that testing after 4 weeks of cough or following antibiotics increases false-negative results, and (3) maximizing DNA recovery by obtaining samples via aspiration or posterior nasopharyngeal swab (12,13).

Finally, serologic testing can be used for diagnosis, but only in the later stages of disease (2 to 8 weeks after the onset of cough) (12).

KEY TESTING

- CBC: predictive of severe disease with leukocytosis >20,000 and a lymphocytic predominance or "right shift"
- Chest x-ray: with a perihilar infiltrate or "shaggy" heart border
- Culture of nasopharyngeal secretions: if within first 2 weeks of illness
- PCR of aspirated nasal secretions: if within first 3 weeks of illness and observing CDC best practices
- Serology: if between 2 to 8 weeks of symptoms

ED MANAGEMENT

In addition to watching for apnea, overall ventilation, and oxygenation should be carefully assessed and monitored. Patients should be observed both during paroxysmal coughing and between paroxysms. Suctioning the oropharynx with a catheter large enough to permit aspiration of tenacious secretions may be helpful during

paroxysms. Apneic infants may require active airway management. Children younger than 6 months old are more likely to be hospitalized, tend to have longer hospitalizations, and are more likely to require intensive care monitoring.

The paroxysmal coughing episodes may prove exhausting, and avoiding factors that provoke such attacks may be helpful. Early recognition of hypoxia or bradycardia is critical. Corticosteroids and bronchodilators such as albuterol are not routinely recommended for treatment of pertussis, although some have suggested they may reduce paroxysms of coughing (3). Maintenance of hydration and nutritional status is of utmost importance for optimal recovery, especially in infants with severe disease or posttussive vomiting.

Antimicrobial agents, if given early during the course of illness, may ameliorate the symptoms. Because of delays in definitive diagnosis, empiric treatment is often started early in the illness course. However, once paroxysmal coughing is established, antibiotics have no effect on the course of illness, but are still recommended to limit transmission. Macrolide antibiotics are the first line of treatment. Erythromycin was the traditional first-line choice, but azithromycin and clarithromycin are equally effective and have fewer side effects (5). In addition, administration of erythromycin has been associated with pyloric stenosis in infants aged 1 month and younger (10,14,15). For patients allergic to macrolides, trimethoprim–sulfamethoxazole is an acceptable alternative. See Table 262.1 for dosing guidelines (14).

TABLE 262.1
Antimicrobial Treatment Guidelines for Pertussis

Azithromycin	Children <5 mos 10 mg/kg daily for 5 d
Azithromycin	Patients >5 mos 10 mg/kg (max 500 mg) on day 1 5 mg/kg (max 250 mg) daily on days 2–5
Clarithromycin	15 mg/kg/d (max 1 g/d) divided into two daily doses for 7 d
Erythromycin	40–50 mg/kg/d (max 2 g/d) divided into four daily doses for 14 d
Trimethoprim—sulfamethoxazole	8/40 mg/kg/d (max 320/1,600 mg/d) divided into two divided doses for 14 d (contraindicated for infants <2 mos)

From Shah S, Sharieff GQ. Pediatric respiratory infections. *Emerg Med Clin North Am*. 2007;25: 961–979.

In addition to standard precautions, droplet precautions are recommended for 5 days after initiation of effective antimicrobial therapy. Chemoprophylaxis is recommended for all household contacts, irrespective of age and immunization status. The treatment regimen for postexposure prophylaxis is the same as that to treat active disease (14).

With the resurgence of pertussis in adolescents and adults with diminishing immunity, there has been increased focus on vaccination maintenance. Two Tdap vaccines (Tetanus toxoid, diphtheria toxoid and acellular pertussis vaccine, adsorbed), Boostrix and Adacel, were licensed in 2005. The Centers for Disease Control recommends Tdap vaccination instead of Td in adolescents and adults who require tetanus vaccination for wound management. In 2012, the Advisory Committee on Immunization Practices (ACIP) expanded their recommendation to include immunizing adults over the age of 65. Either Boostrix or Adacel is acceptable (16). The dosage of Tdap is 0.5 mL IM (1).

Cocooning, or immunization of adults and adolescents who will be in close contacts with infants <12 months, is recommended with a standard dose of Tdap. ACIP also recommends Tdap for pregnant patients during *EACH* pregnancy. The vaccine may be given at any time during pregnancy but is preferred between 27 and 36 weeks to maximize the level of maternal antibodies. No risk has been

demonstrated to the administration of vaccine during pregnancy (17,18).

CRITICAL INTERVENTIONS

- Recognize that infants may not exhibit the classic "whoop" of pertussis.
- Recognize that infants are at risk for apnea with pertussis.
- Treat all household contacts of patients with pertussis.
- Maintain current immunization status with Tdap throughout life.

DISPOSITION

Patients with severe disease and those younger than 6 months of age with significant clinical evidence of pertussis should generally be hospitalized because of the high rate of complications in this age group. The immunization history of siblings should always be reviewed. Older children and those with milder forms of illness may be discharged home after appropriate evaluation and initiation of antimicrobials. Parents should be instructed to call if breathing difficulties occur, if there is any evidence of cyanosis or restlessness, dehydration, or if medications are not tolerated. Close follow-up is essential.

Common Pitfalls

- Failure to recognize and diagnose pertussis, especially when it presents in an atypical fashion.
- Failure to recognize that infants younger than 6 months of age are at particular risk for severe illness.
- Failure to administer chemoprophylaxis to contacts.
- Incorrect specimen collection and delay in plating secretions on appropriate media.
- Failure to immunize appropriate patients with Tdap vaccine.

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CHAPTER 263
Asthma

Jeffrey F. Linzer, Sr.

Asthma can simply be defined as recurrent reversible bronchospasm due to a trigger (Table 263.1). There is an underlying complex of inflammatory and neural mechanisms that make the airways more sensitive to the triggers and result in bronchial hyperresponsiveness and varying degrees of multicellular inflammation. Recruitment and activation of mast cells, macrophages, dendritic cells, neutrophils, eosinophils, and T-lymphocytes result in an inflammatory and cellular infiltration into the airways, causing the airway epithelium to become fragile and denuded. The epithelial sub-basement membranes thicken, mucus production and viscosity increase, and endothelial leakage results in mucosal edema. Clinicians should avoid outdated terms such as extrinsic (allergic) and intrinsic (late onset) asthma and instead adopt the terminology set out by the National Heart, Lung, and Blood Institute and the Global Initiative for Asthma: Mild intermittent, mild persistent, moderate intermittent, and severe persistent (Fig. 263.1).

TABLE 263.1
Triggers of Asthma Symptoms in Various Age Groups

	Infancy	Early Childhood	Late Childhood	Adolescence
Viral infections	++++	+++	±	+++
Exercise	+	++	+++	+++
Irritants	+	++	+++	+++
Foods	++	+	( )	( )
Indoor inhalants	±	+++	+++	+++
Pollens	( )	++	+++	++
Emotions	( )	+	+	+

Adapted from Pearlman DS, Lemanske RF Jr. Asthma (bronchial asthma): Principals of diagnosis and treatment. In: Bierman CW, Pearlman DS, Shapiro GG, et al., eds. *Allergy, Asthma and Immunology from Infancy to Adulthood*. Philadelphia, PA: WB Saunders, 1996:492.

Level of severity (Columns 2–5) is determined by events listed in Column 1 for both impairment (frequency and intensity of symptoms and functional limitations) and risk (of exacerbations). Assess impairment by patient's or caregiver's recall of events during the previous 2–4 weeks; assess risk over the last year. Recommendations for initiating therapy based on level of severity are presented in the last row.

Components of Severity		Intermittent			Persistent								
					Mild			Moderate			Severe		
		Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years
Impairment	Symptoms	≤2 days/week			>2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤2x/month		1–2x/month	3–4x/month		3–4x/month	>1x/week but not nightly		>1x/week	Often 7x/week	
	SABA* use for symptom control (not to prevent EIB*)	≤2 days/week			>2 days/week but not daily	>2 days/week but not daily and not more than once on any day		Daily			Several times per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
	Lung function		Normal FEV_1 between exacerbations	Normal FEV_1 between exacerbations									
	➔ FEV,* (% predicted)	Not applicable	>80%	>80%	Not applicable	>80%	>80%	Not applicable	60–80%	60–80%	Not applicable	<60%	<60%
	➔ FEV,/FVC*		>85%	Normal†		>80%	Normal†		75–80%	Reduced 5%†		<75%	Reduced >5%†
Risk	Asthma exacerbations requiring oral systemic corticosteroids‡	0–1/year			≥2 exacerb. in 6 months, or wheezing ≥4x per year lasting >1 day AND risk factors for persistent asthma	≥2/year		Generally, more frequent and intense events indicate greater severity.			Generally, more frequent and intense events indicate greater severity.		
		Consider severity and interval since last asthma exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV,*											
Recommended Step for Initiating Therapy (See "Stepwise Approach for Managing Asthma Long Term," page 7)		Step 1			Step 2			Step 3	Step 3 medium-dose ICS* option	Step 3	Step 3	Step 3 medium-dose ICS* option or Step 4	Step 4 or 5
								Consider short course of oral systemic corticosteroids.					
The stepwise approach is meant to help, not replace, the clinical decisionmaking needed to meet individual patient needs.		In 2–6 weeks, depending on severity, assess level of asthma control achieved and adjust therapy as needed. For children 0–4 years old, if no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternate diagnoses.											

FIGURE 263.1 Terminology set out by the National Heart, Lung, and Blood Institute and the Global Initiative for Asthma. (From National Heart, Lung, and Blood Institute, National Institutes of Health. Expert panel report 3: Guidelines for the diagnosis and management of asthma. NIH Publication No. 07–4051, Bethesda, MD: National Institutes of Health, 2007.) Key: EIB, exercise-induced bronchospasm; FEV, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; SABA, short-acting

β_2-agonist. †Normal FEV1 /FVC by age: 8 to 19 years, 85%; 20 to 39 years, 80%; 40 to 59 years, 75%; 60 to 80 years, 70%. ‡Data are insufficient to link frequencies of exacerbations with different levels of asthma severity. Generally, more frequent and intense exacerbations (e.g., requiring urgent care, hospital or intensive care admission, and/or oral corticosteroids) indicate greater underlying disease severity. For treatment purposes, patients with ≤ 2 exacerbations may be considered to have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

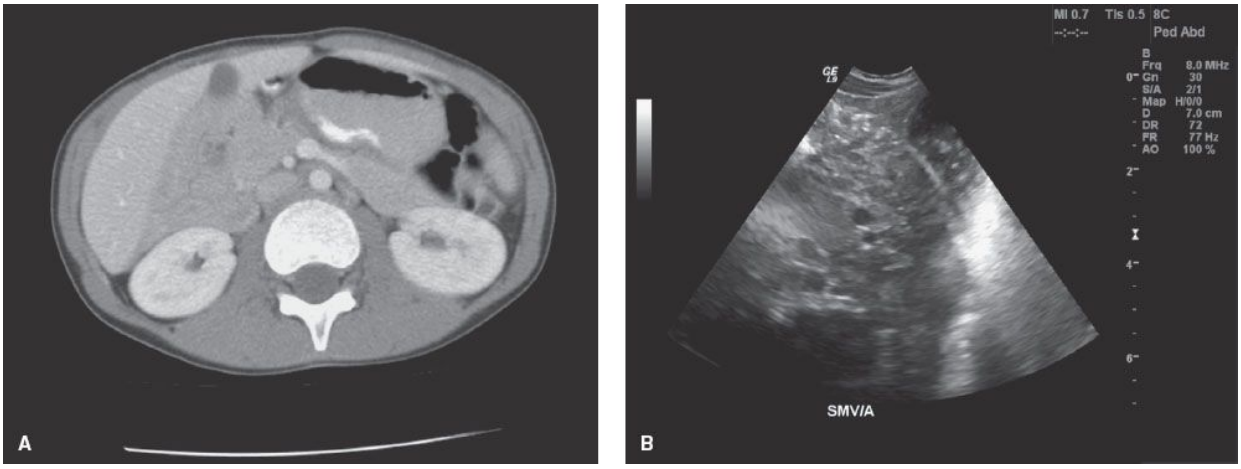

FIGURE 271.1 Images demonstrating position of the SMV in relation to the SMA. In patients with malrotation, the SMV is seen on the left of the SMA **(A)**. In normal orientation, the SMV will lie superiorly and to the anatomic right of the SMA **(B)**. This may be an incidental finding. (Image courtesy of Dr. John Lee.)

According to the Centers for Disease Control and Prevention, in 2011 over 10 million children were diagnosed with asthma. Non-Hispanic black children continue to be the most likely diagnosed (21%) as are children of poor families (18%) (1). Approximately 4.5% of all emergency department (ED) visits by children in 2010 were asthma related.

CLINICAL PRESENTATION

Acute asthma exacerbations vary widely in severity and duration. An asthma attack can be divided into two phases: Early and late allergen responses. The bronchospasm of the early allergen response (EAR) involves release of leukotrienes (LTC4, LTD4, and LTE4) and occurs soon after exposure to a provoking agent. About 50% of patients go on to develop a late allergen response (LAR) induced by a type 2 T-helper cell (Th2) about 4 hours after the initial trigger exposure. The LAR episode usually lasts 12 to 24 hours but may persist up to several days in some children.

Acute asthma attacks can be divided into mild, moderate, severe, and imminent respiratory arrest (Table 263.2). Classically, the child with an acute asthma exacerbation presents with wheezing and respiratory distress. Bronchospasm, however, can also present less characteristically as cough, chest pain, shortness of breath, and fatigue with exertion. There is poor correlation between symptoms, spirometry, and ventilation–perfusion measurements. Spirometry tends to reflect the degree of bronchoconstriction in large and medium airways, best measured by the forced expiratory flow 25% to 75% ($FEF_{25–75}$). Ventilation–perfusion mismatch is more related to obstructive changes in the peripheral airways.

TABLE 263.2
Evaluation of Severity of Asthma Exacerbation

	Mild	Moderate	Severe	Respiratory Arrest Imminent
Symptoms				
Dyspnea/Breathlessness	• Only with activity (assess tachypnea in young children) • Talks in sentences • Can lie down	• Interferes with or limits usual activity and talking (infant softer, shorter cry; difficulty feeding) • Speaks in phrases • Prefers sitting	• Present at rest; interferes with conversation • Able to say few words at a time (infant stops feedings) • Sits upright	• Unable to speak
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Signs				
Respiratory rate	Normal to minimal	Increased	Marked	
0–17 mos	<40	40–60	>60	
18–35 mos	<35	35–55	>55	
3–6 yrs	<30	30–50	>50	
>6 yrs	<20	20–40	>40	
Work of breathing	Normal or mildly increased	Moderate accessory muscle use and retractions	Severe accessory muscle use and retractions	Paradoxical thoracoabdominal movement
		Nasal flaring may be present	Nasal flaring present	
Wheeze	Moderate, often only end expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze, "quite chest"
Cough	No or mild cough	Frequent coughing but with no loss of breath	Frequent coughing with loss of breath	
Functional Assessment				
PEF				
% predicted or % personal best	≥70%	~40–69% or response lasts <2 hrs	<40%	<25%
PaO_2 (on room air)	Normal (test not usually necessary)	>60 mm Hg (test not usually necessary)	<60 mm Hg; possible cyanosis	
and/or				
PCO_2	<42 mm Hg (test not usually necessary)	<42 mm Hg (test not usually necessary)	≥42 mm Hg; possible respiratory failure	
SaO_2% (on air) at sea level	>90%* (test not usually necessary)	>90%*	<90%	
Clinical course	• Usually cared for at home • Prompt relief with inhaled SABA • Possible short course of oral systemic corticosteroids	• Usually requires office or ED visit • Relief from frequent inhaled SABA • Oral systemic corticosteroid; some symptoms last for 1–2 d after treatment is begun	• Usually requires ED visit and likely hospitalization • Partial relief from frequent inhaled SABA • Oral systemic corticosteroids; some symptoms last for >3 d after treatment is begun • Adjunctive therapies are helpful	• Requires ED/hospitalization; possible ICU • Minimal or no relief from frequent inhaled SABA • Intravenous corticosteroids • Adjunctive therapies are helpful

*A SaO_2 >90% is associated with a PaO_2 of 60 mmHg

Note: Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents.

Source: Adapted and modified from National Heart, Lung, and Blood Institute, National Institutes of Health. Expert panel report 3: guidelines for the diagnosis and management of asthma. NIH Publication No. 07-4051, Bethesda, MD: National Institutes of Health, 2007.

With a mild attack, the child usually has been symptomatic for a short period of time and may still be in the EAR phase. There may be some increase in the respiratory rate, with a tight, hacking cough or end-expiratory wheezing. There is good air exchange, with minimal breathlessness and no accessory muscle use. A PaO_2 of 60 mm Hg or greater (reflected by a room air oxygen saturation [SaO_2] of >90%) is acceptable. Examination of lung function (peak expiratory flow rate [PEFR] or FEV in 1 second [FEV_1]) should be >70% of predicted or personal best.

In a more moderate attack, symptoms may have been going on for several hours to days, or unresponsive to treatment, indicating LAR. There is an increase in the work of breathing, with tachypnea and accessory muscle use. Expiratory wheezing may be audible from across the examination room, and inspiratory and expiratory wheezing may be present. The child may become breathless while talking and be somewhat agitated. An infant may have a less vigorous but more irritable cry and pull away from an offered bottle. Oxygen saturation is often in the low normal range, and PEFR/FEV_1 $<$70% of predicted or personal best.

Severe attacks are similar to moderate exacerbations in their time of onset and duration. There is marked respiratory distress, work of breathing, and tachypnea. Accessory muscle use is associated with intercostal and tracheosternal retractions and nasal flaring. Breath sounds can range from inspiratory and expiratory wheezing to a somewhat quiet chest. Emergency physicians must distinguish the child with minimal air movement, and therefore, no wheezing, from the examination of a healthy child with adequate air movement and no wheezing. Between these two extremes lies the child with an active asthma exacerbation, ranging from mild to severe, with audible wheezing. The child's mental status may range from anxious and agitated to somnolent and difficult to arouse, and tends to vary directly with corresponding degrees of air movement; worse air movement corresponds to a less desirable mental status. Infants will range from very agitated to unusually quiet and will refuse to take a bottle. Hypoxia is present, and the $PaCO_2$ may rise above 40 mm Hg. PEFR/FEV_1 is typically $<$40% of predicted or personal best.

It is important to remember that a child may present with symptoms from any and all of the mentioned categories, and that symptoms do not always lend themselves to easy classification. Emergency physicians must become familiar with the subtle nuances of respiratory distress that become appreciable only with frequent clinical reassessments.

DIFFERENTIAL DIAGNOSIS

The clinician's careful history and physical examination can help locate from which part of the respiratory tract the symptoms originate. Asthma is a diagnosis of exclusion in the first year of life and is uncommon during the second year.

Cough or rattling chest sounds that mimic asthma are most commonly heard with upper airway pathology. These sounds occur in children with an upper respiratory infection and in older children and adolescents with allergic rhinitis and sinusitis. Such conditions also may contribute to the severity of a subsequent asthma exacerbation. Similar sounds can be produced in infants with choanal atresia and in children with hypertrophy of the tonsils or adenoids. The examiner should be especially aware of potential foreign bodies in toddlers and young children.

Mid-sized airway pathology can cause not only cough but also wheezing and chest discomfort. Stridor, which is an inspiratory sound, must not be confused with wheezing. Examples of conditions producing stridor include croup, epiglottitis, and pharyngeal foreign bodies. Fortunately, epiglottitis in the post-*Haemophilus influenzae b* vaccination era has become rare in children, although group A streptococcus may produce a similar clinical picture. Unfortunately, laryngotracheobronchitis ("wheezy croup") and tracheal foreign bodies may also produce wheezing which must be distinguished from lower airway disease.

In infants, anatomic conditions causing cough and wheezing include laryngomalacia, tracheomalacia, tracheoesophageal fistula, and hemangiomas. Laryngeal webs, vascular rings, and slings are seen in older infants and toddlers. Vocal cord dysfunction is rare and usually noted only in older children and adolescents. These conditions share an important feature in that there is minimal, if any, improvement in symptom severity with conventional asthma therapy.

The lower airway causes of asthma-like symptoms are more difficult to differentiate from asthma. Cystic fibrosis can present with symptoms that initially respond to asthma treatments. Children with cystic fibrosis can go on to develop digital clubbing, which is rarely seen with asthma. Now less common owing to surfactant therapy,

bronchopulmonary dysplasia can occur in expremature infants who required prolonged ventilatory support. Chronic aspiration and gastroesophageal reflux, which can exacerbate underlying asthma, can produce cough and wheezing on their own. Inhalation of chemical and toxic substances and foreign bodies must also be considered.

Bronchiolitis (both respiratory syncytial virus [RSV] and non-RSV variants) is a common cause of wheezing in children younger than 2 years and especially in children less than 12 months of age. This disease occasionally responds to asthma treatment. Bronchitis should be considered an adult or adolescent disease at best. Chlamydia trachomatis (in infants younger than 3 months), pertussis (especially in infants younger than 6 months), pneumonia, and chronic *Chlamydia pneumoniae* in asthmatics can present similarly or aggravate underlying asthma.

Infections with aggressive forms of common respiratory viruses such as adenovirus and parainfluenza can lead to an asthma-like acute respiratory distress unresponsive to the usual asthma therapies. Infection with these agents can occasionally lead to acute respiratory failure. Other rare lower airway conditions to consider as causes of asthma-like syndromes include complications of congenital cardiac conditions, alpha$_1$-antitrypsin deficiency, pulmonary hemosiderosis, and pulmonary eosinophilia (Löffler syndrome).

ED EVALUATION

Determination of the severity of the attack is based on a rapid initial assessment that includes a brief history and directed physical examination performed in a calm and reassuring manner. Though baseline SaO_2 and measurements of lung function can be useful, the subjective findings on examination provide a better key to the severity of the exacerbation. Formally measuring pulmonary function in the ED may not be possible in many centers and should not be relied upon as a guide to management. Noting work of breathing, patient position and mental status, with frequent reassessment is the key to effectively manage acute asthma exacerbations. An SaO_2 of

<90% on presentation and remaining <91% 1 hour postpresentation, or a PEFR or FEV_1 <70%, can be used to determine severity and the potential need for hospitalization. Though children 5 years and older are capable of performing pulmonary function tests, studies have shown that only 65% can adequately perform one during an acute exacerbation (2).

The presentation and duration of symptoms and response to therapy prior to ED arrival, in addition to identifying contributing factors (e.g., fever, choking), may help to stratify the severity of an exacerbation and to determine the need for ancillary tests see Table 263.2. Assessment should also take into account the frequency and timing of previous episodes. Patients who have had multiple ED visits for asthma exacerbations, have required noninvasive positive pressure ventilation (NPPV), have been endotracheally intubated, have failed to properly use their rescue or controller medication, or have failed ED follow-up care in the past are at increased risk for severe exacerbations and should be treated aggressively.

The physical examination should rapidly determine the child's work of breathing by evaluating the degree of breathlessness, use of accessory muscles (including subcostal and intercostal muscles), and nasal flaring, and by listening to breath sounds. Simply noting the effort of breathing by watching the patient's exposed chest often yields of the most valuable clinical information. Neurologic status, reflected by the degree of irritability and responsiveness to the examiner and caretaker is an equally valuable marker of disease severity.

KEY TESTING

- Chest x-ray is not needed for straightforward asthma attack that improves with ED treatment. Order if there is concern for pneumonia, pneumothorax, or pneumomediastinum.
- Pulse oximetry and noninvasive end-tidal CO_2 monitoring.
- Routine CBC or blood chemistries do not provide useful information in uncomplicated asthma attacks.

ED MANAGEMENT

Short-Acting a-Agonists

Inhaled short-acting selective β_2-agonists (SABAs) remain the mainstay of acute asthma treatment. The inhaled β_2-medications have rapid onset with a maximal peak response at 20 minutes (3). Children respond well to doses higher than those routinely used in adults, and there is a significant relationship between albuterol dosing and improvement in pulmonary function (4). Higher doses and more frequent administration also lead to greater bronchodilation (5). Failure to employ aggressive beta agonist therapy early can result in an unnecessary prolonged ED course or unnecessary hospitalization. Side effects such as tachycardia, tremors, nausea, and vomiting tend to be dose related, but overall, the beneficial effects of beta agonists on acute bronchoconstriction far outweigh the risks of side effects.

β_2-Agents available in the United States include albuterol and levalbuterol for nebulization and albuterol, pirbuterol, and levalbuterol by metered-dose inhaler (MDI). Though part of the NLHBI Expert Panel recommendations, pirbuterol has not been studied in acute pediatric asthma; it is considered about half as potent as albuterol on an mgm-per-mgm basis.

While bronchodilators have traditionally been administered by intermittent small-volume nebulizer, metered-dose inhalers with spacers (holding chambers with a valve) (MDI-S) and continuous nebulization (CN) have both been shown to be at least as effective as small-volume nebulization. MDI-S is a convenient and cost-effective way to administer medication to children of almost any age and appears to have fewer side effects when compared to small-volume nebulization (6,7). Four to eight puffs of a short-acting β_2-agonist (SABA) should be given over a 2- to 5-minute period. CN has an advantage in patients with more severe presentations; doses of up to 30 mg of albuterol per hour can easily be administered to the patient with severe disease or impending respiratory failure (8).

The recommended dosing of inhaled β_2-agents is summarized in Table 263.3. While the question remains somewhat controversial,

there does not appear to be any clinical difference between racemic albuterol and levalbuterol in the acute setting (9).

TABLE 263.3
Dosing of Inhaled a_2-Agents

Medication	Method	Dose[a]	Interval[b]
Albuterol	MDI-S	4–8 puffs (30- to 60-sec intervals)	Every 20 min during the first hr
	SVN	0.15–0.3 mg/kg (2.5 mg minimum)	Every 20 min during the first hr
	Convenience dose	2.5 mg/dose ≤15 kg	
		5 mg/dose >15 kg	Every 20 min during the first hr
	CN	0.5 mg/kg/hr	Every 1–4 hrs
	Convenience dose	7.5 mg/hr ≤15 kg	
		15 mg/hr >15 kg	Every 1–4 hrs
Levalbuterol	MDI-S	4–8 puffs (30- to 60-sec intervals)	Every 20 min during the first hr
	SVN	0.075–0.15 mg/kg (1.25 mg minimum)	Every 20 min during the first hr
	Convenience dose	1.25 mg/dose ≤15 kg	
		2.5 mg/dose >15 kg	Every 20 min during the first hr
	CN	0.25 mg/kg/hr	Every 1–4 hrs
	Convenience dose	3.75 mg/hr ≤15 kg	
		7.5 mg/hr >15 kg	Every 1–4 hrs

CN, continuous nebulization; SVN, small-volume nebulizer; MDI-S, metered-dose inhaler with spacers.
[a]Higher doses of albuterol have been shown to be safe and may be more effective for very severe exacerbations.
[b]As indicated by the patient's response.

Subcutaneous (SQ) or intramuscular (IM) injections of epinephrine or terbutaline have no clinical advantage over the inhaled β-agonists and their use should be limited to patients with severe exacerbations and poor air exchange (3). As a selective β_2-agonist, terbutaline may have a theoretical advantage over the nonselective α-β epinephrine. The SQ or IM dose of terbutaline is 0.1 mg/kg up to a maximum of 0.25 mg, and for epinephrine (1:1,000 solution) 0.01 mL/kg (0.1 mL minimum, 0.3 mL maximum). Doses may be repeated at 15- to 20-minute intervals to a maximum of three doses. The only intravenous (IV) selective β_2-agonist available in the United States is terbutaline. While not FDA-approved, the injectable preparation has been used in children with impending respiratory failure. An IV loading dose of 10 μg/kg (maximum of 1,000 μg) is given over 10 minutes, followed by a maintenance infusion of 0.4 μg/kg/min. The dose is titrated in

increments of 0.2 μg/kg/min until desired respiratory effects are achieved or unacceptable tachycardia occurs. The usual effective infusion dose is 3 to 6 μg/kg/min. The most common side effects, tremors and tachycardia, are dose related.

Ipratropium

Ipratropium bromide is a quaternary ammonium derivative of atropine. This greatly diminishes its systemic absorption and side effects. Its anticholinergic activity does provide an additional mechanism of bronchodilation. By itself, ipratropium has a relatively slow onset but a prolonged duration of action when compared with the β-agonists. It is never given alone as the primary bronchodilator. There is a clinical advantage when given in multiple doses with albuterol in children (10), especially when there is a significant cough component and in moderate to severe attacks.

Ipratropium should be considered with each treatment during the first hour of care or the first three to four nebulizer treatments. Four to eight puffs by MDI-S may be given either as a separate inhaler after the SABA or in an inhaler premixed with albuterol. When used with a nebulizer, 0.25 to 0.5 mg should be combined with each SABA small-volume nebulizer dose or 0.5 to 1 mg in a CN.

Corticosteroids

Systemic corticosteroids (SCS) should be given within 1 hour of presentation to the ED in all but the mildest asthma exacerbations. All routes—oral, IM, and IV—are equally effective (11). The onset of anti-inflammatory activity in all is approximately 4 to 8 hours. Steroids are a vital aspect of treatment in LAR. They decrease inflammation during the acute phase of an asthma exacerbation, and also decrease the relapse rate during the first week after an exacerbation. The route of administration should be chosen based on the patient's condition, the ability to take oral medications, and the risk of noncompliance, which is an important contributor to relapse potential (12).

Prednisone and prednisolone are the most commonly used oral SCS. They are given in a dose of 1 to 2 mg/kg (60 mg maximum). Oral methylprednisolone should be considered in children who are on chronic home SCS therapy, as these patients may be relatively resistant to their baseline former medications. Certain brands of prednisolone are available in a more palatable base that makes it easier for the child to take the medicine. Oral dexamethasone (0.6 mg/kg, 16 mg maximum) may be used as an alternative, especially if compliance is an issue, since a 2-day course is as effective as 5 days of prednisone or prednisolone (13,14). Though not FDA-approved, the parenteral form may be mixed with a flavoring agent and given orally. Otherwise tablets are preferred since the available oral liquid preparations have a very low concentration (0.1 mg/mL) or high alcohol content (30% for 1 mg/mL solution).

Parenteral SCS should be considered for patients who are too ill to take the oral medication or for those in whom there are concerns about compliance. Dexamethasone (0.6 mg/kg, 20 mg maximum) may be given either IM or IV. A single dose of IM dexamethasone can be as effective as a 5-day course of prednisolone (15). Methylprednisolone may be given IM (acetate 10 mg/kg, 160 to 240 mg maximum) or IV (sodium succinate 1 to 2 mg/kg, 125 mg maximum).

Inhaled corticosteroids (ICS) (e.g., budesonide) used concomitantly with a continuously nebulized SABA should be considered for patients with moderate to severe exacerbations. Inhaled steroids provide additional benefits when used with systemic steroids during ED treatment (16). This includes fewer days with symptoms and a trend toward lower hospitalization rates. Though a variety of dosings have been studied, a single dose of 1.5 to 2 mg of budesonide appears to be beneficial.

Oxygen

Children with significant respiratory distress will benefit from oxygen, even those with a normal SaO_2. Low-flow oxygen (1 to 2 L/min) by nasal cannula is usually sufficient to reach the goal of

maintaining SaO_2 >90%. For children requiring higher oxygen concentrations, high-flow oxygen should be administered via a nonrebreather mask. Warm, humidified oxygen is preferable to avoid irritation of the respiratory tree.

Additional Therapies for Severe Exacerbations

Magnesium sulfate has become an increasingly used second-line medication for moderate to severe asthma exacerbations. A dose of 25 to 50 mg/kg of magnesium sulfate (2 g maximum) IV given over 20 minutes may be useful for children who have not responded to conventional therapy, though the higher range appears to be of greater benefit in children (17). Children do not generally require additional hydration or a baseline electrocardiogram.

Heliox (helium-oxygen mixture) has a lower gas density than air or oxygen. Although the role of heliox remains controversial, it is believed that the decreased airway resistance to flow and smaller size or respirable particles result in increased deposition of β_2-agonist in the airways. Children receiving CN driven by either a 70:30 or 80:20 helium:oxygen mixture showed greater clinical improvement than those using room air or oxygen (18).

Ketamine, a dissociative anesthetic, improves pulmonary compliance and decreases airway resistance in moderate to severe bronchospasm. Children tend to tolerate the doses needed to produce bronchodilation better than adults do. Dosing is controversial and an initial dose of up to 1 mg/kg may be needed (19). Maintenance drips should be reserved for pediatric intensive care settings. Side effects, including emergence reactions and hypertension, can be treated with benzodiazepines.

NPPV (bilevel positive airway pressure [BiPAP] or continuous positive airway pressure [CPAP]) have been shown to be an alternative to intubation in children with moderate hypoxia (20). Delivery of β_2-agonist via BiPAP in the ED can stabilize children who otherwise would require admission to the intensive care unit. In a child who has good but incomplete improvement after a CN, a single SVN delivered by positive end-expiratory pressure (PEP) may help

with opening the more distal airways and improve delivery of the medication.

Antibiotics

The routine use of antibiotics is of no benefit in the management of acute asthma. Antibiotics should be used when findings are consistent with pneumonia or other clinical bacterial infection, and are directed to the most likely organism (see Chapter 265, "Pneumonia").

CRITICAL INTERVENTIONS

- SABAs are the mainstay of acute asthma treatment. They should be used early and at frequent intervals (by MDI-S or by CN).
- Ipratropium added to SABA during the first hour is beneficial when there is a cough component or in moderate to severe exacerbations.
- Most children who present to the ED require corticosteroids, and they should receive it within the first hour of ED care.
- Additional treatments, such as magnesium and heliox, should be started early in severe exacerbations.
- Asthma is an inflammatory disease. Viral infections are an important trigger. There is no need to routinely use antibiotics unless there is clearly a bacterial focus of infection.

DISPOSITION

Patient disposition depends on the severity of the attack, the response to treatment, and contributing risk factors. It is important that the patient be reassessed after initial therapy and observed for an appropriate period for relapse before leaving the ED.

A child who has had a mild attack, required no more than one or two albuterol treatments, and whose PEFR or FEV_1 was not $<70\%$ may be sent to home after a short (30-minute) observation period. All other patients should be observed for at least 1 hour for signs of relapse. A child who is breathing comfortably, has no or minimal tachypnea with good air exchange and clear lung fields and who has

a room air SaO_2 >90% may be discharged home. However, certain children are at greater risk of fatal out-of-hospital asthma exacerbations even when they appear clinically well after treatment. Patients who should be considered at high risk include those who have (21):

1. Had three or more ED visits for asthma in the past 12 months
2. Had two or more hospitalizations in the past 12 months or one within the past month
3. Required admission to intensive care because of severity of previous exacerbations
4. Used two or more canisters of SABA in the past month
5. Not been compliant with previous post-ED follow-up and controller use

Admission should be considered for patients with an incomplete or poor response to therapy. This includes children who have a "normal" SaO_2 but still show signs of air hunger and who improve when given low-flow oxygen (clinical hypoxia). The decision to watch a patient in an observation unit or an inpatient ward depends on local policies and capabilities. Children presenting in impending or actual respiratory failure or who have deteriorated in the ED should be admitted to a pediatric intensive care unit.

Children who are discharged should be sent to home with sufficient medication to continue their therapy. The goal is to transition them from scheduled use of SABA to rescue use as quickly as possible (usually within 1 to 2 days) because of the risk of tachyphylaxis and undetected relapse. Children respond well to short courses ("bursts") of SCS and do not need to be "tapered" from the systemic steroid effects. Prednisone, prednisolone, or methylprednisolone is continued at 1 to 2 mg/kg (60 mg maximum) in one or two divided doses. The length of treatment is a 3- to 7-day course, depending on patient's severity and rapidity of response. A second dose of dexamethasone (0.6 mg/kg, 16 mg maximum) is also acceptable. Parents tend to prefer having to give just 1 day of medication, which may result in better compliance (22). The tablets are preferred for home use as the available oral liquid forms have a low concentration (0.1 mg/mL) or high alcohol content (30% for 1

mg/mL solution). Parents can crush the tablets and mix them into a small amount of food or chocolate syrup. A tapering dose of prednisone, prednisolone, or methylprednisolone should be used if the child has taken systemic steroids in the previous 30 to 60 days, has had three bursts in the past 6 months, or four bursts in the past 12 months. The taper should be over 7 to 21 days. The risks of using systemic steroids in children with active varicella (i.e., potential development of disseminated disease) must be carefully weighed against the benefits. Use of appropriate antivirals should be considered.

All children who receive SCS in the ED should be discharged with a 1-month course of low to moderate dose ICS (Table 263.4). It is a cost-effective means of decreasing the rate of relapse (23). Lack of controller medication use after ED care has been shown as a risk factor for near-fatal exacerbations (21).

TABLE 263.4
Daily Dosing of Inhaled Corticosteroids

Drug	Low Dose	Medium Dose	High Dose
Beclomethasone HFA 40 µg/puff 80 µg/puff (in 1–2 doses)	40–80 µg (1–2 puffs) (1 puff)	160–240 µg (4–6 puffs) (2–3 puffs)	>320 µg (≥8 puffs) (≥4 puffs)
Budesonide DPI 200 µg/dose (in 1–2 doses)	200 µg (1 inhalation)	400 µg (2 inhalations)	>600 µg (>3 inhalations)
Inhalation suspension for nebulization 0.25 mg/dose 0.5 mg/dose (in 1–2 doses)	0.25 mg (1 ampule)	0.5 mg (2 ampules) (1 ampule)	>1 mg (>4 ampules) (>2 ampules)
Flunisolide 250 µg/puff (in 2 divided doses)	500–750 µg (2–3 puffs) 160 µg	1,000–1,250 µg (4–5 puffs) 320 µg	>1,250 µg (>5 puffs) >640 µg
HFA 80 µg/puff	(2 puffs)	(4 puffs)	(>8 puffs)
Fluticasone HFA: 44, 110, 220 µg/puff DPI: 50, 100, 250 µg/dose (in 2 divided doses)	88–176 µg (2–4 puffs, 44 µg) 100–200 µg (2–4 inhalations, 50 µg) (1–2 inhalations, 100 µg)	176–352 µg (4–8 puffs, 44 µg) 200–400 µg (4–8 inhalations, 50 µg) (2–4 inhalations, 100 µg)	>352 µg (>3 puffs, 110 µg) (>2 puffs, 220 µg) >400 µg (>4 inhalations, 100 µg) (>2 inhalations, 250 µg)
Triamcinolone acetonide 75 µg/puff (in 3–4 divided doses)	300–600 µg (4–8 puffs)	600–900 µg (8–12 puffs)	>900 µg (>12 puffs)

Adapted from National Heart, Lung, and Blood Institute, National Institutes of Health. Expert panel report 3: Guidelines for the diagnosis and management of asthma. NIH Publication No. 07–4051, Bethesda, MD: National Institutes of Health, 2007.

Children should be sent to home with a written asthma treatment plan that details what treatment the patient received and how any continuing problems at home should be managed. Children 6 years and older should be sent home with a peak expiratory flow meter, to be used two to four times a day; the results are used to guide further treatment.

All children who have had an ED visit for asthma exacerbation should be referred back to their primary care physician or specialist for follow-up. At a minimum, the parent should make phone contact

within 24 hours of discharge to advise the physician of the child's progress.

Common Pitfalls

- Failing to provide early, aggressive treatment can lead to unnecessarily prolonged ED care or hospitalization. Children tolerate relatively higher and more frequent doses of inhaled bronchodilator than adults do.
- Assuming that all children who wheeze have asthma—the conditions are not synonymous. Be alert to other possible etiologies such as foreign-body aspiration or laryngotracheobronchitis.
- Assuming that if a child is not wheezing, there is no asthma attack. Asthma can present as cough (cough variant asthma), chest pain, shortness of breath, and fatigue with exertion.
- Failing to understand which patients are at risk for near-fatal or fatal exacerbations.
- Failing to educate parents and children about potential triggers and how to avoid them. Smoking is a significant environmental trigger and is potentially harmful to the child, even if the parent "smokes outside."
- Failing to send the patient to home with ICS and directed follow-up with the primary care provider within a few days of the ED visit.

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CHAPTER 264 Bronchiolitis

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Each epidemic season, the emergency physician is faced with evaluating, treating, and determining the disposition of infants and young children with bronchiolitis. The American Academy of Pediatrics defines bronchiolitis as “rhinitis, tachypnea, wheezing, cough, crackles, use of accessory muscles, and/or nasal flaring in a child less than 24 months” (3). Unlike children with reactive airway disease, the lower respiratory tract symptoms of children with bronchiolitis are caused by an acute infection causing inflammation of the bronchiolar epithelium. The resultant necrosis of epithelium causes plugging of the smaller airways by cellular debris, resulting in air trapping or atelectasis distal to the obstruction. This results in tachypnea, wheezing, rales, increased work of breathing, and potentially hypoxemia.

Respiratory syncytial virus (RSV) is probably the most important respiratory pathogen in young children and may cause serious morbidity and even mortality. It is the leading cause of infant hospitalization. While the overall hospitalization rates for bronchiolitis have dropped by 17% over the last decade, the number of cases in children with high-risk medical conditions (e.g., prematurity) increased by 34%, and the rate of mechanical ventilation increased by 21% (11,20). More than 50% of infants will acquire RSV infection during their first epidemic season, and 40% of these will progress from upper to lower respiratory tract illness. Three percent of all children <1 year of age will require hospital admission for bronchiolitis (20). The peak incidence of lower airway disease occurs in infants 2 to 5 months of age (9,20). The mean

annual mortality rate is estimated to be 2.8 per 100,000 births, with almost 80% of deaths occurring in patients younger than 12 months old.

Children in high-risk groups are at greatest risk for severe disease and death and require monthly immunoprophylaxis with palivizumab or RSV immunoglobulin during the RSV season. These include (1) those in the first few months of life with a history of prematurity ($\leq$35 weeks' gestational age), (2) those with congenital heart disease (CHD), (especially uncorrected pulmonary hypertension), (3) those who are immunosuppressed, and (4) those with chronic lung disease (CLD) (11,12). Environmental risk factors such as passive smoking, crowded households, and attendance at day care may contribute independently to disease severity.

There are two major subtypes of the RSV virus, strains A and B. Subtype A is commonly associated with more severe disease. Although RSV is the most common pathogen, other viruses, including parainfluenza type III, influenza, adenovirus, rhinoviruses, and mycoplasma, can also cause bronchiolitis (9). Human metapneumovirus (hMPV) is a newly described paramyxovirus associated with upper and lower respiratory tract symptoms similar to RSV bronchiolitis and is responsible for 5% to 10% of hospitalizations (24). Bronchiolitis caused by hMPV is usually found in older infants and is associated with a higher incidence of fever and atelectasis.

CLINICAL PRESENTATION

The presentation of the infant or young child with bronchiolitis ranges from the smiling, interactive child with mild tachypnea and end-expiratory wheezing to the child who presents with impending respiratory failure. Typically, there is a 3- to 5-day history of upper respiratory tract symptoms, including coryza and congestion, before the onset of lower respiratory tract symptoms. The parent may have noted that the child developed a "cold," is not as active, is breathing faster, or has difficulty feeding. Although most patients have tachypnea, cough, wheezing, and increased work of breathing, the

infant under 3 months may simply present with lethargy, irritability, or apnea and have few to no lower respiratory findings. Fever is often present early in the course of illness, but may be absent or low grade at the time lower respiratory tract symptoms develop. Lower respiratory tract involvement usually peaks within 3 to 5 days. Resolution of symptoms overall, including cough, wheezing, and mild hypoxemia, however, may take days to weeks.

DIFFERENTIAL DIAGNOSIS

Emergency physicians must be careful not to anchor on the diagnosis of bronchiolitis in infants during epidemic winter months and should consider other causes of lower respiratory tract illness. While bronchiolitis is a clinical diagnosis, children with atypical presentations, such as severe respiratory distress or absence of viral symptoms, may require more extensive diagnostic evaluation to investigate potential other causes. Congenital heart disease (CHD) and congestive heart failure are initially thought to be bronchiolitis, given that infants may present with symptoms very similar to those of bronchiolitis including poor feeding, tachypnea, rales, and wheezing. Congenital airway lesions, such as vascular rings, slings, teratomas, or bronchogenic cysts, may also present with symptoms suggestive of bronchiolitis. Aspiration from gastroesophageal reflux or tracheoesophageal “H-type” fistulas can cause symptoms precipitated by feeding that may mimic bronchiolitis. Other diagnostic considerations include congenital infections such as chlamydial or community-acquired pneumonia, foreign body aspiration, and allergic reactions. Recurrent symptoms should lead to consideration of cystic fibrosis, immunodeficiency, or asthma. It is often difficult to distinguish bronchiolitis from asthma (reactive airway disease) in older infants and children. However, the first episode of wheezing with upper respiratory tract symptoms in the young child should be considered to be bronchiolitis. Children with atopy, prior episodes of wheezing responsive to bronchodilator therapy, and a strong family history of asthma may indeed have asthma or be at increased risk of asthma (23). Children who have

wheezing beyond 12 months of age, are atopic, or have eosinophilia may be at increased risk of developing asthma as well (23). It is unclear whether children who develop lower respiratory tract illness have a predisposition to reactive airway disease or whether the viral infection itself causes pulmonary damage or immunologic changes leading to the development of asthma. On the other hand, repeated episodes of bronchiolitis are not uncommon, and infants who have had RSV bronchiolitis may be more prone to repeated episodes in the first year of life independent of their baseline risk for asthma. Therefore, in the absence of a strong family history, repeated wheezing episodes during the first year of life should be attributed to bronchiolitis and not asthma.

ED EVALUATION

No single fact or finding during emergency department (ED) evaluation is sensitive enough to predict which child will develop severe disease. A combination of history and physical examination findings is crucial in assessing any patient's risk for significant morbidity (Table 264.1). The history must include the gestational age at birth and whether there were any perinatal complications, such as CLD (formerly called *bronchopulmonary dysplasia*). As mentioned previously, underlying diseases or anomalies such as CHD, cystic fibrosis, or immunodeficiency, may also put the infant at increased risk. It is vital to determine whether the child is in the first few days of illness, in which case the disease may continue to progress and become more severe, or beyond the 3- to 5-day peak which marks the beginning of the convalescent stages of the illness. Social issues must also be considered as part of risk stratification, including the mother's ability to care for a sick infant or to return for additional care if the disease progresses.

TABLE 264.1
Risk Factors Associated with More Severe Disease

Moderate Risk	High Risk
Historic Factors	
Prematurity 34–37 wks	Prematurity <34 wks
Age <3 mos	History of cyanosis or witnessed apnea
Ill appearing on first 3 d of illness	Underlying condition:
	Pulmonary disease
	Congenital heart disease (pulmonary hypertension)
	Immunodeficiency
Physical Examination Findings	
General appearance: ill, not toxic	General appearance: toxic
Moderate accessory muscle use	Marked accessory muscle use
Respiratory rate: 60–70/min	Respiratory rate: >70/min
Oxygen saturation: <94%	Oxygen saturation: <90%
	Mottled, Prolonged capillary refill

The child's overall appearance is a sensitive indicator of disease severity. It is important to evaluate the respiratory rate, accessory muscle use for breathing, air exchange, and hydration status at presentation and after therapeutic trials. The oxygen saturation, as determined by pulse oximetry, is the single most objective predictor of more severe disease and should be measured on all infants and children presenting to the ED with bronchiolitis. Hydration status, as determined by physical examination (moistness of mucous membranes, capillary refill at the fingertip, presence or absence of tears), is crucial to assess since bronchiolitis-associated tachypnea accelerates insensible fluid losses and inhibits oral intake, sometimes leading to significant dehydration. Level of hydration as well as respiratory status play an important role in determining patient disposition.

Radiographs are not routinely indicated in infants or young children with bronchiolitis unless an alternative diagnosis is suspected or when there is severe disease. The majority of routine bronchiolitis radiographs show some degree of hyperaeration or peribronchial thickening (19). Infiltrates occur in $<10\%$ of children presenting for outpatient evaluation; the risk of airspace disease appears to be greater in children with oxygen saturation $<92\%$ or

severe distress. There is limited and controversial evidence that atelectasis on a chest x-ray correlates with progression to severe disease. More importantly, though, routine radiography may actually increase unnecessary use of antibiotics when atelectasis is misinterpreted as an infiltrate (19,25).

Evaluation of fever in infants younger than 2 or 3 months of age should be performed as per usual practice (see Chapter 222). Although the rate of bacteremia is low in infants with bronchiolitis, it may still occur in about 1% of RSV-positive infants. Furthermore, the risk of urinary tract infection is reduced in RSV-positive infants, but is still common enough to require screening (15). For infants older than 2 months of age with classic bronchiolitis, fever is unlikely to indicate serious bacterial illness and is more likely to be due to early viral illness, pneumonia, or otitis media (4,13,25). Therefore, routine culture of the blood or urine may be unnecessary. Complete blood cell counts are *rarely* useful and are weak screening tools. Microbiologic testing to determine viral etiology is indicated only for those with, or at significant risk of, severe disease (CLD, CHD) or for the purposes of infection control and isolation.

KEY TESTING

- Bronchiolitis is a clinical diagnosis based on history and physical examination findings. Chest radiography, blood tests, and viral testing are not routinely recommended for ED patients.

ED MANAGEMENT

To date, there is no strong evidence supporting the effectiveness of *any* single treatment for bronchiolitis (1,3,25). Most children presenting with bronchiolitis have mild or moderate severity of disease. Those with mild disease require only supportive therapy, which includes maintenance of hydration and respiratory support. Intravenous fluids may be required because of insensible losses due to respiratory distress, combined with poor oral intake. Normal saline boluses of 20 mL/kg and additional maintenance fluid may be required for those with signs of dehydration such as tachycardia,

sunken fontanel, and prolonged capillary refill. Oxygen supplementation is indicated if the patient's SpO_2 level is consistently below 90% or if the patient is in severe distress despite an adequate SpO_2. Suctioning may be helpful, but there is no evidence for the benefit of deep suctioning (3). There is some suggestion in the literature that nebulized 3% normal saline may be beneficial in breaking up secretions (14,25). The role of heliox in the management of bronchiolitis remains uncertain (3). Chest physiotherapy is not recommended.

The use of bronchodilators such as nebulized albuterol for bronchiolitis is controversial. (1,3,8). Clinical practice guidelines recommend that bronchodilators *not* be used routinely in the management of bronchiolitis. Although bronchodilators produce small short-term improvements in clinical scores, this must be weighed against the costs and adverse effects of these agents. Infants and children with bronchiolitis may undergo a trial of an inhaled bronchodilator, however—albuterol 0.15 mg/kg via nebulizer or 4 to 6 puffs via MDI with spacer and facemask. The effects should be assessed within 1 hour for objective improvement in oxygen saturation, lowering of the respiratory rate, or improved aeration. For those who do not improve, there is no need to continue further treatments (3). Nebulized racemic epinephrine has been considered more effective than β_2-agonists in several clinical trials and may be tried for those who do not respond to albuterol and will require hospitalization, but a number of recent studies do not support the routine use of epinephrine (3,8,10,21,25). A trial dose of 0.05 mL/kg of 2.25% epinephrine is an option for children who do not respond to albuterol, but treatment should not be continued in the absence of a clinical response within 1 hour.

Oral corticosteroids are not recommended in the treatment of bronchiolitis since there is no consistent evidence supporting their use (1,3,5–7,17,18,25). However, corticosteroids may provide some benefit in combination with racemic epinephrine and this suggests there may be a future role for them in combination with other therapies (17,25). Steroids should be considered for children with

multiple episodes of wheezing responsive to bronchodilator therapy, those with atopy, and those with a strong family history of asthma. Antibiotics are indicated only when a bacterial infection has been diagnosed, or for febrile neonates. Of note, more than 60% of children with bronchiolitis develop bacterial ear infections (4). Inhaled corticosteroids montelukast, cromolyn sodium, ribavirin, and immunoglobulins have all shown little evidence of clinical efficacy for bronchiolitis and are not recommended.

Children with moderate or severe respiratory distress should be allowed to assume a position of comfort, and 100% oxygen should be delivered. Suctioning of copious nasopharyngeal secretions may relieve some distress caused by airway obstruction. A trial of bronchodilators and/or racemic epinephrine should be delivered. Heated humidified oxygen administered by high-flow nasal cannula or nasal continuous positive airway pressure may be effective in preventing intubation and mechanical ventilation in severe cases of bronchiolitis (16). However, additional studies are necessary to determine what role these modalities should play in the management of severe bronchiolitis. Intubation is required for the child with severe respiratory distress or failure to respond to these measures.

CRITICAL INTERVENTIONS

- Use pulse oximetry to identify children with hypoxemia. This is the most specific and objective indicator of more severe disease. Cyanosis detectable on physical examination does not occur until the oxygen saturation is $<85\%$!
- Beware of dehydration, as infants with respiratory distress and copious secretions are at risk for poor feeding and have increased water losses due to fever and increased work of breathing.
- Suction the infant to help improve airway obstruction.
- Keep the infant in the position of comfort as long as possible and avoid agitating the patient.

DISPOSITION

Most infants and children with bronchiolitis do not require admission. Clearly, those in respiratory distress or with hypoxia or dehydration require intervention and admission. Among those with mild or moderate disease, no single factor can predict the need for admission (1,3,25). Children at high risk for developing more severe disease (see Table 264.1) should be considered for admission or close outpatient observation. Hospitalization should be strongly considered for infants at risk for apnea: premature infants younger than 37 weeks and <48 weeks after conception, full-term infants younger than 1 month of age, and infants with a prior apnea episode witnessed either by the family or the practitioner (23). Children who are early in the course of the illness or have moderate severity of illness that does not require admission should have follow-up arranged in 24 hours. Criteria for discharge include the following:

- No signs of severe respiratory distress.
- Caretaker is comfortable using bulb suctioning.
- Patient does not require supplemental oxygen.
- Patient's oral intake is adequate to prevent dehydration.
- Caretaker is comfortable and has resources available to take care of patient at home.
- Anticipatory guidance has been reviewed.
- Close primary care follow-up can be achieved.

Children with underlying medical conditions should have their subspecialist physicians consulted about treatment and indications for admission. For example, the pediatric cardiologist can determine whether the child with CHD has significant uncorrected pathology that creates a higher risk of deterioration. If the diagnosis of bronchiolitis is not clear, a pediatrician may offer further help with the differential diagnosis or workup.

Children with respiratory failure requiring intubation should be transferred to a facility with a pediatric intensive care unit. Children with underlying medical conditions or at high risk for severe disease

or mortality should also be transferred to a facility with pediatric subspecialists and a pediatric intensive care unit.

Common Pitfalls

- Failure to identify that the child is in the first few days of illness and may become progressively worse. Children who appear to have mild illness may progress over the next hours or days and thus require close outpatient follow-up. The caregiver should be given specific instructions of what to look for and when to return.
- Failure to assess the child's hydration status and to treat with intravenous fluid when indicated.
- Failure to identify the child with an underlying condition or a history of prematurity that put him or her at high risk for morbidity and mortality.
- Persistence in using bronchodilators despite no evidence of response. Less than 50% of infants with bronchiolitis respond to bronchodilators. If they have mild disease, they should be sent home with symptomatic care instructions and follow-up arrangements.
- Overuse of routine laboratory tests or radiographs in the infant or young child with bronchiolitis. Testing should be tailored to the individual patient.

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CHAPTER 265 Pneumonia

Ian McCaslin

Pneumonia is an inflammatory process of the pulmonary parenchyma. It is commonly the result of community-acquired infections both viral and bacterial including *Mycoplasma pneumoniae* and *Chlamydophila* species (formerly known as *Chlamydia*). Although mortality rates from childhood pneumonia in the United States have declined over the past half century, worldwide pneumonia kills approximately 1.2 million children annually, making it the leading cause of death in children under the age of 5 (1,2). Pneumonia is frequently diagnosed in US children, with outpatient visit rates ranging from 74 to 92 per 1,000 children <2 years old to 35 to 52 per 1,000 children 3 to 6 years old (3). Children in the first 2 years of life have higher attack rates, but children in the 2- to 4-year-old age group have a higher incidence of pneumonia complicated by empyema (4).

Low socioeconomic status, poor nutrition, underlying disease, crowded living conditions, and smoke exposure as well as immunocompromise including malignancy, sickle cell disease, HIV, or genetic disorders have all been implicated in increased risk of pneumonia.

Pneumonia may be divided into bacterial and other etiologies (i.e., viruses, fungi, or parasites), but in the majority of cases a microbiologic agent is never identified. Since children do not produce sufficient sputum to obtain an adequate sample for culture, differentiation of infection from colonization is problematic. Nasopharyngeal culture is rarely useful in identifying a presumed bacterial pathogen. Rapid and reliable diagnostic methods are rarely

available to the practicing physician. There are well-recognized seasonal variations in respiratory illness with late fall and winter peaks of lower respiratory tract illness due to viruses such as respiratory syncytial virus (RSV) and influenza A or B, but bacterial pneumoniae exhibit less seasonal variation.

A number of epidemiologic studies (5,6) have confirmed the importance of *Streptococcus pneumoniae* as the agent responsible for the majority of serious bacterial pneumoniae across all age groups beyond the newborn period. Introduction of the heptavalent pneumococcal conjugate vaccine in 2000, followed by the 13-valent vaccine in 2010, have resulted in dramatic reductions in the overall rate of invasive pneumococcal disease, including pneumonia in children <1 year of age (7,8). Rates of mixed infection of *S. pneumoniae* with either *M. pneumoniae* or *Chlamydophila pneumoniae* are relatively frequent in older children, suggesting that the historical classification of clinical pneumonia into "typical" and "atypical" categories should be discouraged. Viruses cause relatively more disease in younger infants and children, whereas *M. pneumoniae* and *C. pneumoniae* infections become more prevalent in the school-aged population. The most common viral agent is RSV, and evidence of coinfection of *S. pneumoniae* with RSV is common, particularly in younger children. Human metapneumovirus infection is a relatively common cause of respiratory infection in young children, with a spectrum of disease similar to that of RSV (9). *Staphylococcus aureus,* including community-associated methicillin-resistant *S. aureus* (CA-MRSA), causes abrupt and severe pneumonia and should be particularly considered during influenza season or in the presence of severe disease (10). *Mycobacterium tuberculosis* may cause pneumonia in healthy children and is often linked to high-risk exposures. Anaerobic bacteria may be implicated in a host who is susceptible to aspiration, particularly if there is evidence of abscess formation.

CLINICAL PRESENTATION

Symptoms and signs of pneumonia in children vary with age, duration of illness, and underlying condition rather than by bacterial versus viral etiology. Many children with early pneumonia do not have specific respiratory complaints and do not appear severely ill. The “classic” presentation of sudden onset of fever, chills, chest pain, and productive cough is very rare. In fact, febrile children who are ultimately found to have pneumonia frequently present with nonspecific historical and physical examination findings (11). Infants younger than 2 months of age may present with fever and tachypnea and no signs of pulmonary consolidation or clinical evidence of sepsis. Young children usually exhibit some combination of fever, tachypnea, and focal lung findings, associated with a chief complaint of cough, upper respiratory infection symptoms, decreased activity, and poor intake. Older children typically demonstrate a short period of prodromal symptoms, including rhinitis, low-grade fever, decreased appetite, and decreased activity. The proportion of cases of pneumonia due to *M. pneumoniae* and *C. pneumoniae* increases in children after 5 years of age (12). Infections with these organisms characteristically progress slowly over 3 to 5 days, with fatigue, sore throat, low-grade fever, and cough. Occult bacterial pneumonia presenting with abdominal pain, vomiting, and dehydration may be mistaken for acute appendicitis.

Few findings on physical examination exhibit good interobserver reliability. No single physical examination finding or combination of findings demonstrates adequate sensitivity for the clinical identification of pediatric pneumonia. Fever, respiratory rate, and pulse oximetry are objective, reproducible parameters that may help in the clinical diagnosis of pneumonia, and most children with either bacterial or viral pneumonia exhibit some fever and cough by history or examination (11,13). World Health Organization criteria for the clinical diagnosis of pneumonia are based primarily upon the presence of tachypnea and retractions and demonstrate poor sensitivity for the diagnosis in a US-based population (14). The definition of tachypnea varies with age and is conservatively suggested to be a respiratory rate of >60 per minute in infants,

>40 per minute in young children, and >20 per minute in those 5 years and older. While the respiratory rate alone is a poor predictor of pneumonia, infants and children ultimately diagnosed with pneumonia are more often tachypneic than not (15). The presence of hypoxemia, defined as saturation <90% at sea level, is difficult to detect on physical examination (16). Given that hypoxemia is well established as a risk factor for poor outcome in patients with respiratory disease, the simple measurement of oxygenation by pulse oximetry should be included in the initial evaluation of all symptomatic infants and children.

Certain combinations of clinical findings are characteristics of complicated lower respiratory tract disease. Grunting respirations with fever are nonspecific but should prompt further investigation. Rales, retractions, and localized diminished breath sounds are highly correlated with parenchymal disease. The presence of an associated pleural effusion is suggested by unilateral decreased breath sounds and dullness to percussion.

DIFFERENTIAL DIAGNOSIS

A number of conditions may be mistaken for community-acquired pneumonia. Lower respiratory illness characterized by cough, rhinitis, fever, and either wheezing or dry crackles on examination in children younger than 2 years of age is characteristic of bronchiolitis. Caused principally by RSV and human metapneumovirus, bronchiolitis is not improved with antibiotics, and can run a protracted course over 1 to 2 weeks. Sudden onset of high fever and signs of pneumonia after several days of lower respiratory symptoms consistent with RSV should prompt concern for bacterial superinfection and warrants antibiotic treatment. More severe disease can present with cyanosis and signs of respiratory failure, particularly in infants with underlying medical conditions such as congenital heart disease. Reactive airways disease affects nearly 10% of children, and acute episodes of difficulty breathing and cough, particularly at night, are commonly triggered by viral respiratory infections.

Foreign body aspiration, heart disease, and other conditions may be mistaken for infectious pneumonia. A history of a choking episode should be sought in all young children presenting with suspected pneumonia.

Myocarditis is frequently initially misdiagnosed as pneumonia; an ill appearance that suggests pneumonia but is not accompanied by a diagnostic chest film should prompt clinical suspicion and an EKG, and possibly an echocardiogram.

Congenital heart disease is suggested by evidence of diminished peripheral perfusion, congestive heart failure, or evidence of poor growth on examination. Depending upon the specific defect, cardiomegaly on chest radiography or diminished pulse oximetry readings that do not respond to oxygen administration are often supportive of the diagnosis.

ED EVALUATION

In most instances the diagnosis of pneumonia is based upon the history and physical examination alone. A chest radiograph is not required but may be helpful in establishing the diagnosis and excluding noninfectious causes. Radiographs ordered empirically for febrile children younger than 10 years of age with no lower respiratory tract findings, signs of respiratory distress, tachypnea, or hypoxia will reveal an occult infiltrate in approximately 5% of cases (11). Extreme dehydration or early clinical presentation may lead to false negative chest radiography in children subsequently diagnosed with acute bacterial pneumonia.

Chest radiography does not establish the etiology of a community-acquired pneumonia in children. Diffuse peribronchial thickening with hyperinflation of the lungs from air trapping is, however, more consistent with bronchiolitis or a viral etiology in the younger child, whereas focal lobar consolidation and pleural effusion in the older child suggests *S. pneumoniae* or, less likely, *M. pneumoniae.* Chest radiographs should always be obtained in patients with suspected or documented hypoxemia who are in respiratory distress. Both blood culture and complete blood count (CBC) with differential should be

obtained for the hospitalized patient but are not routinely indicated in the outpatient management of pneumonia. The contribution of routine laboratory testing to patient outcomes can be variable. Knowledge of the peripheral white blood cell count or other acute-phase reactant levels at the time of presentation generally does not assist selection of specific therapy or consideration for admission (16). The prevalence of bacteremia is low, and most positive blood cultures are contaminants (17). Moreover, while bacterial disease is suggested by a peripheral white blood cell count $>20{,}000/mm^3$, the CBC does not reliably differentiate between specific etiologies of pneumonia.

ED rapid testing for influenza A and B viruses is recommended during seasonal outbreaks; a positive test can significantly reduce the number of laboratory tests and radiographs ordered, and likewise reduces the number of antibiotic prescriptions (18). Other diagnostic tests such as serology, antigen assay, PCR, and nasopharyngeal swab for culture are considered investigational and are of little benefit in clinical decision making in the outpatient setting (19). Thoracentesis and culture of pleural effusion should be reserved for ill-appearing children or those with immunocompromise who require critical care admission, and in cases where chest tube drainage or operative management is recommended for suspected empyema or abscess.

KEY TESTING

- Early pulse oximetry determination, and oxygen supplementation if $<92\%$
- Influenza A and B rapid diagnosis testing during seasonal outbreaks
- Chest radiography if more severe disease is suspected
- Complete blood count and blood culture if hospitalization is considered

ED MANAGEMENT

After a careful history and physical examination, coupled with a judicious use of radiography and laboratory markers, the emergency physician's primary tasks are to initiate therapy and determine patient disposition. Ill-appearing patients should be placed on continuous cardiorespiratory monitoring while in the ED and dehydrated patients with pneumonia should be given an intravenous (IV) saline fluid bolus of 20 cc/kg. Initial pulse oximetry readings $<92\%$ on room air or an ill appearance should prompt oxygen administration by non-rebreather mask until the response to therapy can be determined. A trial of bronchodilator aerosols may be considered for patients with associated wheezing or history of reactive airways. Antitussive agents are generally ineffective and are not recommended. Purified protein derivative (PPD) placement should be considered for all patients with newly diagnosed pneumonia.

CRITICAL INTERVENTIONS

Infants younger than 8 weeks of age should be hospitalized after culture of blood, urine, and CSF, and empiric administration of IV ampicillin and cefotaxime. Infants aged 8 weeks to 3 months with uncomplicated pneumonia should be admitted to the hospital after culture of urine and blood in the ED followed by administration of IV cefotaxime or ceftriaxone. Narrow-spectrum IV penicillin or ampicillin may be administered to fully immunized children requiring hospitalization in areas where local epidemiologic data demonstrate low-level penicillin resistance for invasive *S. pneumoniae*. Parenteral antibiotic therapy may be initiated with cefuroxime or ceftriaxone for hospitalized children who are not fully immunized, in regions of higher-level penicillin resistance, or for children with severe infections, including those with empyema (16). Inpatient treatment for infections suspected to be caused by either *M. pneumoniae* or *C. pneumoniae* may include IV azithromycin. Children with severe pneumonia require additional empiric coverage for *S. aureus* , including CA-MRSA. Initial treatment should include IV vancomycin in addition to IV

ceftriaxone. These children should be considered for admission to an intensive care unit. Emergency providers should maintain awareness of regional antimicrobial susceptibility reports.

DISPOSITION

Most children with pneumonia can be managed as outpatients, and antibiotic therapy is not indicated for patients with suspected bronchiolitis or if findings are consistent with a viral syndrome. Children beyond 3 months of age with uncomplicated pneumonia may be treated for 10 days with amoxicillin, cefuroxime, or clindamycin in penicillin-allergic patients (16).

For school-aged children where *M. pneumoniae* and perhaps *C. pneumoniae* are possible etiologic agents in addition to *S. pneumoniae,* macrolides including azithromycin or erythromycin are acceptable options. Though not approved for pediatric use, oral levofloxacin appears safe and effective in children with pneumonia if significant resistance to *S. pneumoniae* is suspected (20). Children in whom fluid intake or compliance is a concern may be given parenteral ceftriaxone (50 mg/kg as a single dose) for coverage of initial 24 hours of therapy.

Printed language-appropriate discharge instructions should be reviewed with caretakers prior to discharge from the ED. Attention to adequate hydration, fever control, medication compliance, and observation for worsening condition should be emphasized. The emergency physician may wish to communicate directly with the primary care provider prior to patient discharge. All children with pneumonia diagnosed in the ED should be reevaluated within 24 hours. Fever often persists for 48 hours into the course of treatment of bacterial pneumonia.

Indications for admission include age younger than 4 months, respiratory compromise, persistent oxygen requirement, inability to retain oral fluids or medication, concerning underlying medical condition, and uncertain home environment. Patients with immunocompromise, large pleural effusion, respiratory distress, evidence of hypoxemia requiring FiO_2 greater than feasible in a

general care setting, or suspicion of CA-MRSA pneumonia should be admitted to an intensive care unit or transferred to a facility where appropriate monitoring and critical intervention is ensured.

Common Pitfalls

- Failure to diagnose a patient with foreign body aspiration or myocarditis.
- Treating for bacterial pneumonia in the young well-appearing wheezing child.
- Failure to ensure understanding of discharge instructions, including follow-up in 24 hours.

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CHAPTER 266 Arrhythmias in Children

Syana Sarnaik

Pediatric patients present with three basic categories of rhythm disturbance—fast, slow, or absent. Asystole and bradyarrhythmias are primarily seen in resuscitation settings and are discussed in Chapter 217. This chapter discusses dysrhythmias unique to pediatric patients outside the realm of critical resuscitation.

SUPRAVENTRICULAR TACHYCARDIA

Paroxysmal supraventricular tachycardia (SVT) is the most common pediatric tachydysrhythmia, and may present to the emergency department (ED) in children of almost any age. Infants may tolerate SVT well for 12 to 24 hours, but if the rhythm is sustained for longer periods, signs of congestive heart failure (CHF) may develop (1). Manifestations of CHF in infants include irritability, tachypnea, and poor feeding and, in more severe cases, mottling and cyanosis. Once CHF develops, the infant's ability to compensate is compromised, and the condition can deteriorate rapidly. Older children may have chest pain, palpitations, syncope, fatigue, and dyspnea. In general, the longer SVT continues, the more severe the symptoms. Because of decreased diastolic filling time, tachycardia can lead to decreased stroke volume and therefore decreased cardiac output. Sustained tachycardia is also associated with increased myocardial oxygen demand and decreased time for diastolic myocardial perfusion. Thus, SVT can lead to CHF even after the tachycardia has resolved.

There are three main categories of SVT: AV reentrant tachycardia; atrial tachycardia; and junctional tachycardia. The majority of SVTs are due to reentrant tachycardia. Atrial tachycardias include atrial flutter (characterized by reentrant circuits within the atria), atrial fibrillation, and ectopic atrial tachycardia. Junctional tachycardia is exceedingly rare outside the immediate postoperative phase of open heart surgery.

The etiology of the SVT varies by age group. In infants, more than 50% is idiopathic, and 10% to 20% is associated with Wolff–Parkinson–White (WPW) syndrome (2). The remainder of cases occur after cardiac surgery or in association with congenital heart defects that predispose to SVT, such as Ebstein anomaly, single ventricle physiology, and congenitally corrected transposition of the great arteries. Older children are more likely to have WPW, concealed bypass tracts, or congenital heart disease. Young infants are more likely to present with CHF.

Electrocardiographic Findings

The typical electrocardiogram (ECG) of a patient with SVT shows a rapid rate, a narrow QRS complex, and an absence of identifiable P-waves (Fig. 266.1). In reentrant SVT, the circuit is usually too short to generate a substantial P-wave deflection or the P-wave may be buried in the QRS or T-wave. However, when P-waves are visible, the P-axis is usually abnormal. In reentrant tachycardia, the rhythm is usually regular, with a rate of 220 to 320 beats/min in infants and 150 to 250 beats/min in older children. If the rate varies over time, the rhythm is less likely to be reentrant and more likely to be sinus tachycardia secondary to fever, pain, agitation, dehydration, or possibly an ectopic atrial tachycardia.

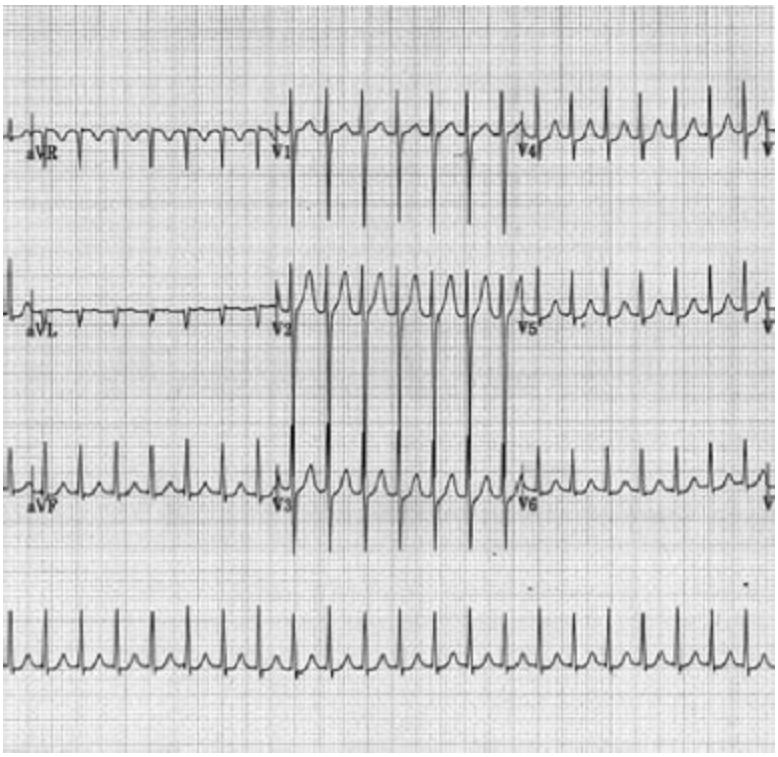

FIGURE 266.1 Supraventricular tachycardia.

ED MANAGEMENT

In an asymptomatic hemodynamically stable patient, the initial approach is to perform vagal maneuvers, followed if necessary by pharmacologic or electrical cardioversion. The effectiveness of vagal maneuvers is related to the patient's age, with the success rate lower in infants and young children (3,4). Nevertheless, the occasional conversion justifies their initial trial. For infants and young children, the application of a bag of crushed ice to the face (to induce the diving reflex) for up to 30 seconds is an effective vagal stimulus. Older children may be asked to blow into an occluded straw or to perform a Valsalva maneuver, which requires cooperation and usually a sustained effort of 15 seconds. Because of the risk of retinal detachment, ocular compression is not a recommended vagal maneuver. The majority of SVTs are reentrant and respond to intravenous adenosine (5). Since its hemodynamic side effects are typically mild and very brief, a diagnostic dose of adenosine can be

given safely if the type of underlying rhythm is not clear (Fig. 266.2).

FIGURE 266.2 Adenosine dose uncovering atrial flutter.

Adenosine causes transient AV block by hyperpolarizing the AV node. This may cause some patients to have an uncomfortable sensation but lasts only a few seconds. The initial recommended dose of adenosine is 0.1 mg/kg (initial maximum of 6 mg, followed by repeat doses of 12 mg) as a rapid bolus, followed immediately by a rapid flush of 5 to 10 mL of normal saline. Given adenosine's very short half-life of <1.5 seconds, it is important to use a three-way stopcock for a rapid flush immediately after the drug is administered. When administering adenosine, an ECG should be obtained prior to, and during, the conversion so as to document the underlying rhythm.

The patient may have a short break in the tachycardia due to adenosine followed by early recurrence requiring additional doses of adenosine. Infants may require up to 0.3 mg/kg by rapid intravenous push in a peripheral intravenous line, preferably positioned in the right arm. The adenosine dose can generally be lower if central venous access is obtained.

In general, calcium channel blockers are contraindicated in infants, as they may produce extreme bradycardia and hypotension in children younger than 1 year (6). In stable patients, other medications can be used, with input from a pediatric cardiologist. These include amiodarone (5 mg/kg), which slows AV nodal conduction and interrupts reentrant circuits, and procainamide (15 mg/kg over 15 minutes). Amiodarone and procainamide should not

routinely be given together, as hypotension and QT prolongation may occur. A pediatric cardiologist should also be involved after successful conversion of SVT for further management and prevention of recurrence. Since patients with SVT by definition have an acquired or anatomic defect of the conduction system, and since they may deteriorate rapidly, it is prudent to have equipment immediately available for airway management and defibrillation.

Immediate synchronized cardioversion with 0.5 to 1 J/kg is indicated if the patient is hemodynamically unstable. Cardioversion may not be successful in the presence of hypoxia or an acid–base disorder, so there should be careful attention to concurrent management of airway, breathing, and circulation (ABCs). Cardioversion can induce ventricular dysrhythmias in patients who are taking digoxin. In cases of digoxin-related ventricular arrhythmia, lidocaine can be used (1).

COMPLETE HEART BLOCK

Complete heart block may be either congenital or acquired. It may be associated with structural heart defects or occur postoperatively after repair of a congenital heart lesion, especially Tetralogy of Fallot (TOF) or ventricular septal defect (VSD). Maternal collagen vascular disease (e.g., lupus) may also result in transplacental passage of maternal immunoglobulins that result in an abnormal fetal conduction system. Infants typically present with bradycardia and a ventricular rate usually less than 75 beats/min. ECG findings include dissociation between atrial and ventricular depolarization and either a wide or a narrow QRS, depending on whether the escape beats are junctional or ventricular. The clinical presentation in infants may range from asymptomatic to frank CHF. Older children may have syncope, fatigue, and decreased exercise tolerance. In unstable patients, management focuses on stabilization of the ABCs and consideration of an infusion of isoproterenol (0.02 to 0.5 μg/kg/min) or epinephrine (0.05 to 0.5 μg/kg/min) to increase the junctional or ventricular escape rate, pending pacemaker placement. Improving AV nodal conduction with

atropine can be considered in first- and second-degree heart block but is not helpful in third-degree heart block. An external pacer should be applied while awaiting more definitive management.

VENTRICULAR DYSRHYTHMIAS

Isolated premature ventricular contractions (PVCs) may occur in up to 15% of normal newborns, 33% of normal adolescents, and 66% of patients with repaired heart disease (e.g., TOF, VSD, AV canal defects, transposition of the great vessels, and aortic stenosis) (7). An incidental finding of isolated PVCs is not worrisome, provided the remainder of the ECG is normal and the frequency of PVCs decreases with bedside exercise. However, multiform or complex ectopy (couplets, triplets), especially in an ill-appearing or febrile child, can be a presenting sign of myocarditis.

Ventricular tachycardia (VT) is defined as a series of three or more PVCs at a rate of 120 to 200 beats/min. QRS complexes are wide, and T waves have a polarity opposite the QRS. VT does not occur in children with normal hearts and usually indicates serious underlying myocardial pathology, dysfunction, or toxicity. Although uncommon, hemodynamically unstable ventricular arrhythmia requires immediate aggressive treatment. Cardiac output is seriously compromised in VT, and the rhythm is vulnerable to rapid deterioration to ventricular fibrillation. In the occasional patient who is stable, amiodarone should be given slowly, at a dose of 5 mg/kg over 20 to 30 minutes to avoid hypotension.

Unstable patients with VT require immediate synchronized cardioversion with 2 to 4 J/kg. Patients with pulseless VT require immediate defibrillation starting at 2 J/kg.

Electrolyte abnormalities should be considered in patients who are refractory to cardioversion. Drug ingestions causing dysrhythmias may require specific therapy (e.g., bicarbonate in patients with tricyclic overdose). In patients with digoxin toxicity, synchronized cardioversion should be avoided and treatment with digoxin-specific Fab fragments initiated.

ATRIAL FIBRILLATION

Atrial fibrillation is usually associated with structural heart disease such as dilated atria, myocarditis, digitalis toxicity, or previous intra-atrial surgery (e.g., Fontan procedure for hypoplastic left heart syndrome).

The ECG is characterized by an extremely fast atrial rate or a lack of recognizable atrial activity and an irregularly irregular ventricular response with narrow QRS complexes. Rate control can be accomplished by cautious administration of a beta blocker or calcium channel blocker. Digoxin may be started for longer-term control but is not effective acutely. In patients with atrial fibrillation and WPW syndrome, there may be rapid conduction to the ventricles and a risk of deterioration with drugs that preferentially slow AV node conduction, such as calcium channel blockers. Consultation with a cardiologist is strongly recommended (2).

For rhythm conversion, class I antiarrhythmic agents (i.e., quinidine, procainamide, flecainide) or the class III agent amiodarone may be used. Unstable patients require synchronized cardioversion, using 0.5 J/kg.

CRITICAL INTERVENTIONS

- Stabilize ABCs.
- Run a rhythm strip while administering adenosine to convert SVT.
- Be prepared for deterioration of dysrhythmia or patient's overall condition.

Common Pitfalls

- Rapid administration of amiodarone in stable patients.
- Failure to recognize complete heart block and failure to place a pacemaker as needed.
- Intravenous calcium channel blockers are almost always contraindicated in infants.

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of Syana Sarnaik and Ajit Sarnaik to the content of this chapter.

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CHAPTER 267 Cardiac Murmurs

David G. Nelson

Heart murmurs are common in infants and children. Although most murmurs are benign, a few may be signs of serious heart disease, either congenital or acquired. The emergency physician must be able to determine which patients need emergency department (ED) evaluation, should be referred to their primary care provider, or be seen by a pediatric cardiologist.

CLINICAL PRESENTATION

Most cardiac murmurs are the result of normal turbulence and are therefore physiologic, also referred to as *benign, innocent,* or *functional.* In this case, the infant or child generally does not have signs or symptoms of systemic or cardiac disease. However, patients with pathologic murmurs may be ill-appearing or may have features of cardiac disease that must be evaluated and managed acutely in the ED. Evaluation begins with a thorough history and cardiovascular examination, including evaluation of murmur characteristics, peripheral perfusion, and associated signs and symptoms. It is unusual for a murmur to be the only sign of serious cardiac disease in a child without systemic signs or symptoms, with the exception of neonates or infants who have yet to display fulminant disease.

DIFFERENTIAL DIAGNOSIS

Benign Functional Murmurs

As the name indicates, these common benign murmurs of childhood are caused by blood flow within the normal heart (or by vibrations of

normal intracardiac structures) and share a number of common characteristics. They tend to be short, systolic not holosystolic, and soft and vibratory. In addition, they tend to vary with patient position, hydration status, and respiration. Patients have normal ECG and x-ray findings. These murmurs are often associated with particular age groups, locations in the chest, and other characteristics described in Table 267.1.

TABLE 267.1
Innocent Murmurs

Murmur	Approximate Age	Timing and Grade	Origin	Best Heard	Factors
Peripheral pulmonic stenosis (PPS)	Newborn–3 mos	Systolic ejection Soft grade 1–2/6	Bifurcation of pulmonary artery	LUSB–transmits to axillae and back	Increased with increased flow (anemia, fever, exercise, excitement)
Stills (vibratory) most common	3–6 yrs	Systolic ejection Grade 2–3/6	Vibration from left heart	Mid LLSB and cardiac apex	May disappear with Valsalva maneuver
Venous hum	3–6 yrs	Continuous Grade 1–2/6	Jugular vein and SVC	Supra and infraclavicular areas	Heard when patient is upright. Extinguished when patient is supine or head turned
Pulmonary ejection	8–18 yrs	Systolic ejection Soft grade 1–3/6	Pulmonary valve	LUSB	Increased with increased flow (anemia, fever, exercise, excitement)

LUSB, left upper sternal border; LLSB, left lower sternal border.

Pathologic Murmurs

Pathologic (or organic) murmurs are the result of turbulent blood flow through abnormal cardiac structures or vessels (Table 267.2). *Systolic murmurs* are due to either regurgitation or ejection. Regurgitation murmurs begin with the first heart sound (S1) and are caused either by insufficiency of an atrioventricular valve or by a left-to-right shunt through a ventricular septal defect (VSD). Ejection murmurs also start just after the S1 heart sound and are caused by a stenotic valve (see Table 267.2). *Diastolic murmurs* begin with the second heart sound (S2) and are caused either by the flow of blood from the aortic or pulmonary artery back into the ventricle, or by increased flow across a normal or stenotic mitral or tricuspid valve. These are almost always associated with underlying heart disease.

TABLE 267.2
Features Suggestive of a Pathologic Murmur

Any diastolic murmur
Systolic murmurs louder than 3/6, continuous, or associated with a thrill
Murmurs associated with clicks, rubs, abnormal splitting, or asymmetric pulses
Cyanosis or respiratory distress
Abnormal cardiac size or silhouette on chest radiograph
Abnormalities on electrocardiogram

ED EVALUATION

The evaluation of murmurs is largely based on clinical history and physical examination findings. More detailed historical elements appear in Table 267.3. It is vital to document whether a murmur is known to the family or patient and, if so, how long the patient had it and whether it has been evaluated by a cardiologist or treated surgically. Does the murmur result in associated symptoms such as poor feeding, edema, cyanosis, or shortness of breath? Does the older child have difficulty keeping up with friends while playing? Is there any family history of Marfan syndrome or sudden death?

TABLE 267.3
Questions to Ask Regarding a Patient with a Heart Murmur

Is it a known murmur? For how long? Has it been evaluated? Do you know what it is? How often does the child need to see the cardiologist? Has there been cardiac surgery?
Family history: Congenital heart disease, sudden cardiac death, Marfan disease
Associated symptoms such as edema, cyanosis, difficulty breathing, poor feeding, poor weight gain, congenital defects
Does the patient tire easily? Have trouble climbing stairs? Is the child unable to run during recess or gym class? Any syncopal or presyncopal episodes?
Recent illnesses (e.g., sore throat, viral infections) preceding the onset of murmur, especially in older children or adolescents. History of Kawasaki disease or syndrome

The murmur itself is characterized by four qualities: Timing, intensity, quality, and location. The timing is based on the murmur's relationship to the first (S1) and second (S2) heart sounds. Systolic murmurs are heard between S1 and S2, whereas diastolic murmurs are between S2 and S1. Continuous murmurs persist through S2. Murmur intensity (or loudness) is based on a scale of 1 to 6. Grades 1 to 2 are hardly appreciable, grades 3 to 5 are easily heard with a stethoscope, and grade 6 is audible with the stethoscope off the

chest. Murmur quality describes the murmur with such terms as musical, rumbling, harsh, vibratory, soft, blowing, or high-pitched. The location of the murmur on the chest is often helpful in establishing its etiology (see Table 267.4).

TABLE 267.4
Auscultation Locations of Common Systolic Murmurs in Children

Left upper sternal border: Pulmonic area
Pulmonic valvular stenosis
Atrial septal defects
Innocent pulmonic ejection murmur
Innocent peripheral pulmonic stenosis
Patent ductus arteriosus
Left lower sternal border
Innocent stills (vibratory) murmur
Ventricular septal defects
Endocardial cushion defects
Tetralogy of Fallot
Hypertrophic cardiomyopathy
Apex
Innocent stills (vibratory) murmur
Mitral regurgitation
Aortic stenosis
Hypertrophic cardiomyopathy
Right upper sternal border: Aortic area
Aortic valvular stenosis
Coarctation of the aorta

Associated signs and symptoms, beyond vital signs and oxygen saturation, can be helpful (Table 267.5). These include four-extremity blood pressures (looking for coarctation of the aorta). The routine physical examination of neonates and infants should include palpation for femoral pulses to detect otherwise occult cases of aortic interruption. In addition, clinicians should look for associated signs of heart failure, including edema, distended neck veins, liver enlargement, and respiratory distress. Dysmorphic features or evidence of growth retardation are other indicators that a murmur may be pathologic in nature.

TABLE 267.5
Associated Signs and Symptoms

Respiratory
Tachypnea or grunting may be a sign of failure
Auscultate for crackles
Fever
Consider infective endocarditis
May accentuate an innocent murmur
Cyanosis
Differentiate cardiac versus respiratory etiology
Assess for chronic hypoxia with clubbing of fingers
Pulses
Decreased, especially femoral
Cardiac failure
Cardiogenic edema is more likely to be pitting
Neck vein distention
Hepatosplenomegaly
Nutritional status
Poor weight gain or weight loss

KEY TESTING

- Neonates or infants (less than 6 months)—benign or pathologic murmur
  - Oxygen saturations, four-extremity blood pressures
  - Chest x-ray
  - If ill—cardiology consultation, echocardiogram
- Children and adolescents (pathologic murmur or systemic signs or symptoms of cardiac disease)
  - Oxygen saturation
  - Chest x-ray, EKG
  - Cardiac consultation or echocardiogram

ED MANAGEMENT

The management of a heart murmur detected in the ED depends on whether there are associated signs or symptoms suggestive of underlying cardiac disease. A number of ancillary diagnostic tests are available to aid in the diagnosis (Table 267.6).

TABLE 267.6
Ancillary Diagnostic Tests

Chest x-ray
Heart size and silhouette
Pulmonary vasculature (normal, diminished, or increased)
Electrocardiogram
Often normal
Dysrhythmias
Ventricular or atrial enlargement
Practitioner should be aware of significant differences in "normal" based on age
Blood tests
Complete blood count, sedimentation rate, blood culture, ASO (when considering rheumatic heart disease, endocarditis or Kawasaki syndrome)
Blood gases
Echocardiography
Provides definitive diagnosis
Not routinely used in emergency department except for ill patients or those with signs of heart failure or congenital heart disease

These tests need not be ordered routinely, but may be considered if the history and physical examination suggest a pathologic murmur. Some tests (e.g., chest x-ray and ECG) may be obtained as a baseline to help with assessment and to assuage parents' anxiety.

CRITICAL INTERVENTIONS

- Detailed history to identify historical or physical signs of heart disease.
- Consider infective endocarditis or rheumatic heart disease if a new murmur is noted in an older child with fever.
- Order an ECG and chest x-ray if any other signs or symptoms of pathology are present.
- If there is cardiomegaly on x-ray or the patient is ill-appearing, order a stat echocardiogram.

DISPOSITION

The emergency physician's primary goal is not to definitively diagnose the underlying lesion responsible for a murmur, but to assess the patient and provide a safe disposition. If it is determined a murmur is innocent, the child may be safely discharged home with

routine follow-up with the pediatrician or family practitioner. However, as with many conditions in pediatrics, the parents' anxiety may persuade the clinician that follow-up with a pediatric cardiologist is advisable. If it is suspected that the murmur is pathologic but the patient is clinically stable and the family is reliable, a call to the pediatric cardiologist is indicated to formulate an outpatient treatment plan, including prompt follow-up.

Common Pitfalls

- Failure to recognize a diastolic murmur, which is typically pathologic.
- Failure to recognize associated subtle signs and symptoms such as tachycardia, tachypnea, or failure to thrive as signs of serious heart disease.
- Failure to consult a cardiologist for pathologic murmurs.
- Failure to order an echocardiogram in an ill-appearing patient with a murmur.

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of Edward J. Bayn, Annalise Sorrentino, and Steven Baldwin to the contents of this chapter.

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CHAPTER 268

Congenital Heart Disease and Congestive Heart Failure

Ann M. Dietrich, Leslie Mihalov, and Katherine Mizelle

Congenital heart disease occurs in nearly 1% of live-born infants and must be recognized as early as possible in order to guide definitive medical and surgical management. At least 15% of congenital heart defects (CHDs) are associated with genetic conditions and about 20% to 30% of people with a CHD have other physical, developmental, or cognitive disorders (1). Routine neonatal examination fails to detect over half of infants with congenital heart disease. Many are discharged from the nursery before having a diagnosis made, and almost one-third of infants with critical heart lesions present to medical attention during the first week of life at the time of closure of the ductus arteriosus (2). Initial presentations range from the subtle (poor feeding) to the fulminant (shock or profound cyanosis), making congenital cardiac disease an important consideration in the differential diagnosis of any ill infant or young child. Congenital cardiac lesions can be classified by their mode of presentation and for the purposes of this chapter will be discussed in the following order: (1) cyanotic heart disease, (2) acyanotic heart disease, and (3) congestive heart failure (CHF).

CYANOTIC HEART DISEASE

CLINICAL PRESENTATION

Cyanosis is relatively infrequent in pediatric patients and is more commonly due to lung disease than heart disease. Cardiac lesions leading to cyanosis result from one of the three mechanisms: (1) obstruction of blood flow to the pulmonary circulation, (2) return of deoxygenated systemic blood back to the systemic circulation without passing through the lungs, or (3) inability of pulmonary venous blood to return to the left atrium and thence to the systemic circulation.

It is vital to differentiate between peripheral cyanosis (acrocyanosis, or discoloration of the extremities), which is particularly common in neonates (e.g., in a cold child or in a child with decreased peripheral perfusion), and central cyanosis (likely secondary to central nervous system depression, pulmonary disease, sepsis, metabolic disease, toxic ingestion, or cardiac disease).

The most common causes of cyanotic congenital heart disease are transposition of the great arteries (TGA), tetralogy of Fallot (TOF), tricuspid atresia, and obstructed total anomalous pulmonary venous return (TAPVR). Pulmonary atresia/critical stenosis and truncus arteriosus may also cause cyanotic congenital heart disease, but are less common and not discussed here. Table 268.1 lists typical radiographic and electrocardiographic findings in patients with cyanotic congenital heart disease.

TABLE 268.1
Cyanotic Congenital Heart Disease

Diagnosis	Chest Radiograph	ECG Findings
Tetralogy of Fallot	Normal/large heart with decreased PVMS "boot-shaped" appearance	Right ventricular hypertrophy, RAD (+120 to +150), right atrial hypertrophy
TGA	Mildly enlarged heart with increased PVMS "egg on a string" appearance	RAD, right ventricular hypertrophy
Tricuspid atresia	Normal/large heart with decreased PVMS	Leftward-superior axis, decreased right ventricular forces, LVH
TAPVR (with pulmonary venous obstruction)	Small heart with pulmonary edema	RAD, RVH

ED EVALUATION

The underlying physiology and presentations of cyanotic heart lesions, while seemingly complex, relies heavily on appreciating the importance of maintaining communication between the right- and left-sided circulatory systems in ductal-dependent lesions. Finally, the majority of children living with cyanotic heart disease as they progress through the course of multiple procedures have room air oxygen saturations of <90%. It is important to query caregivers about the patient's baseline oxygen saturations to have an informed sense of how to stratify the severity of a patient's current presentation (Table 268.1)

Transposition of the Great Arteries

TGA is the most common cyanotic congenital heart lesion to present in the neonate, and the second most common cyanotic congenital cardiac abnormality (6). It accounts for 5% of all congenital heart disease, and is more common in males. In a heart with D-transposition of the great vessels, the pulmonary and systemic circulations are isolated and in effect independent of one another, making a connection between the two systems via either an atrial/ventricular septal defect (ASD/VSD) or a patent ductus arteriosus (PDA) critical for survival.

Patients typically present in the newborn period with cyanosis and tachypnea but are not generally dyspneic. On auscultation, there is a loud, single S2. A systolic murmur may also be appreciated if an associated VSD is present or if there is pulmonary stenosis. Radiographically, TGA may present with mild cardiomegaly and increased pulmonary vascular markings, with a narrowed mediastinum ("egg on a string" appearance), but the majority of newborns with TGA have a normal-appearing chest x-ray. The electrocardiogram (ECG) is generally not diagnostic, showing the expected rightward axis and prominent right ventricular forces seen in neonates.

Management focuses on stabilization and allowing mixture of blood between the two circulatory systems. A prostaglandin E1

(PGE1) infusion can improve oxygenation by opening the ductus arteriosus to allow bidirectional mixture of the blood (see ED Management). Early involvement by a pediatric cardiologist is critical. Patients may require an emergent procedure for stabilization, such as a Rashkind atrial balloon septostomy, followed by definitive operative repair. Operations used for TGA include the Mustard, Senning, and arterial switch procedures. The arterial switch procedure is preferable because the right ventricle functions poorly as a normal systemic ventricle as the child ages, and there is a higher incidence of arrhythmias with procedures dependent on intra-atrial baffle procedures. To date, survivors of the arterial switch operation have much lower morbidity.

Tetralogy of Fallot

TOF is the most common form of cyanotic congenital heart disease beyond early infancy, representing 6% to 10% of all children with a CHD. Males and females are affected equally. The four defects comprising the tetralogy are: (1) VSD, (2) pulmonary stenosis, (3) right ventricular hypertrophy, and (4) overriding aorta.

In the newborn period patients typically present with a murmur. Clinical symptoms depend on the degree of right ventricular outflow tract (RVOT) obstruction. Initially, most infants are asymptomatic and only mildly cyanotic. As the RVOT obstruction progresses, the infant becomes increasingly cyanotic. Only about 25% of infants with TOF are markedly cyanotic at birth, and this subset can present in the first few days of life with acidosis due to severe cyanosis as a result of closure of the ductus arteriosus. On physical examination, the infant may have a right ventricular heave on palpation, a single S2 (pulmonic valve closure not heard), and a systolic ejection murmur at the left mid to upper sternal border (the intensity of which varies inversely with the degree of RVOT obstruction). A continuous murmur due to a PDA or collateral vessels may also be present. An ECG will generally demonstrate right axis deviation and right ventricular hypertrophy. A chest radiograph characteristically shows a normal heart size with decreased pulmonary vascular

markings, and a deficient main pulmonary artery segment resulting in a “boot shape” appearance of the heart.

Cyanotic or hypoxemic episodes “tet spells” are seen in some patients with TOF and typically consist of hyperpnea, irritability, and increasing cyanosis along with a decreased intensity of the underlying heart murmur. These episodes are frequently initiated by crying, and can also be precipitated by acute hypovolemia and tachycardia. During a “tet spell,” the murmur of pulmonary stenosis will markedly decrease in intensity. A decrease in systemic vascular resistance along with increased resistance to flow across the RVOT increases the right-to-left shunting across the VSD, which causes hyperpnea; the subsequent, increase in systemic venous return further promotes an increase in right-to-left shunting (see ED Management).

All patients with TOF will ultimately require surgical intervention. In a very young infant with severe RVOT obstruction and recurrent “tet spells,” palliative surgery to augment pulmonary blood flow involves surgical placement of a shunt, either a Blalock–Taussig shunt (subclavian artery to the ipsilateral pulmonary artery, or a central shunt [aorta to pulmonary artery]). Definitive surgical repair includes patch closure of the VSD and relief of the right ventricular outflow obstruction. A Rastelli procedure may be necessary in patients whose anatomy requires a conduit to bypass the RVOT obstruction.

Tricuspid Atresia

Tricuspid atresia has an incidence of 1% to 2% with no gender predominance. Children with tricuspid atresia, in addition to a missing valve, have a variable degree of underdevelopment of the right ventricle and pulmonic valve. Associated lesions include a VSD, pulmonary stenosis, and transposition of the great vessels. As there is no flow from the right atrium into the right ventricle, an ASD as well as a VSD are critical for survival in the newborn. If there is significant pulmonary stenosis present, a PDA is necessary to ensure adequate pulmonary blood flow. Common presentations

include severe cyanosis, poor feeding, and tachypnea. On physical examination there is a single S2, but patients with an accompanying VSD will have a grade 2–3/6 systolic murmur best heard at the left lower sternal border. Severe pulmonary stenosis will present with a loud systolic ejection murmur at the left upper sternal border. If a PDA is also present, the patient may have a continuous murmur and if there is obstruction to flow across the ASD, the infant will likely have hepatomegaly. The ECG has a characteristic leftward and superior QRS axis, along with evidence of right atrial and left atrial hypertrophy (RAH and LAH), as well as left ventricular hypertrophy. The chest radiograph will show a normal to slight increase in heart size along with decreased pulmonary vascular markings. Like all patients with abnormal development of two ventricles, these patients need multiple palliative surgeries to normalize oxygenation levels.

Ebstein Disease

Ebstein disease is a rare cause of cyanotic congenital heart disease, and consists of malformation of the septal and posterior leaflets of the tricuspid valve. Severe Ebstein disease presents in the neonate with marked cyanosis and tachypnea. The lesion is characterized on examination by a split S1, a triple or quadruple gallop, and a systolic murmur along the left mid to lower sternal border from severe tricuspid valve regurgitation. In severely cyanotic neonates, management consists of PGE1 to keep the ductus arteriosis patent until pulmonary vascular resistance decreases after infancy. Surgery in infancy is reserved for patients with persistent severe cyanosis and acidosis. After infancy, patients are generally asymptomatic with a variable degree of cyanosis. The ECG is notable for marked right atrial enlargement, and a right bundle branch block. Pre-excitation is seen in up to 25% of patients. The chest radiographic is pathognomonic, with massive cardiomegaly from right atrial dilation, and decreased pulmonary vascular markings.

Total Anomalous Pulmonary Venous Return

In TAPVR, the pulmonary veins bring the blood from the lungs to the right atrium instead of the left atrium. This entity may be divided into four anatomic groups, depending on the course of pulmonary venous drainage: (1) supracardiac, (2) cardiac, (3) infracardiac, and (4) mixed types. Patients with infracardiac drainage generally have significant pulmonary venous obstruction, and present with severe cyanosis and respiratory distress. In addition to pallor and decreased pulses due to decreased cardiac output, there is frequently hepatomegaly. The cardiac examination tends to reveal a loud single S2 with a gallop rhythm. The ECG demonstrates sinus tachycardia, right axis deviation, and right ventricular hypertrophy. A chest radiograph will show a small cardiac silhouette with pulmonary edema due to pulmonary venous congestion. Obstructed TAPVR is a surgical emergency, and immediate stabilization and repair is indicated.

KEY TESTING

- The hyperoxia test in patients with undifferentiated congenital disease
- Chest radiograph
- ECG
- Echocardiogram if available

ED MANAGEMENT

The initial management should focus on stabilization of the airway, breathing, and circulation. Once a diagnosis of congenital heart disease is suspected, a call to a tertiary care center, pediatric ED, or pediatric cardiologist is appropriate. If the child has a suspected ductal-dependent lesion, a PGE1 infusion should be initiated at a rate of 0.05 to 0.1 μg/kg/min. Adverse effects associated with PGE1 infusions include apnea (12%), fever, hypotension, and seizures. Because of the frequent occurrence of apnea, elective intubation should be considered prior to initiation of the PGE1 infusion.

The hyperoxia test. This is a useful bedside test to determine the etiology of a child's cyanosis (respiratory vs. cardiac). With the

application of 100% oxygen, an increase in pO_2 to >100 mm Hg suggests pulmonary disease, whereas a pO_2 <100 mm Hg suggests cyanotic congenital heart disease. The test can also be performed by measuring the oxygen saturation before and after the application of 100% oxygen, although this can be misleading because pulse oximetry is not as consistently accurate. The oxygen saturation should increase by at least 10% in the presence of a pulmonary process.

In patients with TOF and a hypercyanotic spell, a variety of maneuvers to improve oxygenation should be performed emergently. The child may benefit from being placed in the knee-to-chest position. All children should receive supplemental oxygen. Morphine sulfate at a dose of 0.1 mg/kg intramuscularly or subcutaneously may be given. IV access should be established, as these children are at high risk for recurrent episodes. An IV fluid bolus of 10 to 20 mL/kg may then be given. In refractory cases, phenylephrine 0.02 mg/kg IV should be considered to increase systemic vascular resistance and promote pulmonary blood flow. The dose may need to be titrated for effect. Sodium bicarbonate and propranolol may also be effective. In completely unresponsive cases, general anesthesia and paralysis may be considered. These children invariably require urgent surgical intervention.

ACYANOTIC HEART DISEASE

CLINICAL PRESENTATION

Acyanotic cardiac disease is composed primarily of lesions causing left to right shunting and left ventricular outflow tract (LVOT) obstructions. Lesions causing acute left to right shunting comprise almost 50% of all congenital heart disease and include (1) VSDs, (2) ASDs, (3) PDA, and (4) endocardial cushion defects. Infants with significant LVOT obstruction generally present in the first few weeks of life with symptoms of shock due to inadequate cardiac output after closure of the ductus arteriosus. The timing of presentation of a left-sided obstructive lesion depends upon the degree of obstruction

and upon ventricular function. The most common lesions presenting emergently are: (1) critical aortic stenosis, (2) critical coarctation of the aorta, (3) interrupted aortic arch (IAA), and (4) hypoplastic left heart syndrome (HLHS).

ED EVALUATION

Left–Right Shunts due to Structural Lesions

Depending on the degree of shunting from the systemic to the pulmonary side, consequences of significant pulmonary overcirculation can develop, including left ventricular dilation and hypertrophy, decreased ventricular function, and signs of CHF. In the neonate, high pulmonary vascular resistance initially limits the amount of left-to-right shunting, but as pulmonary vascular resistance drops in the first few weeks of life, pulmonary blood flow increases. Large left-to-right shunts (except ASDs) will eventually result in the development of pulmonary hypertension and the Eisenmenger complex if not diagnosed and surgically repaired in a timely fashion.

Clinically, patients will have a murmur characteristic of a specific defect. There is frequently a diastolic rumble or gallop. Pulmonary overcirculation may be the cause of the patient's tachypnea (with or without respiratory distress), pallor or mottling of the extremities, and underlie a history of feeding difficulties and poor weight gain. The differential diagnosis should include sepsis; however, the distinguishing features of the heart murmur, an S3 gallop, and enlarged heart on chest radiograph will help identify CHF in patients with shunt lesions. Pulse oximetry may demonstrate mildly decreased oxygen saturations due to pulmonary edema. Supplemental oxygen therapy should be used judiciously since it can accelerate CHF symptoms by lowering pulmonary vascular resistance and further enabling pulmonary blood flow.

Left-Sided Obstructive Lesions

Critical Aortic Stenosis and Critical Coarctation of the Aorta

The age of presentation of patients with aortic valve stenosis (AS) depends on the severity of the obstruction to flow across the aortic valve. Approximately 10% to 15% of patients present before 1 year of age (4). The typical presentation of severe aortic stenosis in infancy is CHF, but there can be cardiogenic shock in the setting of critical AS (ductal-dependent systemic blood flow). The latter patients present acutely and appear ashen, with markedly decreased or absent pulses, and are severely acidotic and obtunded. These patients may be cyanotic due to pulmonary venous desaturation. The classic murmur of AS is typically a loud and harsh systolic murmur with transmission to the neck. Patients presenting with severe aortic stenosis may have minimal, if any, murmur because of associated diminished cardiac output from ventricular dysfunction. Patients with reasonable cardiac output and aortic stenosis may also have an ejection click and a systolic thrill in the region of the upper right sternal border, suprasternal notch, or carotid arteries.

Infants with critical coarctation generally present before 2 weeks of age owing to progressive ductal closure and manifestations of obstructed arterial flow, whereas older children and adolescents with less severe coarctation may present with a murmur and hypertension that may have been longstanding in nature. Unlike patients with critical aortic stenosis who present with diminished pulses throughout, patients with severe or critical coarctation of the aorta and IAA should have unequal upper and lower extremity pulses (higher in the upper extremities). Four-limb blood pressures can be diagnostic. Simultaneous pulse oximetry readings in the right hand and a foot in patients with coarctation may show significantly lower oxygen saturation in the foot, due to perfusion of the lower extremities with desaturated blood from the PDA. A pulse oximetry reading in the leg of $<92\%$ on room air or more than a 7% difference between the leg and arm was found in 85% of infants with left heart obstructive disease and in 79% with other forms of congenital heart disease (5,6). ECG findings in critical aortic stenosis and critical coarctation are similar, with biventricular hypertrophy, ST-segment changes, and inverted T waves in lead V6.

The radiographic findings of patients with left-sided obstructive lesions vary. Infants who present in failure may have cardiac dilation and pulmonary venous congestion. Older children with aortic stenosis generally have a normal-appearing chest x-ray, and those with isolated coarctation of the aorta can have evidence of collateral blood vessels, characterized by rib notching.

Hypoplastic Left Heart Syndrome

HLHS accounts for 1% of all CHDs, and is more common in males. As in infants with critical coarctation of the aorta and critical aortic stenosis, systemic perfusion depends on a PDA. Clinical presentation after birth can initially be subtle, with no murmur, intermittent pallor, and a complaint that the infant is "not acting right." As the ductus constricts, tachypnea, respiratory distress, and metabolic acidosis occur. The closure of the ductus results in rapidly progressive cardiogenic shock and circulatory collapse. In addition, there can be significant obstruction to systemic blood flow if there is restriction of the obligatory left-to-right shunt across the patent foramen ovale. Surprisingly, infants with HLHS may have normal radiographic findings. ECG findings vary considerably but commonly there is RVH.

ED MANAGEMENT

The initial management should focus on acute stabilization of the airway, breathing, and circulation. Once a diagnosis of congenital heart disease is suspected, a call to the tertiary care center, pediatric ED, or pediatric cardiologist is indicated. Management of symptomatic shunt lesions is discussed in the next section on CHF. If there is concern regarding a left-sided obstructive lesion, initiation of PGE1 at 0.05 to 0.1 μg/kg/min may help to maintain patency of the ductus in an infant. The goal should be to maintain adequate systemic blood flow via the ductus without hyperperfusing the pulmonary vasculature. This balance can be achieved by methods to increase the pulmonary vascular resistance, such as controlled hypoventilation and positive end-expiratory pressure.Supplemental

oxygen should be limited, with acceptance of lower oxygen saturations, to avoid a dramatic drop in pulmonary vascular resistance. Sodium bicarbonate may be indicated in patients with severe acidosis. Prompt referral to a pediatric cardiologist or pediatric cardiovascular surgeon is indicated. Treatment may include staged or definitive surgery, or interventional cardiac catheterization (e.g., for aortic stenosis).

CONGESTIVE HEART FAILURE

CLINICAL PRESENTATION

Ninety percent of cases of CHF in children occur during the first year of life and it is frequently the final common pathway for congenital lesions that have progressed to critical stages. The CHDs most commonly associated with CHF are those that result in pulmonary overcirculation through a large left-to-right shunt (VSD, PDA, atrioventricular [AV] canal defect). Patients with significant shunts typically present between 3 and 8 weeks of age, following the physiologic drop in pulmonary vascular resistance, which allows pulmonary overcirculation to develop. The pathophysiology of CHF in these children starts with increased pulmonary blood flow and progresses to pulmonary interstitial edema, and volume overload of the left heart. A chest radiograph should be considered for any "first-time wheezer" who fails to improve with conventional treatment. Hyperinflation from bronchiolitis should be associated with a normal or small cardiac silhouette. Cardiomegaly in a child with wheezing suggests "cardiac asthma" due to cardiomyopathy, pericardial effusion, pulmonary overcirculation, or other cardiac etiologies. Children presenting with symptoms of CHF later in life should be suspected of having an acquired problem (e.g., cardiomyopathy) rather than a congenital heart disease. In contrast, CHF in the first day of life is usually secondary to cardiac muscle dysfunction from hypoxia, hypoglycemia, hypocalcemia, myocarditis, sepsis, or infarct (e.g., from an anomalous left coronary artery).

Left-to-right shunt lesions with pulmonary overcirculation, and some left ventricular outflow obstructive lesions, should be appropriately identified based on history, physical examination, and the timing of clinical presentation. Infants with CHF typically present with tachypnea, tachycardia, and diaphoresis. Because the bulk of work performed by infants and small children occurs during feeding, many of these children also have feeding intolerance and failure to thrive. Toddlers and older children usually have tachycardia, tachypnea, fatigue, and exercise intolerance. In older children, peripheral edema and venous distension may be apparent, but they are unusual and are associated with significant right-sided heart failure. Physical examination findings of CHF may include hepatomegaly and a gallop rhythm, with decreased peripheral pulses. On chest x-ray, there is typically cardiac enlargement and increased pulmonary vascular markings, with pulmonary edema. Significant cardiomegaly in the absence of pulmonary vascular congestion should raise suspicion of pericardial effusion.

ED EVALUATION

Structural Congenital Heart Defects

Cardiomyopathy and Myocarditis

Clinical signs of diminished cardiac output and CHF may occur in patients with poor myocardial function due to cardiomyopathy or myocarditis. A cardiomyopathy can be the result of ischemia due to a coronary artery anomaly, a glycogen storage disease, a previous viral infection, muscular dystrophy, an inherited or idiopathic myopathy, or incessant tachyarrhythmia. The degree of symptomatology is usually related to the degree and duration of cardiac dysfunction. The patient with mild dysfunction may present with only mild symptoms of tachypnea and poor feeding (or weakness and fatigue in older patients), whereas the patient with end-stage cardiomyopathy may present in florid CHF and require emergent resuscitation. The child with acute myocarditis may present with severe cardiac dysfunction and an associated tachyarrhythmia (e.g., sinus tachycardia, premature ventricular

contractions, ventricular tachycardia) or bradyarrhythmia (e.g., second- or third-degree heart block).

The classic radiographic findings in these patients include cardiomegaly and, frequently, pulmonary edema. Patients with sustained tachyarrhythmias can have cardiac enlargement as a result of LV failure. Patients with a "dilated," poorly functioning cardiomyopathy may show ECG findings of atrial enlargement, LVH, and occasionally RVH, in addition to, ST-segment or T-wave changes. Children with glycogen storage diseases, such as Pompe disease, may have a short PR interval with very large precordial QRS voltages. Decreased amplitude, manifested as a *low-voltage QRS* (<5 mm total in each frontal lead), suggests myocarditis with decreased contractility or restrictive disease. One also must consider a large pericardial effusion as the cause for low QRS voltage. Patients with an anomalous left coronary arising from the pulmonary artery may have ECG evidence of an ST elevation myocardial infarction (STEMI).

ED MANAGEMENT

In general, the treatment of CHF includes both respiratory and inotropic support. CHF cannot be treated the same in all pediatric patients, due to the wide variety of potential etiologies (7). Infants with cardiogenic shock and septic shock can present similarly, with poor perfusion and metabolic acidosis. However, septic shock requires fluid resuscitation and possibly vasopressors, whereas cardiogenic shock often requires the use of PGE1 infusion.

The approach in the acute care setting should be as follows: (1) to remove any precipitating or aggravating factors (i.e., transfuse for severe anemia, treat dysrhythmias, and possibly restrict fluids), (2) to reduce metabolic demands (reduce fever, sedate agitated patients, consider endotracheal intubation and ventilation), (3) to relieve pulmonary congestion (diuresis, mechanical ventilation with positive end-expiratory pressure, morphine sulfate), and (4) to improve myocardial performance and oxygen delivery (inotropes, afterload reduction, preload reduction, oxygen [which must be used

carefully since it can worsen pulmonary overcirculation], PGE1 [specifically for ductal-dependent left heart obstructive lesions] and correction of metabolic acidosis). In the acute care setting dobutamine and the phosphodiesterase inhibitor milrinone have been successfully used. Dobutamine should be initiated as a continuous infusion at 5 to 10 μg/kg/min. Low-dose dopamine (3 to 6 μg/kg/min) may also be of assistance by promoting diuresis. Milrinone has gained favor in the management of children with myocardial dysfunction; its major advantage is the lack of chronotropic stimulation while assisting with afterload reduction. However, proarrhythmic effects have been reported. Agents such as epinephrine and norepinephrine can be used in the patient with ventricular dysfunction; however, they may aggravate the sympathetic overstimulation of fulminant CHF and also are proarrhythmic.

If the etiology of low cardiac output appears to be poor myocardial function, the initial focus should be on maximizing oxygenation and improving cardiac output through inotropic support, including afterload reduction. In addition, oxygen consumption should be minimized via maintenance of normothermia, normal hemoglobin levels, and preventing or reversing tachycardia.

Unique Complications of Pediatric Congenital Heart Disease

Children with congenital heart disease are at risk for unique complications. Patients with baseline limited pulmonary blood flow are extremely sensitive to acute alterations in pulmonary vascular resistance, and simple respiratory infections (e.g., acute bronchiolitis) are potentially life-threatening in this subset of patients. Patients with defects that limit pulmonary or systemic blood flow require close monitoring for common viral illnesses, such as viral gastroenteritis, as they typically do not tolerate dehydration well.

The Fontan procedure may be performed palliatively in children with complex CHDs. In this staged procedure, systemic venous blood is diverted to the pulmonary arteries without passing through the right ventricle. These patients are at increased risk for pulmonary embolism and for a protein-losing enteropathy that may present with ascites, peripheral edema, and pleural effusions. Patients with shunt-dependent lesions (e.g., pulmonary atresia with a systemic-to-pulmonary shunt) may present with sudden and severe cyanosis and acidosis (and an absence of a continuous shunt murmur on physical examination) owing to thrombotic obstruction of the shunt. Patients with existing right-to-left shunts (either pre- or postoperative) are at risk for stroke, particularly children with polycythemia or chronic cyanosis. These children should have filters on all IV lines to decrease the risk of air emboli. Finally, all children with known cyanotic or complex structural heart disease, or those who have had prosthetic materials inserted, are at increased risk for bacterial endocarditis.

A patient who has had surgery involving the atrium, including the Mustard and Senning operation, is at risk for atrial tachyarrhythmias and sinus node dysfunction. Unlike the typical atrial flutter seen in adults, these patients can manifest atrial tachycardia at a wide range of rates. Ventricular tachycardia is a significant risk of morbidity and mortality in patients with previous ventriculotomy, especially patients with a previous repair of TOF.

CRITICAL INTERVENTIONS

- In addition to congenital heart disease, consider sepsis in a child with poor perfusion and cyanosis.
- Timely prostaglandin infusion for suspected cyanotic ductal-dependent lesions, presenting most commonly within the first week of life. Benefits outweigh the risks even if there is ultimately no cardiac lesion.
- Use supplemental oxygen judiciously in patients where pulmonary vascular resistance must be considered as part of the hemodynamics of an obstructive left-sided lesion.

- Differentiate cardiac from respiratory disease via the hyperoxia test when indicated.

DISPOSITION

Patients with acute problems related to congenital heart disease almost universally require emergent cardiology consultation or critical care admission. If patients are not at a tertiary pediatric center with cardiologic expertise, use of a Neonatal/Pediatric Critical Care Transport Team may be indicated.

Common Pitfalls

- Failure to recognize that cardiogenic shock and septic shock can present similarly, with poor perfusion and metabolic acidosis. Septic shock requires fluid resuscitation and possibly vasopressors, whereas cardiogenic shock in infancy often requires the use of PGE1 infusions.
- Failure to consider a potential cardiac etiology in infants presenting with complaints that include poor feeding, lethargy, dehydration, or septic appearance.
- Delay in institution of prostaglandin infusion.

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CHAPTER 269

Appendicitis

Maureen D. McCollough

Appendicitis is the most common surgical emergency in childhood. Despite the decline in mortality since the introduction of antibiotics, over the past 40 years morbidity secondary to delayed diagnosis and perforation has remained unchanged. Perforation rates in children are higher than those in adults and 50% to 70% in preschoolers versus 10% to 20% in adults (1). The clinical progression of symptoms and signs is also more rapid in children. What starts as vague abdominal complaints can quickly progress to ileus, nausea, vomiting, fever, tachycardia, localized pain, and finally peritonitis. The inability of the omentum in young children to wall off localized infections contributes to the development of diffuse peritonitis, which further emphasizes the importance of early intervention (1).

CLINICAL PRESENTATION

The primary cause of appendicitis is obstruction of the appendiceal lumen, caused most commonly by a fecalith (calcified fecal material). Other less common causes of obstruction include inflamed lymphoid tissue, vegetable or fruit seeds, intestinal worms (especially Ascaridae), bacterial infection (with *Yersinia, Salmonella,* or *Shigella*), anomalies of mucous-secreting glands (as in cystic fibrosis), and rarely, retained barium from previous radiographic studies (2).

Luminal obstruction of the appendix causes distention and increased intraluminal pressure, resulting in obstruction of the blood supply. Bacterial invasion occurs and ultimately the ischemic

appendix becomes gangrenous and perforates. Bacteriologic cultures of perforated appendices have revealed polymicrobial organisms, including *Escherichia coli, Bacteroides fragilis,* and enteric streptococci.

Obstruction and distention stimulate appendiceal stretch receptors, relaying pain to the tenth thoracic ganglion, resulting in the perception of periumbilical pain. Bacterial invasion and inflammation then lead to fever, nausea, or vomiting in up to 80% of children. As inflammation extends to surrounding tissues, pain depends on the anatomic location of the appendix. Up to one-third of appendices are located in areas other than the usual location, with the result being that up to 30% of children have pain localized to areas other than the right lower quadrant. A retrocecal location may cause back or flank pain, a pelvic appendix may cause suprapubic pain, and a retroileal location may cause pain referred to the testicle.

If appendicitis is allowed to progress appendiceal rupture will occur. In this case the child is typically ill-appearing, toxic, and dehydrated. Particularly in younger children, the incompletely developed greater omentum is incapable of walling off the inflammatory process, resulting in pain that is more diffuse. The pain may decrease in intensity just after perforation, but typically becomes more severe as peritonitis spreads.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of abdominal pain in children comprises a lengthy list of disorders. The list may divided into five broad categories: (1) intestinal diseases, (2) uterine, tubo-ovarian, or testicular pathology, (3) urinary tract infection or obstruction, (4) systemic illness (respiratory, vasculitic, endocrinologic, and hematologic), and (5) trauma (2).

1. *Intestinal diseases:* Mesenteric adenitis, viral and bacterial enteritis, constipation, Meckel diverticulitis, intussusception, enteric duplication

2. *Uterine, tubo-ovarian, or testicular pathology:* Ovarian or testicular torsion, acute epididymitis, pelvic inflammatory disease, ectopic pregnancy, endometriosis, mittelschmerz
3. *Urinary tract infection or obstruction:* Acute pyelonephritis, cystitis, renal stones
4. *Systemic illness (respiratory vasculitic, endrocrine, hematologic):* Basal pneumonia, Henoch–Schönlein purpura, sickle cell crisis, diabetic ketoacidosis
5. *Trauma:* Accidental or nonaccidental injury

It has been reported that 20% to 40% of children with acute appendicitis are given the wrong diagnosis on the first physician visit (1). The most common erroneous diagnoses, in descending order of frequency, accounting for more than 75% of all missed diagnoses, include acute mesenteric lymphadenitis, no organic pathologic condition, acute pelvic inflammatory disease, ovarian cyst, mittelschmerz, and acute gastroenteritis.

Acute Mesenteric Lymphadenitis

Mesenteric adenitis is often confused with acute appendicitis in children. A careful history in these patients almost invariably reveals the presence of upper respiratory symptoms. Laboratory studies are usually of limited value in differentiation, although a relative lymphocytosis may suggest mesenteric adenitis or a generalized viral syndrome. The abdominal pain is usually more diffuse and less severe than with appendicitis, and generalized lymphadenopathy may be noted on physical examination.

Pelvic Inflammatory Disease

A history of vaginal discharge in a sexually active adolescent can often be elicited. Interviewing adolescents alone, without parental presence, may provide a more informative history regarding sexual activity. Pain is most often bilateral and lower in location than with appendicitis. Physical examination reveals pain with motion of the cervix.

Acute Gastroenteritis

Acute gastroenteritis usually can be differentiated from appendicitis. There is often a history of other ill contacts. These patients have nausea, vomiting, watery diarrhea, and intermittent, crampy abdominal pain. Often, the vomiting precedes the diarrhea by 24 hours. Localizing signs on the abdominal examination are usually absent.

Constipation

Constipation is one of the most significant mimics of appendicitis frequently presenting with abdominal pain localized to the right lower quadrant (see Chapter 230). Often there is a history of hard, pellet-like stools, or decreased stool output. The pain is often colicky and waxes and wanes, but overall, the child appears well between colicky episodes. If the diagnosis is in question or appendicitis is still high on the differential, a mineral oil enema or pediatric Fleet enema may be useful to relieve the pain of constipation.

Meckel Diverticulitis

Preoperative differentiation is unnecessary, because the signs and symptoms of Meckel diverticulitis are similar to those of acute appendicitis, and surgical treatment is indicated for both.

Intussusception

Distinguishing between intussusception and acute appendicitis relies significantly on the age of presentation for each disease. Appendicitis is rare in children younger than 2 years of age, whereas nearly all intussusceptions occur in children younger than age 2. Intussusception typically occurs suddenly in an otherwise healthy infant. The infant “doubles up” with apparent colicky pain, but is usually pain-free between attacks. While a bloody mucoid stool may passed several hours after the onset of pain, this is rare and is an indicator of advanced disease. Physical examination may reveal a sausage-shaped mass in the right lower quadrant.

Occasionally, infants with intussusception present with altered mental status. The diagnosis can be made using ultrasound. In patients between the ages of 1 and 3 years, both of these two entities should carry equal weight in the differential diagnosis until an imaging study such as ultrasound can help clarify the clinical picture. Treatment of intussusception is reduction by barium or air enema (see Chapter 270).

Henoch–Schönlein Purpura

Henoch–Schönlein purpura, a diffuse vasculitis, classically presents with joint pain and swelling and purpura. Abdominal pain may also be a prominent symptom. Rectal examination should be performed for occult blood, and a urinalysis to evaluate for hematuria due to nephritis.

Mittelschmerz

Patients with mittelschmerz are at the midpoint of their menstrual cycle. The pain of mittelschmerz is usually of sudden onset and may be either localized, generally to one of the lower quadrants, or diffuse.

Ovarian or Testicular Torsion

These are often accompanied by anorexia, nausea, and vomiting. The correct diagnosis in boys can always be made by including the genitalia in the physical examination, which usually reveals the subtle findings of asymmetry in gonadal size or position. In girls, ultrasound can be used to make the diagnosis of ovarian torsion more likely if decreased or absent vascular flow is seen unilaterally. And, it should be remembered that normal examination of the ovary, or normal testicular size or position, does not completely rule out the diagnosis of torsion.

Urinary Tract Infection

Urinary bacteria or white blood cells may be present in children with acute appendicitis if the appendix lies near the ureter or bladder. However, with the exception of an elevated specific gravity due to dehydration, the urinalysis is normal in more than 80% of children with acute appendicitis.

ED EVALUATION

The most important steps in the correct diagnosis of appendicitis are eliciting a thorough history and performing a complete physical examination, including examining the external genitalia in boys and performing a pelvic examination in adolescent girls. The diagnostic value of the rectal examination in children is limited; rectal tenderness is present in half of all children with or without appendicitis, and rectal examination should thus be limited to children with rectal complaints.

Examining a young child with abdominal pain can be challenging. Young children are often frightened of doctors and "white coats," but observing the child from the doorway or across the room can be very revealing and yield important clues. Clinicians must not underestimate the value of information gleaned during this early subjective assessment. A young child who is ambulating easily around the room, interested in his or her surroundings, is less a cause of concern than a child who is ill-appearing and lying very quietly. A slight limp when the child walks, hesitation to climb onto the examination table, and inability to stretch the right leg may suggest appendicitis even before the full evaluation. The child usually prefers to lie still in the supine position with the thighs, particularly the right one, drawn up. Vital signs are typically normal, but a child with simple appendicitis may have a mild temperature elevation. Tachycardia may be present if the child is dehydrated, febrile, or in pain.

Abdominal palpation should start away from the painful area. Examination of the abdomen for bowel sounds and tenderness can often frighten young children. Distraction, for example by using a hand puppet or other toy, may help to improve the quality of the

examination. The classic physical finding is point tenderness at McBurney point (3 to 5 cm from the anterior–superior iliac spine on a straight line drawn from that process to the umbilicus) (2). Muscular resistance to palpation of the abdomen parallels the severity of the inflammatory process. Early in the disease, resistance if present consists of voluntary guarding alone. With the progression of peritoneal irritation, muscle spasm increases and becomes involuntary. Bowel sounds are usually normal in early appendicitis, but advanced inflammation, perforation, or both, usually results in an ileus and a quiet abdomen.

Physical signs classically associated with acute appendicitis include Rovsing sign, psoas sign, and obturator sign (3). Rovsing sign tests for peritoneal inflammation by ascertaining the degree of referred right lower quadrant tenderness elicited from palpation of the left lower quadrant. To elicit the psoas sign, the child should lie on the left side and stretch the psoas muscle by slowly extending the right thigh. Alternatively, the child may lie supine and flex the right hip against a hand placed just above the knee. Pain elicited by either maneuver may indicate an irritating focus in proximity to the psoas muscle. Finally, a positive obturator sign occurs when, in a supine patient, passive internal rotation of the thigh (with the hip flexed to 90 degrees) produces right-sided abdominal pain, indicating irritation around the obturator internus muscle. A positive psoas or obturator sign suggests retrocecal or retrocolic inflammation. Although these three signs are often cited as being associated with appendicitis, few studies have evaluated the accuracy of the clinical examination for appendicitis (3).

Given the breadth of the differential diagnosis evaluations must be stratified for age. An abdominal pain evaluation for a 2-year old must include consideration not only of appendicitis, but also of intussusception. On the other hand, in an adolescent female ovarian pathology must be considered far more strongly than intussusception. Selected laboratory tests, including a urinalysis and CBC, may be indicated along with selected imaging studies including ultrasound, CT, or possibly MRI.

The interpretation and integration of findings from the physical examination, laboratory, and imaging studies does not guarantee that every diagnosis will be made, and the literature on the reliability of signs, symptoms, laboratory markers, and imaging in pediatric appendicitis is limited. A systematic review assessing the reliability of common clinical signs for ruling in appendicitis noted that those with the highest positive likelihood ratios were fever, rebound tenderness, and migration of pain to the right lower quadrant. The clinical signs with the highest negative likelihood ratios for ruling out appendicitis were absence of fever and absence of rebound tenderness (4). A history of previous similar pain also seemed to lower the likelihood of appendicitis. Patients with appendicitis, however, do not always present with the "most reliable signs with the highest positive likelihood ratios." Becker et al. specifically studied atypical features in children with confirmed appendicitis to quantify their frequency and investigate which features had the strongest negative predictive value. They noted that 44% of patients presented with six or more atypical features, the most common include (1) lack of fever, (2) absence of Rovsing sign, (3) increased or normal bowel sounds, (4) absence of rebound, (5) lack of pain migration, and (6) lack of abrupt onset of pain. The atypical signs with strongest negative predictive properties based on likelihood ratios included (1) WBC $<10{,}000$ mm^3, (2) an ANC $<7{,}500$ mm^3, (3) absence of guarding, (4) lack of percussive tenderness, and (5) lack of nausea or emesis (5).

A number of clinical decision rules (CDRs) have been developed to help clinicians manage the diagnostic uncertainties of pediatric appendicitis (6). The MANTRALS score by Alvarado dates back to 1986 and was originally developed for adult appendicitis, but has been modified and studied in cohorts of pediatric patients as well. Other scores of note include the Pediatric Appendicitis Score and that by Kharbanda et al. (6). These scores all harness the high-yield indicators of pediatric appendicitis discussed above, including RLQ tenderness, rebound tenderness, leukocytosis, and nausea or emesis. Collectively, however, their performances vary widely and none has proven reliable as a single diagnostic tool that is more accurate than

the clinical intuition of an experienced physician (Mandeville, 2011). Alvarado scores and PAS scores of greater than 7 and 6, respectively, place patients at significantly greater risk for appendicitis but still only achieve sensitivities of 76% and 88%, respectively (Mandeville, 2011).

The application of CDRs in acute appendicitis must therefore fit into a larger picture that includes diagnostic imaging and observation. Ultrasound should be considered a primary modality for the diagnosis of acute appendicitis, in light of the radiation exposure risks associated with CT scans. In children, ultrasound has been reported to have an overall sensitivity and specificity of 90% and 97%, respectively, with an overall accuracy of 96% (7,8). Ultrasound's greatest liability, however, is the variability of its performance across different users and at different centers. Rates of visualization of the appendix, even at experienced pediatric institutions, is only 56%, and at less experienced centers the rate can be as low as 26% (9). Likewise, the sensitivity of ultrasound may vary widely at different centers, ranging from 69% to 86% in experienced centers and from 35% to 52% in institutions where ultrasound is used less frequently or is less available. Specificity, however, appears to be similar across centers, ranging from 96% to 99% (9). Thus, if a normal appendix can be visualized, appendicitis can be ruled out. If the appendix is not visualized, however, or the findings are equivocal, additional evaluation is warranted.

Relative to ultrasound, CT of the abdomen is more sensitive and nearly as specific, with sensitivity and specificity both $>95\%$ and a negative predictive value of 97% (8,10). CT also has been shown to reduce the number of inpatient prediagnosis observation days, operations, and negative laparotomies (11). To balance the superior and more consistent test characteristics of CT against the radiation risk it entails, clinical pathways have been developed that couple CDRs with imaging that stratifies patients and selects imaging modalities according to the likelihood of disease. This maximizes the use of ultrasound as a first-line modality and reserves the use of CT for only the most equivocal cases, which increases its yield. Fleischman et al. published such a pathway that produces a nearly

50% reduction in CT use, from 13% to 7% of cases. Interestingly, their study showed that the accuracy of either a high-risk or a low-risk scoring system was not increased over the clinical impression of an experienced clinician (12).

The newest modality for imaging for appendicitis in young children is focused magnetic resonance imaging (MRI) scanning. Although there are as yet only limited studies (13,14), it appears that MRI provides a sensitivity comparable to that of CTs, but without the radiation exposure. Limitations of MRI include its decreased availability in most medical centers and prolonged scanning time. It should be noted, however, that a less-than-10-minute scanning protocol also appears to be diagnostically successful (15).

Indicated laboratory studies include a complete blood count with differential and urinalysis. Moderate leukocytosis (10,000–18,000 white blood cells [WBC] per mL) with a predominance of polymorphonuclear cells is classically seen but does not necessarily correlate with the severity of the disease (16). A left shift in the differential may precede a total leukocytosis in children. A recent study looked at the use of the WBC and the C-reactive protein (CRP) in the diagnosis of appendicitis in children (17). Used alone, the tests had a sensitivity ranging from 60% to 86%. Used together (either test elevated), there was a sensitivity of 98%, but the 95% CI was as low as 95.3%. It must be noted that a normal WBC or normal CRP does not rule out the diagnosis of appendicitis.

Abdominal radiographs are not particularly helpful, since a fecalith is shown in only 10% to 20% of children with appendicitis. Nonspecific findings on plain abdominal films include isolated distended loops of bowel in the right lower quadrant and obliteration of the psoas shadow. Because lesions that irritate nerves at the T10 to T12 level may simulate the referred pain distribution of appendicitis, a chest film may be required to rule out right lower lobe pneumonia, especially if signs or symptoms of lower respiratory tract disease exist.

There is a higher incidence of perforation in younger children and those with a history of prolonged symptoms. Findings suggestive of

perforation include (1) duration of symptoms >36 hours, (2) temperature >102°F, white blood cell count of >15,000/mL, and (3) physical findings of peritonitis.

The surgical consultant should be contacted as soon as the diagnosis of acute appendicitis is entertained, to avoid the complication of late diagnosis and perforation. Perforated appendicitis has a mortality rate of 5% and a morbidity rate of up to 46% in some series, compared with a mortality rate of 0.1% for nonperforated appendicitis (18).

KEY TESTING

- CBC
- Urinalysis
- Ultrasound
- CT only if indicated
- Observation in the face of equivocal findings

ED MANAGEMENT

Appendicitis is a surgical emergency. All children thought to have an abdominal surgical emergency should be seen by a surgeon as soon as possible. The initial emergency department (ED) management of simple and perforated appendicitis is essentially the same. Once the diagnosis is made, the child must be fluid-resuscitated intravenously and kept NPO.

It was previously believed that the use of analgesic medication such as narcotics in a child with abdominal pain would mask the diagnosis and make the evaluation of the child more difficult. Just as with adults, this has been shown to be untrue (19,20). Multiple studies have found no difference in time to surgical decision, number of perforated appendices, or the rate of negative laparotomies when morphine was compared to placebo in children with diagnosed appendicitis (21).

The same can be said for antiemetics in children. It was believed that children given antiemetics such as prochlorperazine or metoclopramide would be overly sedated and would experience

more dystonic reactions, making the diagnosis more difficult. However, a survey of pediatricians, emergency physicians, and pediatric emergency physicians reveals that the majority use antiemetics in children who are being evaluated for appendicitis (22). The risk of side effects also appears to be lower than first thought (23).

Ondansetron, a serotonin 5-HT3 receptor antagonist, has been shown to be an effective antiemetic in children presenting to EDs with acute gastroenteritis and other conditions, including appendicitis (24,25).

In a child who has been vomiting, obtaining serum electrolyte levels should be considered while intravenous fluid therapy is started. Children who have clinical signs of dehydration should receive 0.9 NaCl or Ringer lactate boluses at 20 mL/kg to maintain urine output at 1 to 2 mL/kg/hr. Once the child is considered fluid-resuscitated, dextrose 5% in 0.45 normal saline and 20 mEq/L KCl at 1.5 times maintenance should be given, as long as the child is not oliguric. If the child is febrile, an antipyretic can be given orally with a small amount of water allowed.

The use of routine antibiotic coverage in children with uncomplicated appendicitis continues to be debated. It appears that short-term perioperative antibiotic prophylaxis in children with acute nonperforated appendicitis may decrease the rate of postoperative infectious complications (26). Absolute indications for extended therapy and a broader spectrum of antibiotic coverage are systemic signs of toxicity, sepsis, suspected perforation, and the presence of underlying conditions predisposing the patient to complications of bacteremia (i.e., infants younger than 6 months of age and children with congenital or acquired cardiac anomalies, sickle cell disease, diabetes mellitus, chronic renal failure, or other states of immune suppression). One commonly used regimen includes ampicillin, gentamicin, and clindamycin. This regimen ensures coverage of aminoglycoside-resistant enterococci, gram-negative bacilli, and anaerobes, respectively. Monotherapy or other antibiotic combinations can be used as long as the same microbial coverage is obtained in the setting of acute uncomplicated disease.

Single-agent treatment with ceftriaxone, piperacillin/tazobactam, or cefoxitin being used with increasing frequency. These appear to be equally efficacious and may result in shortened lengths of stay and reduced hospital charges.

CRITICAL INTERVENTIONS

- Maintain a high index of suspicion for appendicitis in all children with abdominal pain. A retrocecal appendix may cause back or flank pain, a pelvic appendix may cause suprapubic pain, and a retroileal location may cause pain that is referred groin or scrotum.
- Stratify patients and select imaging that balances test performance against the risks of ionizing radiation. After equivocal test results, observation is a valid test.
- Administer 0.9 NaCl or Ringer lactate boluses at 20 mL/kg in children with clinical signs of dehydration to maintain urine output at 1 to 2 mL/kg/hr.
- Obtain a surgical consult as soon as possible to avoid the complications associated with late diagnosis and perforation.

DISPOSITION

All children with appendicitis should be admitted to the hospital for surgical exploration. Laparoscopic appendectomy may be an option is some situations. In certain cases of appendiceal abscess, a surgeon may opt for admission to the hospital for intravenous antibiotics or percutaneous drainage, with an interval appendectomy several weeks later.

If there is doubt about the correct diagnosis but the suspicion for appendicitis is still high, the child should be admitted to the hospital for serial physical examinations. If the suspicion is low but still a consideration, the child may be discharged with clear instructions to return in 6 to 8 hours for a reexamination of the abdomen. If there is any doubt about the ability of the child to return for a revisit, the child should be admitted to the hospital for serial physical examinations.

The child may require transfer to another facility if appropriate surgical staff is unavailable at the initial hospital. This should be done expediently after resuscitation has been started.

Common Pitfalls

- Failure to appreciate atypical presentations of acute appendicitis in children.
- Failure to consider urologic or gynecologic conditions in children.
- Failure to appreciate risk-benefit ratios of different imaging modalities and how they affect decision-making.
- Failure to appreciate the importance of observation as a valid diagnostic test.

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CHAPTER 270

Intussusception

Vanessa Tamas and Paul Ishimine

Intussusception is an invagination of any segment of the intestine. This occurs when the proximal portion of the intestine invaginates into the distal, adjacent part. The majority of pediatric intussusceptions are ileocolic in origin (1).

Intussusception is the most common cause of intestinal obstruction in children, occurring with a frequency of 56 per 100,000 children per year (2) Typically, intussusception occurs in children less than 2 years of age, with most episodes occurring between the fifth and the ninth month. However, intussusceptions have been reported throughout the age spectrum, from the neonatal period through adulthood (3).

Idiopathic intussusceptions account for more than 90% of cases (4). Viral illness, immunization against rotavirus, and pharmaceuticals that include promotility medications and oral antibiotic agents have been implicated in these patients (5). In up to 10% of cases, a cause for intussusception is found, usually a well-defined pathologic lead point. A lead point is found with some frequency after 4 years of age, and is found consistently after 14 years of age (6). Conditions associated with intussusception include lymphoma, Henoch–Schonlein purpura, hemolytic-uremic syndrome, Meckel diverticulum, familial polyposis, Peutz–Jeghers syndrome, mesenteric adenopathy, and inverted appendiceal stumps. The possibility of an underlying lead point should be considered in patients who present with recurrent episodes, those out of the typical age range, and those with small bowel–small bowel intussusception. Irrespective of cause, early diagnosis is

essential; the duration of intussusception before treatment bears a close relationship to its morbidity and mortality.

CLINICAL PRESENTATION

The cardinal symptoms of intussusception are abdominal pain, vomiting, and rectal bleeding (1). In a typical case, there is a sudden onset of severe abdominal pain that may last several minutes. After an asymptomatic interval, repeated paroxysms will cause the child to cry out again. The child may be impossible to console or may seem comfortable only in a knee-chest position in the arms of a caregiver. Vomiting may occur either with the initial painful episode or soon after. Concurrent with vomiting, the child usually has one or more bowel movements, which may vary from thin liquid to formed stools. Within 12 to 24 hours, mucus, blood, or both may be passed per rectum (7).

Only 25% to 65% of patients present with the classic triad of paroxysmal pain, vomiting, and rectal bleeding; most patients develop only colicky abdominal pain and vomiting. (2,4,7). Nonbilious vomiting may become bilious as bowel obstruction progresses. Rectal bleeding is a less constant historic feature and may be found in as few as 40% of patients (8). Frank blood, or blood-streaked stools, may be present in a few hours of the first painful episode. “Currant jelly” stools account for a minority of bloody stools and are typically observed only after prolonged illness (9).

Recognition of the stereotypic history facilitates the diagnosis. However, less-than-classic presentations are frequent and contribute to diagnostic uncertainty and increased morbidity. Among the main factors that contribute to misdiagnosis are altered mental status and listlessness. Valuable time may pass during a well-considered evaluation for altered mental status that is not focused on an abdominal etiology. Altered mental status with intussusception is frequently associated with a prolonged course of illness (10). Furthermore intussusception may be considered late or not at all in patients presenting outside the conventional window of the first 2

years of life. A painless event may occur in 15% of cases (11). Occasionally no blood passes per rectum. The rectal examination early in the course may show show that is normal in appearance, and guaiac testing may be negative.

The vital signs and physical appearance of an affected child may be variable. Most children will be alert and hydrated. Those with advanced disease complicated by either fluid or electrolyte imbalance, or blood loss, may appear less responsive. Not uncommonly, a child with a very brief history of enteric manifestations may be obtunded at presentation. It is speculated the decreased level of consciousness observed in some patients is due to the release of natural endorphins from the intussusceptum.

On inspection, the abdomen may appear scaphoid and the right lower quadrant may seem empty. A sausage-shaped mass, sometimes ill-defined, can be palpated occasionally in the right upper quadrant. Rectal examination may reveal blood, ranging from occult blood noted on guaiac testing to frankly bloody stools. Rarely, rectal prolapse may be noted.

DIFFERENTIAL DIAGNOSIS

Because the signs and symptoms of intussusception overlap with many other clinical diagnoses the differential diagnosis is broad. Conditions that are commonly confused with intussusception include gastroenteritis and constipation. Other entities that should be considered, especially in infants, include malrotation with volvulus, incarcerated hernia, necrotizing enterocolitis, allergic or infectious colitis, and gastroesophageal reflux.

Gastroesophageal reflux, the most common cause of emesis in infants can be misinterpreted as intussusception when it is accompanied by abdominal pain. Bloody stools in infants can also be indicative of underlying allergic colitis; however, patients with allergic colitis generally appear well without vomiting or abdominal pain. Appendicitis can present similarly, with abdominal pain and vomiting and is one of the most challenging entities to differentiate from intussusception.

In patients who present primarily with lethargy, the differential diagnosis is similarly broad and complex. Electrolyte abnormalities, notably hypoglycemia and hyperglycemia should be ruled out. Primary neurologic diseases such as intracranial masses, hemorrhage, ingestion, or seizures need to be considered.

If a right upper quadrant mass is present, other causes of abdominal mass in children in this age should be considered. Wilms tumor is generally characterized as painless and is not usually associated with vomiting. The presence of hematuria would differentiate this from intussusception. Hepatoblastoma can be felt originating from the liver. In patients with neuroblastoma, there can be a history of weight loss, flushing, irritability, diarrhea, and possible electrolyte abnormalities such as acidosis and hypokalemia. If neuroblastoma invades or encroaches upon the spinal cord, lower extremity hyperreflexia and flaccidity may be present.

ED EVALUATION

There are no laboratory tests that can confirm the diagnosis of intussusception, but testing can assist with risk stratification of patients in whom this diagnosis is considered. A stool examination for occult blood has a high benefit-to-cost ratio. A negative guaiac should not be used to exclude the diagnosis, yet a positive stool guaiac should reduce the threshold for further evaluation and management decisions. Other laboratory tests are generally used to exclude other conditions that may have similar presentations. Tests that may help narrow the differential diagnosis include a complete blood count, C-reactive protein, glucose, electrolyte panel, liver function testing, urine analysis, and stool culture. In an ill-appearing child in whom there is concern for underlying peritonitis, sepsis, or perforation, an arterial or venous blood gas, lactate level, and coagulation studies may be helpful. Urine drug screen and computed tomography scan should be considered in patients who have painless intussusception presenting as profound lethargy. The child who appears septic should undergo blood, urine, and cerebrospinal fluid testing.

When intussusception is considered, abdominal radiographs can be utilized to help with risk stratification. Most centers perform two-view radiographs, including supine and left lateral decubitus, but the addition of a third prone view has been argued to further assist in diagnosis (12). Common findings on radiographs that are consistent with intussusception include the presence of a soft tissue mass (typically in the right upper quadrant, often with loss of the visible liver margin), a target sign (concentric radiolucent circles overlying the right kidney), a crescent sign (the cap of the intussusceptum seen within the lumen of the intussuscipiens), paucity of air within the ascending colon or right lower quadrant, and evidence of small bowel obstruction. However, radiographs may be normal, especially early in the course of the disease, or equivocal (13,14). Interobserver reliability among radiologists remains imperfect as well. Thus, negative plain abdominal x-rays do not rule out intussusception and should be followed by ultrasound if intussusception is suspected clinically. The presence of free air precludes reduction by enema.

Children in whom the history and physical examination are highly suggestive of intussusception, should proceed directly to an abdominal ultrasound. Ultrasound is superior to abdominal radiographs, with a sensitivity and specificity that both approach 100%. Ultrasound has been successfully performed by both radiologists and pediatric emergency physicians (15). Ultrasound findings consistent with intussusception include a “target sign” on transverse scan, as well as a “pseudokidney” or “sandwich” sign on longitudinal scan. Ultrasound is the initial diagnostic study of choice for most patients, as it provides a rapid diagnosis without exposure to radiation and allows for evaluation of possible pathologic lead points or alternative diagnoses. Studies have shown that emergency physicians, with limited training, can accurately diagnose idiopathic ileocolic intussusception utilizing bedside ultrasound. If ultrasound is not available, or if the ultrasound results are equivocal, either a barium or contrast enema can be performed, since it is both diagnostic and therapeutic. Abdominal computed tomography scans can accurately detect intussusception, but because of the significant

associated radiation exposure involved, ultrasound is preferred when the suspicion for intussusception is high.

KEY TESTING

- Abdominal ultrasound
- Air or contrast enema

ED MANAGEMENT

Most patients who have suspected intussusception require the placement of an intravenous line. These patients should undergo fluid resuscitation as well as correction of any underlying electrolyte imbalances. Although not universally performed, pending imaging procedures, a nasogastric tube should be considered. All patients should be made NPO (i.e., nothing by mouth).

Once intussusception has been confirmed, the patient should be referred for reduction, either via pneumatic or barium enema. Successful reduction rates are variable, but reported to be as high as 80% to 95% (16). Pneumatic enemas are currently favored over barium enemas given the risk of chemical peritonitis if perforation were to occur. Perforation is more likely to occur in patients who are diagnosed later, presumably owing to the higher degree of bowel edema and friability. Surgical reduction is indicated in patients in whom the diagnosis has been delayed or in those in whom reduction cannot be completed by enema. Patients who present with recurrent intussusception should also be considered for surgical reduction, to allow for exploration for a pathologic lead point (17). Surgical options for reduction are at the discretion of the surgeon and include both open and laparoscopic techniques. In patients in whom sepsis, peritonitis, or perforation is suspected, immediate fluid resuscitation, antibiotics, and surgical consultation should be obtained immediately. Antibiotics are not routinely recommended for patients in whom perforation is not suspected.

CRITICAL INTERVENTIONS

- There should be a low threshold for ordering an ultrasound to evaluate for intussusception.
- Children with apparent intussusception require hemodynamic stabilization before undergoing imaging.
- After stabilization, further treatment of intussusception is directed at reduction of the intussusception, most commonly by air or contrast enema.
- Appreciating the importance of timely reduction after the diagnosis is made—"time is bowel."

DISPOSITION

Well-appearing patients who have undergone successful contrast enema reduction can be discharged after a period of observation and successfully tolerating oral intake (18,19). If the patient continues to appear ill or dehydrated admission is warranted for further resuscitation. If the enema reduction was particularly difficult, indicating delayed diagnosis and more severe ischemia, observation should be considered. Parents should be counseled that in approximately 10% of children (20), intussusception recurs, the majority of which occur in the first 24 hours. Parents should be advised to return to the ED if pain or vomiting recurs.

Common Pitfalls

- Obstacles to accurate diagnosis include failure to recognize the typical history, failure to perform a rectal examination, reluctance to accept the diagnosis in a well-appearing child with a prolonged history, and failure to consider the disease in older children.
- Marked variation from the classic picture may lead to misdiagnosis. The absence of pain, lack of a mass, presence of bright red rectal bleeding, or altered mental status should not dissuade one from considering the diagnosis.
- A normal plain abdominal radiograph in a suspected case of intussusception should not deter performance of further imaging studies such as ultrasound.

ACKNOWLEDGMENT

The authors of this chapter wish to credit the previous edition author, Dr. Adam Singer for is past contributions.

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CHAPTER 271

Malrotation and Midgut Volvulus

Maybelle Kou

Intestinal malrotation with midgut volvulus is a form of torsion in which the small intestine wraps around the superior mesenteric artery (SMA). It is a diagnostically challenging condition particularly in infants causing significant morbidity and mortality if not diagnosed and corrected in a timely fashion (1). This congenital defect may not be symptomatic unless coupled with a midgut volvulus which leads to potentially catastrophic bowel ischemia. Bilious vomiting is the hallmark feature of malrotation with midgut volvulus, and is a complaint that must be evaluated thoroughly in all cases.

Intestinal malrotation is reported to occur in 1/200 to 1/500 live births, although *symptomatic* malrotation may occur in only 1/5000 live births (2–4), most commonly in the first few months or the first year of life (3). Despite the preponderance of early presentations, malrotation may remain asymptomatic for years, with a likely higher prevalence than reports suggest. Cases of malrotation with midgut volvulus have been described in the adult literature, and should be considered in the differential diagnosis of an adolescent or adult presenting with UGI obstruction or undifferentiated intermittent abdominal pain (1).

EMBRYOLOGIC AND ANATOMIC CONSIDERATIONS

Malrotation results from the abnormal embryologic rotation positioning and anchoring of the intestinal midgut with respect to the SMA.

Critical anatomic structures associated with intestinal malrotation are the duodenojejunal and cecocolic midgut; these are portions of the intestine proximal and distal to the SMA. During the 5th week of embryologic development, after extrusion and rapid lengthening through the abdominal wall, the intestine makes two distinct 270-degree turns in a counterclockwise direction upon return into the peritoneal space by the 12th week (3,4). Proper embryologic rotation allows fixation of the proximal midgut (duodenum) in the left upper quadrant at the ligament of Treitz, the junction at which the duodenum transitions from the retroperitoneum to become the jejunum (duodenal–jejunal junction [DJJ]). The distal midgut (cecum) comes to lie in the right iliac fossa. The intermediate intestine lies anteriorly, encased in a "fan" of omentum." In the most common form of malrotation, this counterclockwise rotation is incomplete, the position of the proximal midgut anchoring posteriorly relative to the SMA and the distal portion anchoring anteriorly with additional colonic attachments to the right retroperitoneum, known as Ladd bands. *Midgut volvulus occurs with the twisting of the midgut about a narrow pedicle in the axis of the SMA placing bowel supplied by the SMA at risk for ischemia.* There are a number of anatomic variants that complicate the diagnosis of malrotation. Ladd bands, for example may compress the duodenum and create intermittent symptoms similar to but not necessarily midgut volvulus (3).

CLINICAL PRESENTATION

The clinical presentation of children with intestinal malrotation is variable and dependent on the presence or absence of volvulus which can be notoriously episodic. Symptoms may or may not include bilious vomiting, intermittent abdominal pain and distension (2). While most cases of malrotation with midgut volvulus will present in small children, the diagnosis must still be

entertained in older children presenting with UGI obstruction whose early courses may have been more indolent or asymptomatic.

Neonatal Presentations

Vomiting in infancy is a common emergency department (ED) chief complaint, however, *an infant with bile-stained vomit has malrotation with midgut volvulus until proven otherwise.* The range of presentations can be widely variable. Infants with bilious emesis alone may have an unremarkable initial examination and appear well. The least challenging and most obvious presentation in the neonatal age group is of bilious vomiting, and abdominal distension. Bloody diarrhea has been described and infants may present with crying spells or symptoms of dehydration including lethargy and fatigue. Infants who have progressed to bowel ischemia and infarction may appear to be in shock with the appearance of sepsis.

Infant and Childhood Presentations

Older infants and children with intermittent volvulus may present with intermittent pain with or without vomiting. While bilious vomiting is an ominous sign and may suggest UGI obstruction and/or volvulus, it is not always present. Malrotation should be suspected in a child with chronic intermittent idiopathic abdominal pain, chronic malabsorption and/or diarrhea, however, in a well-appearing child with no acute impending intestinal catastrophe a less emergent work-up can be arranged.

DIFFERENTIAL DIAGNOSIS

In addition to conditions described above, the differential diagnosis of a neonate with bilious vomiting and abdominal distension should also include NEC, duodenal webs, strictures, intestinal ileus, and Hirschsprung disease. Infants and children with intussusception can also present with symptoms of UGI obstruction, vomiting, and shock due to intestinal ischemia that may be impossible to distinguish clinically. Incarcerated hernias may also paint a picture of bowel obstruction. The diagnosis must also be entertained in infants with

failure to thrive, such as those that exhibit poor feeding or persistent intermittent nonbilious vomiting. This may be mistaken for conditions such as milk intolerance, pyloric stenosis or GERD. Infants with "heterotaxy" (congenital cardiac defects) may also be at high risk for intestinal malrotation due to visceral anatomic abnormalities. Finally, there is a clear association between children with intestinal malrotation and other congenital anomalies (3).

ED EVALUATION

The evaluation of infants or children with bilious vomiting and the suspicion of malrotation with midgut volvulus should include rapid assessment for dehydration and shock. Those presenting in shock should have prompt initiation of intravenous fluid resuscitation and gastrointestinal decompression, including airway protection and nasogastric tube placement. A detailed feeding history should be performed on any infant with vomiting to elicit relationship to feeding, weight gain, history of prematurity, stooling patterns, and concurrent illness. Physical examination should be performed carefully, noting presence of abdominal bowel sounds, peritoneal signs, and other anatomic considerations such as hernias and imperforate anus.

The ill-appearing child with evidence of ongoing symptoms and dehydration, may exhibit electrolyte disturbances, however in well-appearing children, blood work may be unrevealing. In ill-appearing children laboratory work is unlikely to compliment medical decision making and should not delay radiographic studies or surgical consultation. The literature does not describe utility of inflammatory markers for this condition, although serum lactates have long been used in the diagnosis of intestinal ischemia in adults their utility in children is not proven and not currently recommended. In short there is no definitive laboratory study for the diagnosis of malrotation with midgut volvulus; diagnosis relies on timely radiographic evaluation.

UGI Series: The current gold standard test for diagnosis of malrotation and midgut volvulus is the contrast UGI series, the

purpose of which is to document the position of the DJJ and cecum and attempt to measure the mesenteric base (5). The radiology literature stresses the need for meticulous technique in acquiring these images, with a false-positive rate of up to 15% of patients (3) and reports of false-negatives (6). It is important that ED physicians understand the limitations of available testing (6,7). Most institutions follow local protocols with a combination of pulsed and still fluoroscopic images of the passage of orally administered contrast. This is followed with a delayed (5 minutes) AP view, the small bowel follow through. A confirmatory study may reveal a "double bubble" that is caused by Ladd bands compressing the duodenum, or the downward "corkscrew" appearance of the obstructed distal duodenum and proximal jejunum (Fig. 271.2). A shortened mesenteric base is associated with a higher risk of volvulus. In a retrospective study of 163 children the sensitivity of a UGI to diagnose malrotation was reported at one institution to be as high as 96%, and to detect volvulus 79% (7). This study stresses the importance of a true lateral view to document the position of the duodenum, and of a small bowel follow through to determine the position of the cecum in indeterminate cases. The overfilled stomach can also displace bowel, so a baby should not be overfed contrast (3). Delayed films in stable patients may also be helpful in diagnosis of in determinant cases.

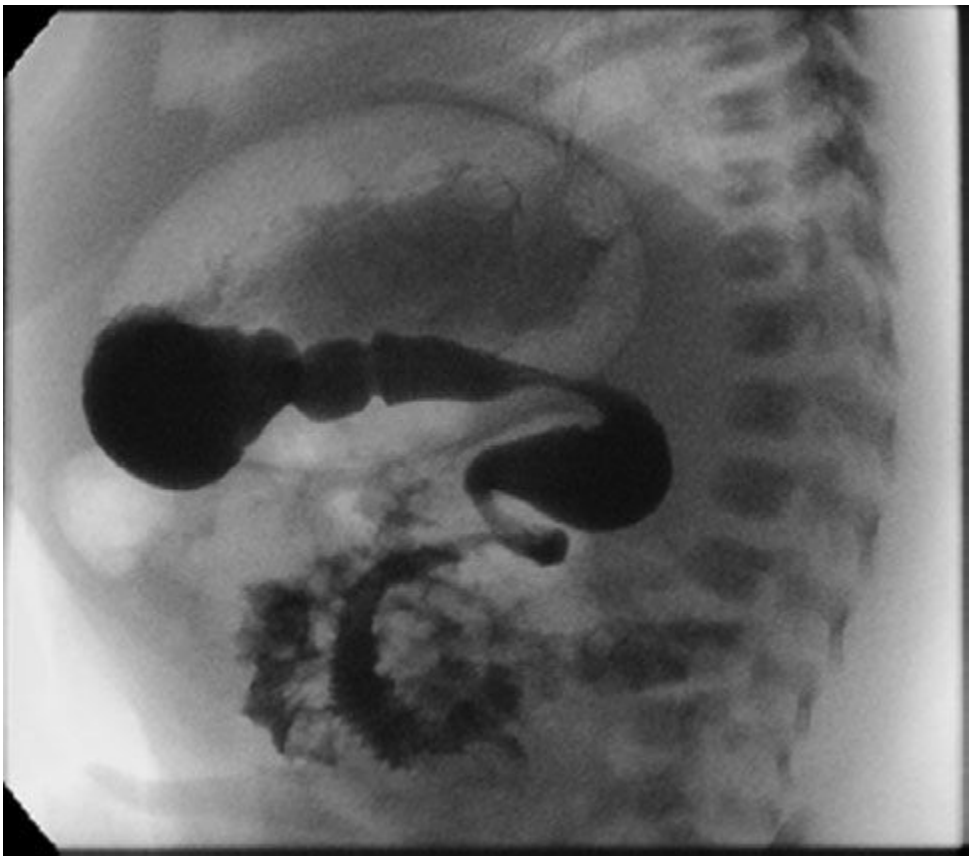

FIGURE 271.2 This image demonstrates the "corkscrew" appearance of a midgut volvulus. (Image courtesy of Dr. John Lee.)

Ultrasound: Although ultrasound has become increasingly popular in conjunction with the UGI series for the diagnosis of malrotation and volvulus, studies in the literature are limited with no prospective comparisons of UGI series to US. The purpose of ultrasound is to document the relationship of the superior mesenteric vein and artery (SMV/SMA) orientation, which may not always be visualized, and to detect the "whirlpool" sign seen in volvulus that suggests but is not always present (case reports of the whirlpool sign *without* volvulus have been published). Sensitivities of US alone are insufficient for its use without UGI, however it may be helpful in cases where UGI is not confirmative. Limitations of US notwithstanding, the study must be performed accurately, is operator dependent and may not be available at all institutions (8).

Plain radiography: A paucity of bowel gas may be suggestive of malrotation but also of many other things as well. While not sensitive for malrotation, plain radiography may be helpful to rule out other causes of abdominal distension, including NEC, megacolon, or free air (6,7) (Fig. 271.3) demonstrate a double bubble.

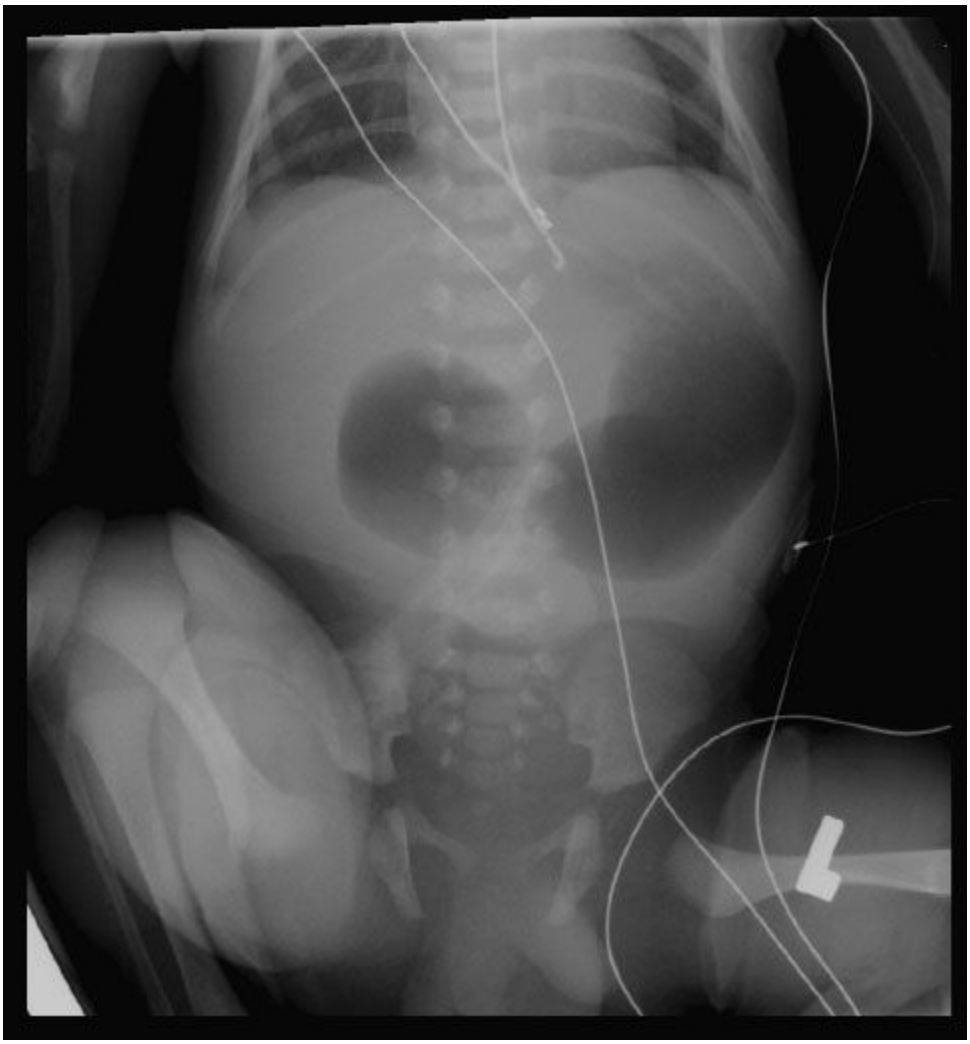

FIGURE 271.3 *Double-bubble sign: This image demonstrates gastric distension and paucity of air in the distal bowel, suggestive of midgut volvulus. (Image courtesy of Dr. John Lee.)

Computed tomography and barium enema are not currently considered first-line tests in the diagnosis of malrotation in children, however, may be employed if gold standard tests are unsuccessful in

making a diagnosis in a stable patient in whom the suspicion is high.

KEY TESTING

- UGI must be performed on any infant less than a year old with a history of bilious vomiting. This must demonstrate passage of contrast beyond the ligament of Treitz.
- Ultrasound may be used in conjunction with UGI.
- Abdominal x-ray does not replace the UGI.
- CBC, electrolytes, type, and cross.

ED MANAGEMENT

If the suspicion for malrotation is high enough based on clinical presentation, and primary assessment and fluid resuscitation have been initiated, further management depends largely on institutional capability and protocols. **If diagnostic tests are not available, the child should be transferred to the closest full service pediatric facility.** Temporizing measures must include intravenous fluid resuscitation, via IO if necessary, and nasogastric decompression. Antibiotics should be administered urgently in patients with peritoneal signs or evidence of infection. Antiemetics, such as ondansetron, may quell symptoms of nausea. Analgesia should be considered. Time is of the essence in the treatment of this entity.

CRITICAL INTERVENTIONS

- Low threshold for ordering UGI in infants with a history of bilious vomiting
- Recognition of volvulus, dehydration, impending shock
- IV fluid resuscitation via IO if necessary
- NG decompression/management of SBO
- IV antibiotics if suspicion of peritonitis
- Urgent or emergent radiologic evaluation
- Transfer to appropriate facility if tests and treatment are not immediately available

DISPOSITION

Intestinal malrotation and volvulus is a time-sensitive surgical emergency requiring immediate definitive surgical intervention. The most commonly performed procedure is named for William Ladd who pioneered the treatment (4). The Ladd procedure involves operative detorsion of the volvulus and division of Ladd bands to mobilize the cecum. Once the bowel is detorsed, and blood supply restored, the intestines are repositioned. In septic-appearing patients the discovery of frankly infarcted bowel is undesirable, and must be sacrificed if reperfusion is unsuccessful. Recurrent volvulus, although rare, has been described both immediately postsurgery and years later. A case report of successful use of thrombolytics in two neonates with volvulus and mesenteric thrombi has recently been described (9). Well-appearing, asymptomatic patients with incidental findings of malrotation can be managed with surgical consultation and follow-up.

Common Pitfalls

- Failure to consider malrotation in patients who do not present with bilious vomiting.
- Failure to consider malrotation if there is no vomiting or only intermittent volvulus.
- Failure to consider malrotation in any neonate presenting with bilious or intractable vomiting or reflux symptoms.
- Failure to consider malrotation in an infant or child with a grossly distended abdomen and symptoms of UGI obstruction.

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CHAPTER 272 Pyloric Stenosis

Ronald A. Furnival and Marissa A. Hendrickson

Hypertrophic pyloric stenosis is the most common surgical etiology of nonbilious vomiting in young infants presenting to the emergency department (ED) and the most common indication for abdominal surgery before 6 months of age (1). Pyloric stenosis occurs in 2 to 5 of every 1,000 infants, affecting four to five males for every female. The etiology of pyloric stenosis appears to be multifactorial, with a number of genetic, biochemical, and environmental associations (2). Erythromycin treatment during the first 2 weeks of life has been associated with a moderately increased risk for developing pyloric stenosis (2,3). Regardless of the underlying cause, pathologic gastric outlet obstruction results from hypertrophy of the pyloric muscle, leading to vomiting, dehydration, poor weight gain, and eventual hypochloremic metabolic alkalosis as the "classic" presentation.

CLINICAL PRESENTATION

The typical infant with pyloric stenosis has symptoms beginning on average at 3 weeks of age, with gradually worsening nonbilious vomiting. Pyloric stenosis is relatively rare among newborns younger than 1 week of age or infants older than 3 to 4 months of age; premature infants may present according to their corrected age (4). The progressive vomiting of pyloric stenosis is often characterized as "projectile" in nature, although it is not necessarily a key consideration in diagnosis and can be difficult to pinpoint historically (5). The infant with pyloric stenosis may also have a history of blood-streaked or "coffee-grounds" emesis from gastritis,

weight loss or poor weight gain relative to the birth weight, and physiologic jaundice (1).

As infants with pyloric stenosis present at an earlier age, often without significant complications, their physical examination findings have become correspondingly more subtle. These infants often appear continuously hungry, even after vomiting an attempted feed. With more advanced cases, the infant may appear thin-limbed and cachectic, with reduced subcutaneous fat stores, weight loss, and evidence of dehydration in up to 30% of cases (6). Visible peristaltic waves may be noted in the epigastrium (5). There has been a decrease in the proportion of infants presenting with the classic findings of hypochloremic alkalosis, weight loss, and a palpable pyloric muscle mass or "olive" in the right epigastrium (7). The use of a sucrose-dipped pacifier, ventral decubitus positioning or flexed-hip positioning, nasogastric (NG) or orogastric tube placement for gastric emptying, and a very gradual approach may improve the likelihood of successful palpation of the olive (5). However, with the advent of modern imaging the frequency with which a palpable olive is documented has decreased from as high as 99% of cases in the 1970s to 13% currently (7).

DIFFERENTIAL DIAGNOSIS

The most common cause of nonbilious vomiting in the otherwise healthy infant is gastroesophageal reflux. The infant with reflux may have a history of overfeeding, positional variation in symptoms, or respiratory complications in the more advanced cases (8). Other common medical conditions presenting with nonbilious vomiting include viral gastroenteritis or an occult urinary tract infection, although both usually would have a history of shorter duration, with fever or other associated symptoms. Central nervous system disorders (hydrocephalus, intracranial hemorrhage, meningitis) may present with vomiting but seldom without associated neurologic findings in a healthy-appearing infant. Less common medical causes of nonbilious vomiting during infancy include congenital adrenal hyperplasia, inborn errors of metabolism, or renal insufficiency,

which may present with characteristic electrolyte abnormalities (i.e., hyponatremia and hyperkalemia with the salt-wasting form of adrenal hyperplasia) or specific diagnostic laboratory findings (9).

Though pyloric stenosis is the most common surgical consideration associated with nonbilious vomiting in early infancy, other surgical conditions (intestinal malrotation with volvulus, intussusception, Hirschsprung disease, tracheoesophageal fistulas, esophageal or duodenal webs, duodenal atresia or stenosis, appendicitis, incarcerated hernia) must also be considered. Most infants with pyloric stenosis are initially well and *gradually* develop progressive vomiting over time. Congenital abnormalities of the upper gastrointestinal tract generally present early in the newborn period, without a progressive history of feeding difficulty. The infant with evidence of abdominal pain, abdominal distention, or bilious (either yellow- or green-stained) emesis must be considered to have an emergent surgical condition until proven otherwise. Immediate surgical consultation should be arranged, and imaging studies should be performed as necessary for diagnosis (10).

ED EVALUATION

If the infant's history and physical examination raise the possibility of pyloric stenosis, carefully attempt to palpate the olive for diagnosis. If the olive can be felt, no further diagnostic work up is required, and the surgeon can be notified. An imaging evaluation is appropriate if the abdominal examination does not reveal the diagnosis.

Abdominal imaging is performed in 70% to 90% of infants with pyloric stenosis, including those with a palpable olive. Though an increased use of imaging is credited with the earlier diagnosis and improved clinical condition of today's infants with pyloric stenosis, imaging is not necessary for those with a clear diagnostic examination. Upper gastrointestinal contrast imaging has been used, but ultrasound has increasingly become the modality of choice (11). With growing experience in ultrasonography among surgeons and emergency physicians, bedside ultrasound is emerging as a

possibility (12–14). In patients with pyloric stenosis, ultrasound shows a thickened and elongated pylorus, with a thickness of 3 mm or greater, and pyloric length of 15 mm or longer, having 100% sensitivity and 97% to 99% specificity for the diagnosis (15).

KEY TESTING

- Infants suspected of having pyloric stenosis should be evaluated with focused abdominal ultrasound to establish diagnosis.
- Assess serum glucose and electrolytes for hypoglycemia, metabolic alkalosis, hyperchloremia, and hypokalemia.

ED MANAGEMENT

Once the diagnosis of pyloric stenosis is clear, intravenous (IV) access should be obtained, and the infant should remain NPO. NG tube placement for gastric decompression is controversial as it may increase complications, so it is generally not recommended (16). Blood should be obtained for the measurement of serum glucose and electrolytes. With earlier recognition of the condition electrolyte abnormalities, ranging from metabolic acidosis early on, to the classic hypochloremic metabolic alkalosis with more advanced illness, are uncommon (<15% of cases) (7). Infants presenting with elevated serum bicarbonate (>25 mEq/L) and severe hypochloremia (<99 mEq/L) generally have had a longer duration of vomiting, with more severe dehydration and greater weight loss, and as a result may have longer hospital stays (5,7).

The primary goals of preoperative care are IV fluid resuscitation and correction of any electrolyte and acid–base imbalances. Preoperative fluid resuscitation should consist of one or two initial 20 mL/kg IV boluses of normal saline, followed by 5% dextrose and one-half normal saline at 1.5 times the infant's maintenance rate. If the serum potassium is not elevated, 20 mEq/L of KCl should be added to the IV infusion. Complete fluid resuscitation with correction of alkalosis prior to surgery decreases the risk of postoperative apnea (5).

CRITICAL INTERVENTIONS

- The dehydrated infant with suspected pyloric stenosis should receive 20 mL/kg IV normal saline boluses and have a serum glucose and electrolyte panel sent to the lab while awaiting surgical consultation or imaging studies.
- Adjust the IV fluid infusion to 5% dextrose and one-half normal saline at 1.5 × the maintenance rate after the initial boluses. Include 20 mEq/L KCl if the serum potassium is not elevated.
- Keep the infant NPO.

DISPOSITION

The infant with diagnosed pyloric stenosis must be hospitalized for fluid resuscitation and surgical intervention. The Ramstedt extramucosal pyloromyotomy remains the standard approach, with excellent cosmetic and functional outcomes, minimal morbidity, and very low mortality (<0.5%) (17–22). Though the open procedure has had a record of remarkable success and longevity, laparoscopic pyloromyotomy is gaining favor. A number of recent studies have shown small improvements in some outcomes with the laparoscopic approach, including shorter stays, improved cosmesis, and better cost-effectiveness (19,22–26). Excellent outcomes for either procedure appear to be volume dependent for both the surgeon and the institution, with fewer complications noted for those with larger numbers of procedures (17,20,21) and in children's hospitals compared to general hospitals (27). Early postoperative feeding protocols have reduced the total hospital length of stay for the average infant with pyloric stenosis to 48 hours, with few complications. Post-pyloromyotomy vomiting is common, with coexisting gastroesophageal reflux present in 10% to 15% of affected infants. This vomiting usually resolves within 1 to 2 weeks after surgery; persistent vomiting may represent the very rare failed pyloromyotomy. Nonsurgical medical therapy for pyloric stenosis with IV atropine has been studied primarily in Europe and Japan, but it requires a significantly longer hospital stay than pylorotomy,

has an unacceptably high failure rate, and is rarely used in North America (28).

Common Pitfalls

- Assuming that bilious vomiting in the infant <2 months of age is pyloric stenosis. Bilious emesis mandates an immediate UGI for possible malrotation and volvulus, as well as prompt surgical consultation.
- Inadequate IV fluid resuscitation in the infant with hypochloremic metabolic alkalosis.

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CHAPTER 273
Foreign Bodies

Tim Young and Lance Brown

The emergency department (ED) management of foreign bodies can be simple and rewarding. There are three basic elements of management: (1) attempted removal, (2) reassurance, and (3) consultation. The plan will depend on the body cavity, the foreign body, and the clinical presentation. This chapter discusses foreign bodies of the ear, nose, airway, and gastrointestinal tract. Management of pediatric vaginal foreign bodies is discussed in Chapter 287.

EAR FOREIGN BODIES

CLINICAL PRESENTATION

Children of all ages have been described with foreign bodies in the ear canal (median age 6 years) (1,2). Presenting complaints may include pain, discomfort, decreased hearing, and bleeding (1). Ear foreign bodies include insects, paper, beads, seeds, eraser tips, earring parts, toy parts, and disk or button batteries (1–4).

DIFFERENTIAL DIAGNOSIS

It is usually easy to identify foreign bodies in the ear canal. Impacted wax and rare ear canal masses may be mistaken for foreign bodies. Chemicals released from disk or button batteries can cause an intense localized inflammation that can mimic otitis externa (3).

ED EVALUATION AND MANAGEMENT

The ED evaluation of a suspected ear foreign body is almost always straightforward and involves visual inspection of the ear canal with an otoscope. If a button battery is suspected, radiography can easily identify this metallic foreign body.

Most ear canal foreign bodies can be removed by emergency physicians in the ED (1,2). The most commonly described techniques involve grasping the object with forceps, using a hook, loop, or curette to drag the object out of the ear canal and irrigation to wash the object out (1,5). A loop may be fashioned from a paperclip when more specialized tools are not available (6). Irrigation should only be undertaken if the tympanic membrane is intact (7). Cyanoacrylate applied to the blunt end of a cotton swab may be useful to remove a round smooth object such as a bead in a child who is cooperative or sedated (8). It is critical that the child be still and that the cyanoacrylate be used sparingly to avoid applying the adhesive to the ear canal. Procedural sedation improves the chances of successful removal in the ED (1).

Button batteries in the ear canal must be removed urgently to avoid continued tissue destruction (3), In the event that an ear canal foreign body other than a button battery cannot be removed in the ED, the patient may be referred to an ear, nose and throat (ENT) surgeon for removal using an otomicroscope in the clinic or operating room (9).

NASAL FOREIGN BODIES

CLINICAL PRESENTATION

Nasal foreign bodies tend to present in young children (median age of 2 to 3 years) (1,10). These children are asymptomatic about 50% of the time (1,10). Less common complaints include a foul odor, persistent nasal discharge, pain, discomfort, and bleeding. In about 10% of cases, unilateral nasal discharge is the sole presenting complaint (1,10). The most commonly encountered nasal foreign bodies include beads, plastic toy parts, corn kernels, and beans (10).

Children may also present to the ED with button batteries in their noses (4). Bilateral nasal magnets may adhere across the nasal septum causing pressure necrosis and perforation (11).

DIFFERENTIAL DIAGNOSIS

Young children with unilateral nasal discharge should be treated as if they have a nasal foreign body until proven otherwise (5). Nasal polyps may be mistaken for foreign bodies. Children who have a foul odor emanating from the mouth or nose may have halitosis, purulent pharyngitis, sinusitis, or a dental infection.

ED EVALUATION AND MANAGEMENT

A nasal foreign body can be identified by visually inspecting the nasal passages. Good lighting and a pediatric nasal speculum may be helpful.

The vast majority of nasal foreign bodies can be managed in the ED by emergency physicians (1,10). Sedation may be helpful in uncooperative children with large or adherent foreign bodies (1). The techniques for removal include grasping the object with forceps, using a hook, loop, or curette to drag the object forward, and suction applied directly to the foreign body (5). A positive pressure technique may be used whereby the parent applies pressure to the contralateral nostril and then blows into the mouth to expel the foreign body (12). Another technique is to insert a balloon catheter (such as a 6-French silicon Foley catheter or Fogarty vascular catheter) past the foreign body, inflate the balloon, and then withdraw the catheter with the balloon inflated. This is a good choice for large, round objects that are difficult to grasp and friable or fragmented materials such as clay or paper. Bilateral nasal magnets adherent across the nasal septum may be removed by placing the metal handle of a pair of forceps in each nostril to break the magnetic attraction and individually remove the magnets (13).

Essentially all children with nasal foreign bodies are discharged home (1). If a foreign body cannot be removed in the ED, outpatient referral to an ENT surgeon is appropriate in all cases except button

batteries and magnets adherent across the nasal septum, which require urgent removal to avoid tissue necrosis.

AIRWAY FOREIGN BODIES

CLINICAL PRESENTATION

Although aspirated foreign bodies are uncommon (5), they are most commonly seen in toddlers, and the most common symptoms include choking or coughing (5,14). Other signs and symptoms include dyspnea, fever, and wheezing. Stridor, hemoptysis, or completely asymptomatic presentations are uncommon. The most commonly reported aspirated objects are food-related, with peanuts accounting for about one-third of cases (5).

DIFFERENTIAL DIAGNOSIS

Symptoms associated with aspirated foreign bodies are nonspecific and may describe a wide variety of common pediatric ailments including viral upper respiratory tract infections, bronchiolitis, croup, asthma, pneumonia, and hydrocarbon aspirations.

ED EVALUATION AND MANAGEMENT

Definitively determining whether a child has aspirated a foreign body can be difficult because radiography and the physical examination are insensitive diagnostic tools (15). If the object is radiopaque, a two-view chest x-ray can clearly reveal the location of the foreign body in the trachea or bronchus. Unfortunately, about 85% of aspirated foreign bodies are radiolucent. If the radiology technologist can time it properly, inspiratory and expiratory chest x-rays may be helpful, revealing a normal symmetric inspiratory study but hyperinflation on the expiratory film on the side of the foreign body. Bilateral lateral decubitus films may reveal a failure of the mediastinum to shift downward toward the affected side. However, these techniques are insensitive and have high false positive rate (15). A careful history and physical examination and re-assessments

can help determine disposition in uncertain cases. Bronchoscopy is often both diagnostic and therapeutic (14).

Once an aspirated foreign body has been identified or is strongly suspected, consultation for bronchoscopy is indicated. A variety of pediatric specialists perform this procedure, including pulmonologists, intensivists, otolaryngologists, and surgeons. Aspirated foreign bodies and children with a clinical picture suspicious for aspirated foreign bodies should undergo urgent bronchoscopy.

GASTROINTESTINAL FOREIGN BODIES

CLINICAL PRESENTATION

Swallowed foreign bodies are common (16). Most children with subdiaphragmatic foreign bodies are asymptomatic, including those who ingest batteries (5,17). Developmentally delayed children may ingest large or sharp foreign bodies, present in an atypical fashion, or provide a limited history as a result of communication difficulties (18). The most widely studied esophageal foreign bodies are coins (5). More than 90% of children with esophageal coins are symptomatic before or at the time of presentation to the ED (5). Symptoms of esophageal foreign bodies include drooling, substernal pain, and a foreign body sensation. Recent years have seen an increase in magnet ingestion presentations to the ED commensurate with the increasing availability of small, high-powered rare earth magnets in the form of toys and accessories for both children and adults (19). Multiple ingested magnets can trap adjacent bowel loops and cause intestinal wall necrosis. The child may present with abdominal pain without fever, or symptoms of obstruction, volvulus, or perforation (19).

DIFFERENTIAL DIAGNOSIS

Although usually asymptomatic, subdiaphragmatic foreign bodies may present with abdominal pain or rectal bleeding (20). Conditions such as appendicitis, intussusception, Meckel diverticulum,

intestinal polyps, or other rare causes of abdominal pain must be included in the differential diagnosis.

ED EVALUATION AND MANAGEMENT

A traditional approach for evaluating a child with an ingested foreign body is to obtain x-rays from the nasopharynx to the bottom of the pelvis, looking for radiopaque foreign bodies. If a foreign body is identified, the critical question is whether the foreign body is esophageal, since these typically require treatment. If a child is asymptomatic, can eat and drink without apparent pain or difficulty, and has a negative set of x-rays, a subdiaphragmatic radiolucent foreign body is assumed. If the child has persistent foreign body sensation or pain in the substernal area or neck and the x-rays are unrevealing, the child may need to undergo esophagoscopy to evaluate for esophageal abrasions or a radiolucent esophageal foreign body. The use of handheld metal detectors has also been described in the evaluation of ingested coins. When used by emergency physicians, they are highly sensitive and specific for coin presence and highly accurate for coin localization (21). When the coin is localized to the stomach or beyond, children have been discharged without adverse events (22). This approach may save time and radiation exposure.

Subdiaphragmatic foreign bodies, including sharp objects and intact batteries, pass spontaneously the vast majority of the time in children with normal anatomies (18,23). Exceptions include very large or very long and pointed objects (typically ingested by developmentally delayed older school-aged children), children with abnormal gastrointestinal anatomy (e.g., an ileostomy), with multiple magnets in the intestines (19), with intestinal batteries that could be damaged or appear to be fragmenting on x-ray (17), and symptomatic children with evidence of peritonitis.

The vast majority of ingested foreign bodies, especially those that have been confirmed to be subdiaphragmatic, can be managed expectantly without further intervention unless symptoms such as vomiting, bloody stools, or abdominal pain develop. Although it has

been historically recommended that parents sift through stools until the foreign body is identified as having been passed, this process does little more than punish the parents. Children who have ingested multiple magnets typically require a laparotomy for magnet removal (19). Esophageal foreign bodies, especially button batteries, tend to need removal to avoid esophageal erosion (Fig. 273.1) (5). Coins above the thoracic outlet generally have low rates of spontaneous passage and risk airway compromise and obstruction; therefore, they should be removed urgently by a qualified specialist (24). Children with acutely ingested esophageal coins below the thoracic inlet may be observed for up to 16 hours for spontaneous passage, which occurs in up to 40% of cases (25).

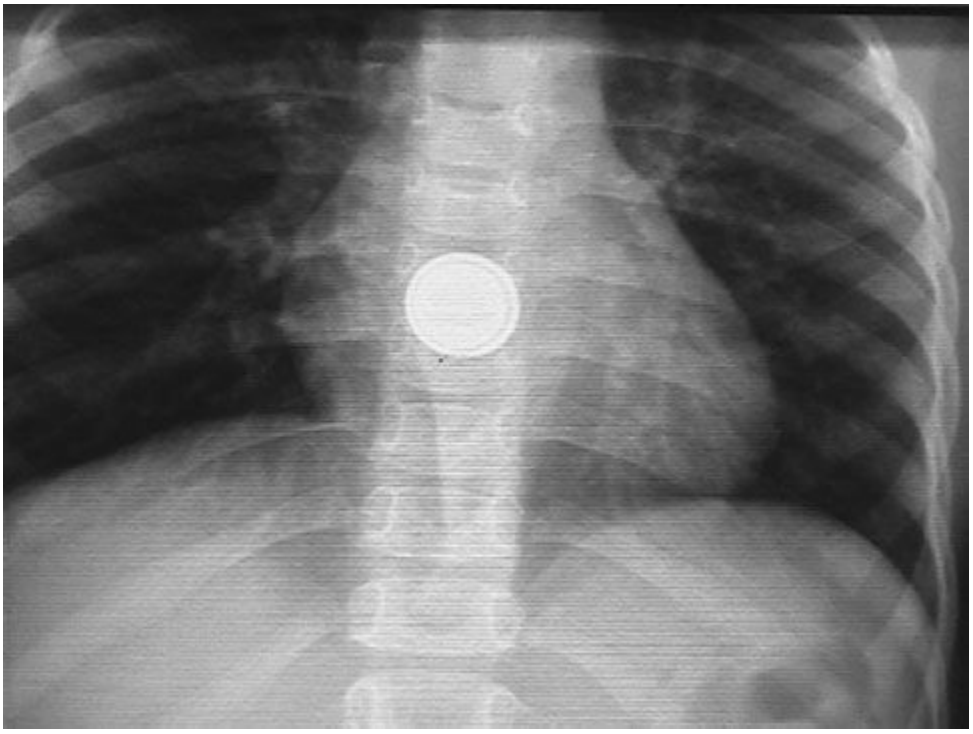

FIGURE 273.1 Radiograph of a large, flat disk battery in the distal esophagus of a young child. Note the faint circular area of relative radiolucency near the periphery of the object shadow. This characteristic target appearance distinguishes this object from the more homogeneous appearance of an ingested coin. (Photograph by Lance Brown, MD, MPH.)

CRITICAL INTERVENTIONS

- Arrange for urgent removal of button batteries in the ears, nose, or esophagus.
- Consider use of sedation to remove ear foreign bodies if not accomplished easily on first attempt.
- Arrange for urgent removal of multiple magnets that may adhere across tissue planes causing pressure necrosis. This may occur across the nasal septum or in the GI tract.

Common Pitfalls

- Delaying management of a disk battery or multiple magnet ingestion.
- Failure to use procedural sedation and appropriate equipment to manage ear foreign bodies.
- Failure to consider foreign body as the cause of unilateral nasal discharge.
- Relying on radiography to rule out an aspirated foreign body.

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CHAPTER 274 Diabetic Ketoacidosis

Cristina M. Estrada and Timothy G. Givens

Diabetic ketoacidosis (DKA) is caused by either an absolute or a relative insulin deficiency accompanied by increased action of four counterregulatory hormones: glucagon, epinephrine, cortisol, and growth hormone (1,2). Counterregulatory hormone activity increases the patient's insulin resistance, thus compounding the effects of insulin deficiency. The results of this imbalance are hyperglycemia, dehydration, ketosis, and acidosis.

Precipitating events for this cascade include acute infection, inflammatory reactions, trauma, psychological stress, or medical noncompliance in patients known to have insulin-dependent diabetes mellitus (IDDM); recurrent DKA almost always occurs because of failure to take insulin as prescribed. Approximately 30% of cases of new-onset IDDM present as DKA (3); a high index of suspicion is required to make the initial diagnosis in infants and children. Mortality in DKA is most often associated with the development of cerebral edema, which occurs more frequently in children than adults (4–7).

CLINICAL PRESENTATION

Children with DKA may present variably making the diagnosis challenging in patients not previously known to be diabetic. Acutely, the child may appear moderately dehydrated and be misdiagnosed as having viral gastroenteritis or a urinary tract infection. Presenting symptoms include nausea, vomiting, abdominal pain, hyperpnea, fruity breath odor, dehydration,

lethargy, or coma. Polyuria, polydipsia, and polyphagia, three classic features of diabetes, coupled with weight loss should alert physician to consider DKA.

DIFFERENTIAL DIAGNOSIS

All patients presenting with vomiting should be queried for underlying histories of polyuria and polydipsia because new-onset diabetes with DKA may easily be mistaken for a routine case of gastroenteritis or a urinary tract infection. Occasionally, dehydrated children with gastroenteritis will have hyperglycemia and glucosuria caused by stress but do not have IDDM; since they are usually nonketotic (8).

The degree of hyperglycemia appears to be significantly associated with the severity of illness. However, the evidence is unclear as to whether patients with stress-induced hyperglycemia are at risk for future development of IDDM (8,9). If a history of diabetes is unclear or unavailable in a child with altered mental status, the differential diagnosis should widen to include intoxication, inborn errors of metabolism, Reye syndrome, sepsis, meningoencephalitis, nonketotic hyperglycemic coma, or hypoglycemic coma (10). In children with known IDDM, the differential diagnosis should focus on potential precipitants of DKA, such as bacterial infections, viral gastroenteritis, appendicitis, pancreatitis, or other acute intra-abdominal disorders.

ED EVALUATION

The evaluation of any child presenting with suspected DKA must address the following issues in a timely manner: (1) establishing the diagnosis, (2) assessing and correcting dehydration and electrolyte imbalance, (3) providing adequate insulin to restore normal metabolism, (4) searching for the precipitant cause of DKA, and (5) avoiding complications of therapy including cerebral edema, hypoglycemia, and hypokalemia.

DKA, as the name implies, has three components; hyperglycemia, ketosis, and acidosis. Patients may present with hyperglycemia

alone and with none of the other elements early in their course. Alternatively, they may present further along the continuum of illness and be hyperglycemic with ketonuria but have not yet become acidotic. It is therefore important to assess patients using clear criteria for hyperglycemia, ketonemia, and acidosis. Traditionally, patients have been deemed to be in DKA when the serum glucose level is greater than 300 mg/dL, ketonuria is detected by urine dipstick, and the pH measured via venous blood gas (VBG) is less than 7.30 or the serum bicarbonate is less than 15 mEq/dL. Patients who present earlier in their course of illness and are not in fulminant DKA may be candidates for less aggressive treatment. This may include additional doses of subcutaneous insulin on a sliding scale with close monitoring of glucose and urine ketones in consultation with an endocrinologist or primary care provider. It is important to appreciate the spectrum of presentations of DKA and how these may affect the ED evaluation and management.

Following a primary survey, the patient's degree of dehydration must be assessed. Estimates of dehydration are often underestimated, given the hyperosmolarity of the extracellular fluid in DKA patients. Relying solely on physical signs that correlate with extracellular volume loss (e.g., hydration of mucous membranes, skin turgor, and temperature) can be misleading and in general, one should assume at least 10%, or moderate, dehydration in all patients with DKA (1).

The interpretation of serum electrolyte levels must take into account the underlying physiologic derangements that accompany DKA. Measured serum sodium levels are often low secondary to the hyperosmolar state caused by hyperglycemia, which osmotically draws fluid into the intravascular space resulting in pseudohyponatremia. Correction of the serum sodium can be expected to occur without specific treatment as glucose levels fall during treatment for DKA. Serum potassium levels, on the other hand, may be elevated despite the patient's total body stores being depleted. In the presence of acidosis intracellular potassium ions are exchanged for extracellular hydrogen ions that may be lost via osmotic diuresis. Low-normal potassium levels in DKA may be

indicative of extreme total-body potassium depletion and continuous electrocardiographic monitoring for potassium-related cardiac dysrhythmias may be warranted.

KEY TESTING

- Initial serum testing including glucose, electrolytes, creatinine and urea nitrogen, blood gases, and hematocrit.
- A urinalysis should document the presence of ketones.
- The diagnosis of DKA is confirmed by the findings of hyperglycemia BG >300 mg/dL), a metabolic acidosis (pH <7.3 or HCO3 <15 mEq/L), ketosis.

ED MANAGEMENT

Treatment protocols for pediatric DKA vary considerably (10). Fluid replacement and correction of dehydration should begin as soon as possible. Formerly, volume expansion with a bolus of isotonic fluid such as normal saline, 20 mL/kg, was recommended during the first 1 to 2 hours of therapy. Because overly vigorous administration of fluids may precipitate a rapid fall in plasma osmolarity and is associated with the potential development of cerebral edema; pediatric treatment protocols now advise more conservative fluid replacement, on the order of 10 mL/kg during the first hour (11). Unless the patient is severely hemodynamically compromised, larger fluid boluses should be avoided (4).

Once the diagnosis of DKA has been confirmed, insulin administration should begin. Although insulin administration has been effective using intramuscular or subcutaneous routes, continuous low-dose intravenous infusion allows for slower, more even correction of hyperglycemia and is associated with fewer episodes of hypoglycemia than other routes of insulin administration (4). There is no evidence an initial bolus of intravenous insulin is helpful, and it may be harmful (1). Thus, a continuous intravenous infusion of insulin at a rate of 0.05 to 0.1 U/kg/hr is recommended. When mixing the insulin for infusion, the concentration of insulin should be at least 0.5 U/mL, and the

infusion line should be primed to overcome the effect of insulin binding to the intravenous infusion equipment. The addition of a single dose of the long-acting analogue insulin glargine to initial low-dose insulin infusion therapy may hasten resolution of acidosis and smooth the transition to subcutaneous insulin administration (12). Plasma glucose levels should be measured hourly and serum electrolyte concentrations and VBG every 2 to 4 hours. Calcium and phosphate concentrations should be checked every 8 hours. The rate of decrease in glucose should be no faster than 50 to 100 mg/dL/hr (1).

After the first hour, fluids should be adjusted to correct the free water deficit over the next 48 hours. This is accomplished with a solution of 0.45% sodium chloride (which closely approximates the fluid lost in DKA), with the addition of 40 mEq/L of potassium as either the chloride or phosphate salt. Some authors suggest that isotonic saline may be the most appropriate fluid for the first 24 hours of therapy (13). The overall guiding principle, independent of the particular choice of fluid, is the gradual correction of fluid and electrolyte deficits, with frequent monitoring of serum chemistries (1,14).

Dextrose is added to fluids when the plasma glucose levels approach 300 mg/dL; the desired goal is to maintain a glucose level between 200 and 300 mg/dL. At this point it is vital not to wean the insulin drip if the patient still has a clinically important anion gap. Glucose levels should be supported by the addition of dextrose-containing fluids and not by the tapering of insulin therapy. Some institutions use a “two-bag system” to easily titrate the dextrose concentration of intravenous fluids between 0% and 10% in response to the patient’s current serum glucose (15). In this technique, two bags of saline solution are prepared, one with 10% dextrose and the other 0% dextrose (simple normal saline solution). By regulating the rates of fluid administration from each bag, the amount of fluid can be maintained constant, whereas the glucose content of infusion can be adjusted to respond to changes in the patient’s serum glucose.

Hypophosphatemia and deficiency of 2,3-diphosphoglycerate are well-known features of DKA. They occur because of osmotic diuresis and phosphate competition with glucose for reabsorption at the renal tubules. Potassium phosphate has thus been proposed as an alternative to potassium replacement with the chloride salt. Correction of phosphate deficits has not been shown to clinically benefit children with DKA (2).

Both the benefits and the risks of the use of bicarbonate in the treatment of DKA remain unproven (16). The potential advantages of bicarbonate are improved myocardial function, reduction of potential for dysrhythmias, decreased insulin resistance, and a more rapid correction of acidosis. The major disadvantages of bicarbonate use are its potential for paradoxical central nervous system acidosis (caused by the increased diffusion of carbon dioxide across the blood–brain barrier), increased hemoglobin affinity for oxygen (which increases tissue hypoxia, because of reduced off-loading), and promotion of hypokalemia. Recent data show that bicarbonate therapy offers little benefit in terms of reducing the severity of acidosis, improving mental status, or correcting hyperglycemia (16). Rapid infusions of bicarbonate may produce hypokalemia and exacerbate the hyperosmolarity and have been associated with an increased incidence of cerebral edema in children (4). Therefore, bicarbonate, if is used at all, should be reserved only for severe and refractory acidosis or life-threatening hyperkalemia.

In spite of improvements in DKA management, mortality caused by cerebral edema has not changed (7). Data suggest a large percentage of patients in DKA have subclinical cerebral edema on computed tomography scans (3); however, clinically significant cerebral edema is reported in $<1\%$ of cases of DKA (5). Typically, signs of increased intracranial pressure present several hours into therapy, as the patient experiences a sudden decline in sensorium, headache, sluggish pupillary reflexes, or a change in vital signs despite improvement in metabolic and other clinical parameters.

Although cerebral edema has been thought to be related to aggressive fluid resuscitation in early DKA, there is no strong or consistent evidence implicating fluid administration as a primary

cause (17). What is known, however, in spite of a paucity of mechanistic evidence, is that children with new-onset IDDM and/or a prolonged period of untreated DKA are at increased risk for ultimately developing cerebral edema (3,17).

Once clinically apparent, cerebral edema is associated with a mortality rate of 60% to 80% and long-term neurologic morbidity in the majority of the rest. Hence, if cerebral edema becomes clinically evident, the patient should receive rapid aggressive intervention to reduce intra-cranial pressure—with intravenous mannitol (1 g/kg) or with 2 to 5 mL/kg of 3% saline (11). Intubation with mild hyperventilation should also be considered. Because of the devastating outcomes in patients who develop this complication, the need for frequent neurologic reassessments and early intervention cannot be over emphasized.

CRITICAL INTERVENTIONS

- A history of polyuria and polydipsia should be sought in every case of a child who is vomiting, particularly in very young children.
- Pediatric treatment protocols advise conservative fluid replacement, 10 mL/kg during the first hour.
- An initial bolus of intravenous insulin is not recommended because of concern about lowering the blood sugar too rapidly. A continuous infusion of intravenous insulin at a rate of 0.05 to 0.1 U/kg/hr is recommended.

DISPOSITION

Children in moderate-to-severe DKA should be admitted to a pediatric intensive or intermediate care unit because of the frequency and extent of monitoring required (1). Patients with new-onset IDDM should be admitted to a facility where age-appropriate diabetes education can be given.

Patients who can retain oral intake without vomiting and who are not significantly dehydrated or acidotic (pH >7.25) may be discharged home from the emergency department if appropriate

follow-up care can be arranged. Follow-up includes frequent telephone contact during the ensuing 24 hours with an individual knowledgeable in diabetes management.

Common Pitfalls

- Failure to administer adequate insulin, which may result from errors in insulin dilution or infusion. Concerns about therapy-related hypoglycemia are addressed by adding dextrose to the fluid replacement, not by slowing or stopping the insulin infusion.
- Failure to treat the precipitating process. Patients with refractory DKA should be thoroughly reexamined for a source of infection or intra-abdominal disorder, such as pancreatitis or appendicitis.
- Inadequate volume expansion from failure to monitor the patient's fluid input and output.
- Too-rapid correction of the hyperosmolarity may lead to cerebral edema and brainstem herniation.
- Inadequate potassium replacement during correction of acidosis, which leads to a shift of potassium into the cells and resultant hypokalemia.

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CHAPTER 275

Metabolic and Endocrine Disorders

Jeffrey Hom

Metabolic disorders can be acquired or congenital, and early consideration is important in previously healthy neonates with apparent metabolic derangements that are not attributable to infectious, neurologic, toxicologic, or endocrinologic causes. This chapter focuses on the general approach to metabolic disorders and their diagnosis in the emergency department (ED).

CLINICAL PRESENTATION

Children with metabolic disorders frequently present with nonspecific symptoms. Differences in presentation can be subtle, especially in the neonatal period. Vomiting, alterations in neurologic status, and feeding difficulties are perhaps the most prominent features of metabolic diseases. Frequently, these patients are evaluated for common diagnoses, such as sepsis, that do not quite "fit." In neonates and young infants, although sepsis is always a consideration, metabolic disorders should also be considered, based on known historical and laboratory findings. Metabolic diseases often present with derangements that are discovered on a basic chemistry panel. These include abnormalities of glucose, sodium, potassium, and bicarbonate (the latter suggesting metabolic acidosis). Each of these abnormalities is linked to a disease or a constellation of symptoms that clinicians must recognize and address promptly.

DIFFERENTIAL DIAGNOSIS

Hypoglycemia

In children, infants, and term neonates older than 1 to 2 days of life, hypoglycemia is defined as a serum glucose concentration less than 40 to 45 mg/dL (1,2). The laboratory value should be interpreted in the context of the patients' clinical presentation and not as an isolated numerical value. Thus, symptomatic patients with a glucose level of 50 to 60 mg/dL warrant treatment. Glucose is the primary energy substrate for the brain. Its blood levels represent a balance between exogenous supply, endogenous gluconeogenesis, and glycogenolysis. Mobilization of glucose is mediated primarily by insulin, which stimulates glucose uptake in cells and glycogen synthesis; its actions are opposed by glucagon, cortisol, epinephrine, and growth hormone.

Symptoms of hypoglycemia generally fall into two categories: (1) those associated with activation of the autonomic nervous system (adrenergic) and (2) those associated with decreased cerebral glucose utilization (neuroglycopenic). Adrenergic symptoms are usually seen when there is a rapid decline in blood glucose and are accompanied by findings of tachycardia, tachypnea, vomiting, and diaphoresis. More familiar are neuroglycopenic symptoms, which are usually associated with slower or more prolonged hypoglycemia. These include poor feeding, altered mental status, lethargy, and seizures; they are usually evident in older children and adults, but in infants the presentation may be subtle and include only hypotonia, hypothermia, or poor feeding. Early detection hypoglycemia in newborns and infants lessens the risk of permanent brain damage. Hypoglycemia that requires acute resuscitation or intensive care unit management is associated with increased mortality in children (3,4). Persistent hyperinsulinemic hypoglycemia of infancy is a common cause of neonatal hypoglycemia and should be considered from the newborn period to 6 months of age (5). Causes of hypoglycemia are listed in Table 275.1.

TABLE 275.1
Causes of Hypoglycemia

Decreased Production/Availability of Glucose
Low glycogen stores
  Small for gestational age, prematurity
Malnutrition/fasting
  Malabsorption/diarrhea

Increased Utilization of Glucose
Hyperinsulinemic states
  Infant of diabetic mother
  Persistent hyperinsulinemic hypoglycemia of infancy
    Nesidioblastosis
    Islet cell adenoma/hyperplasia
  Beckwith–Wiedemann syndrome
Stress
  Infection/sepsis

Combined or Other Mechanism
Inborn errors of metabolism
Hormone deficiency
  Adrenal (glucocorticoid) insufficiency
  Growth hormone deficiency
  Glucagon deficiency
Iatrogenic
  Insulin/oral hypoglycemic therapy
  Poisoning (ethanol, propanolol, salicylates)
  Reye syndrome

Hyponatremia

Hyponatremia is one of the most common electrolyte abnormalities in hospitalized and critically ill children (1,6,7). It is defined as a serum sodium level less than 125 to 130 mEq/L, although clinical symptoms are not usually seen until the serum sodium falls below 120 mEq/L. Hyponatremia is caused by salt-losing states, including vomiting and diarrhea, diuretic excess, and adrenal insufficiency, or by excess total body water states, such as infection-induced syndrome of inappropriate secretion of antidiuretic hormone (SIADH), nephrotic syndrome, and cirrhosis. Factitious, or pseudohyponatremia, can occur in the context of hyperglycemia, hyperlipidemia, or hyperproteinemia. In children, hyponatremia is

commonly caused by excess gastrointestinal (GI) losses from prolonged vomiting or diarrhea or from inappropriately diluted formulas. Pyridoxine-dependent seizures are a rare cause of intractable seizures in neonates.

Symptoms of hyponatremia may include altered mental status, lethargy, vomiting, diarrhea, seizures, and circulatory collapse. Vomiting can be both a cause and a manifestation of hyponatremia. The presence of symptoms is dependent in part on the rate of change in serum sodium. Gradual or chronic progression of hyponatremia may not become clinically evident even at levels less than 110 mEq/L; conversely, less severe levels of hyponatremia may be symptomatic if the decline in serum sodium is rapid. Treatment should be geared toward the underlying disorder, and aggressive treatment with hypertonic saline should be initiated *if the patient is acutely symptomatic* (i.e., seizures or circulatory collapse). Central pontine myelinolysis is a potential complication of too rapid correction of hyponatremia, although it has been less frequently described in children than adults (2,6). Hyponatremia in the pediatric population tends to occur acutely rather than chronically, and most cases of central pontine myelinolysis occur after sodium is rapidly corrected in the context of chronic hyponatremia.

Metabolic Acidosis

Metabolic acidosis occurs via three major mechanisms: (1) loss of bicarbonate from the kidney or GI tract, (2) excess acid from endogenous production or an exogenous source, or (3) underexcretion of acid by the kidneys. Neonates and infants are more susceptible than older children and adults to acidosis due to a lower ability to reabsorb bicarbonate and limited maximum net acid excretion.

The significance of metabolic acidosis depends on whether it is a normal anion gap (AG) acidosis or an increased AG acidosis. The AG is the difference between serum sodium and the sum of serum chloride and bicarbonate $Na^+ - (Cl^- + HCO_3^-)$. The normal range of the AG is somewhat age dependent but in children is 12 ± 4. Causes of metabolic acidosis based on AG are listed in Table 275.2.

TABLE 275.2
Causes of Metabolic Acidosis

Normal ANION GAP
Gastroenteritis/diarrhea
Renal tubular acidosis
Adrenal (mineralocorticoid) insufficiency
Increased ANION GAP
Mudpiles
Methanol, uremia, DKA, paraldehyde, iron or INH, lactic acidosis, ethylene glycol, salicylates
Inborn errors
Carbohydrate, amino acid, or fatty acid metabolism
Starvation
Chronic renal insufficiency

Clinical manifestations of metabolic acidosis are nonspecific and include altered mental status, vomiting, and poor perfusion. Tachypnea as a compensatory mechanism can be an important sign alerting the ED physician of possible metabolic acidosis. Breathing quality and depth can range from mild and shallow to the deep Kussmaul respirations of the severely acidotic patient. Treatment consists of appropriate fluid resuscitation and specific therapy of the underlying cause of the acid–base disturbance.

Diagnostic Entities

Adrenal Insufficiency

Adrenal insufficiency is either acquired or inherited and caused by primary adrenal disease or secondary to pituitary suppression. Congenital adrenal hyperplasia (CAH) is one of the primary causes of newborn primary adrenal insufficiency, whereas Addison disease is a more common cause in children and adolescents. Secondary adrenal insufficiency is more common in older children and frequently is a sequel of exogenous steroid use. Acute adrenal insufficiency or crisis occurs when the adrenal glands, in response to stress, fail to produce adequate glucocorticoid and mineralocorticoid. The common ED presentation involves a patient treated for a chronic disease, such as

asthma, who has recently discontinued steroids and is exposed to a precipitating stressor (e.g., infection). In patients with unexplained electrolyte abnormalities or hypotension, a careful history eliciting previous steroid use is the key to diagnosis.

CAH refers to a group of inherited defects in adrenal biosynthesis of cortisol. Low cortisol production stimulates pituitary production of adrenocorticotropic hormone (ACTH), which causes the characteristic hyperplasia of the adrenal cortex. Depending on the affected enzyme in the biosynthetic pathway, the synthesis of other steroids such as mineralocorticoids (aldosterone) or androgens may also be affected, and clinical expression of disease varies correspondingly. Deficiency of 21-hydroxylase (21-OH) accounts for up to 95% of CAH cases, and discussion here is limited to this particular form of CAH which occurs in 1 in 10,000 to 20,000 live births worldwide (8). Up to 75% of affected newborns have the "classic" salt-losing virilizing variant, which is associated with aldosterone deficiency and androgen overproduction; up to 25% have the nonsalt-losing virilizing type. The degree of virilization and other clinical signs is usually greater in the salt-losing variant.

Many states now screen newborns for CAH; however, these results may not be available for several weeks, and an acute adrenal crisis may occur during this time. Males are particularly prone to a missed diagnosis since their genitalia may appear normal at birth, in contrast to females, who usually exhibit ambiguous genitalia. Another physical examination sign is hyperpigmentation, which is caused by the accumulation of a corticotropin precursor that stimulates melanocytes; hyperpigmentation may be present in the axilla and scrotal or labial areas. Symptoms of the classic salt-losing type may begin 1 to 2 weeks after birth and include weight loss, poor feeding, vomiting, polyuria, and dehydration.

Acute adrenal insufficiency, whether acquired or secondary to classic CAH, is associated with hyponatremia, hyperkalemia, and hypoglycemia. A normal anion gap metabolic acidosis is often seen due to aldosterone deficiency. Unexplained hypotension unresponsive to intravenous (IV) fluids is another sign of steroid deficiency. In cases involving infection or trauma, the clinical

progression can be rapid and fulminant, leading to altered mental status, hypotension, or death. Treatment should be geared toward aggressive fluid resuscitation and rapid initiation of stress doses of corticosteroids. Prior to treatment, blood should be collected, if possible, for nonemergent testing of specific endocrine hormones and metabolites.

Thyroid Disorders

Hyperthyroidism in children is almost always caused by Graves disease (diffuse toxic goiter), an autoimmune disorder that produces thyroid-stimulating hormone (TSH) receptor antibodies, causing increased thyroid hormone secretion (9). Nearly 5% of all patients with hyperthyroidism are adolescents younger than 15 years of age. Unlike adults, children with hyperthyroidism usually have months of indolent symptoms prior to diagnosis. Personality or emotional disturbances may be the earliest symptoms, followed by more classic symptoms of weight loss, heat intolerance, diaphoresis, palpitations, diarrhea, and amenorrhea. A goiter is present in nearly all cases, and exophthalmos, tachycardia, and hypertension are common. Thyroid storm can occur in the pediatric population; it consists of extreme signs and symptoms of hyperthyroidism combined with fever and altered mental status. A stressor such as infection, trauma, or dehydration usually precipitates thyroid storm. Thyroid storm is life-threatening, and management, as in adults, should be early and aggressive.

Neonatal thyrotoxicosis (also known as congenital hyperthyroidism) is caused by in utero passage of thyroid-stimulating immunoglobulins from mother to fetus. In most cases, it is caused by maternal Graves disease and occurs in up to 10% of infants born to these mothers (10). Euthyroid mothers treated for hyperthyroidism remain at risk for having a newborn with thyrotoxicosis. These infants are commonly born preterm with low birthweight, microcephaly, and craniosynostosis. The infants usually present within a few days of life, but sometimes 10 days or more after birth. Symptoms are transient and last less than 6 to 12 weeks; the duration depends on the persistence of maternally transmitted

immunoglobulins. Symptoms include vomiting, diarrhea, poor feeding, weight loss, sweating, and irritability. Most have a goiter, and many also have exophthalmos, hyperthermia, tachycardia, hepatomegaly, and jaundice. Although transient, neonatal thyrotoxicosis can be life-threatening, usually from heart failure, with a reported mortality of up to 20% (11).

Hypothyroidism does not occur with acute signs or symptoms and is rarely classified as an emergent condition. Because of laboratory errors in newborn screening, congenital hypothyroidism may occasionally be missed, making early ED detection and treatment (within the first few weeks of life) important to prevent irreversible brain damage. Classic symptoms include prolonged jaundice, poor feeding, constipation, somnolence, and hypothermia. Classic signs include coarse puffy facies, large fontanelles, macroglossia, hypotonia, jaundice, and a distended abdomen with umbilical hernia.

Inborn Errors of Metabolism

These diverse hereditary disorders all involve gene mutations, of an enzyme or transport system, causing clinically significant blocks in metabolic pathways that result in accumulations of toxic metabolites. Because of the large number of inborn errors of metabolism (IEMs), the reported incidence of these disorders varies greatly, ranging from 1 in 15,000 for PKU to 1 in 100,000 for organic acidemias (12,13). It is now possible to screen for many of these defects prior to birth. Many IEMs manifest clinically in the newborn period or shortly thereafter, and failure to make an early diagnosis may lead to permanent brain damage and death if specific treatment is not initiated. There are only a few IEMs that are amenable to specific emergency treatment. The most common clinical manifestations in the neonatal period include vomiting, neurologic abnormalities, metabolic acidosis, and hypoglycemia (1). These nonspecific findings can mimic many other disorders, including sepsis or adrenal crisis. An IEM should be considered, however, in a previously normal neonate who presents with an acute clinical deterioration. The presence of infection does not exclude the possibility of an IEM, as

patients with IEM may deteriorate and become septic quickly. Standard laboratory values, particularly blood ammonia, electrolytes, and urinalysis, can be helpful in further classifying the IEM and tailoring treatment in the ED (see Fig. 275.1).

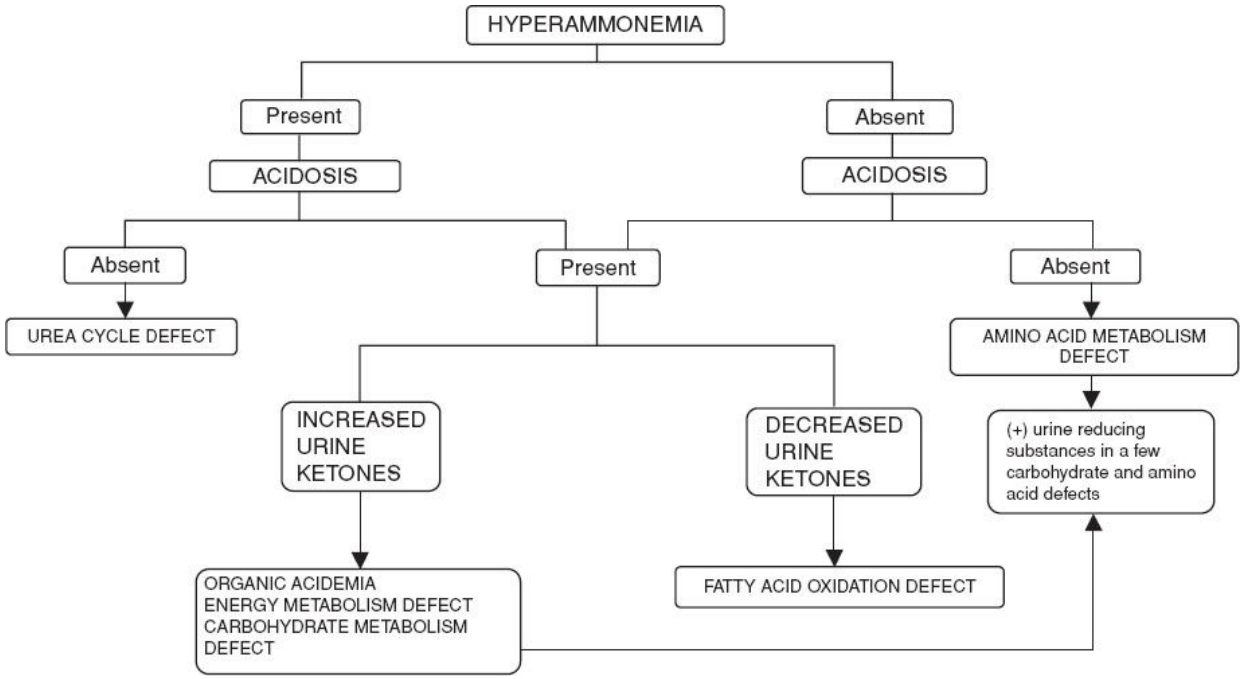

FIGURE 275.1 Diagnostic pathway for inborn errors. Note: Exceptions to above pathway exist. (Modified from Brousseau T, Sharieff G. The critically ill newborn. *Crit Dec Emerg Med.* 2003;18:1–7.)

IEMs can be divided into disorders of amino acid metabolism (phenylketonuria, nonketotic hyperglycinemia); fatty acid oxidation or metabolism (acyl-coenzyme A dehydrogenase deficiency, primary carnitine deficiency), energy metabolism (primary lactic acidemias); and carbohydrate metabolism (glycogen storage diseases, galactosemia). The organic acidemias (methylmalonic, propionic, and isovaleric acidemias, maple syrup urine disease) are a specific group of disorders of amino and fatty acid metabolism in which high levels of nonamino organic acids accumulate in the serum and urine.

Most patients with IEMs exhibit symptoms as newborns after feedings have been initiated, but a minority may go undetected into

childhood demonstrating only psychomotor delay until a stressor causes their condition to deteriorate. Recurrent vomiting, dehydration, and acute metabolic encephalopathy are common clinical manifestations. Neurologic symptoms can range from hypotonia to seizures to frank coma. Intractable seizures are characteristic of nonketotic hyperglycinemia and pyridoxine-dependent seizures. Hepatomegaly is a common physical examination finding and can be pronounced in glycogen storage diseases and galactosemia. The risk of *Escherichia coli* sepsis and liver failure is also increased in patients with galactosemia. A particular odor in body fluids is associated with certain specific disorders. Maple syrup urine disease is named for its characteristic sweet sugar odor; isovaleric acidemia is associated with a "sweaty feet" scent; and methylmalonic and propionic acidemias can result in a fruity ketotic odor similar to that of diabetic ketoacidosis. Metabolic acidosis with an increased AG is common in many IEMs. Hypoglycemia is also common and can be pronounced, particularly in glycogen storage diseases and defects of fatty acid oxidation (14).

Hyperammonemia is most commonly seen in organic acidemias and urea cycle defects. Urea cycle defects are a specific class of IEMs that are associated with hyperammonemia caused by the inability to detoxify ammonia and convert it to urea. These include ornithine transcarbamylase (OTC) deficiency, arginase deficiency (argininemia), and argininosuccinic acid synthetase deficiency (citrullinemia). The clinical manifestations parallel those seen in other IEMs. Neonates frequently present after a few days of protein feeding (of either breast milk or formula); older infants and children may present with recurrent vomiting, ataxia, or developmental delay. Tachypnea is common because ammonia may stimulate the respiratory center. The degree of hyperammonemia tends to be greater than that seen in organic acidemias. Blood ammonia is usually more than 200 μmol/L (generally greater than three to five times the upper range of normal) (1,2). Although sicker infants tend to have higher ammonia levels, there is no strict correlation between the ammonia level and clinical severity of disease. The degree of neurologic impairment is thought to be related to the rate of increase

and duration of hyperammonemia. Blood urea nitrogen (BUN) is usually low, but a normal BUN does not exclude a urea cycle defect. Metabolic acidosis does not occur with these disorders unless there is concurrent dehydration from another illness. The lack of acidosis is helpful in differentiating urea cycle defects from many of the other IEMs.

ED EVALUATION

Questions about prenatal care and maternal medications may yield clues to the diagnosis of an endocrine disorder. Newborn screening test results, as well as a history of consanguinity or sudden infant death in the immediate family, are important to know when considering a potential IEM. Feeding difficulties, weight loss, or association of symptoms with dietary intake or particular types of food are always important historical elements in newborns. Vomiting is a prominent feature in most metabolic disorders.

The physical examination should focus on the neurologic and circulatory status. Alterations in consciousness can range from mild lethargy to seizures and coma. Hypotonia with poor suck and Moro reflexes are frequently seen. Dehydration with tachycardia, poor perfusion, or hypotension should be recognized early and treated aggressively. Tachypnea is a characteristic sign in acidotic patients, and the degree of tachypnea frequently correlates with the severity of acidosis. Unusual or peculiar body fluid odors suggest IEMs. Hepatomegaly and jaundice may be prominent in glycogen storage diseases and galactosemia.

Emergent diagnostic testing should begin with bedside glucose testing, which should be verified by standard laboratory testing. Electrolytes, and calculation of the AG, help with diagnostic classification (see Table 275.2). Acid–base status can be more precisely measured with an arterial blood gas, although in the absence of hypoxia or poor perfusion, a venous or capillary measurement may be adequate in infants (15,16). An increased AG is the most sensitive and specific sign for organic academia, especially when the AG is greater than 20 (1). Serum calcium, magnesium, and liver function tests should also be obtained. Urinalysis will reveal the

presence or absence of ketones, which can help to differentiate particular metabolic disorders; the lack of an appropriate ketonuric response to metabolic acidosis is indicative of a fatty acid oxidation defect. The pH of urine is normally less than 5 in organic acidemias, while the most common urea cycle defect, ornithine transcarbamylase deficiency, may contain urinary orotic acid crystals. The finding of urine reducing substances in the absence of glycosuria is indicative of galactosuria and presumptive galactosemia. Urine reducing substances can also be seen in a few disorders of amino acid metabolism, such as tyrosinemia. Urine electrolytes and osmolality can better classify a hyponatremic disorder. Serum osmolality, both measured and calculated along with drug screens and levels, can help to exclude a toxicologic cause. Concurrent with these studies should be standard investigations for infection, including a complete blood count (CBC), cerebrospinal fluid studies, and body fluid cultures.

Blood ammonia level should be obtained in any altered patient in whom metabolic disease is suspected. Ammonia is significantly elevated in urea cycle defects and many of the organic acidemias. Mild transient elevation of ammonia is common in asymptomatic neonates, especially premature infants. To avoid falsely elevated levels, ammonia testing must be completed within 30 minutes of the blood draw. Lactate and pyruvate levels can be of use, although both acids can be elevated in sepsis and IEMs. The lactate-to-pyruvate ratio tends to be increased in sepsis ($>$10:1), whereas in many IEMs, such as primary lactic acidosis, the ratio is usually normal. Because stat thyroid function testing is now available in many laboratories, these tests should be initiated in the ED when indicated. Testing should include levels for TSH and free thyroxine (T_4).

Additional archival body fluid samples should be appropriately collected and stored if an undiagnosed metabolic disease is considered in the ED, preferably prior to initiation of treatment. For adrenal insufficiency and CAH, additional blood studies to consider include cortisol, ACTH, 17-hydroxyprogesterone, aldosterone, renin, insulin, and growth hormone. For organic acidemias and other defects in amino acid and fatty acid metabolism, quantitative levels

of blood amino acids and urinary amino and organic acids will aid in definitive diagnosis. Although these tests are not emergent, the emergency physician may on occasion be requested to order these studies by a consultant.

KEY TESTING

- Initial bedside fingerstick
- Basic metabolic panel
- Arterial blood gas (if not available, obtain venous blood gas)
- Ammonia level

ED MANAGEMENT

ED management begins with the standard ABCs (airway, breathing, and circulation). Poorly perfusing or hypotensive patients require IV fluid resuscitation, and antibiotics should be administered empirically for suspected sepsis. Overaggressive fluid resuscitation should be avoided in normotensive infants, as well as in patients with diabetic ketoacidosis because of the suspected risk of cerebral edema.

Acute treatment for hypoglycemia begins with IV glucose. The recommended bolus dose ranges from 0.25 to 1 g/kg. A midlevel dosing range of 0.4 to 0.5 g/kg glucose translates to approximately 4 mL/kg of 10% dextrose-containing solution, 2 mL/kg of 25% dextrose-containing solution, or 1 mL/kg of 50% dextrose-containing solution. Generally, a 10% solution is used in neonates and infants to minimize the risk of causing vascular injury with more concentrated fluids. In toddlers and children a 25% solution may be used and in adolescents a 50% solution. Continuous glucose infusion should follow bolus administration, especially in neonates, to maintain normal glucose levels. The normal glucose requirement in a neonate is 6 to 10 mg/kg/min, which is roughly equivalent to an infusion of 10% dextrose-containing solution at 1.5 times maintenance rate. Glucose levels should be rechecked frequently (every 1 to 2 hours) and the infusion rate adjusted accordingly. If hypoglycemia persists despite boluses and infusions in an infant, a hyperinsulinemic state

should be considered; this may be treated with glucagon 0.1 to 0.2 mg/kg (up to 1 mg) parenterally. Because it can be given intramuscularly, glucagon can be particularly helpful when IV access is difficult or delayed. Glucagon is not effective in patients lacking adequate glycogen stores (e.g., those with inherited storage diseases) (17). Hydrocortisone 2 to 3 mg/kg or 25 to 50 mg/m^2 can also be considered for refractory hypoglycemia (2).

Hyponatremia should be treated with 3% hypertonic saline (514 mEq/L) only if there are seizures or coma. A dose of 5 mL/kg over 10 to 15 minutes should raise the sodium level by approximately 5 mEq/L; smaller additional doses of 2 to 3 mL/kg can be considered if no clinical improvement is seen. Acute correction to 125 mEq/L should alleviate symptoms in most cases. Following the acute correction, sodium levels should be slowly corrected to normal at a rate of 0.5 mEq/L/hr (maximum 12 mEq/L/d) using a 0.9% normal saline infusion. If SIADH is suspected, consider fluid restriction to two-thirds maintenance and administration of furosemide 1 to 2 mg/kg. Pyridoxine 100 mg IV should be considered for neonates with intractable seizures where isoniazid overdose is a possibility (2,18).

Acute adrenal insufficiency is treated with stress doses of corticosteroids; Table 275.3 lists various options. Hydrocortisone is the steroid of choice, having equal glucocorticoid and mineralocorticoid effects; cortisone is an alternative but cannot be given IV. The stress dose of hydrocortisone, three to four times the physiologic dose, is 25 to 50 mg/m^2 (approximately 2 to 3 mg/kg). Dexamethasone has no mineralocorticoid effect and thus does not interfere with diagnostic ACTH-stimulation testing; it is therefore preferred over hydrocortisone in normotensive patients with an unconfirmed diagnosis. An oral mineralocorticoid such as fludrocortisone can be started after initial stabilization with IV fluids and glucocorticoids. Hyperkalemia should self-correct with fluids and steroid therapy and rarely requires specific treatment.

TABLE 275.3
Corticosteroids for Adrenal Insufficiency

Drug	Dose	Potency Effect (per mg)	
		Glucocorticoid	Mineralocorticoid
Glucocorticoid			
Hydrocortisone	25–50 mg/m^2 IV/IM Or Infant: 25 mg Child: 50 mg Teen: 75 mg	1	1
Cortisone	1 mg/kg IM	0.8	1
Dexamethasone	0.1–0.2 mg/kg IV/IM	40	none
Mineralocorticoid			
Fludrocortisone	0.1 mg PO daily	15	400

IV, intravenous; IM, intramuscular; PO, by mouth.

There are many available therapeutic interventions for neonatal hyperthyroidism and thyroid storm. β-Adrenergic blockade can be achieved with propanolol 0.01 mg/kg/dose IV titrated to clinical effect; alternative oral dosing is 2 mg/kg/d in three to four divided doses. Thyroid hormone synthesis can be blocked using propylthiouracil 5 to 10 mg/kg/d or methimazole 0.5 to 1 mg/kg/d, both in three divided oral doses. Iodine can be given in the form of Lugol solution (8 mg iodine/drop) 1 to 3 drops daily. Iodine should be started at least 1 hour after administering an antithyroid drug such as propylthiouracil to avoid increasing thyroid gland stores before the antithyroid effect occurs. Glucocorticoid treatment with hydrocortisone or prednisone may also be helpful in severe cases.

Treatment for IEMs consists of general measures as well as specific medications if a probable type of IEM is suspected. Unless the infant has a known IEM and is already on a special formula, all dietary intakes should be withheld and feedings reintroduced only after consultation with a specialist. IV fluid that contains dextrose may be indicated, particularly if a urea cycle defect is suspected, because stimulating endogenous insulin will minimize protein catabolism and ammonia production. After appropriate fluid boluses of normal saline

to correct shock, most IEMs can be managed with a standard IV fluid consisting of 10% dextrose in normal saline at 1.5 times maintenance. Metabolic acidosis unresponsive to IV fluids should be treated with sodium bicarbonate boluses of 1 to 2 mEq/kg. The rapid removal of toxins may be life saving in some cases, particularly with severe hyperammonemia. Hemodialysis to remove excessive ammonia is more effective than peritoneal or other extracorporeal routes (1,2). Temporizing empiric therapy with arginine, with or without sodium benzoate/phenylacetate, can reduce ammonia levels acutely in most urea cycle defects. Table 275.4 lists specific therapies to consider when suspecting particular IEMs.

TABLE 275.4
Specific Therapies for Inborn Errors of Metabolism

Drug	Dose	Indication
Arginine HCL 10%[a]	210–600 mg/kg IV	Urea cycle defects
Biotin	10 mg IV or PO	Organic acidemias
Carnitine	50–100 mg/kg IV or PO	Fatty acid defects, organic acidemias
Pyridoxine	100 mg IV	Pyridoxine-dependent seizures
Sodium benzoate[a] and/or phenylacetate[a]	250 mg/kg IV	Urea cycle defects
Thiamine	25–100 mg IV	MSUD, primary lactic acidosis

[a]Can infuse over 1 to 2 hours in dextrose-containing solution.
IV, intravenous; PO, by mouth.
Data from Kwon (2) Ozand (14), and Weiner (13).

CRITICAL INTERVENTIONS

- Bedside glucose testing and frequent glucose monitoring (every 1 to 2 hours based on diagnosis).
- Dextrose solution greater than 12.5% will require central access.
- Recognition of the signs and symptoms of thyrotoxicosis or thyroid storm in an infant.
- Correction of hyponatremia in cases of dehydration and GI losses with normal saline over 24 hours

- Sodium bicarbonate for severe refractory metabolic acidosis if an IEM is suspected.
- Rapid treatment of severe hyperammonemia with arginine and emergent hemodialysis.

DISPOSITION

Most symptomatic patients with a known or suspected metabolic disorder require hospitalization, typically in an intensive care setting for frequent monitoring of metabolic parameters and neurologic status. Prompt consultation should be initiated with a pediatric endocrinologist or metabolic specialist. If appropriate resources are unavailable, transfer should be arranged with a pediatric center skilled in managing metabolic disorders. This should be done expeditiously after resuscitation and empiric treatment for suspected disorders have been started. In the event of a failed resuscitation or imminent death in a patient with suspected IEM, permission for autopsy and specimen testing should be discussed with parents. Perimortem samples to consider include frozen blood and urine specimens, skin biopsy, and needle liver biopsy (1). These studies may allow for appropriate genetic counseling for family members and future siblings.

Common Pitfalls

- Failure to consider a metabolic disorder in a previously healthy infant with acute clinical deterioration.
- Delayed recognition and treatment of hypoglycemia and hyperammonemia.
- Failure to recognize acute adrenal insufficiency in a patient with refractory hypotension.

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CHAPTER 276 Kawasaki Disease

James A. Wilde

Kawasaki disease (KD), also known as *mucocutaneous lymph node syndrome,* was first described in Japan in 1967 (1) and reported in the United States literature in 1974 (2). Although initially thought to be a new disease, KD was soon recognized to be clinically indistinguishable from infantile periarteritis nodosa (3). The disease is primarily a vasculitis that affects the coronary arteries most significantly, but it can also produce pathology in the central nervous system, liver, gallbladder, lungs, and digits.

Three to five thousand cases of KD are estimated to occur in the United States annually (4). Children younger than 5 years of age account for 80% of cases, but the disease has also been reported in young adults (5,6). The peak incidence is in the second year of life. Intensive efforts to identify the causative agent have failed to yield an etiology, although certain clinical and epidemiologic features favor an infectious cause.

No specific diagnostic assay can definitively identify a case of KD, so the diagnosis must be made presumptively based on clinical features and laboratory findings. Some children have been described with an incomplete form of KD that does not fit the classic case definition, making identification still more challenging (7–9). About 25–30% of untreated patients with KD develop coronary artery ansurysms, compared to 5% to 8% of those treated with the currently recommended regimen of intravenous immune globulin (IVIG) and aspirin (10). The overall mortality rate is 1% to 3% in untreated KD, (11) but as low as 0.08% with treatment.

CLINICAL PRESENTATION

Classic KD is diagnosed by clinical criteria originally described by Kawasaki, with only slight modifications. These criteria include fever of at least 5 days duration, at least four of five physical findings, and no other explanation for the illness (Table 276.1). The fever is generally >39°C, spiking, remittent, and prolonged in untreated patients, with some children remaining febrile for 2 to 4 weeks. Another commonly reported finding is extreme irritability beyond that seen in more common febrile illnesses (12).

TABLE 276.1
Diagnostic Criteria for Kawasaki Disease

Fever of at least 5 days duration
PLUS
Presence of four of five physical findings:
Bilateral, nonpurulent conjunctival injection
Inflammatory changes of the lips and oral mucosa
Erythema or swelling of the hands or feet
Nonvesicular rash, primarily truncal
Cervical lymphadenopathy, usually unilateral
AND
Illness not explained by other known disease

The conjunctivitis is primarily bulbar, spares the area around the limbus, and is not associated with an exudate. Changes in the lips may include erythema, bleeding, dryness, and fissuring. The oral mucosa may show erythema with a strawberry tongue, but exudates and oral ulcerations are not found. Hands and feet may show edema, erythema, or both, primarily on the palms and soles, with characteristic desquamation 1 to 2 weeks after the onset of the illness. The rash can be quite variable, but it is most commonly diffuse, maculopapular, and erythematous.

Cervical lymphadenopathy is usually unilateral, is nonfluctuant, and is defined by a node diameter of at least 1.5 cm. Each of the clinical criteria described above is found in approximately 90% of

cases, with the exception of cervical lymphadenopathy, which is noted in only 50% to 75% of cases.

Multiple organ system involvement has been reported, including pericarditis, myocarditis, arthritis, cerebrospinal fluid pleocytosis (13), peripheral extremity gangrene (14), pulmonary infiltrates, and hydrops of the gallbladder (12). A desquamated, erythematous, perineal rash in the first 3 to 4 days of illness is an early finding that can potentially be helpful in making the diagnosis, although it is not specific for KD (15).

Approximately 1 to 2 weeks after the onset of the acute symptoms, resolution of the fever, rash, and lymphadenopathy can be expected, although the conjunctival injection often persists. It is during this subacute stage that desquamation of the digits occurs. This is also the stage at which coronary artery aneurysms develop and the risk of sudden death is highest.

Incomplete KD, formerly known as atypical Kawasaki disease, was first described in a number of case reports and case series in the early 1980s (7). Most of these patients were younger than 6 months of age, but cases in older children have also been reported (9). Incomplete KD is a febrile illness that does not meet the case definition for KD but can result in cardiac sequelae at least as severe as those of typical KD (16). In most cases reported to date, one to three of the physical findings typical of KD have been present, but several cases of incomplete KD have been manifested solely by fever.

DIFFERENTIAL DIAGNOSIS

There are several diseases that can mimic KD, but careful attention to the clinical criteria, as outlined above, can help to avoid misdiagnosis. Among these diseases are scarlet fever, measles, toxic shock syndrome, Stevens–Johnson syndrome, leptospirosis, and Rocky Mountain spotted fever. Tonsillar exudates suggest an illness caused by group A streptococci, such as scarlet fever, as does the characteristic scarlet fever rash. Prominent respiratory symptoms, particularly cough, should suggest measles. Many of the symptoms

of toxic shock are similar to those of KD, but hypotension is an uncommon finding in KD unless heart failure secondary to severe carditis has developed.

Recent exposure to inciting drugs, the presence of oral lesions, an exudative conjunctivitis, and the typical “target lesion” rash can serve as clues to the diagnosis of Stevens–Johnson syndrome. The centripetal spread of a petechial rash that begins on the hands or feet, severe myalgias, and seasonal and epidemiologic clues may point to Rocky Mountain spotted fever. Chills, myalgia, and abdominal pain may lead to the diagnosis of leptospirosis. Serologic tests are of limited value in the acute stage of any of these illnesses, but they can be helpful during the recovery phase for retrospective diagnoses.

In the emergency department (ED), the diagnosis of KD is usually one of exclusion and is often not considered until the patient has presented to a clinic or emergency setting multiple times. In one recent study, there was a mean of 7.9 days between onset of illness and diagnosis. Independent predictors of delay in diagnosis included age younger than 6 months and a presentation of incomplete KD (17).

ED EVALUATION

Immediate workup of a suspected case of KD should include a complete blood count and differential, platelet count, blood cultures, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), and a chemistry panel including serum transaminases, total protein, and albumin. Elevation of acute phase reactants such as ESR or CRP is virtually always present during the acute stage (12) and strongly supports the diagnosis of KD or incomplete KD when seen in combination with a consistent set of clinical signs and symptoms. White blood cell counts are usually elevated, with polymorphonuclear cell predominance, and leukopenia is uncommon. Platelet counts are usually normal in the acute stage but after a week may be markedly increased, occasionally to more than 1 million per microliter.

Laboratory values may yield mixed results, but a few findings are worthy of note. A GGT level may be elevated in up to 70% of children at risk for KD. In addition, serum transaminases are often two to three times normal in patients with KD. Marked rises in serum immunoglobulin levels in the acute stage may result in an elevation in the total serum protein level; serum albumin is often decreased. Urinalysis may reveal sterile pyuria, with ≤10 white blood cells per high-power field. Urine should be collected without a catheter because the pyuria is a reflection of urethral inflammation. Last, a lumbar puncture may reveal aseptic meningitis (13).

Further workup in patients with likely KD should include a baseline electrocardiogram to identify evidence of myocarditis or pericarditis. A baseline echocardiogram should also be obtained but should not delay therapeutic interventions.

Young children and infants with unexplained prolonged fever should be evaluated for incomplete KD. The American Academy of Pediatrics and the American Heart Association have suggested a laboratory-based algorithm to aid clinicians in making this diagnosis (Table 276.2) (12).

TABLE 276.2
Algorithm for the Diagnosis of Incomplete Kawasaki Disease

Fever ≥5 days *and* two to three clinical criteria consistent with KD *and* no symptoms inconsistent with KD *and* CRP ≥3.0 mg/dL and/or ESR ≥40 mm/h *and*

≥3 supplemental laboratory criteria*:

- Albumin ≤3.0 g/dL
- Elevation of alanine aminotransferase
- Platelets after 7 days illness ≥450,000/mm^3
- White blood cell count ≥15,000/mm^3
- Urine ≥10 white blood cells per high-power field

*Infants ≤6 months old and fever ≥ 7 days without explanation can be diagnosed with IKD without additional clinical criteria or supplemental laboratory criteria if they have a positive echocardiogram.

Source: From Newburger JW, et al. (18)

ED MANAGEMENT

Children who meet the clinical case definition of KD and who have evidence for inflammation as demonstrated by an elevated ESR or CRP should be admitted to the hospital and treated for KD. High-dose IVIG when administered early in the course of disease at a dose of 2 g/kg over a 10-hour period has been shown to substantially reduce the incidence of coronary artery aneurysms (11). High-dose aspirin at 100 mg/kg/day in four doses is also started on admission and is continued until the acute phase has resolved. Corticosteroids are not currently recommended for initial therapy but may play a role in refractory cases (19).

In the ED, uncomplicated KD requires no more than supportive management such as an antipyretic for fever and intravenous fluids for rehydration and maintenance, although more serious manifestations such as cardiovascular decompensation may require more aggressive supportive treatment.

Infants and children who present with prolonged fever and fewer than four of the classic clinical findings of KD may have incomplete KD. Those meeting the criteria for incomplete KD should be managed similarly to patients with typical KD. Abnormal laboratory findings are of critical importance in making this diagnosis.

CRITICAL INTERVENTIONS

- Order a baseline electrocardiogram to assess for evidence of myocarditis or pericarditis.
- Recognize that the diagnosis of KD may be based entirely on clinical presentation.
- Ensure timely initiation of high-dose IVIG and aspirin therapy.
- Perform a full fever evaluation even if it is suspected that fever is caused by KD.

DISPOSITION

Children with a presumptive diagnosis of KD or incomplete KD should ideally be admitted to a tertiary care pediatric center where pediatric cardiologists and infectious disease consultants are

available. Transfer to a pediatric intensive care unit should be considered for patients with signs of cardiac decompensation.

Common Pitfalls

- Failure to consider KD in the differential diagnosis of prolonged fever in young children
- Failure to consider incomplete KD in prolonged fever in infants and young children
- Failure to monitor for or identify cardiac decompensation
- Failure to use laboratory screening tests, such as ESR, to help differentiate KD from common childhood viral exanthems
- Failure to recognize the importance of early admission, institution of therapeutic interventions such as IVIG and aspirin, and cardiology consultation

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CHAPTER 277 Cellulitis

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Cellulitis is a common, acute, rapidly spreading, nonsuppurative inflammation of the epidermis, dermis, and subcutaneous fat that is usually caused by bacterial infection. The age of the patient, the history, and the location of the infection all serve as important determinants of the most likely causative bacterial organisms. Cellulitis may occur by local tissue invasion after minor traumatic skin breaks and bite wounds or by hematogenous dissemination of a pathogenic organism. It may also be the presenting sign of disease states such as septic arthritis, osteomyelitis, sinusitis, or pyomyositis (1). Neonatal omphalitis (infection of the umbilical stump and surrounding tissues) and neonatal mastoiditis are unique to the newborn period.

Recent studies have demonstrated a dramatic increase in the incidence of soft-tissue infections in the United States and concomitant emergency department visits (2). These increasing infection rates are due to the emergence of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA), which affect otherwise healthy children (3,4). Most of the culture-proven CA-MRSA infections present as superficial abscesses or and carbuncles.

In most instances, children with cellulitis recover uneventfully. However, the recent resurgence of invasive group A β-hemolytic *Streptococcus* (GABHS) infection, characterized by bacteremia, toxic shock, and necrotizing fasciitis, emphasizes both the potential for serious complications and the need for accurate diagnosis and appropriate management of pediatric cellulitis.

EPIDEMIOLOGY

During the course of normal play, children routinely incur minor injuries with breaks of the skin. Any injury or skin opening that disrupts the protective barrier of the skin can serve as a portal of entry for pathogens, most commonly GABHS or *Staph aureus.* The role of MRSA in cellulitis without obvious purulence is unclear because cultures are rarely obtained from children with these infections, but CA-MRSA has emerged as an increasing cause of purulent soft-tissue infections in children (4). The incidence and prevalence of CA-MRSA vary geographically. In surveillance conducted in areas of Maryland, Georgia, and Minnesota in 2001 and 2002, the proportion of all MRSA infections that were caused by CA-MRSA ranged from 8% to 20% (4). Factors common in outbreaks of CA-MRSA include crowding; frequent skin-to-skin contact between people; participation in activities that result in abraded or compromised skin surfaces; sharing of potentially contaminated personal items such as towels, sporting equipment, and razors; and limited access to health care. One explanation for these increased infection rates is related to virulence characteristics that are more common in this organism. One such factor is thought to be a cytotoxin, Panton-Valentine leukocidin, that destroys leukocytes by creating pores in the cell membranes. CA-MRSA should be considered a potential cause of every infection presenting to the hospital or clinic, emphasizing the need for practitioners to be aware of local antibiotic resistance patterns.

Puncture wounds by a contaminated object such as a nail penetrating a shoe may predispose to infections with pathogens such as *Pseudomonas* species. Likewise, animal and human bites are associated with an increased likelihood of *Pasteurella multocida* and *Eikenella corrodens* infections, respectively.

Omphalitis, infection of the umbilicus, with accompanying erythema of the abdomen, is a diagnosis unique to the newborn period that usually occurs in the first few weeks of life. Neonatal mastitis is an infection of the breast tissue in prepubertal children, limited to the first 2 to 5 weeks of life (5). Female infants are

affected twice as often as males. Hormonally induced hypertrophy of the glandular tissue facilitates bacterial entry and abscess formation. The most common pathogen is *Staph. aureus,* including CA-MRSA; however, occasionally gram-negative enteric organisms are involved.

The epidemiology of childhood facial cellulitis has changed dramatically since the introduction of the *Haemophilus influenzae* type B vaccine in 1985. *H. influenzae* type B (HIB) had been the cause of more than 50% of cases of facial cellulitis but, in the post-vaccine era, it has become rare. In fact, there has been an approximately 90% decrease in the incidence of HIB disease (6). Any child who has received the second dose of HIB vaccine more than 7 days prior is unlikely to have HIB disease. Currently, common organisms for facial cellulitis include *Streptococcus pneumoniae,* GABHS, and *Staph. aureus.* As more children become completely immunized with the conjugated pneumococcal vaccine it is anticipated there will be a decrease in cellulitis due to *Strep. pneumoniae* vaccine and nonvaccine serotypes. Facial and periorbital infections caused by HIB and *Strep. pneumoniae* are usually spread hematogenously and hence can be isolated by blood cultures. Primary dental infection may also lead to bacterial seeding of adjacent facial soft tissues by a variety of aerobic and anaerobic bacteria such as *Bacteroides, Prevotella, Fusobacterium,* and *Peptostreptococcus* (7).

Important pre-existing conditions that may predispose to cellulitis include other traumatic injuries, particularly crush injuries, pre-existing vascular or lymphatic compromise, chronic cutaneous conditions such as eczema, and immunocompromised states. More recently, there has been an increase in case reports of necrotizing fasciitis due to GABHS infection occurring in conjunction with varicella infection (8).

CLINICAL PRESENTATION

The most reliable way to diagnose cellulitis is to recognize the characteristic clinical features: Localized erythema, warmth, edema,

and pain. Demarcation between involved and adjacent normal skin may be indistinct. Most often, cellulitis involves the extremities, with the leg affected three times as often as the arm (1). There may be associated lymphangitis, appearing as red streaks radiating from the margin of the lesion, and also enlargement and tenderness of regional lymph nodes, particularly with streptococcal infection. The white blood cell (WBC) count is usually normal. In 10% to 20% of cases, cellulitis is associated with fever and other systemic symptoms such as chills, malaise, myalgias, and emesis. When fever is present, a concomitant bacteremia should be presumed leukocytosis is expected.

More recently, increasing childhood purulent infection rates due to CA-MRSA, and the inability to distinguish these infection from methicillin-sensitive strains, have necessitated the development of new evaluation and management schemata for these infections, such as that recommended by the American Academy of Pediatrics (Fig. 277.1) (9).

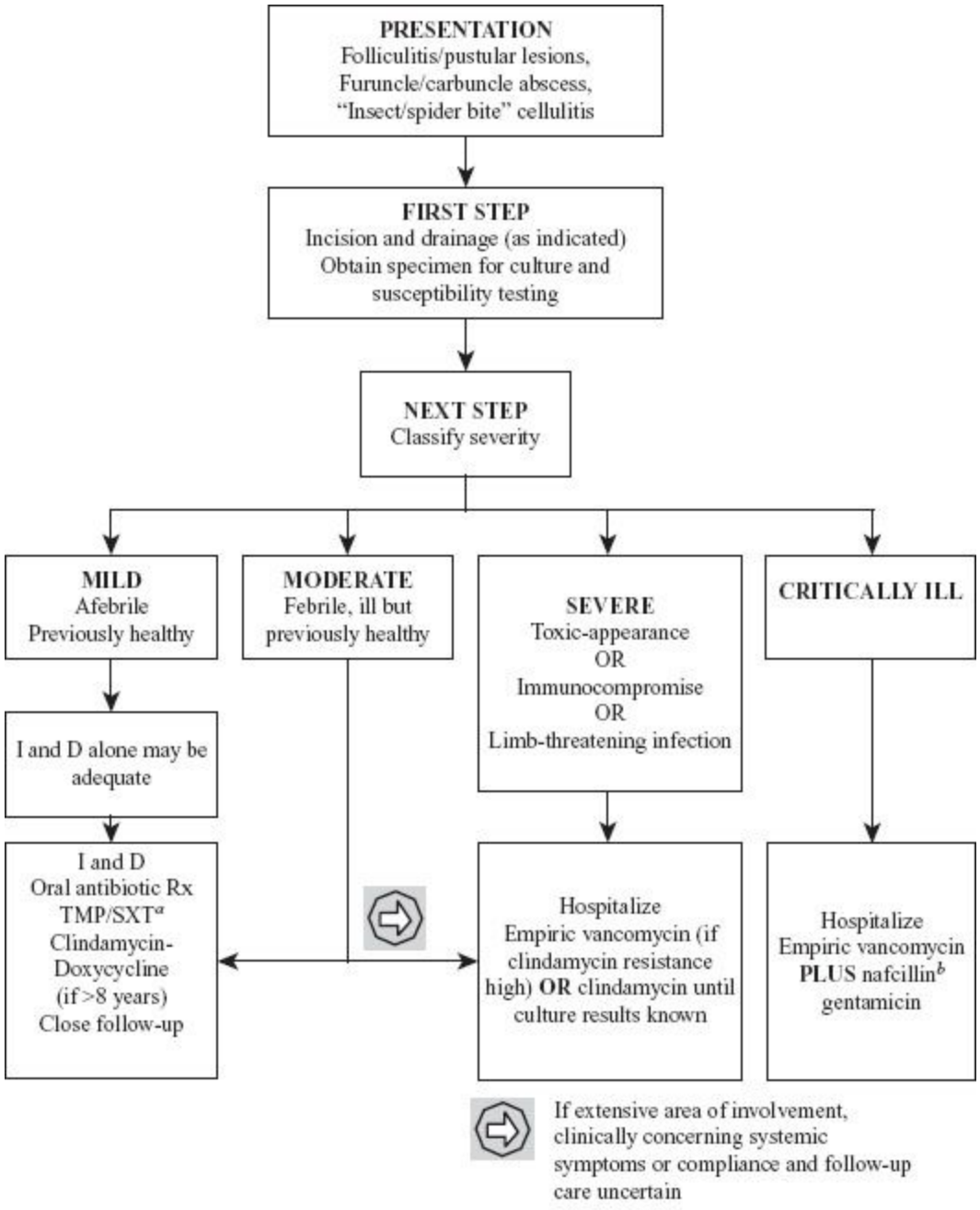

FIGURE 277.1 Initial outpatient management of suspected CA-MRSA skin and soft-tissue infections schematically illustrated. Assumes CA-MRSA strains are prevalent in a community.

Erysipelas is a superficial cellulitis predominantly affecting the upper dermis. It is characterized by tender, rapidly enlarging,

erythematous, indurated plaques with sharply demarcated borders, with extensive lymphatic involvement. Patients tend to be young children, and most cases involve the legs and feet (10,11). Symptoms also include toxic appearance with fever and chills (12). Facial erysipelas may occur after streptococcal upper respiratory tract infection (10). GABHS is the most common cause of erysipelas, in addition to other streptococcal groups including groups B, C, and G. Historically, erysipelas has rarely been linked to staphylococci. Current investigations still acknowledge the possibility of CA-MRSA as a causative agent but data supporting its existence remains weak (13).

Buccal cellulitis presents as a tender mildly erythematous swelling of the cheek in children between 6 and 24 months, most often not associated with previous trauma. Hematogenous seeding by oropharyngeal or middle-ear bacteria is suggested as the pathogenesis (6). Previously, HIB was by far the most common etiologic agent, with rare cases caused by *Staph. aureus* and *Strep. pneumoniae.* As a result of routine immunization with HIB vaccine, the incidence of buccal cellulitis has decreased (12). Of note, in infants younger than 3 months of age, facial cellulitis may be the only presenting sign of GBS bacteremia.

Ludwig angina is a cellulitis of the submandibular and sublingual space. Patients often present with rapidly progressive, tense, and painful induration of the submental area and neck, along with drooling, dysphonia, high fever, and leukocytosis. It is important to recognize the potential for airway compromise in such patients (12). Predisposing factors include poor dental hygiene, recent dental extractions, and impacted foreign bodies in the oral cavity. Infections tend to be polymicrobial, involving oral flora.

Periorbital or preseptal cellulitis is an infection presented anterior to the orbital septum and is usually seen in children younger than 5 years old (6,14). It typically presents with sudden onset of unilateral eyelid and periorbital tenderness, swelling, and erythema; extraocular eye movements and visual acuity are preserved and there is no evidence of proptosis (12). More than half cases are secondary to local extension from a nearby facial wound infected

with either GABHS or *Staph. aureus*. In general, children appear nontoxic, but bacteremia and leukocytosis may occur, particularly when infection is due to *H. influenzae* or *Strep. pneumoniae* infections.

In contrast, *orbital cellulitis,* which is less common than periorbital cellulitis, is postseptal and involves the orbit itself (14) (see Chapter 253). Ethmoid sinusitis is most commonly the source of infection as the ethmoid sinus is separated from the orbit by the rather thin bony structure known as the *lamina papyracea* (14).

Omphalitis presents in the newborn as purulent, foul-smelling discharge from the umbilical stump and as erythema of the abdominal wall. However, both of these clinical findings may occur without infection, thus making the diagnosis challenging at times. Suggestive findings include anterior abdominal erythema and circumferential erythema of the umbilicus (5). The cord stump may serve as a portal of entry for *Staph. aureus,* CA-MRSA, GABHS, group B *Streptococci* (GBS), or gram-negative enteric organisms. Infection is clinically diagnosed when induration and erythema of the anterior abdominal wall are present. Fever, temperature instability, lethargy, and irritability may be seen late as signs of sepsis. Laboratory studies such as WBC count may be normal in early localized infections. Omphalitis is rare in developed countries where the usual cord care in the neonatal period avoids most infections.

Neonatal mastitis presents as enlargement of the breast bud with associated tenderness, warmth, erythema, and purulent nipple discharge (5). Hormonally induced hypertrophy of the breast tissue does not present as erythema or tenderness and is associated only with a milky white discharge. About one-fourth of infants will present with fever and ill appearance. Since the infection tends to be well localized, the WBC is normal in most cases, and blood cultures are negative.

Wound-related cellulitis is the most common cause, of cellulitis of the extremities, especially in older children and adolescents (12). The involved area is red, warm, and tender, and systemic signs of fever, chills, and leukocytosis are often present. Lymphangitic streaking and regional lymphadenopathy are more common than in

cases of erysipelas. Children with cellulitis of an extremity may have limitation of movement of the affected limb or refusal to walk because of pain. Infections tend to be polymicrobial and are age related, with GBS more common in infants younger than 3 months old, *Strep. pneumoniae* and HIB in patients aged 6 to 24 months (still undergoing primary vaccination series), and *Staph. aureus,* CA-MRSA, and GABHS most likely in children older than 24 months (1). With GBS, *Strep. pneumoniae,* and HIB, high fever, WBC above 15,000, and bacteremia are not uncommon.

Necrotizing fasciitis (NF) is an uncommon but potentially devastating infection of the subcutaneous and fascial tissues (11). Children may be predisposed as a result of traumatic skin lesions, or those of varicella zoster infection, eczema, or burns (12,15,16). Necrotizing fasciitis may initially present as a cellulitis, but develops rapidly into dusky, painful, indurated plaques and progresses to purpura, blistering, and necrosis. Crepitance may develop within the tissues. The infection spreads rapidly along fascial planes between subcutaneous tissue and superficial muscle fascia (15). The initial diagnosis may be difficult to make because there are often only modest skin changes early in the course of disease. However, extreme pain that is out of proportion to examination findings is very suggestive. Patients may present with fever and marked fussiness and may refuse to bear weight or move the affected limb. Severe systemic toxicity with tachycardia, hypotension, and multiorgan system failure are common in fulminant cases. The child may be lethargic, disoriented, and in profound septic shock. When necrotizing fasciitis occurs in conjunction with streptococcal toxic shock syndrome (STSS), the mortality rate is particularly high (15).

STSS may be associated with NF in as many as 50% of cases (10). The syndrome presents with a generalized, fine, scarlatiniform rash and hyperemia of the conjunctivae or other mucous membranes, along with fever, tachycardia that out of proportion to fever, hypotension, and possibly altered mental status and respiratory distress, vomiting, diarrhea, and renal and hepatic dysfunction are often present (10,15).

A similar toxin-mediated syndrome affecting young children is *staphylococcal scalded skin syndrome* (SSSS). Skin manifestations are age related and include the spectrum of bullous impetigo, scarlatiniform eruption, and widespread exfoliation (11). Generalized SSSS, called *Ritter disease,* usually occurs in patients younger than 5 years of age; older children tend to have more localized infections. Following a purulent conjunctivitis, upper respiratory infection, or localized superficial skin infection, a generalized orange-red macular erythema resembling sunburn develops. During the subsequent scarlatiniform phase, the skin becomes extremely tender. Within 1 to 3 days, the skin becomes wrinkled, and large flaccid bullae develop in flexural areas or around orifices. During this phase, Nikolsky sign is present—the epidermis pulls away from the dermis with gentle traction, leaving raw, weeping, and denuded skin underneath (12). As the skin dries, large flakes are formed, leading to widespread desquamation with complete recovery in 10 to 14 days. Dehydration and superinfection may occur due to loss of the dermal barrier during exfoliation.

DIFFERENTIAL DIAGNOSIS

Any tender, erythematous swelling of the skin and subcutaneous soft tissue may resemble cellulitis. Trauma, insect bites or stings, localized urticarial eruptions, lymphadenitis, swelling overlying a sprain or fracture, or a joint with septic arthritis may all be mistaken for cellulitis. Mosquito bites may induce significant lymphedema surrounding the bite site, which develops over hours. The bites are usually described as pruritic rather than painful. Bee stings and spider bites may also cause significant lymphedema, warmth, and even tenderness and therefore may be more difficult to distinguish from cellulitis.

"Popsicle panniculitis" can mimic facial cellulitis. Thought to be a cold-induced histamine response from drinking ice water, typically the skin involvement begins at the labial crease and spreads outward with a warm, mildly tender cheek. Insect bites and stings,

panniculitis, and orthopedic injuries all lack accompanying systemic signs such as fever or ill appearance.

Localized specific soft-tissue infections, such as folliculitis (infection of a hair follicle), furuncles and carbuncles (deep follicular abscess, either solitary or multiseptate and loculated), impetigo (vesiculopustular lesions), ecthyma (impetigo involving the dermis), and others, should be differentiated from cellulitis by their characteristic clinical appearances.

Extremity cellulitis, as mentioned earlier, may limit range of motion of the affected limb; making it difficult to distinguish deeper tissue infections (such as osteomyelitis or septic arthritis) from cellulitis.

ED EVALUATION

In most cases, cellulitis is a clinical diagnosis. Blood culture and WBC counts should be reserved for immunocompromised patients or those presenting with fever or other signs of systemic illness. Clinical judgment and patient age should be used to determine the need for lumbar puncture for culture, particularly with cellulitic infections of the head and neck region (6). In infants with facial cellulitis who have not been fully immunized a lumbar puncture should be strongly considered (6).

Many clinical features are specific enough for clinical decisions to be made based on appearance alone; however, given the rapid increase in frequency of CA-MRSA, cultures may become more necessary. Erysipelas, with its characteristic rapidly advancing, raised, sharply demarcated margin, is usually caused by GABHS. A bluish or violaceous discoloration of the affected area suggests infection by *H. influenzae* or *Strep. pneumoniae.* Cellulitis in the perineal or buccal area, or cellulitis in an area involving devitalized or necrotic tissue should raise concern for polymicrobial anaerobic organisms or CA-MRSA. Cellulitis caused by pet bites is often associated with *P. multocida,* whereas human bite infections are often associated with *E. corodens.* Cellulitis due to water-contaminated wounds is usually caused by *Mycobacterium marinum*

or *Aeromonas* and *Vibrio* species (17). Systemic symptoms in any patient with cellulitis should suggest the possibility of concurrent bacteremia. Immunocompromised states should alert the clinician to the possibility of atypical infectious agents and to neutropenia potentially masking the actual depth and extent of infection.

While varicella is relatively rare because of routine immunizations against it, invasive GABHS should be considered in children with varicella who have fever on or beyond the fourth day of the exanthem (8). With the re-emergence of suppurative GABHS infections, it is vital to distinguish early streptococcal necrotizing fasciitis from cellulitis. Although the combination of clinical features and epidemiologic considerations may suggest the etiology of cellulitis, definitive bacteriologic diagnosis requires isolation of the causative organism. In the past, because of the high prevalence of *H. influenzae,* bacteremia, blood cultures were routinely obtained in children with cellulitis. In the post-HIB vaccine era, however, the association of bacteremia with cellulitis in children has been dramatically reduced, and recent studies indicate that it is not necessary to obtain blood cultures routinely (18). Of note, positive blood cultures are most commonly associated with younger age, active varicella, and deeper tissue infections such as osteomyelitis or septic arthritis.

Needle aspiration of the cutaneous lesion, accompanied by gram stain and culture, is a rapid and specific tool for establishing a bacteriologic diagnosis. Aspiration is performed by inserting a 22-gauge needle attached to a 1-cc syringe into the advancing edge of the cellulitis. If no material is aspirated, 0.1 mL of normal saline may be injected into the area, followed by immediate aspiration. The yield of needle aspiration, however, can be modest; positive aspiration rates vary from 5% to 50%.

If underlying deeper trauma or infection is suspected, appropriate imaging should be ordered, especially in patients with suspected orbital cellulitis (19). Patients with cellulitis involving the midface are also susceptible to cavernous sinus thrombosis.

Complications of cellulitis may result from direct extension, seeding of an underlying joint space, or hematogenous spread.

Meningitis, endocarditis, or other serious complications, although rare, may develop, especially in immunocompromised patients.

KEY TESTING

- CBC, blood culture, and wound cultures in patients with atypical presentations, ill appearance, or immunocompromise
- CT scan for patients with suspected orbital cellulitis
- CT, MRI, or ultrasonography to investigate potential joint infections or osteomyelitis

ED MANAGEMENT

Antibiotic therapy is warranted in most cases, except in the mildest forms of cellulitis. See Figure 277.1 for management of purulent infections (9). Given the low yield of microbiologic testing, in most situations antibiotic therapy is empiric but should be based on sound clinical judgment.

The presence of pus should prompt a high index of suspicion for CA-MRSA, and incision and drainage with packing should be performed. Any fluid aspirated should be cultured, including MRSA typing. Hospital admission and parenteral antibiotic therapy should be strongly considered in any febrile child. Application of warm compresses and elevation of the affected limb are useful adjunctive therapies. Analgesics may be necessary for pain control, and antipyretics for relief of fever.

All neonates with suspected omphalitis or mastitis should be promptly admitted and started empirically on parenteral antibiotics for *Staph. aureus* and CA-MRSA, GABHS, GBS, and gram-negative enteric organisms. In infants younger than 3 months of age with facial or extremity cellulitis should be admitted and treated with parenteral penicillin and an aminoglycoside. Between 3 months and 3 years of age, *Staph. aureus, H. influenzae,* or *Strep. pneumoniae* may be causative organisms, and third-generation cephalosporins (ceftriaxone or cefotaxime) should be administered, as well as clindamycin. In ill-appearing children, clinicians should consider the possibility of a more invasive infection and have an increased

suspicion for CA-MRSA (16). Vancomycin is required if meningitis is suspected.

Patients with orbital cellulitis require hospital admission. Multispecialty involvement by otorhinolaryngology, infectious diseases, and ophthalmology is warranted, since surgical drainage of an abscess or a sinuses may be required. Patients should be started empirically on intravenous antibiotics to cover respiratory pathogens; ampicillin–sulbactam is a reasonable choice (14). Intravenous antibiotics for a total of 7 days, followed by a course of oral antibiotics for 14 days, are recommended.

Patients suspected of a severe infection with GABHS should receive parenteral clindamycin in addition to penicillin, intravenous immunoglobulin, an immediate surgical consultation for emergent débridement, and close cardiorespiratory monitoring for signs of septic shock. Aggressive fluid resuscitation may be required. Surgical intervention must not be delayed by radiologic investigations when the clinical likelihood of sever disease is high (10,15,16).

Immunocompromised patients often develop cellulitis caused by atypical organisms such as *Corynebacterium, Pseudomonas,* atypical mycobacteria, and even fungi. A microbiologic diagnosis should be vigorously pursued in these patients, particularly when initial empirical therapy fails to produce a satisfactory response.

Beyond 3 years of age, patients with well-localized cellulitis and without fever or systemic illness may be treated as outpatients with antistaphylococcal and anti-GABHS oral agents. Consider the addition of anaerobic coverage with clindamycin for cases of bite wounds, oral infections, or wounds with devitalized tissue. Caregivers of children who are treated as outpatients require instruction about the necessity of close follow-up within 48 hours and about signs and symptoms that necessitate prompt return to the ED.

Susceptibility patterns of CA-MRSA to clindamycin and trimethoprim–sulfamethoxazole differ in various regions of the country. Generally, either of these agents can be used to treat mild-to-moderate cellulitis due to such MRSA. In the case of severe

infection with CA-MRSA, empiric, parenteral vancomycin is recommended (20).

A patient with cellulitis who shows severe systemic toxicity or does not improve within 48 hours of oral antibiotic therapy should receive high-dose intravenous broad-spectrum antibiotic therapy covering both streptococci and staphylococci. Newer recommendations favor changing empiric therapy to include CA-MRSA coverage. Antibiotic recommendations for possible CA-MRSA infection are presented in Table 277.1.

TABLE 277.1
Antibiotic Doses for the Treatment of Infections Caused by CA-MRSA

Antibiotic	Daily Dose (mg/kg/day)	Interval (H)
Vancomycin	40–60 (IV)	6–8
Clindamycin	30–40 (IV or PO)	8
Gentamicin[a]	3 (IV)	8
Rifampin[a]	20 (IV)	12
Trimethoprim–sulfamethoxazole	10–12 (IV or PO)	12
Linezolid	30 (IV or PO)	8 for children <12 year
	20 (IV or PO)	12 for children >12 year
Minocycline[b]	100 (PO)	12

[a]Used for synergy in combination with vancomycin; not used alone.
[b]For children older than 8 years of age; represents total dose, not per kilogram.

Patients who respond promptly to parenteral antibiotics may be switched over to oral antibiotics but in most cases the total duration of therapy should be a full 10 days.

CRITICAL INTERVENTIONS

- Recognize that patients with necrotizing fasciitis present with pain out of proportion to physical examination findings.
- Arrange follow-up within 48 hours for patients with cellulitis who are treated on an outpatient basis.
- Recognize that patients with purulent infections should be cultured and treated as if they have CA-MRSA.

- Recognize that mastitis and omphalitis are serious forms of cellulitis in the neonatal period that mandate emergent evaluation and treatment.

DISPOSITION

Most children with simple cellulitis can be started on oral antibiotics on an outpatient basis, with follow-up arranged at 48-hour intervals. With the decreasing incidence of *H. influenzae* and *Strep. pneumoniae* cellulitis and the availability of potent oral antibiotics, more and more patients with cellulitis can be safely managed as outpatients.

Admission should be strongly considered in infants younger than 6 months old. Any child, who appears to be ill, has extensive lesions or is immunosuppressed should also be admitted. Patients with facial cellulitis and a fever of $>38.5^{\circ}C$ or those with extremity cellulitis and a fever of $>39^{\circ}C$ and a WBC count $>15{,}000/mL$ are likely to require intravenous antibiotics.

Patients with necrotizing fasciitis require surgical débridement in the operating room. Children with severe systemic manifestations need aggressive treatment and admission to a pediatric intensive care unit. Wound management in cases of extensive SSSS may be best accomplished in a pediatric burn unit.

Common Pitfalls

- Failure to recognize that CA-MRSA infection in children without identified risk factors is increasing in prevalence
- Failure to include orbital cellulitis in the differential diagnosis of periorbital cellulitis
- Failure to recognize that in immunocompromised patients with cellulitis, atypical and opportunistic infections are common and that a microbiologic diagnosis should be actively pursued

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of Christopher S. Kennedy and Mary E. Moffatt to the content of this chapter.

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CHAPTER 278 Meningitis and Encephalitis

James A. Wilde

Central nervous system (CNS) infections are a source of significant morbidity and mortality and are often considered in the differential diagnosis of a febrile child. Bacterial meningitis and viral disease presenting as meningitis, encephalitis, or meningoencephalitis are the most common forms of CNS infection in children. Because of their low prevalence and often subtle presenting signs and symptoms and because of the overwhelming nature of CNS infections, these diseases present a formidable challenge to emergency physicians, both diagnostically and therapeutically.

The organisms most commonly isolated in cases of bacterial meningitis vary with the age of the patient. Among neonates, group B *Streptococcus* (GBS) is by far the most commonly isolated bacterium. Other less common but significant organisms include *Listeria monocytogenes* and gram-negative enteric bacilli such as *Escherichia coli, Klebsiella* and *Enterobacter* species, *Citrobacter diversus,* and *Salmonella* species. GBS and *L. monocytogenes* typically present as "late-onset" meningitis at 1 to 12 weeks of life, whereas meningitis caused by the gram-negative enteric bacteria often presents during the first 2 weeks. Beyond the age of 3 months, *Streptococcus pneumoniae* and *Neisseria meningitidis* are the major pathogens, with *S. pneumoniae* predominating from 2 months to 10 years and *N. meningitidis* predominating from 11 to 17 years. Meningitis caused by *Haemophilus influenzae* type B (HIB) is now rare in the United States owing to a highly effective vaccine (1).

The leading pathogens caused an estimated 1,400 cases of bacterial meningitis in US children younger than 18 years in 2007 (1). This represents a dramatic decline associated with the near-eradication of HIB meningitis following the introduction of Hib conjugate vaccine in 1990. Two-thirds of patients with bacterial meningitis in 1986 were between 1 month and 5 years of age, but by 1995 meningitis in this age group had dropped by 87%, and the median age of bacterial meningitis cases rose from 15 months to 25 years. A second sharp decline in bacterial meningitis was noted with the introduction of the pneumococcal conjugate vaccine in 2000.

Bacterial meningitis is almost always preceded by a hematogenous spread of bacteria. The mechanism whereby bacteria gain access to the intravascular space is unclear, although some data suggest that viral upper respiratory infections may cause a breach of the normal mucosal barriers. It is also unclear how bacteria, once in the bloodstream, gain access to the CNS. Bacterial meningitis can also result from direct invasion of the CNS after trauma or erosion through an infected sinus, but this is a much less common mechanism.

Most instances of bacteremia do not progress to invasion of the CNS. However, once in the CNS, bacteria can initially multiply relatively unimpeded because of the poor immunologic defenses within normal cerebrospinal fluid (CSF) (2). It is only after local release of bacteria-associated chemotactic factors that the CNS mounts a significant defense. The resulting inflammation, edema, and CNS dysfunction are seen clinically as severe headache, nuchal rigidity, photophobia, or seizures. A patient with fever can be anywhere on this continuum but, without CSF for evaluation, it is generally not possible to state definitively when or if the child has reached the meningitic stage.

Aseptic meningitis (i.e., meningitis without the evidence of a bacterial pathogen in the CSF) may be caused by a number of infectious or noninfectious agents. Enteroviruses (ECHO and coxsackievirus) and the mumps virus are among the most common infectious etiologies. Encephalitis is an inflammation of the brain that can occur as a primary pathologic event, as in arbovirus

encephalitis, or as a simultaneous event with primary meningitis. The latter is more correctly termed *meningoencephalitis* and is common in bacterial meningitis. Among the many viral causes of encephalitis are the enteroviruses, arboviruses (West Nile virus, La Crosse strain of the California encephalitis virus [CEV], St. Louis encephalitis), herpes simplex virus (HSV), varicella virus, and mumps virus. Infections caused by enteroviruses and arboviruses occur primarily during the warmer months, with the arbovirus infections paralleling mosquito activity. Infection by CEV is typically seen in young boys exposed to hardwood forests or small pools of stagnant water, where mosquitoes breed (3). HSV encephalitis can occur at any age, including a neonatal form that presents during the second to third week of life.

CLINICAL PRESENTATION

Owing to the protean clinical manifestations of bacterial meningitis in infants and young children, physicians must maintain a high index of suspicion for the disease. Inflammation of the meninges can be manifested by headache, nausea and vomiting, fever, photophobia, mental confusion and lethargy, or excessive irritability, none of which are specific for meningitis. Other clinical findings that are suggestive of meningitis include seizures, focal neurologic signs (hemiparesis, quadriparesis, cranial nerve palsies, visual-field defects), and ataxia, though no single sign is pathognomonic. The symptoms and signs of meningitis vary and depend in part on the patient's age, the duration of illness, and the host's response to the infection. Clinical findings, especially in neonates and young children, may be subtle and nonspecific, including disinterest in feeding, lethargy, respiratory distress, or jaundice. *Fever is commonly absent in neonates with bacterial meningitis.*

A change in the child's affect or state of alertness is one of the most important signs of bacterial meningitis. In one study, depending on the patient's age, 36% to 60% of meningitic children were described as toxic or moribund, and 73% to 100% as lethargic or comatose (4). Interestingly, these findings were generally not present in infants younger than 3 months. *Lethargy* refers to a decreased level

of consciousness with an inappropriate response to stimuli bordering on unconsciousness. However, a child who is sleepy is not necessarily lethargic. Likewise, a febrile child who is playful, smiling, and interactive is unlikely to have bacterial meningitis in the absence of other suggestive signs or symptoms.

Seizures are noted at presentation in 20% to 30% of children with bacterial meningitis (5). *Seizures are rarely the sole manifestation of meningitis in febrile children.* Most children with seizures secondary to bacterial meningitis have a significant, prolonged alteration in their level of consciousness or focal findings on physical examination (6). This is in marked contrast to children with simple febrile seizures who, after a short postictal period, usually return quickly to their baseline mental status and have no neurologic deficits on examination.

Bacterial meningitis in infants and children can present either insidiously over several days or acutely and fulminantly over several hours. The prognosis may be worse for the second group (7), who are not generally not difficult to recognize at presentation. Despite physicians' best efforts, delays in diagnosis are common in those with more insidious presentations. It is unclear whether these delays contribute to subsequent morbidity or mortality (8,9).

Enteroviral infection is typically insidious in onset and may have a biphasic course extending over 10 days or more. Furthermore, the patient with enteroviral meningitis does not usually appear seriously ill unless the infection occurs during the neonatal period.

Differentiating HSV infection from bacterial meningitis may be difficult because the nonspecific symptoms just described are found in both infections. Helpful clues include the absence of bacteria on CSF Gram stain, negative cultures of blood and CSF, the presence of focal seizures, and difficult-to-control seizures. Cutaneous vesicles are found at presentation in only 30% to 50% of infants with neonatal HSV and are uncommon at any stage of HSV encephalitis in older children. St. Louis encephalitis and La Crosse encephalitis can present either in a mild form, consisting of a 2- to 3-day prodrome of low-grade fever, headache, malaise, and vomiting with subsequent development of higher fever, lethargy, and meningeal signs, or in a

severe form, characterized by the abrupt onset of fever and headache followed rapidly by generalized or focal seizures, focal neurologic signs, and coma. HSV encephalitis in the older child may be similar to this severe form of arboviral encephalitis.

An altered state of consciousness is apparent in most children with encephalitis owing to inflammation of the brain parenchyma. This may be manifested by lethargy or delirium, but in severe cases lethargy may progress to a stuporous state or frank coma.

DIFFERENTIAL DIAGNOSIS

While not always apparent at presentation, nuchal rigidity is the clinical sign physicians most associate with meningitis. It is, however, associated with a wide variety of illnesses including:

- *Infections:* Meningitis, encephalitis, brain abscess, epidural abscess, Guillain–Barré syndrome, transverse myelitis, acute cerebellar ataxia, poliomyelitis, tetanus, cervical adenitis, retropharyngeal abscess, vertebral body osteomyelitis, discitis, epiglottitis, trichinosis, tonsillitis, otitis media, pyelonephritis, mumps, hepatitis, shigellosis, malaria, typhoid fever.
- *Vascular abnormalities:* Subarachnoid hemorrhage, intracranial venous thrombosis.
- *Neoplasms:* Meningeal leukemia, intracranial and brainstem tumors, tumors of the cervical vertebrae (osteoid osteoma, eosinophilic granuloma).
- *Metabolic disorders:* Infantile Gaucher disease, maple syrup urine disease, kernicterus.
- *Bony or muscular disorders:* Vertebral anomalies; subluxations, dislocations, and fractures of the cervical spine; myositis; fibromyositis; congenital torticollis.

Children with common, self-limited viral infections may present with symptoms that mimic meningitis. Headache, somnolence, and decreased activity are common symptoms in many childhood infectious diseases. Children with these non-CNS infections may appear toxic on initial presentation but often become alert and playful if the fever responds to antipyretics. *Symptoms of bacterial meningitis generally do not abate with antipyretics alone.*

ED EVALUATION

A careful history can help to differentiate a child with a serious systemic bacterial infection such as sepsis or meningitis from one with a self-limited viral infection. It is important to note that the overwhelming majority of children with fever do not have bacterial meningitis, which is now a rare disease. If each child between 2 months and 2 years of age had only one febrile illness per year of life, the expected rate of bacterial meningitis would be <1 case per 14,000 febrile episodes. Most children in this age group have more than one febrile illness per year, so the actual rate is much lower. Information gathered from the history and physical examination can help the physician to decide who requires LP for further evaluation (Table 278.1).

TABLE 278.1
Indications for Lumbar Puncture and/or Immediate Empiric Treatment for Meningitis

Recommended	Strongly Consider
Unexplained fever and:	Unexplained fever and:
Lethargy	Seizure in child <18 months or >5 year of age
Coma	Severe headache
Shock	No obvious source for fever, child <3 month of age
Extreme irritability in infant	Poor feeding in infant
Age <1 month	Increased sleep in infant
New neurologic deficit	Petechial or purpuric rash
Nuchal rigidity	Any afebrile, toxic-appearing child with symptoms from either column
Photophobia	
Uncontrolled seizure	
Seizure in child <6 months of age	
New-onset focal seizure	

Bacterial meningitis leads to inflammation of the brain and meninges, which causes symptoms such as extreme irritability, photophobia, vomiting, headache, lethargy, and seizures. Excessive

sleep or poor feeding may be observed in infants. The emergency physician should initially focus on these elements of the history in the assessment of a febrile child. Their absence does not rule out meningitis but does make it less likely. Conversely, their presence should heighten suspicion for meningitis.

In addition, questions should be directed toward establishing a source for the fever. Are there any ill contacts with fever? Are there signs or symptoms that are temporally related to the fever and that together constitute a self-limited viral illness? Prior or current antibiotic administration is another important historic item to ascertain.

In the evaluation of a neonate with fever, the mother should be questioned about infections during pregnancy or at delivery. The physician should ask about pruritic or burning vaginal lesions, antibiotic use during pregnancy, ingestion of raw dairy products during pregnancy (listeriosis), parental history of or exposure to HSV, perinatal complications in the mother or child, prolonged care in the nursery after delivery, the mother's GBS status at the time of delivery, and any antibiotic use in the child since birth.

In all febrile children, a history of exposure to someone with sepsis or meningitis should be sought. Travel history and animal contact are important factors to consider when dealing with the less common causes of CNS infections. Mosquito bites may suggest an arbovirus infection.

Parents tend to use the word *lethargic* to describe their children when, in fact, true lethargy is not present. A child who is less playful or more sleepy than usual is not necessarily a lethargic child. Decreased play and increased sleep are almost universally present in young children with febrile illnesses.

A complete physical examination is critical in the evaluation of a febrile child to detect a CNS infection or to establish a reasonable alternative explanation for fever. The following are important questions to ask: Does the child have signs of an acute upper respiratory infection? Does the child have an obvious pharyngitis or oral lesions consistent with herpangina or herpetic gingivostomatitis? Is there a rash consistent with a clear etiology, such as varicella or

the sandpaper rash of scarlet fever? Does the child have conjunctivitis or otitis? Hypotension or prolonged capillary refill time in the absence of dehydration suggests a potentially life-threatening bacterial infection.

The chest, abdomen, and extremities should be examined to search for the evidence of serious bacterial infections such as pneumonia, peritonitis, pyelonephritis, septic arthritis, cellulitis, or osteomyelitis. Look for the presence of a bulging anterior fontanelle in infants in the seated position, an indication of increased intracranial pressure (ICP). Although the funduscopic examination is usually normal in acute CNS infections, the presence of papilledema should raise concern for a brain abscess, subdural empyema, or venous sinus thrombosis. A complete neurologic examination is important to determine the presence and severity of a CNS insult and to document a baseline against which the response to therapy can be monitored.

In all patients with suspected CNS infection, signs of meningeal irritation are sought by examining for nuchal rigidity and Kernig and Brudzinski signs. Especially in a very young child who is frightened by the ED setting, forceful flexion of the neck can be misleading, because the child's natural tendency is to resist the examiner. A toy or flashlight placed at the sitting child's umbilicus usually causes the child to flex the neck spontaneously and may be more helpful in excluding nuchal rigidity. Kernig sign is positive when pain is elicited by extension of the knee from its initial flexed position, with the patient supine and the leg flexed at the hip. The Brudzinski sign consists of spontaneous flexion of the lower extremities after passive flexion of the neck. Meningeal signs are almost invariably present at the time of diagnosis in children older than 13 months with bacterial meningitis but are only rarely present in children younger than 6 months (10).

Careful attention to the child's affect or state of alertness is critical to distinguish those who should undergo LP for further evaluation from the vast majority who need no further invasive tests. The emergency physician should carefully document the general appearance of the child.

The definitive diagnosis of meningitis requires CSF analysis after performance of an LP. This procedure should include an opening pressure, if available, cellular analysis, glucose (including simultaneous serum glucose) and protein determinations, Gram-stained smear, and appropriate bacterial cultures. Viral, mycobacterial, and fungal cultures should be reserved for special circumstances and are not considered routine in otherwise healthy children.

The LP should be delayed if there are signs of significantly increased ICP, evidence of bacterial infection in or around the LP site, coma, focal seizures, new focal neurologic deficits, signs or a history of a bleeding disorder, or cardiopulmonary compromise. If the LP is to be delayed, blood cultures should be obtained and empiric antibiotics administered immediately; lifesaving therapy takes priority over diagnostic procedures.

The laboratory diagnosis of bacterial meningitis rests on demonstration of bacteria or inflammation in the CSF. Though early antibiotics may prevent the isolation of bacteria in subsequent CSF culture, obvious laboratory markers of inflammation persist for days to weeks in most cases. In addition, bacteria can be isolated from blood culture in up to 80% of patients with bacterial meningitis. The various rapid antigen diagnostic tests, including countercurrent immunoelectrophoresis, latex particle agglutination, and enzyme-linked immunosorbent assay, also may be helpful in establishing the etiologic agent if antibiotics have already sterilized the CSF.

A head computed tomography (CT) scan is not necessary before performance of LP (11) if the clinical scenario is consistent with uncomplicated meningitis or encephalitis. However, if the patient has focal neurologic findings, has signs of severely increased ICP, or is comatose (making neurologic examination unreliable), it is prudent to order a brain imaging study such as a contrast-enhanced CT to identify an abscess or other space-occupying lesion that might be considered a contraindication to performance of the LP.

The results of CSF analysis can give important clues to the etiology of the CNS infection **(Table 278.2).** However, in approximately 1% of cases of bacterial meningitis, CSF cell counts, glucose, and protein

are normal, and there are no organisms on Gram stain (12). A "normal" CSF profile thus does not completely rule out the possibility of bacterial meningitis, but it does render the diagnosis very unlikely. Viral infections of the CNS are typically associated with fewer than 500 white blood cells per microliter in the CSF and a lymphocytic predominance. CSF glucose and protein concentrations are usually normal. However, the initial CSF examination in a child with acute enterovirus meningitis may reveal a predominance of polymorphonuclear leukocytes, and the cell count may rarely exceed 1,000/μL.

TABLE 278.2
Typical CSF in Infants and Children

Component	Normal Children	Normal Newborn	Bacterial Meningitis	Viral Meningitis	Herpes Meningitis
Leukocytes/μL	0–6	0–30	>1,000	100–500	10–1,000
Neutrophils (%)	0	2–3	>50	<40	<50
Glucose (mg/dL)	40–80	32–121	<30	>30	>30
Protein (mg/dL)	20–30	19–149	>100	50–100	>75
Erythrocytes/μL	0–2	0–2	1–10	0–2	10–500

The values shown should be used only as a guide to diagnosis, because there is considerable overlap in CSF values for the different etiologic categories.
Source: Modified from Wubbel L, McCracken GH. Management of bacterial meningitis 1998. *Pediatr Rev.* 1998;19:78–84.

Interpretation of a traumatic tap is difficult, and previous recommendations for estimating the number of white cells on the basis of ratio of white to red cells in peripheral blood may be inaccurate (13).

In addition to blood culture and CSF analysis, the minimum laboratory evaluation should also include a complete blood count with differential and platelet count, coagulation studies if thrombocytopenia is present, serum electrolytes, urine sodium concentration, urinalysis, and, in some cases, a chest radiograph.

In suspected cases of encephalitis, helpful additional studies include viral cultures of CSF and mucosal surfaces, specific viral detection in CSF by polymerase chain reaction, electroencephalogram, and brain imaging studies (14).

KEY TESTING

- LP: Gram stain, protein, glucose, bacterial culture
- CBC with differential and platelet count
- Blood culture
- Serum electrolytes
- Urinalysis

ED MANAGEMENT

Supportive care and stabilization are of the utmost importance with CNS infections. Among the initial complications encountered are septic shock with its associated metabolic derangements, coagulopathy, intracranial hypertension, seizures, and hyponatremia resulting from the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. The ED physician must be prepared to support the patient with acute meningitis and manage complications until an intensive care unit (ICU) setting can be arranged for definitive care.

Septic Shock

Simultaneous shock and cerebral edema present a theoretic therapeutic dilemma, because the treatment of one may adversely affect the other. Fluid resuscitation is an integral part of the management of septic shock, and treatment of systemic hypotension must take priority, often requiring massive amounts of crystalloid or colloid.. If there is no response after intravenous infusion of 40 to 60 mL/kg, pharmacologic support should be instituted with pressor agents such as dopamine. Patients who require this level of intervention should ideally be managed in an ICU setting, with a central venous pressure line, Foley catheter, and cardiorespiratory monitors.

Previous recommendations for the fluid management of children with meningitis have stressed fluid restriction to avoid cerebral edema resulting from SIADH (15). More recent data, however, have led to the hypothesis that an elevated anti-diuretic hormone and the concomitant increase in extracellular water may be part of a compensatory mechanism to overcome elevated ICP and maintain

adequate cerebral blood flow (16,17). Routine restriction of fluids should no longer be considered standard (1). If the patient is not dehydrated, the cardiovascular system is stable, and the serum sodium is above 135 mEq/L, maintenance fluids can be initiated using a solution containing one-fourth to one-half normal saline in 5% dextrose.

Increased ICP

The upper limit of normal ICP is about 50 mm H_2O in neonates and 85 mm H_2O in older infants and children, but it can be much higher in CNS infections. In patients with suspected intracranial hypertension, the head of the bed is elevated 15 to 30 degrees. Although the practice is somewhat controversial, some physicians use mannitol (0.25 to 1.0 g/kg infused over 10 minutes), with or without diuretics, to treat intracranial hypertension. Hyperventilation is another effective means to temporarily decrease ICP in the severely affected patient. If hyperventilation is utilized, the $PaCO_2$ should be maintained at 25 to 30 mm Hg. ICP should be monitored continuously in patients requiring hyperventilation and mannitol infusions.

Several authors have advocated the use of adjunctive dexamethasone therapy for bacterial meningitis, particularly in cases of HIB (18,19). However, subsequent research has failed to demonstrate any improvement in neurologic or developmental outcome in children who received steroids for bacterial meningitis (20). Other authors, however, have pointed out that, in light of the low incidence of side effects and the potential benefits, administration of steroids remains appropriate (21), particularly if CSF Gram stain or epidemiologic clues point to a likely case of HIB meningitis. The American Academy of Pediatrics Committee on Infectious Diseases has suggested the use of dexamethasone in suspected bacterial meningitis but has stopped short of recommending it as routine therapy unless disease is caused by HIB (22). If dexamethasone is used, it should be given only to children older than 6 weeks of age with suspected bacterial meningitis, at a

dose of 0.15 mg/kg intravenously just before the first parenteral dose of antibiotic.

Seizures

Early seizure activity occurs in 20% to 30% of patients with bacterial meningitis. Effective anticonvulsants include diazepam or lorazepam acutely and phenobarbital or phenytoin as maintenance. Seizures associated with hyponatremia require infusion of hypertonic sodium solutions. Generally, 4 mL/kg of 3% NaCl is infused over 10 minutes; repeat doses may be necessary if the seizure continues.

Disseminated Intravascular Coagulation

Treating the underlying disease process and correcting the shock and metabolic derangements constitute the best approach to reversing disseminated intravascular coagulation (DIC). If the patient is actively bleeding from peripheral sites or from the gastrointestinal or urinary tract, treatment options include: (1) platelet transfusions to increase the count to above 50,000/μL, (2) vitamin K to correct a prolonged prothrombin time, and (3) infusions of fresh-frozen plasma to correct a prolonged activated partial thromboplastin time. Heparin therapy may be considered in cases of DIC with thrombotic manifestations, although its use in this setting is controversial.

Antimicrobial Therapy

Table 278.3 lists the antibiotics and dosages suggested for the initial therapy of suspected bacterial meningitis. Because penicillin- and cephalosporin-resistant pneumococci have been reported throughout the United States, vancomycin should be added to the regimen any time infection caused by *S. pneumoniae* is suspected. Previous concerns about reduced penetration of vancomycin into the CNS after administration of dexamethasone appear to be unwarranted (23).

TABLE 278.3
Initial Antimicrobial Therapy for Suspected Bacterial Meningitis

Age	Drug	Dosage (mg/kg)
Newborn: to 30 days	Ampicillin	50–75
	and	
	Gentamicin	2.5
	or	
	Cefotaxime	50
30 days to 3 months	Ampicillin	
	and	
	third-generation cephalosporin	50–75
	• Ceftriaxone	50
	• Cefotaxime	75
>3 months	Ceftriaxone or cefotaxime	
	and	
	Vancomycin	15

Sometimes, the results of the initial CSF examination do not distinguish between a bacterial and a viral process. If patients have been pretreated with antibiotics, are younger than 6 months, or are clinically unstable, they should be initially managed as if bacterial meningitis were present.

If HSV encephalitis is suspected, acyclovir therapy is instituted at 20 mg/kg every 8 hours.

CRITICAL INTERVENTIONS

- Consider bacterial meningitis and perform an LP in lethargic or irritable infants, even in the absence of classic signs of meningitis.
- Consider repeat LP if the evolving clinical setting suggests meningitis, even if a CSF culture obtained hours or days earlier was negative.
- Obtain a blood culture before instituting antibiotic therapy for suspected bacterial meningitis.
- Initiate antibiotics prior to CT scanning and the availability of CSF results in any patient with suspected meningitis.

DISPOSITION

Pediatric infectious disease consultation may be warranted for the management of CNS infections in children. Neurosurgical consultation for placement of an ICP-monitoring device may also be required.

Patients with bacterial meningitis or HSV encephalitis require immediate hospitalization with intensive monitoring. CNS infections of probable enteroviral or arboviral origin may require hospitalization for diagnostic purposes or for supportive care.

If clinical signs and symptoms and laboratory analysis of CSF suggest viral meningitis, outpatient management may be appropriate (24). Some authors suggest observation for 4 to 8 hours, followed by a second LP to help confirm the diagnosis (10). If the second CSF analysis reveals lymphocyte predominance, no significant worsening of pleocytosis, normal glucose and protein, and continued absence of bacteria on Gram stain, bacterial meningitis is highly unlikely. A recently validated bacterial meningitis score has been shown to have a high negative predictive value for bacterial meningitis and can also be used to identify candidates for outpatient therapy (Table 278.4) (24).

TABLE 278.4
Risk Factors for Bacterial Meningitis: The Bacterial Meningitis Score[a]

Bacteria detected on CSF gram stain
CSF absolute neutrophil count ≥1,000 cells/μL
CSF protein ≥80 mg/dL
Peripheral blood absolute neutrophil count ≥10,000 cells/μL
History of seizures before or at the time of presentation

[a]No risk factors = very low risk, negative predictive value for bacterial meningitis 99.9%.

Source: From Nigrovic LE, Kuppermann N, Macias CG. Clinical prediction rule for identifying children with cerebrospinal fluid pleocytosis at very low risk of bacterial meningitis. *JAMA*. 2007;297:52–60.

Transport to a pediatric referral center should be strongly considered for any child with bacterial meningitis. If the LP has been performed, an aliquot of the CSF should be sent with the patient,

along with documentation of clinical management up to the point of transfer.

CONTACT PROPHYLAXIS

If meningitis is caused by *N. meningitidis* or HIB, rifampin chemoprophylaxis should be considered for the child's household contacts. The dosage regimen is 10 mg/kg (maximum dose, 600 mg) every 12 hours for four doses and 20 mg/kg (maximum dose, 600 mg) once daily for 4 days, respectively. Chemoprophylaxis is given to household contacts of children with HIB meningitis only if there is at least one unvaccinated household member younger than 48 months. Rifampin should not be given to a pregnant patient. Medical personnel exposed to a patient with meningococcal infection need chemoprophylaxis only if that exposure was intimate (e.g., mouth-to-mouth resuscitation). The use of appropriate isolation precautions (mask and gown, hand washing) for suspected cases of meningococcal disease eliminates any need for prophylaxis in most situations.

Common Pitfalls

- Failure to consider meningitis in infants with fever without a source.
- Failure to consider CNS infection in children with vomiting.
- Excluding the diagnosis of bacterial meningitis despite strong clinical clues, even when the CSF white cell count is normal or the Gram-stain is negative for bacteria
- Failure to order a Gram-stained smear of the CSF when bacterial meningitis is suspected.
- Failure to consider a CNS infection in a child who has had a simple febrile seizure. Although LP is not mandatory, it should be considered in a child younger than 18 months of age, especially if the child has not returned to baseline mental status.
- Failure to document the physical examination thoroughly, particularly the child's general appearance.
- Failure to provide adequate discharge instructions, especially reasons for immediate return to the emergency department.

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of William J. Barsan to the content of this chapter.

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CHAPTER 279 Human Immunodeficiency Virus

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In the early 1980s, children were identified with clinical features similar to severe combined immunodeficiency (SCID) but with distinct epidemiologic and pathologic findings. These first cases of pediatric acquired immunodeficiency syndrome (PAIDS) were reported in 1982. By 1983, the causative agent of AIDS was identified as human immunodeficiency virus (HIV) (1).

HIV is an RNA retrovirus that selectively infects T-cells and cells of the monocyte lineage. The host cell targets of HIV are critical components of the immune system (2). When confronted with pathogens, these cells normally produce a coordinated, protective effector response. The molecular signals that activate normal cell responses to pathogens are read by the HIV proviral DNA as signals to initiate replication.

Three pathologic consequences of HIV infection induce recognizable patterns of clinical disease: progressive immunologic attrition and immune deficiency, central nervous infection, and uncontrollable immune activation (3). Because functional CD4+ T-cells are required for the generation of protective, antigen-specific T-cell and antibody responses, T-cell loss and impaired T-cell production eventually induce an acquired severe immune deficiency and progressive susceptibility to opportunistic infections (OIs). Neurons in the central nervous system (CNS) are not specific targets for HIV, although it infects and activates local microglial cells. These activated macrophage-like cells generate a variety of cytokines that

cause activation-induced programmed cell death of adjacent neurons, resulting in signs and symptoms of neuroencephalopathy. HIV may also induce an inappropriate and uncontrolled activation of infected target cells, producing a variety of proliferative disorders such as lymphoid interstitial pneumonitis (LIP), lymphadenopathy, hepatosplenomegaly, and systemic features of chronic infection, including fatigue, fever, and wasting.

In 2008 the Centers for Disease Control and Prevention (CDC) redefined the criteria for HIV infection and *acquired immunodeficiency syndrome* (AIDS) in children less than 13 years of age (4). Although in the revised definitions, children less than 18 months old whose mother is HIV positive and have an AIDS defining condition (see Table 279.1) are considered to have been infected, confirmatory testing is still strongly encouraged. Children 18 months of age and older must have laboratory confirmed evidence of infection even if they have an AIDS defining condition, in order to be considered infected with the virus. The CDC also has developed a specific classification system to describe the immunologic and clinical features of the disease in children (Table 279.2). These categories are combined to provide a pediatric HIV classification which defines patients at their worst clinical and immunologic states; the assigned class is not be upgraded even if a patient improves with treatment (Table 279.3) (5).

TABLE 279.1
AIDS-Defining Conditions in Children <13 Years

Bacterial infections, multiple or recurrent	LIP or PLH complex
Candidiasis of esophagus, bronchi, trachea, or lungs	Lymphoma, Burkitt (or equivalent term), immunoblastic (or equivalent term, or primary, of brain
Coccidioidomycosis, disseminated or extrapulmonary	*M. avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary	*Mycobacterium tuberculosis* of any site, pulmonary, disseminated, or extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month's duration)	*Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month	*Pneumocysti jirovecii* pneumonia
Encephalopathy, HIV related	Progressive multifocal leukoencephalopathy
Histoplasmosis, disseminated or extrapulmonary	*Salmonella* septicemia, recurrent
Isosporiasis, chronic intestinal (>1 month's duration)	Toxoplasmosis of brain, onset at age >1 month
Kaposi sarcoma	Wasting syndrome attributed to HIV
Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)	

Source: From Schneider E, Whitmore S, Glynn KM, et al.; Centers for Disease Control and Prevention (CDC). Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years - United States, 2008. *MMWR Recomm Rep.* 2008;57(RR10):1–12.

TABLE 279.2
CDC Immunologic Categories Based on Age-Specific CD4+ T-Lymphocyte Counts and Percent of Total Lymphocytes for HIV-Infected Children

	Age of Child					
	<12 month		1–5 year		6–12 year	
Immunologic Category	**Cells/μL**	**(%)**	**Cells/μL**	**(%)**	**Cells/μL**	**(%)**
No evidence of suppression	≥1,500	(≥25)	≥1,000	(≥25)	≥500	(≥25)
Evidence of moderate suppression	750–1,499	(15–24)	500–999	(15–24)	200–499	(15–24)
Severe suppression	<750	(<15)	<500	(<15)	<200	(<15)

Source: From Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *Morb Mortal Wkly Rep.* 1994;43(RR-12):4.

TABLE 279.3
CDC Classification System for HIV-Infected Children <13 Years of Age

Immunologic Category	Clinical Categories[a]			
	N: No Signs/ Symptoms	A: Mild Signs/ Symptoms	B: Moderate Signs/Symptoms	C: Severe Signs/ Symptoms
No evidence of suppression	N1	A1	B1	C1
Evidence of moderate suppression	N2	A2	B2	C2
Severe suppression	N3	A3	B3	C3

[a]For definitions of mild, moderate and severe symptoms, see Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR Morb Mortal Wkly Rep.* 1994;43(RR-12):1–10.

With recommendations for universal HIV screening of all pregnant women and effective pre- and post-natal therapy of "at risk" babies, maternal to child transmission is less than 2%. However, adolescents and young adults (13 to 29 years old) accounted for 39% of all new HIV infections in 2009. The HIV infection rate in children under 13 years has remained relatively stable between 2008 and 2011 at ~0.4% (6). The majority of infections are still acquired perinatally. Fortunately, the estimated rate of PAIDS is >0.01%

CLINICAL PRESENTATION

The initial presentation and assessment of an HIV-infected child may differ depending upon whether or not the diagnosis of HIV infection has been made previously (3,7). The child with perinatally acquired HIV may appear to be growing normally and to have no more than the usual number of routine childhood infections. Therefore, previously undiagnosed HIV-infected children may present through the emergency department (ED) with their first clinical manifestations of HIV-associated disease, and a degree of suspicion must be kept for HIV even in relatively healthy older children.

Additionally, as teens engage in high-risk behavior, they too may present to the ED with complications of previously undiagnosed HIV infection.

HIV infection should be considered in children who present with unexplained poor growth or developmental delay or with recurrent or chronic infections. Recurrent infections do not need to be severe or debilitating, and the most common infections seen early in the course of HIV-associated immunodeficiency are frequent otitis media, sinusitis, bacterial pneumonia, adenitis, and diarrhea. Any OI

immediately suggests an underlying immune deficiency. The most common presenting physical findings in previously undiagnosed HIV-infected children are lymphadenopathy, especially involving cervical and axillary lymph nodes, and hepatic or splenic enlargement. Parotid gland enlargement may also be seen. The presence of recurrent or chronic oral candidiasis especially in a child older than 1 year suggests immune deficiency. Common hematologic findings in HIV-infected children include anemia, neutropenia, and, in approximately 5% of undiagnosed HIV-infected children, "idiopathic" thrombocytopenia. Blood chemistry abnormalities may include nonspecific liver enzyme elevations, hypoalbuminemia, and hyperproteinemia with an increased globulin fraction. The erythrocyte sedimentation rate is often markedly elevated.

Acute manifestations of an OI may be the initial presenting process in a child with undiagnosed HIV. *Pneumocystis jiroveci* pneumonia (PJP) remains the most common presenting OI in undiagnosed children. Although typically presenting at <2 years of age, PJP may occur in a child at any time and depends upon the status of an individual patient's T-cells. Symptoms of PJP include dyspnea, tachypnea, cough, and fever that may be slowly progressive over several weeks. Physical examination often reveals clear lung sounds and disproportionate hypoxemia. The severity of symptoms may range from a mild repetitive cough to severe respiratory distress. Chest radiography shows a diffuse interstitial pattern often disproportionately mild compared to the patient's hypoxemia and respiratory distress. Lymphoid interstitial pneumonitis (LIP) and pulmonary lymphoid hyperplasia (PLH) also cause respiratory symptoms and may mimic infection or reactive airway disease. In contrast to PJP, LIP and PLH often have radiographic findings worse than respiratory symptoms would suggest. Children with this process often have generalized lymphadenopathy and hepatosplenomegaly and may display digital clubbing. The most common organisms causing respiratory infections in HIV-infected children remain the typical pediatric respiratory pathogens such as *Streptococcus pneumonia, Haemophilus influenzae,* and *Moraxella catarrhalis.*

Children with profound immune deficiency may present to the ED with a variety of other OIs. *Mycobacterium avium* complex presents with prolonged fevers, night sweats, chronic diarrhea, abdominal pain, and weight loss. Chronic oral thrush is common, and esophageal candidiasis should be suspected in a child with oral thrush accompanied by dysphagia, irritability, and weight loss. Diarrhea is common. Although at times related to persistent gastrointestinal infections with "routine" organisms such as Salmonella, Shigella, and Campylobacter, HIV-infected children are particularly at high risk for *Clostridum difficile, Giardia,* cryptosporidium, and cytomegalovirus (CMV) enteritis. Disseminated toxoplasmosis, histoplasmosis, and cryptococcosis, although uncommon, may be seen in children. Herpes virus infections—herpes simplex virus (HSV), varicella-zoster virus (VZV) and CMV—are often particularly severe and may present as disseminated disease. CMV retinitis, a common cause of vision loss in adult HIV patients, is uncommon in children but can occur with advanced disease and may present to the ED as acute blurry vision. Malignancies, especially B-cell lymphomas, occur at an increased rate with HIV infection and may occur in the CNS or gastrointestinal tract. Kaposi sarcoma, however, is rare in children. Acute cardiac and renal manifestations are uncommon, but cardiomyopathy with congestive heart failure and acute renal failure has been described. Chronic HIV-associated encephalopathy and developmental delay are common in untreated children, and acute CNS manifestations such as infection, space-occupying lesions, and thromboembolic events may occur. Infected children are at risk for sepsis and meningitis with the usual pediatric pathogens, and patients may be particularly susceptible because of compromised ability to respond to routine immunizations.

Less-acute but common presentations to the ED include infectious skin eruptions, such as molluscum, verrucae, and drug eruptions. The child with HIV-associated immune compromise is at greater risk for severe HSV and VZV infections and may present with recurrent or persistent chicken pox, varicella zoster, or mucocutaneous herpes simplex infections. Oral aphthous ulcers are common and present as

painful, shallow oropharyngeal ulcers that often result in decreased oral intake, weight loss, and, at times, dehydration. Aphthous ulcers need to be differentiated from oral HSV lesions, as corticosteroids are useful in the treatment of the former and contraindicated in the latter.

Children known to be infected with HIV often present to the ED with a different constellation of chief complaints (7). Patients who are adherent to their highly active antiretroviral therapy (HAART) are very unlikely to develop an OI, and acute infections most often reflect routine childhood illnesses. More commonly, ED visits are associated with adverse effects of patients' treatment regimens. Acute pancreatitis can be seen with several antiretroviral (ARV) agents and can be severe and life threatening. Drug eruptions ranging from mild nonspecific erythroderma and urticaria to overwhelming Stevens–Johnson syndrome may be seen with agents used for PJP prophylaxis (trimethoprim–sulfamethoxazole [TMP–SMX]) or ARV agents (e.g., abacavir and nevirapine). Nausea, vomiting, and liver function abnormalities are commonly seen in patients on HAART. Drug-induced hematologic abnormalities that may present to the ED include thrombocytopenia-associated bleeding, anemia-associated congestive heart failure, and granulocytopenia-associated secondary infections, such as those caused by *S. aureus* and *Pseudomonas aeruginosa.*

DIFFERENTIAL DIAGNOSIS

Any of the SCID syndromes may present identically to HIV. Children with either autosomal recessive or X-linked SCIDs often present with overwhelming infections within the first 6 months of life, although later presentation may occur. Patients with DiGeorge syndrome may develop OIs, but these patients usually have associated conotruncal congenital heart disease, hypocalcemia, or typical facial dysmorphisms. Primary antibody deficiencies including X-linked agammaglobulinemia and common variable immune deficiency typically present with recurrent upper and lower respiratory tract infections caused by encapsulated bacteria. *Giardia* and enteroviral disease are also commonly seen in these patients.

Lymphoma, leukemia, and other malignancies can present with weight loss, organomegaly, lymphadenopathy, cytopenias, and OIs. Cystic fibrosis is also associated with recurrent pneumonias, sinus disease, chronic diarrhea, and poor weight gain. Autoimmune diseases such as systemic lupus erythematosus and systemic juvenile rheumatoid arthritis and metabolic and mitochondrial diseases may present with multiple features suggestive of immune deficiency. Many chronic conditions may be associated with secondary immunodeficiency including protein calorie malnutrition, zinc deficiency, nephrotic syndrome, inflammatory bowel disease, and protein-losing enteropathies.

In infants younger than 3 months, TORCH infections (toxoplasmosis, rubella, CMV, HSV, syphilis) may present with features similar to HIV.

ED EVALUATION

Assessment in the ED will depend upon whether the patient is known to be infected with HIV or is presenting with a suspected but undiagnosed immune deficiency (7). A careful physical examination and history should assess factors listed in Table 279.4. However, absence of known risk factors should not override clinical suspicion for HIV. A child with findings strongly suggestive of immune deficiency should be considered for hospitalization for comprehensive evaluation. There are several highly sensitive and specific rapid HIV tests approved for use in the United States. Fourth-generation immunoassays detect IgM and IgG antibodies and p24 antigen and are highly sensitive at detecting early infection. Unfortunately, results are not immediately available with these newer assays. Although not as sensitive for early detection, several second-generation devices that detect antibody only are designed for point-of-care testing and provide results within 20 minutes.

TABLE 279.4
Indications for HIV Testing in Children Presenting to the ED

History of parental HIV infection
Signs of congenital viral infection
Suspected OI
History of recurrent, severe, bacterial infections
Hepatosplenomegaly, lymphadenopathy
Unexplained wasting, myopathy, hepatitis, carditis, nephritis, developmental regression, neuropathy, encephalopathy

For the child with known HIV infection, ED evaluation should address the presenting problems in the context of the patient's immunologic status. The risk of OI is related to the degree of immune deficiency and adherence to a HAART regimen. In general, children who are in CDC category 1 (no evidence of immune suppression) may receive the same evaluation as a noninfected child with similar clinical symptoms. Children in more advanced categories are at higher risk of serious illness, and more intensive evaluations are indicated.

Although potentially a sign of underlying malignancy, fever is usually an indication of secondary infection. In most children, a routine complete blood count, appropriate cultures, and indicated radiographs should be performed. In children with severe immune compromise, blood cultures should also be obtained for acid-fast bacilli, CMV, and adenovirus. Pulse oximetry or blood gases are indicated for patients with cough, wheeze, or respiratory distress. Nasal pharyngeal washings for rapid viral diagnostic assessment should be sent, and sputum should be obtained in older children. For acute diarrheal disease, stool examinations are indicated for routine bacterial and rotavirus infections, ova, and parasites *Giardia* and *C. difficile*. In children with advanced HIV disease, evaluation for cryptosporidium, acid-fast bacilli, CMV, and adenovirus would be added to this list. Where dehydration is a consideration, serum electrolytes, calcium, and magnesium levels should be monitored. For children presenting with acute abdominal pain, serum amylase and lipase and tests of liver function should be ordered. Abdominal imaging may be indicated for patients with severe or persistent pain. For acute rashes suggestive of drug hypersensitivity, a history of recent medication changes should be sought. Skin lesions appearing infectious in origin should be cultured. Children with acute CNS

symptoms should have appropriate imaging and lumbar puncture if deemed safe and appropriate.

HIV infection is often associated with generalized lymphadenopathy. Differentiation from chronic parotid gland involvement is sometimes difficult. Acute infectious lymphadenitis or focal bacterial parotitis may complicate long-term lymphadenopathy or parotid gland swelling. HIV-associated B-cell lymphoma may present as a rapidly growing local adenopathy in a patient irrespective of T-cell level.

Adverse medication reactions are very common in HIV patients and may develop acutely or after prolonged exposure to ARV drugs. The primary side effects associated with ARV agents are listed in Table 279.5 (8). The long-term adverse impact of ARV agents on metabolism and bone is being seen more frequently. Many agents may cause acute, severe lactic acidosis. HIV-associated lipodystrophy known to affect adults is now being seen more commonly in children and is associated with increased abdominal girth, dorsocervical fat accumulation, and peripheral fat loss characterized by thinning of the face, extremities, and buttocks. Metabolic complications include insulin resistance leading to frank diabetes, hyperlipidemia with elevated cholesterol, and triglyceride levels, leading potentially to early coronary artery disease, and osteopenia with increased risk for spinal compression and extremity fractures. ARV agents, particularly the protease inhibitors, have pharmacologic interactions with many other agents (e.g., prolongation of activity of midazolam). Many other drug interactions have been documented, and clinicians must exercise caution when adding new drugs to an HIV-infected patient's treatment regimen.

Current guidelines from the Health and Human Services panel on ARV therapy and medical management of HIV-infected children recommend discontinuing all components of a child's drug regimen in severe or life-threatening toxicity. The toxic effect and the suspected ARV should clearly be documented in the medical record. Unless the recent results of therapeutic drug monitoring showing concentration above the normal therapeutic range are available to

the ED physician, dose reduction is not considered an option in the setting of ARV toxicity (8).

KEY TESTING

- Known HIV infection
  - Fever: Degree of immune suppression
    - None: Evaluate as if noninfected
    - Moderate: Complete blood count, appropriate cultures, rapid respiratory viral testing
    - Severe: As above plus test for acid-fast bacillus, cytomegalovirus, and adenovirus
  - Respiratory symptoms: Chest X-ray, rapid respiratory viral testing, and sputum culture
  - Acute gastrointestinal illness: Serum electrolytes, calcium, and magnesium levels, stool culture, rotavirus antigen test, adenovirus rapid test
    - Ova and parasites test, *Giardia* and *C. difficile* toxin should be considered for primary diarrheal illness
  - Acute abdominal pain: Serum amylase and lipase and liver function testing
- HIV exposure evaluation: Rapid HIV1/2 test, hepatitis B surface antibody and antigen, hepatitis C test

ED MANAGEMENT

Three principles guide ED management of children with HIV: HIV is not spread by routine clinical contact with patients or their families; the risk of any acute process being a serious one is inversely related to the patient's T-cell count; and close communication with the patient's HIV specialist is crucial.

Presenting illness in an HIV-infected child with intact T-cells can generally be managed in a manner similar to that of the same process in a noninfected child. For other HIV-infected children, the degree of immune suppression (CD4+ T-lymphocyte count or percentage) (Table 279.2) needs to be considered when ED management is initiated. Importantly, ED-identified physical or

laboratory abnormalities may be known to the primary HIV health-care provider as chronic conditions, and the primary service may be aware of psychosocial factors unique to the patient and family that need to be incorporated into ED management.

TABLE 279.5
Primary Side Effects Associated with ARV Agents

ARV Class/Agent	Primary Side Effects and Toxicities
Nucleoside Reverse Transcriptase Inhibitors	
Zidovudine (Retrovir; ZDV; AZT)	Anemia, neutropenia, nausea, headache, insomnia, muscle pain, and weakness
Lamivudine (Epivir; 3TC)	Abdominal pain, nausea, diarrhea, rash, and pancreatitis
Emtricitabine (Emtriva; FTC)	
Stavudine (Zerit; d4T)	Peripheral neuropathy, headache, diarrhea, nausea, insomnia, anorexia, pancreatitis, increased liver function tests (LFTs), anemia, and neutropenia
Didanosine (Videx; ddI)	Pancreatitis, lactic acidosis, neuropathy, diarrhea, abdominal pain, and nausea
Abacavir (Ziagen; ABC)	Nausea, diarrhea, anorexia, abdominal pain, fatigue, headache, insomnia, and hypersensitivity reactions
Tenofovir (Viread; TNV; TDF)	Nausea, diarrhea, vomiting
Nonnucleoside Reverse Transcriptase Inhibitors	
Nevirapine (Viramune; NVP)	Rash (including case of Stevens-Johnson syndrome), fever, nausea, headache, hepatitis, and increased LFTs
Delavirdine (Rescriptor; DLV)	Rash (including case of Stevens-Johnson syndrome), nausea, diarrhea, headache, fatigue, and increased LFTs
Efavirenz (Sustiva; EFV)	Rash (including cases of Stevens-Johnson syndrome), insomnia, somnolence, dizziness, trouble concentrating, and abnormal dreaming.
Protease Inhibitors	
Indinavir (Crixivan; IDV)	Nausea, abdominal pain, nephrolithiasis, and indirect hyperbilirubinemia
Nelfinavir (Viracept; NFV)	Diarrhea, nausea, abdominal pain, weakness, and rash
Ritonavir (Norvir; RTV)	Weakness, diarrhea, nausea, circumoral paresthesia, taste alteration, and increased cholesterol and triglycerides
Saquinavir (Invirase [formerly Fortovase]; SQV)	Diarrhea, abdominal pain, nausea, hyperglycemia, and increased LFTs
Amprenavir (Agenerase; APV) Fos-Amprenavir (Lexiva; *f*-APV)	Nausea, diarrhea, rash, circumoral paresthesia, taste alteration, and depression
Lopinavir/Ritonavir (Kaletra; LPV/RPT)	Diarrhea, fatigue, headache, nausea, and increased cholesterol and triglycerides
Atazanavir (Rayataz; ATV)	Jaundice, hyperbilirubinemia, nausea, vomiting, headache, diarrhea, rash
Tipranavir (Aptivus; TPV)	CNS hemorrhage, hepatitis, rash, increased cholesterol and triglycerides
Darunavir (Prezista; DRV)	Nausea, diarrhea, abdominal pain, headache, lipodystrophy, increased cholesterol and triglycerides
Entry Inhibitors	
Enfuvirtide (Fuzeon; T-20)	Injection site reactions; household exposure to contaminated needles/syringes
Maraviroc (Selzentry; MVC)	Cough, rash, muscle and joint pain, abdominal pain, dizziness
Integrase Inhibitor	
Raltegravir (Isentress; RAL)	Diarrhea, nausea, headache, increased creatine kinase

The insight of the patient's HIV provider will help guide the empiric antibiotic treatment of a child presenting to the ED with fever. The specific antibiotic regimen is based on the source of infection, likely organisms, and degree of T-cell compromise. Children with normal T-cells may be treated with oral antibiotics alone. Parenteral ceftriaxone (50 to 75 mg/kg) followed by a course of oral antibiotics effective against beta-lactamase positive agents is a good choice for community-acquired pneumonia, acute otitis media, or sinusitis in a patient with mild-to-moderate immunologic

suppression but stable T-cell numbers. Children with advanced HIV disease require more aggressive antibiotic intervention. Initial treatment should be with high-dose parenteral ceftriaxone (75 to 100 mg/kg); additional antibiotics including vancomycin or piperacillin and tazobactam may also be considered. Fever with granulocytopenia, which may develop at any time as a complication of ARV therapy, requires broad-spectrum antibiotic coverage, as does the patient with fever and an indwelling central venous catheter. The ED physician should have a low threshold for admission to a facility with specialists in PAIDS, especially for the child with severe immune suppression.

Antiviral chemotherapy often is needed in children with HIV. Empiric influenza treatment should be started on any HIV-infected children with a febrile viral illness during influenza season regardless of the result of a rapid flu test. Acyclovir may be used for outpatient management for varicella prophylaxis following exposure.

Although HIV-positive infants younger than 1 year may develop PJP at any T-cell level, older patients with severe T-cell suppression are at particular risk for this complication, particularly if adherence to prescribed prophylaxis is inconsistent. Patients with PJP usually present with a history of progressive cough, tachypnea, shortness of breath, dyspnea, and intermittent fever, which may be low grade. Auscultation of the chest often reveals an expiratory grunt without other adventitious sounds. Hypoxemia is demonstrable with pulse oximetry and may be exacerbated with simple exercise. Chest radiograph may show only minimal changes; marked interstitial infiltration reflects very advanced disease and a guarded prognosis. Any patient suspected of having PJP should be hospitalized at a center familiar with the management of this disorder. Bronchoalveolar lavage is particularly useful in confirming the diagnosis. TMP-SMX is the antibiotic of choice, and systemic corticosteroids are indicated as adjunctive therapy in these patients. HIV-infected children, even those with T-cells sufficient to avoid OIs, are at increased risk for pneumonias and other respiratory tract infections with “routine” organisms including *S. pneumoniae, M. catarrhalis,* and *H. influenzae.* They are also at risk for reactive airway

disease, and more than 30% of patients require bronchodilators or more intense therapy for asthma. Differentiating between an acute asthma attack and a serious acute infectious process is essential.

The most common cause of diarrhea in HIV-infected children is their ARV therapy. Dietary changes and loperamide are usually sufficient to control symptoms. Dehydration is treated with oral or intravenous rehydration depending on severity. Because of the increased risk for infectious enteritis, HIV-positive children presenting to the ED with diarrhea should be screened for salmonella, shigella, Campylobacter, and parasitic infections with *Giardia lamblia* and cryptosporidium. *C. difficile* and intestinal candidiasis may be complications of long-term prophylactic antibiotics. Nonspecific enteritis commonly seen in children with long-term HIV disease may be associated with electrolyte imbalance, malabsorption, and wasting.

It is not appropriate to institute or make changes in an individual's ARV therapy, prophylactic therapy, or other chronic medical treatment in the ED. Any such changes should be made only after discussion with patient's HIV health-care provider.

CHEMOPROPHYLAXIS AFTER EXPOSURE TO HIV

Children may present to the ED after exposures that put them at risk for HIV infection. Examples include accidental puncture wounds during play with discarded needles or from needles in the home and sexual abuse. Nonoccupational post-exposure prophylaxis (nPEP) is recommended for children after substantial exposure risk to blood, genital secretions, or other potentially infected body fluids of a person known to be HIV infected. Nonoccupational PEP should also be considered in the situation where the HIV status is unknown, such as following a sexual assault (Fig. 279.1). The most effective outcomes occur when nPEP is started within 72 hours of exposure when transmission of the virus is more likely to be interrupted (9). However, nPEP may be started more than 72 hours post-exposure if, in the clinicians' judgment, there is a serious risk of transmission and the benefits of therapy outweigh the risks.

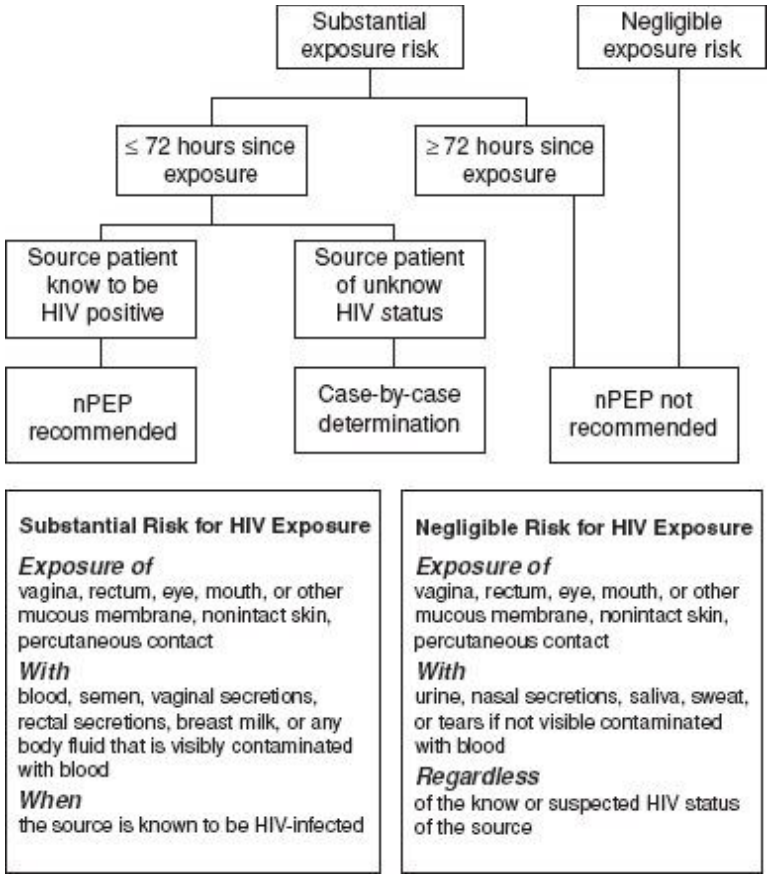

FIGURE 279.1 Algorithm for evaluation and treatment of possible nonoccupational HIV exposures. (From Centers for Disease Control and Prevention. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: Recommendations from the U.S. Department of Health and Human Services. *MMWR Recomm Rep.* 2005;54[RR-2]:8.)

Generally a three-drug HAART regime is used to provide maximal suppression of virus replication. There is no clear evidence which regimen provides the best outcome. Current recommendations include use of either a nonnucleoside, protease inhibitor or integrase inhibitor combined with two nucleoside reverse transcriptase inhibitors (Table 279.6) (9–11). The course of therapy is for 28 days. Compliance may be improved if the child is sent home with a 3- to 5-day supply of medications. The child should be tested for HIV antibodies at the initiation of post-exposure prophylaxis to confirm the absence of pre-existing HIV infection. Post-exposure prophylaxis

should be offered in conjunction with appropriate counseling as to the risks and benefits of ARV therapy and the infectious risk of the exposure and after arrangements are made for ongoing counseling and follow-up testing.

TABLE 279.6
Postexposure Prophylaxis Regime for Children

Regime Type	Nucleoside Reverse Transcriptase Inhibitors (One Drug from Each Column)	
Nonnucleoside: Efavirenz (EFV)	Lamivudine (3TC) or Emtricitabine (FTC)[a]	Zidovudine (ZDV) or Tenofovir (TDF)[a]
Protease inhibitor: Lopinavir/Ritonavir (LPV/r) (Kaletra®)	Lamivudine (3TC) or Emtricitabine (FTC)	Zidovudine (ZDV)
Integrase inhibitor: Raltegravir (RAL)	Emtricitabine (FTC)[a]	Tenofovir (TDF)[a]

[a]FTC and TDF are available in a combination formulation (Truvada®), approved for children ≥12 years and ≥35 kg.

Source: From Smith DK, Grohskopf LA, Black RJ et al.; U.S. Department of Health and Human Services. Centers for Disease Control and Prevention. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: Recommendations from the U.S. Department of Health and Human Services. *MMWR Recomm Rep.* 2005;54(RR–2):1–20; New York State Department of Health AIDS Institute. HIV post-exposure prophylaxis for children beyond the perinatal period. Available online at: http://www.hivguidelines.org/clinical-guidelines/infants-children/hiv-post-exposure-prophylaxis-for-children-beyond-the-perinatal-period. Accessed September 1, 2013.

CRITICAL INTERVENTIONS

- Patients suspected of having immune deficiency should not be given live virus vaccine; all blood products required by such patients should be irradiated and CMV negative.
- Fever in an HIV-infected patient suggests infection. Appropriate investigations (such as complete blood count, blood culture, chest radiograph, urinalysis, lumbar puncture) are indicated.
- Consider HAART side effects as the cause of symptoms such as rash, abdominal pain, and other gastrointestinal symptoms.
- In an HIV-infected patient, the risk for a more serious disease is inversely related to the patient's T-cell count. Immunosuppressed children should receive more intensive evaluation and treatment interventions than immunologically normal children.
- A child at risk for HIV by either history or suggestive clinical findings should be offered rapid HIV testing and managed

accordingly.

DISPOSITION

As with any chronic disorder, children with HIV are best followed up by a primary service experienced in the multidisciplinary management of the disease. Children who are suspected of having undiagnosed HIV and who do not have compelling clinical findings should be referred to a pediatric infectious disease or other HIV specialist for urgent consultation. Discussion with the consultant prior to discharge from the ED can help assess whether the child can be safely discharged and to arrange follow-up. Known HIV-infected children who are manageable at home may be discharged from the ED after consultation with the primary HIV health-care service and arrangement for follow-up.

Children requiring hospitalization should be carefully evaluated to determine whether admission to an intensive care or regular inpatient unit is required. If the hospital is not equipped to manage seriously ill HIV-infected children or if the necessary specialists are not available, the patient should be transported to an appropriate center by qualified transport personnel.

Common Pitfalls

- Failure to appreciate the clinical latency from infection to manifestation of HIV disease may be years. Perinatally infected children may present with their first complications at 10 years or older.
- Failure to question histories. Not all parents will volunteer that their child is HIV infected, and others may deny their own risk factors. Decisions to test or treat a child as HIV infected may need to be based on clinical suspicion alone.
- Failure to recognize OIs in patients with known or suspected immune deficiency. In any suspected immune-deficient patient younger than 1 year, the presence of tachypnea and hypoxia suggest PJP, and empiric therapy should not be withheld while waiting for a definitive diagnosis. Children prescribed appropriate

PJP prophylaxis may develop the disease if they are nonadherent to their prophylaxis regimen.

- Failure to appreciate the significance of oral thrush. Any child older than a year with persistent or recurrent oral thrush should be considered to be immune deficient.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Ronald M. Ferdman to the content of this chapter.

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CHAPTER 280

Sickle Cell Disease in Children

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Sickle cell disease (SCD) represents a spectrum of inherited hemoglobin defects that are characterized by dysmorphic red blood cells, impaired homeostatic balance involving the vascular endothelium and nitric oxide, and subsequent microvascular occlusion. It is one of the most common severe monogenic disorders (1). The molecular basis of the disease is the substitution of 17th nucleotide from thymine to adenine forming valine instead of glutamic acid in the sixth position of the globin beta chain (1). This change causes the crystallization of the hemoglobin molecules in conditions of relative hypoxia, low pH, cold, dehydration of the RBCs, and infections (1).

These patients may present with signs and symptoms involving any organ. The majority of emergency department (ED) visits are because of recurrent vaso-occlusive crisis, invasive infections, acute chest syndrome (ACS), stroke, and priapism (5). The severity of clinical manifestations of these syndromes depends on the presence of specific type of hemoglobinopathy (Table 280.1). As life expectancy has been increasing for patients with SCD, the number of ED visits per year has risen (3).

TABLE 280.1
Sickle Cell Syndromes (Specific Hemoglobinopathy and Associated Findings)

Hemoglobinopathy	Clinical Presentation	Hb (g per dL)	Hb S (%)	Hb A (%)	Hb A_2 (%)	Hb F (%)
SCT (carrier)	Asymptomatic	Normal	40	60	<3.5	0
SCD (different variants)						
Hb SS (sickle cell anemia)	Severe	6–8	>90	0	<3.5	<10
Hb S beta°—thalassemia	Moderate/severe	7–9	>80	0	>3.5	<20
Hb S beta—thalassemia	Mild/moderate	9–12	>60	10–30	>3.5	<20
Hb SC	Mild/moderate	10–15	>50	0		0

Sickle cell trait (SCT) is found in 8% to 10% of African Americans. Sickle cell anemia occurs in 1 in 400 to 600 newborns. The disease is seen less commonly in the Hispanic, southern European, and Middle Eastern populations (1).

Hemoglobin electrophoresis provides rapid and accurate diagnosis of hemoglobinopathies. However, the sickle cell prep (Sickledex) can produce false-negative results before 4 and 6 months of age owing to the presence of normal maternal hemoglobin, and it also cannot differentiate between SCD with SCT.(4).Today, state-mandated newborn screening programs allow for early diagnosis of these disorders (5) Nevertheless, unexplained anemia in African American children should raise the suspicion of a hemoglobinopathy. The hemoglobin electrophoresis and HPLC identifies the various types of hemoglobin and allows for the differentiation of SCT and SCD.

Clinical symptoms may begin as early as 3 to 4 months of age, when significant amounts of hemoglobin S present. Early recognition and aggressive ED management can decrease the morbidity and mortality associated with these disorders. Long-term care is best provided by physicians familiar with the disease and its complications. SCD presentations generally fall into one of the six categories: (1) vaso-occulsive crisis, (2) dactylitis, (3) sepsis, (4) aplastic crisis, (5) acute splenic sequestration, and (6) ACS.

ACUTE PAINFUL VASO-OCCLUSIVE CRISIS

CLINICAL PRESENTATION

Acute painful vaso-occlusive (VOC) episodes are the most common manifestation of SCD and the most common reason for ED presentation and hospital admission (6). Pain is the result of tissue ischemia and infarction caused by micro vascular occlusion and may

be severe, unpredictable, and relentless. Precipitating factors include infection, dehydration, high altitude, and extremes of temperature. Often, however, no precipitating factor is identified (6).The frequency of such episodes increases with advancing age, alpha thalassemia trait, high hemoglobin concentration, high ferritin level, higher median tricuspid regurgitation jet velocity, lower parasympathetic activity and greater sympatho-vagal imbalance, and higher blood viscosity (7).The frequency of painful episodes is a marker of disease severity and correlates, ultimately, with increased mortality (6).

The average rate of painful crisis per patient is 0.8 episodes per year, although 1% of patients experience more than six episodes per year, and 5% of patients account for 33% of all episodes (8). Recent data has shown 17% having more than three episodes and a re-hospitalization rate of 33%.

The pain of VOC most often involves the lower back, chest, femoral shafts, hips, knees, and abdomen. In children, the hands, feet, fingers, and toes are more commonly involved. In individual patients, pain tends to recur in a limited number of sites (6). Given the propensity of symptoms involving the chest, abdomen, and extremities, the emergency physician must always consider other diagnosis in SCD patients presenting with acute pain such as ACS, septic arthritis, bone fractures, or acute surgical abdomen. In the absence of complications, physical examination in acute VOC is usually unremarkable which emphasize the need of thorough history and high index of suspicion for serious occult illness.

VOC is a medical emergency. Patients in acute pain presenting to the ED usually have exhausted all home care options and require parenteral opioid analgesia (9). There remains variability in the ED management of painful crisis, and barriers to optimal management persist (9). Implementation of a Clinical Practice Guideline (CPG) to manage VOC enables a standardized approach for the cost-effective care of patients with SCD (10). VOC usually vary in intensity and duration at different times. Painful crises are treated episodically in the ED by health-care providers with whom the patient has no established relationship. Patients often report severe pain but lack

objective findings, health professionals often fear iatrogenic opioid addiction, and patients may demonstrate behavior resulting from undertreated pain that is then perceived as drug-seeking in nature (6). Interestingly, it has been shown that although SCD patients receiving opioids may develop physiologic dependence and tolerance, the rate of addiction is no greater than in the general population.

ED MANAGEMENT

ED management has traditionally consisted of supplemental oxygen and fluids. There is no evidence that either therapy improves outcome in the nonhypoxic, euvolemic patient, and the chronic anemia and renal impairment that occurs in many patients with this condition puts them at risk of pulmonary edema if too vigorously resuscitated with isotonic fluid (11).

The mainstay of ED management is parenteral opioid analgesia (12). The intravenous route is preferred although the subcutaneous route can be used if venous access is difficult. The intramuscular route is not appropriate as this is painful and drug absorption is unpredictable. Morphine and hydromorphone are effective. Effective pain management requires some form of titration to effect pain relief, which means attempts should be made to objectify the severity of the patient's pain using a pain scale. One approach involves an initial bolus dose of morphine (Table 280.2) followed by repeated small boluses at intervals of 15 to 30 minutes until pain is relieved (12). Patients should be carefully observed for respiratory depression and hypotension. Monitoring of vital signs, oxygen saturation, intake and output should also be monitored. Pain relief is then maintained with bolus doses on a fixed schedule. If pain relief is maintained, the patient is discharged on an equianalgesic dose of an oral opioid until outpatient reassessment. If pain is not maintained after two to three bolus doses, hospital admission is required. Adjunctive medications such as antihistamines and antinauseants may be necessary to mitigate opioid side effects. Parenteral ketorolac cannot be routinely recommended; it does not consistently relieve pain and has potential for renal toxicity (11).

TABLE 280.2
Suggested Approach to Pain Control in Patients with Vaso-Occlusive Crisis

ED management of pain in VOC
Initial bolus morphine 0.1–0.15 mg/kg IV
1/4–1/2 of bolus dose q15–30 min until pain relief
Morphine bolus q2 hourly to maintain pain relief
If pain relief is maintained, discharge with oral analgesics and arrange for outpatient follow-up
If pain relief is not maintained, admit

The emergency physician must be aware of the role of hydroxyurea in VOC. Although not indicated in the management of the acute painful event, treatment with hydroxyurea has been shown to decrease the incidence of VOC by 44% and is indicated in patients experiencing more than three episodes per year.

DACTYLITIS (HAND&NDASH;FOOT SYNDROME)

CLINICAL PRESENTATION

The hand–foot syndrome commonly presents between 6 and 24 months of age in children with SCD. It is often the first manifestation and these children usually present with low-grade fever and swelling of hands or feet or both, secondary to infarction of the metacarpals and metatarsals. The children usually present with the irritability, inability to bear weight on the affected joint along with swollen and tender joint on examination. Hematologic values are usually unchanged. Radiographs at the outset show only soft-tissue swelling, but osteolytic and periosteal changes become evident 2 to 3 weeks after the onset of symptoms. This classic presentation must be differentiated from osteomyelitis (either unifocal or multifocal) and trauma.

ED MANAGEMENT

Therapy consists of hydration at 150% to 200% maintenance (with either oral or intravenous fluids) and pain management. Pain and

swelling commonly resolve in 2 to 5 days. As the patient ages the collateral vascular supply to these bones develops making recurrence uncommon, especially, after 2 years of age.

SEPSIS

CLINICAL PRESENTATION

In spite of current vaccination and prophylactic antibiotic regimens, sepsis is the leading cause of morbidity and mortality in SCD patients (1). These patients suffer from functional asplenia (occurring at age 5 months to 5 years) secondary to progressive splenic auto-infarction, resulting in deficient antibody production and impaired phagocytosis. SCD patients are, consequently, susceptible to potentially life-threatening infections by encapsulated organisms (Table 280.3) such as *Streptococcus pneumonia* which is the most common cause of sepsis and meningitis in children younger than 3 years old and carries a mortality rate of 20% to 50%. Bacterial meningitis and septicemia are 600 times more common in children with sickle cell anemia than in normal children (13).

TABLE 280.3
Various Microorganisms Causing Lethal Infections in Patients with SCD

Microorganism (Bacterial)	Infection	Remarks
Streptococcus pneumoniae	Septicemia	Common despite prophylaxis and vaccine
	Meningitis	Low frequency compared to pre-vaccine era
	Pneumonia	Rare except in children
	Septic arthritis	Uncommon
Haemophilus influenza type b	Septicemia	—
	Meningitis	—
	Pneumonia	Low frequency compared to pre-vaccine era
Salmonella species	Osteomyelitis	Most common cause of bone and joint infection
	Septicemia	—
Escherichia coli and other gram-negative enteric pathogens	Septicemia	Urinary tract infection
Staphylococcus aureus	Osteomyelitis	Uncommon
Mycoplasma pneumoniae	Pneumonia	Pleural effusions; multilobe involvement
Chlamydia pneumoniae	Pneumonia	—
Viral organisms		
Parvovirus B19	Aplastic crisis	Marked bone marrow suppression
Hepatitis viruses (A, B, and C)	Hepatitis	Hyperbilirubinemia

Vaccination and daily penicillin prophylaxis starting at 2 months of age have been shown to reduce the incidence of pneumococcal sepsis (14). The effectiveness of the 23-valent pneumococcal polysaccharide vaccine among children with SCD is 80% to 90%. Penicillin prophylaxis in children younger than 3 years is 125 mg orally twice daily (15) and 250 mg orally twice daily for ages 3 to 5 years. The role of prophylaxis after the age of 6 years remains controversial given concerns regarding the growing prevalence of penicillin resistance pneumococci.

Early recognition of a febrile episode and prompt administration of IV antibiotics can lower the risk of severe pneumococcal sepsis. However, resistant strains of pneumococcus have emerged, necessitating an alternative antibiotic regimen incorporating vancomycin (Table 280.4).

TABLE 280.4
Management of Sepsis in Patients with SCD

Evaluation
History: Immunization and penicillin prophylaxis
Labs: Complete blood count, electrolytes, Hgb S levels,
–Cultures (blood, urine, throat, cerebrospinal fluid) as indicated
–Chest X-ray
Treatment
IV Ceftriaxone 75 mg/kg
Add vancomycin 15 mg/kg if meningitis is suspected
Hydration

Haemophilus influenzae type b is the second most common organism responsible for sepsis in SCD patients. *H. influenzae* vaccine given during early infancy provides excellent protection against this organism.

Salmonellosis and osteomyelitis occur more commonly in patients with SCD than in normal children, probably secondary to infection of the infarcted bone (1). Osteomyelitis is typically caused by Salmonella and *Staphylococcus aureus.* There are now reported cases of rare fulminant infections with nontuberculous mycobacterium (16).

ED MANAGEMENT

The ED management of SCD patients presenting with fever (with or without an obvious focus of infection) includes administration of IV ceftriaxone (50–75 mg/kg per dose up to 2 g), after a complete blood count, reticulocyte count, and blood culture are obtained. Patients can be classified as low risk (age >1 year, well-appearing, white blood cell count between 5,000 and 30,000/cubic mm, temperature <104°F, absence of pulmonary infiltrates, and a reassuring Hb) or high risk. Low-risk patients can be managed in an outpatient setting with 24-hour follow-up. High-risk patients are admitted for inpatient treatment (17).

Children younger than 1 year of age with fever are typically admitted for intravenous antibiotics. Children with a temperature >103°F, toxic appearance, missed doses of prophylactic penicillin, respiratory distress, uncertain follow-up, previous episodes of severe

sepsis or meningitis and segmental/lobar infiltrates on chest X-ray should also be admitted. Older children with a temperature <103˚F and no focal source of infection may be discharged to home after obtaining appropriate cultures and receiving ceftriaxone, but reliable follow-up must be ensured.

APLASTIC CRISIS

CLINICAL PRESENTATION

To maintain baseline hemoglobin levels, bone marrow erythroid activity is increased in SCD patients (reticulocyte activity >10%). An aplastic crisis occurs when this increased erythropoietic activity is interrupted by various infections (such as parvovirus B19) causing acute cessation of RBC production. An aplastic crisis is characterized by a drop in hemoglobin, a low reticulocyte count (<1%), and a decrease in marrow activity. Parvovirus B19 accounts for 68% of episodes of aplastic crisis (18), followed by *S. pneumoniae,* Salmonella, and Epstein–Barr virus. Packed red blood cell transfusions may be necessary until erythroid production returns, usually within a few weeks. The patients with aplastic crises can present with fatigue, GITgastrointestinal symptoms, and signs of upper respiratory tract infections.

ED MANAGEMENT

Patients with aplastic crisis require close monitoring to avoid life-threatening anemia where the hematocrit falls to < 10% within a few days. By enlarge these patients do well with supportive treatment after a timely diagnosis. Hydroxyurea has been shown to reduce the occurrence of aplastic crisis.

ACUTE SPLENIC SEQUESTRATION

CLINICAL PRESENTATION

Splenic sequestration is a life-threatening condition seen in young children before the onset of splenic autoinfarction. Children with Hb

SS have an incidence of 30%, carrying a 15% mortality rate and often occur within the context of a viral illness. Over a period of hours, a significant portion of the circulating blood volume is sequestered in the spleen because of vaso-occlusion within the splenic vein. This usually occurs when a bacterial or viral infection is associated with a massive coinciodental intrasplenic trapping of erythrocytes. This sequestration of erythrocytes within the spleen contributes to a remarkable fall in hemoglobin levels. Patients may present with hypovolemia, pallor, massive splenomegaly, and occasionally shock and death.

ED MANAGEMENT

Treatment is aimed at sustaining blood volume until the condition spontaneously reverses, releasing the sequestered blood cells to free circulation. Careful monitoring and, often, a transfusion of 10 mL/kg of packed red blood cells may be required (18). Sequestration may recur in 50% of cases making splenectomy after resolution strongly recommended. Parents should be educated on how to palpate for an enlarged spleen, especially during viral illness, to promote early detection of this fulminant condition.

ACUTE CHEST SYNDROME

CLINICAL PRESENTATION

The ACS in SCD is a clinical syndrome with multiple etiologies sharing a common pathophysiologic endpoint of acute lung injury (19,20). ACS is defined by the presence of a new segmental pulmonary infiltrate on chest radiograph accompanied by at least *one* of the following clinical symptoms or signs: (a) temperature $>38.5^{\circ}C$, (b) chest pain, (c) cough, (d) wheezing, (e) tachypnea, or (g) worsening anemia (19).

The pathophysiology of acute lung injury in SCD is multifactorial, with a final common pathway of pulmonary micro-vascular obstruction, tissue hypoxia, ischemia, and infarction (19). Recurrent episodes of acute lung injury may lead to chronic restrictive lung disease (19,20). A large multicenter trial found the most common

causes of ACS to be related to fat embolism from infarcted bone marrow, respiratory infection, and isolated lung infarction. The most common pathogens identified in this study were chlamydia, mycoplasma, and respiratory viruses. Interestingly, the rate of fibrin thromboembolism is no greater in patients with SCD than in the general population, and thromboembolism is very difficult to distinguish from sickle vaso-occlusion by chest computed tomography scan or radionuclide perfusion scanning (19).

ACS is the leading cause of death among patients with SCD and the second leading cause of hospitalization (19). One-half of all patients with SCD will have one episode of ACS, and some patients will experience multiple events. One-half of all cases of ACS occur after hospitalization for an acute pain crisis. The peak incidence is between the ages of 2 and 4 (19). There is a higher incidence of ACS in those with Hb SS disease and in patients with higher baseline white blood cell counts. Patients with higher Hb F levels have a lower incidence of ACS, which may account for the lower incidence in patients younger than 2 years of age and in patients taking hydroxyurea.

The clinical presentation of ACS in the ED is variable and may mimic that of other chest syndromes in the general population, particularly bacterial pneumonia. It is important to be aware that the clinical course of ACS differs from that of the general population presenting with similar findings. Patients with ACS may present with a transient benign illness or may present in respiratory failure requiring intubation and mechanical ventilation. In one study, the average length of hospital admission was 10.5 days, and 13% of patients required mechanical ventilation (19). During hospitalization, 11% experienced neurologic symptoms, and 9% of those older than age 20 died. Factors predictive of a more severe course are age older than 20, pain in the arms and legs on presentation, platelet count $<200{,}000/\mu L$, and multilobar involvement or pleural effusion on chest radiograph. Clinical findings in ACS appear to be age dependent. Although fever is the most common presenting finding in all patients, children younger than 10 years of age are more likely to present with cough and wheezing, whereas adolescents and adults

more commonly present with chest and extremity pain. Bacteremia is more common in children with ACS, and *S. pneumoniae* is the most common isolate. Initial chest radiographs may be negative in nearly half of the cases. In children, upper and middle lobe infiltrates are more common, whereas adults are more likely to have isolated lower-lobe involvement and pleural effusions (19).

ED MANAGEMENT

The management of ACS is essentially supportive and aims to maintain alveolar ventilation and gas exchange and to prevent further pulmonary injury (Table 280.5). Patients should receive supplemental oxygen to maintain oxygen saturation >92% (19,20). Fluid deficits should be corrected with normal saline infusion, which is then changed to hypotonic fluid such as 5% dextrose in one-fourth normal saline at 1.5 times the maintenance requirement. Overaggressive hydration should be avoided to prevent pulmonary edema. Patients should receive prompt antibiotic therapy to cover the most common organisms identified in this syndrome, with consideration given to local sensitivity patterns. A respiratory quinolone alone, or a third- or fourth-generation cephalosporin in combination with a macrolide, should provide adequate coverage (19,20). Bronchodilators should be given, as all patients have been demonstrated to have some degree of airflow obstruction even in the absence of wheezing (19,20). Pain should be aggressively managed with parenteral opioids and incentive spirometry prescribed to prevent atelectasis since ventilation may be compromised by pain secondary to ischemia or infarction of ribs and/or thoracic vertebrae. The role of transfusion therapy in the ED management of patients with ACS is not clearly defined. However, red blood cell transfusion early in the course of ACS is the only treatment that has been shown to stabilize acute lung injury (5). Simple transfusion is indicated when there is a need to increase oxygen-carrying capacity with the objective of decreasing cardiac workload and improving patient comfort. Urgent exchange transfusion should be considered in patients with poor prognostic factors, where it may lead to rapid resolution of ACS and who are at risk for respiratory failure (19,20).

TABLE 280.5
ED Management of Acute Chest Syndrome

1. O_2 to keep SaO_2 >92%
2. IV D5:1/4 NS at 1.5× maintenance
3. Antibiotics
   Levofloxacin 500 mg IV or
   Ceftriaxone 2 g IV and
   Azithromycin 500 mg PO
4. Morphine IV titrated to pain relief
5. Salbutamol 2.5–5 mg q1–4h
6. Incentive spirometry
7. Simple or exchange transfusion
8. Admission

Patients with ACS are prone to rapidly deteriorating clinical courses and should be admitted.

CEREBROVASCULAR ACCIDENT

CLINICAL PRESENTATION

Patients with SCD suffer from neurologic injury with a spectrum ranging from silent cerebral infarcts (SCI) to overt strokes. SCI are the most common form of neuronal damage in toddlers (<4 years old), and the cumulative incidence increases until 14 years of age. Kinney et al. (21) identified 266 infants with SCD and followed them up for 14 years with a minimum of one magnetic resonance imaging MRI at 6 years or older and showed an incidence of 22% SCI in patients without overt stroke (21). These SCI infarcts result in progressive neuronal damage, resulting in lower intelligence and other neurocognitive defects. A history of seizure, leukocyte count $>11.8 \times 10^9$ and the presence of the Senegal-3 globin gene haplotype are associated with an increased risk of SCI. SCI is diagnosed on the basis of an abnormal MRI (focal 3-mm or larger area of abnormal signal intensity) with a normal neurologic examination result and without a history or physical findings suggestive of an overt stroke. No therapy has been established for the

treatment of SCI. Preliminary data from the STOP trial indicated that in patients with SCI and an elevated transcranial Doppler (TCD) ultrasound velocity measurement, blood transfusion resulted in a 100% relative risk reduction (Table 280.6) (15). Currently, a large trial funded by the National Institutes of Health is investigating the role of blood transfusion in patients with SCI and normal TCD measurements.

TABLE 280.6
Management of Stroke in Patients with SCD

Evaluation
–CBC, electrolytes, high S levels, sample for red cell antigens
–Urgent CT or MRI (identify thrombotic vs hemorrhagic infarction, cerebral aneurysm, and intracranial bleed)
Arteriography is not indicated as it can precipitate sickling crisis
Treatment
–1½–2 volume exchange transfusion to reduce Hgb S less 30%
–ICU admission
–Neurology and hematology consultations

CBC, complete blood count; CT, computed tomography; MRI, magnetic resonance imaging; ICU, intensive care unit.

Overt stroke occurs at a rate of 1 in 600 to 100,000 patient years, resulting in a prevalence of 10% by the age of 50 (22). In the younger child, the event is usually thrombotic; in the adolescent it may be hemorrhagic. Patients at increased risk for stroke include those with familial propensity, parvovirus infection, prior stroke or SCI, or increased TCD velocity measurement. Silent stroke is the strongest risk factor for overt stroke.

ED MANAGEMENT

In the ED, any untoward neurologic event in a sickle cell patient is considered a cerebrovascular accident until proven otherwise. Early recognition and aggressive treatment result in improved outcomes. Long-term treatment necessitates hypertransfusion for several years to reduce the 66% chance of a recurrent cerebrovascular accident

(18). Hydroxyurea therapy has also been shown to be effective for prevention of recurrent stroke in sickle cell patients.

PRIAPISM

CLINICAL PRESENTATION

Priapism is defined as a sustained, painful, and unwanted erection and is a well-recognized complication of SCD (23). It is an unpredictable and recurrent complication that has potentially devastating consequences for future erectile function and quality of life. At least one episode of priapism is described by 30% to 45% of adult patients with SCD, and it occurs most commonly in patients with HbSS disease. The mean age of occurrence is 12, and the mean duration of episodes is 125 minutes (23).

Priapism is believed to occur because of sickling and sludging of erythrocytes in the corpora cavernosa, with subsequent deoxygenation, acidosis, further sludging, increased intercavernosal pressure, penile ischemia, and, finally, fibrosis resulting in impotence (23). Episodes most commonly occur during sleep but may be triggered by sexual activity, alcohol, or drug use (23).

The emergency physician should document the time of episode onset and inquire about potential triggers. Physical examination reveals an erect penis with a soft glans. Priapism is a urologic emergency. There is a high risk of ischemic injury if symptoms continue beyond 4 hours (23). Urology consultation should thus be obtained early in the ED course.

ED MANAGEMENT

The goals of ED management are pain relief, resolution of erection, and preservation of future erectile function. All patients should receive parenteral opioid analgesia and may receive intravenous hypotonic fluids at 1.5 times the maintenance rate. Patients arriving in the ED whose episode has already lasted 4 hours require immediate urologic consultation with penile aspiration and irrigation using a dilute solution of epinephrine or phenylephrine (23). Patients who arrive earlier in an episode may receive a trial of oral vasoactive

agents such as terbutaline or pseudoephedrine (Table 280.7), which have been shown to be effective in pharmacologically induced priapism but have not been studied in SCD (23). Patients whose erections resolve in the ED should be educated on the importance of seeking early medical care if priapism recurs, of avoiding of triggers, and of following up with their primary care provider.

TABLE 280.7
ED Management of Priapism

1. IV D5:1/4 NS at 1.5 maintenance
2. Parenteral opioid analgesia
3. If >4 hours duration:
   - *Urgent* urology consultation
   - Cavernosal aspiration and irrigation
   - Exchange transfusion/surgical shunt in resistant/recurrent cases

   If <4 hours duration:
   - Trial of vasoactive agents
   - Terbutaline 2.5–5 mg PO
   - Pseudoephedrine <10 year: 30 mg PO >10 year: 60 mg PO
   - Urology consultation if persistent

KEY TESTING

- CBC
- Consider Type and Screen for patients likely to be transfused
- Reticulocyte count
- CXR when considering acute chest syndrome
- CT head for any alteration in mental status
- Pulse oximetry monitoring

CRITICAL INTERVENTIONS

- Prompt administration of antibiotics to all febrile sickle cell patients.
- Rapid titration of opioid analgesia for patients with acute vaso-occlusive crisis.

- Early recognition and aggressive management of hypoxia and hypoventilation in ACS.
- Immediate blood transfusion for aplastic and splenic sequestration crisis.
- Exchange transfusion in patients with cerebrovascular accidents and ACS.
- Emergent cavernosal aspiration in priapism of >4 hours duration.

Patients can be discharged from the ED if the child does not require supplemental oxygen is tolerating fluids orally, and has follow up with family or primary physician.

DISPOSITION

Patients with SCD are prone to a variety of complications and can rapidly deteriorate. ED physicians should be cautious in the disposition of these patients and maintain a low threshold for inpatient management. It is essential that the patient's primary care physician and hematologist be advised of the patient's emergency visit and consulted regarding the discharge plan.

Common Pitfalls

- Failure to appreciate the immunocompromised status of patients with SCD.
- Failure to recognize that symptoms may present as early as 3 to 4 months of age.
- Failure to recognize that the sickle prep is inaccurate before 4 to 6 months of age.
- Failure to consider a cerebrovascular accident when evaluating any acute neurologic event in a patient with SCD.
- Failure to consider aplastic crisis and acute splenic sequestration in the acutely anemic sickle cell patient.
- Failure to appreciate the severity of pain in acute VOC.
- Failure to appreciate the potential for rapid deterioration associated with ACS.
- Failure to ensure rapid urology consultation and cavernosal aspiration in the patient with priapism of more than 4 hours

duration.

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CHAPTER 281

Urticarial, Maculopapular Lesions

Barry Gilmore and Rudy Kink

Urticarial and maculopapular lesions account for a large percentage of dermatologic complaints. Their prevalence is eclipsed only by the breadth and variety of pathology they represent, which ranges from allergic reactions to conditions such as measles and rubella. Although many presentations are benign, there are some where early identification may have a significant impact on infection control or require immediate treatment.

URTICARIA

Urticaria (hives) is a common skin condition affecting virtually all age groups but is more prevalent in children and young adults. It is estimated that 15% to 25% of the population will have an episode in their lifetime (1). Urticaria represents a vascular reaction of the skin characterized morphologically by transient, typically pruritic, red or white, smooth, elevated patches (wheals) which may change shape and location over time. Urticaria results from the release of histamine, bradykinin, leukotriene C4, prostaglandin D2, and other vasoactive agents released from basophils and mast cells. There is a transient extravasation of plasma into the superficial dermis, causing intense pruritus from the histamine release (2). This distinguishes urticaria from angioedema, which involves the deep dermis and results in deep tissue swelling and pain. The lesions may present in ring-like configurations or may coalesce over larger areas.

Urticaria can be classified by the duration of symptoms. Acute urticaria is defined by symptoms lasting less than 6 weeks; chronic urticaria lasts more than 6 weeks. Chronic urticaria typically requires further evaluation to rule out an underlying systemic medical condition. The causes of urticarial can be divided into several broad categories (see Table 281.1).

TABLE 281.1
Classification of Urticaria

Physical	Insects
Cholinergic	Inhalants
Dermatographism	Drugs
Pressure	Transfusion related
Cold	PUPP[a]
Solar	Idiopathic
Vibratory	Urticarias in chronic disease
Aquagenic	Systemic vasculitis/collagen vascular disease/malignancy
Heat	Infections
Adrenergic	Genetic
Contact	
Food	

[a]PUPP, pruritic urticarial papules and plaques.

Clinical Presentation

A key feature is their polymorphic appearance and waxing and waning of individual lesions. Dermatographism (exaggerated triple response of Lewis) may also be noted; wheals occur within 10 minutes of moderate stroking and fade by 30 minutes.

There are many identified triggers of urticaria; the more common ones are summarized in Table 281.2. Typical triggers include foods, medications, infections (both viral and bacterial), environmental factors, latex, cold, heat, emotional stress, pregnancy, and exercise (3).

TABLE 281.2
Agents Known to Cause Urticaria

- Medications
  - ACEi
  - Anesthetic muscle relaxants (i.e., succinylcholine)
  - Narcotics
  - Penicillins
  - Cephalosporins
  - Sulfas
  - Diuretics
  - Aspirin
  - NSAIDs
  - Iodides
  - Bromides
  - Quinidine
  - Chloroquine
  - Vancomycin
  - Isoniazid
  - Antiepileptic drugs
- Infections
  - Viral
  - Amebiasis
  - Malaria
- Foods
  - Shellfish
  - Eggs
  - Cheese
  - Chocolate
  - Nuts
  - Berries
- Environment
  - Extremes of temperature
  - Dander
  - Dust
  - Molds
  - Water
- Pregnancy
- Contact
  - Nickel
  - Latex
  - Nail polish
  - Chemicals
- Exercise
- IV dye/contrast

ACEi, NSAID, nonsteroidal anti-inflammatory drug.

Medications are a significant cause of urticarial reactions, which tend to start as macules and papules on the trunk and extremities and spread outward. The onset may be 1 to 2 weeks following the start of a new medication but can occur much sooner if there have been previous exposures. Penicillin, cefaclor, amoxicillin, and aspirin are most frequently incriminated. Individuals who are aspirin intolerant may see an onset of symptoms with 15 minutes of ingestion, or after a delay of as long as 20 hours. These patients are also likely to have flushing, rhinorrhea, wheezing, and increased bronchial secretions (4,5).

Food allergies account for about 20% of cases of acute urticaria and are mediated by IgE-specific food proteins. The most common offending foods in adults are shellfish and nuts, whereas in children they tend to be peanuts, nuts, eggs, wheat, soy, and shellfish. The onset of symptoms may be within minutes of ingestion but can be delayed by several hours. A less common cause is scombroid fish poisoning caused by the ingestion of heat-stable toxins found in certain partially spoiled dark-meat fish such as tuna, salmon,

swordfish, and bluefish. Bacterial decomposition of histidine produces histamine that can induce nonwheal urticaria as well as other allergic responses (4,5).

Infections may be associated with urticaria, but less commonly so than other etiologies; in adults, when this occurs there tends to be an association with chronic urticaria. Children, however, may have hive-like rashes associated with the first 3 to 5 days of a viral illness and resolving as the infection clears. Urticaria has also been associated with hepatitis, infectious mononucleosis, herpes simplex, streptococcal infections, and parasitic infections (4,5).

Contact urticaria represents a reaction to a substance that comes in contact with an individual's skin. A multitude of agents have been found to trigger such a reaction, including metals, hair and beauty products, and foods.

In the healthcare setting, latex allergy has become a more commonly identified cause. Sensitized patients can progress very rapidly from a local reaction to angioedema and life-threatening anaphylaxis. Furthermore, patients with chronic medical conditions have a higher incidence. Thus, many institutions and offices have moved completely away from all latex-containing products.

Physical causes of urticaria are less common and are identified through a careful history and physical examination. *Dermatographism,* a reaction of the skin secondary to moderately firm stroking of the skin, comes on quickly (<10 minutes) and is usually gone within 30 minutes. *Pressure urticaria,* because of sustained contact, is characterized by localized pain and pruritus. Although the onset is typically delayed (6 to 72 hours), the location of the lesions is often a helpful clue in establishing the clinical connection. *Cold urticaria* is caused by exposure of skin to extreme cold, damp, and/or windy conditions and has an onset within minutes. Severe reactions resulting in massive histamine release have been reported with swimming in cold water. When an ice cube is placed on the forearm, a distinct hive may develop, helping to make the diagnosis at least in its more severe forms. Standard antihistamines show little effect, although improvement has been reported with cyproheptadine, doxepin, and ketotifen. Cold urticaria tends to affect 18 to 25 year

olds and may last for 5 to 6 years. There is also a rare hereditary form with delayed onset involving the entire body. *Cholinergic or stress urticaria* is triggered by any stimulus that causes an increased core temperature; the lesions are small, pruritic, and generally short lived (6). *Solar urticaria* occurs on areas exposed to ultraviolet or visible light; the onset is within minutes and wanes rapidly (1 to 3 hours) when the skin is no longer exposed (6). Miscellaneous types of urticaria include aquagenic (water exposure), vibratory, and those caused by insect bites and blood transfusions. Urticaria associated with blood transfusions has an incidence of 1% to 3%. This is not a transfusion reaction but an antibody-mediated response to the donor's plasma; they respond well to antihistamines.

Pruritic urticarial papules and plaques of pregnancy (PUPP) is a hive-like rash that affects some women during their pregnancy. It typically starts on the abdomen and spreads peripherally to the extremities. Although irritating, it is not considered a threat to mother or fetus.

Other systemic conditions are more commonly associated with chronic urticarial. These include malignancies (lymphoma, chronic lymphocytic leukemia), collagen vascular diseases, cryoglobulinemia, serum sickness, C1 esterase inhibitor deficiency, and hypo- and hyperthyroidism.

Differential Diagnosis

Initially it is critical to recognize developing anaphylactic shock with bronchospasm and progressive cardiovascular collapse (3,7). If anaphylaxis is not an issue, narrowing down the diagnosis is based on a detailed history and physical examination. Urticarial lesions can be confused with a number of common conditions listed in Table 281.3.

TABLE 281.3
Urticaria Differential Diagnosis

Anaphylactic Shock	Respiratory distress and CV collapse
Angioedema	Deep tissue swelling, mucous membrane involvement, abdominal symptoms
Atopic dermatitis[a]	Scaly, more maculopapular
Bullous pemphigoid[a]	Older adults, progresses to blistering
Contact dermatitis[a]	Areas of contact, popular, erythematous, vesiculation can occur
Cutaneous vasculitis[a]	Lesions >72 h
Dermatitis herpetiformis[a]	Papulovesicular lesions, extensor surfaces, associated with gluten intolerance
Erythema marginatum	Raised ring like lesions, extensor surfaces, spares face, wax and wane for months
Erythema multiforme[a]	Target lesions, long lasting, +/– Fever
Henoch–Schonlein purpura	Purpuric, lower extremities and buttocks, systemic symptoms
Juvenile arthritis	Salmon colored rash, typically on trunk, fever, fatigue, joint pain/swelling
Mastocytosis[a]	Dark brown, fixed lesions, fatigue, abdominal pain, nausea/vomiting
Morbilliform drug reactions[a]	Medication, more maculopapular
Pityriasis rosea (early lesions)	Herald patch, "Christmas tree" distribution, lasts weeks
Serum sickness	1–2 wks delayed onset, fever, arthralgias
Urticarial vasculitis	Painful, lesions last 1–2 days, purpuric, residual hyperpigmentation
Viral exanthemas	Fever, prodrome, specific lesions last days (do not come and go)

[a]Typically pruritic

ED Evaluation

Life-threatening conditions such as anaphylactic shock or critical angioedema must be ruled out early in any evaluation of urticaria. Once this has been done, a careful history and physical examination should be performed. The physical examination should note any signs or symptoms of upper airway involvement, including tongue swelling, stridor, or wheezing. The skin and extremity examination should discriminate between deep tissue edema suggesting angioedema urticaria, which is more superficial in nature.

In addition to a complete review of symptoms, clinicians must obtain a detailed history focusing on timing, onset, and progression of symptoms. The exposure history should focus on potential environmental agents, foods, medications, recent illnesses, and any past or family history of previous similar episodes. Often this information, along with the size, shape, location, and progression of

the lesions, can focus the evaluation and identify potential triggers. In the majority of cases, the trigger or underlying cause is never specifically identified.

Detailed laboratory evaluation is not warranted unless an underlying systemic condition is being considered, for example, when symptoms have been going on for 6 weeks (chronic urticaria). In this situation, current guidelines suggest a baseline CBC, liver function tests, erythrocyte sedimentation rate, urinalysis, and possibly TSH.

KEY TESTING

For chronic urticaria:
- CBC, ESR, LFTs, UA, and TSH

For acute urticaria:
- No specific testing

ED Management

Treatment is centered on removing possible offending agents and treating acute symptoms with H1 (histamine) blockers. The first-generation agents (diphenhydramine, hydroxyzine, chlorpheniramine, and cyproheptadine) have been used for quick relief of associated itching but have other side effects (sedation, dry mouth, confusion, trouble concentrating) that may be problematic for pediatric patients. The second-generation antihistamines (loratadine, desloratadine, fexofenadine, cetirizine, and levocetirizine) are now recommended as initial treatment options because of their less sedating properties as well as once-daily dosing. A mixture of first- and second-generation agents can be considered based on the patient's symptoms (3,8).

Adding an H2 blocker (cimetidine, famotidine, or ranitidine) has shown some mild benefit for the acute symptoms. A short course of steroids (oral prednisone at 0.5 mg to 1 mg/kg per day given for 3 to 7 days with a taper) may be helpful for those with significant symptoms or to help accelerating improvement, but data on effectiveness is limited (Table 281.4).

TABLE 281.4
Treatment of Urticaria

Class	Medication	Adult Dosing	Pediatric Dosing	Considerations
H1 blockers First generation	Diphenhydramine (Benadryl)	25–50 mg PO/IM/IV q6h	1 mg/kg PO Q6h	Sedating, avoid with MAOI's
	Hydroxyzine (Vistaril)	25–100 mg PO/IM QID	0.5 mg–1 mg/kg/dose IM q4–6h 2 mg/kg/24 h PO divided tid	Sedating, No IV
	Cyproheptadine (Periactin)	4 mg PO tid	0.25 mg/kg divided tid	Sedating
	Chlorpheniramine	4 mg PO q4h	6–11 y/o 2 mg po q4–6h (max 12 mg/day) > 12 adult dosing	Sedating
Second generation[a]	Cetirizine (Zyrtec)	5–10 mg PO qd	2–5 y/o 2.5–5 mg PO qd >6 y/o 5–10 mg PO qd	Chewable Tabs, Nonsedating
	Fexofenadine (Allegra)	180 mg PO qd	6 m–2y/0 15 mg PO bid 2–11y/o 30 mg BID >12 y/o adult dosing	Nonsedating, do not give with fruit juice, renal dosing
	Loratadine (Claritin)	10 mg PO qd	2–5 y/o 5 mg PO qd >6 y/o adult dosing	Nonsedating renal and hepatic dosing
Corticosteroids	Prednisone	40–60 mg PO qd < 6 day no taper needed	1–2 mg/kg divided bid	Caution in diabetics
	Methylprednisolone (Solu-Medrol)	125 mg IV/IM	0.5–2 mg/kg, IV/IM/PO (max 60 mg)	Caution in diabetics
	Hydrocortisone	100–500 mg IV	5–10 mg/kg IV (max 500 mg)	Caution in diabetics
H2 blockers	Cimetidine (Tagment)	400 mg PO qd 300 mg IV/IM qd	Infants 10–20 mg/kg/day PO/IM/IV divided q6–12h Children 20–40 mg/kg/day PO/IM/IV divided q6h	Use with H1 blockers
	Ranitidine (Zantac)	50 mg IV/IM or 150 mg PO bid	0.5 mg/kg/day PO/IV divided q6–12h	Use with H1 blockers
	Famotidine (Pepcid)	20 mg PO/IV qd/bid	1–2 mg/kg/day PO/IV divided bid (max 40 mg) Start with 1 mg/kg	Use with H1 blockers
Leukotrienes	Montelukast (Singular)	10 mg PO qd	6–14 y 5 mg PO qd >15 y adult dosing	Use with H1 for chronic/cold urticaria
	Zafirlukast (Accolate)	20 mg PO bid	5–11 y 10 mg PO bid >12 y adult dosing	Use with H1 for chronic /cold urticaria, caution with hepatic impairment

[a]Chronic urticaria may consider 2–4 × standard dose

Treatment of chronic urticaria occurs over a period of weeks. The initial treatment is the same as for acute urticaria, concentrating on the second-generation antihistamines at standard doses. If there is no improvement by 2 weeks, doubling or quadrupling the dose is suggested. If symptoms persist after another 1 to 4 weeks, switching agents, or adding a first-generation medication, H2 blocker, leukotriene antagonist, or brief steroid burst may be warranted. Referral to a dermatologist should be strongly considered (3,8).

CRITICAL INTERVENTIONS

- Epinephrine (SC/IM), antihistamines, steroids, and albuterol for life-threatening urticaria accompanied by cardiovascular collapse, bronchospasm, or laryngeal edema.
- Antihistamines are the initial treatment of urticaria.

Disposition

Most patients can be discharged home if they have acute uncomplicated urticaria that has responded to treatment. An observation period of 2 to 6 hours has been suggested, and most patients respond within 2 hours of treatment. Patients with rebound symptoms, anaphylaxis, hypotension, or airway swelling should be admitted for close observation. Antihistamines (H1 or H2 blockers) should be continued for 2 to 5 days and steroids, if used, for 5 to 7 days.

MACULOPAPULAR RASHES

Maculopapular exanthems comprise both flat discolored areas of skin and papules; these rashes often consist of large red areas with small confluent bumps (Table 281.5).

TABLE 281.5
Features of Selected Diseases with Maculopapular Eruptions

Disease	Age Most Affected	Typical Season	Type/Distribution of Lesions	Associated Signs and Symptoms	Complications
Measles	Children, young adults	Winter, spring	Skin—Purple-red maculopapules spreading from hairline down, confluent on face and neck oral mucosa—Koplik spots	Prodrome of high fever, coryza, cough, conjunctivitis	Common: Otitis media, pneumonia Rare: Encephalitis, laryngotracheitis
Rubella	Children, young adults	Winter, spring	Skin: Discrete, pink-red maculopapules spreading from face down Soft palate: Forchheimer spots	Children: Lymphadenopathy, mild fever Adolescent/adult: Febrile prodrome, joint pains	Common: Arthritis in older patients Very rare: Encephalitis, purpura
Erythema infectiosum	2–12 year	Late winter, spring	"Slapped-cheek" malar rash which spreads to the trunk and extremities	Asymptomatic or nonspecific illness (fever, chills, myalgias, malaise and headache)	Rare: Arthritis (especially in adults), hemolytic anemia, encephalitis, fetal loss
Scarlet fever	3–12 year	Winter, spring	Skin: Face flushed with circumoral pallor, trunk/extremities with "sandpapery," blanching pinpoint red rash most prominent in creases, Pastia lines Mucosal-pharyngitis/tonsillitis, palatal, petechiae, strawberry tongue	Fever, sore throat, vomiting, headache, abdominal pain, tender anterior cervical nodes	Early: Otitis media, peritonsillitis, cervical adenitis, sinusitis Late: Rheumatic fever, glomerulonephritis
Staphylococcal scalded Skin	Early childhood before age 5 year or immunocompromised adults or those with renal insufficiency	Year-round	Bullae formation and diffuse desquamation often resulting from hematologic spread of toxins, Nikolsky sign	Fever, malaise and general symptoms of upper respiratory tract infection	Skin desquamation with resulting hypovolemia, hypothermia, and secondary infection

Measles

Measles is a highly contagious disease caused by an RNA paramyxovirus. It is spread by direct droplet contact; the incubation

period is 6 to 19 days, with a median of 13 days. Patients are infectious from 1 to 2 days prior to the onset of the illness until 4 days after the rash appears. Natural measles infection allows for lifelong immunity, and measles vaccination is highly protective against the infection. There have been recent outbreaks of measles because of decreased vaccination rates. In 2011, a large measles outbreak occurred in Quebec, Canada, and in the United States (9,10). Of the 222 cases of measles reported in the United States, 85% were unimmunized individuals (10).

ED Evaluation and Management

Measles initially presents with 3 to 5 days of fever followed by cough, coryza, and conjunctivitis; collectively known as the "3Cs." The exanthem phase of infection is marked by the appearance of discreet 1 to 3 mm white plaques (Koplik spots) on the erythematous mucous membranes around the lower premolar area (Fig. 281.1). Other symptoms include headache, malaise, and decreased appetite.

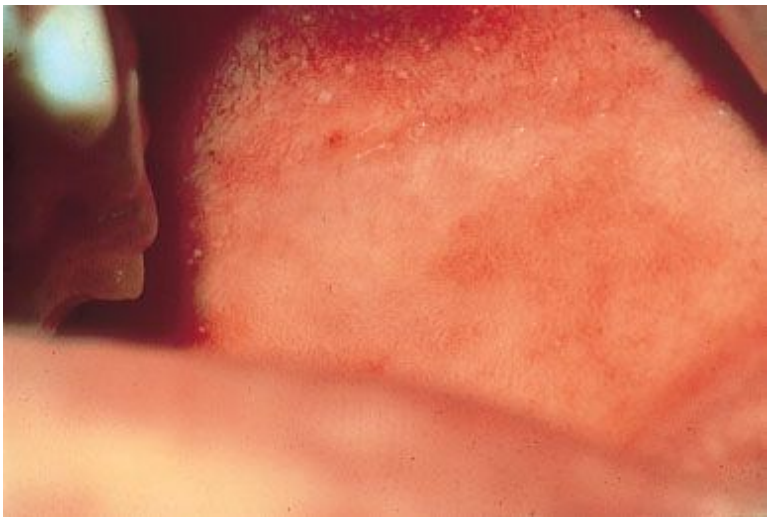

FIGURE 281.1 Koplik spots. (The Wellcome Trust, National Medical Slide Bank, London, UK.)

The viral exanthema usually appears 3 to 5 days after fever onset and is a blanching maculopapular rash starting around the hairline and progressing caudally to include the extremities; palms and soles are rarely affected (Fig. 281.2). The rash typically fades after 3 to 4

days, leaving a brown discoloration and desquamation. There is complete resolution by day 10 (11).

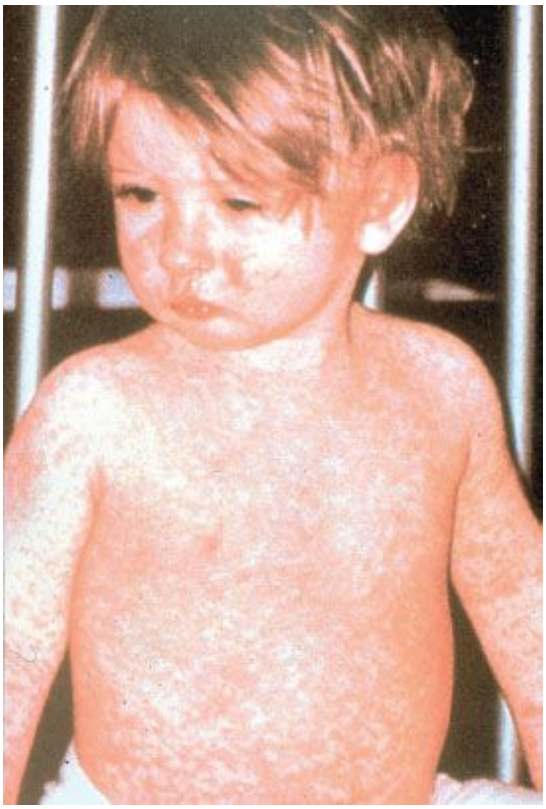

FIGURE 281.2 Measles. Morbilliform rash of measles. (Photo courtesy of Centers for Disease Control and Prevention.)

Measles can affect multiple organ systems, including pulmonary, neurologic, gastrointestinal, and cardiac. These complications can be life threatening. In children, otitis media, croup, bronchopneumonia, and diarrhea are commonly reported. Complications such as acute encephalitis, acute disseminated encephalomyelitis, and severe pneumonia are rare but may be life threatening. Other complications include myocarditis, pericarditis, hepatitis, Stevens–Johnson syndrome, appendicitis, and subacute sclerosing panencephalitis. The latter is a degenerative disease of the central nervous system caused by a mutant form of the measles virus. It occurs 2 to 10 years after the initial infection and is characterized by behavioral changes, seizures, intellectual decline, memory loss, and eventually death for the majority of patients (12).

The differential diagnosis of a maculopapular rash with fever includes mononucleosis, pityriasis rosea, Rocky Mountain spotted fever, syphilis, drug eruption often caused by penicillin, nonsteroidal anti-inflammatory drugs or phenytoin, as well as reactive conditions such as urticaria, erythema multiforme, and Kawasaki disease.

The treatment of measles is primarily supportive. A Cochrane review of randomized trials on the use of vitamin A concluded there was no overall significant reduction in mortality, but there was evidence that two doses were associated with a reduced risk of mortality and pneumonia-specific mortality in children under the age of 2 years. For those with secondary bacterial infection, appropriate antibiotic directed therapy is indicated (13). Patients presenting to the emergency department who are suspected of having measles should immediately be placed in isolation to decrease exposure of other patients. At risk patients, including infants, immunocompromised individuals, and pregnant women exposed to measles, can receive immunoglobulin intramuscular injections up to 6 days post-exposure. The dosage is 0.25 mL/kg IM or 0.5 mL/kg (maximum, 15 mL) for immunocompromised patients (14).

Rubella

Rubella (German measles or third disease) is caused by an RNA Ribivirus, belonging to the Togavirus family. It is spread by direct contact or droplets from nasopharyngeal secretions of an infected individual and can also be transplacentally transmitted to the fetus, with potentially serious consequences. The infection in children is typically mild and can even be asymptomatic. Infected individuals are contagious from a few days before rash onset to 7 days after rash onset. Infants who acquired rubella prenatally can become reservoirs and spread the virus for up to a year after birth (15).

ED Evaluation and Management

Patients with rubella have a low-grade fever, an erythematous maculopapular rash, and generalized lymphadenopathy. The rash typically starts on the face and spreads caudally to the extremities and lasts approximately 1 to 5 days. Infected patients can also have

conjunctivitis and/or Forschheimer spots (a viral exanthem occurring on the soft palate as erythematous areas with petechial macules). Symptoms in adolescents and adults include malaise, headache, pharyngitis, conjunctivitis, cough, coryza, and arthalgias. Adolescent females may experience monoarticular arthritis or arthalgias involving the fingers, wrists, and knees. Rare complications include encephalitis and thrombocytopenia (Fig. 281.3).

FIGURE 281.3 Rubella. Maculopapular rash of rubella. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

The fetus is particularly vulnerable to rubella infection. The earlier in the pregnancy the gravid patient is exposed, the more severe the infection is for the fetus. Structural defects typically occur if the fetus is exposed to rubella prior to 16 weeks of gestational age (16,17). Defects associated with congenital rubella involve the eye (congenital glaucoma, cataracts, and retinopathy), the brain (mental retardation, meningoencephalitis, and behavioral problems), the

heart (pulmonary stenosis, patent ductus arteriosus), the ears (sensorineural impairment), and the skin (purpuric skin lesions, blueberry muffin appearance) along with growth retardation, thrombocytopenia, hepatosplenomegaly, and bone disease (18) (Fig. 281.4).

FIGURE 281.4 Congenital rubella. Blueberry muffin rash of congenital rubella. (Photo courtesy of Centers for Disease Control and Prevention.)

Postnatal rubella infection is typically a mild infection requiring only supportive care including antihistamines for itching and nonsteroidal anti-inflammatory drugs for arthritis. Because rubella can cause devastating effects to fetuses, rapid diagnosis is critical if the patient is pregnant. If a pregnant woman is exposed to the virus, rubella antibodies should be obtained. If negative, antibodies should be obtained again in 2 to 3 weeks, and again 6 weeks post-exposure. Increases in antibody titers indicate a recent infection. Immunoglobulin (0.55 mL/kg IM) may be given, but it does not

guarantee prevention of fetal infection (19). Patients diagnosed with rubella infection should be placed on droplet precautions and be excused from school or daycare for 7 days from the time the rash started.

Roseola Infantum

Roseola (exanthem subitum or sixth disease) typically occurs in children between the ages of 6 months and 2 years and presents 3 to 5 days of high fever and then develops a morbilliform rash (20). The most common cause of roseola infantum is HHV-6, which is a double-stranded DNA human herpes virus. HHV-7 is a less frequent cause. HHV-6 has been associated with febrile seizures in 10% to 15% of patients (21). The majority of patients who have HHV-6 infections present with a fever, but they can have respiratory or gastrointestinal symptoms as well.

ED Evaluation and Management

Though roseola is a common infection, only 20% of patients present with the classic symptoms. Other symptoms of HHV-6 infection include malaise, palpebral conjunctivitis, uvula palatoglossal junctional macules or ulcers (sometimes called Nagayama spots), upper and lower respiratory symptoms, vomiting, diarrhea, and a bulging fontanelle. The rash is characterized by rose-pink macules or maculopapules that occur mainly on the trunk and neck and then may spread to the rest of the body (Fig. 281.5). The rash lasts approximately 1 week (22). The rash is similar to that caused by Epstein–Barr virus, adenovirus, parvovirus B-19, and other viral illnesses. The diagnosis is largely clinical.

FIGURE 281.5 Roseola. Maculopapular rash of roseola. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

Typically the infection is self-limited and resolves uneventfully. Rare complications include encephalitis, fulminant hepatitis, thrombocytopenia, and hepatosplenomegaly (22). Infants and children presenting with fever and bulging fontanelle are often evaluated for meningitis. Supportive care includes fever management and encouraging adequate hydration.

Erythema Infectiosum

Erythema infectiosum (fifth disease) is a common infection caused by human parvovirus B19 and seen predominantly in children ages 5 to 15 years (Fig. 281.6) (23,24).

FIGURE 281.6 Erythema infectiosum. "Slapped Cheeks" with perioral pallor. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

It was first discovered in 1975 and associated with the clinical disease in 1981. There are now three identified genotypes, with the first two found in Western countries and the third in sub-Saharan Africa and South America (25). It is normally transmitted via respiratory droplets but can also be transmitted via blood product transfusion, bone marrow and organ transplantation, and vertically from mother to fetus. It begins with a nonspecific illness consisting of low-grade fever, chills, myalgias, malaise, and headache, which is followed by a characteristic exanthem within 7 to 10 days. The contagious stage occurs approximately a week before the onset of rash.

The exanthem initially is an erythematous, raised rash over the malar areas of the face (giving a "slapped cheek" appearance) with associated circumoral pallor. It fades within 3 to 5 days. This is followed by a lacy, often pruritic rash occurring on the trunk, which in turn spreads peripherally to involve the buttocks and extremities (Fig. 281.7) (26). The rash can later recur when provoked by sunlight, heat and other environmental changes, exercise or emotion. Outbreaks tend to occur in school-age children but have been described in adults. The rash is not a feature of the disease in adults,

in whom it may present as acute arthritis and edema, primarily of the small joints (27). In children, in addition to the rash there may be other clinical manifestations, including arthropathy and a transient aplastic episode that is seen most often in patients with hemolytic anemia, hemoglobinopathies, or other abnormalities in red cell production or structure.

FIGURE 281.7 Erythema infectiosum. "Lacy Rash" of erythema infectiosum. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

ED Evaluation and Management

In an otherwise healthy patient, only supportive care is necessary (23,24). Laboratory testing is not indicated unless there is a concern for aplastic anemia or exposure in pregnancy. Patients with clinical hematologic effects such as an aplastic episode may require blood transfusions; immunocompromised patients may benefit from immune globulin intravenous infusion. Isolated pleural and pericardial effusions, intrauterine growth retardation, and fetal hydrops can contribute to fetal demise in 2% to 6% of cases of parvovirus B19 infection during pregnancy (especially in the second trimester). Pregnant healthcare workers should be advised of the

potential fetal risks and should adhere to strict infection control measures to avoid exposure to respiratory tract secretions and blood from infected patients.

Differential Diagnosis

The differential diagnosis includes measles, roseola, hepatitis, Epstein–Barr virus, and other viral exanthems; scarlet fever; Lyme disease; drug eruption; allergic hypersensitivity reaction; acute rheumatic fever; and other rheumatologic disorders.

Scarlet Fever

Scarlet fever (scarlatina) is caused by the pyrogenic exotoxins produced by anaerobic group A beta hemolytic streptococci (GABHS) (28,29), one of the many manifestations of GABHS. The spectrum of presentation is broad and includes pharyngitis, sinusitis, pneumonia, meningitis, superficial skin infection (such as perianal dermatitis), and, less commonly, immune-mediated sequelae such as rheumatic fever, Sydenham chorea, neuropsychiatric disorders (PANDAS), reactive arthritis, and glomerulonephritis. Classically, patients present with fever, sore throat, headache, and vomiting. The typical "sandpaper" rash begins within 1 to 2 days of the onset of fever.

This nonpruritic micropapular and macular rash begins on the lower face, chest, and axilla and spreads in the next 6 hours to involve the rest of the trunk and extremities. It often resolves in 1 week and is followed by desquamation 7 to 10 days later, with the hands and feet being most noticeably affected (Fig. 281.8). Other distinguishing features include circumoral pallor, increased intensity of erythema in the skin folds of the axilla and groin, and transverse streaks in the skin folds known as Pastia lines. The characteristic oropharyngeal findings are an erythematous pharynx and tonsillar exudates. The palate has scattered petechial and punctuate lesions. In addition, there is initially a "white strawberry tongue," which evolves into a "red strawberry tongue" by day 4 or 5.

FIGURE 281.8 Scarlet fever. Desquamation of hands from scarlet fever. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

Differential Diagnosis

The differential diagnosis of scarlet fever includes viral syndromes such as Epstein–Barr virus, measles, and rubella. Bacterial infections including staphylococcal infections, Hemophilus influenzae, and secondary syphilis, as well as toxic shock syndrome, drug hypersensitivity reactions, juvenile rheumatoid arthritis, Kawasaki's disease, and acute systemic lupus erythematous, should also be considered.

ED Evaluation and Management

The diagnosis of scarlet fever is based on the clinical examination. A rapid streptococcal antigen test may be ordered to confirm or document the cause of infection if needed. The treatment of choice is oral penicillin V or intramuscular benzathine penicillin (30). Amoxicillin is also equally effective. Macrolides can be used for penicillin-allergic patients and cephalosporins are an alternative unless there is a history of an immediate or Type 1 hypersensitivity reaction, in which case clindamycin should be used. Antibiotic treatment can help improve fever and constitutional symptoms

within 2 days and can almost eliminate the risk of acute rheumatic fever. However, the role of proper antimicrobial therapy in preventing acute post-streptococcal glomerulonephritis remains uncertain.

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) is caused by the acute exfoliatins, exotoxin A and B, produced by catalase-positive *Staphylococcus aureus* (30,31). Through hematogenous spread, these epidermolytic toxins act at distant skin sites, leading to a separation of the intraepidermal layers, formation of bullae, and diffuse desquamation. In addition to exfoliatins, *Staph. aureus* can produce coagulase and clumping factor, as well as other destructive tissue factors (30). Coagulase causes the clotting of plasma through interaction with fibrinogen, facilitating abscess formation, and clumping factor induces clumping of the organisms, which prevents effective phagocytosis by the host's immune system.

Typically, *Staph. aureus* colonizes the skin and nasal passages of healthy hosts without untoward effect. Young children typically cannot mount an effective immune response or metabolize and excrete toxins related to *Staph. aureus,* and thus SSSS is usually a disease of early childhood (usually before age 5). Generalized exfoliation has also been known as Ritter disease, and in neonates it is known as pemphigus neonatorum. SSSS in children begins with malaise, fever, and upper respiratory tract symptoms. The exfoliatin-induced rash follows, with generalized and sometimes tender erythema worse in the flexures but sparing the mucous membranes. Classically, shearing of the upper epidermal layers with gentle pressure (Nikolsky sign) is observed and is followed by bullae formation and diffuse desquamation (Figs. 281.9 and 281.10).

FIGURE 281.9 Nikolsky sign. (From Fleisher GR, Ludwig S, Baskin MN. *Atlas of Pediatric Emergency Medicine.* Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

FIGURE 281.10 Staph scalded skin. Bullae and diffuse desquamation of skin. (From Avery GB, Fletcher MA, MacDonald MG. *Neonatology:*

Pathophysiology and Management of the Newborn. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.)

Differential Diagnosis

The differential diagnosis of SSSS includes Kawasaki disease, epidermolysis bullosa, toxic shock syndrome, impetigo, scarlet fever, toxic epidermal necrolysis (TEN), and graft-versus-host disease. TEN is often caused by an immunologic reaction to specific viruses, mycoplasma, or drugs. Unlike SSSS, TEN almost always involves the mucous membranes, and the Nikolsky sign is only present in damaged areas of skin. TEN also causes full thickness skin splitting at the dermo-epidermal junction, in contrast to SSSS which causes splitting within the granular layer of the epidermis without necrosis.

ED Evaluation and Management

Microbial analysis of material obtained from skin lesions or bacterial foci such as abscesses can provide evidence of infection and guide antimicrobial therapy. *Staph. aureus* is never normally isolated from otherwise sterile body fluids, such as blood or cerebral spinal fluid, so isolation of the organisms is clear evidence of disease. Complications of severe SSSS include hypovolemia, hypothermia, and secondary infection. Standard treatment includes antistaphylococcal antibiotics, fluid and electrolyte management, and supportive care. In severe cases, patients require admission to an intensive care unit or burn unit.

CRITICAL INTERVENTIONS

- Establish that an urticarial rash is not caused by anaphylaxis.
- Establish that urticaria is not angioedema.
- Obtain clear and detailed exposure histories.
- Document MMR immunization history.
- Perform effective exposure control for pregnant patients and immunocompromised patients potentially exposed to suspected measles and rubella.

Common Pitfalls

- Extensive workups are usually not needed. Focus on a detailed history and physical examination.
- Not all urticaria is benign. Lymphoma, SLE, vasculitis, and other systemic diseases may present with urticarial.
- Failure to confirm immunization status.
- Failure to recognize that patients with suspected or diagnosed measles who exhibit mental status changes or respiratory distress are at high risk for encephalitis or pneumonia.
- The use of amoxicillin or ampicillin for pharyngitis when the illness is caused by Epstein–Barr virus can result in a morbilliform rash.

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CHAPTER 282

Rashes: Vesicular, Pustular, and Scaly Lesions

Martin I. Herman, W. Ricks Hanna, Jr., and Mindy Longjohn

Skin disorders displaying vesicles, pustules, or scales may be caused by wide variety of diseases. Most commonly rashes in this category are caused by Herpes simplex, Varicella, Coxsackie, Herpes zoster, and other enteroviruses. They may also due to entities such as, eczema, atopic dermatitis (AD), seborrheic dermatitis and impetigo, among many others (see Tables 282.1 and 282.2).

TABLE 282.1
Diseases Associated with Vesicles by Pathologic Class

Infectious	Allergic, Auto-Immune	Metabolic	Deficiency Disorders
Chicken pox	Dermatitis medicamentosa	Congenital erythropoietic porphyria	Pellagra, acrodermatitis enteropathica
Coxsackie virus, hand foot and mouth disease	Dermatitis, contact	Erythropoietic protoporphyria variant	Vegetative, autonomic, endocrine disorders
Disseminated GC	ID reaction	Hematoerythrpoietic porphyria	Dishidrosis
Herpes simplex, labialis, genitalis	TEN	Developmental	Toxicologic
Herpes zoster	Pemphigus, bullous	Neonatal acne	Poison ivy/oak/sumac
		Miliaria, erythema toxicum	Caterpillar dermatitis
			Chronic mercurialism
Scabies	Pemphigus, vulgaris		
Staphylococcal/scalded skin	Dermatitis herpetiformis		
Tinea pedis, capitis, cruris, corporus	PUPP syndrome of pregnancy		
Rickettsial pox	Drug-induced photodermatitis		
Monkey pox	Linear IGA dermatosis		
Small pox			

TABLE 282.2
Eczematous Rashes

Eczematous Rash	Age Group Mostly Affected	Characteristics
Seborrhea	Infancy, adolescents, adults	Nonpruritic, erythematous to salmon-colored plaques, scaly or greasy; on scalp, face, retroauricular, intertriginous area
Psoriasis	Children, adults	Round erythematous plaques with loosely adherent silvery or grayish scales, nail pitting, (irregular and large size), extensors, genitalia and scalp
Guttate psoriasis (droplet-like)		Symmetrically distributed plaques over trunk and proximal extremities; may be associated with streptococcal infection
Scabies	Children, adults	Linear burrows, nodules to vesicles; along the web spaces between the fingers and toes, may be on scalp, hands and feet in infants
Cutaneous candidiasis	Neonates, infants	Diaper area and skin folds, papules to pustules at the margins of erythematous plaques, satellite lesions (papules with fine scales)
Nummular (discoid) eczema	Adolescents	Chronic coin-shaped (>5 cm), erythematous base with papules and vesicles, no clearing in center (central clearing seen with tinea); can be generalized, on extensor surfaces in teenagers and fingers in young females
Dyshidrotic eczema	Teenagers, adults	Palms, soles, lateral fingers, clustered vesicles (tapioca-like), pruritic, with later stage of painful fissures and erosions
Tinea	Children, adults	Scaling plaque with raised vesicular or pustular margin, central clearing
Dermatophytid reaction (id reaction)	Children, adults (reaction to fungal antigen)	Redness of skin to red papules to oval plaques; face, neck, proximal extremities, trunk
Granuloma annulare	Children, young adults	Papules and plaques, shiny, erythematous or violaceous or skin-colored, single or confluent, ring-shaped; hands, feet, elbow, knees along dorsal surface
Asteatotic eczema (eczema craquelé)	Adolescents, old age (overbathing, winter months, low humidity)	Dry, cracked skin with red fissures, extensor surfaces
Pityriasis rosea	Children (spring and autumn)	Herald patch followed by papular to plaque-like rash in the skin line distribution (Christmas tree along the back); may be inverse in African-American children, with the rash along the extremities and sparing the trunk
Allergic contact dermatitis	More likely after 3 yrs of age (delayed hypersensitivity reaction)	Papules and vesicles in linear pattern (poison oak or Rhus dermatitis); direct contact areas (e.g., nickel dermatitis)
Irritant contact dermatitis	Any age (caused by direct irritant contact)	Well-demarcated rash on face caused by contact with saliva in infants, diaper dermatitis caused by contact with ammonia in stool, juvenile plantar dermatosis caused by occlusive shoes
Wiskott–Aldrich syndrome	Male infants (X-linked recessive disorder)	Severe eczematous rash, petechiae (caused by thrombocytopenia), increased susceptibility to pyogenic infections, elevated serum IgA and reduced serum IgM
Hyper IgE syndrome (Job syndrome)	Infancy (autosomal dominant disorder)	Chronic dermatitis, recurrent staphylococcal or streptococcal skin, sinus, pulmonary infections, markedly elevated IgE (greater than 2,000 IU/mL), defective neutrophils chemotaxis, cold abscess
Phenylketonuria	Neonates	Eczematous rash, associated features of mental retardation, seizures, photosensitivity, hypopigmentation
Acrodermatitis enteropathica	Infancy (enzyme deficiency in absorbing oral zinc)	Bright red plaques, vesiculobullous rash along perianal and perioral area; associated diarrhea and failure to thrive
Hartnup disease	Infancy (autosomal recessive disorder, defect in tryptophan absorption)	Rash in light exposed area, well-marginated eczematous scaly lesions; associated with cerebellar ataxia
Pellagra	Children, adults (niacin deficiency)	Dermatitis, diarrhea, dementia, rash in areas of sun exposure or around skin friction, symmetric, erythematous
Histiocytosis X (Letterer–Siwe Disease)	Infancy	Seborrheic rash on scalp, retro-auricular and intertriginous areas (papules to plaques; yellow to reddish brown or purplish hemorrhagic appearance, vesicles)

Diagnostic accuracy can be enhanced by keeping a broad differential in mind and not limiting oneself to those rashes that are common and familiar (1). Always start with a detailed history. When did symptoms start? Where did the rash first start? Has the rash changed since first being noticed? Has it migrated since initial presentation? Are there associated signs and symptoms? Is there a history of recent exposure to infectious disease, chemicals, or plant toxins, travel, or new or recent medication use? What interventions have already been tried to treat the condition? Is anyone else affected? Are there any underlying medical conditions? Is there any prior history of similar rash? Other factors, such as age, will also help to formulate a working diagnosis.

The physical examination should focus on the characteristics of the lesions, their location and color, the appearance of the surrounding tissue, size of the lesions, their shape, and tendency to cluster or coalesce. Associated signs or symptoms including fever, lymphadenopathy, and general appearance are also helpful. Look for the presence of dermatologic signs like Koebner phenomena (appearance of lesions in areas of recent trauma), Nikolsky sign (separation of epidermis from dermis with shearing pressure), or the Aspitz sign (punctate bleeding after scale removal) (1). Laboratory testing is occasionally necessary for diagnosis by culture, polymerase chain reaction, or other indicated tests, depending on the differential diagnosis.

DISEASES WITH VESICULAR OR PUSTULAR LESIONS

Herpes Simplex

After the neonatal period, infection with herpes simplex virus (HSV) is often asymptomatic. The most common manifestation is the common cold sore, but the most common ED presentation is acute herpetic gingivostomatitis, often associated with reduced oral intake and dehydration (see Chapter 240, Oral Lesions) (2).

Clinical Presentation

HSV usually presents as discrete vesicles in tight crops or as a confluence of several vesicles in a confined area (Fig. 282.1). Typically, eruptions do not spread, though areas such as the fingers or genitalia can be seeded by autoinoculation. Corneal infection may also occur in association with lesions around the eye (Fig. 282.2). An outbreak may last 1 to 2 weeks and infected children can shed virus for a week or more, spreading HSV to playmates and household contacts. Other less common presentations of HSV infection include herpes gladiatorum and herpes rugbiaforum, which occur in wrestlers and rugby players, respectively (2).

FIGURE 282.1 Crop of vesicular lesions on a cheek.

FIGURE 282.2 Typical HSV lesions on or about the eye lid margins. (Dr. K. L. Hermann, Centers for Disease Control.)

In adolescents and adults, genital herpes (Figs. 282.3 and 282.4) is the most common presentation of HSV. It presents with vesicular or ulcerative lesions of the genitalia and surrounding tissues. In young children there are rare cases of innocently acquired primary herpes simplex infection presenting as herpetic vulvovaginitis; however, the possibility of sexual abuse must be considered in all of these cases.

HSV typing can help to indicate whether the inoculation occurred from a primary site, such as a cold sore on the lip usually associated with HSV-1, or from genital contact, which is often caused by HSV-2. However, there can be substantial overlap. Other primary and recurrent herpes infections, such as herpetic whitlow (Fig. 282.5) and herpes keratoconjunctivitis, may be seen in children. Children with AD may develop extensive herpes simplex infection on eczematized areas (eczema herpeticum).

FIGURE 282.3 Typical small ulcers on labia. (From Willis MC. *Medical Terminology: A Programmed Learning Approach to the Language of Health Care.* Baltimore, MD: Lippincott Williams & Wilkins; 2002.)

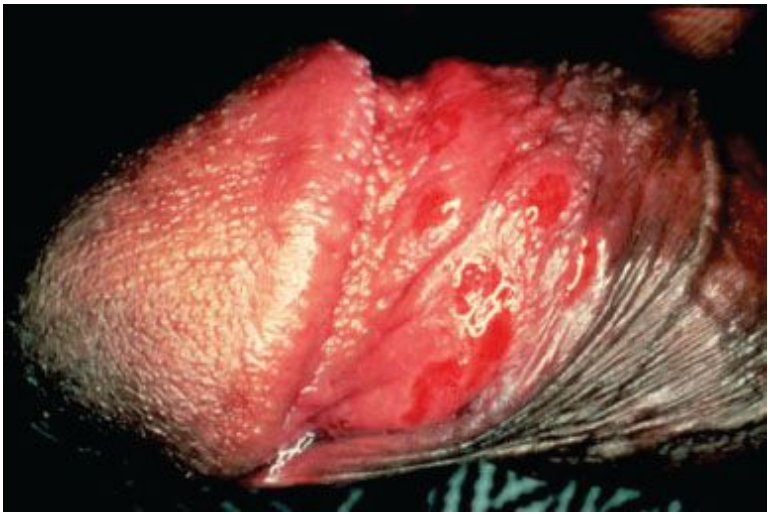

FIGURE 282.4 HSV penile lesions, unroofed revealing shallow ulcers. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

FIGURE 282.5 HSV infection of a finger is called a herpetic whitlow. Grouped, fluid-filled, or pus-filled, blisters are typical. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.) (Copyright Dr. P. Marazzi/SPL/Science Source/Photo Researchers.)

ED Evaluation

Neonatal HSV infection can be associated with severe morbidity or even mortality and hence should not be overlooked. It can present as disseminated disease, especially with pulmonary and liver involvement, which account for 45% of cases. It may also manifest as localized central nervous system (CNS) disease (30% of cases) or as an infection localized to the skin, eyes, and mouth (SEM) (25% of cases). Neonatal HSV may occur up to the age of 4 weeks from birth and should be part of the differential diagnosis for neonates with fever. Many HSV-infected babies do not have skin lesions at presentation, as skin lesions tend to present later than disseminated disease (2).

If vesicles are seen and HSV is suspected, it can be confirmed through the use of viral cultures, fluorescent antibody staining, or enzyme immunoassay. Polymerase chain reaction (PCR) can detect HSV DNA in the CSF. Swabs should be taken from the mouth, nasopharynx, conjunctivae, and rectum. Cultures should be collected from skin vesicles, urine, blood, and CSF.

Suspected corneal infection with HSV mandates consultation with an ophthalmologist or, at a minimum, fluorescein staining of the cornea to look for dendritic keratitis (Fig. 282.6). The diagnosis can be verified by immunofluorescence, PCR, or Giemsa stain (3).

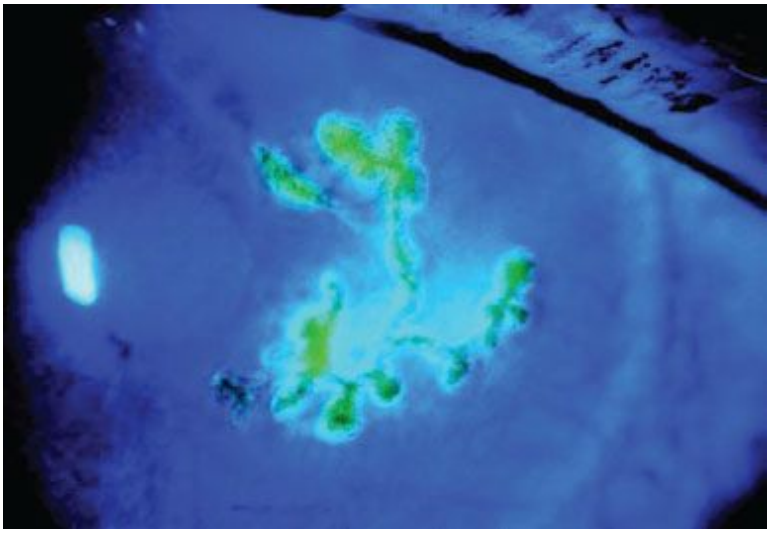

FIGURE 282.6 The hallmark of herpes simplex keratitis is the dendrite, a branching, epithelial ulceration with swollen, raised edges and terminal bulbs. (From Tasman W, Jaeger E. *The Wills Eye*

Hospital Atlas of Clinical Ophthalmology. 2nd ed. Lippincott Williams & Wilkins; 2001.)

For patients with presumed genital herpes, the diagnosis should be confirmed by culturing material from the lesions and ordering serologic testing. Other sexually transmitted diseases should also be tested, as they commonly occur together.

ED Management

Neonatal HSV can be a medical emergency; hence, neonates are usually admitted for evaluation and treatment. HSV infections after the neonatal period involving skin and mucus membranes can be treated with analgesics and, if recommended, antiviral agents.

Acyclovir, valacyclovir, famciclovir, or penciclovir may be used to treat genital herpes. Penciclovir topically, or acyclovir or valacyclovir orally, can help quell cold sores as well. HSV of the cornea or eye should be treated with topical antiviral agents; 1% trifluridine, 0.1% iododeoxyuridine, or 3% vidarabine have been shown to be effective for HSV keratitis (2). Providers should check treatment guidelines available from the CDC, the Infectious Disease Society, or the AAP Red Book for the most recent recommendations.

Varicella

Clinical Presentation

Varicella (chicken pox) is a highly infectious disease caused by the varicella-zoster virus (VZV, also known as HHV 3) (4). In the pre-vaccine era, nearly 90% of cases involved children younger than 15, with the majority of cases occurring in preschool and early school-aged children. Prior to the introduction of the VZV vaccine in 1995, varicella occurred, with an average annual incidence of approximately 150 cases per 1,000 patient years or 15 to 16 cases per 1,000 population. In the post-vaccine era, the reported incidence is down to 15.8 cases per 1,000 patient years, representing an approximately 90% reduction (5).

Signs and symptoms of varicella develop in healthy children after an average incubation period of 14 to 16 days (range, 10 to 21).

Following a 1 to 2 day prodromal state characterized by fever, headache, anorexia, cough, coryza, sore throat, and cutaneous itching, varicella skin lesions (in an unvaccinated individual) begin to appear in crops (6). The lesions begin as macules that rapidly progress to papules, then vesicles that eventually rupture and crust over. The classic early vesicle is small with circumscribed erythema, often referred to as a *dewdrop on a rose petal.* The first lesions often develop on the face and scalp and as the rash spreads, lesions of all stages (papules, vesicles, crusts) are characteristically present within a single affected area (Fig. 282.7). Shallow ulcers often occur in the mouth and may appear on other mucous membranes. Pruritus is common, and scarring may result if lesions are aggressively scratched or become superinfected.

FIGURE 282.7 Dew drop on rose petals, lesions in various stages of progression. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

Unvaccinated patients typically have 250 to 500 lesions in various stages, whereas vaccinated patients may have less than 50 (5). Chicken pox is contagious from 1 to 2 days before the onset of rash until all lesions are crusted over, which is typically 4 to 7 days after the onset of rash. VZV remains dormant in sensory nerve ganglia and can be reactivated later in life causing herpes zoster (i.e., shingles).

The epidemiology and clinical characteristics of varicella have changed with the implementation of the varicella vaccine program. Varicella that develops more than 42 days after vaccination (i.e., breakthrough varicella) typically is mild, with fewer than 50 skin lesions, minimal fever, and a shorter (4 to 6 days) duration of illness. The rash is predominantly maculopapular rather than vesicular in most cases (7).

Complications of varicella are rare but can be serious. The most common complications seen in children are secondary bacterial skin infections, usually caused by group A beta-hemolytic streptococcus (GABHS) or *Staphylococcus aureus.* There have been reports of chickenpox-associated invasive group GABHS infections, including necrotizing fasciitis and streptococcal toxic shock syndrome (8,9). GABHS infection should be suspected in children with varicella who develop localized skin swelling, warmth, redness, or pain. Most importantly, it should be considered in patients with fever persisting beyond the fourth day of illness or with a recurrence of fever after becoming afebrile (10). Other serious complications in children include acute cerebellar ataxia, encephalitis, encephalopathy, and post-viral transverse myelitis. Varicella pneumonia is rare in immunocompetent children but may occur in adolescent and adult patients. Deaths from varicella have diminished significantly since the VZV vaccine program was instituted dropping to only 112 in a 5-year period (10).

Patients with altered cell-mediated immunity, such as children with leukemia who are on chemotherapy, are susceptible to disseminated varicella and may have hemorrhagic lesions, pneumonitis, and encephalitis. Children with HIV can develop chronic or recurrent varicella, with new lesions appearing over the course of months. Severe varicella has also been reported in healthy children receiving intermittent courses of corticosteroids for treatment of asthma or other illnesses (2).

Differential Diagnosis

The differential diagnosis of varicella can be quite extensive and includes Herpes simplex, Herpes zoster, and rickettsial pox, as well

as zoonotic pox viruses. Other entities associated with vesicular-bullous lesions should also be included in the differential (see Tables 282.1 to 282.3). Shingles or zoster is caused by the same virus that causes chickenpox, when a previously dormant VZV infection is reactivated. The lesions look similar to those of varicella but are limited to the dermatome of the affected nerve roots. Several of the enteroviruses and parechoviruses cause vesicular skin lesions, the best known being hand–foot–mouth disease (HFMD) (Fig. 282.8). These lesions are similar to those of varicella, but their characteristic distribution sets them apart. The lesions of scabies, with associated excoriation secondary to intense itching, may appear similar to late-stage varicella lesions. Insect bites resulting in papular urticaria (e.g., from bedbugs) may also mimic early varicelliform lesions or atypical varicella. The variable manifestations of drug reactions, erythema multiforme, and syphilis should also be considered.

TABLE 282.3
Differential of Vesicular–Pustular Lesions

Varicella	Secondary syphilis
Herpes zoster	Acne
Herpes simplex	Scabies and other insect bites
Vaccinia (vaccine reaction)	Impetigo
Enterovirus	Drug rash
Molluscum contagiosum (especially HIV pts)	Erythema multiforme
Monkey pox	Contact dermatitis

FIGURE 282.8 Subtle clear vesicles on erythematous bases located on the fingers, toes, hands, feet, lips and oral mucosa.

ED Evaluation

Patients should be placed in isolation, with respiratory precautions (including a mask). Contact with caretakers who might be pregnant or immunocompromised should be avoided. A vaccine record is helpful in determining whether the case is vaccine related or atypical. Identify complications of varicella such as pneumonia, keratitis, meningoencephalitis, or secondary skin infection and initiate treatment if indicated. If corneal involvement is suspected, consultation with an ophthalmologist is strongly suggested. Classic varicella is usually easily recognized, and laboratory testing is usually not needed. When the diagnosis is in doubt, a viral culture is the recommended standard. In both varicella-zoster and herpes simplex infection, Tzanck smears prepared from vesicle scrapings may demonstrate single- or multi-nucleated giant cells with intranuclear inclusions. PCRs are very sensitive and specific for viral DNA. Direct fluorescent antibody tests are more rapid and sensitive than culture, but less sensitive than PCR testing. “Real-time” PCR tests show very high sensitivity and specificity and may in time replace direct tests or viral cultures (2).

ED Management

Children suspected of having chicken pox usually do not require more than fever control and symptomatic treatment of pruritus. Varicella may be associated with thrombocytopenia, making ibuprofen and other nonsteroidal anti-inflammatory drugs contraindicated; however, acetaminophen remains an appropriate antipyretic. Topical measures such as cool baths, calamine lotion, and colloidal oatmeal baths may help alleviate pruritus. Oral antihistamines may be helpful for severe itching; topical antihistamines, however, are less desirable because of the risks of sensitization and excessive systemic absorption through nonintact skin.

Antiviral medications have a limited window of opportunity for treatment of varicella-zoster infection. Some patients who are at risk for moderate to severe illness (age over 12 years, chronic cutaneous or pulmonary disorders, current treatment with inhaled steroids or chronic salicylates) may benefit from a prescription for oral acyclovir if it is administered within 24 hours of the onset of rash. Intravenous acyclovir is recommended for immunocompromised patients with varicella-zoster infection and should be initiated early.

If the history, examination, or laboratory testing indicates the presence of complicating factors, these should be addressed. Symptomatic dehydration requires fluids, ideally administered orally, but intravenously if the patient refuses to drink. The presence of secondary bacterial infections mandates treatment with antibiotics. In the era of methicillin-resistant staphylococcus (MRSA), treatment with antibiotics such as clindamycin, ceftriaxone, cefuroxime, linezolid, or vancomycin may be necessary, depending on the severity of the illness and local antibiotic susceptibilities. Airborne and contact precautions are recommended for patients with varicella for a minimum of 5 days after onset of the rash and for as long as vesicular lesions are present. Post-exposure prophylaxis includes either varicella-zoster-immune globulin (VariZIG) within 96 hours for high-risk susceptible persons, or varicella vaccine within 72 hours after varicella exposure for susceptible children (see the CDC guidelines or the AAP *Red Book* for current recommendations).

Most patients may be discharged home with fever control and antipruritics. Hospitalization may be needed if the patient cannot maintain hydration or requires oxygen or intravenous medications.

Herpes Zoster

Herpes zoster (shingles) is caused by a reactivation of latent VZV in sensory ganglia. Children are less commonly affected than adults, and younger patients tend to have a less painful course and little post-herpetic neuralgia (11). Risk factors for shingles include varicella acquisition in utero or prior to 18 months of age, general aging, and immunosuppression. Roughly 15% to 30% of the population will experience zoster at some point in their lives.

Clinical Presentation

The characteristic findings include grouped vesicular lesions in a dermatomal distribution (Figs. 282.9 and 282.10) accompanied by pain and tenderness along the course of the involved nerves. The most common sites are the areas supplied by the trigeminal nerve and the thoracic ganglia. Fever and local lymphadenopathy are common.

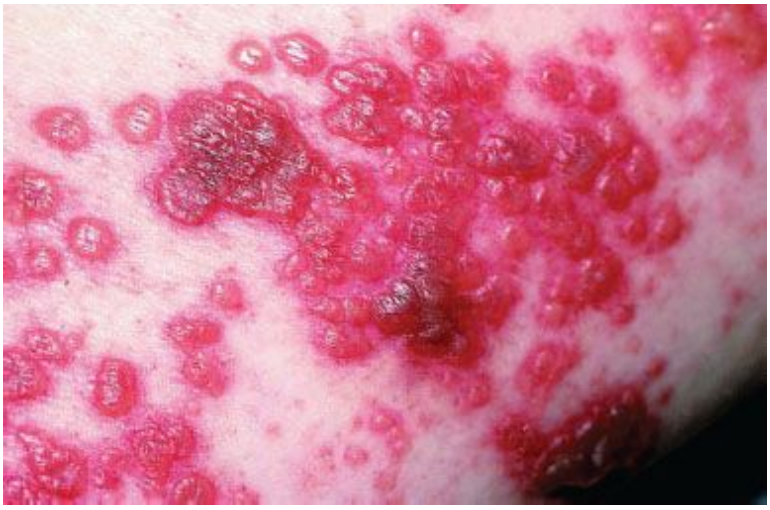

FIGURE 282.9 Discrete and confluent small vesicles with an erythematous base. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

FIGURE 282.10 Shingles demonstrating a right thoracic dermatomal distribution.

ED Evaluation

The history and physical should concentrate on the location and duration of the eruption, and whether symptoms are indeed dermatomal. A common history is of recent contact with a child who has chickenpox. Multi-dermatomal distribution usually represents disseminated infection, which is more common in immunocompromised individuals. If there is any suggestion of eye involvement, such as lesions on the tip of the nose or eyelids, the patient should be evaluated by an ophthalmologist.

Reactivation of VZV can also cause aseptic meningitis, cerebellar ataxia, encephalitis, or encephalopathy. Ancillary diagnostic testing such as lumbar puncture, brain CT or MRI, and or supplemental treatment may be required (11).

ED Management

Adequate analgesia, with opioids if necessary, is an important component of care (Calamine lotion does not appear to be beneficial for VZV-related pain (12)). Famciclovir, valacyclovir, or acyclovir

may be helpful. Acyclovir 20 mg/kg (max 800 mg/dose) can decrease healing time and decrease associated pain (11) (note: Famciclovir and valacyclovir are licensed for use only in adults) (1). Most patients with shingles can be sent home with analgesics and antihistamines such as diphenhydramine to reduce itching.

Enteroviruses

Clinical Presentation

HFMD (see Fig. 282.8) is a distinctive clinical syndrome that is usually caused by Coxsackie A16 or enterovirus 71. Sporadic cases have been associated with Coxsackievirus A4-A7, A9,10, B1–3, and B5 (6).

A 2- to 4-day prodromal stage of fever, anorexia, sore throat, and abdominal pain occurs prior to the appearance of the rash. The lesions are typically 2 to 8 mm, large, oval, gray blisters noted on the sides of the fingers as well as the palms and soles, and usually with an erythematous halo. Apthous ulcers may be seen on the palate, tongue, and buccal mucosa. The rash generally lasts 5 to 10 days (4). Complications of HFMD include aseptic meningitis, encephalitis, paralysis, and death. Outbreaks of HFMD associated with neurologic complications and death have been linked with enterovirus 71 (13).

ED Evaluation

The diagnosis of an enteroviral infection is usually based on the clinical findings. Confirmatory testing may be desired, however, and can be done for many of the agents. Cell culture is the standard method; specimens obtained from the rectum, stool, or throat have the highest yield, but the virus may be recovered from CSF, blood, and urine as well. PCR assays are available for enteroviruses and are more rapid and sensitive than cell culture.

ED Management

Fever control and hydration are particularly important issues and are the mainstays of management. Patients should be adequately hydrated, and their ability to drink, especially in patients with mucous membrane involvement, should be carefully assessed. If the patient is unable or unwilling to drink, intravenous fluids should be

given. Analgesics should be provided as necessary, but the use of topical anesthetics like viscous lidocaine in younger patients should be discouraged, as aspiration and toxicity may result. Application of aluminum hydroxide and magnesium hydroxide or sucralfate may be helpful in ameliorating stomatitis-related pain (14), though controlled studies have not shown a clear benefit (15).

Most patients with HFMD, herpangina, or other enteroviral infections may be discharged home if they can demonstrate their ability to take adequate fluid. Fever can be managed with antipyretics at home. Spread of the enteroviruses should be contained by meticulous hand washing, disinfection of surfaces, and avoiding the popping of any vesicles. Patients with CNS infection and an altered level of consciousness or muscle weakness should be hospitalized. Cardiac monitoring in the hospital is appropriate for patients with myocarditis or pericarditis caused by enteroviral infection. Vaccines are being researched as are chemotherapeutic agents, but thus far none has been approved for use in the United States.

Impetigo

Impetigo is an infection of the superficial epidermis by *Staphylococcus aureus* and/or *Streptococcus pyogenes* that presents with multiple vesicular lesions on an erythematous base, which usually crust over. The infection is highly contagious; humidity, crowding, and poor hygiene all contribute to its spread. Children ages 2 to 5 years are most often affected (16,17). It is most common on exposed areas of the body, including the face, extremities, and scalp. Minor skin abrasions, minor trauma, burns, insect bites, diabetes mellitus, varicella infection, HIV infection, and pre-existing skin disease are all predisposing risk factors.

Clinical Presentation

There are two types of impetigo: nonbullous and bullous (Figs. 282.11 and 282.12). Nonbullous impetigo is more common and is usually secondary to a mixed infection with *Staph. aureus* and *Strep. pyogenes*. It begins as a single red macule or papule that becomes

vesicular. The vesicle ruptures, forming an erosion, and the contents of the vesicle dry, leading to the classic thick honey-colored crust. Nonbullous impetigo is spread to adjacent areas by autoinoculation, especially in areas subject to environmental trauma, such as the face and extremities. This leads to clustering of the vesicles before the breakdown and crusting of the lesions. Pain and pruritus are not common but may occur. Regional lymphadenopathy may be an isolated finding.

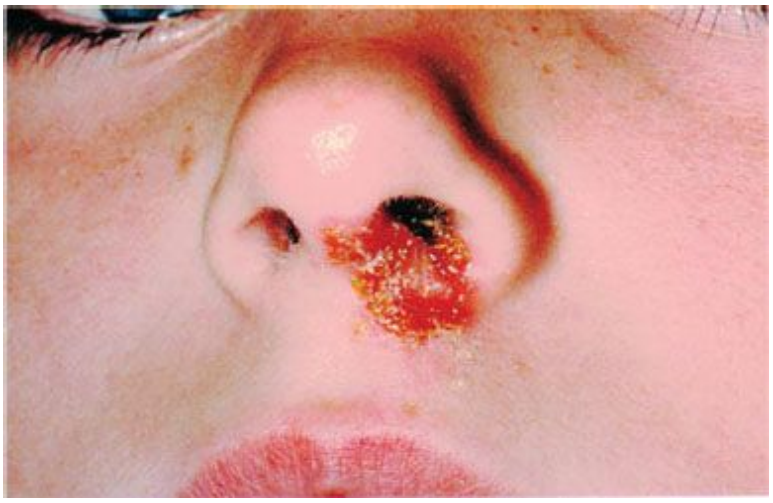

FIGURE 282.11 Typical honey-colored crusts. (From Smeltzer SC, Bare BG. *Textbook of Medical-Surgical Nursing.* 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2000.)

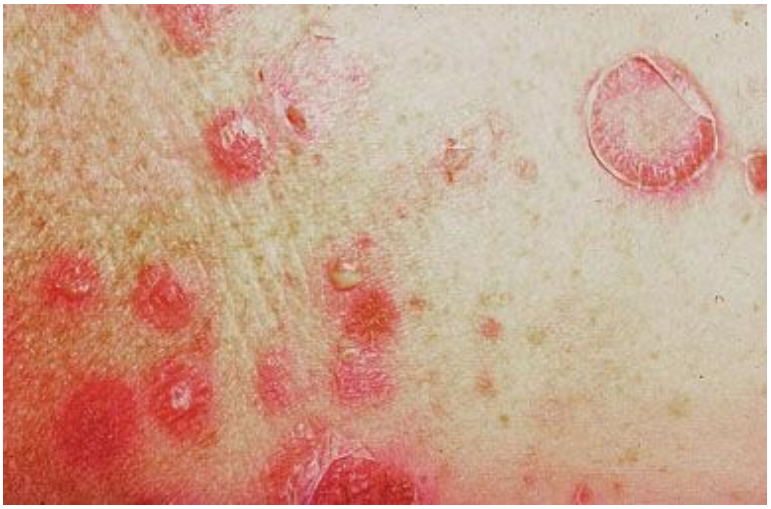

FIGURE 282.12 Blebs, bullae, and coin-shaped lesions that remain after the bleb is removed.

Common or impetiginous impetigo (also called secondary impetigo) is a subtype of nonbullous impetigo (16). This is a complication of systemic diseases such as diabetes mellitus and acquired immunodeficiency syndrome or may be secondary to processes that cause a break in the skin, such as insect bites or herpes simplex. Secondary impetigo proceeds similarly to nonbullous impetigo.

Bullous impetigo is less common and is usually seen in newborns and infants but can occur in any age group. The bullous form is caused by toxin-producing *Staph. aureus* and is considered a localized form of staphylococcal scalded skin syndrome. Bullous impetigo begins as vesicles that progress to enlarging, flaccid bullae with sharp margins and no surrounding erythema. The bullae are filled with yellow fluid that crusts over after rupture. A collarette of scale surrounding the blister roof at the periphery of ruptured lesions is pathognomonic (Fig. 282.13) (16). Bullous impetigo is common in moist body areas, including the diaper area, axilla, and neck folds. There are usually no systemic symptoms, and regional lymphadenopathy is rare. As compared to the nonbullous form, cases of bullous impetigo are less contagious and tend to be sporadic.

FIGURE 282.13 Collarette of scale surrounding the blister roof at the periphery of ruptured lesions is pathognomonic. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

Differential Diagnosis

The differential diagnosis of nonbullous impetigo includes AD, candidiasis, contact dermatitis, dermatophytosis, discoid lupus erythematosus, herpes simplex, insect bites, pemphigus, scabies, Sweet syndrome, and varicella infection. The presence of the honey-colored crust and the distribution of the lesions are important differentiating factors in impetigo.

Varicella infection is unique in that the vesicles appear in crops and that there are usually lesions of different ages present concurrently. Sweet syndrome is a rare skin condition presenting with fever, arthritis, and the sudden appearance of bluish-red tender papules located asymmetrically on the arms, legs, and face.

Bullous impetigo can mimic cigarette or thermal burns and can be mistaken for child abuse (16). It is also important to differentiate bullous impetigo from Stevens–Johnson syndrome and toxic epidermal necrolysis (TEN). These diagnoses represent a continuum and are potentially life threatening. Stevens–Johnson is a blistering process that by definition involves mucosal surfaces, usually the mouth and eyes, among others. TEN is the continuation of the blistering of Stevens–Johnson with detachment of the epidermis.

ED Evaluation

The diagnosis of impetigo is usually made on the basis of history and clinical presentation. If the diagnosis is uncertain, the organism(s) can be identified by Gram stain and culture of the lesions or the associated fluid. The lesions should be de-crusted aseptically to obtain the exudative material beneath for the appropriate studies.

ED Management

If left untreated, most cases of impetigo are self-limited with no residual scarring (16,17). The main goals of therapy are relief of discomfort, prevention of autoinoculation, limiting of spread of the

disease, and improved cosmetic appearance. Topical antibiotic therapy with mupirocin has the advantage of being applied only where needed, minimizing potential side effects. Side effects of topical antibiotics are uncommon and are usually mild if present, with skin sensitization occurring in susceptible individuals.

Oral antibiotic therapy may be needed for patients who cannot tolerate topical antibiotic therapy or who have extensive or systemic disease. Oral antibiotics are typically prescribed for 10 days and should have antistaphylococcal activity. Common oral antibiotic choices include amoxicillin/clavulanate and cephalosporins, with clindamycin and trimethoprim–sulfamethoxazole used for suspected MRSA. Combining topical and oral antibiotics is not necessary.

Approximately 1% to 5% of patients will develop acute post-streptococcal glomerulonephritis as a serious complication of nonbullous impetigo (16). Antibiotic treatment has not been found to decrease the risk of glomerulonephritis. Other more rare complications include sepsis, osteomyelitis, arthritis, endocarditis, pneumonia, cellulites, toxic shock syndrome, and staphylococcal scalded-skin syndrome. Rheumatic fever has not been associated with impetigo.

Most patients with impetigo can be discharged from the ED with topical or oral antibiotic therapy. In cases of severe infection or concerns for Stevens–Johnson syndrome or aggressive MRSA, inpatient therapy may be necessary. Follow-up should be arranged to guarantee complete and complication-free resolution.

Eczema and AD

AD is the most common chronic inflammatory skin condition in the pediatric age group (18,19). Its prevalence is 10% to 15% among children in the United States and Europe, and the incidence is noted to be increasing worldwide (20,21). AD is a chronic relapsing dermatitis that is relentlessly pruritic and often progresses to eczematous patches, with crusting and fissuring. AD affects the patient's quality of life because of intractable pruritus, loss of sleep, decreased appetite, and mood changes. The families of patients with

AD are also adversely affected through parental sleep disturbance, anxiety, depression, and the impact on the care of siblings (18,20).

AD is considered an allergic condition. Allergic disorders in children are likely to develop in genetically predisposed children after exposure to environmental triggers. The *atopic triad* (21) refers to the presence of AD, allergic rhinitis, and asthma. AD can be a lifelong condition; most cases present between the ages of 2 and 5 years. Some evidence suggests that AD may be more common in Black and Asian children (18).

Clinical Presentation

The presentation of AD is similar to most inflammatory skin conditions: Pruritus, erythema, dry skin, scaling, and eventually lichenification. Lesions may be acute, subacute, or chronic, and all stages may be present at the same time. The initial symptom is usually intense pruritus, which eventually leads to micro-trauma in the epidermis and the formation of erythematous papules with dry skin and a light scale. As AD progresses from this mild form, intense erythema and small vesicles form. Chronic changes include lichenification, especially at the skin lines and eventual fissuring (Fig. 282.14).

FIGURE 282.14 Lichenification, excoriation, hyperpigmentation of antecubital folds.

In infants, AD is typically seen on the face, scalp, trunk, and the extensor surfaces of the extremities. The perioral and periorbital areas tend to be spared. As patients grow older, the common areas are the flexor surfaces of the extremities, face, neck, wrist, and ankles. In addition to the rash, almost all patients have xerosis, or dry skin, that is exacerbated by dry climates and winter weather. Patients may also exhibit nonpigmented hyperkeratotic papules (keratosis pilaris), which form around hair follicles. Keratosis pilaris is most often found on the extensor surfaces of the upper arms, the buttocks, and the anterolateral thighs.

With repeated excoriation, the rash associated with AD can become secondarily infected, most often with *Staph. aureus* and *Strep. pyogenes* (21). Because the normal skin barrier is compromised, AD makes the patient more susceptible to cutaneous infections. Herpes simplex is among these infections; widespread herpes infection complicating AD is known as eczema herpeticum (19).

Differential Diagnosis

The differential diagnosis of AD includes other papulosquamous conditions including contact or irritant dermatitis, lichen simplex chronicus, pityriasis rosea, and psoriasis. The rash associated with allergic dermatitis is usually found on exposed areas and can also be acute, subacute, or chronic, depending on the length of the exposure. Common causes include poison ivy, nickel, rubber, latex, soaps, detergents, and cosmetics. The exposure history and the resolution of the rash with removal of the offending agent are typical clues to the diagnosis. The herald patch associated with pityriasis rosea may be confused with AD (19). Pityriasis rosea is usually not pruritic, and the typical distribution of the rash helps to differentiate it from AD. The rash associated with psoriasis is an erythematous plaque with an adherent silvery scale, giving the area a greasy appearance (19). Psoriasis is usually located on the extensor surfaces, whereas AD typically involves the flexor surfaces.

ED Evaluation

AD is usually diagnosed by history and physical examination. The most striking feature is the pruritus, which is almost universally

present. Other associated features are a history of atopy, family history of atopy, the relapsing nature of the dermatitis, and the typical appearance and distribution of the skin findings.

ED Management

The mainstays of treatment are hydration of the skin, avoidance of irritants, and the application of topical anti-inflammatory agents (21). AD is a chronic condition, and although treatment is often begun in the ED, long-term care should be coordinated through the patient's primary care provider or dermatologist. Hydration of the skin is begun with the use of lotions and creams as emollients, applied at least three to four times a day and especially after bathing. Patients should be instructed to decrease the frequency and duration of bathing since prolonged bathing may worsen the condition. Any identified skin irritants such as environmental or food allergens should be avoided; others, like winter weather or low humidity, may be difficult to avoid.

Topical corticosteroids (TCSs) have historically been the most common first-line anti-inflammatory treatment for AD and its flares (18,21). TCSs are effective in treating the acute manifestations of AD, but prolonged and unmonitored use should be avoided because of their local and systemic side effects. These side effects include the local effect of skin atrophy and systemic suppression of the hypothalamic-pituitary-adrenal axis. Young children, with their large skin surface area–body mass ratio, are at increased risk of systemic side effects owing to cutaneous absorption.

Superinfection of AD requires treatment with antibiotics effective against *Staph. aureus* and *Strep. pyogenes* along with routine skin care. Eczema herpeticum requires acyclovir and occasionally hospitalization for its control.

It is important to remember AD is a chronic relapsing condition that affects not only the patient but the entire family unit. When treating AD, it is important to take the time to discuss the importance of skin care and the various treatment options. Close follow-up is essential for children using TCSs or immunomodulators.

Pityriasis Rosea

Pityriasis rosea (PR) is a self-limited papulosquamous eruption that is common in children and young adults (22). The etiology of PR remains unclear, but there are features that suggest a role for human herpesvirus 7 (19,22,23). Cases are known to cluster within populations and are typical in the late fall and winter, with a peak in early spring. PR most commonly affects adolescents, especially between 10 and 35 years, and there is a slight female predominance.

Clinical Presentation

Patients with PR typically present after a viral prodrome (i.e., an upper respiratory tract infection, fever, malaise, arthralgias, and headache). The herald patch presents in most patients and precedes the rash. It is a 2- to 10-cm, oval-to-round plaque that is salmon colored and surrounded by a dark red rim. The center is clear and is separated from the rim by a scaly collar or "collarette." The secondary rash occurs days to weeks after the herald patch and is characterized by 5- to 10-mm, oval, and salmon-colored lesions, with the same scaly "collarette." It is found on the chest, back, abdomen, and extremities along the lines of skin tension or Langer lines; it commonly takes on a "Christmas tree" pattern on the back. Pruritus in noted in only 25% of patients (23) (Fig. 282.15). The rash usually lasts from 2 to 6 weeks but can persist for as long as 3 months.

FIGURE 282.15 Typical Christmas tree distribution with a herald patch on the right forearm. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

Differential Diagnosis and ED Evaluation

PR is usually diagnosed on the basis of history and the appearance and distribution of the lesions. The most important disease in the differential diagnosis is secondary syphilis. The rash associated with secondary syphilis can mimic PR, but in secondary syphilis, the palms and soles are often affected, whereas they are spared in PR. If a patient is sexually active or the diagnosis is in question, serologic testing for syphilis should be considered.

Other conditions in the differential diagnosis include nummular eczema, especially when only the herald patch is present. Other entities to be considered include tinea, guttate psoriasis, lichen planus, pityriasis lichenoides, and Kaposi sarcoma. Rarely, drug reactions have been confused with PR; some authors have searched for a causal link, but none have been found.

For pruritus, antihistamines, oatmeal soaks, and occasionally topical steroids are recommended. For severe cases of pruritus, systemic steroids may be useful.

ED Management

The patient and family should be reassured that the disease is not contagious, is self-limited, and can be expected to resolve within several weeks. Patients should be encouraged to see their physician if the rash lasts longer than 3 months. Black patients can exhibit hypopigmentation following the resolution of the rash.

CRITICAL INTERVENTIONS

- Treatment with acyclovir should be initiated in neonates who are febrile, irritable, displaying lethargy or have physical signs of HSV infections.
- Patients should receive adequate pain control.

- An eye examination should be performed in patients with disseminated disease.
- Test for syphilis in patients who present with a rash resembling pityriasis rosea.

Common Pitfalls

- Mistaking hand–foot–mouth for varicella.
- Recommending topical diphenhydramine, especially if in addition to recommending oral diphenhydramine to control itching.
- Failing to recognize that lesions on the nose may signal involvement of the cornea.
- Failure to recognize that bullous impetigo can mimic cigarette or thermal burns and can be mistaken for child abuse.
- Failure to recognize systemic HSV and to consider CNS HSV in an infant.
- Failure to realize that enteroviral infections can be associated with serious complications such as a polio-like illness, seizures, or death.
- Failure to determine the patient's or parents' ability to maintain hydration.
- Failure to recognize that high-potency steroids should not be used routinely in the perineal area.

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CHAPTER 283 Common Pediatric Infestations

Jesse Walck and Martin I. Herman

Infestations refer to a state of being lived in or on as a parasite. Although infestations occur commonly they are not a cause of significant morbidity but, because of the symptoms they can produce and the near hysteria they can invoke, they are often seen in the emergency department. The following sections address some of the more common infestations.

CUTANEOUS LARVA MIGRANS

CLINICAL PRESENTATION

Cutaneous larva migrans (CLM), or creeping eruption, refers to a hookworm infection that produces a characteristic intensely pruritic serpiginous rash (Fig. 283.1) (1). The usual cause is the larvae of cat and dog hookworms found in warm climates near beach areas. CLM is a disease of children, gardeners, utility workers, sunbathers, or anyone who comes in contact with sand or soil contaminated by cat or dog feces (2,3).

FIGURE 283.1 Cutaneous visceral larva migrans. (From Farr WE, Wood MJ, Innes JA, et al. *Infectious Diseases Text and Color Atlas.* 2nd ed. New York, NY: Gower Medical Publishing; 1992.)

The larvae gain access to the human skin most commonly in the lower extremities and form a pruritic reddish papule at the site of entry. If exposed to heavily contaminated soil several papules may develop. The larva migrates within the dermis of the skin advancing several millimeters a day until they eventually die within 1 to 2 weeks. Rarely the larva can disseminate hematogenously to the lungs producing patchy infiltrates and blood eosinophilia producing a condition referred to as Loeffler syndrome (4).

Patients usually present with an intensely pruritic characteristic serpiginous erythematous rash about 2 to 3 mm in diameter. The rash is usually raised and typically occurs on the lower extremities. Some lesions may appear fluid filled or crusted and have associated nodules and blisters (4). Lesions can become secondarily infected.

DIFFERENTIAL DIAGNOSIS

CLM may be mistaken for the rash seen with tinea pedis, herpes simplex, contact dermatitis, scabies, cutaneous leishmaniasis, and myiasis (botfly skin infestation) (4).

ED EVALUATION

The diagnosis is made clinically. Biopsies or laboratory testing is not indicated.

CRITICAL INTERVENTIONS

- The infestation is self-limited after several weeks to months. Treatment is indicated to relieve symptoms and to prevent secondary infection. Ivermectin 200 μg/kg PO QD for 1 to 2 days or Albendazole 400 mg PO QD for 3 days is effective (5). Symptoms typically disappear within 1 week of treatment often before the rash resolves. Topical preparations of albendazole or thiobendazole are effective but difficult to obtain. Loeffler syndrome is treated orally at the same doses mentioned previously (4).
- Suspected secondary infections can be treated with appropriate antibiotics.

DISPOSITION

Patients can be discharged to initiate treatment at home.

Common Pitfalls

- Failure to recognize the infestation
- Attempting to extricate the worm by dissection
- Treating with topical agents

SCABIES

CLINICAL PRESENTATION

Scabies is an infestation of the skin caused by the mite *Sarcoptes scabiei* that produces a pruritic skin rash with a characteristic distribution (6).

The female mite burrows in the upper dermis of the skin creating small linear burrows. Sensitization to the mite and its eggs and feces are responsible for the pruritic reaction (6).

The infestation is contagious and obtained from human contacts or dogs. The incubation period for persons without prior exposure is 2 to 6 weeks, but in a reinfestation, symptoms may appear in as early as a few days. Norwegian or crusted scabies occurs most commonly in immunocompromised patients, is characterized by crusted or warty lesions with minimal pruritus but with high concentrations of highly contagious mites (7).

Patients usually present with an intensely pruritic erythematous rash often with characteristic burrows. However the rash is variable and can also present with papules, pustules, or nodules and burrows may not be visible due to excoriation or secondary infection. Adults often have lesions in the fingers (Fig. 283.2), web spaces and flexor surfaces of the wrists, axilla, and genital areas. Infants and young children most commonly have lesions on the face, head, neck, scalp, palms, and soles (Fig. 283.3) and the lesions are often more inflammatory than in adults (8).

FIGURE 283.2 Scabies—web spaces. (From Fleisher GR, Ludwig S, Baskin MN. *Atlas of Pediatric Emergency Medicine.* Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

FIGURE 283.3 Scabies—infants. (From Fleisher GR, Ludwig S, Baskin MN. *Atlas of Pediatric Emergency Medicine.* Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

Crusted scabies can present with crusted or warty lesions with minimal pruritus.

DIFFERENTIAL DIAGNOSIS

When considering scabies as the diagnosis, one must also include atopic dermatitis, seborrheic dermatitis, contact dermatitis, impetigo, syphilis, drug reaction, pityriasis rosea, histiocytosis X in the differential as they may appear very similar.

ED EVALUATION

The diagnosis is made or suspected based on the clinical presentation. A history of household contacts with similar symptoms makes scabies more likely. Skin scrapings can confirm the diagnosis by direct visualization of the mites by light microscopy and can be done by gently scraping a burrow with a scalpel and mineral oil and transferring to a slide.

CRITICAL INTERVENTIONS

- Permethrin cream 5% is the initial treatment for infants, young children, and pregnant or nursing women. The cream should be applied to the entire body including the head and left on for 8 to 14 hours before bathing. A second application may be needed 1 week later. Oral ivermectin given as a single dose at 200 μg/kg has been shown to be effective for treatment of scabies. It is not recommended in children under 15 kg or in pregnant or lactating women.
- Treatment of crusted scabies may require more aggressive treatment with daily topical permethrin 5% for 7 days in addition to oral ivermectin 200 μg/kg/dose on days 1, 2, 8, 9, and 15 (6,9,10).
- Pruritus may persist for days after successful treatment due to the inflammatory response to the dead mites and can be managed with antihistamines. Secondary infections if present should be treated with appropriate antibiotics.

DISPOSITION

Patients can be discharged to initiate treatment at home. Bedding and clothes should be washed in hot water or bagged for several days since the mites can only survive a few days away from the human host. Family members and close contacts should be treated at the same time. Affected individuals may return to work or school after treatment (8).

Common Pitfalls

- Failure to recognize or suspect the infestation especially in infants.
- Failure to apply the topical treatments as directed.
- Failure to recognize crusted scabies in immunocompromised patients.

PINWORMS (ENTEROBIUS VERMICULARIS)

CLINICAL PRESENTATION

Pinworms are the most common helminthic infection in the United States with prevalence estimates of up to 40 million people affected (11,12). Pinworm infections occur most frequently in preschool and school-aged children, infestations are uncommon under the age of 2 years. Infestation also occur in clusters within families and in institutionalized individuals. The eggs are transmitted via the fecal–oral route or by contamination of the hands. Sharing toys, bedding, clothing, toilet seats, and baths may promote spreading of the infection (13).

Once the eggs are ingested they hatch in the duodenum, mature and migrate to the cecum. The female pinworm migrates to the perineum at night and lays up to 10,000 eggs. Once the eggs are laid on the perineum the patient can auto infest or spread the infection to others. Scratching may collect eggs under the fingernails and lead to autoinfestation or transmission to others. The infestation usually lasts 4 to 6 weeks in the absence of autoinfestation (14).

Most infestations are asymptomatic. However patients often present to the ED with nocturnal pruritus ani. Prepubertal females may also present with pruritus vulvae and in some cases vulvovaginitis. Scratching of the rectum and vagina can lead to secondary bacterial infections. Occasionally worm burdens may be so high as to cause abdominal pain, nausea, or vomiting (13).

DIFFERENTIAL DIAGNOSIS

Any condition that leads to excoriation from scratching may be mistaken for pinworms. For example, poor hygiene, nonspecific vaginitis, UTI, sexual abuse, and streptococcal perianal infection may present with perianal abrasions, and excoriations similar to this seen with pinworm infestation.

ED EVALUATION

Diagnosis can be made by the direct visualization of the thread-like worms in the perineal region and are usually best seen at night about 2 to 3 hours after the patient has fallen asleep (14). Clear tape can be used to touch the perineal area in the morning to collect any eggs

and worms that may be present. The tape can then be viewed under a low power microscope to confirm the diagnosis (Fig. 283.4).

FIGURE 283.4 Pinworm eggs with clear tape. (From Koneman EW, Allen SD, Handa WM, et al. *Color Atlas and Textbook of Diagnostic Microbiology*. 5th ed. Philadelphia, PA: Lippincott; 1997. Fig. 20.3G.)

CRITICAL INTERVENTIONS

Pinworm infestation can be treated with albendazole 400 mg or pyrantel pamoate 11 mg/kg up to 1 gm (OTC). Both are given as a single dose and are repeated in 2 weeks with a cure rate greater than 90% (15). Oral antihistamines can be used to control pruritus.

DISPOSITION

Patients can be discharged to initiate treatment at home. Good hand and fingernail hygiene, cleaning of all bedding and showering in the morning should help prevent reinfestation. Household contacts should be treated as well.

Common Pitfalls

- Failure to treat household contacts.
- Failure to recognize pinworms as a possible cause of vaginitis in prepubertal females.

HEAD LICE

CLINICAL PRESENTATION

Pediculosis capitis (head lice) is an infestation caused by the head louse *Pediculus humanus capitis* and commonly affects children and adults. Head lice are not indicative of personal hygiene and can affect all socioeconomic classes. Head lice are less common in African Americans possibly due to the suspected ability of the louse to preferentially grasp certain shapes or widths of hair. Lice live close to the scalp and the female lays about 10 eggs/day usually within 4 cm of the scalp. The eggs or nits are firmly attached to the hair shafts and hatch within about 10 to 14 days (Fig. 283.5). As the louse sucks blood from the scalp an immunologic response occurs on the scalp which is responsible for the pruritis (6,16).

FIGURE 283.5 Head lice (nits). (Courtesy of Hans B. Kersten, MD.)

Lice have not been shown to carry communicable disease. Lice can be spread by direct contact and by shared clothing, combs, brushes, or bedding. Lice do not jump.

CLINICAL PRESENTATION

The patient with head lice may present with pruritus to the scalp, behind the ears or at the nape of the neck. Cervical and occipital lymphadenopathy may be present (16). The lice and nits are visible on inspection. Head lice may be asymptomatic and be found as an incidental finding. Secondary infections may be present.

DIFFERENTIAL DIAGNOSIS

Seborrheic dermatitis, tinea capitis, and folliculitis should be considered in making the diagnosis. Other types of lice infestations may occur such as body lice (*Pediculus humanus humanus*) and crab lice (*Pthirus pubis*), these may be differentiated by their morphology (see Fig. 283.6).

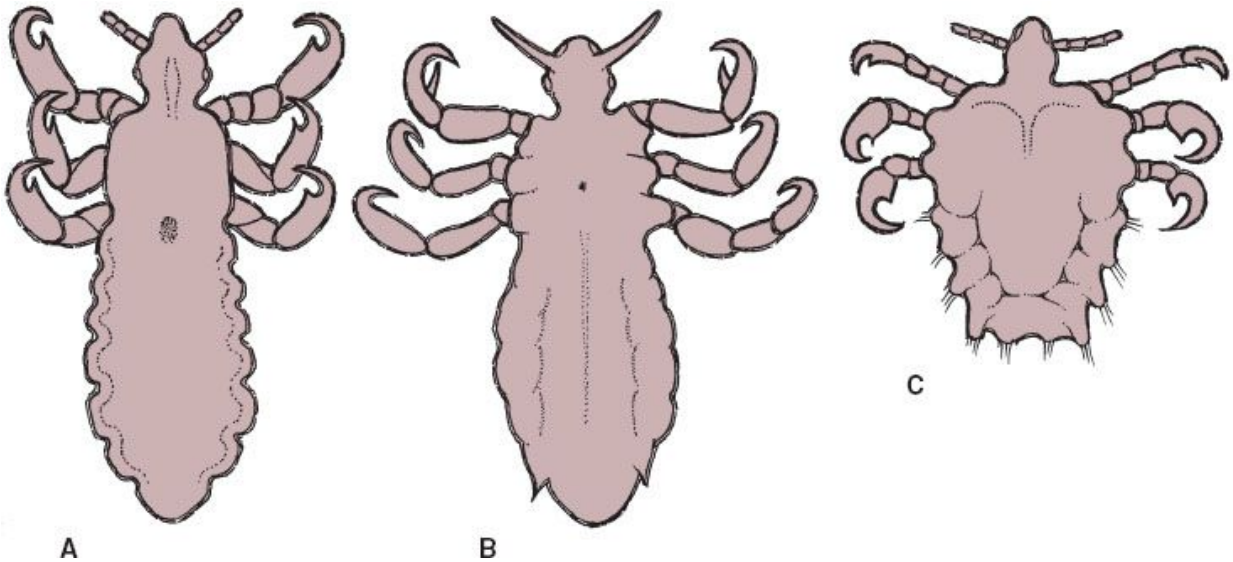

FIGURE 283.6 Common lice of humans; **(A)** head louse (*Pediculus humanus capitis*), **(B)** body louse (*Pediculus humanus humanus*), **(C)** public louse (*Pthirus pubis*). (From Stedman's Medical Dictionary. 28th ed. Philadelphia, PA: Lippincott Williams & Wilkins.)

ED EVALUATION

Diagnosis is made by visualization of nits and live lice. Presence of nits alone does not diagnose an active infestation (8). Lice fluoresce a pale blue under the woods lamp (6).

CRITICAL INTERVENTIONS

- Several treatments are effective and available. See Tables 283.1 and 283.2 (5,6,8,16).
- The effectiveness of head lice treatment by suffocation with occlusive agents such as mayonnaise, peanut butter, petroleum jelly, oil, or butter has not been adequately studied. Shaving hair has not been studied as a treatment to eradicate head lice.
- Oral antihistamines can be used for the pruritus.
- Head lice and eggs are killed by exposure to temperatures achieved by hot water washers and hot air dryers.

TABLE 283.1
Topical Treatments

Topical	Age	Dose	Consideration
Permethrin 1% lotion (Nix)	>2 mos	Apply for 10 min	Kills live lice only Reapply in 1 wk if live lice seen
Pyrethrins (RID, Pronto, TripleX) OTC	>2 yrs	Apply for 10 min	Kills live lice only Reapply in 1 wk
Malathion	>6 yrs	Apply for 8–12 hrs	Kills lice and partially ovicidal Reapply in 1 wk if live lice seen Flammable
Benzyl alcohol 5% lotion	>6 mos	Apply for 10 min	Kills lice and partially ovicidal Reapply in 9 d if live lice seen
Ivermectin 0.5% lotion	>6 mos	Apply for 10 min	Single application
Spinosad suspension 0.9%	>4 yrs	Apply for 10 min	Contains benzyl alcohol and spinosad Reapply in 7 d if live lice seen
Lindane 1% shampoo	No longer recommended for infants or children	Potentially neurotoxic if swallowed	Kills lice and ovicidal

TABLE 283.2
Oral Treatment for Pediculosis

Oral	Age	Dose	Considerations
Ivermectin 200–400 µg/kg	>15 kg	One-time dose	Usually reserved for infestations resistant to topical therapy May need second dose in 1 wk
Trimethoprim-sulfamethoxazole 10 mg/kg/d TMP-divided BID	>2 mos	10-d course	Used in combination with topical permethrin for resistant infestations

DISPOSITION

Patients can be discharged and treatment initiated at home. Surviving nits and lice are killed by exposure for greater than 5 minutes to temperatures of greater than 53.5°C, therefore clothing worn by the infested person over the 2 to 3 days before treatment can be washed. Extensive housecleaning is not necessary since lice cannot survive for more than 1 to 2 days if unable to feed (5,17).

Common Pitfalls

- Assumption that presence of lice is a sign of poor hygiene.
- Overestimation of lice's ability to be transferred from person to person.
- Failure to repeat treatment if needed.

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CHAPTER 284

Immunizations

Sandra L. Grossman and Marla J. Friedman

Immunizations have been instrumental in reducing the incidence, morbidity, and mortality of preventable diseases throughout the world. Childhood immunization has been a cornerstone of pediatric health care since the first American Academy of Pediatrics (AAP) policy statement on immunization practices was released in 1977. Despite recommendations of universal immunization, only 77% of children in the United States aged 19 to 35 months received their routine immunization series in 2011 (1,2). Adolescent vaccination coverage, however, has increased, with Tdap coverage reaching the *Healthy People 2020* target of 80% (3). Most concerning are children living below the poverty level, whose immunization rates are reported to be as low as 64% (4). Although most routine immunizations are administered in a primary health care setting, many view an emergency department (ED) visit by an underimmunized child as an opportunity to vaccinate.

CLINICAL PRESENTATION

Recent Recommendations and Controversies

The schedule in Table 284.1 represents the most recent recommendations from the AAP, the Centers for Disease Control and Prevention (CDC), and the American Academy of Family Physicians (AAFP) for routine childhood immunizations. This schedule is reviewed and updated annually to include new vaccines and revised recommendations. Combination vaccines and their approved uses are presented in Table 284.2. Interim information on vaccines,

schedules, and adverse events can be found on the AAP website (www.aap.org), the AAFP website (www.aafp.org), and the CDC website (http://www.cdc.gov/vaccines). The national immunization hotline is available to answer immunization-related questions from both health care personnel and the public (1–800–232–4636).

TABLE 284.1
Childhood Immunization Schedule—United States, 2013

Birth	1 mo	2 mos	4 mos	6 mos	12 mos	15 mos	18 mos	24 mos	4–6 yrs	11–12 yrs	15–18 yrs
Hepatitis B	HepB 1[a]										
		HepB 2				HepB 3			catch-up series		
DTaP		DTaP	DTaP	DTaP		DTaP			DTaP	Tdap	catch-up series
Hib		Hib	Hib	Hib[b]		Hib					
Polio		IPV	IPV			IPV			IPV	catch-up series	
MMR						MMR			MMR	catch-up series	
Varicella					Varicella				catch-up series		
Pneumococcal (PCV13)		PCV	PCV	PCV		PCV			high-risk groups[c]		
Influenza					Influenza (Annually)						
Rotavirus		Rota	Rota	Rota							
Hepatitis A	Hep A (2 doses)						high-risk groups[d]				
Meningococcal	high-risk conditions					MCV4					
HPV	HPV								catch-up series		

Children 9 mos–10 yrs of age with anatomic/functional asplenia, terminal complement deficiencies, travel to or residence in areas of epidemic meningococcal disease.
[a]If mother is Hepatitis B surface antigen negative.
[b]Not required if vaccine containing PRP-OMP (Comvax, PedvaxHIB) given at 2 and 4 mos.
[c]High-risk groups: Sickle cell disease, HIV, asplenia, diabetes, heart/pulmonary disease.
[d]High-risk groups: Chronic liver disease, clotting disorders, travel to developing countries, illicit drug use, homosexual adolescent males.
DTaP: Diphtheria, Tetanus, acellular Pertussis; Tdap: Tetanus and diphtheria toxoids, acellular pertussis; Hib: *Haemophilus influenzae type b;* MMR: Measles, Mumps, Rubella; HPV: Human Papillomavirus.
Adapted from recommendations of the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, and the American Academy of Family Physicians.

TABLE 284.2
Combination Vaccines

	Approved Use	Notes
Pediarix (DTaP, IPV, hepatitis B)	Ages 6 wk–6 yr	Only for three-dose primary series Do not use for booster doses Given at 2, 4, 6 mos
MMRV (ProQuad) (measles, mumps, rubella, varicella)	12 mo–12 yr	Two doses ≥3 mo apart
Comvax (Hib, hepatitis B)	6 wk–71 mo born to HbsAg mothers	Three doses; given at 2, 4, and 12–15 mo
Kinrix (DTaP-IPV)	4–6 yr	Booster for fifth dose of DTaP, fourth dose of IPV
Twinrix (hepatitis A, hepatitis B)	Age ≥18 yr	Three doses on a 0-, 1-, and 6-mo schedule
Pentacel (DTaP-IPV/Hib)	6 wk–4 yr	Four doses; given at 2, 4, 6, and 15–18 mo

DTaP, diphtheria, tetanus, acellular pertussis; IPV, inactivated poliovirus vaccine; Hib, *Haemophilus influenzae type b*.

There has been much controversy regarding the safety of immunization, particularly the development of neurologic sequelae after certain vaccinations. The questionable association between measles–mumps–rubella (MMR) vaccine and autism has received much press and has heightened parental anxiety toward vaccination. Both the Institute of Medicine and an AAP panel of experts have independently concluded that the increasing diagnoses of autism *cannot* be attributed to the MMR vaccine. Several comprehensive reviews have also concluded that autism is not linked to MMR (5–7). Moreover, the 1998 study linking the MMR vaccine to autism has since been retracted (8–12).

No causative association was found between diphtheria–tetanus–pertussis (DTP) vaccine and infantile spasms, sudden infant death syndrome (SIDS), or permanent neurologic injury (13). The Immunization Safety Review Committee has concluded that the evidence does not support a causal relationship between thimerosal-containing vaccines and autism or other neurodevelopmental disorders (14–16). The Committee also stated that the benefits of vaccination are proven and the widespread rejection of vaccines

would lead to an increased incidence of serious infectious diseases. These and other committee reports regarding vaccine safety can be accessed on the Institute for Vaccine Safety website (http://www.vaccinesafety.edu). Health care providers can receive the most up-to-date information electronically by signing up at www.immunize.org/subscribe and www.cdc.gov/mmwr/mmwrsubscribe.html.

There are many misconceptions about contraindications to vaccine administration. However, a few true contraindications do exist. Table 284.3 reviews common myths that should not be misconstrued as contraindications to vaccination. Several of the recommended vaccinations have precautions associated with their administration. In these cases, the physician must decide whether the benefit of the immunization outweighs the risk of complications. The contraindications and precautions associated with each vaccine are discussed in the following sections.

TABLE 284.3
Not Contraindications to Immunization

Mild local reaction (soreness, redness, swelling) to previous vaccination
Fever after previous vaccine dose
Mild acute illness with or without fever
Current antimicrobial therapy
Prematurity (infants should receive same dosage and schedule as full-term infants)
Recent exposure to infectious disease
Nonimmunized household contact
Immunocompromised or pregnant household contact
HIV infection (unless low CD4+ counts)

Diphtheria–Tetanus–Pertussis

Acellular pertussis vaccine (DTaP) has been recommended for primary immunization in the United States since 1997, as it causes fewer local and systemic reactions than the whole-cell pertussis vaccine (DTP) (13). DTaP should be given at ages 2 months, 4 months, 6 months, 15 to 18 months, and 4 to 6 years, with a booster

dose at 11 to 12 years. If the fourth dose of DTaP is delayed until after the fourth birthday, the fifth dose is not recommended.

The most common reactions to DTaP vaccine include mild local reactions (redness, induration, and tenderness at the injection site), and constitutional symptoms (fever $< 40.5^{\circ}C$, fussiness, drowsiness, crying). These manifestations usually present within several hours of vaccination and resolve spontaneously without sequelae. Seizures were fairly common after vaccination with whole-cell vaccine but occur much less commonly after administration of acellular DTaP (13). When seizures do occur, they are brief, generalized, and self-limited. The vaccine-associated seizures do *not* increase the child's risk of developing epileptic seizures or other neurologic sequelae.

Haemophilus influenzae type b

The Hib vaccines are well tolerated, with mild local skin reactions being the most common adverse event reported. Anaphylaxis after a prior dose of the vaccine or any of its components is a contraindication, and moderate or severe acute illness is a precaution to vaccination.

Hepatitis A

Hepatitis A vaccines (containing inactivated virus) first became available in the United States in 1995. Hepatitis A vaccination is recommended for all children 12 to 23 months old, given as a two-dose series at least 6 months apart. Reports estimate that protective levels of antibody after vaccination could be present for $\leq$14 to 20 years in children (13). Soreness at the injection site is the most frequently reported adverse effect after vaccination.

Hepatitis B

Recombinant hepatitis B vaccines contain hepatitis B surface antigen protein. The various vaccine products available in the United States differ in the concentration of protein, but all are 90% to 95% effective in preventing hepatitis B virus infection. Long-term studies indicate that vaccine protection lasts for at least 15 years, and no

routine booster doses are recommended at this time for children and adults with normal immune status. Universal immunization beginning at birth is now recommended. The vaccines are well tolerated, with pain at the injection site being the most common adverse effect.

Influenza

All currently available influenza vaccines are trivalent and thus contain three strains of influenza virus (two types of influenza A virus and one type of influenza B virus). One or two strains are changed yearly in anticipation of the most prevalent disease-causing strains circulating in the United States at that time. There are two types of influenza vaccines currently available. The *trivalent inactivated vaccine* (TIV), given intramuscularly or intradermally, is the more widely used. The most common side effect is soreness at the vaccination site. Fever, myalgia, malaise, and other systemic symptoms occur more commonly in those receiving the vaccination for the first time. The intradermal formulation of TIV is licensed for use in those aged 18 to 64 years. The most common adverse reactions are induration, redness, swelling, pain, and itching at the site of administration. Headache, myalgia, and malaise may also occur (13). The *live attenuated influenza vaccine* is an intranasal mist (FluMist) approved only for healthy nonpregnant persons of ages 2 to 49 years. The most common adverse effect is rhinorrhea; however, headache, emesis, fever, and myalgias may also occur. Quadrivalent live and inactivated influenza vaccines are both anticipated to be available during the 2013 to 2014 influenza season (18,19).

Vaccine protection is variable, ranging from 50% to 95% depending on the match of vaccine strain to the circulating virus strain. Yearly influenza vaccination is currently recommended for all persons aged $\leq$6 months.

Influenza vaccination with TIV has been associated with a slight increase in cases of Guillain–Barré syndrome (GBS) in adults. Although this has not been confirmed in children, development of GBS within 6 weeks of immunization with TIV should be considered a precaution to future vaccination.

**Recommendations for the influenza vaccine are constantly being updated. Please refer to http://www.cdc.gov/flu/professionals/acip/ for the most up-to-date recommendations from the Advisory Committee on Immunization Practices (ACIP).

Measles–Mumps–Rubella

There has been a dramatic decline in the incidence of measles and its complications since licensing of the first vaccine in 1963. Most recipients are immune after receiving a single dose of the live-attenuated vaccine after 12 months of age, but universal immunity is almost always conferred after two doses (13).

There was a resurgence of measles in the United States between 1989 and 1991 because of decreasing immunization rates in preschool-age children. With the renewed efforts for universal vaccination, the incidence of measles in the United States is once again low, with most cases now being seen only in immigrants from countries where measles disease is endemic.

Children may develop a transient rash or fever $\leq 39^{\circ}C$ at 6 to 12 days after vaccination with MMR or MMRV. The fever usually lasts between 1 and 5 days and presents with no other symptoms. Febrile seizures 5 to 12 days after immunization may also occur. Local hypersensitivity reactions to MMR/MMRV vaccine may occur, but anaphylaxis is rare. Transient thrombocytopenia has been reported within 2 months of vaccination and should be considered a precaution to future vaccination.

Meningococcus

Four meningococcal vaccines are currently licensed and available in the United States, the newest of which is combined with Hib and approved as a four-dose series for use in children 6 weeks through 18 months of age. The most frequent reaction to vaccination is pain and redness at the injection site. Previous anaphylaxis to the vaccine or to any of its components including diphtheria or tetanus toxoid is a contraindication to receiving further doses.

Pneumococcus

There are currently two pneumococcal vaccines licensed for use in children in the United States; PCV13 (Prevnar13) and PPSV23—(Pneumovax23)284. Mild local reactions and fever within the first 2 days after injection are the most common adverse effects reported (Table 284.4).

TABLE 284.4
Children at Risk for Invasive Pneumococcal Infections

High risk
Sickle cell disease and/or asplenia
Immunodeficiency
Chronic renal, cardiac, or pulmonary disease
Diabetes
Cochlear implants
Moderate risk
Children younger than 2 yrs of age
Children 36–59 mo in out-of-home day care
African American or American Indian children ages 36–59 mo
Low socioeconomic status
Homelessness
Chronic exposure to tobacco smoke
History of recurrent otitis media or tympanostomy tubes

Polio

Disease due to wild poliovirus has virtually been eradicated in the United States since the implementation of universal vaccination in 1979. After that, several cases of oral vaccine–associated paralytic polio (VAPP) had been reported in the United States annually. An inactivated poliovirus vaccine (IPV), which does not carry a risk of paralysis, was introduced into the routine immunization schedule in 2000. The oral polio vaccine is no longer available in the United States. IPV contains poliovirus inactivated with formaldehyde. Immunity after vaccination is expected to be lifelong. IPV is well tolerated, with no serious adverse effects reported.

Rotavirus

Two rotavirus vaccines are licensed for use among infants in the United States. A live, oral, pentavalent rotavirus vaccine (RV-5-RotaTeq) was licensed for use in the United States in 2006.

A rhesus-based tetravalent rotavirus vaccine (RotaShield) was used for routine vaccination of infants in 1998, but it was withdrawn from the market within 1 year due to its association with intussusception. Accordingly, there has been public anxiety regarding the use of current rotavirus vaccines. Some studies performed outside the United States have detected a slight increased risk of intussusception shortly after the first dose of rotavirus vaccine, but the level of risk is substantially lower than after immunization with RotaShield (13).

The most frequently reported adverse effects after vaccination are fever, diarrhea, vomiting, rhinorrhea, cough, and ear infection.

Varicella

The live-attenuated varicella vaccine was introduced in the United States in 1995 for use in patients older than 1 year who have not had varicella disease. Quadrivalent measles–mumps–rubella–varicella (MMRV) vaccine is licensed for use in healthy children 12 months to 12 years of age. The vaccines are more than 95% protective against moderate-to-severe disease. Both vaccines are given subcutaneously in two doses. The most common adverse event after vaccination is a mild local reaction with pain, redness, and swelling at the injection site. A small percentage of children may develop a mild varicella-like illness with the development of fewer lesions and lower rates of fever than nonimmunized children with varicella disease. Children who develop a postvaccination rash may rarely transmit the virus to others. There is a slightly increased risk of febrile seizures following the first dose of MMRV compared with MMR and monovalent varicella.

ED EVALUATION

The risks of natural disease in nonimmunized children should be discussed with parents. They should further be informed of the risks

and benefits associated with preventive immunization. The National Childhood Vaccine Injury Act (NCVIA) of 1986 included strict legal requirements for administering immunizations. A vaccine information statement (VIS) detailing the risks and benefits of each vaccination must be provided to the parent prior to immunization. Copies of current VISs can be obtained from the CDC, AAP, vaccine manufacturers, local health departments, or by calling the national immunization hotline. The NCVIA further requires health care personnel record in the patient's medical record the vaccine manufacturer, lot number, and date of administration, and the name and address of the person giving the vaccine. Although current VISs do not require a parent's signature, both the CDC and the AAP recommend a note be made in the patient's chart indicating the VIS was provided and discussed with the legal guardian. The AAP further recommends the site and route of administration and the expiration date of the vaccine be documented as well (13). If vaccinations are administered in the ED, emergency physicians should notify primary care providers of the immunizations given either by facsimile or by inserting a page into the child's immunization book.

Although all vaccines are considered safe and effective, some children will experience adverse reactions. Most reactions are minor and inconsequential, but some may rarely be serious and life-threatening. The most common events associated with vaccination are mild febrile and local reactions. Sterile abscesses may occur at the site of an intramuscular injection. Nerve and vascular injuries are uncommon. Serious adverse effects, such as encephalopathy and permanent neurologic damage, are rarely vaccine-associated events. The cause of a neurologic event that occurs temporally related to vaccination is often difficult to ascertain, as immunizations are given during a time when most neurologic problems first present.

Unexpected adverse events occurring soon after immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Several similar events documented after administration of a certain vaccine can be used in conjunction to determine causation between immunization and adverse reaction. There is no time limit for reporting an adverse event. Disease that occurs in an immunized

child should also be reported to the VAERS. Reports to the VAERS can be submitted electronically (http://vaers.hhs.gov/index). The occurrence of a vaccine-preventable disease should be reported to the local or state health department.

The National Vaccine Injury Compensation Program is a no-fault system that provides compensation to people who have experienced severe or fatal vaccine complications. Claims must be filed within 36 months of the appearance of the first symptom after vaccination. All vaccines that are recommended as part of the routine childhood immunization schedule are included in the compensation program (13).

CRITICAL INTERVENTIONS

- Be aware of each child's immunization status. Do not miss an opportunity to vaccinate.
- Know contraindications and precautions to vaccinations
- Document vaccine side effects; ask about prior vaccine reactions
- Decide whether benefits of immunization outweigh risks of complications
- Report unexpected postvaccination adverse events to VAERS

DISPOSITION

When a severe or unexpected immunization reaction is suspected, consultation with a pediatrician, neurologist, or infectious disease expert should be obtained. Severe unexpected vaccine complications must be reported to the VAERS. Children with significant neurologic findings, anaphylaxis, or other serious vaccine complications should be hospitalized. Transfer to a tertiary pediatric facility should be considered if further subspecialty consultation or intensive care is needed. The child's primary physician should be notified of the possible immunization reaction.

Common Pitfalls

- Minor febrile illness is not a contraindication to routine immunization.

- Current antimicrobial therapy is not a contraindication to vaccination.
- HIV infection is not an absolute contraindication to live vaccination.
- Mild local and febrile reactions are not contraindications to further doses of vaccine.
- Do not automatically attribute fever occurring after immunization to vaccination. Thoroughly examine the child for a treatable focus of infection.
- Allergic reactions after vaccination are rare; always consider other causes.

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CHAPTER 285 Nursemaid's Elbow

Evan J. Weiner

CLINICAL PRESENTATION

Radial head subluxation, also known as *nursemaid's elbow,* is a common orthopedic injury occurring in early childhood. The peak incidence is in the toddler years; however, the condition also occurs in the first year of life and has been described as late as age 6 (1–3). The left arm is more commonly affected, as are females (1,3–5).

The most commonly described mechanism of injury is that of axial traction on the extended arm usually occurring when an adult pulls up or swings a child by the arm (2–4,6,7). However, a history of this pulling mechanism may not be present in up to half the cases (2,3,7). Occasionally the history of a fall may be provided (2).

Children with nursemaid's elbow present because of refusal to use the affected arm and will be noted to hold the arm at their side with the forearm in a pronated position. Because of their young age, they are often unable to localize their pain. The examiner should have difficulty detecting any point of tenderness but will note that the child resists and has pain with any movement at the elbow joint. It is helpful to use good distraction tools when examining these young anxious children. It is important to note that patients with nursemaid's elbow do not have any swelling, warmth, or ecchymosis. If these findings are present, radial head subluxation is unlikely to be the cause.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of decreased arm use in a child includes, but is not limited to, fractures of the clavicle, humerus or forearm, septic joint, osteomyelitis, and brachial plexus injury. The presence of fever, swelling, bruising, or other skin changes involving the affected arm is an indication for radiography and possible further laboratory studies.

ED EVALUATION

The history elicited from the caregiver should include the timing and mechanism of injury, the presence of fever, and any prior episodes of a similar problem with the arm. Any history of chronic medical conditions predisposing the child to bone or joint disease should also be sought (e.g., hemophilia, sickle cell anemia, osteogenesis imperfecta, immune disorders), as this may indicate another more likely cause.

During examination of the upper extremity, it is often helpful to have the child placed on the parent's lap in a sitting position facing the examiner. Before touching the child, produce a toy or colorful object to see whether the child will reach for it with each arm. Visually inspect the arm for any swelling, skin changes, or signs of trauma. It may be helpful to compare one arm to the other. Begin with palpation of the bones, beginning with the clavicle and working downward toward the hand, noting any areas of particular tenderness or warmth. Assess distal pulses and perfusion. Sensation and motor function should also be assessed if the child is able to cooperate with a neurosensory examination.

Radiographs should be performed prior to reduction attempts in cases in which aspects of the history (e.g., witnessed direct trauma to the upper extremity) and examination findings (e.g., swelling, bruising, warmth over the joint) suggest that infection or fracture are more likely than radial head subluxation. Patients who present with a history and examination findings consistent with nursemaid's elbow need not undergo radiography prior to reduction attempts. Not uncommonly, a child with a nursemaid's elbow who is sent for

radiographs of the arm will undergo an incidental reduction in the radiology suite during the repositioning of the arm for the study.

KEY TESTING

Although radiographs are not needed in classic presentations of nursemaid's elbow, radiographs should be performed in patients with atypical examination findings (e.g., swelling, ecchymosis, redness, fever, point tenderness). These radiographs should include three views of the elbow, including a good quality 90-degree lateral view. In general, radiographs should also include a joint proximal and distal to the injury.

- Three-view elbow radiographs, including 90-degree lateral
- Radiographs of a joint above and below injury (e.g., two-view forearm and two-view humerus)

ED MANAGEMENT

There are two different methods commonly used for reducing a nursemaid's elbow. Prospective studies comparing the two methods reveal that the hyperpronation technique has a significantly higher initial success rate than the supination/flexion technique (1,4). Furthermore, there is growing evidence that the hyperpronation method is less painful for the patient (1,8). Both techniques are described here.

Hyperpronation Technique

The hyperpronation method involves the examiner cradling the child's elbow with one hand (with thumb or forefingers overlying the radial head) while the examiner's other hand is used to hyperpronate the child's forearm by holding and turning the child's hand into a hyperpronated position (Fig. 285.1). With successful reduction, a "click" will be felt by the examiner. The child usually experiences some momentary discomfort during the procedure.

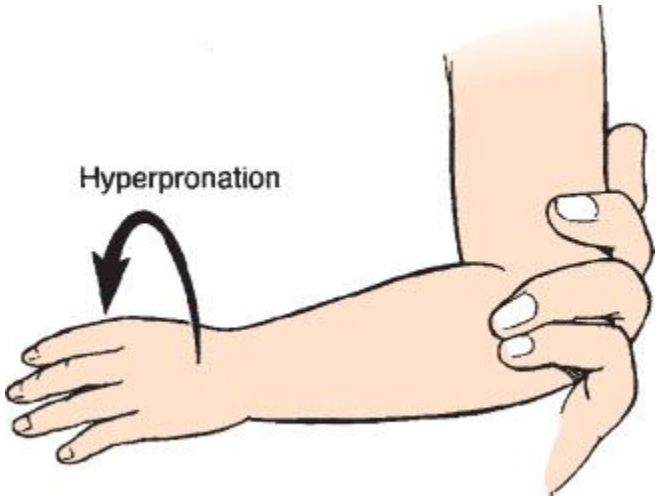

FIGURE 285.1 Hyperpronation technique. Pronation at the wrist. (From Macias CG, Bothner J, Wiebe R. A comparison of supination/flexion to hyperpronation in the reduction of radial head subluxations. *Pediatrics.* 1998;102:e10, with permission.)

Supination/Flexion Technique

The supination/flexion technique involves the examiner cradling the child's elbow with one hand (again with thumb or forefingers over the radial head) and with the other hand supinating the patient's hand completely until the palm faces the ceiling. The examiner then fully flexes the child's elbow by bringing the supinated hand up toward the shoulder (Fig. 285.2). With successful reduction, a "click" will often be felt. The child experiences momentary discomfort at the time of the procedure.

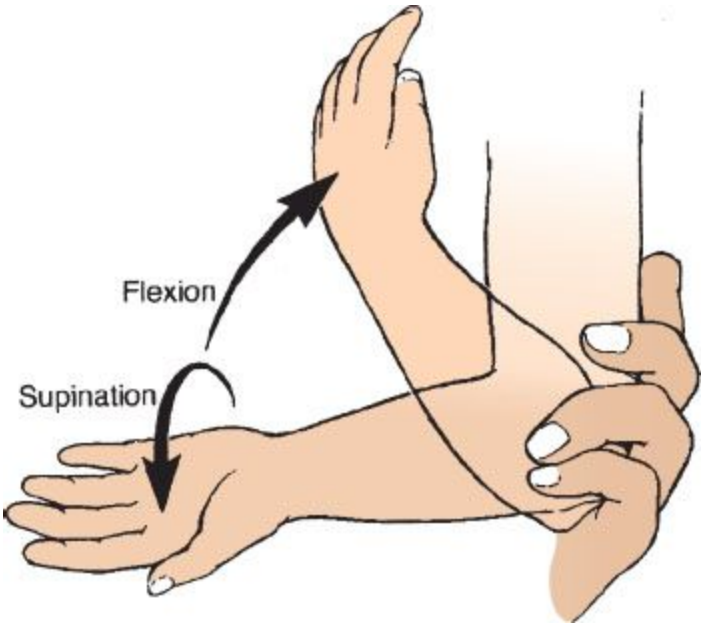

FIGURE 285.2 Supination/flexion technique. Supination at the wrist followed by flexion at the elbow. (From Macias CG, Bothner J, Wiebe R. A comparison of supination/flexion to hyperpronation in the reduction of radial head subluxations. *Pediatrics*. 1998;102:e10, with permission.)

Regardless of which reduction technique is used, it may be 15 minutes or longer before the child begins to use the arm normally again. Again, the examiner should see if the child can reach for a toy or similar object. A failed reduction attempt should be followed by a second attempt using either the same or alternate technique. This second attempt often meets with success (4). After two or three failed reduction attempts, radiographs of the upper extremity should be obtained to help exclude fracture or other pathology as the cause of the child's symptoms.

DISPOSITION

The child with a successfully reduced nursemaid's elbow does not need specific follow-up with the primary caregiver unless symptoms (pain or disuse of the arm) return. Parents and caregivers should be cautioned about refraining from any activity that involves pulling

on the child's arm, since the condition recurs in about one-fourth of children who have experienced at least one episode (5).

The patient who does not respond to reduction attempts will require splinting of the arm with a posterior long-arm splint and orthopedic consultation.

Common Pitfalls

- Attempting a nursemaid reduction in any child who has swelling, ecchymosis, or deformity of the extremity, as these findings are not consistent with a nursemaid's elbow and manipulation could result in further injury and unnecessary pain.
- Assuming that a patient cannot have a nursemaid's elbow simply because there is not a clear history of a pull on the child's arm; this history is lacking in a large percentage of cases (2).

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CHAPTER 286
Renal Emergencies

Madeline Matar Joseph and Carmen J. Martinez

Renal emergencies may present with a wide spectrum of acuity and may be the first identified manifestation of significant underlying systemic disease. This chapter focuses on hematuria and two important renal diseases, glomerulonephritis (GN) and nephrotic syndrome.

HEMATURIA AND GLOMERULONEPHRITIS

CLINICAL PRESENTATION

Hematuria is the presence of blood in the urine, which can be macroscopic (visible to the naked eye) or microscopic. Microscopic hematuria represents one of the most frequently encountered genitourinary abnormalities in children. There are many causes of hematuria (1). It is important to first determine the source of bleeding in the presenting child. In infants, blood on the diaper can originate from the vagina or rectum and be confused with hematuria. The “red diaper syndrome” in infants has two causes: One is a group of healthy infants whose soiled diapers develop a red color after 24 to 36 hours, which is attributed to *Serratia marcescens;* the second is due to urate crystals. The former is rarely seen, owing to the popularity of disposable diapers. In the menstruating girl, vaginal bleeding can be confused with urinary blood. It is often necessary to obtain a catheterized urine specimen to determine the source of the bleeding. Up to 50% of cases of hematuria in children (more so than adults) are glomerular in origin. Glomerular bleeding tends to be associated with cola-colored urine (30% of patients), whereas lower

tract bleeding colors the urine red or pink. The passage of blood clots in the urine usually points to the bladder or urethra as the source of bleeding.

Acute glomerulonephritis (AGN) results from immunologic effects on the glomerular tissue and is divided into three broad categories: (1) Postinfectious, (2) intrinsic renal disease, and (3) systemic disease (Table 286.1). Poststreptococcal acute glomerulonephritis (PSAGN) is one of the most common causes. Poststreptococcal GN is most common in children aged 5 to 12 years and uncommon before the age of 3 years. PSAGN is known to follow infections of the skin (part of an epidemic, summer time, particularly in the southern regions of the United States accounting for two-thirds of cases) or pharyngitis with certain nephrogenic strains of streptococci, which are virtually always group A streptococci (2,3). The incidence of clinically detectable GN during an epidemic is up to 10% of children with pharyngitis and 25% of children with impetigo. One study reported a change in the epidemiology of PSAGN and found that pharyngitis has replaced impetigo as the predominant cause of PSAGN (4).

TABLE 286.1
Causes of Glomerulonephritis

Postinfectious	Renal Systemic
Streptococcus	*Membranoproliferative GN*
	Wegener granulomatosis
GAS	Type I and II
	Hypersensitivity vasculitis
Other bacteria:	*IgA nephropathy* (Berger disease)
	Cryoglobulinemia
Staphylococcus, mycobacteria, salmonella	*Idiopathic rapidly progressive GN*
	Systemic lupus erythematosus
Viral: CMV, Coxsackie, EBV, hepatitis	Type I: Antiglomerular basement membrane
	Polyarteritis nodosa rubella, mumps disease
Fungal:	Type II: Mediated by immune complexes
	Henoch–Schönlein purpura
Coccidioides immitis	Type III: Antineutrophil cytoplasmic antibodies
	Goodpasture syndrome
Parasite: Plasmodium spp, Schistosoma mansoni, Toxoplasma gondii, filariasis, trichinosis, trypanosomes	

CMV, cytomegalovirus; EBV, Epstein–Barr virus.

Characteristically, there is a latent period between the onset of the streptococcal infection and the onset of nephritis that ranges from 8 to 14 days for pharyngitis and 14 to 21 days for skin infections (2). The onset of GN less than a week after streptococcal infection is highly suggestive of pre-existing renal disease (5). Of note, hypertension under these circumstances usually does not require antihypertensive treatment and resolves with treatment of associated fluid retention.Table 286.2 includes the clinical manifestations in PSAGN in order of frequency.

TABLE 286.2
Clinical Symptoms of Glomerulonephritis

Most Frequent	Less Frequent
Edema (periorbital most common)	*Urinary tract syndrome* (Flank pain, dysuria, frequency)
Hematuria (Microscopic to gross)	*Circulatory congestion* (Mild CHF, pulmonary edema
Hypertension (Mild–moderate) in 75% of patients	*Hypertensive encephalopathy*
Oliguria	*Acute renal failure*
Nonspecific systemic symptoms (Anorexia, nausea, fever, malaise, abdominal pain)	

CHF, congestive heart failure.

Dysuria, frequency, or abdominal pain suggests a urinary tract infection (UTI). A history of recent trauma, strenuous exercise, menstruation, or bladder catheterization or of masturbation, excessive bicycle riding, or urethral foreign body insertions (particularly in adolescents) may account for transient hematuria and exclude the need for further workup. A recent or earlier history of renal colic or passage of a stone in the urine and a family history of hypercalciuria and renal stones should be elicited. Associated symptoms such as hemoptysis (Goodpasture syndrome) or the triad of sinusitis, AGN, and pulmonary infiltrates (Wegener granulomatosis) could aid in the diagnosis. History should include the use of antibiotics, chemotherapy, radiation for malignancies, exposure to tuberculosis, and the use of over-the-counter medications, which may cause interstitial nephritis. Umbilical catheterization in the neonatal period can cause renal vein or artery thrombosis, which may result in hematuria (6). A family history of hearing deficits and renal failure can lead to the diagnosis of Alport syndrome. Other diseases that carry a genetic origin include systemic lupus erythematosus (SLE), sickle cell anemia, hemophilia, and other coagulation factor deficiencies. Nephrolithiasis and IgA nephropathy also have a familial association.

Acute complications may arise from hypertension secondary to acute renal dysfunction. Hypertension is seen in 60% of such patients and is associated with hypertensive encephalopathy in 10% of cases. Although the neurologic sequelae are often reversible with

appropriate management, severe prolonged hypertension can lead to intracranial bleeding. Other potential complications include heart failure, hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, seizures, and uremia. Acute renal failure may require dialysis with the acute phase generally resolving within 6 to 8 weeks (2). Although urinary protein excretion and hypertension usually normalize by 4 to 6 weeks after onset, persistent microscopic hematuria can persist for 1 to 2 years after the initial presentation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for childhood hematuria can be remembered by using the alphabetical sequence A through I (see Table 286.3) (1).

TABLE 286.3
The Differential Diagnosis of Childhood Hematuria

***A*natomy**/vascular (renal cysts, arteriovenous malformations, obstruction with hydronephrosis)

***B*oulders** (renal stones, hypercalciuria, and hyperuricosuria)

***C*ancer** (Wilms tumor or adenocarcinoma and infiltration of the kidney by leukemia or solid tumors)

***D*rugs/Dehydration** (over-the-counter or illicit drugs, methicillin, cyclophosphamide, anticoagulants)

***E*xercise**-induced hematuria

***F*oreign body, familial** (Alport) or **factitious**

***G*lomerulonephritis (GN):** Primary: Poststreptococcal GN, IgA nephropathy (Berger Disease), membranoproliferative GN. Secondary GN: HSP, HUS, SLE

***H*ematology** (hemoglobinopathy, coagulopathy)

***I*nfection** (cystitis caused by adenovirus, tuberculosis, schistosomiasis in patients with recent travel to the Middle East or Africa)

ED EVALUATION

In the absence of gross hematuria, the primary tool for hematuria screening is a urine dipstick. Blood +1 and greater is considered positive. The dipsticks used for detection of blood in the urine are very sensitive in detecting red blood cells (RBCs) and minute amounts of free hemoglobin and myoglobin. All positive dipstick

screens should be confirmed by a microscopic examination of the urine to confirm the presence of RBCs. Causes of false-positive dipstick reactions include myoglobinuria, (rhabdomyolysis); hemoglobinuria (seen in conditions causing hemolysis); oxidizing contaminants, such as bacterial peroxidases from a UTI; delay in reading the dipstick; and interfering compounds, such as beets or aniline dyes. A false-negative dipstick result can occur in urine with high specific gravity and in urine containing large amounts of reducing substances such as ascorbic acid. Screening dipstick urinalyses are still being performed on school-aged children despite the fact that the American Academy of Pediatrics is no longer recommending it for school-aged children to detect chronic kidney diseases (7,8).

The physical examination of the patient with hematuria is largely nonspecific; however, an accurate blood pressure is essential. The presence of elevated blood pressure should alert the clinicians to the possibility of a more severe underlying condition. The height and weight of the child should also be plotted carefully to assess for failure to thrive associated with long-standing acidosis or chronic renal insufficiency. A funduscopic examination should be performed, looking for evidence of long-standing hypertension or lenticonus as seen in Alport syndrome. In children, periorbital edema is the most common location of edema associated with glomerular disease. The chest should also be examined for signs of fluid overload. Costovertebral angle tenderness may indicate a UTI or recent trauma can be detected by findings of flank bruises and pain. Examining the abdomen for masses is critical for the identification of malignancies (Wilms tumor), polycystic kidneys or hydronephrosis. The examination of the skin and joints can give evidence of arthralgias and pallor or rashes. This may be significant in diseases such as hemoglobinopathies (leukemia, Henoch–Schönlein purpura, petechial or purpuric lesions on the lower extremities), and SLE (malar rash). The genital examination should be included to identify abuse or trauma, discharge, and meatal stenosis, all of which can cause hematuria.

Renal imaging should be performed (computed tomography [CT] with IV contrast) for any child with gross hematuria and a history of abdominal trauma to detect and grade any renal injury. Gross hematuria is not the only presentation for significant renal injuries. Significant injuries may present with either microscopic hematuria or with a normal urine analysis. Therefore, imaging decisions for the diagnosis and grading of renal injuries should not be based solely on urine analysis results without consideration of clinical status or mechanism of injury (9). Patients presenting with gross hematuria after minimal-force blunt abdominal trauma should be considered at risk for pathologic lesions of the urinary tract. The diagnostic and therapeutic approach to blunt renal trauma should be modified in these cases (10). Some authors recommend a CT scan of the abdomen and pelvis should be performed in patients with 50 or more RBCs on urinalysis, hypotension at the time of emergency department (ED) presentation, or if there is a serious mechanism of injury such as high-speed motor vehicle accident with evidence of deceleration injuries (11). If blood is noted at the urethral meatus, a retrograde urethrogram must be done prior to catheterization to verify urethral integrity.

A urine culture must be sent if dysuria, urinary frequency, or the presence of systemic signs (fever, vomiting, diarrhea, and abdominal pain) suggests the possibility of a UTI. UTIs are the most common cause of macroscopic hematuria, and a third of UTIs are associated with hematuria; making the urine culture especially important in children with white blood cells on microscopic urinalysis (1). If the culture is negative and signs and symptoms are strongly suggestive of cystitis, alternative causes include adenovirus or a chemical cystitis due to bubble bath. The child with gross hematuria and sudden colic flank or abdominal pain associated to nausea and vomiting should raise the suspicion for urolithiasis. In younger patients, symptoms can be less specific. In this case, the initial workup consists of radiologic imaging, urinalysis, and urine culture. Radiologic imaging consists of an abdominal x-ray, a renal sonogram or noncontrast abdominopelvic spiral CT. Of these, the most sensitive and specific for diagnosis is the noncontrast spiral CT (12).

Gross hematuria and the presence of proteinuria suggest GN. Proteinuria should not exceed 2+ if the only source of protein is from the blood. Pertinent laboratory evaluation includes serum electrolytes (potassium), renal function (BUN, creatinine) complete blood count (for hemolytic–uremic syndrome), and culture from the throat and skin should be sent to isolate a nephrogenic strain of *Streptococcus*. Hematuria is the most consistent urinary abnormality in AGN, but the urinalysis can be normal. Rising antistreptolysin-O (ASO) titers suggest previous recent streptococcal infection; however, the ASO may not rise after pyoderma. Therefore, anti-DNAse B is the best single test to detect recent streptococcal infection. The complement C3 level is low in acute poststreptococcal GN, membranoproliferative GN, and SLE but returns to normal in 6 to 8 weeks (2). Complement levels and antinuclear antibody tests may be helpful if a diagnosis of underlying systemic disease is being entertained. Evaluation also includes serum creatinine, potassium concentrations, and chest radiographs, which may reveal cardiomegaly, pulmonary edema, pleural effusions, and edema of the soft tissues.

Less common causes of gross hematuria include hypercalciuria, nephrocalcinosis, sickle cell trait, and glomerular basement membrane defects. Diagnosis begins with a urine Cr/Ca ratio or a 24-hour urinary calcium excretion, serum creatinine, and renal sonography. Consultation with a pediatric nephrologist is recommended.

KEY TESTING

- Urinalysis, dipstick for blood and microscopic evaluation
- Urine culture if infection is suspected
- CT or US in cases of trauma or urolithiasis
- BUN, creatinine, CBC
- Culture of skin lesion, throat culture, ASO titers for suspected GN
- Complement levels and antinuclear antibody for suspected collagen vascular disease

ED MANAGEMENT

The patient with hematuria should be managed according to the etiology of the disease condition. Asymptomatic hematuria does not need acute management in the ED with the exception of UTIs. Acutely emergency physicians must address pain in the uncomfortable child. Nonsteroidal anti-inflammatories and/or narcotics can be used for pain control related to urolithiasis. Ketorolac has been used for renal colic, but contrary to the adult literature, there are no studies evaluating its effectiveness in children.

A recent Cochrane review compared different antibiotic agents, routes, frequencies, and durations of therapy in children aged 0 to 18 years with proven UTI and acute pyelonephritis. Twenty-three studies (3,295 children) were eligible for inclusion. No significant differences were found in duration of fever and persistent renal damage at 6 months between 10- and 14-day oral antibiotic therapy and 3-day IV therapy followed by 10-day oral therapy. Therefore, children with acute pyelonephritis can be treated with oral antibiotics (cefixime, ceftibuten, and amoxicillin/clavulanic acid) or with short courses (2 to 4 days) of IV therapy followed by oral therapy. If intravenous therapy is chosen, effective agents include ceftriaxone, cefotaxime, ampicillin, and gentamicin; single daily dosing with aminoglycosides is considered safe and effective (13). Patients aged 2 months to 2 years with their first febrile UTI can be treated with a second- or third-generation cephalosporin or sulfamethoxazole-trimethoprim (SMZ-TMP) (13–15).

In most cases of PSAGN much of the treatment is supportive, there is no specific therapy influencing healing of glomerular lesions. Antibiotics do not alter the course of the disease but may decrease the spread of nephrogenic strains of *Streptococcus* in patients with positive cultures. Prompt treatment of hypertension, or hyperkalemia is indicated for the child in acute renal failure. This may include pharmacologic treatment of hyperkalemia and fluid restriction or diuretics (16). As many as 60% of these patients will have hypertension, with up to 10% having hypertensive encephalopathy presenting with headache, nausea, vomiting, seizures, and transient

cortical blindness (2). For hypertensive emergencies in children with PSAGN, therapy should be gradual and controlled. Hypertensive encephalopathy is a hypertensive emergency therefore because of their rapid onset of action diazoxide, hydralazine, labetalol, loop diuretics, and calcium channel blockers may be necessary. Overly aggressive blood pressure correction by more than 20% to 25% can contribute to decreased cerebral perfusion and potential hemorrhage or stroke.

In patients with nonstreptococcal GN, the nephrology consultant may recommend corticosteroids or cytotoxic agents.

Less common causes of hematuria can be pursued in the ED as resources allow and based on level of suspicion raised by the history and physical examination (17,18). Conditions requiring advanced workup (Table 286.4) should be referred to a pediatric nephrologist or urologist.

TABLE 286.4
Evaluation of the Child with Hematuria

Initial evaluation of child with hematuria
History/family history/physical examination
Urinalysis with microscopy, protein measurement
Red blood cell morphology
Urine culture
Calcium–creatinine ratio
Sickle cell screen, if applicable
Complete blood count, creatinine and blood urea nitrogen levels
Urine of first-degree relatives
Renal ultrasound
Advanced evaluation of child with hematuria
Complement level (membranoproliferative, SLE, postinfectious GN) Antistreptolysin-O and anti-DNAase B (Acute poststreptococcal glomerulonephritis)
Antinuclear antibody (SLE)
Audiogram (Alport syndrome)
Antiglomerular basement membrane antibodies
Antineutrophil cytoplasmic antibodies (Active crescenteric glomerulonephritis)
Tuberculosis testing
Renal biopsy

SLE, systemic lupus erythematosus.

CRITICAL INTERVENTIONS

- When there are signs and symptoms of UTI, a urine culture should be sent regardless of the results of the urinalysis.
- The decision to order renal imaging after blunt trauma should be based on clinical status history and mechanism of injury and not on the urinalysis alone.

DISPOSITION

Hospitalization is necessary for the following patients with UTI: Patients who are septic, ill appearing, have signs of urinary obstruction or significant underlying disease, who are unable to tolerate adequate oral fluids or medications, infants younger than 2 months with febrile UTI (presumed pyelonephritis), all infants younger than 1 month with suspected UTI even if afebrile.

Referral to a pediatric nephrologist should occur if the child has gross hematuria, a coexistent significant proteinuria, hypertension,

abnormal kidney function tests, persistent hypocomplementemia, findings suggestive of systemic disease, or a family history of GN, nerve deafness, chronic renal failure, end-stage renal disease, or familial hematuria. If parental anxiety is high, referral to a pediatric nephrologist may help alleviate compounding fears and serve as additional reassurance to the family that dangerous and treatable conditions have been ruled out. Parents are often concerned their child is losing large amounts of blood based on the color of the urine; they should be reassured that as little as 1 mL of blood in 1 L of urine can make the urine red (19).

Patients with newly diagnosed renal disease should be admitted with pediatric nephrology consultation to monitor for possible complications, such as hypertension, hyperkalemia, and acute renal failure.

It is important to remember the most common causes of microscopic hematuria without casts or proteinuria are benign and do not require treatment. The prognosis for these children is very good while a poor prognosis tends to be associated with proteinuria at presentation, persistent hematuria, and hypertension.

Common Pitfalls

- Failure to perform a urine dipstick and urinalysis to confirm the presence of blood in the patient with "red urine." This can lead to unnecessary further laboratory testing.
- Failure to obtain relevant historical information such as a history of recent pharyngitis, trauma, or renal stones
- Failure to detect proteinuria, hypertension, or subtle signs of fluid overload
- Failure to include AGN in the differential diagnosis of hematuria, particularly when there are other signs such as edema

NEPHROTIC SYNDROME

CLINICAL PRESENTATION

The nephrotic syndrome is characterized by proteinuria and hypoalbuminemia that is often associated with edema and hypercholesterolemia. A small number of patients may also have hypertension, hematuria, and decreased glomerular filtration rate. This combination of clinical findings may be found alone or in association with a number of systemic illnesses such as diabetes, amyloidosis, and lupus erythematosus or viral infections (e.g., Hepatitis B, Hepatitis C, and HIV) or preeclampsia (19). The primary pathophysiologic issue in nephrotic syndrome is the increased permeability of the glomerular capillary wall to plasma proteins leading to an excessive albuminuria.

The incidence of nephrotic syndrome is two to seven new cases per 100,000 children (15 years of age and younger) per year. The peak age of onset is 2 to 3 years, and 75% of children are younger than 10 years (19). The nephrotic syndrome is categorized into primary (>90% of cases) and secondary forms (Table 286.5). Minimal-change nephrotic syndrome is the most common form accounting for 80% to 85% of primary cases, followed by focal segmental glomerulosclerosis and membranoproliferative glomerulonephropathy (19).

TABLE 286.5
Etiology of Nephrotic Syndrome

Primary/minimal change
Congenital: Steroid responsive, Steroid resistant
Secondary
Associated with systemic disease: SLE, Henoch–Schönlein purpura, sickle cell disease, diabetes mellitus, lymphoma, Berger disease/IgA nephropathy, amyloidosis
Postinfectious glomerulonephritis: Syphilis, malaria, HIV, CMV, toxoplasmosis, hepatitis
Associated with medications: NSAIDS, heroin, gold salts, tridione
Associated with toxins/allergens: Bee sting, poison oak, vaccinations, food allergy

CMV, cytomegalovirus; NSAID, nonsteroidal anti-inflammatory drug; SLE, systemic lupus erythematosus.

A renal biopsy revealing minimal glomerular abnormalities, yields a better prognosis and 92% of these patients will respond to corticosteroid therapy (20). Regardless of the histopathologic abnormalities, edema is the most prominent clinical manifestation of the nephrotic syndrome in most children. This may be initially seen in the periorbital area and often follows a flu-like illness so it may often be confused with allergies or sinusitis. It is pitting in nature and typically seen in dependent areas, so facial swelling may be observed in the morning, whereas lower extremity edema is exhibited in the evenings. Oliguria may be seen but is more common in relapses (21). Other symptoms such as anorexia, abdominal pain (thought to be due to bowel wall edema), vomiting, diarrhea, and fatigue can also be present. With anasarca and abdominal distention, patients may have respiratory distress, umbilical and inguinal hernias, and/or rectal prolapse. Pleural effusions and, less often, pericardial effusions may be present. Ascites has been described and can be a source of infection in children presenting with fever. On rare occasions, a child may present with signs of thrombosis secondary to a hypercoagulable state associated with nephrotic syndrome.

The initial of nephrotic syndrome, and subsequent relapses, may follow a viral upper respiratory tract infection. Microscopic hematuria occurs in approximately 20% of children with minimal-change nephrotic syndrome and in 50% of those with membranoproliferative disease. The presence of macroscopic hematuria should prompt investigation for underlying causes. Blood pressure is usually normal in minimal-change nephrotic syndrome but hypertension in up to 13% of patients (above the 98th percentile for age) has been reported. Persistent hypertension is uncommon and is suggestive of a diagnosis other than minimal-change nephrotic syndrome.

DIFFERENTIAL DIAGNOSIS

The complete differential diagnosis of nephrotic syndrome is listed in Table 286.5. Although nephrosis may be the presenting symptom in the secondary forms, there is usually accompanying evidence related

to the underlying diagnosis. This includes a number of disorders commonly seen in the pediatric ED including, Henoch–Schönlein purpura, sickle cell disease, diabetes mellitus, lymphoma, HIV, hepatitis, bee sting, poison oak, vaccinations, and food allergies among others.

ED EVALUATION

Laboratory findings diagnostic of the nephrotic syndrome include (1) proteinuria: >40 mg/m^2/d ($>2+$ on urine dipstick) and spot urine protein to creatinine ratio greater than two, (2) hypoproteinemia: Serum albumin <2.5 g/dL, (3) hyperlipidemia with elevated serum levels of triglycerides, cholesterol, and total lipids, (4) normal serum creatinine, (5) normal or slightly elevated serum blood urea nitrogen, and (6) increased hemoglobin (seen frequently owing to hemoconcentration). Secondary findings include hypocalcemia (with a normal ionized fraction), hyperkalemia, hyponatremia, and hypercoagulability (22).

Many children with nephrotic syndrome are apparently healthy and have edema as their only obvious presenting abnormality. A thorough physical examination is indicated; however, to assess for respiratory difficulties secondary to ascites and pleural effusions or complications related to infection and thrombotic phenomena. The presence of edema can be deceptive, giving the impression of fluid overload when, in fact, many patients are, secondary to their hypoproteinemia, intravascularly volume depleted.

Depending on the clinical findings, other laboratory studies may be performed such as antinuclear antibodies, ASO titer, syphilis serology, hepatitis B surface antigen, testing for the human immunodeficiency virus, and skin testing for tuberculosis. There are no radiographic studies routinely recommended, but a chest x-ray may be helpful in evaluating for pleural effusions.

KEY TESTING

- Urinalysis
- Serum albumin
- Serum electrolytes, including Ca

- CBC
- Serum triglycerides, cholesterol, and total lipids

ED MANAGEMENT

Typically, the treatment of the initial presentation of nephrotic syndrome is not an emergency; however, children are admitted to the hospital for therapy and further testing. Patients who have relapsed may present to the ED but may not require admission. General measures to treat the edema of nephrotic syndrome include salt restriction (no-added-salt diet) and occasionally diuretics. Furosemide (Lasix) is the diuretic of choice for nephrotic patients with severe discomfort due to fluid retention. It is given orally or intravenously in a dose of 1 to 2 mg/kg and may require giving an infusion of salt-poor albumin for optimal benefit. A useful regimen is to give furosemide intravenously, then 1 g/kg of 25% salt-poor albumin solution intravenously over 2 hours followed by a second dose of furosemide at the end of the infusion. Patients should be observed closely for hypotension or hypertension. Diuretics should be used cautiously, given the high risk of intravascular volume depletion and thrombosis. Some patients will require thoracentesis for relief of respiratory distress secondary to pleural effusions. To avoid the risk of peritonitis secondary to paracentesis the procedure should be reserved for ascites causing respiratory compromise.

Treatment consists of prompt restoration of the intravascular volume by rapid intravenous fluid administration preferably albumin containing solution. In addition, patients presenting with hypovolemic shock require hospitalization for close fluids and electrolytes monitoring following the initial fluid resuscitation.

Infections and related complications account for up to 70% of deaths in patients with nephrotic syndrome. Because of relative immune compromise they are at high risk of invasive *Streptococcus pneumoniae* infections. These patients are also susceptible to gram-negative organisms such as *Escherichia coli, Pseudomonas,* and *Haemophilus influenza* and at risk for severe varicella infections. Therefore, febrile children with nephrotic syndrome may need to be

admitted to the hospital for treatment with broad spectrum antibiotics.

Hypoalbuminemia leads to a decrease in protein-bound calcium, but ionized calcium levels can also be decreased secondary to excessive loss of vitamin D–binding protein in the urine and decreased calcium absorption. Symptomatic hypocalcemia is rare; however, bone demineralization and osteomalacia may occur and occasionally, a patient will present to the ED with tetany or muscle cramps. Such a patient should be placed on a cardiac monitor and given an initial dose of 0.5 to 1 mL/kg of a 10% solution of calcium gluconate intravenously over 3 to 5 minutes. Calcium gluconate is preferable to calcium chloride because it is less sclerosing to the veins. When symptoms are relieved, calcium gluconate may be added to the intravenous solution at a dose of 100 mg of elemental calcium/kg/d or administered orally (10% calcium gluconate contains 9-mg elemental calcium/100 mg of the salt).

Increased risk of vascular thrombosis is a rare but serious complication of the nephrotic syndrome. Routine anticoagulation is generally not recommended; however, a patient with evidence for thrombosis or additional risk factors (e.g., prolonged immobility), most likely will warrant anticoagulant medication. Renal vein thrombosis should be suspected in any patient with acute flank pain, renal enlargement, hematuria, unexplained deterioration in renal function, oliguria, or renal failure.

Corticosteroid therapy is cornerstone of treatment for nephrotic syndrome in patients with no contraindications to the use of high-dose steroids (e.g., active bacterial infection or positive tuberculin skin test) (19). The typical starting dose is 2 mg/kg/d for the first 4 to 6 weeks. Typical side effects include cushingoid faces, increased appetite, and hirsutism, which subside with decreasing doses (22). The majority of patients (~90%) will experience complete clearing of their urine on this regimen. Maintenance therapy (with slow tapering of the steroid dose) is then continued for a total of about 28 weeks, which is associated with a reduced risk of relapse. Nonsteroidal agents, such as cyclophosphamide or cyclosporine, are sometimes used in steroid-resistant patients (19). New

immunosuppressive agents, like calcineurin inhibitors have less adverse effects while inducing and maintaining remission, have also been recommended for steroid-resistant patients (23).

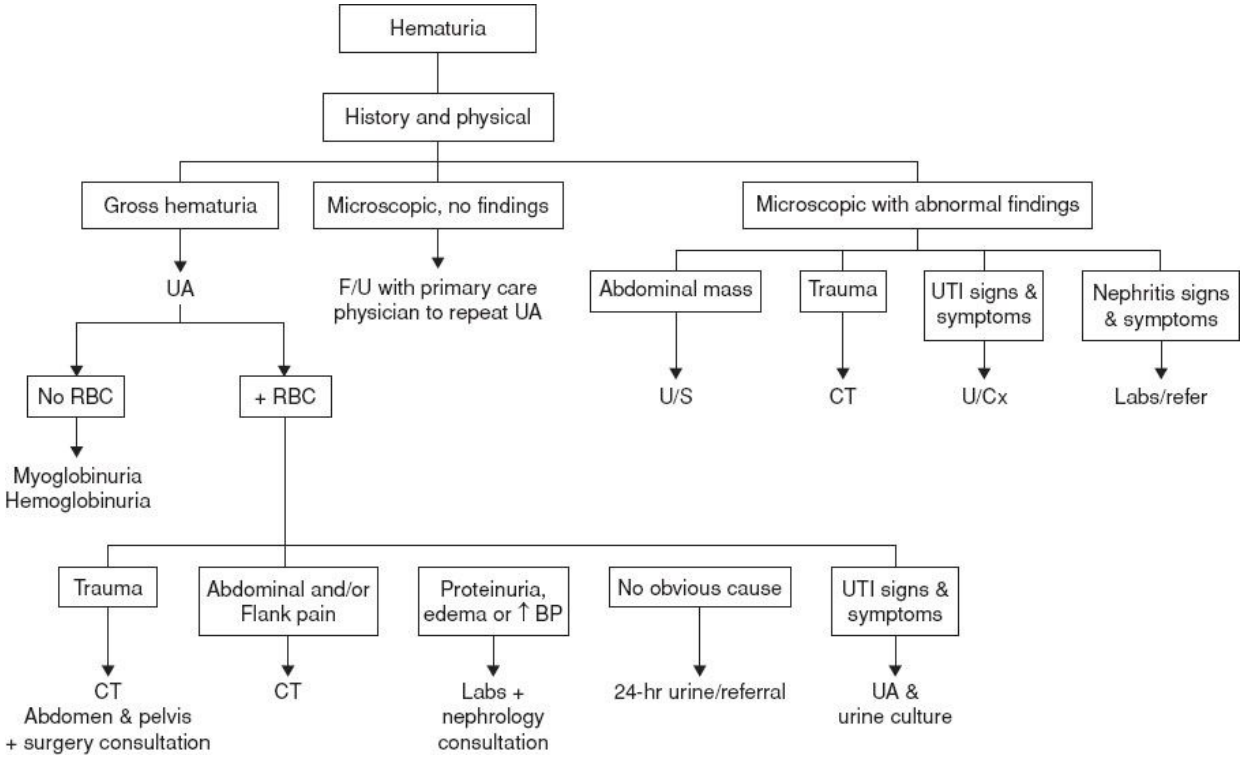

FIGURE 286.1 Approach to the diagnosis of hematuria in children.

CRITICAL INTERVENTIONS

- Patients with nephrotic syndrome may present with edema despite being intravascularly volume depleted. Diuretics should be used with caution to avoid severe hypovolemia.
- Overaggressive correction of hypertension can be dangerous, and patients must be monitored closely during treatment. A continuous infusion of nitroprusside or labetalol allows titration to desired effect.

DISPOSITION

Most children with new-onset nephrotic syndrome are admitted to the hospital for initiation of steroid therapy and aggressive education of the patient and family. A thorough history regarding tuberculosis

exposure and a chest x-ray should be performed in the ED. If these are negative, steroid therapy may be initiated. Children presenting with a relapse may be discharged to home if stable. Children older than 6 years and those with hypertension, hematuria, or evidence of impaired renal function should be admitted for further evaluation to determine the underlying cause of their disease. Mild edema may be treated with salt restriction at home. Discharge instructions should include warnings regarding fever, tachypnea, abdominal pain, chest pain, vomiting, increasing edema, and decreasing urine output.

Common Pitfalls

- Incorrectly diagnosing periorbital edema as allergy related or due to sinusitis
- Overaggressive treatment of edema in nephrotic syndrome
- Overaggressive treatment of hyponatremia in nephrotic syndrome
- Failing to take seriously fever or other signs of infection in children with nephrotic syndrome. These patients are relatively immune compromised, even before initiation of steroids.

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CHAPTER 287 Genitourinary Disorders

Genevieve Santillanes and Marianne Gausche-Hill

Pediatric genitourinary and gynecologic evaluations pose specific challenges to the emergency practitioner. The physician must incorporate knowledge about stages of development, likely diagnoses for different age groups, and the patient's specific history to tailor an appropriate examination. Any child presenting with abdominal pain should undergo a genitourinary examination. In addition, the emergency physician should maintain a high index of suspicion for sexual abuse as children who are abused may present with unusual or vague complaints.

FEMALE GENITOURINARY DISORDERS

The response of the premenarchal female to the genitourinary examination depends upon her stage of development. Younger children generally cooperate easily, whereas older children tend to be more private, especially in the early stages of puberty. Putting the child at ease to make the evaluation as atraumatic as possible is crucial. Infants can be examined in a parent's lap. Older girls are more easily evaluated on the examination table. Two positions commonly used to facilitate evaluation of young girls are the frog-leg position and, for girls old enough to cooperate, the knee-chest position. In the frog-leg position, the child is supine on the table with her heels together with her knees and hips flexed (Fig. 287.1). With gentle lateral and outward traction on the labia majora, the hymen and introitus are more easily visualized. The knee-chest position generally affords a better view of the vaginal vault. The child is

instructed to get on her hands and knees, fold her arms, rest on her elbows, and place her head on her arms.

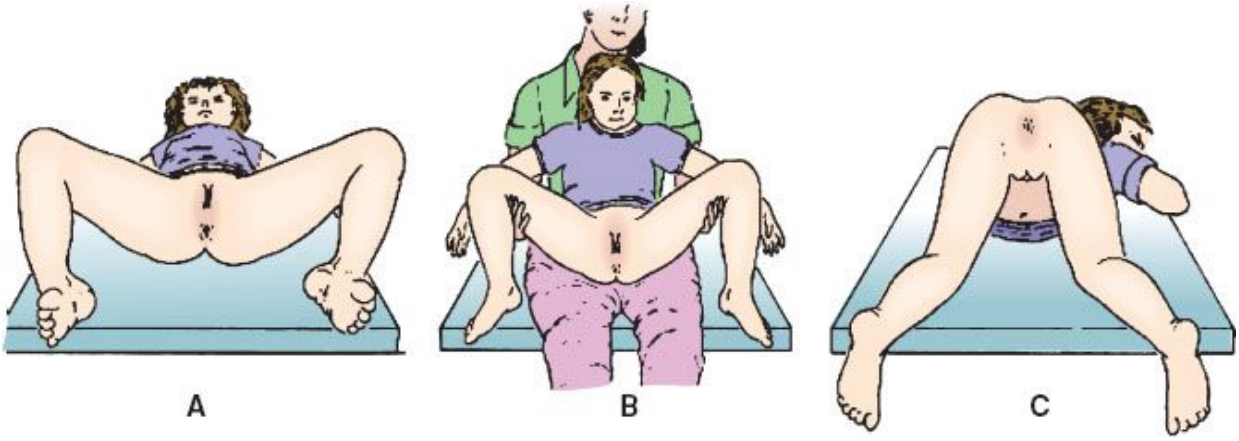

FIGURE 287.1 Positions for genitourinary examination of the female child. **A, B:** Frog-leg position and **(C)** knee-chest position.

A thorough gynecologic examination under procedural sedation or anesthesia may be necessary in young children if vaginal bleeding is present without an obvious source on external examination, if a vaginal foreign body is suspected but not visualized, or if significant trauma is suspected. For most complaints in premenarchal girls, a careful history and physical with a thorough evaluation of the external genitalia and culture of any vaginal discharge is adequate.

When evaluating an adolescent with a genitourinary complaint or abdominal pain, the history must include age of menarche, menstrual history, sexual activity, pregnancies, history of sexually transmitted diseases, and contraception. The adolescent should be interviewed alone. Every postmenarchal girl should have a pregnancy test performed. Virginal females will rarely require bimanual or speculum examinations as pelvic pain in virginal girls generally can be evaluated with transabdominal ultrasonography. Sexually experienced adolescents require a full gynecologic evaluation, given the high rate of sexually transmitted infections in this age group.

PEDIATRIC VULVOVAGINITIS

CLINICAL PRESENTATION

Inflammation of the vulva and vagina is the most common gynecologic complaint in the prepubertal female. Prepubertal patients are predisposed to inflammation due to the absence of labial fat pads and pubic hair for protection and a low estrogen level, leading to a more alkaline vaginal pH. In addition, vaginal proximity to the anus and poor local hygiene increase the risk of inflammation. There generally is no appreciable physiologic vaginal discharge from approximately 1 month of age until the initiation of puberty, although estrogen effects passed from the mother to the female child may last through infancy. Thus, a prepubertal girl with the chief complaint of vaginal discharge warrants a medical evaluation. Patients may also present with pruritus, vaginal redness, soreness, and, rarely, bleeding (1). The postpubertal female may present with a change in vaginal discharge, pruritus, or pain. Frequency and dysuria can be associated symptoms.

The normal prepubertal vaginal flora has not been well studied, and thus the determination of a causative agent can be difficult. Classically, the etiology of vulvovaginitis in pediatrics is usually divided into two groups, specific and nonspecific. Nonspecific vaginitis is usually attributed to poor hygiene, chemical irritation, or tight-fitting clothing. The majority of cases of vulvovaginitis in prepubertal girls are due to nonspecific vaginitis (2). Nonsexually transmitted infections thought to cause vulvovaginitis include Group A β-*hemolytic streptococcus, Staphylococcus aureus,* and *Shigella* (2,3). *Candida albicans* is a rare cause of vulvovaginitis in the prepubertal patient.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis varies depending upon the age and the patient's risk factors. An infant is more likely to have neonatal leukorrhea, diaper dermatitis, impetigo, chemical–mechanical irritation, seborrheic dermatitis, or a genitourinary malformation. Vaginal foreign bodies are generally seen after infancy. Chronic irritation may be secondary to lichen sclerosis, labial adhesions, or a vaginal foreign body. Pinworms that migrate to the vagina can lead

to vulvovaginitis, and should be suspected when nighttime symptoms predominate or there is associated anal pruritis. Pinworms are discussed in greater detail in Chapter 284. In adolescents, urethritis, cervicitis, or pelvic inflammatory disease should be considered.

ED EVALUATION

Visible discharge in a premenarchal patient should be sent for wet mount, cytology, and bacterial cultures. Cultures may be obtained with a moist swab placed in the introitus. The prepubertal hymen and clitoris are extremely sensitive so a small swab should be used, avoiding contact with the hymen, or lidocaine jelly can be applied for analgesia. A culture for chlamydia is usually sent only if other cultures are negative or sexual abuse is suspected. Urine tests are now available for gonorrhea and chlamydia, and can be used to screen for disease. Because diagnosis of a sexually transmitted infection in a prepubertal child is an evidence of sexual abuse, highly specific tests that will be acceptable as evidence in legal proceedings should be obtained before treatment of sexually transmitted infections (4). Appropriate forensic testing is discussed in Chapter 292. Patients who have been sexually active should have a bimanual and speculum pelvic examination and should be tested for sexually transmitted infections.

ED MANAGEMENT

Culture-proven–specific vaginitis can be treated with targeted antimicrobial therapy. Isolation of sexually transmitted organisms in a prepubertal child necessitates child abuse workup and reporting. The treatment of nonspecific vaginitis is focused on proper hygiene (i.e., front-to-back wiping), sitz baths, and avoidance of chemical irritants such as bubble bath and harsh detergents. A diagnosis of candidal vaginitis in a toilet-trained prepubertal patient is unusual, and a workup for diabetes or immunodeficiency should be considered.

DISPOSITION

Patients should follow-up with their pediatrician for culture results and to ensure that symptoms have resolved or with a subspecialist as indicated.

IMPERFORATE HYMEN

CLINICAL PRESENTATION

Imperforate hymen is a rare disorder. In infants and young girls, it is most often discovered incidentally during physical examination. In the neonate, circulating maternal hormones stimulate vaginal mucus secretion. If the imperforate hymen is not recognized at birth, it may present within days to weeks of life when the obstructed vagina becomes distended, resulting in hydrocolpos or mucocolpos. If the distension extends to the uterus, it is referred to as *hydrometrocolpos.* The infant may present with a lower abdominal mass or mass at the introitus, urinary retention secondary to extrinsic obstruction, or constipation. Girls who remain undiagnosed in childhood will present during or after menarche when the vagina fills with blood resulting in hematocolpos or hematometrocolpos. They will have normal pubertal development with primary amenorrhea. The chief complaint may be lower abdominal pain that may or may not be cyclic, back pain, a pelvic mass, constipation, or urinary retention (5).

DIFFERENTIAL DIAGNOSIS

The diagnosis of imperforate hymen is generally made upon examination of the external genitalia. However, other causes of vaginal obstruction must be considered. Transverse vaginal septum, labial adhesions, pelvic mass, agenesis of the vagina, testicular feminization, and Gartner duct cysts should be included as possible diagnoses. Sexual or physical abuse also rarely mimics the presentation of imperforate hymen.

ED EVALUATION

A thorough history and physical should lead to the diagnosis. In infants, imperforate hymen may appear as a whitish bulging membrane. Infants should be evaluated for the complications due to mass effect including evaluation for respiratory distress, inferior vena cava compression, and hydronephrosis. A urinalysis should be performed to assess for concomitant infection. Hematocolpos in adolescents is classically described as a bulging membranous dark blue mass at the introitus. An adolescent with severe pain may require an ultrasound evaluation, as case reports of ruptured hematosalpinx have been documented (5).

ED MANAGEMENT

The treatment for imperforate hymen is surgical incision and resection. The urgency of gynecology consultation or referral is based on patient symptoms.

DISPOSITION

Asymptomatic infants and prepubertal children can be scheduled for elective repair. Patients with complications such as renal insufficiency, respiratory distress, or shock from inferior vena compression require admission to the hospital and emergent intervention. Adolescents with hematocolpos should undergo surgical treatment promptly. In addition, all female siblings should undergo an external examination, as familial occurrences have been reported (6).

URETHRAL PROLAPSE

CLINICAL PRESENTATION

Urethral prolapse is a disorder seen in prepubertal girls and postmenopausal women. In children, the diagnosis is most commonly seen in prepubertal African American girls. The patient presents with painless vaginal bleeding, a vaginal mass, or urinary symptoms of straining or dysuria. The mass is generally swollen, purple or deep red, and doughnut shaped. A central depression representing the

lumen of the urethra may or may not be evident. The area may have evidence of thrombosis and necrosis.

DIFFERENTIAL DIAGNOSIS

Urethral processes that can present similarly are urethral polyps, prolapsed ureteroceles, and rarely urethral carcinomas. Dermatologic causes include condylomata and hemangiomas. Accidental and nonaccidental trauma can cause a hematoma that mimics prolapse. Imperforate hymen and hair tourniquets are other possibilities. An important entity on the differential that must be excluded is botryoid sarcoma, as it requires immediate referral and management.

ED EVALUATION

If the origin of the mass is in question, a catheter can be passed through the mass to verify the diagnosis.

ED MANAGEMENT

Appropriate treatment is debated in the literature with some experts recommending surgical treatment in all cases and others advocating conservative treatment for most patients. In general, if the prolapse is small, without evidence of necrosis and asymptomatic or only mildly symptomatic, sitz baths or warm moist compresses can be recommended. A topical estrogen cream applied twice a day for 2 weeks may aid in resolution. If there is evidence of extreme congestion, necrosis, or if symptoms are significant, a urologic evaluation is indicated for reduction under anesthesia and/or excision (7).

DISPOSITION

The uncomplicated urethral prolapse will generally resolve in 3–6 weeks but may take up to 3 months. Follow-up should be given to all patients to ensure resolution has occurred. Patients with necrosis, severe symptoms or failure to resolve need urologic referral.

VAGINAL FOREIGN BODY

CLINICAL PRESENTATION

The classic presentation of a retained foreign body is vaginal bleeding or blood-stained or foul-smelling vaginal discharge. A prepubertal girl with chronic vaginal discharge should have a thorough workup for vaginal foreign body (8). More commonly reported foreign bodies in prepubertal girls include toilet paper, cloth, and other small items. Adolescents are more likely to present with retained tampons and condoms.

DIFFERENTIAL DIAGNOSIS

The presenting symptoms of a patient with a vaginal foreign body include vaginal bleeding, discharge, and abdominal/pelvic pain. Vulvovaginitis, urethral prolapse, dysfunctional uterine bleeding, labial adhesions, tumor, trauma, and urinary tract infection (UTI) can all present similarly.

ED EVALUATION

The patient should undergo a full genitourinary evaluation. The knee-chest position with a good light source will facilitate the best vaginal examination of a premenarchal patient. The use of an otoscope placed carefully into the hymen may enhance visualization. If a vaginal foreign body is highly likely but not visualized with the foregoing methods, an examination under procedural sedation or anesthesia may be indicated. Postmenarchal patients can undergo a speculum and bimanual examination. An x-ray or ultrasound can be considered, although the objects found are generally not radiopaque.

The relationship between vaginal foreign bodies and sexual abuse has not been well studied or described in the literature. A retrospective case review suggests a possible correlation in some cases; therefore, patients should be questioned about and screened for signs of sexual abuse, especially if the patient has recurrent vaginal foreign bodies (8).

ED MANAGEMENT

If a vaginal foreign body is suspected, a gentle vaginal lavage should be performed. A 50-mL syringe with the plunger removed can be attached to a catheter that is inserted in the introitus. Normal saline poured into the syringe will provide a continuous flow to flush the object out of the vagina. If this procedure is not tolerated or fails to remove the object, a gynecologist can perform vaginoscopy under anesthesia.

DISPOSITION

Most patients are managed as outpatients. Patients with persistent complaints of vaginal discharge or bleeding should be referred to a gynecologist for further evaluation (9).

LABIAL ADHESIONS

Adhesions of the labia minora are a common entity encountered in the pediatric patient. Labial fusion is thought to be due to irritation and inflammation of unestrogenized epithelium with adhesions forming during the healing process. The incidence in prepubertal girls is reported to be less than 5% (10). Most patients are between 1 and 6 years of age. Symptoms may include urinary complaints, recurrent UTIs, vaginitis, or leakage of urine. Labial adhesions may also be noted by parents or on examination by a health care provider. The diagnosis is generally made clinically, with labial tissue with a central line or raphe obstructing the view of the introitus and hymen. The characteristic central thickened line differentiates the diagnosis from congenital malformations.

Appropriate treatment of labial adhesions is controversial. Traditional treatment of labial adhesions was surgical or manual separation of adhesions, or application of topical estrogen cream. Estrogen cream is associated with side effects including vaginal bleeding and breast bud development. Newer literature suggests that betamethasone cream may be more efficacious and associated with fewer side effects than topical estrogen (10). The natural history of labial adhesions is resolution in early puberty when estrogen levels rise. Thus, asymptomatic patients do not require treatment. If the patient is having complications or symptoms, estrogen or

betamethasone cream can be applied sparingly to the adhesions at bedtime for several weeks to months. After separation, zinc oxide or petroleum jelly should be applied at bedtime for an additional 2 weeks. Patients should be followed up closely for failure of separation and recurrence. At that time, manual or surgical separation may be performed.

KEY TESTING

Suspected Disorder	Testing	Consultations/Referrals
Vulvovaginitis	• If discharge present: Wet mount, cytology, culture	• If persistent discharge: Gynecology to rule out foreign body and other serious disease • If child abuse suspected: Child protective services, law enforcement, and child abuse team for further workup and appropriate STI testing
Imperforate hymen	• If severe pain: Ultrasound to assess for complications • If symptoms suggestive: Urinalysis	• Gynecology for surgical repair (urgency based on symptoms)
Urethral prolapse	• Generally none	• If necrotic tissue, severe symptoms or no resolution: Urology
Vaginal foreign body	• Generally none	• If unable to remove or if foreign body suspected, but not visualized: Gynecology • If suspicion of abuse: Child abuse team
Labial adhesions	• If symptoms suggestive: Urinalysis	• If symptomatic and no resolution with topical therapy: Gynecology or Urology

CRITICAL INTERVENTIONS

- Rule out pregnancy in every postmenarchal patient with genitourinary symptoms.
- Evaluate prepubertal pediatric patients diagnosed with a sexually transmitted infection for sexual abuse

- Evaluate infants with hydrocolpos for signs of hydronephrosis, respiratory insufficiency, and compression of the vena cava

Common Pitfalls

- Failure to take a complete sexual history or perform a genitourinary examination because of inaccurate assumptions of low risk
- Failure to recognize that candidal infections in prepubertal patients are unusual and may be associated with diabetes or an immune disorder
- Failure to evaluate pediatric patients with recurrent or chronic vaginitis for a vaginal foreign body or other serious pathology

MALE GENITOURINARY DISORDERS

Any male with abdominal or genitourinary complaints must undergo a complete examination. This section focuses on common testicular and foreskin complaints in pediatric patients.

TESTICULAR TORSION

CLINICAL PRESENTATION

Testicular torsion is a critical diagnosis to make in the ED. Testicular torsion has been reported in all ages from in utero through adulthood, but nearly all cases occur before the age of 25 (11). It is most common during adolescence. Patients classically present with acute onset of severe, unilateral, progressive scrotal pain and swelling. Diffuse scrotal erythema, a horizontal lie, or a high-riding testis may be seen. Patients may also present with atypical features, including pain which is intermittent or bilateral or lower abdominal. It is common for patients to have associated nausea and vomiting. The cremasteric reflex is usually absent; however, the cremasteric reflex is commonly subtle or absent in healthy young boys (12). The presence of a cremasteric reflex is suggestive that torsion is not the correct diagnosis; however, its presence in patients with torsion has been reported (13,14). Patients with an undescended testis have a

higher incidence of torsion and the diagnosis should be considered in males with undescended testicles presenting with abdominal pain or vomiting (15).

Torsion in adolescence is due to improper attachment of the testicle to the tunica vaginalis resulting in the "bell clapper" deformity. The result is a free-hanging testicle, predisposing to twisting of the spermatic cord. The abnormal attachment is usually bilateral.

DIFFERENTIAL DIAGNOSIS

Two other diagnoses which present as atraumatic acute scrotal pain and swelling in pediatric patients are epididymitis and torsion of a testicular appendage. Epididymitis tends to have a more gradual onset of symptoms, an intact cremasteric reflex, and a vertically oriented testis. None of these findings are diagnostic for epididymitis, however. Torsion of a testicular appendage usually presents with less severe symptoms than testicular torsion. With torsion of a testicular appendage, a firm tender nodule can be palpated on the upper pole of the testis and a "blue-dot sign" may be visualized. Delayed diagnoses of testicular torsion frequently result in testicular loss; therefore, testicular torsion must be considered in any patient who presents with scrotal pain. Table 287.1 lists other causes of painful scrotal swelling.

TABLE 287.1
Causes of Scrotal Swelling and Masses

Painful	Generally Painless
Testicular torsion	Inguinal hernia
Torsion of appendix testis	Hydrocele
Epididymitis	Varicocele
Incarcerated hernia	Tumor/metastases
Trauma	Henoch–Schönlein purpura
Edema	

ED EVALUATION

If the patient presents with a history and physical examination most consistent with torsion, immediate urologic evaluation is warranted without further studies. Only if the diagnosis of torsion is uncertain should imaging be performed. Color Doppler ultrasonography has become the imaging modality of choice as it is noninvasive, uses no radiation, and is readily available. Recently published studies have found that color Doppler ultrasound has 94% to 100% sensitivity and 96% to 97.9% specificity for the diagnosis of testicular torsion (15–17).

Additional information that may aid in diagnosis is a urinalysis. If significant pyuria is demonstrated, a diagnosis of epididymitis becomes more likely. However, the presence of pyuria does not rule out testicular torsion.

ED MANAGEMENT

Testicular torsion is a surgical emergency. If the diagnosis is likely, emergent urologic evaluation should be obtained and the patient should undergo scrotal exploration in the operating room. Imaging studies should not delay urologic evaluation or surgical exploration. The survival of the testis is correlated with duration of symptoms. Manual detorsion to increase blood flow to the testis can be attempted as a temporizing measure if the patient cannot be taken to the operating room promptly. Analgesia should be administered prior to the manual detorsion. This maneuver is performed by facing the patient and rotating the involved testicle outward as if one were opening a book: The left testis is rotated clockwise and the right counterclockwise until the symptoms improve. One study demonstrated that the degree of rotation of torsed testes ranged from 180 to 1,080 degrees, with a median of 540 degrees (18). The classically described torsed testis is rotated in the medial direction; however, the same study reported that one-third of the torsed testes were laterally rotated, a fact that should be kept in mind when undertaking detorsion maneuvers (18). Emergent surgical exploration with detorsion and orchiopexy is the definitive treatment.

DISPOSITION

The patient with testicular torsion must undergo surgical exploration of both testes and bilateral orchiopexy.

EPIDIDYMITIS

CLINICAL PRESENTATION

Acute epididymitis is a common cause of acute scrotal pain. The pain of epididymitis is usually gradual in onset. It may be associated with swelling and erythema of the scrotum, fever, vomiting, and urinary symptoms. It is more common in adolescent males; however, the diagnosis is not uncommon in prepubertal boys. The tenderness is generally posterior and lateral to the testis. The cremasteric reflex is usually intact.

DIFFERENTIAL DIAGNOSIS

The main entity that must be distinguished from epididymitis is testicular torsion. Patients with testicular torsion generally have a more acute onset of symptoms, no fever, and fewer urinary complaints.

ED EVALUATION

Urinalysis may demonstrate white blood cells. A urine culture should be sent. If the patient is sexually active, gonorrhea and chlamydia testing should be performed. If the diagnosis of torsion cannot be excluded, color Doppler ultrasonography should be performed to rule out torsion. Increased blood flow to the epididymis will be visualized on ultrasound.

ED MANAGEMENT

The treatment for acute epididymitis depends upon the patient's age. Traditional teaching is to treat all cases of prepubertal epididymitis with antibiotics. Younger children with evidence of an associated UTI on urinalysis should be treated with oral antibiotics to cover common urinary organisms (*Escherichia coli, Klebsiella pneumoniae,*

and *Pseudomonas aeruginosa)* (see Chapter 290). However, recent studies have demonstrated that most prepubertal cases of epididymitis are not associated with UTI (19,20). Therefore, prepubertal children without evidence of UTI or suspicion of a sexually transmitted disease can be treated with supportive care. Although there is little data on young infants with epididymitis, the authors believe that infants younger than 1 month of age should be admitted for inpatient antibiotics and infants between 1 and 3 months of age should be treated with oral antibiotics until cultures are negative (20). Admission should also be considered for patients who appear ill. Most cases of epididymitis in adolescents are due to sexually transmitted infections, and the patient should be empirically treated for *Neisseria gonorrhoeae* and *Chlamydia trachomatis.* Recommended treatment is a single dose of 250 mg of ceftriaxone intramuscularly and 100 mg of doxycycline twice daily for 10 days (4).

DISPOSITION

The patient should be prescribed analgesics, sitz baths, and scrotal elevation, as age permits. Antibiotics should be prescribed as outlined earlier, with a low threshold for admitting young infants. Urologic follow-up should be arranged.

HYDROCELE

CLINICAL PRESENTATION

Hydroceles are common findings in infants and young children. The usual presentation is a painless swollen scrotum that tends to increase in size throughout the day and decrease when supine. The fluid collection may appear after coughing or straining. A simple hydrocele is a fluid collection without a patent processus vaginalis. A communicating hydrocele has a patent processus vaginalis and generally has greater fluctuation in size. Communicating hydroceles may be associated with an indirect inguinal hernia (21).

DIFFERENTIAL DIAGNOSIS

See Table 287.1 for the differential diagnosis of nonpainful scrotal swelling.

ED EVALUATION

Palpation of the scrotum should reveal a normal testis and spermatic cord above the mass. To aid in distinguishing a hydrocele from an inguinal hernia, it should be noted that the spermatic cord above the hydrocele should not feel thickened. A hydrocele is fluid filled and should transilluminate (Fig. 287.2). Testicular tumors pathology may be associated with hydroceles, so if a tumor cannot be ruled out by physical examination, ultrasound evaluation is recommended.

FIGURE 287.2 Hydrocele with transillumination of fluid-filled scrotal sac.

ED MANAGEMENT

If the hydrocele is tense or painful, the patient should undergo a surgical evaluation. If the mass fluctuates in size rapidly or the examination is consistent with a communicating hydrocele, the patient should be referred to a surgeon to rule out an inguinal hernia.

DISPOSITION

A small uncomplicated hydrocele can be managed conservatively, as most resolve spontaneously. Failed resolution at age 2 years warrants a surgical referral for repair (21). Any communicating hydrocele with an associated hernia needs surgical closure. It is recommended that parents be counseled on the signs and symptoms of incarceration.

TESTICULAR TUMORS

CLINICAL PRESENTATION

Testicular tumors present as an abnormally large testis or mass and are generally painless, although there may be associated scrotal heaviness or abdominal pain. Lymphadenopathy may also be present.

DIFFERENTIAL DIAGNOSIS

A testicular or paratesticular mass should be evaluated under the assumption that it is a malignancy. Other entities including hernia, hydrocele, varicocele and in neonates, prenatal testicular torsion, may present as painless scrotal enlargement. Rhabdomyosarcomas, teratomas, epidermoid cysts, and yolk sac tumors present as testicular or paratesticular masses (22).

ED EVALUATION

A full physical evaluation should be performed examining carefully for lymphadenopathy and location of the mass. Testicular and paratesticular masses should be evaluated by ultrasound. β-Human chorionic gonadotropin (β-HCG) is rarely elevated in prepubertal testicular tumors, but a urine or serum β-HCG can be checked (22). Alpha-fetoprotein (AFP), is elevated in yolk sac tumors; however, AFP levels in healthy infants may be elevated (22).

ED MANAGEMENT AND DISPOSITION

A pediatric surgeon or urologist should be consulted for further workup and management. Patients should be admitted or very close follow-up must be arranged.

INGUINAL HERNIA

Approximately 15 in 1,000 births result in an abdominal hernia, with a higher incidence in premature infants. Inguinal hernias are more common in males, with bimodal peaks before 1 year of age and then again after age 40. An indirect inguinal hernia occurs when the processus vaginalis does not obliterate in infancy and abdominal contents invaginate through this patent sac. These hernias are more common on the right side. Entrapment of mesentery, bowel, intraperitoneal organs, and the hernial sac can occur and are more common with small hernias. If the contents of the hernia can be returned to their anatomic position, the hernia is termed *reducible;* if it remains entrapped, it is termed *incarcerated* or *irreducible.* Hernias that remain incarcerated can result in strangulation, with resultant bowel necrosis.

CLINICAL PRESENTATION

Patients with incarcerated hernias may present with pain, edema extending to the scrotum, nausea, vomiting and low-grade fever. Physical examination may reveal bowel sounds in the scrotal sac. If the inguinal mass can be palpated separately from the testes, then it is possible to diagnose an inguinal hernia clinically. A strangulated hernia can present as a tense, blue mass in the scrotum.

ED MANAGEMENT AND DISPOSITION

The patient should be placed in the Trendelenburg position with an ice pack placed on the groin, as tolerated, to reduce swelling; pain medication or sedation may be necessary before reduction. Slow gentle pressure should be applied to reduce the hernia. The parent or child may assist in applying. If the hernia cannot be reduced or strangulation is suspected, the patient should receive fluid resuscitation and broad spectrum parenteral antibiotics, and surgical consultation should be obtained (21).

Patients with reducible hernias should be referred for outpatient surgical repair.

PHIMOSIS

Phimosis occurs when the foreskin cannot be retracted over the glans. When caused by normal physiologic adhesions, it is called *primary phimosis.* Phimosis is normal in infants and young children, with resolution generally by 6 years of life. Secondary phimosis may occur owing to scarring of the foreskin after inadequate circumcision or due to irritation or infection. Patients generally are asymptomatic. However, in some patients, the constriction causes voiding difficulty, UTI, and local infection of the foreskin and glans.

Physical examination establishes the diagnosis. If symptoms of a UTI are present, urinalysis and urine culture are warranted. Renal function tests and a bedside or formal renal ultrasound should be performed if significant urinary obstruction is suspected.

No treatment is needed for asymptomatic patients younger than 6 years of age. Symptomatic phimosis can be treated with topical steroids, or if conservative treatment fails, with circumcision. Steroid treatment has been shown to be effective in 75% to 88% of boys (23–25). Betamethasone 0.05% or other steroid cream applied to the stretched foreskin twice daily for 1 month is commonly recommended. Symptomatic patients and older boys should have urologic follow-up.

PARAPHIMOSIS

Paraphimosis is a condition seen in uncircumcised males when the foreskin is retracted over the glans for a prolonged period. This leads to edema and venous congestion of the foreskin and glans and eventually impairs blood flow to the glans. The patient presents with increasing swelling and pain. Paraphimosis can occasionally occur in males with a history of circumcision if insufficient foreskin tissue was removed. The diagnosis is made clinically, systematically ruling out hair tourniquet syndrome.

Treatment requires reduction of the foreskin to restore its normal position over the glans. This is best accomplished with effective pain control. Options include oral or parenteral pain medication, procedural sedation, topical anesthetic creams, or a penile block. Controversy exists as to methods of reduction of the foreskin. Reduction is facilitated by first reducing swelling by manual compression, use of sugar-soaked solutions to the area, or aspiration of the fluid in the edematous tissue (24,26). The physician should then place both thumbs on the glans with the index and middle fingers on the distal end of the foreskin. Simultaneous persistent pressure is applied to the glans with the thumbs and to the rolled edge of the foreskin with the fingers so as to return the foreskin to its proper position. If the foreskin cannot be reduced, emergent urologic consultation is necessary. If phimosis is successfully reduced in the ED, urologic follow-up is recommended for possible circumcision.

BALANITIS AND BALANOPOSTHITIS

A break in the foreskin caused by local trauma or poor hygiene can lead to posthitis. Extension of the cellulitis or inflammation to the glans is referred to as *balanoposthitis*. The patient presents with swelling, erythema, and penile pain. Purulent discharge may be present. A culture of any discharge may be sent for identification and proper antibiotic treatment.

The responsible organisms are typically skin flora (i.e., *Staphylococcus* and *Streptococcus*). Treatment includes sitz baths and topical antibiotics. In more severe cases, cephalexin (25 to 50 mg/kg/d divided three times daily for 7 days) can be added (24). Follow-up is recommended, as treatment failures, repeated episodes,

and scarring can lead to phimosis. Patients not in diapers with *candidal* balanitis or balanoposthitis should be evaluated for diabetes mellitus. Patients with swelling severe enough to cause obstruction or concern for a more invasive infection should be admitted for urologic evaluation and intravenous antibiotics.

KEY TESTING

Suspected Disorder	Testing	Consultations/ Referrals
Testicular torsion	• None if diagnosis is likely • Ultrasound if signs/ symptoms make torsion possible but less likely	• Emergent urologic consult
Epididymitis	• Urinalysis and culture • Sexually transmitted infection testing for sexually active males • Ultrasound to confirm diagnosis	• Outpatient urologic follow-up
Hydrocele	• Ultrasound if testis not adequately palpated	• Outpatient pediatric surgery follow-up if persistent past age 2 years or if associated with a hernia
Inguinal hernia	• Generally none	• Emergent surgical consult if strangulated or if unable to reduce incarcerated hernia • Outpatient pediatric surgery follow-up for reducible hernias
Phimosis	• Generally none	• Outpatient urology follow-up in older children or if symptomatic
Paraphimosis	• Generally none	• Consider outpatient urologic follow-up
Balanitis and balanoposthitis	• Consider culture if discharge present • Glucose level if Candidal infection present in toilet-trained child	• Outpatient urologic follow-up if recurrent

CRITICAL INTERVENTIONS

- In patients with suspected testicular torsion, obtain immediate urologic evaluation without waiting for ultrasound confirmation of diagnosis.

- Order an ultrasound in patients with hydroceles if adequate palpation of the testis is not possible as hydroceles can be associated with testicular tumors.
- Obtain an emergent urologic consultation for patients with paraphimosis that cannot be reduced.

Common Pitfalls

- Failure to perform a complete abdominal and GU examination on all males with a complaint of abdominal pain or vomiting
- Delay of urologic consultation in patients with suspected testicular torsion
- Failure to consider testicular torsion in patients with abdominal pain or vomiting and an undescended testicle

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CHAPTER 288

Urinary Tract Infections in Children

Nazreen Jamal and Kathleen Brown

CLINICAL PRESENTATION

Urinary tract infections (UTIs) are the most common serious bacterial infection in infants and young children. However, the diagnosis can be challenging as the clinical presentation and prevalence of UTI varies with age. Children under 2 years of age usually present with fever alone or nonspecific symptoms such as vomiting, diarrhea, failure to thrive, irritability, and jaundice. Preschool children may present with more specific symptoms such as suprapubic pain, urgency, dysuria, and frequency, though some children in this age group may also present with only nonspecific symptoms. Enuresis in a previously continent child may be an indicator of possible infection. In the school-age child with a UTI, symptoms associated with the urinary tract are usually present. Fever may or may not be present, and although it suggests upper tract disease, fever can be present in patients with cystitis and may be absent in a patient with significant renal involvement. Though parental report of malodorous urine is associated with an increased likelihood of UTI, the sensitivity and specificity is not sufficient to be diagnostic (1).

Given the variability in presentation, an understanding of prevalence among subgroups of children can help to better inform the decision to test children for UTI. A meta-analysis showed an overall prevalence of 7% in febrile infants and 7.8% among older

children with urinary complaints. The rates varied significantly, however, based on the child's age, race, gender, and circumcision status. The highest prevalence of UTI was found in febrile uncircumcised males <3 months of age and febrile females <12 months of age (2).

DIFFERENTIAL DIAGNOSIS

In infants, UTI should be included in the differential diagnosis of fever, irritability, gastroenteritis, failure to thrive, and sepsis. When preschool-age and older children present with urgency, dysuria, or frequency, the differential diagnosis for this complex of symptoms should include urethritis, pinworms, vaginitis, and child abuse. Physical examination of the genitalia is necessary to assess for the presence of these problems. Children with constipation are at increased risk of UTIs, and the diagnosis should also be considered in these patients. In the adolescent patient, the presence of sexually transmitted diseases needs to be considered. In addition, patients with group A *Streptococcus* infection, Kawasaki disease, and appendicitis may also present with fever, abdominal pain, and pyuria. A complete history and physical examination can help in the differentiation of these illnesses.

ED EVALUATION

The diagnosis of UTI in children requires the presence of pyuria or bacteriuria on a urinalysis (UA) *and* at least 50,000 colony-forming units per mL of a known uropathogen from a urine sample obtained by urine catheterization or suprapubic aspiration (SPA) (3). Therefore, both UA and urine culture should be obtained when considering a diagnosis of UTI in children. In addition, the presence and risk for short-term complications such as sepsis or meningitis needs to be evaluated, especially in the young infant. The overall risk of bacteremia is highest in children less than 6 months of age (8%), and meningitis in children less than 2 months of age (4–7). As with any pediatric patient, the need for supportive therapy,

including intravenous (IV) hydration, and laboratory studies (to assess renal function) should be considered as clinically indicated.

Who Should Be Screened for UTI?

In 2011, the American Academy of Pediatrics (AAP) issued a revision of its clinical practice guidelines for the diagnosis and management of first time UTIs in children 2 to 24 months. While the previous recommendation advocated for UTI screening of all girls and uncircumcised males less than 2 years with unexplained fever, the most recent guidelines recommend screening based on risk factor stratification (3). The risk factors include (1) child's gender, (2) circumcision status in males, (3) patient race, (4) duration of fever greater than 24 hours, (5) height of fever greater than 39°C, and (6) absence of an alternative source of fever. UTI screening is recommended for children who are not at low risk defined as either $<1\%$ or $<2\%$, depending on clinical scenario and number of risk factors a given patient possesses (Table 288.1). These guidelines do not apply to children with a previous history of UTI, for which the threshold for screening should be lower, nor for ill-appearing children who are determined to require immediate empiric antibiotics, for which urine specimens should be obtained prior to antibiotic administration.

TABLE 288.1
Prevalence of UTI in Children Varies Based on Age, Gender, Race, and Circumcision Status

Febrile Males <3 mos	
Circumcised	2.4% (CI: 1.4–3.5)
Uncircumcised	20.1% (CI: 16.8–23.4)
Febrile Females	
0–3 mos	7.5% (CI: 5.1–10)
3–6 mos	5.7% (CI: 2.3–9.4)
6–12 mos	8.3% (CI: 3.9–12.7)
12–24 mos	2.1% (CI: 1.2–3.6)
Race	
White	8% (CI: 5.1–11)
African American	4.7% (CI: 2.1–7.3)
<19 yrs with urinary symptoms	7.8% (CI: 6.6–8.9)

Modified from Shaikh N, Morone NE, Bost JE, et al. Prevalence of urinary tract infection in childhood: A meta-analysis. *Pediatr Infect Dis J*. 2008;27(4):302–308.

Notably, the absence of another source for fever is included as a risk factor for UTI, but the presence of a diagnosis of a viral infection does not preclude a concomitant UTI. Two large, prospective, multicenter studies evaluated the risk of serious bacterial infection in febrile infants ≤60 days of age with proven viral infections with influenza and respiratory syncytial virus (RSV). Krief et al. (8) noted febrile infants with influenza had a significantly lower (but not absent) rate of UTI (2.4%) than influenza-negative infants (10.8%). Similarly, in a study comparing rates of serious bacterial infections in febrile infants with and without RSV, infants with RSV were found to have a significantly lower rate of UTI (5.4%) compared to those without RSV (10.1%). While rates of UTI may be lower in young febrile infants with viral infections, the presence of a concomitant UTI must still be considered (9).

How Should Specimens Be Collected?

A clean catch sample (obtained with the help of an adult) is an acceptable means of obtaining a specimen for culture and screening tests in children who are continent of urine. In these children, cleaning of the perineum has been shown to significantly decrease

the rate of contaminated specimens (10). However, in children who are not yet continent of urine other methods of collection must be utilized. The recent AAP guidelines offer two options for urine testing in children less than 24 months of age. The first is to obtain a UA and urine culture by urethral catheterization or SPA. The second is to collect a screening UA through the "most convenient means," followed by a UA and urine culture through catheterization or SPA if the initial UA is suggestive of a UTI (3).

Urine obtained by SPA or transurethral catheterization is unlikely to be contaminated and therefore is the preferred specimen for documenting UTI. Both techniques have limited risks but require some skill and experience, particularly in small infants, girls, and uncircumcised boys. Many physicians and parents perceive these procedures as unacceptably invasive and prefer to collect urine specimens from a bag affixed to the perineum. If a UA collected in this manner is negative, further testing can be avoided. However, positive results require confirmation since bagged specimens are likely to yield a high rate of false-positive results no matter how well the perineum is cleaned.

Both options are acceptable in situations where immediate empiric antibiotic therapy is not clinically indicated. However, if immediate antibiotic treatment is clinically indicated, urine should be obtained by SPA or catheterization prior to administration of antimicrobials, as the opportunity to confirm the presence of a UTI may otherwise be lost.

KEY TESTING

- UA and urine culture
  - Catheterized specimens recommended for patients who are not yet continent of urine
  - Bag specimens can be used for screening UA, but should be followed with catheterized specimens for repeat UA and urine culture if positive
- Blood cultures and lumbar puncture in febrile infants <4 weeks of age and when otherwise clinically indicated

• Renal function tests only as clinically indicated

ED MANAGEMENT

The major considerations in managing a child with a possible UTI include assessing for need for hydration, antibiotic therapy, and inpatient admission.

Who Should Be Treated in the ED?

The gold standard for diagnosis of UTI requires both UA and urine culture results. However, screening tests are often relied upon to make treatment decisions in the emergency department because delayed initiation of antibiotic therapy has been associated with increased severity of infection (11,12). A UA that includes microscopy with a hemocytometer is more sensitive and specific than a urine dipstick, however is not always available. A UA positive for leukocyte esterase, nitrite, or microscopy positive for white blood cells or bacteria is considered a positive UA, and is suggestive, but not diagnostic of UTI. The diagnosis of UTI is highly unlikely ($<0.3\%$) when the UA is negative. Initiation of antibiotics is recommended when the UA is positive, with subsequent discontinuation of antibiotics if the urine culture is negative (3).

Who Should Receive Parenteral Antibiotics?

In the past, it has been recommended that all infants with a UTI be hospitalized for IV antibiotic therapy. More recent studies indicate that it may be safe to consider outpatient therapy for otherwise healthy infants older than 1 month of age with a presumptive UTI who do not appear toxic, are tolerating oral fluids, and are likely to be compliant with oral antibiotics (13,14). Initiating therapy with oral or parenteral therapy is equally efficacious under these conditions (Table 288.2) (3). Patients not meeting criteria for admission for IV antibiotics can be safely treated as outpatients with appropriate follow-up.

TABLE 288.2
Indications for IV Antibiotics

Toxic appearance
Age <4 wks
Unable to tolerate oral antibiotics
Require ongoing hydration
Require IV pain control

Which Antibiotic Should Be Used?

Antibiotic selection should be tailored to the age of the child being treated and guided by local antimicrobial sensitivity. A list of antibiotics commonly used in the treatment of UTI is listed in Table 288.3. Knowledge of regional and local resistance patterns is essential to initiating appropriate antibiotics for oral therapy. The antibiotic can later be adjusted once the sensitivity of the isolated uropathogen is available (3). Recent data demonstrate that resistance to many drugs traditionally used to treat UTIs in children is unacceptably high and rising. In a national survey, *Escherichia coli,* the most commonly isolated uropathogen, had the highest resistance rates to ampicillin (45%) and trimethoprim-sulfamethoxazole (24%) (15). First-generation cephalosporins and nitrofurantoin were found to be narrow spectrum drugs with low resistance rates. However, drugs such as nitrofurantoin, which are excreted in the urine but do not reach therapeutic concentrations in the bloodstream, should be avoided in the treatment of febrile UTIs in infants (Table 288.3) as they may be insufficient to treat pyelonephritis or suspected urosepsis (3).

TABLE 288.3
Empiric Antimicrobial Agents for Treatment of UTI

Parenteral	Oral
Ceftriaxone	Amoxicillin-clavulanate:
75 mg/kg, every 24 hrs	20–40 mg/kg/d in 3 doses
Cefotaxime	Trimethoprim-sulfamethoxazole:
150 mg/kg/d, divided every 6–8 hrs	6–12 mg/kg trimethoprim and 30–60 mg/kg sulfamethoxazole per day in 2 doses
Ceftazidime	Cefixime
100–150 mg/kg/d, divided every 8 hrs	8 mg/kg/d in 1 dose
Gentamicin	Cefprozil
7.5 mg/kg/d, divided every 8 hrs	30 mg/kg/d in 2 doses
Tobramycin	Cefuroxime axetil
5 mg/kg/d, divided every 8 hrs	20–30 mg/kg/d in 2 doses
Piperacillin	Cephalexin
300 mg/kg/d, divided every 6–8 hrs	50–100 mg/kg/d in 4 doses

Modified from Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB. Urinary tract infection: Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128(3):595–610.

How Long Should Patients Be Treated?

Recommendations on the duration of therapy vary. Because short-course and single-dose therapies have been successful with women, short-course regimens may be acceptable for uncomplicated cystitis in adolescent girls. For febrile children 2 to 24 months of age, 1- to 3-day courses of antibiotics have been shown to be inferior to longer courses; the current recommendation is to treat for a total of 7 to 14 days (3,16). Studies of short-course therapy in children have yielded conflicting results and it is often difficult to differentiate uncomplicated cystitis from pyelonephritis in younger children, therefore, most experts still recommend a 7- to 10-day course of antibiotics in prepubertal children with cystitis and up to 14 days when pyelonephritis is suspected. Follow-up within 48 hours should be arranged to ensure children are demonstrating an adequate response to therapy.

CRITICAL INTERVENTIONS

- Screen febrile infants with a high likelihood of UTI based on presence of risk factors
- UA can be obtained by catheterization, suprapubic aspiration, or by urine bag attached to the perineum when screening for UTI. However, the latter requires a second urine sample if screening is positive.
- A positive UA should *always* be confirmed by a urine culture sent from a urine sample obtained by *catheterization or SPA only*
- Assess all children with suspected UTI for the presence of dehydration, sepsis, and renal failure
- Treat children with suspected UTI or pyelonephritis promptly with antibiotics known to have a low rate of resistance in your locality
- Make sure caregivers of young children understand the importance of follow-up and the possible need for repeat urine culture and anatomic evaluation

DISPOSITION

Most patients older than 1 month of age can be safely managed as outpatients. In any patient managed as an outpatient, an initial dose of antibiotic should be given in the ED either orally or parentally. Though early initiation of appropriate antibiotic does not necessarily protect against renal scarring, prompt diagnosis and treatment of UTI continues to be recommended to reduce the risk of renal involvement (12,17). Previously, strategies to prevent renal scarring in children relied upon the use of imaging after UTI to detect abnormalities of the genitourinary tract that would require additional evaluation. However, due to the lack of evidence supporting routine screening with voiding cystourethrograms (VCUG) on all children with febrile UTIs, the AAP recommendations have since been revised. The new guidelines continue to recommend that all children 2 months to 2 years of age with a febrile UTI undergo a renal and bladder ultrasound (US). The US need only be performed during the acute illness *if* the patient is not responding appropriately to antibiotics. A VCUG, however, should be performed

only if abnormalities are noted on the screening US (3). Although these studies would not be performed in the ED, the emergency physician should be cognizant of the latest recommendations to provide appropriate anticipatory guidance and follow-up instructions to families.

Common Pitfalls

- Failure to consider UTI as a source of fever in otherwise asymptomatic children leads to missed or incorrect diagnoses. Viral infections do not preclude UTI as the source of fever in the young child.
- Failure to obtain a urine culture by catheterization or SPA to confirm positive screening UAs may lead to inaccuracies in diagnosis and uropathogen isolation.
- Failure to recognize local antibiotic resistance patterns may lead to ineffective treatment.
- Failure to ensure appropriate follow-up can fail to detect children with treatment failure or progression of disease.

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CHAPTER 289

Psychosocial and Behavioral Emergencies

Cynthia J. Mollen

Mental health disorders in children have become a significant health problem. It is estimated that one of every five children in the United States meets criteria for a mental health disorder with at least some impairment expected over their lifetime (1). These patients frequently present to the emergency department (ED) (2,3). Though the mental health needs of children are quite large, there are many barriers to accessing mental health services for pediatric patients, such as lack of insurance, insufficient numbers of specialists who care for children with mental health problems, and the stigma accompanying mental health disorders (4,5). In addition, barriers specific to care in the ED setting include lack of knowledge about pediatric psychiatric illness, limited time, the use of many ED resources, and frequent revisits, contributing to overcrowding (6,7).

CLINICAL PRESENTATION

Depression and Suicide

Depression-related suicidal ideation is the leading serious psychiatric cause for an ED visit. The prevalence of depression increases through adolescence, with 1-year prevalence estimates of 3% to 8% and a lifetime prevalence of approximately 20% (8,9). Depression can be difficult to diagnose because of fluctuating symptoms or vague presenting complaints (8).

Common symptoms of depression include: Sadness, irritability, boredom, mood swings, anxiety, school refusal, declining grades, and substance abuse. While suicide and depression are closely associated there are multiple suicide-specific risk factors, including a family history of suicide, a personal history of a suicide attempt, and poor school attendance (5,10,11).

Anxiety, Obsessive–Compulsive Disorder, and Posttraumatic Stress Disorder

Anxiety disorders, such as panic disorder, separation anxiety, phobias, posttraumatic stress, or obsessive–compulsive disorder, are the most prevalent type of mental health disease in children and adolescents (12). Anxiety in children is often manifested by nonspecific physical complaints. Therefore, an extremely thorough history to separate organic disease from anxiety-related disorders is vital.

Neurobehavioral

There are numerous visits to the ED by children with known neurobehavioral disorders such as attention deficit hyperactivity disorder (ADHD), often because of worsening symptoms or medication-related problems, such as adverse reactions or abuse of medications. For example, use of stimulant medications for ADHD can lead to loss of appetite and weight loss. Medications can be abused for the purpose of weight loss or for recreational purposes (13). Furthermore, children with ADHD or other behavioral disorders may present to the ED for routine emergency complaints; it is important to consider how their underlying disorder(s) or baseline medications may complicate evaluation and medical management with particular attention toward sedation and prescription medications.

Differential Diagnosis

When considering the potential etiologies of a pediatric mental health emergency, emergency physicians must recognize several organic medical disorders may present as acute behavioral disturbances. Alternative medical diagnoses to consider include many disease categories considered in the evaluation of adult psychiatric patients including intracranial lesion or injury, acute drug intoxication or withdrawal, CNS infection, endocrinopathies (i.e., hyper- or hypothyroidism). Among children additional etiologies to consider should include abuse or neglect, metabolic disturbance, and undiagnosed seizure disorder.

When differentiating between organic and psychiatric etiologies of psychosis, consider organic etiologies in patients with the following: (1) New or sudden onset of symptoms with no previous psychiatric history, (2) altered level of consciousness, or (3) abnormal vital signs, neurologic changes, or physical examination findings.

ED Evaluation

When dealing with a pediatric mental health problem the history is perhaps the most critical aspect of the ED encounter. Children, especially younger ones, are usually unable to provide a clear history of past and current problems, so ED physicians must rely on information from numerous other sources, including parents, siblings, relatives, teachers, and other health care providers.

A standard medical history should be performed, and additional questions should explore the circumstances for the ED visit including escalating behavioral problems, threats to self or others, changes in affect, and school performance can be important indicators of severe disease. When the patient is old enough to engage in the history (often as young as 4 or 5 years old), questions should be directed at the patient, with additional questions to the caretaker. It can often be useful to interview the caretaker alone as well. A detailed medication and substance use history is also important, including questions about compliance and side effects, and a complete physical examination is necessary as well.

Adolescents with mental health complaints require a thorough psychosocial assessment by qualified mental health professionals or physicians and should be interviewed with extreme attention to confidentiality. Several structured interview approaches have been widely accepted as templates for gathering information on all aspects of teenage life. Generally these structured interviews progress slowly from less sensitive topics to more sensitive ones (Table 289.1) (14,15). Prior to the start of the psychosocial interview, it is imperative to clarify with patients when confidentiality will be maintained and when it may be needed to be breached (such as if the patient reveals the possibility of harm to themselves or others or in circumstances where mandatory reporters must alert authorities about potential abuse) (16). The confidential interview is critical as it may be the only mechanism for identifying risk factors linked to depression, including substance abuse, sexual orientation and behavioral issues, and the presence of firearms in the home. In addition, this provides the best setting to screen for suicide, which should be included in all assessments of adolescent patients (5,10–12,17). One approach recommend by the American Academy of Pediatrics (AAP) is to ask a general question such as, "Have you ever thought about killing yourself or wished you were dead," followed by, "Have you ever done anything on purpose to hurt or kill yourself?" These questions should be toward the end of questions about depressive symptoms (10).

TABLE 289.1
Components of the Psychosocial Assessment of Adolescents

Heeadss	Shaddsss
Home	School
Education	Home
Eating	Activities
Activities	Depression/self-esteem
Drug use and abuse	Diet
Sexual behavior	Substance abuse
Suicidality and depression	Sexuality
	Safety

The ED evaluation of mental health complaints must be tailored to the specific problem. In many instances, no laboratory or radiologic imaging will be required, such as in cases of a patient with a known history of depression and an exacerbation of suicidal thoughts but no actions. In contrast, any patient with a change in mental status not accounted for by psychiatric disease, with generalized medical or traumatic complaints, or in whom the diagnosis is uncertain should undergo a focused diagnostic medical evaluation for medically indicated. Selective testing for well-considered medical disorders are much more likely to yield meaningful results than batteries of tests blindly ordered for screening purposes (18).

KEY TESTING

Testing should be guided by the patient's signs and symptoms. Diagnostic tests to consider in appropriate cases may include some or all of the following: Complete blood count; serum electrolytes, blood urea nitrogen, creatinine, and glucose; liver function tests; ammonia level; urine pregnancy test (bHCG) in females; electrocardiogram; chest x-ray; head computed tomography (CT); lumbar puncture; and thyroid function tests. Other tests, such as antinuclear antibody (ANA), are ordered less frequently. Diagnostic testing for patients with mental health complaints should be selective and thoughtful. Not all patients require laboratory evaluation and tests should not be ordered indiscriminately or for screening purposes. Serum and urine toxicologic screens are

frequently a focus of ED testing for mental health patients. Specific agents included on available laboratory screens tend to differ from hospital to hospital, and ED physicians must be aware of local variations. Although many inpatient psychiatric facilities require such testing prior to admission, toxicology testing should never be forced upon a patient simply because of a parent's or caretaker's request (17). Rather, there should be a definite medical or psychiatric indication for testing (16).

ED Management

The ED management of pediatric mental health disorders varies according to the disorder. The ED physician's role is one of advocacy and usually involves evaluating for organic disease and determining the need for consultation and potential transfer to a specialized mental health facility. In the setting of an acute psychiatric or behavioral crisis, the need to provide for safety of patients and caregivers and to limit disruption to the care of patients is paramount. Although rarely necessary in children, physical and chemical restraints are important elements of safety and often complement each other. Many patients can be calmed through techniques other than physical or chemical restraints, such as decreasing stimulation, providing one-to-one support, using relaxation activities, and involving family members. If restraints become necessary, appropriate policies and procedures must be followed.

The AAP statement on the use of physical restraints calls for documentation of the reasons for use of restraint, specific orders (verbal or written) with an attempt to define time limits of use, assessment that restraints are being used properly (not causing physical harm to patient) with close monitoring, and for possible release from restraints when the acute crisis has abated and safety can be assured (19). The practice of patient restraint is carefully regulated by the Joint Commission of Healthcare Organizations. It emphasizes that physical and chemical restraints must be used as a last resort when other methods to control the patient have failed.

The Joint Commission also requires that each health care facility have a written policy and procedure in place to ensure appropriate use (20).

Chemical restraint may be needed when a patient continues to be agitated while in physical restraints or, in specific cases, as an option prior to physical restraint. In children, commonly used medications for chemical restraint are benzodiazepines and butyrophenones. These drugs are useful in the control of agitated behavior and have a long duration of action. An alternative sedative is diphenhydramine; however, this should be used with caution because it may cause paradoxical excitement.

CRITICAL INTERVENTIONS

- Perform a thorough medical evaluation first to exclude organic causes for symptoms
- Consider depression in children who present with a change in their behavior
- Assess thoroughly for suicidal thoughts, intent, and plan
- Question adolescents with an emphasis on privacy and confidentiality
- Document the indication for restraints, if they are needed, and frequently reassess this need

Disposition

A team approach to the ED evaluation of pediatric mental health disorders is considered optimal. Physicians, nurses, social workers, child life personnel, ED technicians, security personnel, and mental health consultants all play a role in establishing an effective evaluation, treatment plan, and safe disposition. However, it is recognized that many EDs will not have this comprehensive set of resources. EDs lacking specific mental health resources should have established referral patterns and a mechanism for transfer or hospitalization. Other potential resources for families with children with mental health needs include primary care physicians, the

school system, clergy, support groups, and community-based mental health centers.

In patients who are considered to be at immediate risk for suicide, one-to-one observation by an ED staff member must be initiated and maintained throughout the ED stay. All pediatric patients who are actively suicidal should have consultation with a mental health provider. If hospitalization is recommended by either the emergency physician or mental health consultant, it is preferred that the parent or patient consent to admission. In cases where the patient is a mature minor and refuses hospitalization, an involuntary commitment order may need to be applied if the patient is considered to be at risk for harm to self or others. An emergency physician or mental health physician is authorized to apply such a commitment. The specifics of involuntary commitments vary from state to state and it is incumbent upon providers to be aware of the state laws governing the commitment of minors for mental health treatment.

Depressed patients who are not actively suicidal and not considered high risk, with no access to lethal methods and a supervising adult who can closely monitor their behavior may be discharged with urgent outpatient follow-up (21). Emergency physicians should take extra precautions to ensure follow-up is prearranged at the time the patient leaves the ED and that an alternative plan is in place if follow-up fails (i.e., primary care visit, return to the ED).

Common Pitfalls

- Failure to aggressively explore nonspecific complaints in a child or adolescent who do not seem to have an organic basis for the possibility of depression/suicide. Depression often masquerades as nonspecific somatic complaints and many depressed and suicidal patients have visited a physician shortly before attempting suicide.
- Failing to enquire about the presence of firearms in the home or access to firearms in general as part of disposition planning. The

presence of firearms in the home is considered a highly lethal risk factor for completion of suicide.

- Failure to detect medical conditions with presenting symptoms that mimic psychiatric disorders. Metabolic, infectious, and toxicologic problems related to acute mental status changes should be assumed to have an organic etiology, particularly, in the case of a first episode or in a younger patient with no known psychiatric or behavioral disorder.

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CHAPTER 290

Child Abuse: Physical, Sexual, and Neglect

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Child maltreatment refers to the abuse and neglect of a child under the age of 18 by a parent or another caregiver, resulting in harm or risk of harm to the child. In 2011, U.S. state and local child protective services (CPS) received an estimated 3.7 million referrals, 681,000 of which were founded (1). Seventy-nine percent were victims of neglect, 18% were victims of physical abuse, 9% were victims of sexual abuse, and 10% were victims of other types of maltreatment (1).

The emergency department (ED) is a common setting for victims of child maltreatment to present. Abused or neglected children may be brought to the ED for common pediatric conditions or in critical condition as a result of abusive injuries and/or neglectful behavior. The history provided by the caregiver and/or patient remains the most important diagnostic tool when assessing for abuse and neglect.

All medical professionals in the United States are mandated reporters of suspected child abuse, with specific requirements in each state. Medical professionals are not required to prove abuse or neglect; law enforcement and CPS will determine if a suspicion is substantiated. No penalty may be brought against medical professionals reporting in good faith; however, serious penalty may result for failure to report suspected child abuse. It is therefore crucial to have a low threshold for reporting concerning injuries to the appropriate authorities.

PHYSICAL ABUSE AND NEGLECT

Child maltreatment can be defined by two categories: (1) An action (commission) or (2) a lack of action (omission) resulting in actual harm or possible harm to a child. Acts of commission include words or actions that harm the child physically, sexually, or emotionally. Acts of omission refer to child neglect. Neglect encompasses the failure to protect a child from harm and/or a failure to provide for a child's basic physical, emotional, or educational needs (2). This section discusses primarily child physical abuse.

Child physical abuse affects children of all ages, genders, ethnicities, and socioeconomic groups. Although the risk of physical abuse increases with age, fatal abuse and serious abusive injuries are more common among children and infants younger than 2 years (3).

CLINICAL PRESENTATION

Physically abused children may present to the ED in virtually any condition ranging from benign and well appearing to critical depending on the type and severity of injury. For some children, an injury is the presenting complaint; for others, an injury, abuse, or neglect is uncovered only during the course of the ED evaluation. What these patients share almost universally are vague, and at time evasive, histories. Emergency physicians must perform careful focused interviews to uncover how an injury may have occurred and to fill in vital missing details to determine if there are any other comorbidities associated with the injury. When evaluating a patient for an injury, the physician must consider the comorbidity of neglect. For example, an infant evaluated for an unexplained leg fracture may also be diagnosed with failure to thrive (3). It is important to appreciate that injuries have many causes and abuse is but one of them; assumptions of guilt should be avoided.

DIFFERENTIAL DIAGNOSIS

To establish whether an injury is accidental or inflicted relies on a plausible history of trauma that is consistent with the child's

developmental status (3). The differential for an injury must include medical conditions that mimic inflicted injuries. Some cutaneous conditions mistaken for abuse include dermal melanocytosis, vascular cutaneous markings (e.g., flame nevi), bullous impetigo, contact dermatitis, chemical burns. When evaluating for fractures, some conditions mistaken for abusive injuries include physiologic subperiosteal new bone formation, nutritional deficiencies, Caffey disease, leukemia, osteomyelitis, and osteogenesis imperfecta (4).

ED EVALUATION

It is important to maintain a neutral professional manner throughout the evaluation with parents and avoid being accusatory or judgmental. Obtaining and documenting a chronologic timeline of events, including behavior and symptoms before and after the injury, is critical to determining if the mechanism is consistent with the injury. The timeline is used to identify when the injury would have happened and provides a framework to compare histories for consistency. If there are multiple caretakers, they should be interviewed separately. The history should include the child's development, previous injuries, birth history (including any trauma during the birth), bleeding tendency, temperament, and any prior ED visits or hospitalization. Of note, the initial history may change if the caretaker perceives any doubt on the part of the healthcare provider (5). The primary medical doctor should also be contacted for additional information.

A complete physical examination should accompany the history and detailed timeline. Examination may reveal additional injuries which may increase the suspicion of child abuse. Examinations where physical abuse is suspected should include external examination of the genitals given the strong association between physical and sexual abuse. Accidental and inflicted injuries may occur together; there are only a very small number of injuries that stand alone as indicators of inflicted injury.

Below are some common manifestations of physical abuse and neglect:

Cutaneous Injuries

Bruises are the most common manifestation of inflicted injury, but are also very common in active healthy children. All skin injuries (e.g., bruises, abrasions, lacerations, bites, and burns) should be described by location, size, and shape, keeping in mind whether they seem to fit a pattern (e.g., human bite mark, hand print, belt mark, etc.). Bruising, in addition to being well described, should be photo documented in the medical chart with a length scale (4). Color can be used for descriptive purposes but should not be relied upon to determine the age of a bruise.

Accidental bruises are more frequent and are located in areas exposed to injury in play, such as elbows, knees, skin over the anterior tibias, and bony prominences. In contrast, inflicted injuries tend to occur at sites away from the bony prominences, including the anterior and posterior neck, head, buttocks, hands, upper extremities; obscure locations include ears and frenula, which makes their inspection critical (3). Any bruising in a nonambulatory infant requires further workup for concern of possible abuse.

Burns are a specific form of cutaneous injury that may be due to child abuse. The majority of childhood burns are accidental. The most common type of inflicted burn is by scalding hot liquid. Accidental scalds typically involve hot liquids pulled and splashed on the child's upper body. To differentiate, inflicted scalds or forced immersion burns typically have a sharp line of demarcation. Inflicted burns may also be the result of the application of hot objects (e.g., cigarette burns or a hot iron) or chemical or electrical injuries (5). The depth of a burn depends on the time of exposure and temperature. For more information, please see Chapter 46.

Fractures

As with any fracture, swelling, tenderness, or disuse of an extremity may indicate underlying fracture. There may not be an overlying bruise. Rib fractures in infants, classic metaphyseal lesions, multiple and complex skull fractures, scapula fractures, fractures of the vertebral body or spinous process, as well as fractures in a

nonambulatory child are concerning for abuse. Rib fractures and metaphyseal fractures may not be clinically evident; therefore, a negative physical examination does not rule out an occult injury (3).

Abusive Head Trauma

"Shaken baby syndrome" is a popular term used to describe injuries resulting from abusive head trauma (AHT). However a greater understanding of the mechanisms and injuries associated with AHT has caused a shift in this terminology. The American Academy of Pediatrics recommends physicians abandon the term "shaken baby syndrome" since it implies a specific back and forth, acceleration–deceleration mechanism. In younger children the acceleration–deceleration more specifically will result in rotation of the head as it sits upon the neck. "Shaken baby syndrome" also does not include blunt impact as another possible mechanism. AHT is a more inclusive term, referring to mechanisms which include but are not limited to shaking (6).

The incidence of AHT during the first 2 years of life has been estimated in various studies to range from 16.1 to 33.8 cases per 100,000 infants per year (5). It is the leading cause of child abuse fatalities in infants (3). Victims of AHT may present with vague, nonspecific, poorly explained symptoms including feeding difficulty, vomiting, irritability, respiratory changes (including apnea), lethargy, seizures, hypothermia, hypotonia, or altered mental status. The most common presentation is of respiratory difficulty, apnea, or unexplained seizures, secondary to increased intracranial pressure.

Victims of AHT may present with soft tissue injuries to the scalp, skull fractures, intracranial bleeding, or parenchymal brain injuries. These injuries can occur in isolation or in combination and the evaluation may detect coexisting injuries unexplained by the mechanism offered for the initial head injury. These coexisting injuries include retinal hemorrhages (RHs), long bone and rib fractures (7).

RHs are present in 70% to 80% of confirmed cases of AHT. RHs are found in less than 10% of non-AHT. With AHT, RH are more

often bilateral and more numerous; found throughout all layers of the retina out to the periphery (ora serata) (7). With non-AHT, they are more frequently unilateral and fewer in number confined to the posterior pole or optic disc. An ophthalmologist with pediatric experience should be consulted to perform a dilated retinal examination to evaluate for RHs (7).

The fractures associated with AHT are a direct result of the mechanism. Skull fractures may be seen as the result of impact on a hard surface. Metaphyseal fractures at the ends of long bones may be seen as the result of the child's extremities flailing around during the injury or due to twisting or pulling of the extremities when the child is mishandled. Rib fractures, especially posterior-medial, may be the result of squeezing as the child is gripped around the chest during the injury. Posterior-lateral rib fractures may also be the result of squeezing, but can also result from blunt impact. With the exception of two-handed CPR in neonates and young infants CPR will usually not result in posterior rib fractures (3).

Abdominal Trauma

Although uncommon, abdominal trauma is among the leading causes of death from physical abuse. Injury can be due to blunt trauma or penetrating trauma. The most commonly injured organ is the liver, followed by spleen, hollow viscus, and pancreas (8). If the intestines, liver, or spleen have been ruptured, guarding or abdominal muscle rigidity may be noted on palpation. Abdominal bruising may be present, but is uncommon (3). Patients with altered mental status being evaluated for abuse with negative head CTs should be evaluated for occult abdominal trauma.

Neglect and Medical Child Abuse

Child neglect is the most common form of child abuse, accounting for nearly half of all child abuse fatalities. Types of neglect include physical (e.g., failure to thrive), medical, dental, poor oversight (e.g., ingestions), emotional, educational, and "other" (including exposure to domestic violence and illegal activities) (5). The

diagnosis of neglect often requires an extensive medical record review and multi disciplinary investigation.

The opposite of neglect, specifically medical neglect, is medical child abuse, formerly referred to as Munchhausen syndrome by proxy. Medical neglect refers to the child *not* receiving adequate medical treatment, while medical child abuse occurs when a child receives *too much* medical treatment (5). Medical child abuse should be considered when a child receives unnecessary and potentially harmful medical care at the insistence of a caretaker (5). As with physical abuse, the history frequently does not match the clinical status of the patient.

As with neglect, the diagnosis of medical child abuse can be difficult to make in the ED. The ED physician should consider it in the patient with multiple ED/hospital visits, multiple rare diagnoses, and the abrupt onset of symptoms with no clear medical etiology. Caretakers may list various concerns, cite diagnoses that are untrue, and request invasive procedures or hospitalization. A high level of suspicion should be maintained, and CPS should be contacted when necessary (9).

KEY TESTING

When physical abuse or neglect is suspected, testing may be indicated for diagnosis, for screening to detect other injuries, or to rule out undiagnosed medical causes to account for the injuries. Testing is based on the injury severity and age of the child.

- Children < 2-year old who have injuries or symptoms suspicious for abuse, should receive a skeletal survey to look for occult injury. A single radiograph of the entire infant ("babygram") is inadequate. Skeletal survey should be followed up in 2 weeks, to look for acute fractures not visualized on initial imaging (4).
- Children > 2-year old should have x-rays of clinically affected limbs to look for fractures (4).
- Children < 1-year old with injuries or history suspicious for abuse should *also* have a noncontrast head CT (NCHCT). Note that if the NCHCT does not yield any information and there is

high suspicion of child abuse, obtain an MRI of the head/neck with T1/T2, echo, and FLAIR (fluid attenuation inversion recovery) sequences (4).

- If AHT is suspected, CBC, PT, PTT, and DIC laboratories may be indicated since intraparenchymal damage may affect coagulation. Laboratory evaluation is guided by the clinical status of the patient and the workup should proceed as it would for any patient in critical condition to stabilize them.
- For suspected abdominal trauma, hepatic enzymes, as well as amylase and lipase should be obtained and a CT scan of the abdomen should be obtained when indicated.
- When a toxic ingestion is suspected as a result of neglect, physical or medical abuse, obtain a urine toxicology screen. There are several limitations of the available testing so a negative test may require follow-up broader more advanced toxicologic screening tests.
- If an underlying medical cause for the patient's presentation is suspected, consultation with a specialist is recommended. For example, bruises in a child do not alone require further testing, however when a bleeding disorder is of concern, screening laboratories may be indicated in addition to consultation with a hematologist.

ED MANAGEMENT

All findings on history and physical examination should be documented clearly in the medical chart. Direct quotes from the child and caregiver should be utilized. Photo documentation should be obtained and clearly labeled with the patient's name and date of presentation to the ED. There should be a clear, precise description of any injuries. All radiologic studies should be reviewed by a pediatric radiologist specifically looking for osteopenia or any indication for an underlying metabolic condition. Though abuse may still have caused the injury, the mechanism in these instances would require less force. Dating of fractures or subdural hematomas

may be imprecise and therefore should be described simply as either acute or healing.

Social work where available should be consulted to perform a family psychosocial assessment and screen for domestic violence, substance abuse, or any contact with CPS in the past. When the decision is made to contact CPS, the physician should calmly inform the parent(s) a report is being made because he or she is required to do so by state law in cases where there is an injury to a child without a clearly understood mechanism. It is generally helpful to explain what is anticipated after the report is made by informing the parents about the steps in the investigative process. Investigators will want to talk with the caretakers, often speaking with each one separately, as well as speaking to the child if he or she is old enough to relate what happened.

CRITICAL INTERVENTIONS

- Complete a thorough history and physical examination with clear documentation, including photographic documentation of injuries.
- Recognize when the history provided is inconsistent with the developmental stage of the child or with the stated mechanism of the injury.
- Consider and investigate diagnoses other than abuse.
- Order appropriate testing based on age and injury severity.
- Maintain a low threshold for contacting CPS to make a report of suspected abuse or neglect.

DISPOSITION

Emergency physicians must assess the degree of imminent risk to the child if they are discharged home. CPS will determine if it is safe for the child to go home with their caregiver(s) or if they should be placed into state custody. The child should not be discharged until there is a safety plan established. Many times if the child is in critical condition, due to AHT for instance, he/she will be admitted to the hospital.

Common Pitfalls

- Failure to identify infants who present with nonspecific symptoms as possible victims of child abuse.
- Failure to take a complete history, including developmental level of the patient, and evaluate for the mechanism of injury.
- Failure to complete a thorough photo documentation of injuries.

SEXUAL ABUSE

The sexual abuse of a child is imposed sexual activity for which the child is not emotionally, intellectually, or developmentally prepared to give consent. The sexual activity can include, but is not limited to, direct physical contact between victim and abuser (i.e., genital, oral–genital, anal–genital, breast contact, fondling, use of objects to penetrate the oral/anal/genital cavities of the victim) or can be without physical contact (voyeurism, production or viewing of child pornography, exhibitionism) (10). Adolescent patients can be victims of sexual abuse just like prepubertal children. This is distinct from adolescent sexual assault which is "any genital, anal, or oral penetration by a part of an individual's body or by an object, using force or without a person's consent" (11). Of note, the age of consent for sexual intercourse and reporting requirements to CPS, parents, or law enforcement vary from state to state (12,13).

The treatment of adolescent sexual assault is approached similarly to adult sexual assault, with some key considerations (e.g., most commonly acquaintance rape, familiarity with your state's statutes surrounding statutory rape, the developmental level of the adolescent as compared to an adult, and physical examination in adolescent is less likely to have findings than in adults) (14). Please see Chapter 135.

CLINICAL PRESENTATION

A sexual abuse victim may present to the ED in a variety of ways. For instance, a clinically stable patient may be taken to the ED after a disclosure of sexual abuse to a parent or caregiver. Alternatively parents may suspect sexual abuse has occurred as a result of unusual

physical or behavioral symptoms leading them to bring the patient to the ED. Most of these signs and symptoms are incredibly nonspecific and are frequently linked to common pediatric issues in nonsexually abused children. Examples include nonspecific abdominal pain, enuresis, encopresis, or genital or rectal itching. Behavioral complaints include sexualized behavior, changes in school performance, sleep disturbances, and phobias (10).

Patients presenting to the ED critically ill (e.g., hemorrhagic shock from vaginal or anal trauma), must initially be stabilized, making forensic evidence collection, questioning, and reporting a secondary priority (10).

DIFFERENTIAL DIAGNOSIS

"Mimics" of findings otherwise concerning for sexual abuse include vaginitis, vulvar dermatitis, labial adhesions, anal fissures, genital/anal infections, foreign bodies, vascular problems, neoplasia, urethral prolapse, ureterocele, and lichen sclerosus (5). Accidental anogenital injury is uncommon with the exception of straddle injuries which generally have clear, unambiguous histories. Normal and developmental variations to the anogenital area should also be considered and referenced, in prepubertal females particularly in terms of hymen anatomy (5).

ED EVALUATION

The vast majority of the time in sexual abuse, the physical examination is normal, making the patient's history critical. It is important to know your local resources and state policies. Assuming that a child advocacy center (CAC) or child abuse pediatrician (CAP) is available, a full forensic interview will take place later under optimized conditions. ED physicians may not have training in forensic interview techniques or the time necessary to conduct such an extensive interview but this should not prevent a thorough medical history from being obtained (5). Before beginning, the physician should explain his/her role, the steps in the evaluation, and all elements of the physical examination, to minimize anxiety

for the patient and family members. The physician should take time to build rapport and trust with the child to facilitate a more relaxed and cooperative examination. When appropriate, a brief history should be obtained from the child directly and separately from the parent for the purposes of medical diagnosis and treatment (5). The child's developmental stage should be considered to ensure that the questions asked can be be reliably answered based on language acquisition. Very young children (ex. less than 6 years old) are susceptible to repeated and/or leading questioning in part because of their dependence on adults. When an adult repeatedly asks a young child the same questions, there is the risk that the child will give different answers to please the adult. It is therefore advisable that very young children not be interviewed in this setting (5). When talking to an older child or adolescent who is developmentally appropriate, questions pertinent for the patient's medical care should include a history of the events—specifically, the frequency of contact, most recent contact, type of contact (penile–oral, penile–vaginal, penile–anal, fondling), any physical symptoms or injuries, condom use, and abuser characteristics (e.g., known to be HIV positive) (5). It is also important to determine the mental state of the patient and screen for suicidal ideation and/or depression where appropriate.

The physical examination should begin with a general examination to check for other physical injuries that may require photo documentation.

If the history provided reveals the last contact occurred within the previous 72 hours or there are symptoms concerning for an acute injury (e.g., anogenital pain, anogenital bleeding), emergent anogenital examination should be performed. When the type of contact would not necessitate evidence collection or examination (e.g., touching without penetration), more than 72 hours has passed, or there are no symptoms (e.g., bleeding, pain, discharge), it is not necessary to perform a genital examination in the ED. As long as the patient is safe, examination by a skilled child abuse pediatrician can be scheduled in the outpatient setting (10).

Emergent anogenital examination is necessary when there are symptoms and/or the patient presents within 72 hours of the last contact. Of note, a speculum examination is not recommended at the time of presentation unless there is vaginal bleeding, and concern for intravaginal injury. Surgery or gynecology should be consulted in that case. Anesthesia will likely be necessary in the prepubertal child and should be strongly considered in the adolescent patient if she is unable to cooperate with the examination (5). It is important to note that, unlike a prepubertal patient, an adolescent patient has the right to refuse any part of the examination.

When anesthesia is not required, the patient should be examined in the most comfortable position possible. For prepubertal females, the supine frog-leg position provides the examiner with a clear view of the anogenital structures (5). When the patient is supine, the examiner can lightly grasp the labia and pull downward, outward, and anteriorly (labial traction). The prone knee-chest position allows better viewing of the posterior hymen and upper vagina. This position should be used to confirm a suspected hymenal injury. The use of a gynecologic examination table in the lithotomy position can be used with older children and adolescents. Always remember to document the patient's Sexual Maturity Rating (5).

The vast majority of the time the genital examination will be normal even if the child gives a clear history of penetration or the abuser confesses to penetration. A normal physical examination neither confirms nor excludes a history of sexual abuse. Examination findings should be documented as nonspecific, suggestive, or indicative of recent trauma. Concerning findings on physical examination of prepubertal victims include vaginal lacerations, complete hymenal transections, deep clefts, bruises or abrasions of the hymen, fossa navicularis, and posterior fourchette (5).

KEY TESTING

- Forensic evidence collection (forensic evidence kit [FEK], aka "rape kit") and laboratory workup should be considered when (1) presentation is within 72 hours of disclosure of the last sexual contact *and* (2) the sexual contact includes penetration, *or* there are findings on physical examination that are suspicious for acute injury.
- Policies and procedures for the FEK collection vary by state. The FEK consists of a series of swabs used to identify potential DNA evidence left from the abuser on the victim (e.g., semen, secretions, saliva, blood, hair). The FEK also collects the child's clothing, including underwear, as well as linens associated with the abuse as these are more likely to yield positive findings on forensic analysis.
- Specially trained, nonphysician medical personnel, such as pediatric sexual assault nurse examiners (pedi-SANEs), are able to assist in the medical and forensic evaluation of children and adolescents. ED physicians should know the protocol at their institutions where pedi-SANEs are available (15).
- Routine screening for STIs, including pregnancy testing, in postpubertal victims is recommended. More selective criteria are applied to prepubertal patients. These criteria include symptoms concerning for an STI, an abuser known to have an STI or is at high risk, the patient's sibling or close contact has an STI, there is evidence of vaginal, anal, or oral penetration, evidence of ejaculation, and parent/patient request (10). If there is evidence for one STI, the child should be tested for other STIs as well.
- Gonorrhea (GC) and Chlamydia (CT) are the most common STIs identified in sexually abused children and adolescents. Cultures are recommended as the test of choice in this population. Of note, recent literature suggests that urine nucleic acid amplification tests (NAATs) for GC and CT are more sensitive than cultures and are less invasive than cultures which may be preferable (11). When cultures are obtained from females, they should be vaginal only (not cervical). Culture remains the preferred method for boys and for nongenital specimens (pharynx and rectum) (12).

- Serologic testing for hepatitis B, hepatitis C, human immunodeficiency virus, and syphilis should be obtained if indicated or if requested by the patient or family. Table 290.1 outlines the implications of various STIs and the relationship with sexual abuse in prepubertal children (10).

TABLE 290.1
Implications of Commonly Encountered STIs for the Diagnosis and Reporting of Sexual Abuse of Infants and Prepubertal Children

STD Confirmed	Sexual Abuse	Suggested Action
Gonorrhea[a]	Diagnostic[b]	Report[c]
Syphilis[a]	Diagnostic	Report
HIV infection[d]	Diagnostic	Report
Chlamydia trachomatis infection[a]	Diagnostic[b]	Report
Trichomonas vaginalis infection	Highly suspicious	Report
Cyanea acuminate infection[a] (anogenital warts)	Suspicious	Report
Herpes simplex (genital location)	Suspicious	Report
Bacterial vaginosis	Inconclusive	Medical follow-up

Unless there is a clear history of autoinoculation.
[a]If not perinatally acquired and rare nonsexual vertical transmission is excluded.
[b]Although the culture technique is the "gold standard," current studies are investigating the use of nucleic acid amplification tests as an alternative diagnostic method in children.
[c]To the agency mandated in the community to receive reports of suspected sexual abuse.
[d]If not acquired perinatally or by transfusion.
From Kellogg N. The evaluation of sexual abuse in children. *Pediatrics*. 2005;116:509, with permission.

ED MANAGEMENT

If a postpubertal female patient presents within 72 hours of last contact, emergency contraception should be offered. In addition, if the postpubertal patient presents within 72 hours or is having symptoms suspicious for an STI, postexposure prophylaxis for STIs should be offered. STI prophylaxis is not routinely recommended in prepubertal females because of the low frequency of acquiring an STI after being sexually abused. Treatment is warranted if the

history or physical examination is strongly suggestive of an STI (10). Please see Chapter 184 for more specific details on STIs and their treatment.

Of note, sexual abuse has resulted in the transmission of HIV. The consideration for HIV postexposure prophylaxis requires the patient present within 72 hours of exposure; victims of sexual abuse are usually exposed over a longer period of time and therefore may not benefit from prophylaxis. With long-standing sexual abuse, assessment of risk factors pertaining to the abuse (e.g., abuser is known HIV positive) and consultation with a pediatric infectious disease specialist is critical (16).

All suspected cases of sexual abuse should be reported to the appropriate law enforcement agency and CPS based on your state's reporting laws.

CRITICAL INTERVENTIONS

- Perform anogenital examination of a prepubertal child only if the child presents within 72 hours of anogenital contact or if the patient is having acute symptoms.
- If last contact was within 72 hours, perform an examination using a FEK, clinically relevant laboratory studies, and prophylaxis when indicated.
- Report all cases of suspected sexual abuse the appropriate law enforcement agency and CPS based on your state's reporting laws.

DISPOSITION

A more detailed forensic interview as well as detailed genital examination with the use of colposcopic magnification is usually performed by appropriately trained personnel at a regional CAC. Follow-up examinations by specialists can affect the interpretation of trauma and detection of STIs. They are recommended to assess healing and provide reassurance. Significant injuries or laboratory test results require follow-up, usually within a week of the initial evaluation (17). In circumstances in which transmission of syphilis,

HIV, or hepatitis B is a concern but baseline tests are negative, repeat testing approximately 6 weeks, 3 months, and 6 months after the last suspected sexual exposure is recommended to allow time for antibodies to develop (12). In addition, mental health referrals should be made.

Common Pitfalls

- Decision to perform examination of genitalia when not indicated.
- Failure to provide medical follow-up as well as mental health referrals.
- Failure to perform FEK, appropriate testing, and administer appropriate prophylaxis when indicated.

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CHAPTER 291

Ventricular Shunt Problems and Technology-Dependent Children

Lila O'Mahony and Rob Cloutier

Children with chronic conditions are a rapidly growing population and require emergency evaluation and care more frequently than other children (1–4). A subpopulation of these children are dependent on medical devices for a broad range of congenital problems or acquired illnesses. These devices include cerebrospinal fluid (CSF) ventricular shunts, tracheostomy tubes, enteral feeding tubes, and indwelling central catheters. Many of these children have complex chronic conditions and may require urgent or emergent transfer to a pediatric center that can provide subspecialty or critical care.

Parents and caregivers are often experts regarding their child's medical conditions and associated equipment, and are often excellent sources of information for the emergency physician. Caregivers are often able to note the mildest of alterations in a child's behavior or mental status and serve as a vital early warning system for illnesses or complications.

CEREBROSPINAL FLUID SHUNTS

CSF shunt placement, usually for the treatment of either congenital or acquired hydrocephalus, is the most common neurosurgical procedure performed in children (5). Untreated hydrocephalus can lead to increased ICP, brain injury, and death (6); however,

complications associated with CSF shunts are relatively common and can also cause significant morbidity and even death (7).

CSF shunts are catheters inserted into the ventricles or other CSF-containing structures in the brain and then threaded under the skin from the skull to the terminal location such as the right atrium, pleural cavity, or (most commonly) the peritoneum. There are three components to the shunt: (a) A proximal catheter that drains one of the cerebral ventricles or areas of CSF accumulation, (b) an extracranial one-way valve to prevent backflow of CSF, and (c) a subcutaneous tunneled distal catheter. Some shunts also have a single or double reservoir system located adjacent to the opening in the skull and can be accessed percutaneously to collect CSF. The catheters and valves have radiopaque markings to enable radiographic visualization (Table 291.1).

TABLE 291.1
Congenital Hydrocephalus and Acquired Hydrocephalus

Congenital Hydrocephalus	Acquired Hydrocephalus
Congenital cysts	Neoplasm
Intraventricular hemorrhage of prematurity	Infection
Congenital brain malformations	Trauma

COMPLICATIONS: SHUNT MALFUNCTION AND INFECTION

The cause of shunt malfunction may be mechanical (e.g., broken tubing) or nonmechanical (e.g., infection), or a combination of the two. Shunt malfunction occurs most commonly in the first 12 months following placement, and accounts for about 10% of all shunt malfunctions (8). After the initial year post-placement, the rate of shunt malfunction falls to about 5% (9).

Obstruction of CSF flow is the most common type of shunt malfunction. The three most common sites of obstruction are the proximal catheter, the proximal valve, and the terminal end of the distal catheter. Shunt catheters can also become disconnected at any point along their trajectory, most commonly in the neck region (10).

Disconnections are often associated with improper use of connectors distal to the valve or fracture of the shunt tubing that can occur with age and calcification over time. A less common complication is *migration* of the tip of the shunt catheter. The catheter tip can migrate into or traverse intra- and extra-abdominal organs including the bladder, rectum, scrotum, and lungs. This is in part due to the extra length of tubing placed in the abdominal cavity to correspond to the child's future growth. Other complications are organ specific and depend on where the catheter terminates, and may include intraperitoneal CSF collections or pseudocysts which may or may not cause peritonitis.

Obstruction, disconnection, and catheter migration often lead to complications associated with inadequate CSF drainage. However, overdrainage can also be a problem. While rare, overdrainage can lead to ventricular collapse and "slit ventricle syndrome," which manifests as orthostatic hypotension, subdural fluid collections, craniosynostosis, ventricular compartmentalization, and cerebellar tonsillar herniation (11).

Shunt infections include the shunt hardware, the overlying tissues, or the distal terminal sites (typically within the peritoneum) and occur primarily through direct contamination or hematogenous seeding. The reported incidence averages 10% to 15% (11), the majority occurring within the first 6 months post-placement (12,13). Like other bacterial infections of the CNS, these infections can be responsible for severe neurologic injury or death (Table 291.2).

TABLE 291.2
Risk Factors for Infection

• Premature birth	• CSF shunt leak
• Patient age <6 mos	• Prior shunt infection
• Shunt placed/revised <6 mos ago	• Revision soon after placement

Data from McGirt MJ, Zaas A, Fuchs HE, et al. Risk factors for pediatric ventriculoperitoneal shunt infection and predictors of infectious pathogens. *Clin Infect Dis*. 2003;36:858–862; Simon TD, Whitlock KB, Riva-Cambrin J, et al. Revision surgeries are associated with significant increased risk of subsequent cerebrospinal fluid shunt infection. *Pediatr Infect Dis J*. 2012;31:551–556.

CLINICAL PRESENTATION

Children may have subtle or fulminant presentations of shunt complications. Paying close attention to the history and concerns relayed by the parents or caregivers cannot be overemphasized (14). Presenting symptoms of a shunt malfunction or obstruction may be subtle (mild irritability) or profound (signs of impending herniation and cardiopulmonary instability). Cranial nerve palsies, visual impairment, and hemiparesis represent atypical presentations (14). Headaches are a common complaint in children with shunts, and the character of the headache may help diagnose malfunction. Severe and progressive headaches are more likely to be associated with increased ICP, whereas postural headaches may be associated with slit ventricle syndrome or low-pressure conditions (Table 291.3).

TABLE 291.3
Shunt Malfunction/Obstruction

Symptoms	Signs
• Lethargy	• Bulging, tense fontanelle
• Irritability	• Widely split sutures
• Headache	• Shunt site swelling
• Nausea/vomiting	• Papilledema
• Visual changes	• Engorged head veins
• Developmental delay	• Cranial nerve palsies
• Incontinence	• Hyperreflexia
• Seizure (late)	• Cushing triad (late)

The presenting symptoms of shunt infection may be nonspecific, or suggestive of other entities, including shunt malfunction. Importantly, fever is not always present and is rarely the sole manifestation of shunt infection. Infection can include any portion of the shunt system. While seizure activity is a negative predictor of shunt malfunction, elevated ICP caused by shunt failure must still be considered (15,16). Lastly, it is important to remember that a patient can have concurrent shunt malfunction and infection and thus present with clinical evidence of both problems (Table 291.4).

TABLE 291.4
Shunt Infection

Symptoms	Signs
• Chills, fever • Nausea/vomiting • Irritability • Abdominal pain • Headache	• Fever • Behavioral change • Erythema or swelling at shunt site or along catheter track • Peritonitis • Signs of shunt malfunction

DIFFERENTIAL DIAGNOSIS

Symptoms of shunt malfunction and infection are largely nonspecific and other common pediatric illnesses, such as acute gastroenteritis, urinary tract infection, and otitis media, should be considered once shunt function has been evaluated.

ED EVALUATION

Important history includes the indication for and date of the initial shunt placement, postoperative complications, and any history of shunt malfunctions, infections, or revisions. It is important to ask about signs and symptoms that may have accompanied previous failures. The shunt itself should be examined and palpated for any signs of infection (warmth, tenderness, or erythema) or malfunction (broken tubing or subcutaneous collection of CSF). The shunt catheter can be located as it exits through a hole in the skull, travels subcutaneously just inferior to and behind the ear, and continues down the neck to the chest. For a ventriculoperitoneal shunt, the catheter travels anterior to the clavicle, passes through the subcutaneous tissue overlying the chest wall, and ultimately enters the peritoneal cavity. Of note, when inspecting shunts that have been recently placed, incision sites should be carefully examined for evidence of infection.

Imaging and laboratory studies are often indicated in suspected shunt malfunction or infection. Standard imaging should include a plain radiograph “shunt series” and either a noncontrast computed tomography (CT) or magnetic resonance image (MRI) of the head to

assess ventricular size and changes from prior studies. Some shunt valves will need to be reprogrammed following an MRI and require an on-site individual trained at this procedure. The shunt series images the entire course of the shunt, including the skull, neck, chest, and abdomen, to reveal catheter fracture, kinking, disconnection, dislocation, or migration. Finally, an abdominal ultrasound or CT scan is indicated if there is concern for an intra-abdominal process such as intra-abdominal pseudocyst around the distal tip.

A complete blood count with differential, blood cultures, electrolytes, and a coagulation screen are commonly recommended for the evaluation of a potential shunt malfunction or infection. A neurosurgeon should be consulted before a diagnostic puncture is performed for aspiration ("tap") of a ventricular shunt. For patients who are not critically ill, a shunt tap is performed to measure the opening pressure and collect CSF for laboratory analysis (cell count, protein, glucose, Gram stain, and culture) to detect possible infection. Rarely, a patient with a ventricular shunt may present to the ED with signs of cardiorespiratory failure due to elevated ICP (unilateral fixed and dilated pupil, posturing, apnea). In this unique circumstance, it may be appropriate to perform a therapeutic shunt tap without first consulting a neurosurgeon.

KEY TESTING

- Head CT or brain MRI
- Radiographic shunt series
- Laboratory studies as indicated by presentation and differential diagnosis

ED MANAGEMENT

The time between the onset of symptoms and coma from shunt failure may be only a few hours (17). A patient with a suspected ventricular shunt problem should be seen in the ED by a neurosurgeon, regardless of the results of diagnostic tests. CT scans can be notoriously unchanged from baseline despite an acute shunt

malfunction. In situations where evaluation by a neurosurgeon is not possible, transferring the patient to another facility where such services are available may be the best option.

For patients with confirmed shunt infection, empiric antibiotics should be administered to cover both common gram-positive and gram-negative pathogens. A third-generation cephalosporin (e.g., ceftriaxone, cefotaxime) and vancomycin are recommended choices for initial therapy to cover typical pathogens (commonly *Staphylococcus* species), and penetrate well into the CNS. Patients with confirmed shunt malfunction or obstruction require a surgical revision. The timing of the revision depends on the patient's clinical condition and the availability of the neurosurgeon; severe symptoms require immediate repair.

KEY INTERVENTIONS

- Obtain history of the reason for and date of shunt placement, prior complications, and infections.
- Obtain a shunt series and noncontrast CT.
- Transport the patient as necessary to a facility where definitive care can be provided.

DISPOSITION

For patients who require interfacility transfer, if possible, complete any invasive procedures that are likely to become necessary (endotracheal intubation, central line placement, etc.) while the patient is still in the ED, since space and personnel advantages greatly increase the chances for success.

Any child with suspected or confirmed shunt infection or malfunction requires hospital admission. If the diagnostic workup for shunt malfunction is negative and the patient is examined and cleared by a neurosurgeon, the child can be safely discharged from the ED. For children discharged home, it is important to provide clear return instructions and recommendations for outpatient follow-up.

Common Pitfalls

- Failure to recognize a shunt malfunction or infection associated with nonspecific patient complaints. Complaints such as "decreased activity" or "poor appetite" may be due to a viral illness, but warrant a focused shunt evaluation in patients with a shunt.
- Failure to review previous head CT or MRI scans.
- Failure to obtain neurosurgical consultation in the ED.

TRACHEOSTOMY TUBES

Tracheostomy tubes share two common attributes: (1) A primary cannula, and (2) an obturator that is inserted into the primary cannula for all replacements, whether routine or emergent. Parents can usually provide specific details about their child's tracheostomy and tracheostomy tube (**Tables 291.5** and **291.6**).

TABLE 291.5
Tracheostomy Tubes

- Single cannula: Neonates, younger children
- Double cannula with outer sheath: Older children
- Fenestrated tubes: Redirects air into upper airway, allows child to speak and breathe through nose and mouth
- Cuffed or uncuffed

TABLE 291.6
Tracheostomy Complications

- Decannulation
- Obstruction
- Granuloma formation at stoma
- Superficial bleeding at cannulation site
- Hemorrhage due to tube erosion into local blood vessel
- Creation of false passage with reinsertion
- Bronchospasm
- Infection
- Tracheitis
- Bronchitis
- Pneumonia

CLINICAL PRESENTATION

Children with an obstructed or dislodged tube (one of the most common complications) (18) range from those who appear well to those with impending respiratory failure. This depends on their degree of tracheostomy dependence, which can range from none to complete dependence on mechanical ventilation. Infection should be suspected if there are acute changes in tracheal secretions such as increased thickness, quantity, new color, or new odor, especially if accompanied by fever.

ED EVALUATION, MANAGEMENT, AND DISPOSITION

In the case of tracheostomy tube obstruction or displacement, it is important to recall that caregivers routinely replace tracheostomy tubes outside the hospital setting. Thus, a patient whose dislodged or obstructed tube has not been easily managed by a parent or caregiver must be considered to have a high-risk airway. Ideally, an otolaryngologist should be consulted prior to attempts at tube replacement in case the tube does not easily pass, if bleeding occurs, or other significant surgical concerns arise, especially with a recently created tracheostomy site. Patient positioning and careful preparation for emergent airway management are critical and should include tracheostomy-specific suction, oxygen delivery, and humidification systems. Place a towel roll under the child's shoulders to hyperextend the neck for optimal visualization of the tracheostomy site and to help open the airway distally. Identify the type and size of tracheostomy needed for replacement, and if possible, have a second device, a half-size smaller, available if edema, scar tissue, or anatomic factors prevent replacement with the original size. If the type of device and tube size are not known, an appropriately sized endotracheal tube may serve as an interim solution, but it should not be advanced more than 2 to 4 cm into the stoma.

An appropriately sized endotracheal tube and airway setup should always be available in case an airway cannot be established through the tracheostomy site and emergent orotracheal intubation becomes necessary (18). Tracheal suctioning may help relieve mucus

plugging, but it is important to limit suctioning to only 10 to 20 seconds to prevent hypoxemia and further respiratory compromise. Humidified oxygen should be administered. Albuterol may be administered liberally by this route if there is thought to be bronchospasm.

Prior to placement of the new tube, verify balloon integrity and lubricate the tip. Similarly, be sure to deflate the balloon on the old tracheostomy tube prior to removing it. Once the old tube has been removed, carefully place the new tube into the recently vacated stoma. To minimize the chance of creating a false passage, do not force the tube into the tract. If there is significant respiratory distress, failure to pass the tube easily should prompt consideration of orotracheal intubation.

If there is concern about tracheitis or pneumonia, tracheal aspirate samples and a chest radiograph should be obtained. Consider empiric antibiotics to cover typical pathogens: *Staphylococcus* species, *Haemophilus influenzae B,* and *Moraxella catarrhalis.* Disposition from the ED depends on the patient's overall clinical status and specific tracheostomy needs. Children requiring new or increased oxygen support, intravenous antibiotics, ongoing pulmonary care, or subspecialty consultation should be hospitalized.

ENTERAL FEEDING TUBES

Enteral feeding tubes are placed for diverse indications. Some children depend on them for primary nutrition and hydration, whereas others have to be used only for supplemental nutrition or medication administration. Feeding tubes placed via the nasopharynx, such as nasogastric (NG) and nasoduodenal (ND) tubes, are typically temporary, while gastrostomy (G) and gastrojejunostomy (GJ) tubes, which are placed through the abdominal wall, are more permanent. Feeding tube complications may be categorized as those related to the anatomical location of the tube and the surrounding tissues, or those related to the tube itself (e.g., dislodgement or breakage) (Table 291.7) (19).

TABLE 291.7
Complications of Enteral Feeding Tubes

All Tubes	Nasogastric/ Duodenal	Gastrostomy	Gastrojejunostomy
Dislodgement	Sinusitis	Gastroesophageal reflux	Diarrhea
Obstruction	Nasoesophageal irritation	Peristomal infection	Tube migration
Gastric distention	Aspiration	Abdominal wall abscess	Bowel perforation
		Peritonitis	Intussusception
		Gastric perforation or hemorrhage	Peritonitis
		Gastrocolic fistula	Peristomal infection
		Gastric ulceration	Abscess
		Gastric outlet obstruction	

Stomal complications include dermatitis, bleeding granulation tissue, peristomal cellulitis, and superficial fungal infection.

CLINICAL PRESENTATION

The majority of children appear well, though others may complain of abdominal distention and pain. Dislodgement, especially of G tubes, is the problem most commonly seen in the ED (20).

ED EVALUATION, MANAGEMENT, AND DISPOSITION

NG and ND tubes can be replaced in the ED. ND tubes are more challenging because the tip must pass through the pylorus; placing the child on his or her right side may help with movement through the pylorus. Dislodged G tubes require urgent replacement to prevent closure of the stoma and tract. A temporary catheter (e.g., Foley catheter) may be inserted in place of the actual device to preserve the stomal tract until a more permanent replacement tube is secured. A G tube that has been placed surgically within 2 months, and especially within 2 weeks, should be replaced by the specialty service that initially placed it, because of the increased risk of creating a false tract within the incompletely healed abdominal wall (21). Analgesia and anxiolysis should be considered prior to tube replacement to help with relaxation of the abdominal wall musculature. Dilators may be required to facilitate replacing the

tube, but recently created tracts (i.e., less than 30 days old) should not be dilated.

GJ tubes require interventional radiology or general surgery consultation for replacement or repair. If there is concern for an abdominal wall abscess, ultrasound is an ideal initial imaging modality. Adjunctive laboratory studies should be obtained only as clinically indicated (e.g., for suspected infection or in an ill-appearing child). Children with enteral feeding tube complications often require admission to the hospital for intravenous hydration, nutritional support, medication administration, or surgery as indicated, until the tube can be satisfactorily replaced. If the tube is replaced in the ED, the position should be verified either clinically or by a contrast-enhanced imaging study; the child can then be discharged home with routine follow-up.

INDWELLING VENOUS CATHETERS

Indwelling venous catheters, often tunneled beneath the skin, may provide access through externalized tubing (e.g., Hickman device), or a subcutaneous reservoir (e.g., Port-a-cath device). They can vary in length, diameter, and number of lumens or access ports. Special equipment and specific procedural steps are necessary to access these lines. Complications may be mechanical, including dislodgement, breakage, or obstruction, or nonmechanical, including infection and air embolism. Overall, the most common complications are obstruction and infection (22).

CLINICAL PRESENTATION

Dislodged, broken, or fractured indwelling catheters may present with bleeding; a bulge, pain, defect, or swelling at the catheter site; head or neck swelling; respiratory distress; arrhythmia; or signs of cardiac tamponade. Obstruction presents with difficulty drawing back, infusing, or flushing through the line. Families will often have tried to troubleshoot this type of complication at home prior to presenting to the ED. A catheter-related infection may present with local signs and symptoms such as erythema and swelling, or the child may have systemic symptoms such as fever and tachycardia.

Immunocompromised children may not be able to mount a local inflammatory response and may present with more subtle symptoms. These patients are at high risk for disseminated infection and should be evaluated promptly. Air embolism should be suspected in patients with an acute onset of tachypnea, tachycardia, hypotension, or altered mental status.

ED MANAGEMENT AND DISPOSITION

Dislodged or broken catheters should be clamped proximally and repaired as per local institutional practices or replaced as indicated by the appropriate surgical service. Obstruction can sometimes be relieved by infusion of a fibrinolytic, but if this is unsuccessful surgical consultation is warranted. Use of these agents should follow individual institutional guidelines. If a catheter or blood infection is suspected, obtain blood cultures and initiate empiric antibiotics. Immunosuppressed children should be evaluated promptly and monitored closely. Further laboratory and imaging studies should be guided by the child's clinical status. If air embolism is suspected, the child should be placed in Trendelenburg position on the left side while the catheter is clamped and oxygen applied. If the catheter cannot be repaired in the ED, or if infection is suspected, hospital admission is likely to be necessary until definitive repair can be scheduled.

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PART 6 • ADMINISTRATIVE AND CLINICAL ISSUES

CHAPTER 292 Pediatric Interfacility Transport

Lila O'Mahony and George A. Woodward

Interfacility transport is an integral component of the continuum between optimal emergency and definitive care of acutely injured or ill pediatric patients, and when executed safely, efficiently, and by appropriately skilled teams, contributes to improved patient outcomes (1–4). Given that 89% of acutely injured or sick children are initially cared for at hospitals that typically do not have pediatric specialty or critical care services (5); a substantial number of children will require transfer to a higher level of pediatric care (Fig. 292.1).

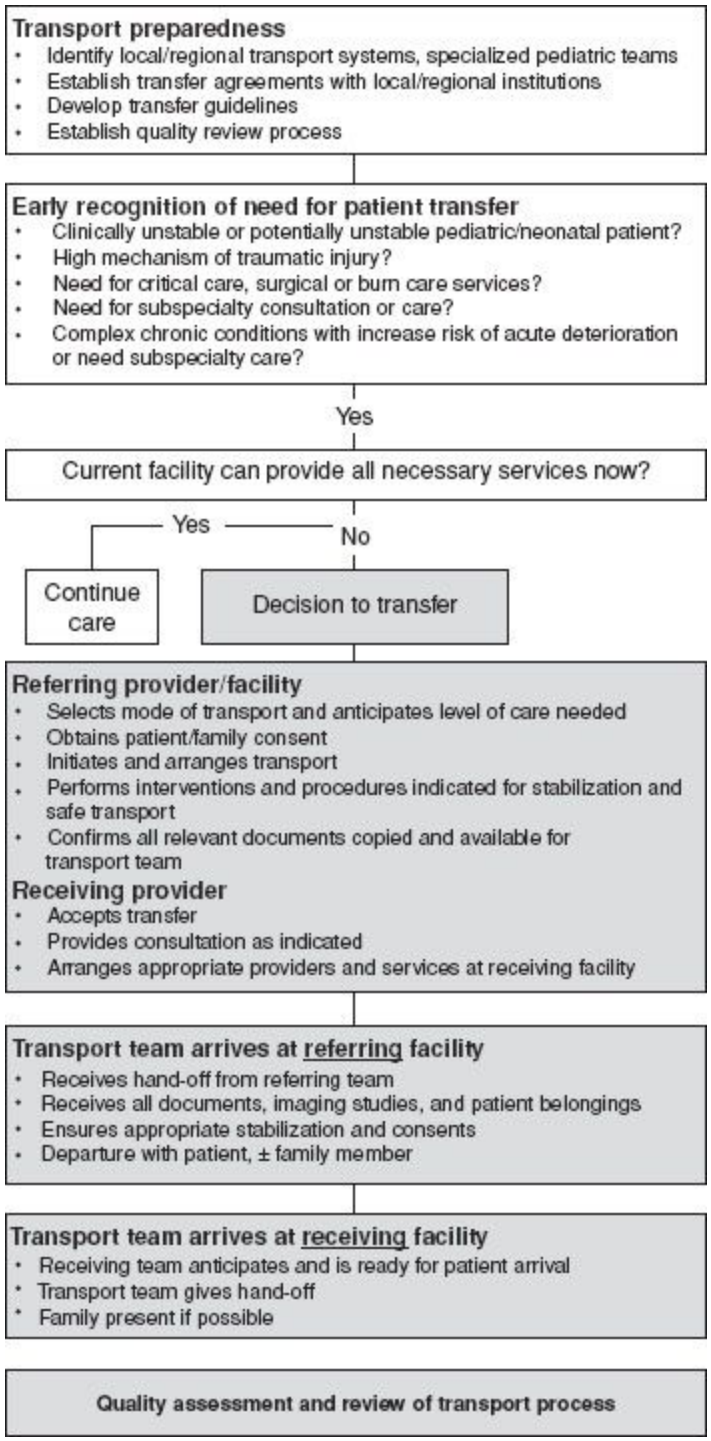

FIGURE 292.1 Pediatric interfacility transfer algorithm.

It is imperative that referring and receiving hospitals have processes and resources to safely and efficiently transfer pediatric patients. Ideally, these should be identified in advance to ensure

optimal preparation. Some hospitals have pre-existing agreements with facilities that have comprehensive pediatric services outlining expectations and conditions, as well as the standard mode of transfer for critically ill or injured patients. A practical resource for the development of such guidelines is the 2013 "Interfacility transfer tool kit for the pediatric patient," published by the Emergency Nurses Association, Emergency Medical Services for Children, and the Society of Trauma Nurses (http://www.ena.org/practice-research/Practice/Pages/Toolkit.aspx).

MEDICAL LEGAL ISSUES FOR REFERRING AND RECEIVING PROVIDERS

The Emergency Medical Treatment and Active Labor Act (EMTALA) is the cornerstone of civil transport regulation. It applies specifically to clinically unstable patients and is meant to (1) protect patients from being denied appropriate care due to an inability to pay and (2) prevent institutions from inappropriately transferring patients due to an inability to pay when the institution is able to provide needed care. Under EMTALA, referring providers are responsible for (1) stabilizing a patient within the capabilities of their institution, (2) initiating the transport process, and (3) selecting the mode of transportation, whether air or ground, and (4) the level of care the patient should be transferred to. In addition, referring providers ensure that patient care during transport remains at the level initiated and does not place the patient at undue risk. On the receiving end, providers and hospitals are responsible for ensuring they are able to provide the services the patient requires. Receiving providers and transport-related supervisors may act as consultants to the referring team to optimize ongoing care and select an appropriate transport mode. However, unless the receiving physician provides medical advice, or is serving as the transport's online medical control physician or provides the transport service, accepting institutions are not legally responsible for patients' care until they arrive at the receiving facility. Under EMTALA, there are

circumstances under which a receiving provider may deny acceptance of a patient transfer. Caution must be taken when considering the determinants of an individual's clinical "stability"; for under EMTALA, unstable patients cannot be denied transfer if the receiving facility has the capability to treat them (Table 292.1).

TABLE 292.1
Acceptable Conditions for Refusing Transfer of a Pediatric Patient

- Risks of transfer outweigh the benefits
- Patient can be realistically and properly cared for at referring facility

MODE OF TRANSPORT AND TEAM COMPOSITION

Referring institutions must appreciate the constraints of geography, traffic, weather, and other pertinent issues affecting transport logistics. These factors must be carefully weighed when selecting the composition of the transport team and the mode of transport.

Not all transport teams have comparable pediatric skills, experience, or equipment. Transport providers and teams lie on a spectrum from volunteers to basic emergency medical technicians with limited pediatric-specific skills to highly trained specialized pediatric and neonatal critical care teams. Awareness of the skill level and clinical capabilities of available transport teams will aid in the selection of the most appropriate transport team and mode (6–8).

When transferring critically ill children, the referring provider should strongly consider a team with specialized pediatric critical care skills since care by such providers is associated with decreased morbidity, improved survival, and better outcomes (1). While use of such a team may result in a longer period of stabilization at the referring facility, it allows for the initiation and continuation of consistent treatment at both facilities and ensures that an appropriately skilled team is able to respond to critical events or changes during transport. This is a fundamental difference from prehospital practice where the concept of rapid transfer and the

“golden hour” to definitive care is often emphasized (9). In locations or circumstances where specialized teams are not available, the referring provider should ensure that a team is selected which can meet the patient’s needs at the highest level without compromising clinical care. Any appropriate treatments initiated at the referring facility should be continued during transport.

Neonatal transfers are often due to critical illness, congenital disorders, and the need for subspecialty or surgical care not available at a referring institution. Critically ill newborns are infrequent patients in most emergency departments, but may present in the context of trauma, a complicated home birth, or an unexpected precipitous delivery. Neonates who are critically ill or who have the potential for acute decompensation, such as those who are premature or of very low birth weight, require providers with special skills in assessment, management, and procedures, including vascular access and neonatal airway management. Thus, these patients should be transported by specialty teams with the highest level of pediatric and neonatal skills and expertise.

Travel distance to a referral center is a major factor to consider. Ground transport is always an option with an appropriately composed team. As a general rule, distances between 20 and 100 miles may warrant rotor wing aircraft and distances greater than 100 miles may dictate the need for rotor or fixed wing aircraft. These rules of thumb must be weighed against many factors. For example, a critically ill patient 10 miles from a referral center may be better served by rotor wing transport than ground transport during rush hour in an urban setting, while the same patient may travel 300 miles by ground in a rural area with dangerous winter weather that precludes flying.

Pediatric patients, their parents, and their healthcare providers will benefit from maintaining a family centered, supportive, and safe environment for the child, which in most circumstances means enabling parents to travel with their child (10).

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CHAPTER 293

Death, Catastrophic Illness, and Parental Presence in Critical Cases

Karen O'Connell, Phyllis L. Hendry, and Mardi Steere

Emergency physicians and prehospital care providers are often faced with the responsibility of telling a family that their child has died or is suffering from a catastrophic illness or injury. In the emergency department (ED), the hectic surroundings and the lack of acquaintance with the family and patient add to the challenge of this intensely difficult situation. Death in an infant or child carries unique emotional, bereavement, and coping challenges for families and staff.

EPIDEMIOLOGY OF INFANT AND PEDIATRIC DEATH

In 2011 in the United States, there were 23,910 reported infant deaths and 20,192 reported child and adolescent deaths (1). Approximately half of all pediatric deaths in the United States occur in the first year of life, with two-thirds of those occurring in the neonatal period (<28 days of life). The 2011 infant mortality rate (IMR) in the United States was reported as 6.05 deaths per 1,000 live births (1). This rate had been steadily declining over the past 40 years and almost halved between 1980 and 1995. In 2002, the IMR started to increase, a change potentially related to the increasing incidence of low birth weight (LBW) (<2,550 g). LBW is one of the most important predictors of infant mortality and correlates with the percentage of preterm births, which has increased by 20% since 1990 and continues to rise. There continues to be wide variation in

IMRs as reported by race and Hispanic origin, with non-Hispanic black newborns more than twice as likely as white and Hispanic infants to die in the first year of life.

More than half of all infant deaths in 2011 were attributable to five leading causes (Table 293.1): congenital malformations (20.8%), disorders relating to short gestation and LBW not otherwise classified (17.2%), sudden infant death syndrome (SIDS) (7.2%), maternal complications of pregnancy (6.6%), and unintentional injuries (4.6%). Patterns of leading causes of infant mortality have not changed over the past decade.

TABLE 293.1
Leading Causes of Infant Mortality in the United States in 2011

Cause of Infant Death	Percentage (%)
Congenital malformations	20.8
Disorders relating to short gestation and low birth weight	17.2
Sudden infant death syndrome	7.2
Maternal complications of pregnancy	6.6
Unintentional injuries	4.6

Adapted from Hamilton BE, Hoyert DL, Martin JA, et al. Annual Summary of Vital Statistics: 2010–2011. *Pediatrics*. 2013;131(3):548–558.

The death rate for children decreases significantly after the first year of life. In 2011, the death rate for children aged 1 to 19 years was 25.6 per 100,000 population (1). Unintentional injures remain the leading cause of death in all children older than 1 year of age, accounting for 35.6% of deaths, followed by assault (homicide) (11.4%), intentional self-harm (suicide) (10.1%), and malignant neoplasms (9.2%). Congenital malformations, diseases of the heart, influenza and pneumonia, and chronic lower respiratory disease such as asthma continue to be major contributing factors in pediatric death. While death rates for unintentional injuries, homicides, heart and cerebrovascular disease have decreased between 2010 and 2011, death rates from suicide continue to climb.

Sudden unexpected infant death (SUID), defined as deaths in infants younger than 1 year of age that occur suddenly and without

any obvious cause prior to extensive investigation, are often encountered by emergency physicians (2). Most infant and child deaths are pronounced in the ED, even if the death occurred in the prehospital setting. SUID claims the lives of approximately 4,000 infants each year in the United States, half of these are due to SIDS (2). The emergency physician should be knowledgeable about the epidemiology and differential diagnosis of SIDS. SIDS is defined as the sudden death of an infant younger than 1 year of age that remains unexplained after thorough case investigation, including performance of a complete autopsy, examination of the death scene, and a review of the clinical history. Most deaths due to SIDS occur between 2 and 4 months of age. Understanding of the etiology of SIDS remains incomplete, despite extensive research in this area (3–5).

SIDS is the third leading cause of infant mortality in the United States and has important implications in pediatric death (2). The rate of SIDS is two to three times more likely in African American and Native American populations. SIDS has been associated with prone sleep position, sleeping on a soft surface, maternal smoking during or after pregnancy, overheating from heavy bedding or clothing, late or no prenatal care, young maternal age, prematurity, LBW, and male gender (2–5). Many states have death review teams for unexplained infant deaths. Deaths caused by carbon monoxide poisoning, asphyxia in mechanically unsafe sleeping environments, and overlying (smothering) are often initially labeled as SIDS until investigation and/or autopsy confirms an alternate diagnosis. SIDS deaths had been slowing declining in the United States during the 1980s until the American Academy of Pediatrics Back to Sleep campaign took off in 1992. Since that time, the SIDS rate has dropped by approximately 50% and continues to decline (2–5). Medical reporting practices have also contributed to the decrease in reported death rates for SIDS, as physicians have begun to use other terms that result in classification of these deaths into the category of “ill-defined or undetermined” causes (1,5). Despite the infant sleep practice changes and improvements in diagnostic and reporting practices, SIDS remains one of the most common reported causes of

death in infants. Emergency physicians should be knowledgeable of the changing epidemiology of pediatric deaths so they can best meet the needs of patients, their families, and hospital staff.

ED EVALUATION

The ED evaluation of a critically ill or injured infant or child begins at transfer of care from the parent or emergency medical services (EMS) and continues throughout the resuscitative efforts and even after death is pronounced. Chapters 214–219, review the specific resuscitative care of children who present to the ED.

The ED physician must be cognizant of details in the medical history or physical examination that would assist in the explanation of the death. A comprehensive history is often not obtained until after death is pronounced, when caregivers are in a state of distress and/or shock. The ED team should make every effort to coordinate history-taking with law enforcement and other agencies. Many larger communities have infant-death scene investigation protocols or teams in place. Information about the scene, including details about bedding, clothing, play equipment, stairs, swimming pools, and other pertinent information may be obtained from EMS providers. For infant deaths, the history should include details regarding recent illnesses, immunizations, medications, feeding, chronic illnesses, and birth history. Family history of neonatal and stillborn deaths, and sudden or unexplained child deaths should be explored (3–8).

The physical examination of infants and children who present with sudden unexplained death or cardiopulmonary arrest should include a search for signs of abuse, metabolic disorders, and congenital syndromes. Presenting signs and symptoms of child abuse may often mimic other medical illnesses and accidental traumatic injuries. Frequency estimates of nonaccidental death that is incorrectly designated as SIDS range from 1% to 5% (4). In addition to a complete examination, particular attention should be given to body temperature, skin markings, pupil size, and dysmorphic features (3–5). When SIDS is suspected, inform the family that SIDS is a diagnosis of exclusion and that other investigations are required.

FAMILY-CENTERED CARE DURING RESUSCITATION

Involving family member presence during pediatric resuscitation in EDs has been a focus of quality improvement and a practice formally endorsed by many healthcare organizations (9,10). Parents and guardians serve as the primary support system for pediatric patients and play an integral role in the health and well-being of the child. The practice of family-centered care incorporates family attitudes and beliefs about autonomy and health care into what was previously an autocratic medical model in which families were excluded from the treatment area.

Awareness of the benefits of family presence and support for the incorporation of family-centered care has increased over the past decade. Patients undergoing invasive procedures and those who survived resuscitations have expressed feelings of comfort, reduced anxiety, and better pain management when families were present (11). For family members, being present helps them advocate for their child in real time and share pertinent medical information (17). Even when their children died, parents who were with them at the time of death experienced a greater sense of closure than parents who were prevented from being present (12). Family presence may also have greater long-term benefits for families. A study evaluating family presence during prehospital resuscitation showed lower posttraumatic stress disorder–related symptoms for family members who witnessed the resuscitation efforts compared to those who did not (13).

Family members are often with their children when they present to the ED but it is not uncommon for them to be separated from their children during the initial phases of resuscitation. Staff should be supportive in encouraging family presence during invasive procedures and resuscitative efforts, but cautious not to force family participation. Family members should be given the option to be present during their child's care and supported in their decisions. It is important to provide a private, quiet, and comfortable space when assisting parents with saying goodbye to their child or viewing the body.

PRONOUNCEMENT OF DEATH AND NOTIFICATIONS

Pronouncement of death should be made by the attending physician, or the most senior physician who was in attendance at the time of death. The attending physician should also be the one to notify the parents or legal guardians. If the family is not present at the time of death, they should be requested to come to the hospital where the information of the death should be given. In the event that the parents cannot be contacted, social services should be utilized to help locate family or next-of-kin. Most emergency physicians feel uncomfortable dealing with death and giving bad news to families, and historically they have received little training in this area. Most physicians are not skilled in how to conduct these important and stressful conversations, but it is imperative that they be competent in these situations. Families may not recall the details of the actual event, but the manner with which it was disclosed will have lasting effects. Breaking bad news is a skill that can be learned and has been shown to improve with communication specific education. Simulation scenarios, role playing, and other educational tools that focus on death and delivering bad news have been incorporated into both Pediatric Advanced Life Support (PALS) and Advanced Pediatric Life Support (APLS) courses, and should continue to be part of medical education and training (14,15). A useful educational tool that uses a 'GRIEV_ING' mnemonic has been shown to improve ED physician competence and confidence in death notification skills (Table 293.2) (14).

TABLE 293.2
GRIEV_ING Mnemonic[a]

- *G*ather the family; ensure that all members are present.
- *R*esources; call for support resources available to assist the family with their grief (i.e., chaplain services, ministers, family, and friends).
- *I*dentify; identify yourself, identify the deceased or injured patient by name, and identify the state of knowledge of the family relative to the events of the day.
- *E*ducate; briefly educate the family as to the events that have occurred in the ED; educate them about the current state of their loved one.
- *V*erify; verify that their family member has died. Be clear! Use the words dead or died.
- (*S*pace); give the family personal space and time for an emotional moment; allow the family time to absorb the information.
- *I*nquire; ask if there are any questions, and answer them all.
- *N*uts and bolts; inquire about organ donation, funeral services, and personal belongings. Offer the family the opportunity to view the body.
- *G*ive; give them your card and access information. Offer to answer any questions that may arise later. Always return their call.

[a]Adapted from Knazik SR, Gausche-Hill M, Dietrich AM, et al. The death of a child in the emergency department. *Ann Emerg Med* 2003;42(4): 519–529, used with permission.

After the pronouncement of death and the notification of family, the parents should be invited to the bedside, if not already, to be with their child and hold him/her if possible. In preparation, the body should be cleaned for family viewing. Adherence to strict guidelines may be required during preparation of the body, especially if the case is a Medical Examiner's case. Monitoring equipment may be disconnected and the body bathed as necessary to remove obvious body secretions. All tubes from the body, including endotracheal tubes, IV access devices, Foley catheters, chest tubes, feeding tubes, etc. should not be removed. Tubes and IVs may be capped to prevent body fluid from leaking and visible wounds may be covered for viewing.

When a child dies in the ED, the attending physician or designee should notify the child's primary care physician, the Medical Examiner's Office, and the regional organ transplant organization. The licensed independent physician (LIP) in attendance at the time of death is often responsible for completing the Death Worksheet at most institutions. All death packet worksheets and documentations should be completed immediately after the death and prior to

transport of the body to the morgue. In Medical Examiner cases, the death certificates are completed by the Medical Examiner. Social work or international services should be also be utilized in cases where patients with religious beliefs require an expedited death certificate.

AUTOPSY AND ORGAN DONATION

ED staff should be aware of state and local requirements for reporting deaths and for organ donation. The physician pronouncing death is often responsible for determining whether or not the death is a Medical Examiner's case, and if so, has the responsibility of notifying the Medical Examiner's Office immediately after the death. If there are questions as to whether or not the circumstances of death meet the definition for a Medical Examiner's case, the local Office of the Chief Medical Examiner should be contacted and consultation obtained.

Postmortem examinations by state medical examiners are often required in all sudden, unexpected, and unexplained deaths not caused by readily recognizable disease. The definition of reportable deaths varies among states and jurisdictions of medical examiners but also usually includes violent causes of death (homicide, suicide, accidents); deaths which might constitute a threat to public health; deaths of persons whose bodies are to be cremated; deaths related to medical or surgical intervention; and deaths under suspicious circumstances. Consent for autopsy must be obtained prior to autopsy for all deaths except for Medical Examiner's cases. Who can give consent for autopsy may vary by state law, but often includes the nearest blood relative (parents) or legal guardians.

Parents should be made aware of the importance of understanding why their child died and whether other or future children might be affected. Autopsies in infant deaths are strongly encouraged to find evidence of familial genetic disease, infection, public health threats, or child abuse and neglect. Genetic disease is a major contributing factor in 15% to 25% of all infant deaths, with more than 400 inborn errors of metabolism having now been identified (16). Autopsy results should be made available to the parents, and it should be

conveyed to them that a final report may require several months to prepare. Postmortem examinations have been shown to alter recurrence risks for future pregnancies by 25%, making neonatal and infant autopsies of crucial importance (16).

The attending physician or designee is responsible for notifying the local or regional transplant organization after the death of a patient and is recommended to do so within 1 hour of the death regardless of organ donation suitability. Organ donations have made more than 28,000 transplants possible and have given another 1 million people tissue transplants that have helped them recover from trauma, spinal injuries, bone damage, burns, and hearing and vision loss (17). An experienced interdisciplinary team should be utilized to help identify potential organ donors and preserve the donation for families in cases where donation is a viable option. Families should be informed of the option of organ donation and the involvement of a specialized team only after the declaration of death has been made. An experienced team from an organ transplant organization will then help determine the suitability of organs for donation and discuss the option with the family in a manner that is considerate of cultural, ethical, and religious practices.

GRIEF REACTIONS

Society often reacts to pediatric death or terminal illness with disbelief, helplessness, and often anger. Cultural and religious background should be taken into consideration when responding to a parent's grief. Physicians should be knowledgeable of local and common cultural and religious beliefs and respect these traditions (Table 293.3) (7,8).

TABLE 293.3
Common Burial Traditions

Religion	Death Practices
Buddhism	The body is left as it is found in death and gently covered with a sheet.
Catholicism	Before or after the time of death, a priest should administer the sacrament of anointing the sick.
Hinduism	Death should be peaceful, and the body must be attended until cremation.
Islam	After the death, the eyes are closed, the mouth is closed with a bandage, and the arms and legs are straightened.
Judaism	The burial is arranged within 24 hours. The body must be attended until the burial. Cremation is not acceptable.

Extreme sadness, anxiety, guilt, disbelief, and anger can be normal reactions to the death of a child. Parents and family members may express prolonged feelings of guilt, especially if the death was a result of accidental injury. Family members may exhibit emotional lability and blame one another if the death was associated with inadequate supervision. Hostility among family members may be increased in cases of divorced or separated parents. Infants and children may also have had a recent primary care visit before a sudden death occurs, and parents may express anger at the last physician who treated the child. Parents may ask the emergency physician why or how there could have been a delay or failure in the diagnosis by their child's primary care physician.

SUPPORT AND COUNSELING

Interventions for helping survivors cope with grief are reviewed in Chapter 169: Bereavement and Grief Reactions. The grieving parent or family member must be supported during the event of breaking the tragic news and during months after their loss by social services and bereavement resources. EDs should have bereavement guidelines in place, including a death plan addressing notification of family, burial arrangements, organ donation, advance directives, autopsy requests, and family support. Although many national resources and protocols for pediatric ED deaths exist, each case must be individually addressed with local or state statutes followed. An example of an ED death protocol is shown in Figure 293.1. An

example of practice guidelines developed by a multidisciplinary panel for coping with death in the ED setting is summarized in Table 293.4 (15). Family support services should provide trained and skilled bereavement counseling, coping assessment, and referral services offered through an interdisciplinary program that protects and respects the religious, cultural, spiritual, psychological, and ethical needs of all family members. The support team may include physicians, nursing staff, social workers, chaplains, the primary care physician, and other local support groups (6). Institutions can also assist families through this event with formal programs that provide follow-up to all families for a designated period of time, Memory Boxes with hand or foot prints, grief support literature and resources for siblings, and consultation to individuals or organizations in the wider community who experience childhood death. National support organizations are listed in Table 293.5.

PROCEDURE: Pediatric Death In The ED
Support For Survivors

Physician Responsibilities

1. Notify chaplain early, as soon as death appears inevitable. Ask clerk or nurse to page chaplain via operator
2. Talk with family (listen!)
   - Intervene early and report progress
   - Answer specific questions to the best of your ability
   - Assure the family that medical care was complete
   - Allay parental guilt
   - Take PA/Nursing staff with you
   - *Remember:* Doing nothing is doing something! Some people just cannot be consoled or reached acutely
3. Allow family to view or hold their child.

Nursing Responsibilities

1. Assign consistent nurse to the family
2. Facilitate ED phase
3. Accompany physician and chaplain
4. Provide a quiet room and rocking chair
5. Complete ED checklist
6. Personally ensure paperwork forwarded to ED Nurse Manager's office
7. Attach letter requesting medical examiner's report to Notice of Death worksheet

Follow-Up Phase

1. Chaplain phone call to parents 1-2 weeks after death to coordinate support group participation
2. Patient relations to coordinate physician/survivor meeting to review autopsy findings or answer questions

Checklist for Pediatric Deaths

Patient name_____Unit #_____Date_____

Relative name_____Address_____

Phone #_____Account #_____

Initial Emergency Department Phase

____ Staff person assigned to family members, who?
____ Ask family if patient has had a primary physican or medical clinic
____ If so, who?
____ Medical examiner notifed
____ Family notification of death and tentative cause (essential family members present in emergency department)
____ Family permitted to see baby/tangible evidence of death offered (eg, lock of hair), special requests honored, if so, what? _____
____ Family allowed to express grief; respond to individual needs
____ Family members understand how they may receive autopsy report
____ Family informed of follow-up procedures and given a phone number to call if they have questions
____ ED chart completed (including ED form)
____ Copy of chart enclosed
____ Organ donation

EMS Office Phase

Family physician/clinic notified of death on_____Phone #_____by_____

Copy of checklist retained in EMS office? _____Yes _____No

Comments_____

Chaplain's Phase

Phone call to family (3–5 days after death) on_____by_____

Comments_____

Phone call to family (2–3 weeks after death) on_____by_____

Comments_____

Support group offered on_____by_____

Comments_____

Patient Relations Phase

Autopsy results requested on_____by_____

Appointment made for follow-up with physician on_____by_____

Appointment date_____Physician_____

Comments_____

Physician/EMS office Phase

Physician's comments after meeting_____

_____

Checklist/chart returned to Chaplain's office by EMS office on_____by_____

Chaplain's Phase

Call made to family (6 months following death) on_____by_____

Comments_____

Checklist/chart returned to EMS office for final filing on_____by_____

Comments_____

FIGURE 293.1 Example of ED death protocol.

TABLE 293.4
Bereavement Practice Guidelines for Healthcare Professionals in the ED[a]

Phase One

Preparing the ED to Help the Family of a Critically Ill or Injured Child Who Dies

- Have protocols and procedures in place (media, police, ME, family presence, death certificate, organ donation)
- Train all the ED staff (physicians, nurses, techs, students, clerks, and security) about the needs of families, including expected reactions, and cultural and religious differences
- Designate a family room with a phone
- Assign a trained FCP, chaplain, or other appropriate staff to work with the family

Phase Two

When the Critically Ill or Injured Child and the Family Arrive in the ED

- FCP should prepare for the arrival of the family if time permits
- FCP should greet the family upon arrival to the ED
- FCP guides family to a private room
- FCP is the liaison between family and staff and remains with family for duration of stay

Phase Three

When a Child Dies in the ED

- Help the family with grief expressions: anger, sadness, fainting, violence, and guilt
- Review all procedures and "what was done" to help their child
- Praise family and allay guilt
- Explain role of ME, autopsy, organ or tissue donation, law enforcement, child abuse and other agencies
- Contact family's religious or spiritual leader
- Give family option of spending time with their deceased child if allowed by law enforcement or medical examiner
- If appropriate, offer funeral resources
- Offer informational and resource brochures to take home

Phase Four

Follow-up After the Death of a Child in the ED

- Follow-up plan
- Letter of condolence
- Meeting to review autopsy or ME results
- Time for questions
- List of bereavement support groups
- Most hospice programs and children's hospitals offer programs and support

Phase Five

Helping Staff Cope with Childhood Deaths

- Proper education and supervision
- Debriefing sessions in some cases
- Recognize outstanding work

ED, emergency department; ME, medical examiner; FCP, family care provider.
[a]Adapted from Lipton H, Coleman M. Bereavement practice guidelines for health care professionals in the emergency department. *Int J Emerg Mentl Health*. 2000;2:1–13, with permission.

TABLE 293.5
National Resource and Support Organizations

The Compassionate Friends Inc. (www.compassionatefriends.org)
1000 Jorie Blvd., Suite 140
Oak Brook, IL 60522-3696
Ph: (630)990-0010; Toll Free: (877)969-0010

Support for bereaved parents, siblings, and grandparents; chapters in all states
American SIDS Institute (www.sids.org)
528 Raven Way
Naples, FL 34110
Ph: (239)431-5425; Toll Free: (800)232-SIDS

Provides crises phone counseling, grief literature, and referrals
SIDS Alliance (www.sidsalliance.org)
First Candle
2105 Laurel Bush Rd. Suite 201
Bel Air, MD 21015
Ph: (443)640-1049; Toll Free Grief Counseling: (800)221-7437

Provides support to those affected by an infant death
Share Pregnancy & Infant Loss Support, Inc. (www.nationalshare.org)
National Share Office
402 Jackson St.
Saint Charles, MO 63301-3468
Toll Free: (800)821-6819
Email: info@nationalshare.org

Offers support, resources, and education on miscarriage, stillbirth, and newborn death: Literature, keepsake items, and sympathy cards available
Partnership for Parents: A Support Network for Parents of Children with Serious Illnesses (www.partnershipforparents.net)
65 Nielson St, #108
Watsonville, CA 95076
Ph: (831)763-3070

SIBLING AND CHILDHOOD BEREAVEMENT

The emergency physician should also be knowledgeable about the grieving process in surviving children. The American Academy of Pediatrics recommends addressing the following questions: What is death? What made the person die? Where is the person? Can it happen to me? Who will take care of me? Table 293.6 lists manifestations of grief in children by age and developmental level.

The child's pediatrician or primary care physician should be involved in monitoring the grief process (18).

TABLE 293.6
Manifestations of Grief in Children

Young Children (<3 yrs of age)	Preschool Children	School-Age Children	Adolescents
Regression sadness	Increased activity	Deterioration of school performance caused by loss of concentration, disinterest, lack of motivation, failure to complete assignments, and day dreaming in class	Depression
Fearfulness	Constipation	Resistance to attending school	Somatic complaints
Anorexia	Encopresis	Crying spells	Delinquent behavior
Failure to thrive	Enuresis	Lying	Promiscuity
Sleep disturbance	Anger and temper tantrums	Stealing	Suicide attempts
Social withdrawal	"Out-of-control" behavior	Nervousness	Dropping out of school
Developmental delay	Nightmares	Abdominal pain	
Irritability	Crying spells	Headaches	
Excessive crying		Listlessness	
Increased dependency		Fatigue	
Loss of speech			

Adapted from American Academy of Pediatrics, Committee on Psychosocial Aspects of Child and Family Health. The pediatrician and childhood bereavement. *Pediatrics*. 2000;105:445–446.

ED PHYSICIAN AND STAFF CONCERNS

Medical resuscitations in the ED require teams to perform under a tremendous amount of pressure, and when poor outcomes or unexpected deaths occur, the stress on providers can become overwhelming. Emergency physicians on average experience a mean of approximately 17 patient deaths per year and are exposed to a much higher death rate than many other subspecialties (19). Pediatric deaths are rare, but depending on the surrounding demographics and subspecialty certification of an ED, emergency staff may be exposed to significantly higher rates of pediatric deaths. Following failed resuscitations of critically ill patients, providers have reported intense feelings of guilt or inadequacy and considerations of alternative professions (6,19). Pediatric deaths are particularly stressful for staff members. Staff should be observed for signs of depression, hostility, burnout, or substance abuse. A crisis intervention team should be considered if an unusual number of pediatric deaths occur or if a mass-casualty incident exposes the staff to many deaths at one time. Death policies and crisis counseling skills should be part of the orientation program for new ED staff members.

Team debriefing after resuscitation is one intervention that has been shown to mitigate stress by fostering an opportunity for reflection and emotional processing (20,21). Debriefing allows healthcare teams to reexamine the clinical event and discuss individual and team performance, identify errors, and develop plans for performance improvement. The facilitated discussion format of medical debriefings promotes a sense of shared responsibility, builds team trust and morale, and helps with future practice improvements (20,22). Given the infrequent occurrence of pediatric resuscitations, emergency teams would benefit from debriefing practice using simulation. Research shows debriefing to be a skill that improves with practice and one that is influenced positively by the use of Debriefing Tools to facilitate the discussion (21,22). The American Heart Association, American Academy of Pediatrics, and the European Resuscitation Council all recommend routine use of debriefing in clinical practice to improve performance (23–24).

Common Pitfalls

- Assuming unexplained infant deaths are caused by SIDS without looking for signs of abuse, underlying illness, congenital disorders, or sepsis.
- Failure to have an organized plan or protocol for childhood deaths in the ED.
- Failure to contact the patient's primary-care or subspecialty physician.
- Failure to attend to grief reactions in parents and siblings.
- Failure to recognize the benefits of debriefing after resuscitation for ED staff.

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CHAPTER 294

Consent for Care of Children, Adolescents, and Emancipated Minors

Samantha L. Rosman

In the United States, with a few exceptions that will be noted, minors (defined as under age 18 in most states) are unable to consent to their own medical care and require a surrogate such as a parent or guardian to consent on their behalf (1). While the majority of children are brought into the emergency department (ED) by their parents and consent is easily obtained, emergency physicians regularly encounter children brought in by an adult who is not a parent or legal guardian, or adolescents who are seeking care on their own. In these situations physicians must decide what care can and should be provided immediately and what care should be withheld until appropriate consent can be obtained.

UNACCOMPANIED MINORS

The American College of Emergency Physicians (ACEP) states in its policy on the treatment of minors that "the evaluation and necessary treatment of a minor in the ED should not be delayed because of consent issues" (2). Indeed, under the federal Emergency Medical Treatment and Active Labor Act (EMTALA), any hospital that receives federal funding for any of its programs must perform an initial medical screening examination (MSE) for every patient seeking treatment. This examination is required regardless of the

patient's ability to pay or the availability of consent for treatment. The screening must determine whether an emergency medical condition exists, defined as life- or limb-threatening, severe pain, or conditions with potential for serious impairment or dysfunction if left untreated (3). A MSE may be as simple as a physician's examination in triage or may require extensive laboratory testing, imaging, and subspecialty consultation to rule out an emergency medical condition. The ACEP policy also states that an emergency is not only a condition that can cause death or disability but may also include urgent conditions that, if not treated immediately, may result in further complications, pain, fever, disease transmission, etc. (2). Consequently, if the parents of a child with an uncomplicated forearm fracture cannot be reached in a timely manner, physicians can in most cases act in the child's best interest to reduce and splint the fracture if it will decrease the risk of future complications. The understanding is that a reasonable parent or guardian would consent to emergency care if able to do so. In other words, under these circumstances physicians may act with "implied consent" and invoke the emergency exception rule to parental consent for treatment of an unaccompanied minor (Table 294.1) (1).

TABLE 294.1
Conditions of Emergency Exception Rule

1. Child's life or health is in danger as a result of the emergency condition;
2. Child's legal guardian is unavailable or unable to provide consent;
3. Treatment cannot be safely delayed until consent is obtained; AND
4. Treatment is administered only for emergent conditions that pose an immediate threat to the child.

Data from Committee on Pediatric Emergency Medicine and Committee on Bioethics. Consent for emergency medical services for children and adolescents. *Pediatrics*. 2011;128;427–433;Tsai AK, Schafermeyer RW, Kalifon D, et al. Evaluation and treatment on minors: Reference on consent. *Ann Emerg Med*. 1993;22:1211–1217.

If the emergency exception rule is invoked, the following should be clearly documented in the chart: (1) The emergent nature of the condition, (2) the reason immediate care was required, and (3) the unsuccessful efforts made to obtain consent. Courts are almost

universally supportive of physicians in these situations if they are perceived as acting in the child's best interest (1).

ADOLESCENT CONSENT ISSUES

Many adolescents seen in the ED remain minors in the eyes of the law and thus require parental consent for treatment. There are several situations, however, in which the law allows adolescents to consent for themselves (Table 294.2).

TABLE 294.2
Adolescent "Minors" Able to Consent for Themselves

1. Emancipated minor;
2. Specific medical condition exception; OR
3. Mature minor exception.

Data from Committee on Pediatric Emergency Medicine and Committee on Bioethics. Consent for emergency medical services for children and adolescents. *Pediatrics*. 2011;128:427–433;Tsai AK, Schafermeyer RW, Kalifon D, et al. Evaluation and treatment on minors: Reference on consent. *Ann Emerg Med*. 1993;22:1211–1217; Holder AR. Minors' rights to consent to medical care. *JAMA*. 1987;257:3400–3402.

Emancipated minor laws vary by state, and it is important to be familiar with the particular laws that apply. Minors are often defined to be "emancipated" when they (1) are legally married, (2) are economically self-sufficient and not living with parents or guardians, (3) are on active duty military, or (4) are pregnant or a parent themselves. Some states require a court to legally declare a minor emancipated rather than allowing circumstances alone to define the minor's status (1,2,4).

Most states allow minors to consent on their own for care for specific medical conditions such as drug or alcohol abuse, mental health issues, sexually transmitted infection testing and treatment, or pregnancy-related issues (1,4). The specific situations vary as to where, and the ages at which, minor consent is allowed for these or similar conditions.

Most states also provide for a mature minor exception. Although in some jurisdictions the court must declare such an exception, the

physician is empowered to make the decision in others. A mature minor is generally an adolescent—age 14 or older—with the maturity and capacity to understand the risks and benefits of a proposed treatment and the ability to make a reasonable decision after considering the information given. Generally, in cases where the physician is empowered to decide whether the minor is mature, the treatment must (1) be to the minor's benefit, (2) be acutely necessary, and (3) not involve serious risks (1,4).

ADOLESCENT CONFIDENTIALITY

Confidentiality from parents is often a very important issue for adolescents seeking care of their own accord. On the federal level, The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule protects the confidentiality of personal health information from disclosure to third parties. Under HIPAA, however, parents or guardians are considered representatives for their minor children and thus generally have access to their children's health information. There are two major exceptions. First, a parent can agree to a confidential relationship between the physician and the adolescent, thereby transferring the right of disclosure to the minor. Second, the parent can lose the right to the minor's health information in cases in which the state law does not require parental consent for treatment (5,6).

Except for information protected from disclosure by the federal Family Planning Act (FPA), the issue of parental access to a minor's health information is not otherwise covered by federal law (1). Consequently, adolescent consent issues are governed by state law. Some states explicitly require parental notification—depending on the circumstances—while others specifically guarantee confidentiality in cases that permit adolescent consent. Once again, it is critical for physicians to be familiar with applicable parental disclosure and confidentiality laws in the jurisdictions in which they practice.

Physician must be honest and candid with their adolescent patients as to what can be kept confidential and what cannot (see

Chapter 289). In most states, parents have a legal right to request their minor child's medical record unless the parents' possession of the records would put the child in danger or the parent has previously agreed to waive the right to such access. In addition, parents, as the primary insurance holders, often receive bills for services that may disclose diagnoses, procedures, or other aspects of the adolescent's care that may at least partially betray confidentiality. Thus, confidentiality can often only be reliably maintained if the adolescent takes on financial accountability for his or her care, and it is important to identify a confidential way of contacting the patient with the results of pending studies or the need for return visits (1,2).

PARENTAL REFUSAL OF TREATMENT

Parents and guardians generally have the authority to make decisions on behalf of their children and, therefore, to consent to or refuse medical care. In most cases, the parents' decision should be honored, but parental authority is not absolute and is limited by parents' duty to ensure the safety and health of their children. If the parent or guardian acts in such a way that the child's health, well-being or life is in jeopardy, the state may intervene under the doctrine of *parens patriae.* Based on society's obligation to protect its most vulnerable members, this doctrine grants the state the right to act *in loco parentis,* in place of the parent, when it is necessary to protect the life and health of those who cannot take care of themselves, including children (1,2,7,8).

The issue often arises with parents of certain religious groups that are opposed to lifesaving medical interventions. For example, this occurs when Jehovah's Witnesses refuse blood products for their children. In the United States, Jehovah's Witness parents often argue that they have the right to refuse blood on their child's behalf under the Free Exercise Clause of the First Amendment. However, American courts have almost universally ruled in favor of child welfare and have rejected the First Amendment argument in these circumstances. The majority of courts hold that while the freedom

to believe is absolute, the right to practice religion freely does not include the right to put a child at risk of serious illness, injury, or death (8).

Similarly, when the state determines medical neglect, it can act *in loco parentis* and assume temporary custody to authorize medical care if this is being done to protect the "health or safety of the child" (1,8–12).

If a physician believes that a parent's decision places a child's life or health in significant danger, every effort should be made to persuade the parent to consent to the proposed lifesaving treatment. If this is unsuccessful, or the situation does not allow for delay, the physician may need to notify both the police and child protective services and have the child placed in temporary protective custody. In these cases, the doctrine of *parens patriae* allows the state to interfere on behalf of the child's welfare. Such authorization extends only to conditions that are serious or life-threatening (1,2,8).

SUSPECTED CHILD ABUSE AND NEGLECT

In cases where there is suspected child abuse or neglect and the parents refuse to consent to evaluation and treatment, *the physician's primary duty is to protect the child's safety and well-being.* In addition to the mandated reporting of the suspected abuse or neglect, the physician will need to involve state child protective services or local law enforcement to obtain *parens patriae* consent to evaluation and treatment (1,2).

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SECTION XXIII
Toxicology

Section Editor: LOUIS J. LING

PART 1 • GENERAL CONSIDERATIONS

CHAPTER 295 Evaluation of the Poisoned Patient

Jerrold B. Leikin

The history and physical examination is the cornerstone of clinical patient management, and while taking a history may be a direct method for toxin exposure identification, quite often it is not reliable. Information obtained may prove minimal in some cases and should be considered partial or inaccurate in suicidal gestures and with illegal drug or chemical use. Thus, obtaining a history of exposure from family, friends, coworkers, or prehospital personnel, may be essential to patient management.

IMMEDIATE CRITICAL INTERVENTION

An immediate decision with regard to stability needs to be made upon patient presentation. Unstable vital signs need to be assessed and addressed in the traditional manner. Supportive measures including the "ABCs" (airway, breathing, circulation) are often required before confirmation of intoxication can be obtained. Intubation is not always necessary when cough and gag reflexes are present and there is adequate spontaneous ventilation; however, when there is a concern regarding airway protection and potential clinical deterioration, it is better to secure the airway. Intubation is indicated in acute respiratory failure. Other specific indications include the need for high levels of supplemental oxygen (e.g., in carbon monoxide poisoning) and the need to protect the airway for gastric emptying or decontamination. Endotracheal intubation

decreases (but does not eliminate) the risk of aspiration (which is approximately 10% in the comatose patient with drug overdose) (1).

The “coma cocktail” (dextrose, oxygen, thiamine, and naloxone) is diagnostic as well as therapeutic, and should be administered empirically to the comatose patient with a suspected toxic exposure (2,3). A rapid bedside blood glucose can determine which patients should receive dextrose, although a low normal value by blood dipstick does not always exclude low serum glucose. The dose is 50 g IV in an adult; 2 to 4 mL/kg body weight of a 25% solution in a child. Thiamine (50 to 100 mg) can treat or avoid Wernicke encephalopathy syndrome, which is particularly important in the nutritionally depleted alcoholic; there is no evidence that dextrose should be withheld until thiamine is administered.

Naloxone rapidly reverses coma, respiratory depression, and hypotension induced by opioids. An initial dose of 0.2 to 0.4 mg in adults is administered IV, subcutaneously, IM, or endotracheally. The intratrachael dosage is diluted to 1 to 2 mL in normal saline. If there is no response, an additional 1 to 2 mg can be repeated. The pediatric dose is 0.1 mg/kg, repeated every 2 to 3 minutes as needed. Use of a higher initial dose may precipitate withdrawal symptoms in opioid-dependent patients. Heroin and morphine are the most sensitive to naloxone, and while some opioid agents such as meperidine, propoxyphene, diphenoxylate, methadone, and pentazocine require larger doses. A lack of response to 10 mg of naloxone generally excludes opioid toxicity (see Chapter 305 for details about naloxone use).

Flumazenil should be considered in cases where benzodiazepine overdose alone is suspected or when reversal of therapeutic conscious sedation is desired. Case reports suggest a risk of precipitating seizures with flumazenil when there is a suspicion of benzodiazepine plus cyclic antidepressant overdose. See Chapter 308 for details on use of flumazenil. The routine use of flumazenil is discouraged, except in cases of acute benzodiazepine overdose presenting as coma or respiratory depression without any coingestants (4).

DIAGNOSTIC APPROACH

A quick and focused physical examination often leads to important clues about the nature of the toxin. These clues can be specific symptom complexes associated with certain toxins and can be referred to as “toxidromes” (Table 295.1) (5).

TABLE 295.1
Common Toxidromes

Toxidrome	Features	Drugs/Toxins
Anticholinergic	Mydriasis	Antihistamines
"Hot as a hare, dry as a bone, red as a beet, mad as a hatter"	Blurred vision	Atropine
		Fever
		Dry skin
	Flushing	Tricyclic antidepressants
	Ileus	Phenothiazines
	Urinary retention	Propantheline
	Tachycardia	Scopolamine
	Hypertension	
	Psychosis	
	Coma	
	Seizures	
	Myoclonus	
Cholinergic "SLUDGE"	*S*alivation	Carbamate
	*L*acrimation	Organophosphates
	*U*rination	Physostigmine
	*D*iarrhea	Pilocarpine
	*G*I cramps	
	*E*mesis	
	Wheezing	
	Diaphoresis	
	Bronchorrhea	
	Bradycardia	
	Miosis (pinpoint pupils)	
β-Adrenergic	Tachycardia	Albuterol
	Hypotension	Caffeine
	Tremor	Terbutaline
		Theophylline
α-Adrenergic	Hypertension	Phenylephrine
	Bradycardia	Phenylpropanolamine
	Mydriasis	
β- and α-Adrenergic	Hypertension	Amphetamines
	Tachycardia	Cocaine
	Mydriasis	Ephedrine
	Diaphoresis	Phencyclidine
	Dry mucous membranes	Pseudoephedrine
Sedative/hypnotic	Stupor and coma	Anticonvulsants
	Confusion	Antipsychotics
	Slurred speech	Barbiturates
	Apnea	Benzodiazepines
		Ethanol
		Meprobamate
		Opiates
Hallucinogenic	Hallucinations	Amphetamines
	Psychosis	Cannabinoids
	Panic	Cocaine
	Fever	Lysergic acid diethylamide/ Indole alkaloid
	Mydriasis	Phencyclidine (may present with miosis)
	Hyperthermia	
	Synesthesia	

Toxidrome	Features	Drugs/Toxins
Extrapyramidal	Rigidity/tremor	Haloperidol
	Opisthotonos	Phenothiazines
	Trismus	Risperidone
	Hyperreflexia	Olanzapine
	Choreoathetosis	
Narcotic	Altered mental status	
	Slow shallow breaths	Opiates
	Miosis	Pentazocine
	Bradycardia	
	Hypotension	
	Hypothermia	
	Decreased bowel sounds	
Serotonin	Irritability	Fluoxetine
	Hyperreflexia	Meperidine
	Flushing	Paroxetine
	Diarrhea	Sertraline
	Diaphoresis	Trazodone
	Fever	Clomipramine
	Trismus	Selective serotonin reuptake inhibitor
	Tremor	Tramadol
	Myoclonus	
Epileptogenic	Hyperthermia	Strychnine
	Hyperreflexia	Nicotine
	Tremors	Lindane
	May mimic stimulant patterns	Lidocaine
		Xanthines
		Isoniazid
		Chlorinated hydrocarbons
		Camphor
Solvent	Lethargy	Hydrocarbons
	Confusion	Acetone
	Headache	Toluene
	Restlessness	Naphthalene
	Incoordination	Trichloroethane
	Derealization	Chlorinated hydrocarbons
	Depersonalization	Petrochemicals
Uncoupling of oxidative phosphorylation	Hyperthermia	Aluminum phosphide
	Tachycardia	
	Metabolic acidosis	Cyanide
		2,4-Dichlorophenol
		Dinitrophenol
		Glyphosate
		Phosphorus
		Pentachlorophenol
		Zinc phosphide

Adapted from Mokhlesi B, Leikin JB, Murray P, Corbridge TC. Adult toxicology. *Critical Care Chest*. 2003;123:577–592.

Vital Signs. Depending on the intoxication, patients may present with hypotension or hypertension, bradyarrhythmias, or tachyarrhythmias. The pathogenesis of hypotension varies and may include hypovolemia, myocardial depression, cardiac arrhythmia, or

systemic vasodilation. Treatment should be individualized, but an initial strategy of rapid intravenous normal saline solution infusion is indicated in most instances. Vasopressors may be required for refractory hypotension. The vasopressor of choice depends on the type of intoxication. For example, norepinephrine appears to be advantageous over dopamine in tricyclic antidepressant-induced hypotension (6). Lipid rescue therapy can be considered in the setting of hemodynamic instability—this is discussed further in Chapter 296. Hypertension occurs with sympathomimetic drugs, anticholinergics, ergot derivatives, phenylpropanolamine overdoses, and withdrawal from nicotine, alcohol, and sedatives. The need to treat the hypertension depends on its chronicity and severity of symptoms and the inciting agent. Hypertension-induced (reflex) bradycardia generally should not be treated.

Anticholinergic and sympathomimetic substances increase heart rate, blood pressure, and temperature. This is particularly true for cocaine intoxication, where hyperthermia may be a particularly ominous sign for mortality. Important clinical signs that differentiate sympathomimetic poisoning from anticholinergic intoxication include dry skin and xerostomia along with absent bowel sounds, which usually occur in anticholinergic but not sympathomimetic poisoning. It should be noted that the antipsychotics and antidepressants with the greatest anticholinergic effects include clozapine, thioridazine, and amitriptyline. In contrast, organophosphates, opiates, barbiturates, β-blockers, benzodiazepines, alcohol, and clonidine cause hypothermia, bradycardia, and respiratory depression. Table 295.2 lists various toxins which alter temperature.

TABLE 295.2
Drugs Affecting Temperature

Hypothermia	Hyperthermia
Akee fruit poisoning	Monoamine oxidase inhibitors
Alcohols	Amphetamines
Barbiturates	Anticholinergics
Clonidine	Neuroleptic malignant syndrome
Colchicine	Lysergic acid diethylamide
Cyclic antidepressants	Antihistamines
Hypoglycemic agents	Cocaine
Lithium	Malignant hyperthermia
Opioids	Cyclic antidepressants
Phenothiazines	Drug withdrawal
Tetrodotoxin food poisoning	Phencyclidine
White Chameleon	Phenothiazines
	Salicylates
	Serotonin syndrome
	Tung Nut
	Cathinone
	Dextromethorphan
	Arsenic
	Strychnine
	Pentachlorophenol
	Dinitrophenol
	Adrenergic agents
	Quinine
	Thyroid medications

Adapted from Mokhlesi B, Leikin JB, Murray P, Corbridge TC. Adult toxicology. *Critical Care Chest*. 2003;123:577–592.

Sensorium. Determine whether the patient is comatose, stuporous, lethargic, or alert. Table 295.3 lists drugs that can directly affect mental status, while Table 295.4 lists toxic causes of delirium. Poisoned individuals presenting with deep coma (Glasgow Coma Scale under 7) have a mortality rate approximately seven times higher than overall mortality from acute poisoning (7). **Tables 295.5** and **295.6** list clinical signs of worsening of toxin-induced coma and poor prognostic signs of coma. Table 295.7 lists drugs that can cause cyclic or relapsing coma.

TABLE 295.3
Selected Drugs Altering Mental Status

Depressed Physiologic State	Agitated Physiologic State
Sympatholytics	Sympathomimetics
Adrenergic blockers	Adrenergic agonists
Antiarrhythmics	Amphetamines
Antihypertensives	Caffeine
Antipsychotics	Cocaine
Cyclic antidepressants	Ergot alkaloids
Cholinergics	Monoamine oxidase inhibitors
Bethanechol	
Carbamates	Theophylline
Nicotine	Anticholinergics
Organophosphates	Antihistamines
Physostigmine	Antiparkinsonian drugs
Pilocarpine	
Sedative/hypnotics	Antipsychotics
Alcohols	Antispasmotics
Barbiturates	Cyclic antidepressants
Benzodiazepines	Cyclobenzaprine
Gamma hydroxybutyrate	Drug withdrawal
Ethchlorvynol	Clonidine
Narcotics	Ethanol
Analgesics	Opioids
Antidiarrheal agents	Sedative/hypnotics
Other	Hallucinogens
Cyanide	Lysergic acid diethylamide
Hydrogen sulfide	
Hypoglycemic agents	Marijuana
Lithium	Mescaline
Salicylates	Phencyclidine
	Other
	Thyroid hormones

Adapted from Mokhlesi B, Leikin JB, Murray P, Corbridge TC. Adult toxicology. *Critical Care Chest*. 2003;123:577–592.

TABLE 295.4
Toxic Causes of Delirium

Medicinal Agents

Acyclovir	Aldesleukin	Alfentanil
Alprazolam	Aminophylline	Amiodarone
Amitriptyline	Amoxapine	Amphotericin B
Atrophine	Belladonna	Belladonna and Opium
Benztropine	Buprenorphine	Bupropion
Butorphanol	Butriptyline	Caffeine
Camphor	Cantharidin	Carbamazepine
Chloral hydrate	Chlorpheniramine	Chlorpromazine
Choline magnesium trisalicylate	Cimetidine	Ciprofloxacin
Clomipramine	Clonidine	Clozapine
Cocaine	Codeine	Colchicine
Cortisone acetate	Cyclobenzaprine	Cycloserine
Cylosporine	Desipramine	Dextroamphetamine
Dibenzepin	Dicyclomine	Digitoxin
Digoxin	Diphenhydramine	Drug withdrawal
Doxepin	Ergotamine	Estazolam
Ethchlorvynol	Ethyl alcohol	Famotidine
Fentanyl	Flumazenil	Flouride
Fluorouracil	Fluoxetine	Fluphenazine
Glutethimide	Heroin	Hydrocodone
Hydrocortisone	Hydromorphone	Hydroquinone
Hydroxyzine	Hyoscyamine	Imipramine
Interferon α-2a	Interferon α-2b	Interferon α-n3
Interferon β-1b	Interferon γ-1b	Ipratropium
Isocarboxazid	Ketamine	Levodopa
Levomethadyl acetate hydrochloride	Levorphanol	Lidocaine
Lithium	Loperamide	Maprotiline
Mefloquine	Meperidine	Mephentermine
Mesoridazine	Methadone	Methamphetamine
Methohexital	Methotrexate	Methyl salicylate
Methyldopa	Metoclopramide	Mianserin
Midazolam	Morphine sulfate	Nalbuphine
Niacin	Nitroprusside	Nizatidine
Nortriptyline	Opium alkaloids (hydrochlorides)	Opium tincture
Oxycodone	Oxymorphone	Para-aminosalicylate sodium
Paraldehyde	Paregoric	Paroxetine
Pentazocine	Pentobarbital	Perphenazine
Phencyclidine	Phenelzine	Phencyclidine
Phenobarbital	Phenylephrine	Phenytoin
Prazepam	Prednisolone	Procarbazine
Prochlorperazine	Promazine	Promethazine
Propoxyphene	Protriptyline	Quinidine
Ranitidine hydrochloride	Rifampin	Salicylate
Salsalate	Scopolamine	Secobarbital
Serotonin syndrome	Sertraline	Sparfloxacin
Stanozolol	Sufentanil	Tacrolimus
Theophylline	Thioridazine	Thiothixene
Tocainide	Tramadol	Tranlcypromine
Trazodone	Triamcinolone	Trifluoperazine
Triflupromazine	Trimethaphan camsylate	Trimipramine
Valacyclovir	Venlafaxine	Vigabatrin
Vinorelbine	Vitamin A	Zolpidem

Nonmedicinal Agents

1-Propanol	Arsenic	Benzene
Bromates	Carbon dioxide	Carbon tetrachloride
DDT	Diethyltoluamide	Ethylene dichloride
Gasoline	Lead	Lysergic acid diethylamide
Mercury	Nerve gases	Nickel carbonyl
Nitrous oxide	Tetrachloroethane	Thallium
Toluene	Triethyltin	

Biologic Agents

Black nightshade	Boxthorn	Cathinone
Chicken soup	Christmas Cherry	Claviceps purpurea
Daphne	Deadly nightshade	Foxglove
Jimson weed	Lantana	Marijuana (Cannabis)
Morning glory	Mushrooms, Toxic	
(Group II) Monomethyl-hydrazines	Mushrooms, Toxic	
(Group III) Cholinergic Mushrooms, Toxic	Mushrooms Toxic	Oleander
(Group V) Anticholinergic	(Group VI) Psychedelic	
Pennyroyal Oil	Potato (Leaves, stems, tubercles)	Sand Brier
Scorpion fish	Stonefish	Turkey fish
Woody Nightshade	Wormwood	

TABLE 295.5
Neurologic Signs of Worsening of Toxic Coma

Loss of spontaneous blinking or induced blink response
Loss of corneal reflex
Loss of cough or swallow reflex
Flexor toe pattern response to plantar stimulation (Babinski sign)
Decerebrate or decorticate rigidity
Apneustic breathing pattern
Autonomic dysfunction

Adapted from Leikin JB, Carlson A. Alterations in consciousness. In: Brent J, et al., eds. *Critical Care Toxicology*. New York: Mosby Elsevier; 2005:213–24.

TABLE 295.6
Poor Neurologic Prognostic Signs from Recovery of Toxic Coma

Loss of pupillary reflexes (up to 1 wk)
Absence of corneal reflexes after Day 1
Lack of oculovestibular response
Absence of eye-opening response at Day 3
Absence of bilateral cortical component of the somatosensory evoked potential responses
Abnormal skeletal muscle tone
Absence of spontaneous eye movement
Low-voltage delta activity (with alpha coma) or isoelectric tracing on EEG

Adapted from Leikin JB, Carlson A. Alterations in consciousness. In: Brent J, et al., eds. *Critical Care Toxicology*. New York: Mosby Elsevier; 2005:213–24.

TABLE 295.7
Drugs Which can Cause Cyclic or Relapsing Coma

Carbamazepine
Ethchlorvynol
Glutethimide
Meprobamate
Barbiturates

Adapted from Leikin JB, Carlson A. Alterations in consciousness. In: Brent J, et al., eds. *Critical Care Toxicology*. New York: Mosby Elsevier; 2005:213–24.

Behavior and Hallucinations. Often the patient's hallucinatory pattern can be specific for certain drugs. For example, with atropine the patient experiences lilliputian hallucinations; with cocaine, there is a simple visual hallucinatory pattern with objects appearing in the periphery of vision; with phencyclidine, complex hallucinations are often indistinguishable clinically from a paranoid psychosis; with LSD, the patient experiences a combination of illusions, hallucinations, synesthesia, and pseudohallucinations.

Motor Signs. Tremors, hypo- and hyperreflexes, and even the nature of seizures can be useful diagnostic tools. Like hallucinations, seizures caused by specific toxins can exhibit certain specific properties. For example, strychnine is unique in that it can cause generalized seizures while the patient is alert, often called a "spinal

seizure." Most toxin-induced seizures (including withdrawal seizures) will respond to benzodiazepines, barbiturates, or propofol. Other drug-induced seizures respond only to specific antidotal therapies and not conventional antiseizure medication. Examples include anticholinergic-induced seizures, which respond to physostigmine, and isoniazid-induced seizures, which respond to pyridoxine. Most drug-induced seizures rarely respond to phenytoin and may require multidrug therapy. Toxins resulting in isolated cranial neuropathies are rare and are listed in Table 295.8.

TABLE 295.8
Agents Causing Cranial Nerve Palsies

Aldicarb	Arizona Bark Scorpion	Botulinum Toxin Type A
Bromophos	Carbaryl	Carbon disulfide
Chlorfenvinphos	Clostridium botulinum food poisoning	Coumaphos
Demeton-S-methyl	Dichlorvos	Dicrotophos
Didanosine	Dioxathion	Disulfoton
Ethion	Ethylene glycol	Fensulfothion
Fenthion	Ketoprofen	King Cobra envenomation
Lead	Malathion	Mercury
Methidathion	Methiocarb	Methomyl
Methotrexate	Mevinphos	Parathion
Phosdrin	Pravastatin	Profenofos
Propoxur	Rabies virus	Terbufos
Tetraethyl pyrophosphate	Toluene	Trichinella spiralis food poisoning
Trichloroethylene	Vincristine	

Adapted from Mokhlesi B, Leikin JB, Murray P, Corbridge TC. Adult toxicology. *Critical Care Chest*. 2003;123:577–592.

Ocular Findings. These can be divided into two categories: pupillary size and reactivity, and demonstration of nystagmus.

Pupillary Signs. Both atropine and cocaine can result in mydriasis, but in cocaine or other adrenergic intoxication the pupils respond to light, whereas with anticholinergics the pupils will not respond. Agents that contribute to miosis include organophosphate

insecticides, narcotics, bromide, clonidine, and nicotine. Phencyclidine has been known to cause either mydriasis or miosis. It should be noted that pontine hemorrhage can result in miosis; Drug withdrawal and serotonin syndrome can cause mydriasis (see **Tables 295.9** and **295.10**).

TABLE 295.9
Agents Causing Miosis

Medicinals		
Alfentanil	Bethanechol	Bunazosin
Buprenorphine	Buspirone	Chloral hydrate
Clonidine	Codeine	Dextromethorphan
Edrophonium	Fentanyl	Guanabenz
Guanidine	Heroin	Hydromorphone
Levomethadyl acetate hydrochloride	Levorphanol	Lidocaine
Loperamide	Meprobamate	Meptazinol
Mathadone	Methyprylon	Morphine sulfate
Nalbuphine	Neostigmine	Nilutamide
Opium alkaloids (hydrochlorides)	Opium tincture	Oxycodone
Oxymorphone	Paregoric	Pentazocine
Phencyclidine	Phenobarbital	Physostigmine
Pilocarpine	Procane	Propoxyphene
Pyridostigmine	Rauvolfia serpentina	Reserpine
Tilidine	Tramadol	Valproic acid and derivatives
Zolpidem		
Nonmedicinals		
2,4-D	2-Methyl-4-chlorophenoxyacetic acid	Aldicarb
Amitraz	Bromoform	Bromophos
Carbaryl	Chenopodium oils	Chlorfenvinphos
Chlorpyrifos	Coumaphos	Diazinon
Dichlorvos	Dicrotophos	Dioxathion
Disulfoton	Endosulfan	Ethion
Fensulfothion	Fenthion	Isofenphos
Malathion	Methidathion	Methiocarb
Methomyl	Mevinphos	Nerve Gases
Parthion	Profenofos	Propoxur
Terbufos	Tetraethyl pyrophosphate	
Biologic		
Betel nut	Castor Bean	Eucalyptus oil
Fire-bellied toad	Mushrooms, Toxi (Group III) cholinergic	Nutmeg
Poison hemlock	Tetrodotoxin food poisoning	

Adapted from Mokhlesi B, Leikin JB, Murray P, Corbridge TC. Adult toxicology. *Critical Care Chest*. 2003;123:577–592.

TABLE 295.10
Agents Causing Mydriasis

Medicinals

Acetaminophen	Amisulpride	Amphetamine
Atropine	Azatadine	Benztropine
Biperiden	Botulinum toxin type A	Bretylium
Bromides	Brompheniramine	Buclizine
Buflomedil	Bupropion	Butriptyline
Caffeine	Camphor	Carbamazepine
Carbinoxamine	Chlormezanone	Chlorprocaine
Chlorpheniramine	Chlorpromazine	Chlorprothixene
Cimetidine	Cocaine	Cyclizine
Cyclobenzaprine	Cyproheptadine	Desipramine
Diazepam	Dibenzepin	Dicyclomine
Diethylpropion	Dimenhydrinate	Diphenhydramine
Disopyramide	Dopamine	Doxepin
Doxylamine	Ephedrine	Estazolam
Ethchlorvynol	Ethyl alcohol	Fenfluramine
Fluoride	Glutethimide	Glycopyrrolate
Hydrocodone and homatropine	Hyoscyamine	Ketamine
Imipramine	Ipratropium	Isocarboxazid
Ivermectin	Lidocaine	Mecamylamine
Meclizine	Meperidine	Meprobamate
Methamphetamine	Midazolam	Naphazoline
Nicotine	Nortriptyline	Oxytocin
Papaverine	Pemoline	Pentoxifylline
Phencyclidine	Phenelzine	Phentermine
Phenylephrine	Phenylpropanolamine	Phenytoin
Pizotyline	Pralidoxime	Procaine
Promethazine	Protriptyline	Pseudoephedrine
Quinidine	Quinine	Scopolamine
Sertraline	Thioridazine	Thyroid
Tolazoline	Trimeprazine	Trimethaphan camsylate
Trimipramine	Tripelennamine	Yohimbine

Nonmedicinals

1,2-Dibromoethane	2-Butoxyethanol	Barium
Benzene	Carbon monoxide	Chenopodium oils
Chloroform	Chloromethane	Coumaphos
Cyanide	Dichlorvos	Disulfoton
Ethylene glycol	Fensulfothion	Hydrazine
Lysergic acid diethylamide	Methaldehyde	Methidathion
Methyl bromide	Methyl ethyl ketone	Pentachlorophenol
Sodium azide	Sodium monofluoracetate	Terbufos
Thallium	Trichloroethylene	Turpentine oil

Biologic		
Box Thorn	Cathinone	Clostridium botulinum food poisoning
Corn lily (Veratrum)	English ivy	Ephedra
Golden chain tree	Goldenseal	Horse chestnuts
Jimson weed	Lantana	Lupine
Marijuana (Cannabis)	Mate	Mescaline
Morning glory	Mushrooms, Toxic (Group V)	Mushrooms, Toxic (Group VI) Psychedelic
Neurotoxic shellfish poisoning	Nutmeg	Peyote
Sassafras Oil	Scotch Broom	Tetrodotoxin food poisoning
Tyramine hydrochloride food poisoning	Valerian	Water hemlock
Wild cucumber	Woody nightshade	Yew

Adapted from CHEST article.

Nystagmus. Alcohols are probably the most common etiology of horizontal nystagmus, although lithium, carbamazepine, solvents, meprobamate, quinine, and primidone can also cause horizontal nystagmus. Though phencyclidine classically causes a combination of vertical, horizontal, and even rotary nystagmus, these can also occur with phenytoin and sedative–hypnotics.

In addition to these physical signs, odors emanating from the patient may also provide important diagnostic clues. For example, a garlic odor is often caused by arsenicals, phosphorus compounds, organophosphates, and insecticides.

Laboratory evaluation. The clinical laboratory evaluation includes the evaluation of the "three laboratory gaps of toxicology": anion gap, osmolal gap, and oxygen saturation gap. What these "gaps" have in common is that a substance is accounting for a difference between the calculated and measured determinations.

The anion gap reflects the difference between the serum or plasma measured cation and anion concentrations and is usually calculated utilizing the following formula: Anion Gap = measured Na^+ concentration – [measure chloride and bicarbonate concentrations] (8). The normal range of anion gap is usually 8 to 12 mEq/L in most

laboratories. An increase in anion gap (>16 mEq/L) suggests lactic acidemia, uremia, ketoacidemia, or selected intoxications (see **Tables 295.11** and **295.12**). A normal anion gap does not preclude intoxication because most toxins do not elevate the anion gap or there may be a coexisting condition that lowers the gap. Common among these conditions is hypoalbuminemia: for every 1 g/L decrease in the plasma albumin, the anion gap falls by 2.5 mEq/L. Clinicians should pay special attention to this correction factor to avoid missing a clinically significant anion gap. Also, in methanol or ethylene glycol poisoning, concurrent ethanol use delays the development of an elevated anion gap metabolic acidosis. In this case, an elevated osmolal gap may be the only early clue to the diagnosis.

TABLE 295.11
Common Causes of Abnormal Anion Gap

Elevated Anion Gap	Decreased Anion Gap
Lactic acidosis (type A)	Increased unmeasured cation
Uremia	Hyperkalemia
Sepsis	Hypercalcemia
Rhabdomyolysis	Hypermagnesemia
Ketoacidosis	Acute lithium intoxication
Diabetic	Elevated IgG (myeloma; cationic paraprotein)
Alcoholic	Decreased unmeasured anion
Starvation	Hypoalbuminemia
Toxic ingestions (See **Table 295.12**)	Drugs
	Bromide
	Iodide
Metabolic alkalosis with volume depletion	Lithium
	Polymyxin B
Anion gap without acidosis: Carbenicillin	Analytical artifact
	Hypernatremia (>170 mEq/L)
	Hyperlipidemia

Adapted from Mokhlesi B, Leikin JB, Murray P, Corbridge TC. Adult toxicology. *Critical Care Chest*. 2003;123:577–592.

TABLE 295.12
Selected Drugs Associated with an Elevated Anion Gap Metabolic Acidosis

2-Butoxyethanol	Acetaminophen (>75 g)
Amiloride	Ascorbic acid
Carbon monoxide	Chloramphenicol
Colchicine	Cyanide
Dapsone	Dinitrophenol
Epinephrine	Ethanol
Ethyl acetate	Ethylene glycol
Formaldehyde	Fructose (IV)
Hydrogen sulfide	Ibuprofen (over 400 mg/kg)
Iron	Isoniazid
Ketamine	Linezolid
Metformin	Methanol
Nalidixic acid	Niacin
Nitroprusside	Nitroprusside
Nonsteroidal anti-inflammatory drugs	Papaverine
Paraldehyde	Pennyroyal oil
Pentachlorophenol	Phenelzine
Phenylbutazone	Propofol
Propylene glycol	Salicylates
Sodium azide	Sorbitol (intravenous)
Strychnine	Terbutaline
Tetracycline (outdated)	Toluene (hippuric acid)
Tranylcypromine	Vacor
Verapamil	Zinc phosphide

Adapted from Mokhlesi B, Leikin JB, Murray P, Corbridge TC. Adult toxicology. *Critical Care Chest*. 2003;123:577–592.

Low–molecular-weight drugs and toxins that are osmotically active can increase the discrepancy between measured and calculated plasma osmolality (9). Normal plasma osmolality is 285 to 295 mOsm. The calculated value is determined as follows:

$$\text{Calculated osmolality} = 2[Na^+] + \text{BUN}/2.8 + \text{glucose}/18 + \text{ethanol}/4.25$$

in which Na^+ (in milliequivalents per liter) is multiplied by 2 to account for accompanying anions (chloride and bicarbonate), and

measured BUN, glucose, and ethanol (in milligrams per deciliter) is divided by the appropriate denominator. The osmolal gap must be interpreted with caution. Measurement of osmolality by vapor pressure osmometry does not detect volatile alcohols such as ethanol and methanol; however, it does detect ethylene glycol (10). Freezing point depression osmometry, the most frequently used method, measures all of these solutes. Therefore, it is important for clinicians to know the method used by their institution. With the standard formula, the normal osmolal gap is large and may range from −9 to +5 mOsm; 10 mOsm is considered the upper limit of normal. However, an osmolal gap of 10 mOsm in a patient who started at −9 mOsm may be significantly elevated and the gap may be missed. Table 295.13 lists agents that can cause an osmolal gap.

TABLE 295.13
Causes of Osmol Gap (>10 mOsm from Baseline Values)

I. Exogenous Causes
Dimethyl Sulfoxide[a]
Ethanol[b]
Ethylene glycol
Glycerol[a]
Glycine[a]
Hypermagnesemia (serum level greater than 9.5 mEq/L)
Iodine (questionable)
Isopropyl alcohol (acetone)
Mannitol
Methanol[b]
Osmotic contrast dyes
Sorbitol[a]
Valproic acid
II. Artificial (Blood Collection Tube)
Lavender top (EDTA)—15 mOsm/L
Gray top (sodium fluoride and potassium oxalate)—150 mOsm/L
Blue top (citrate)—10 mOsm/L
Green top (lithium, heparin)—6 mOsm/L

[a]Through intravenous administration.
[b]Also usually results in an associated anion gap metabolic acidosis.
Values are reported as calculated contributions.

An oxygen saturation gap is present when there is more than a 5% difference between the saturation calculated from an arterial blood gas and the saturation actually measured by co-oximetry. Co-oximetry detects the absorption of four different wavelengths, enabling it to directly measure levels of four types of hemoglobin species: oxyhemoglobin, reduced hemoglobin, carboxyhemoglobin, and methemoglobin. Because arterial blood gas analysis calculates oxygen saturation from the measured pO_2 using a standard oxygen–hemoglobin dissociation curve, an oxygen saturation gap occurs in the presence of carboxyhemoglobin, methemoglobin, and sulfhemoglobin (which is not routinely measured by co-oximetry). Pulse oximetry estimates oxygen saturation by emitting a red light (wavelength of 660 nm) absorbed mainly by reduced hemoglobin, and a near-infrared light (wavelength of 940 nm) absorbed by oxyhemoglobin.

Methemoglobin absorbs almost equally at both these wavelengths. At high methemoglobin levels (over 35%), the oxygen saturation by pulse oximetry tends to regress toward 85% and plateaus at that level despite further increments in methemoglobin levels. Thus, if the actual oxygen saturation by co-oximetry is >85%, pulse oximetry underestimates it; if it is <85% by co-oximetry, it overestimates oxygen saturation. A listing of drugs/toxins causing methemoglobinemia is in Table 295.14 (11,12).

TABLE 295.14
Selected Drugs/Toxins Associated with Acquired Methemoglobinemia

Acetanilide	Nitric oxide
Aluminum phosphide (phosphine)	Nitroethane
Amyl nitrite	Nitrobenzene
Butyl nitrite	Nitroglycerin
Bromates	Nitroprusside
Aniline dyes	Pesticides
Benzocaine	Petrol octane booster
Bupivacaine	Phenacetin
Chlorates	Phenazopyridine
Chloroquine	Potassium ferricyanide
Dapsone	Prilocaine
Flutamide	Primaquine
Herbicides	Pyridium Plus (Warner Chilcott, Inc. Rockaway, NJ)
Isobutyl nitrite	Silver nitrate
Isosorbide dinitrate	Sodium chloride
Lidocaine	Sodium nitrite
Loxosceles gaucho venom	Sulfonamides
Methyl nitrite	
Metoclopramide	

Adapted from Leikin JB. Observation unit toxicology. Chapter 19. In: Graff L, ed. The Textbook of Observation Medicine: The Healthcare System's Tincture of Time. Dallas, TX: American College of Emergency Physicians; 2010.

Since many laboratories do not routinely use co-oximetry, a more commonly seen gap is the disparity between measured oxygen saturation by blood gas and that measured by pulse oximetry. Carbon monoxide has a wavelength absorption coefficient similar to that of oxyhemoglobin and carboxyhemoglobin may be misinterpreted as oxyhemoglobin by pulse oximetry, leading to overestimation of oxygen saturation when compared to co-oximetry. Abnormally high venous oxygen content (arterialization of venous blood) is characteristic of cyanide poisoning.

In spite of providing indirect laboratory evidence of intoxication, urine drug screening tests alter management in less than 5% of cases (13). However, toxicology urine drug screening can identify a specific toxin for which an antidote is available and in some instances quantify a toxin allowing for titrated therapy. Most institutions offer urine immunoassay–based testing for six or seven of the most commonly abused drugs. Table 295.15 lists substances that

can give a false-positive urine drug screen (14,15). Results are generally available in 60 minutes. Urine confirmation with gas chromatography/mass spectrometry can usually be obtained, but frequently take an additional 2 to 3 days. Because of false positives, while mean immunoassay confirmation rates are highest for cocaine (98%) and marijuana (91%), the confirmation rate for amphetamine is only about 50% (16); in addition, the presence of a drug on a screening test does not necessarily confirm that the symptoms are from that drug. Many drugs cause a positive urine drug screen for many days. Cocaine metabolites can be seen for up to 5 days, and marijuana can be detected for up to a month. Probably the most important prognostic function for immunoassay urine drug screening is in the patient with occult barbiturate use to ascertain the potential risk for barbiturate withdrawal. More comprehensive urine screening (usually performed off-site) may take several hours or even days. Testing of gastric contents is rarely helpful in the emergency department.

TABLE 295.15
Causes of False-Positive Results in Urine Drug Screens (Immunoassay)

A. Amphetamine
   1. Polyclonal based
      a. Ephedrine
      b. Pseudoephedrine
      c. Chloroquine
      d. Labetalol
   2. Monoclonal based
      a. Chlorpromazine
      b. Flusipirilene
      c. Pipothrazin
      d. Dimethylamylamine
B. Phencyclidine
   1. Doxylamine
   2. Diphenhydramine
   3. Venlafaxine
   4. Dextromethorphan
   5. Tramadol
C. Cannabinoid
   1. Omeprazole
D. Benzodiazepine
   1. Oxaprozin
   2. Sertraline
E. Tricyclic Antidepressants
   1. Antihistamines
   2. Cyproheptadine
   3. Carbamazepine
   4. Thioridazine
   5. Chlorpromazine
   6. Cyclobenzaprine
   7. Quetiapine
F. Methadone
   1. Antipsychotic agents
   2. Diphenhydramine
   3. Doxylamine
   4. Quetiapine
   5. Verapamil
   6. Tapentadol
G. Opiate
   1. Gatifloxacin

Serum quantification of certain toxins is useful, particularly in cases of alcohol (ethanol, methanol, ethylene glycol), acetaminophen, salicylate, phenobarbital, theophylline, digoxin, iron, and lithium intoxication. The timing of these serum specimens needs to correlate with the timing of the drug's absorption and such an analysis is particularly useful in evaluating substances that may exhibit a delay in the onset of clinical symptoms (Table 295.16). Serum values of selected agents causing coma are listed in Table 295.17. A strong argument can be made for checking serum acetaminophen and possibly salicylate levels in all cases of medication ingestion, given the easy availability of acetaminophen and salicylate, the subtle manifestation of early poisoning, and the existence and importance of specific treatment of these potentially lethal intoxications.

TABLE 295.16
Agents that can Cause Delay in Symptoms

Toxic Ingestion	Toxic Dose	Onset of Major Symptomatology (Latent Period)	Time to Determination of Toxic Serum Levels
Acetaminophen	140 mg/kg	72 hrs (hepatic phase)	4 hrs
Salicylates	150 mg/kg	May not take place for 12–24 hrs	6 hrs
Iron	20 mg/kg	12 hrs (shock, seizures)	2–6 hrs
Theophylline			
Regular formulation	10 mg/kg		5 (±3 hrs)
Sustained released	20 mg/kg		11 hrs
Wafarin	0.5 mg/kg	36 hrs (bleeding)	PT depression at 24 hrs
Digoxin	2 mg (child) 5 mg (adult)	3–6 hrs	4 hrs
Phenytoin	Variable	1–2 hrs	3–12 hr
Methanol	4 cc (100% methanol)	6–24 hrs (visual)	1 hrs
Ethylene glycol	1.4 cc/kg	24–72 hrs (renal effects)	1–4 hrs
Bupropion	10 mg/kg	6-18 hrs (seizures)	3 hrs (immediate release)/ 6 hrs (extended release)

TABLE 295.17
Agents and Blood Concentrations Resulting in Coma

Drug	Conventional Units	Drug	Conventional Units
Acebutolol	20 mg/L	Glutethimide	10 mg/L
Acetaminophen	300 µg/mL	Iron	500 µg/dL
Acetone	500 mg/L	Isoniazid	20 mg
Amitriptyline	2 mg/L	Lead	100 µg/dL
Amobarbital	43 mg/L	Lidocaine	5 µg/mL
Baclofen	1 mg/L	Lithium	3 mEq/L
Barbital	160 mg/L	Lorazepam	0.3 mg/L
Butabarbital	39 mg/L	Loxapine	0.7 mg/L
Caffeine	100 mg/L	Meprobamate	60 mg/L
Calcium	15 mg/dL	Mephobarbital	40 mg/L
Carbamazepine	18 mg/L	Methanol	100 mg/dL
Carboxyhemoglobin	30%	Methaqualone	8 mg/L
Carisoprodol	30 mg/L	Methemoglobin	20%
Cetirizine	2 mg/L	Methyprylon	50 mg/L
Chloral hydrate (Trichloroethanol)	20 mg/L	Nomifensine	10 mg/L
Chlordiazepoxide	20 mg/L	Olanzapine	100 µg/L
Chlormethiazole	7 mg/L	Orphenadrine	3 mg/L
Chlormezanone	60 mg/L	Phenobarbital	65 mg/L
Chloroquine	1 mg/L	Phenytoin	40 mg/L
Chlorpromazine	0.5 mg/L	Propoxyphene	1 mg/L
Chlorprothixene	0.8 mg/L	Quetiapine	13 mg/L
Cimetidine	10 mg/L	Quinine	12 µg/mL
Clonazepam	0.07 mg/L	Salicylates	100 mg/dL
Clonidine	2 µg/L	Secobarbital	7 mg/L
Clozapine	2 mg/L	Sodium	160 mEq/dL
Codeine	5 mg/L	Theophylline	40 mg/L
Diazepam	20 mg/L	Tetrahydrocannabinol	180 µg/L
Diethyltoluamide (DEET)	50 mg/L	Toulene	10 mg/L
Digoxin	4 ng/L	Tramadol	2,000 µg/L
Dothiepin	1 mg/L	Tranylcypromine	1 mg/L
Doxepin	0.4 mg/L	Triazolam	31 µg/L
Ethanol	300 mg/dL	Valproic acid	300 mg/L
Ethchlorvynol	50 mg/dL	Venlafaxine	6 mg/L
Gamma hydroxybutyrate	100 mg/L	Zopiclone	300 µg/L
Glucose	800 mg/dL		

Adapted from *Poisoning and Toxicology Handbook*. In: Leikin JB, Paloucek FP, eds. 4th ed. Boca Raton, FL: CRC Press; 2008.

Radiography is not a reliable method for evaluating toxic exposure and should be utilized only in specific cases. Factors that influence radiodensity include molecular weight, atomic number, relative contrast to surrounding tissues, and compactness of the form of drug. Overall, only about one-third of all drug preparations would be detectable by plain abdominal x-ray, with about 2% of drugs being densely radiopaque (Table 295.18) (18). These cases include evaluation of heavy metal exposure (including leaded paint chips), concretion formation of drugs (such as salicylate, meprobamate, iron, and theophylline), suspected body packing or body stuffing, and the use of digital radiography for extended-release formulations (17).

TABLE 295.18
List of Radiopaque Substances

Medicinal	
Amiodarone	Meclizine
Bismuth subgallate	Neostigmine
Bromides	Penicillin G (aqueous)
Calcium carbonate	Potassium chloride
Chloral hydrate	Protriptyline
Chlorpromazine	Ranitidine
Diethylstibestrol	Salicylate
Ethchlorvynol	Sodium chloride
Glyburide	Spironolactone
Haloperidol	Sustained-release medications
Hydroxyzine	Thiamine
Iron	Zinc sulfate
Nonmedicinal/Biologic	
Arsenic	Methylene chloride
Barium	Needlefish
Carbon tetrachloride	Paradichlorobenzene
Chloroform	Tetrachloroethylene
Iopanoic acid	Thallium sulfate
Lead	Trichloroethylene
Mercury	

Common Pitfalls

- Failing to obtain collateral information regarding potential toxin exposure.
- Overlooking potential toxic causes in patients with anion gap metabolic acidosis.
- Overlooking the possibility of acetaminophen toxicity in patients presenting with gastrointestinal or hepatic complaints.
- Failing to consider drug or ethanol withdrawal in the hyperadrenergic delirious patient.

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CHAPTER 296

General Management of the Poisoned Patient

Jerrold B. Leikin

The general treatment plan is support of the airway, breathing, and circulation before addressing the poisoning specific treatments with an organized approach essentially similar irrespective of the toxic exposure. This basic poison management encompasses the following intervention (Fig. 296.1):

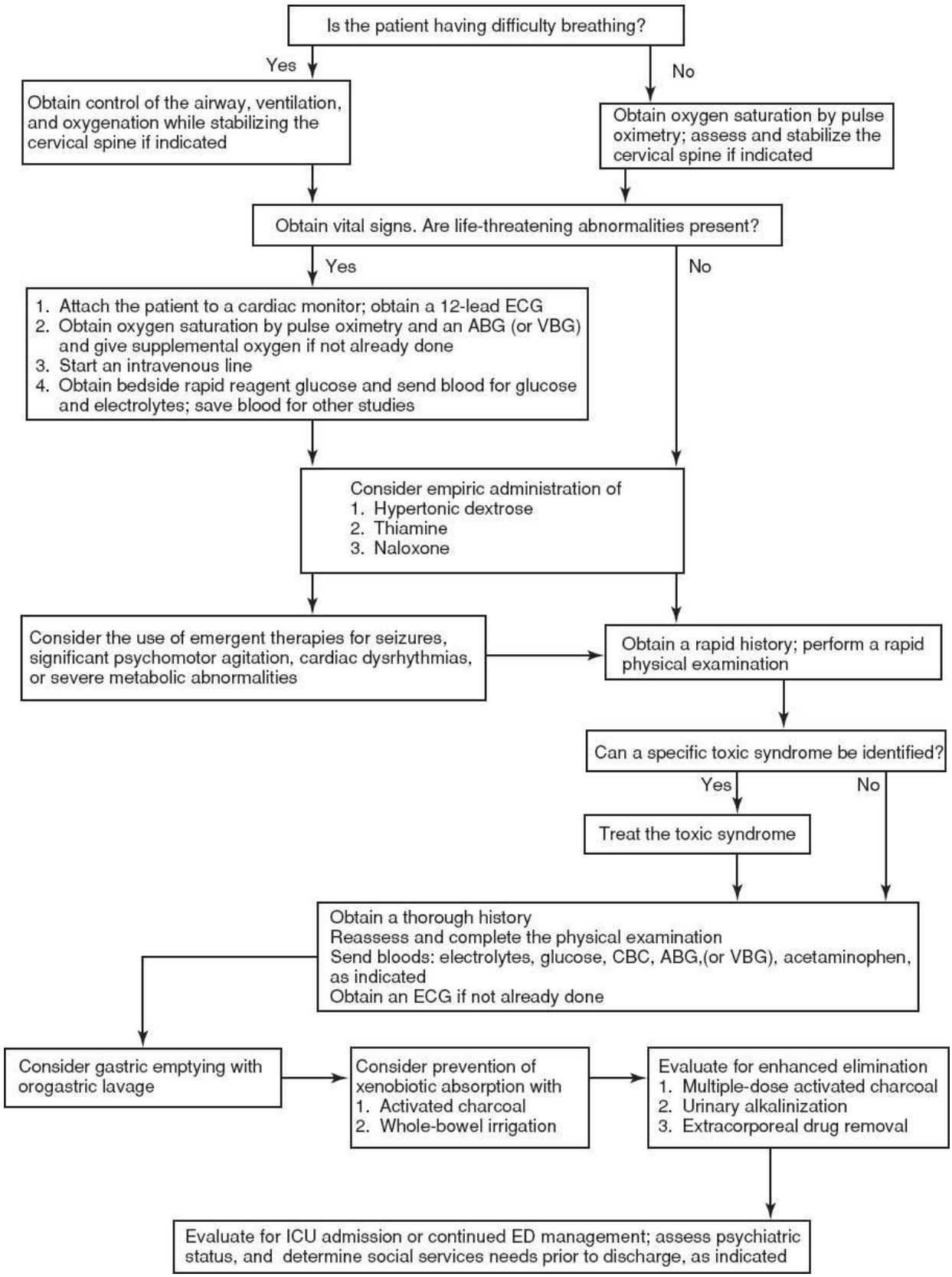
Is the patient having difficulty breathing?
Yes
No
Obtain control of the airway, ventilation, and oxygenation while stabilizing the cervical spine if indicated
Obtain oxygen saturation by pulse oximetry; assess and stabilize the cervical spine if indicated
Obtain vital signs. Are life-threatening abnormalities present?
Yes
No
1. Attach the patient to a cardiac monitor; obtain a 12-lead ECG
2. Obtain oxygen saturation by pulse oximetry and an ABG (or VBG) and give supplemental oxygen if not already done
3. Start an intravenous line
4. Obtain bedside rapid reagent glucose and send blood for glucose and electrolytes; save blood for other studies
Consider empiric administration of
1. Hypertonic dextrose
2. Thiamine
3. Naloxone
Consider the use of emergent therapies for seizures, significant psychomotor agitation, cardiac dysrhythmias, or severe metabolic abnormalities
Obtain a rapid history; perform a rapid physical examination
Can a specific toxic syndrome be identified?
Yes
No
Treat the toxic syndrome
Obtain a thorough history
Reassess and complete the physical examination
Send bloods: electrolytes, glucose, CBC, ABG,(or VBG), acetaminophen, as indicated
Obtain an ECG if not already done
Consider gastric emptying with orogastric lavage
Consider prevention of xenobiotic absorption with
1. Activated charcoal
2. Whole-bowel irrigation
Evaluate for enhanced elimination
1. Multiple-dose activated charcoal
2. Urinary alkalinization
3. Extracorporeal drug removal
Evaluate for ICU admission or continued ED management; assess psychiatric status, and determine social services needs prior to discharge, as indicated

FIGURE 296.1 The algorithm is a basic guide to the management of poisoned patients. A more detailed description of the steps in management may be found in the accompanying text. This algorithm is only a guide to actual management, which must, of course, consider the patient's clinical status.

1. Prevention of absorption or decontamination
2. Antidote administration, if available
3. Removal of absorbed toxin or enhancing elimination
4. Support and monitoring for adverse effects

PREVENTION OF ABSORPTION

The route of entry for toxic substances can be dermal, ocular, GI, inhalational, or parenteral. Skin decontamination requires removal of the toxin with nonabrasive soap and copious irrigation with water. Contaminated clothing may serve as a reservoir for continued exposure and must be removed with caution and placed in plastic bags or other containers that are impervious to the toxin. This will limit exposure to medical personnel and patient. Ocular decontamination may require prolonged periods of irrigation with normal saline solution using a Morgan lens. Inhalational exposure presents a greater challenge since the toxin cannot be accessed and removed. Most irrigant solutions for ocular, dermal, or gastrointestinal lavage are water or saline based with a few exceptions. The vast majority of toxin exposures and poisonings occur through the gastrointestinal (GI) tract (1). There are three methods of GI decontamination including (1) gastric lavage (GL), (2) whole-bowel irrigation (WBI), and (3) activated charcoal (2,3). Syrup of ipecac, previously used, is relegated to medical history or veterinary toxic exposures (4–7).

Gastric Emptying

GL through a 28- to 40-French Ewald tube is aimed at physically removing an unabsorbed toxin (Table 296.1) (8–10). Before inserting the Ewald tube, the mouth should be inspected for foreign material

and equipment should be ready for suctioning. Large gastric tubes are less likely to enter the trachea than smaller nasogastric tubes, and have large holes to facilitate removal of gastric debris. After insertion, proper position should be confirmed by aspirating stomach contents and auscultating the left upper abdominal quadrant during insufflation of air. Nonintubated patients should be alert (and be expected to remain alert) and have adequate gag reflexes. In unresponsive patients, GL should be performed after a cuffed endotracheal tube has been inserted. Intubation for the sole purpose of gastric emptying is reasonable only if there is a high likelihood that a highly lethal agent remains in the stomach. GL is performed by instilling 200-mL aliquots of warmed tap water until there is clearing of aspirated fluid. After clearing, the Ewald tube may be replaced by a nasogastric tube for subsequent intermittent suctioning and/or administration of activated charcoal.

TABLE 296.1
Toxins which Should be Lavaged with Solutions Other Than Water

Gastric	
Aluminum bif luoride	10% calcium gluconate
Aluminum phosphide or zinc phosphide	Avoid water due to release of phosphine
	Lavage with 1:5,000 potassium permanganate
Barium carbonate	Magnesium sulfate or sodium sulfate
Bromates	Sodium bicarbonate (isotonic or 5% concentration)
Zinc phosphide	
Shellfish exposure	
Tetrodotoxin	
Cesium	Berlin/Prussian blue
Chlorfenvinphos	2% Potassium permanganate or 5% sodium bicarbonate
Rubidium	
Chromium	Ascorbic acid 1% solution (10 g in 1 L)
Creosote	Olive oil
DDT	Mannitol
Fluoride	Calcium gluconate (10%)
Iodine	Starch/sodium thiosulfate (1–5%)
Mercury	Sodium formaldehyde sulfoxylate (20 g in a 5% solution)
	A 2–5% solution of sodium bicarbonate can be used as an alternative therapy
Nicotine	1:5,000 to 1:10,000 potassium permanganate (50–100 mg in 1 L water)
Phosphorus	
Physostigmine	
Quinine	
Strychnine	
Paralytic shellfish (saxitoxin)	2% NaHCO3
Paraquat	1–2 g/kg Fuller's earth (15%) or bentonite (7%)
Radium	Magnesium sulfate (10%)
Sodium monofluoroacetate	
Strontium	Avoid contact with water due to thermal reaction
Thallium	1% sodium iodine
Dermal	
Aluminum phosphide, gallium phosphide, zinc phosphide, elemental lithium, sodium, potassium, Rb, Cs, and Fr	Dry wipe (due to explosive hazard), then rinse with water
Calcium oxide	
Chlorosulfonic acid	
Titanium tetrachloride	
Trichlorosilane	
White phosphorus	
Asphalt	Shur-cleanse or De-solv-it
Chlorobenzylidene malononitrile (CS)	Alkaline solution
Cyanoacrylate	Acetone with soaking in water or nitromethane
Phenol	Polyethlene glycol (300 or 400) or isopropyl alcohol (water is not contraindicated)
Skunk musk	Irrigate with sodium hypochlorite (5.25%) diluted 1:5 or 1:10 or can use a that consisting of 1 quart of 3% hydrogen peroxide, ¼ cup of baking soda, and 1 teaspoon of liquid soap
Chloroacetophenone (mace)	Magnesium hydroxide–aluminum hydroxide–simethicome gently blotted over affected area (avoid eyes)
Ocular	
Aluminum phosphide, gallium phosphide, zinc phosphide, elemental lithium, sodium, potassium, Rb, Cs, and Fr	Dry wipe, then irrigate with water (may react violently with water)
Titanium tetrachloride	
Asphalt	Shur-cleanse or De-solv-it
Calcium hydroxide	2% Sodium edetate
Calcium oxide	
Mercury fulminate	Water followed by 2% sodium thiosulfate solution
Radioactive materials	Normal saline
White phosphorus (if burns develop during water irrigation)	3% Copper sulfate solution (several drops)
Zinc chloride (>1%)	Water followed by (within 2 min of exposure) 1.7% (0.5 molar) edetate disodium solution for 15 min

From *Poisoning and Toxicology Handbook*. 4th ed. CRC Press; 2008:1316–1317.

Activated Charcoal

Charcoal is a by-product of the combustion of compounds such as wood, coconut parts, bone, sucrose, rice, and starch. Its adsorptive

capacity is increased or “activated” by removing materials previously adsorbed with steam heating and chemical treatment, increasing the surface area for adsorption to between 1,000 and 3,000 m^2/g. This results in an inert, nontoxic, and nonspecific adsorbent that binds intraluminal drugs soon after ingestion and thus interferes with their absorption. Single-dose activated charcoal is effective against most toxins and drugs but should be used for cases with a higher probability of injury or illness Table 296.2. It is particularly effective in binding high–molecular-weight compounds and is ineffective for small ions such as lithium or potassium, acids, alkali, hydrocarbons, alcohols, and heavy metals Table 296.3. Activated charcoal decreases serum drug levels in some cases by creating a favorable diffusion gradient between blood and gut, often referred to as *Gastrointestinal dialysis* (8,10,11).

TABLE 296.2
Examples of Substances Removed by Activated Charcoal

Acetaminophen	Fluoxetine
Amphetamines	Isoniazid
Antihistamines	Metformin
Barbituates	Methotrexate
β-Adrenergic blocking agents	Paraquat/Diquat
Calcium channel blocking agents	Quinidine/Quinine
Camphor	Salicylate
Carbamazepine	Strychnine
Cardiac glycosides	Sulfonylurea derivatives
Chlordecone	Theophylline
Chloroquine	Tramadol
Citalopram	Tricyclic antidepressants
Colchicine	Valproic acid
Cyanide salts	Venlafaxine
Escitalopram	

Adapted from Mokhlesi B, Leikin JB, Murray P, Corbridge TC. Adult toxicology in critical care: Part 1: General approach to the intoxicated patient. *Chest*. 2003;123:577–592.

TABLE 296.3
Toxins and Drugs Not Absorbed by Activated Charcoal

Alcohols
Hydrocarbons
Organophosphates
Carbamates
Acids
Potassium
Dichloro diphenyl trichloroethane (DDT)
Alkali
Iron
Lithium

Charcoal can be administered after gastric lavage, but it is usually the sole GI decontaminating method (10–12). Airway protection is imperative in stuporous, comatose, or convulsing patients.

Activated charcoal is contraindicated in patients with central nervous system depression with an unprotected airway due to the risk of aspiration. Similarly, hydrocarbon ingestions are also an increased aspiration risk. Individuals at risk for gastrointestinal bleeding or perforation due to previous pathology, recent surgery, or other pre-existing medical conditions may be at increased risk for complications. Activated charcoal should not be administered if endoscopy is being considered. Complications are infrequent; however, charcoal aspiration has been associated with pneumonia, bronchiolitis obliterans, ARDS, and bronchial obstruction, particularly in very young children. Emesis is usually related to use of sorbitol when combined with activated charcoal. Considering the frequency of use of activated charcoal, the complication rate is relatively low but considering the low fatality rate of most poisonings, the greatest benefit is for chemicals or drugs with a high fatality rate such as cyclic antidepressants or calcium channel blockers.

The ideal dose should give a charcoal-to-drug ratio of 10:1. However, since the quantity of poison ingested is usually unknown, the dose is often based on patient weight (0.5 to 1 g/kg). In adolescents and adults, the usual dose is 25 to 100 g. Table 296.2 lists toxins for which charcoal is not particularly effective (13). Based on volunteer studies, the effectiveness of activated charcoal

decreases with time; the greatest benefit is within 3 hours of ingestion although its overall clinical benefit (over that of supportive care) has been challenged (14).

The use of cathartics with activated charcoal may reduce the transit time of drugs and toxins in the GI tract and decrease the constipating effects of charcoal. The two types of osmotic cathartics used are saccharide based (sorbitol) and saline based (magnesium citrate, magnesium sulfate, sodium sulfate. Cathartics may decrease drug absorption but have never been shown to decrease morbidity and mortality or to decrease hospital stay (15–17). Based on available data, the routine use of a cathartic in combination with activated charcoal is not generally recommended (17).

Whole-Bowel Irrigation

WBI with polyethylene glycol electrolyte solution has been used over the past 20 years to prevent toxin absorption by cleansing the gastrointestinal tract. Since no net absorption or secretion of ions occurs, no significant change in water or electrolyte balance would be expected. WBI may have a role in intoxications where activated charcoal is not effective and considered for potentially toxic ingestions of sustained release or enteric-coated tablets, substantial amounts of iron, lead or other metals or ions such as lithium or packets of illicit drugs. The solution is best administered through a small bore 12-French nasogastric tube at age-based dosing: children 9 months to 6 years: 500 mL/hr, children 6 to 12 years: 1,000 mL/hr, adolescents and adults: 1,500 to 2,000 mL/hr. The patient should be seated or the head of the bed elevated to at least 45 degrees to decrease the likelihood of emesis and establish a dependent relationship of the intestines to the stomach. If emesis occurs, the infusion rate can be decreased by 50% for 30 to 60 minutes and then return to the original rate. Metoclopramide (which exhibits both antiemetic and gastric emptying effects) can also be administered.

The solution is administered until the rectal effluent is clear which may take over 5 hours. The technique is time consuming and requires a cooperative patient. Most studies supporting this approach

are limited to case reports, and there are no established specific indications for its use (2,18,19). Contraindications to WBI include ileus, GI hemorrhage, uncontrolled vomiting, bowel perforation, and an unprotected compromised airway.

Antidotes

An antidote is a substance that increases the mean lethal dose of a toxin, or that can favorably affect the toxic effects of a poison. Some are toxic themselves and should be used only when indicated. Only approximately 5% of overdose patients require antidotal administration (1).

Table 296.4 lists antidotes for specific drugs/poisons. These will be discussed in the individual toxin chapters.

TABLE 296.4
Examples of Antidotes

Poison/Drug/Toxin	Antidote
Acetaminophen	N-Acetylcysteine
Carbon tetrachloride	
Other hepatotoxins	
Acetonitrile	Hydroxocobalamin
Acrylonitrile	
Cyanide (e.g., HCN, KCN and NaCN)	
Cyanogenic glycoside natural sources (apricot pits and peach pits)	
Laetrile	
Smoke inhalation (combustion of synthetic cyanogenic materials)	
Pit viper envenomation (e.g., rattlesnakes, cottonmouths, and copperheads)	
Black widow spider envenomation	Antivenom: *Latrodectus mactans* (black widow spider)
Lead	Calcium disodium EDTA
Zinc salts (e.g., zinc chloride)	
Propanolol	Calcium chloride and Calcium gluconate
BlackwWidow spider (*Latrodectus mactans) envenomation*	
Calcium channel blockers	
Fluoride salts (e.g., NaF)	
Hydrofluoric acid (HF)	
Hyperkalemia (not digoxin-induced)	
Hypermagnesemia	
Centruroides scorpion envenomation (grade IV)	Centruroides scorpion antisera
Eastern coral snake	Antivenin—micruros fulvius
Texas coral snake	
Iron	Deferoxamine mesylate
Aluminum accumulation renal failure	
Cardian glycoside–containing plants (e.g., foxglove and oleander)	Digoxin immune fab
Digitoxin	
Digoxin	
Arsenic	Dimercaprol
Copper	
Gold	
Lead	
Mercury	
Benzodiazepines	Flumazenil
Zolpidem	
Methanol	Folic acid
Methotrexate, trimetrexate	Folinic acid (leucovorin)
Pyrimethamine	
Trimethoprim	
2-Butoxyethanol	Fomepizole
2-Chloroethanol	
Diethylene glycol	
Ethylene glycol	
Methanol	
Propylene glycol	
β-Blockers	Glucagon
Calcium channel blockers	
Hypoglycemia	
Hypoglycemic agents	
Carbon monoxide	Hyperbaric oxygen (HBO)
Carbon tetrachloride	
Cyanide	
Hydrogen sulfide	
Brown recluse spider (*Loxosceles recluse or lampona cylindrata) envenomation*	
Ergotamine-induced peripheral ischemia	
Methemoglobin-inducing agents	Methylene blue
Opioids	Naloxone
Tramadol	
Arsenic	D-Pencillamine
Copper	
Gold	
Mercury	
Anticholinergic alkaloid–containing plants and drugs	Physostigmine salicylate
Indanedione derivatives	Phytonadione
Long-acting anticoagulant rodenticide	
Warfarin	
Antimyasthenic agents (e.g., pyridostigmine)	Pralidoxime chloride (2-PAM) and atropine
Nerve agents (e.g., sarin, soman, tabun and VX)	
Organophosphate insecticides	
Tacrine	
Enoxaparin	Protamine sulfate
Heparin	
Acrylamide	Pyridoxine hydrochloride (vitamin B_6)
Cycloserine	
Ethylene glycol	
Hydrazine	
Isoniazid (INH)	
Monomethylhydrazine-containing mushrooms (e.g., Gyromitra)	
Chlorine gas	Sodium bicarbonate
Serum alkalinization for phenobarbitol salicylate	
Agents producing a quinidine like effect as demonstrated by widened QRS complex on EKG	
Arsenic	Succimer
Lead	
Mercury	

Adapted from Mokhlesi B, Leikin JB, Murray P, Corbridge TC. Adult toxicology in critical care: Part 1: General approach to the intoxicated patient. *Chest*. 2003;123:577–592.

ENHANCEMENT OF ELIMINATION

Forced Diuresis and Urinary pH Manipulation

Routine use of volume loading to promote diuresis has not been supported in the literature and is not recommended. Manipulation of urinary pH can be used therapeutically to enhance elimination of some intoxicants (Table 296.5). The limits of urinary pH are 4.5 to

7.5 under conditions of enhanced acidification and alkalinization. Thus, elimination of very strong (negative logarithm of the acid ionization equilibrium constant [p*K*a] <3) or very weak (p*K*a >8) acids is unaltered by urinary pH manipulation. Other acidic or basic drugs do not undergo renal tubular absorption, irrespective of urinary pH, since they are polar in their nonionized form. Urinary alkalinization (pH >7.5) is most often used to eliminate salicylates and phenobarbital (20). It can be achieved by administration of IV sodium bicarbonate (1 to 2 mEq/kg every 3 to 4 hours); this may be administered as two 50-mL ampules of 8.4% sodium bicarbonate (each containing 50 mEq of $NaHCO_3$) per liter of 5% dextrose in water infused at 250 mL/hr. Complications of this therapy include alkalemia (particularly in the presence of concurrent respiratory alkalosis), volume overload, hypernatremia, and hypokalemia. It is particularly important to avoid hypokalemia, which prevents excretion of alkaline urine by promoting distal tubular potassium reabsorption in exchange for hydrogen ion. Accordingly, bicarbonate administration in the presence of significant hypokalemia will not alkalinize the urine, yet will increase the risk of alkalemia. Since urinary alkalinization therapy can cause hypokalemia (due to alkalemia-induced intracellular potassium shift and increased urinary potassium loss with alkaline diuresis), addition of potassium chloride to the bicarbonate infusion is frequently required. Acetazolamide should not be used to alkalinize urine. Resultant metabolic acidosis can increase toxicity of certain poisonings (particularly with salicylate poisoning).

TABLE 296.5
Toxins Eliminated by Urinary Alkalinization

2,4 Dichlorophenoxy acetic acid
Chlorpropramide
Fluoride
Mephobarbital
Methotrexate
2-methyl-4-chlorophenoxyacetic acid (MCPA)
Phenobarbital
Primidone
Quinolone antibiotics
Salicylic acid
Uranium

Adapted from Mokhlesi B, Leikin JB, Murray P, Corbridge TC. Adult toxicology in critical care: Part 1: General approach to the intoxicated patient. *Chest*. 2003;123:577–592.

Multiple-Dose Activated Charcoal

Multiple-dose activated charcoal (MDAC) can be an effective way to enhance the elimination of toxins that have been absorbed (21). The mechanism by which this modality accomplishes enhancement of elimination is either by interrupting the enterohepatic/enterogastric circulation of drugs or through the binding of any drug that diffuses from the circulation into the gut lumen (called *GI dialysis*). However, it has limited application because the toxin must have a low volume of distribution, low protein binding, prolonged elimination half-life, and low p*K*a, which maximizes transport across mucosal membranes into the GI tract. Although optimal dosage and frequency of administration following the initial dose of activated charcoal is not well established, most experts recommend a dose of approximately 0.5 g/kg every 2 to 4 hours for at least three doses. Cathartics are generally not administered to avoid hypernatremia, hypokalemia, and hypermagnesemia. MDAC should be used with caution in patients with decreased bowel sounds, abdominal distension, and persistent emesis. Unless a patient has an intact or protected airway, the administration of multidose charcoal is contraindicated. A review of the literature reported that although MDAC enhances drug elimination significantly, it has not yet been evaluated in a controlled trial of poisoned patients with the objective of demonstrating a reduction in morbidity and mortality. Table 296.6

provides a list of drugs and toxins where there may be a role for MDAC. However, based on experimental and clinical studies, it should be considered in patients with a life-threatening ingestion of carbamazepine, dapsone, phenobarbital, quinine, or theophylline.

TABLE 296.6
Toxins and Drugs Eliminated by Multiple Dosing of Activated Charcoal[a]

Amitriptyline	Meprobamate
Amoxapine	Methyprylon
Baclofen (?)	Nadolol
Benzodiazepines (?)	Nortriptyline
Bupropion (?)	Phencyclidine
Carbamazepine	Phenobarbital
Chlordecone	Phenylbutazone
Dapsone	Phenytoin (?)
Diazepam	Piroxicam
Digitoxin	Propoxyphene
Digoxin	Quinine
Disopyramide	Salicylates (?)
Glutethimide	Sotalol
Maprotiline	Theophylline

[a]? Represents equivocal data.
Adapted from *Poisoning and Toxicology Handbook*. 4th ed. CRC Press; 2008:1234.

Extracorporeal Removal of Toxins

Although clear proof that extracorporeal toxin removal favorably alters the course of any intoxication is generally lacking, it should be considered when the intoxication is projected to undergo delayed or insufficient clearance because of either organ dysfunction, the intoxicating agent produces toxic metabolites, or delayed toxicity is characteristic of the intoxication. Three methods for extracorporeal removal of toxins are possible: (1) dialysis (usually hemodialysis rather than peritoneal dialysis), (2) hemoperfusion, and (3) hemofiltration (22,23). Plasmapheresis is rarely used although effective in reducing plasma levels of several drugs with high plasma protein binding (>80%) and a low volume of distribution (<0.2

L/kg) (Table 296.7) (24,25). Exchange transfusion has been used for neonatal/infant exposures (Table 296.8); therapeutic plasma exchange (TPE) with fresh frozen plasma has been used to remove toxins that are protein bound and not removed by dialysis (i.e., organophosphate insecticides, mushrooms) (26,27).

TABLE 296.7
Toxicants in which Plasmapheresis Has been Shown to Enhance Elimination

Amanita phalloides (mushrooms)
Amphotericin B
Amytriptylline
Caffeine
Carbamazepine
Diltiazem
L-Thyroxine
Maprotyline
Mercury
Paraquat (decreased level by 80%)
Pentachlorophenol
Phenytoin
Propranolol
Theophylline
Tobramycin
Vanadate
Verapamil

Adapted from *Poisoning and Toxicology Handbook*. 4th ed. CRC Press; 2008:1234.

TABLE 296.8
Toxicants for which Exchange Transfusions May be Helpful

Parathion
Acetaminophen
Iron (serum levels >1,000 µg/dL)
Caffeine
Methyl salicylate
Propafenone
Ganciclovir/acyclovir
Methemoglobin producers[a]
Lead (with chelation therapy)
Pentachlorophenol
Phenazopyridine hydrochloride
Pine oil
Theophylline (serum levels >90 µg/mL)
E. Coli 0157: H7 associated with hemolytic–uremic syndrome

[a]Especially patients with G6PD or NADPH-dependent Methemoglobin reductase deficiency and/or to methylene blue therapy with methemoglobin levels >70%.
Adapted from *Poisoning and Toxicology Handbook*. 4th ed. CRC Press; 2008:1231–1232.

Hemodialysis

Hemodialysis is the primary extracorporeal method to remove toxins or drugs. Ideal toxins for hemodialysis have a low molecular weight (<500 d), water soluble, low protein binding (<70% to 80%), and a small volume of distribution (<1 L/kg). It is also effective in correcting concomitant electrolyte abnormality and metabolic acidosis. Toxins in which hemodialysis may be required in an early stage of intoxication include methanol, ethylene glycol, boric acid, salicylates, and lithium. Others are listed in Table 296.9. Hemodialysis can also be used for heavy metal chelation in patients with renal failure.

TABLE 296.9
Some Toxins and Drugs Removed by Hemodialysis

Bromide
Ethylene glycol
Isopropanol
Metformin
Methanol
Lithium
Phenobarbital
Salicylate
Valproic acid

Adapted from *Poisoning and Toxicology Handbook*. 4th ed. CRC Press; 2008:1231–1232.

Hemoperfusion

Hemoperfusion is essentially the parenteral analog of oral activated charcoal. Most drugs are extractable by hemoperfusion, which is particularly suitable for extracorporeal removal of toxins that are of high molecular weight, highly protein bound, or lipid soluble. It has been effectively used to enhance elimination of theophylline, phenobarbital, phenytoin, carbamazepine, paraquat, and glutethimide. Due to the lack of availability of charcoal cartridges, this modality is rarely available.

Hemofiltration

Hemofiltration achieves drug and toxin removal by convection. It transports solutes through a highly porous membrane that is permeable to substances with weights of up to 6,000 d, including virtually all drugs. In some cases, hemofiltration membranes are permeable to substances weighing up to 20,000 d. Although the application of this technique has not been vigorously studied in poisoned patients, there are increasing numbers of case reports of extracorporeal intoxicant removal by continuous arteriovenous or venovenous hemofiltration methods. Hemofiltration is potentially useful for removal of substances with a large volume of distribution, slow intercompartmental transfer, or extensive tissue binding. Specific highly porous hemofiltration cartridges are useful for removal of large–molecular-weight solutes or complexes, such as

combined digoxin–Fab fragment complexes, or desferoxamine complexes with iron or with aluminum.

Lipid Rescue Resuscitation

Lipid emulsion infusion was first demonstrated in 1998 to improve resuscitation due to cardiovascular collapse from bupivacaine overdose (28). Since then, successful treatment of cardiovascular toxicity from a wide range of lipophilic drugs (such as calcium channel blocking agents, β-adrenergic blockers, tricyclic/SSRI antidepressants, and other local anesthetics) has been achieved by lipid or intralipid rescue. The therapeutic mechanisms of lipid emulsion infusion has been postulated to be (28): (1) lipid emulsion capture of drug ("lipid sink"), (2) mitochondrial uptake of fatty acid (metabolic effect), (3) Interference of cellular membrane sodium channel, (4) cytoprotection by inhibition of glycogen synthase kinase, and (5) calcium entry promotion through voltage-dependent calcium channels resulting in a cardiac inotropic effect.

The suggested dosage of a 20% lipid emulsion is a 1.5 mL/kg bolus over 2 to 3 minutes followed by an infusion of 20% lipid emulsion at a rate of 0.25 mL/kg/min (29,30). For asystolic patients, or those who do not respond to the bolus, the dose may be increased if hemodynamic instability remains. Whenever possible, lipid emulsion therapy should be terminated within 1 hour. Hyperamylasemia and hypertrilyceridemia have been reported following lipid emulsion therapy; however, this therapy has otherwise been shown to be relatively free of complications (27,30). Thus, the therapeutic profile of this intervention is quite promising and its use will likely increase to emergently reverse the cardiovascular effects of drug toxicity (30).

DISPOSITION

Indications for ICU Admission

In the current healthcare climate, the practice of routinely admitting the poisoned patient to the ICU is being questioned. Brett et al. (31) identified eight clinical risk factors that can predict ICU interventions: (1) $PaCO_2$ >45 mm Hg, (2) need for endotracheal

intubation, (3) toxin-induced seizures, (4) cardiac arrhythmias, (5) QRS duration ≤0.12 seconds, (6) systolic BP <80 mm Hg, (7) second- or third-degree atrioventricular block, and (8) unresponsiveness to verbal stimuli . In this retrospective study, if a poisoned patient did not exhibit any of the eight characteristics, no ICU interventions (intubation, vasopressors or antiarrhythmics, and dialysis or hemoperfusion) were required (31). Other indications for ICU admission include a Glasgow Coma Scale score <12, need for emergency dialysis or hemoperfusion, progressive metabolic acidosis, and a cyclic antidepressant or phenothiazine overdose with signs of anticholinergic cardiac toxicity (32). An important critical care intervention is extracorporeal membrane oxygenation (ECMO). Even though it has been used since 1972, recent advances in ECMO technology have rendered it more biocompatible. Thus it is increasingly being used as a salvage therapy for acute respiratory distress syndrome and circulatory shock, for up to 3 days, in certain exposures such as calcium channel antagonists, β-adrenergic blockers, tricyclic antidepressants, chloroquine, colchicine and hydrocarbons/inhalation toxic exposure (33). Severe hyperkalemia, wide alterations in body temperature, and the need for continuous infusion of naloxone are also reasons to admit a patient to an ICU. Hypotension on admission is the most significant predictor of fatality (34,35). In addition, staffing issues such as the availability of a "sitter" in cases of attempted suicide may impact patient disposition. Table 296.10 provides a list of criteria for ICU admission.

TABLE 296.10
Criteria for Admission of the Poisoned Patient to the ICU

Respiratory depression ($Paco_2$ >45 mm Hg)
Emergency intubation
Seizures
Cardiac arrhythmia (second- or third-degree atrioventricular block)
Systolic Blood Pressure <80 mm Hg in adults
Unresponsiveness to verbal stimuli
Glasgow Coma Scale score <12
Need for emergency dialysis, hemoperfusion, or ECMO
Increasing metabolic acidosis
Pulmonary edema induced by toxins (including inhalation) or drugs
Hypothermia or hyperthermia including neuroleptic malignant syndrome
Tricyclic or phenothiazine overdose manifesting anticholinergic signs, neurologic abnormalities, QRS duration >0.12 s, or QT >0.5 s
Body packers and stuffers
Concretions caused by drugs
Emergency surgical intervention
Administration of pralidoxime in organophosphate toxicity
Antivenom administration in Crotalidae, coral snake, scorpion, or arthropod envenomation
Need for continuous infusion of naloxone
Hypokalemia secondary to digitalis overdose (or need for digoxin-immune antibody Fab fragments)
Administration of Lipid Rescue Therapy
Cerebral edema
Monoamine oxidase inhibitor toxicity
Significant aspiration pneumonitis in the elderly
Delirum tremens

ECMO, extracorporeal membrane oxygenation.

In addition, the physician should be aware of certain ingestions, that in a single-dose form, can be potentially catastrophic to a toddler (Table 296.11) (36,37).

TABLE 296.11
Toxins/Medications that Could Cause Fatality in a Toddler (Under 20 kg Weight) if Ingested in a Single Dose Form

A. Tablets/Capsules
Amantadine
Amoxapine
Amphetamines
Benzonatate
β-Adrenergic blockers
Buspirone
Calcium channel blockers
Chloroquine (>20 mg/kg)
Chlorpramazine (>25 mg/kg)
Clonidine
Clozapine
Codeine (>1 mg/kg)
Colchicine
Cyclobenzaprine
Diflunisal
Diltiazem
Disopyramide (>15 mg/kg)
Ecstacy (3,4-methylenedioxy-methamphetamine)
Flecainide (>25 mg/kg)
Haloperidol
Hydrocodone (>2.5 mg)
Hydroxychloroquine (>20 mg/kg)
Hypoglycemic agents (sulfonylureas)
Imipramine
Isradipine (>2.5 mg)
Lithium
Lomotil
Loxapine (>30 mg/kg)
Mefanamic acid
Meprobamate
Methadone (>1 mg/kg)
Mollindone
Monoamine oxidase inhibitors
Nifedipine (>15 mg/kg)
Olanzapine (>10 mg/kg)
Phenothiazines
Prazosin
Procainamide
Quinidine
Quinine (>80 mg/kg)
Terazosin
Theophylline (>8 mg/kg)
Thioridazine (15 mg/kg)
Trazadone
Verapamil

B. Ointments/Cream
Camphor (>100 mg/kg)
Doxepin
Methyl salicylate (oil of wintergreen)
Theophylline

C. Patches
Clonidine
Fentanyl
Nicotine
Nitroglycerin

D. Opthalmic
Atropine
Imidazoline
Scopalomine
Acetonitrile
Ammonia (>10% concentration)
Ammonium fluoride
Arsenic (inorganic)
Benzocaine
Boric acid
Butyrolactone
Diethylene glycol
Ethylene glycol (>1 mL/kg)
Formaldehyde
Hydrofluoric acid
Mercury (inorganic)
Methyl alcohol
Methylene chloride
Nicotine sulfate
Nitroethane
Pennyroyal oil
Selenious acid
Strychnine
Thallium
Toluene
Zinc chloride

E. Miscellaneous
Boric acid
Bromates (over 2% concentration)

Common Pitfalls

- Failure to consider decontamination procedures upon presentation.
- Failure to consider delayed onset of the effects of certain toxins.
- Failure to institute extracorporeal removal techniques in a timely manner.
- Failure to consider seriously certain medications, which in a single-dose form, can be lethal to a toddler.

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PART 2 • ALCOHOL-RELATED AGENTS

CHAPTER 297

Ethanol

Michael A. Darracq and Binh T. Ly

Ethanol, or ethyl alcohol, is a two-carbon chain alcohol with the chemical formula CH_3CH_2OH. Ethanol is often commonly referred to as simply "alcohol." However, other alcohols such as ethylene glycol (Chapter 299), methanol (Chapter 300), and isopropyl alcohol (isopropanol) (Chapter 301) also have significant and individual toxicities. Ethanol is unique among potential drugs of abuse in that it is legally and culturally accepted in most societies of the world and is therefore ubiquitous.

A standard "drink" contains about 14.4 g of ethanol. This is the amount of ethanol found in 1.5 oz of 80-proof liquor (40% alcohol by volume), 5 oz of wine (12% alcohol), or 12 oz of beer (5% alcohol). Ethanol is also found in many other commercially available products, including mouthwash, aftershave, cooking ingredients (e.g., vanilla extract), pharmaceutical agents (e.g., elixirs and tinctures), and gel- or foam based hand-sanitizers.

The American Psychiatric Association (APA) *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* defines alcohol use disorders according to the following 11 criteria: (1) Taking the substance (ethanol) in larger amounts or for longer than was intended; (2) wanting to cut down or stop but not managing to; (3) spending a lot of time getting, using, or recovering from use; (4) cravings and urges to use the substance; (5) not managing to do what one should at work, home or school, because of use; (6) continuing to use, even when it causes problems in relationships; (7) giving up important social, occupational or recreational activities

because of use; (8) using ethanol again and again, even when it puts the user in danger; (9) continuing to use, even when the user knows they have a physical or psychological problem that could have been caused or made worse by use; (10) needing more of the substance to get the effect wanted (tolerance); (11) development of withdrawal symptoms, which can be relieved by taking more of the substance (1). The DSM V allows classification of the severity of the disorder on the basis of how many symptoms are identified. Two or three symptoms indicate mild use disorder, four to five symptoms indicate moderate, and six or more symptoms indicate a severe disorder.

Ethanol is rapidly absorbed from the gastrointestinal (GI) tract with up to 90% of an ingested dose absorbed within 1 hour. Twenty percent of ingested ethanol is absorbed in the stomach, with the remainder absorbed by the small intestine (2). Enhanced absorption occurs in the presence of rapid gastric emptying, absence of other gastric contents, carbonation and ethanol concentration in solution with a 20% ethanol solution most readily absorbed. Delays in absorption may occur with higher concentrations of ethanol due to pylorospasm, presence of food in stomach, congestion of other drugs and other individual variability (2).

Ethanol is principally eliminated by the liver. Only a small portion of absorbed ethanol is excreted unchanged in the urine. Alcohol dehydrogenase (ADH) is the primary enzyme for alcohol metabolism (3) which begins prior to systemic absorption. When ethanol contacts the gastric mucosa, a subtype of ADH located in the stomach begins oxidation of ethanol to acetaldehyde. Once absorbed, ethanol is oxidized to acetaldehyde by an additional class of ADH located in the liver. Acetaldehyde is subsequently metabolized by aldehyde dehydrogenase (ALDH) to acetate. Acetate is eliminated as carbon dioxide and water. Genetic polymorphisms in ADH and ALDH determine the extent to which acetaldehyde accumulates after alcohol consumption and affect individual susceptibilities to the toxic effects of ethanol and tendencies toward alcohol dependence and abuse (3). ADH is saturated at relatively low blood-ethanol concentrations ($<$10 mg/dL) (4). Saturation results in elimination converting from first-order to zero-order

kinetics and a longer half-life. The 70-kg adult male metabolizes 7 to 10 g of alcohol per hour, corresponding to an hourly decrease of the blood-ethanol level of approximately 15 to 20 mg/dL/hr (5).

The enzyme catalase and cytochrome P450 enzymes also oxidize ethanol to acetaldehyde. Under normal physiologic conditions, catalase contributes only a minor role to ethanol metabolism. Cytochrome P450 (CYP) 2E1 accounts for the majority of non-ADH metabolism of ethanol in the liver. CYP1A2 and 3A4 also contribute to ethanol metabolism to a lesser extent. While ADH is responsible for the majority of ethanol metabolism, CYP2E1 is inducible and its enzymatic activity increases in the presence of higher ethanol concentrations and after extended ethanol intake (3).

In the oxidation of ethanol to acetaldehyde (ADH) and acetaldehyde to acetate (ALDH), nicotinamide adenine dinucleotide (NAD^+) is used as a hydrogen acceptor. The accumulation of NADH impairs the cell's ability to perform oxidative reactions and can lead to numerous metabolic abnormalities, including impairments of gluconeogenesis (Fig. 297.1). Although this has minimal consequence in normal adults, it may lead to significant hypoglycemia in children and malnourished alcoholics who have limited glycogen stores, particularly. The conversion of NADH back to NAD^+ requires oxygen. When large amounts of ethanol are metabolized, oxygen requirements in the centrilobular areas of the liver exceed its delivery, resulting in a relative hypoxia in these areas, which is believed to contribute to hepatic damage.

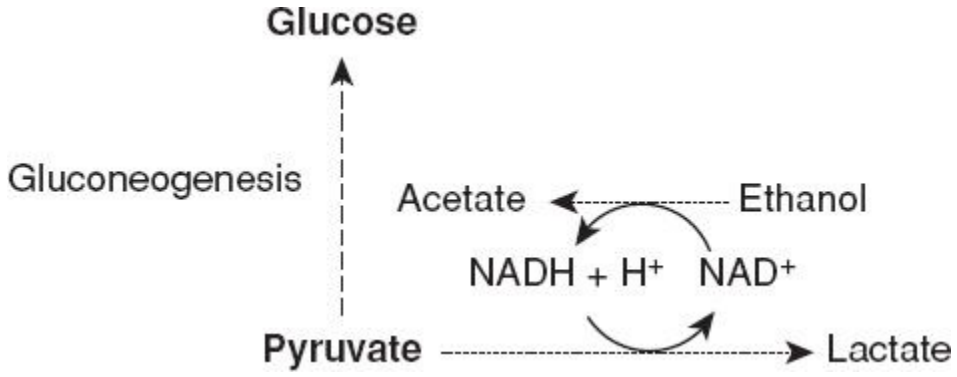

FIGURE 297.1 Mechanism of ethanol-induced hypoglycemia. During the course of ethanol metabolism, the formation of NADH

favors the conversion of pyruvate to lactate rather than to glucose.

Increased oxygen demand also shifts the oxidation–reduction potential of the cell. The result of this shift is an increased ratio of lactate to pyruvate, which favors glycolysis and depletes available glycogen stores. The increase in free hydrogen ions (H^+) tends to favor ketone formation and fatty acid generation. Excess H^+ depresses the citric acid cycle and decreases the use of free fatty acids as an energy source. Ethanol-induced metabolic derangements, especially with poor nutritional status, increase the risk of developing ketoacidosis and hypoglycemia. Renal magnesium wasting, secondary to ethanol's inhibitory effect on magnesium resorption, combined with intestinal malabsorption of magnesium, contribute to development of hypomagnesemia in chronic alcoholics. Pyruvate, which is normally converted to acetyl coenzyme A using thiamine as a cofactor, is converted instead to lactate (Fig. 297.1). Thiamine is a water-soluble nutrient with a limited 10-day supply in the body. Thiamine deficiency, usually because of poor nutrition, may lead to life-threatening lactic acidosis.

The exact mechanisms of ethanol inebriation are still unclear, but current theories suggest that ethanol acts upon a variety of neurotransmitters. Specific receptors for ethanol have not been identified but ethanol enhances the inhibitory effects of γ-amino butyric acid (GABA) at subtype A ($GABA_A$) receptors while blocking the N-methyl-D-aspartate (NMDA) subtypes of excitatory glutamate receptors (6). Ethanol may appear to be stimulating when it selectively depresses inhibitory mechanisms in the brain.

If ethanol is coingested with other sedative-hypnotic agents, it increases the sedative effects of these agents and increase CNS and respiratory depression. These include benzodiazepines, phenothiazines, barbiturates, γ-hydroxybutyrate (GHB), chloral hydrate, cyclic antidepressants, antihistamines, and opioids, among others.

Ethanol is one of the most common substances involved in drug-facilitated sexual assault (DFSA). This most commonly occurs as a result of voluntary ethanol consumption by the victim. Additional substances may or may not be added to the victim's drink leading to further psychomotor depression and amnesia (see Chapter 309).

CLINICAL PRESENTATION

Clinical manifestations following acute ethanol consumption are variable and caution must be employed when trying to attribute ethanol-related signs or symptoms to any specific serum ethanol concentration. The effects of ethanol are dependent on the degree to which the drinker has been habituated. Without knowing the pattern of individual ethanol use, it is difficult to associate a particular ethanol concentration with specific clinical symptoms.

At lower dosages, ethanol's depression of inhibitory pathways in the brain may lead to CNS stimulation through disinhibition. These effects are most pronounced in mildly to moderately intoxicated individuals who engage in functions requiring higher degrees of cortical integration. Individuals may exhibit euphoria, gregariousness, verbosity, or emotional lability. Frequently, disinhibited behavior reflects the individual's basic personality and results in more boisterous or aggressive behavior. Other clinical manifestations may include ataxia, nystagmus, and impairments in reaction time. With deeper levels of intoxication, disinhibition and impairment of cognitive integration may be progressive. Overt displays of hostility and aggressiveness emerge. With severe ethanol intoxication, profound CNS depression, coma, and respiratory depression occur with an increased risk of morbidity as concomitant loss of airway-protective reflexes may ensue.

An acutely ethanol-intoxicated patient may present with classic features that include flushed skin, diaphoresis, tachycardia, hypothermia, hypoventilation, vomiting, dysarthria, and incoordination. Diplopia, visual disturbances, and nystagmus may be evident which may occur from the direct toxic effects of ethanol or may represent Wernicke encephalopathy. Acute heavy ethanol

consumption may be associated with myocardial ischemia in patients with underlying but otherwise stable cardiac disease (4).

The association between ethanol use and cardiac dysrhythmias in otherwise healthy individuals has been referred to as “holiday heart syndrome.” This syndrome was first described in individuals with heavy but sporadic ethanol ingestion such as on holidays and weekends. The most common dysrhythmia is atrial fibrillation, which typically resolves within 24 hours. Although dysrhythmias may occur, they are usually benign and rate control may be the only acute intervention necessary. Long-term antidysrhythmics are not generally necessary.

Hypoglycemia may develop because gluconeogenesis is impaired by rising levels of NADH produced during ethanol metabolism, particularly in the malnourished adult or the young child. Ethanol-induced hypoglycemia may lead to altered sensorium and seizures.

Clinical findings and systemic effects suggestive of chronic alcohol abuse are listed in Table 297.1. Memory difficulties and other cognitive impairments may occur in alcoholics who are otherwise able to function socially or occupationally. GI dysfunction (including abdominal pain, diarrhea, vomiting, hematemesis) because of direct gastric irritation by ethanol or secondary processes such as pancreatitis or hepatitis may occur. Respiratory complaints, frequent infections, weakness, polysubstance use, withdrawal, or recurrent trauma may also occur.

TABLE 297.1
Clinical Manifestations of Alcohol Abuse

Nervous System
Inebriation
Seizures
Dementia
Coma
Wernicke–Korsakoff psychosis
Polyneuropathy
Amnesia
Hallucinosis
Withdrawal

Cardiovascular System
Autonomic dysfunction
Congestive cardiomyopathy
Holiday heart (dysrhythmias)
"Wet" Beriberi (thiamine deficiency)

Gastrointestinal System
Alcoholic hepatitis
Steatosis
Alcoholic cirrhosis
Esophagitis
Gastritis
Peptic-ulcer disease
Gastrointestinal bleeding
Chronic diarrhea
Pancreatitis (acute or chronic)
Pancreatic pseudocyst
Varices and hemorrhoids
Ascites
Malabsorption and malnutrition
Cancers of the gastrointestinal tract (mouth, pharynx, esophagus, larynx)
Boerhaave syndrome
Mallory Weiss tear

Genitourinary System
Uric-acid nephropathy
Acute tubular necrosis
Hepatorenal syndrome
Hypogonadism
Impotence
Infertility

Hematologic
Myelosuppression
Coagulopathies
Microcytic anemia
Megaloblastic anemia
Thrombocytopenia
Leukopenia

Infectious
Pneumonia
Spontaneous bacterial peritonitis

Metabolic
Ketoacidosis
Electrolyte abnormalities
Vitamin deficiencies
Hypothermia
Hypoglycemia
Malnutrition
Hypertriglyceridemia

Musculoskeletal
Myopathies
Gout
Rhabdomyolysis

Pulmonary
Sleep apnea
Chronic respiratory insufficiency
Tuberculosis

Psychiatric
Anxiety
Insomnia
Irrational behaviors
Borderline personality
Polysubstance abuse

Adolescents may present to the ED with a myriad of nonspecific complaints, none of which may directly point to alcohol abuse as a possible underlying etiology. Obtaining a history from family members can be invaluable. The adolescent may have recently undergone significant changes in personality, behavior, peer contacts, or peer relations. College-aged alcoholics, who may use the ED as their only source of healthcare, can present with vague flu-like symptoms, headache, insomnia, chest palpitations, trauma, GI disturbances, or psychiatric complaints. Young, otherwise healthy males presenting with chest palpitations, showing paroxysmal atrial fibrillation, atrial tachycardia, or frequent atrial extrasystoles, should be questioned about their ethanol use. Geriatric alcoholics may be brought to the department by their families with altered mental status, daytime sleepiness, and irrational behavior.

Occasionally, chronic alcoholics are treated with disulfiram (Antabuse) to encourage abstinence. Disulfram blocks ALDH and allow accumulation of acetaldehyde so that small amounts of ethanol may induce an adverse reaction. Signs and symptoms of the disulfiram-ethanol reaction (DER) include flushing of the face and body, tachycardia, sensations of warmth, urticaria, pruritus, light-headedness, headache, nausea, and vomiting. Complaints of palpitations, chest pain, and shortness of breath are common. In addition, disulfiram may cause inhibition of dopamine-β-hydroxylase, blocking the conversion of dopamine to norepinephrine, which may lead to hypotension and hypoperfusion. Myocardial ischemia is usually only associated with severe hypotension. In general, deaths attributable to DERs are extremely rare. Manifestations of DER usually begin within 30 minutes of ethanol exposure and may last for several hours. A number of other compounds may induce a disulfiram-like reaction in the presence of ethanol (Table 297.2). The source of ethanol exposure may be elusive because ethanol-containing products in the home are ubiquitous. A high percentage of Asians have a genetic lack of ALDH and have an identical reaction to taking disulfram with ethanol exposure. Similar findings may result from exposure unrelated to

ethanol, such as niacin, monosodium glutamate, rifampin, vancomycin, boric acid, and scombroid poisoning.

TABLE 297.2
Causes of Disulfiram-Like Reactions Following Ethanol Exposure

Mushrooms	*Coprinus* sp. mushrooms
Chemicals	Carbon disulfide
	Carbon tetrachloride
	Tetramethylthiuram (thiram)
	Trichloroethylene
Medications	Antimicrobials
	Cephalosporins
	Cefamandole
	Cefmenoxime
	Cefoperazone
	Cefotetan
	Trimethoprim-sulfamethoxazole
	Chloramphenicol
	Griseofulvin
	Nitrofurantoin
	Sulfonylureas
	Chlorpropamide
	Tolbutamide
	Chloral hydrate
Genetic	Aldehyde dehydrogenase (ALDH) deficiency

DIFFERENTIAL DIAGNOSIS

Acute altered mental status in the setting of ethanol intoxication must be carefully evaluated for other causes of altered sensorium unrelated to ethanol intoxication. In the appropriate clinical setting, head injuries, CNS infections, and encephalopathy merit consideration as sources of alteration in mental status or cognitive impairment. The differential diagnosis can include hypoglycemia, sepsis, drug or other toxin exposures, carbon monoxide poisoning, Wernicke–Korsakoff syndrome, tumors, blunt traumatic injury,

meningitis, epidural or subdural hematoma, subarachnoid hemorrhage, and dementia, among others. Ethanol abuse typically increases the risk for trauma, illness and these may occur concomitant to ethanol intoxication or as a result of ethanol intoxication. Coingestion of other sedating drugs also may contribute to more pronounced CNS depression (see Chapters 307–310). There is always the danger that a chronic ethanol abuser may substitute ethanol with other potentially lethal intoxicants particularly when deprived of access to ethanol. These other toxic alcohols (see Chapters 299 and 300) may create similar signs and symptoms of inebriation, however a failure to recognize the separate and unique toxicities of these agents may result in renal, visual, and other negative consequences for the patient.

EMERGENCY DEPARTMENT EVALUATION

Obtaining an accurate and thorough history may be impossible when a patient is acutely intoxicated. A thorough medical and surgical history should be sought when possible. In the lucid and cooperative patient, information such as the type, amount, and time of last ethanol use should be obtained. Additional information from friends, family members, or witnesses may be helpful in assessing the risk for trauma, other organ system involvement, presence of medical or psychiatric comorbidities, and potential coingestants.

The initial evaluation of the acutely intoxicated patient or chronic alcohol abuser is identical to the evaluation of any other potentially ill patient. Patients with altered mental status require bedside fingerstick blood glucose determination. A complete set of vital signs, including core temperature and oxygen saturation should be obtained and continuously monitored or frequently reassessed especially if respiratory depression is possible. The patient should be disrobed and carefully examined for signs of trauma or other medical illnesses. During initial evaluation, signs of head trauma, pupil size, appropriate response to voice, hemotympanum, and tenderness to any palpation should be noted. Signs of trauma or coexistent pathology may become more apparent as the patient

becomes less intoxicated. Patients with abnormal vital signs, cardiorespiratory complaints, chest or abdominal pain, or nonspecific constitutional symptoms should have continuous electrocardiographic monitoring and consideration of a 12-lead electrocardiogram (ECG) to evaluate for ischemia and dysrhythmias, particularly atrial fibrillation. Particularly in patients who are unable to offer a medical history, clinicians must be vigilant when performing a physical examination and consider other diagnostic adjuncts such as computed tomography (CT) of the head or abdomen and laboratory testing in unstable patients. Finally, if the clinical examination fails to improve as expected, clinicians should assess for the presence of associated pathology.

Determination of ethanol concentrations in the setting of otherwise uncomplicated acute ethanol intoxication remains controversial. Clinical sobriety may occur in ethanol tolerant individuals at blood-alcohol concentrations that are elevated. In addition, alcohol withdrawal may occur in some tolerant individuals at these elevated blood-ethanol concentrations. Some clinicians do not find ethanol blood or breath concentrations to be helpful in determining patient disposition and avoid levels that may be misinterpreted in potential medical-legal proceedings. Because ethanol intoxication can mimic as well as mask disease and injury, other clinicians argue that obtaining a blood- or breath-ethanol level may aid in estimating the contribution of alcohol in all patients with systemic complaints. Breath-alcohol levels may be helpful in confirming the presence of ethanol; however, accurate sampling is dependent on patient cooperation with obtaining a satisfactory end-expiratory sample. A number of medications contain ethanol and may result in spurious values of the breath-ethanol level. Multidose inhalers, mouthwashes, some gel and foam sanitizers contain significant amounts of ethanol, and sampling of mouth air after vomiting may transiently cause elevations of ethanol concentration. The absence of ethanol or a low ethanol level on breath testing may prompt a search for other conditions that may mimic ethanol intoxication. An accurate blood-ethanol level may help the clinician estimate a reasonable time for observation while the patient

metabolizes the absorbed dose and in the appropriate clinical scenario, additional laboratory or radiographic studies may be avoided. Comatose patients with lower blood-ethanol levels than expected for the level of consciousness may therefore be considered for more extensive diagnostic evaluation that may include CT of the head and lumbar puncture, especially if signs of trauma or infection are present. Because chronic ethanol consumption is associated with both trauma and coagulopathies, the threshold for obtaining head CTs should be low in patients with chronic ethanol use or abuse.

KEY TESTING

- Bedside blood glucose determination with altered sensorium
- Breath- or blood-ethanol concentration
- Electrolytes including calcium and magnesium
- Osmol gap in patients with metabolic acidosis, elevated lactate, low or undetectable ethanol concentration in the setting of profound inebriation or if methanol, ethylene glycol, or isopropanol intoxication is suspected
- Low threshold for brain imaging (CT head) in patients with head trauma and history of chronic alcohol use

Other blood tests may be helpful in the evaluation and treatment of the alcohol intoxicated patient. A rapid point-of-care blood glucose test, complete blood count, electrolytes, blood urea nitrogen (BUN), creatinine, ketones, acetone, lipase, aspartate (AST) and alanine (ALT) aminotransferases, international normalized ratio (INR), ammonia, calcium and magnesium should be considered. The decision to obtain these tests will depend upon specific clinical scenarios and should be guided by patient history and physical examination. An anion gap metabolic acidosis and elevated serum ketones may signify acute alcoholic ketoacidosis (AKA) and warrants measurement of serum osmolality and calculation of the osmol gap. If available, measurement of serum β-hydroxybutyrate concentration may be useful to diagnose AKA (7). The contribution of ethanol to the osmolality can be estimated by dividing the serum

ethanol level in milligrams per deciliter by 4.6. *The formula for calculating Osmol Gap = measured serum osmolality – calculated osmolarity – measured serum ethanol concentration /4.6.* (For further discussion on the osmol gap see Chapters 299 and 300.)

Ethanol-like intoxication in a patient with an osmol gap unexplained by the amount of ethanol present should raise suspicion of acetone, isopropanol, methanol, or ethylene glycol ingestion and should prompt measurement of these agents; however, the absence of an osmol gap cannot exclude the presence of a toxic alcohol, particularly in the case of ethylene glycol.

Chronic alcoholism itself can be difficult to diagnose. Laboratory abnormalities have been linked to chronic alcohol intake, but sensitivities and specificities vary from study to study. γ-Glutamyltransferase, the most sensitive indicator of hepatic injury, rises in patients who have had more than five drinks a day for several weeks. An elevated red blood cell mean corpuscular volume (MCV) may also indirectly hint at protracted ethanol ingestion (Table 297.3).

TABLE 297.3
Laboratory and Radiographic Evaluation

Laboratory	Radiographic
Complete blood count	Chest radiograph
Cell counts for evaluation of marrow function	Pneumonitis
Indices for folate, iron, pyridoxine, B_{12} deficiencies	Aspiration
Serum chemistries	Tuberculosis
Anion gap	Pneumothorax
Hypoglycemia or hyperglycemia	Fractured ribs/trauma
Renal failure	Cardiac size
Electrolyte imbalance (Na, K, Mg, Ca)	Abdominal radiograph
Hypophosphatemia	Pancreatic calcifications
Hyperphosphatemia	Free air
β-hydroxybutyrate	Limb radiograph
Arterial blood gas with carbon monoxide oximetry	Fractures
Hypoxemia	Dislocations
Hypercarbia	Osteomyelitis
Metabolic disturbances	Foreign bodies
Carbon monoxide exposure	Spine radiographs
Anticonvulsant drug levels	Fractures
Urinalysis	Dislocations
Crystalluria	Instability
Myoglobinuria	Computed tomography
Hemoglobinuria	Extra-axial hemorrhage
Liver function tests	Intracerebral hemorrhage
GGT elevation	Intracerebral contusion
AST elevation	Cervical spine injuries
ALT elevation	
Intra-abdominal pathology	

GGT, γ-glutamyltransferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

ED MANAGEMENT

As with all patients with acute mental status changes, rapidly reversible causes such as hypoglycemia, hypoxia, and opioid intoxication should be identified and addressed. Supplemental oxygen should be administered if the patient is hypoxic. Intravenous naloxone, thiamine and dextrose should be administered as indicated. Abnormal vital signs should be noted and stabilized. If trauma is suspected, cervical spinal immobilization and

radiographic imaging may be indicated until the patient is sober and can cooperate with a thorough clinical examination. Agitated or combative patients should be restrained with physical and pharmacologic interventions such as intravenous or intramuscular benzodiazepines or butyrophenones such as haloperidol or droperidol. Caution should be exercised with benzodiazepines as they may act additively with ethanol in the depression of respiratory function. Repeated assessments should be performed to assess for clinical deterioration. Patients who do not demonstrate an appropriate improvement in mental status as they metabolize the absorbed ethanol should be considered for further investigation and therapeutic interventions such as airway management. Intravenous fluids, caffeine, coffee, naloxone, or flumazenil have not been demonstrated to reverse the effects of ethanol or promote more rapid elimination (8).

Treatment of DERs is also supportive. Intravenous crystalloids should be administered. Antiemetics can be given for nausea and vomiting. Antihistamines such as diphenhydramine (H_1 subtype) may help alleviate cutaneous flushing. Benzodiazepines may be helpful in alleviating associated anxiety and dysphoria. Most DERs can be managed in the ED. Patients can be discharged once they become asymptomatic and vital signs normalize, provided there are no cardiac complications or further evaluation of chest complaints is not indicated.

Chronic alcoholics who are malnourished or suspected of Wernicke encephalopathy should receive intravenous thiamine 100 mg, as well as hydration with a balanced electrolyte solution containing dextrose. Significant cost savings is possible with oral repletion, and those who are frequent ED patients do not need to receive vitamins on every visit. Concomitant medical or surgical problems are treated through standard measures, and treatment of ethanol withdrawal (Chapter 298) may be required.

CRITICAL INTERVENTIONS

- Test for and treat hypoglycemia.

- Frequently reevaluate to assure a clinical course consistent with uncomplicated intoxication.
- If level of consciousness is not consistent with the ethanol level, consider alternative explanations including infection, metabolic disturbances, trauma, and cointoxicants.
- Administer thiamine to alcoholic patients with altered mental status, cerebellar ataxia, or cranial neuropathy.
- Advise or arrange for counseling or detoxification in patients with suspected alcohol abuse or dependence.

DISPOSITION

A patient with uncomplicated intoxication can be discharged after a period of observation when the patient is deemed clinically sober enough to walk with a stable gait, make sound decisions, and provide self-care. Because clinical sobriety does not correlate with measured ethanol levels, particularly in tolerant patients, a repeat ethanol level is not necessary before discharge. Serial assessments of cognitive and neurologic function should occur however to avoid premature discharge of a patient who is still clinically intoxicated. When a safe destination with a responsible adult is available, discharge may be considered for a patient who is still clinically intoxicated but otherwise stable and improving with intact protective reflexes. Such patients should not be discharged until after an appropriate medical evaluation has been completed. Prior to discharge, the patient should be offered available social assistance, medical follow-up, and referral to detoxification programs.

Indications for hospitalization include prolonged and inappropriately depressed mental status, metabolic derangements not correctable in a timely manner, persistently abnormal vital signs, associated major trauma, severe withdrawal, mixed overdose, and concomitant medical processes such as GI bleeding, pancreatitis, pneumonia, or severe acute hepatitis. A lower threshold for admission should be applied to those patients who are homeless, lack social support or who have baseline organic brain

syndromes that may be related to chronic ethanol abuse. If the patient is admitted, the potential for ethanol withdrawal (Chapter 298) needs to be anticipated, and therapy with benzodiazepines should be provided in the appropriate clinical setting.

Common Pitfalls

- Failure to consider medical, psychiatric, and traumatic conditions in the ethanol intoxicated patient.
- Failure to obtain a blood- or breath-alcohol concentration when the history is unclear or inconsistent with clinical findings.
- Failure to obtain a complete set of vital signs and to fully undress and examine the alcoholic patient.
- Failure to reevaluate the patient frequently and prior to discharge.
- Failure to refer intoxicated patients for counseling or detoxification.

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CHAPTER 298 Ethanol Withdrawal

Mark Su

Alcohol is the most commonly abused drug in the world. Alcohol abuse is the third leading lifestyle-related cause of death in the United States and the economic cost associated with alcohol use is estimated to be in the hundreds of billions of dollars (1,2). The effects of alcohol and its association with clinical syndromes are well known (see Chapter 297). However, problems associated with acute alcohol abstinence and alcohol withdrawal require particular attention. Most ethanol-dependent patients typically present to the emergency department (ED) for another reason but develop "alcohol withdrawal" during the course of their management. Recognizing the various clinical manifestations of the alcohol withdrawal syndromes and their appropriate treatment is important to avoid significant patient morbidity and mortality.

Alcohol is a sedative–hypnotic that has multiple effects on the central nervous system (CNS). As with other sedative–hypnotic agents, the inhibitory tone increased by alcohol is mediated via gamma-aminobutyric acid (GABA). With chronic alcohol use, the GABA receptors undergo downregulation, leading to the development of tolerance. *Tolerance* is the pharmacologic effect whereby either increasing doses or increasing frequency of alcohol intake is required to achieve the same physiologic effect. Tolerance to alcohol is necessary for withdrawal to occur. *Dependence* is the altered physiologic state resulting from chronic alcohol use and is also a prerequisite for withdrawal. Continued alcohol use is also associated with inhibition of the excitatory glutaminergic pathways and subsequent upregulation of the *N*-methyl-D-aspartate (NMDA)

receptors. When alcohol intake is abruptly stopped, the result is excess excitatory tone and sympathetic stimulation. This is in large part due to decreased inhibition (GABA effects) and increased excitation (glutamate effects), although the exact mechanism has not been fully elucidated. Decreased dopaminergic activity during acute withdrawal may contribute to hallucinations (3).

CLINICAL PRESENTATION

Alcohol withdrawal presents with a wide spectrum of clinical signs and symptoms. For classification purposes, there are four distinct withdrawal syndromes: *(1) Alcoholic tremulousness, (2) alcoholic hallucinosis, (3) alcoholic withdrawal seizures, and (4)delirium tremens* (4). The first three of these clinically distinct entities may occur in isolation, or simultaneously, in any combination (Fig. 298.1).

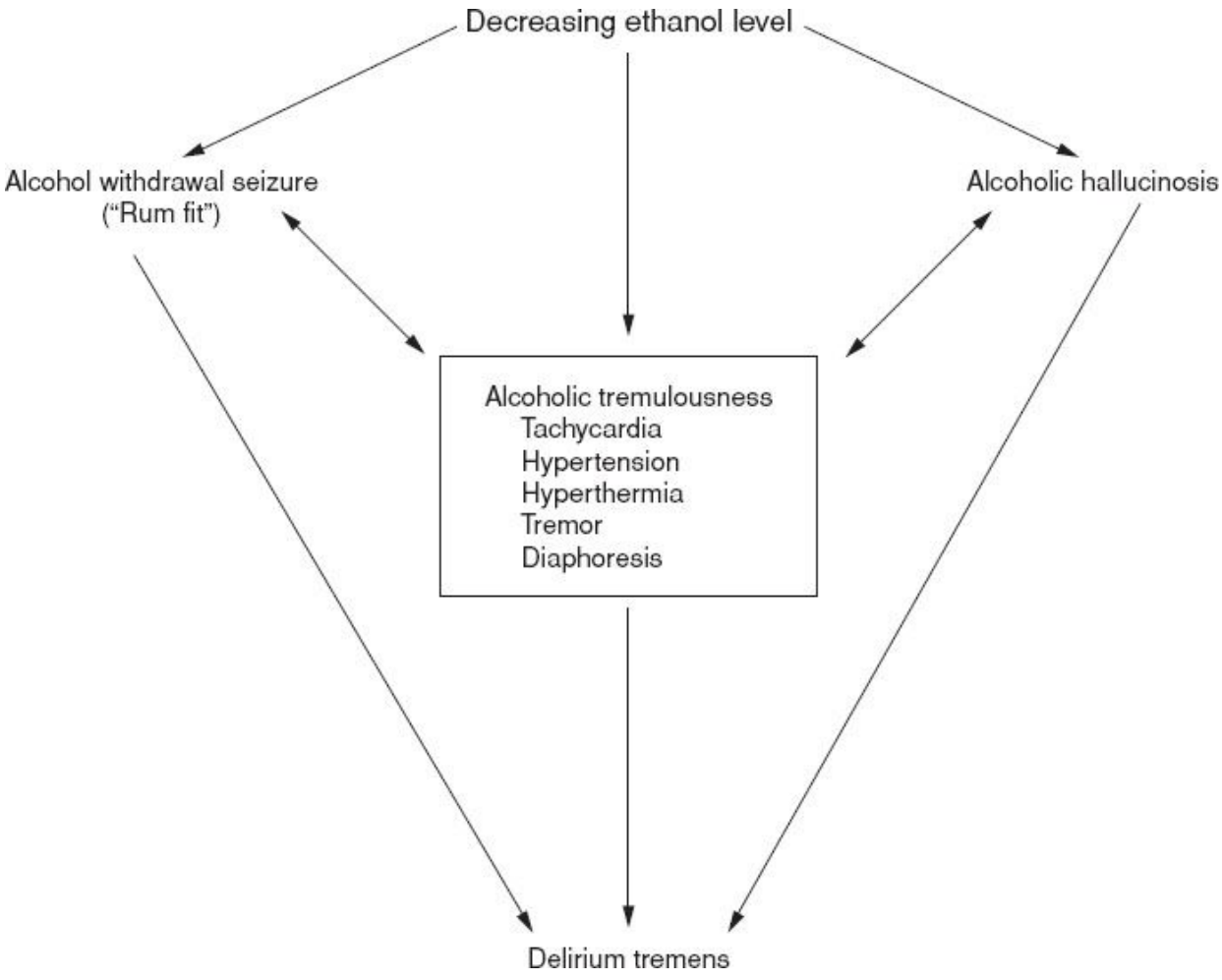

FIGURE 298.1 Adapted from Goldfrank's *Toxicologic Emergencies*. 7th ed.

Alcoholic tremulousness is characterized by catecholamine excess as a result of abstinence. Patients present to the ED with hypertension, tachycardia, diaphoresis, tremor, fasciculations, mild hyperthermia, agitation, and insomnia 4). The patient appears to be extremely uncomfortable but usually has a normal mental status. Symptoms may begin as early as 6 hours after the last drink, and most patients will be symptomatic within 24 to 48 hours after the last intake of alcohol (4). Symptoms are delayed up to 7 days in a few patients (4).

Alcoholic hallucinosis is characterized by frequently visual or sometimes auditory hallucinations that may be persecutory in nature. Formication, the sensation of insects or snakes crawling on the skin, may also occur. The onset is often within a few hours of alcohol cessation and can occur with normal vital signs and without any other manifestations of withdrawal (4).

Alcohol withdrawal seizures, or "rum fits," are the acute onset of a single seizure or a brief flurry of seizures that peak within 24 hours after the last drink. Most patients have a single seizure characterized by a brief postictal state; status epilepticus is rare (4). As with alcoholic hallucinosis, other signs of alcohol withdrawal may occur either before or after the seizures. About one-third of patients with seizures who are untreated progress to delirium tremens (4).

Delirium tremens is the most severe form of alcohol withdrawal. It includes all of the manifestations of the acute withdrawal syndrome in combination with delirium. Only 5% of patients with alcohol withdrawal progress to delirium tremens (4). Signs of delirium tremens include extreme autonomic hyperactivity and alteration in sensorium. Delirium tremens usually occurs within 48 to 72 hours after the last drink and has a typical duration of 3 to 7 days (4). In the past, mortality from delirium tremens was 15% to 20% from fluid and electrolyte abnormalities, seizures, and/or infection. Today, the mortality rate is only 5% in properly treated patients (4).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of alcohol withdrawal is extremely broad because of the many clinical manifestations that occur in isolation or simultaneously and the progression of the condition if left untreated. Furthermore, because patients often suffer from other illnesses, the diagnosis of alcohol withdrawal may be initially overlooked. Consequently, it is crucial to be aware of other etiologies that may mimic the spectrum of alcohol withdrawal (Table 298.1).

TABLE 298.1
Differential Diagnosis of Major Withdrawal Symptoms

Tremor	Seizures	Hallucinations	Delirium
Withdrawal	Withdrawal	Withdrawal	Withdrawal
Ethanol	Ethanol	Ethanol	Ethanol
Sedative–hypnotics	Sedative–hypnotics	Sedative–hypnotics	Sedative–hypnotics
Intoxications	Intoxications	Intoxications	Intoxications
Theophylline	Cocaine	LSD	Cocaine
Caffeine	Anticholinergics	Mescaline	Amphetamine
Beta agonists	Phenothiazines	Mushrooms	Phencyclidine
Mercury	TCAs	Peyote	Anticholinergics
Lithium	Theophylline	Phencyclidine	LSD
TCAs	Camphor	Anticholinergics	Infectious
Phenytoin	Isoniazid	Ergot	Meningitis
Metabolic	Phencyclidine	Nutmeg	Encephalitis
Hypoglycemia	Lidocaine	Infectious	Sepsis
Thyrotoxicosis	Organophosphates	Meningitis	Metabolic
Structural	Infectious	Encephalitis	Thyrotoxicosis
Cerebellar disease	Meningitis	Sepsis	Hypoglycemia
Other	Encephalitis	Metabolic	Hyperglycemia
Parkinsonism	Metabolic	Hypoglycemia	Hypocalcemia
	Hypoglycemia	Hypoxia	Hypoxia
	Hypoxia	Structural	Thiamine deficiency
	Hypothyroidism	CNS hemorrhage	Structural
	Thyrotoxicosis	Tumor	Head trauma
	Hypocalcemia	Psychiatric	CNS hemorrhage
	Hyperosmolar state	Schizophrenia	Tumor
	Hepatic failure	Bipolar disorder	Psychiatric
	Uremia	Other	Other
	Structural	Seizures	Seizures
	Head trauma	Heat-related illness	Heat-related illness
	CNS hemorrhage		
	Tumor		
	CVA		
	Other		
	Idiopathic epilepsy		
	Posttraumatic epilepsy		
	Degenerative disease		

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ED EVALUATION

The clinical presentation of alcohol withdrawal may be extremely unpredictable and depends on the particular patient. Most alcohol-dependent patients do not intentionally stop drinking without a new medical illness (such as recurrent pancreatitis, head trauma) or social

barrier (such as new homelessness or losing money in a robbery) that prevents continued consumption. Therefore, when patients are identified in alcohol withdrawal, it is crucial to determine the underlying reason for alcohol abstinence.

Patients should have a fingerstick glucose and oxygen saturation measured. A relevant history includes substance abuse, previous withdrawal episodes, and all current and former medications. If possible, family, friends, and prehospital personnel are interviewed to gain additional information. Vital signs, including rectal temperature, are recorded and closely monitored. Examination of the skin, abdomen, eyes, and pulse rate may help to identify a distinct toxidrome (e.g., anticholinergic, sympathomimetic). Attention should be paid to any signs of chronic liver disease or intravenous drug use.

Substance abusers are at high risk for concomitant trauma because they are unstable, at risk for falling, and often possess poor judgment. Consequently, traumatic injury should always be considered, especially in patients with an altered sensorium. Patients should also be evaluated for other complications of ethanol and drug abuse, such as pneumonia, skin abscesses, bacterial endocarditis, acquired immunodeficiency syndrome, pancreatitis, liver disease, ascites, and gastrointestinal bleeding.

Laboratory studies are useful to screen for concomitant illness and may included: complete blood count; electrolytes, glucose, blood urea nitrogen, and serum creatinine; aminotransferases; coagulation studies; and serum ethanol concentration and urinalysis for ketones. Ethanol concentrations are likely to be negligible or low in most patients in withdrawal; however, measurable serum ethanol concentrations in patients experiencing alcohol withdrawal correlate with the severity of symptoms (5). Since withdrawal occurs with a relative decrease in consumption, some patients who always have a high blood ethanol level can still have withdrawal symptoms at a lower level before getting to zero. Patients with delirium tremens, especially without a previous history, may need computed tomography of the brain and, if negative, a subsequent lumbar puncture to rule out organic CNS pathology as the cause of their altered mental status.

KEY TESTING

- There are no specific tests for ethanol withdrawal
  - Screening laboratory testing includes serum chemistry, transaminases, complete blood count, coagulation studies, urinalysis, and ethanol concentration
- Patients with altered mental status may require CT of the brain
- If infection is considered, obtain blood cultures, chest x-ray, and urine culture
- Lumbar puncture may be required to rule out meningitis or subarachnoid hemorrhage

ED MANAGEMENT

In any patient with an altered sensorium, a toxicologic cause is always possible. Intravenous dextrose is indicated if the patient has hypoglycemia (usually <90 mg/dL). Chronic alcohol use is commonly associated with hypoglycemia for several reasons. Alcoholics are often nutritionally depleted and may have insufficient glycogen stores from liver dysfunction. Chronic ethanol use also leads to an impaired redox potential from the accumulation of NADH and subsequent depletion of pyruvate, one of the major precursors of gluconeogenesis.

Thiamine (vitamin B_1) is also considered for patients with an altered sensorium and patients with a history of alcohol abuse because of the possibility of Wernicke encephalopathy (triad of ataxia, dementia or confusion, and ophthalmoplegia). This condition is rare but may occur as a result of nutritional deficiency. Alcoholics have also been shown to be thiamine deficient (6). The standard initial dose of thiamine is 100 mg intravenously. For patients who are known alcoholics and often malnourished, other multivitamin preparations and magnesium sulfate may also be administered, but their benefit is unproven (7).

Intravenous fluids are often necessary and important for the treatment of alcohol withdrawal, because alcohol induces a diuresis and leads to volume depletion (4). Alcohol withdrawal is often due to an underlying medical condition (e.g., pneumonia, pancreatitis,

head trauma) that prevents the usual alcohol intake. These patients may require aggressive volume resuscitation for the treatment of this concurrent condition.

Agitated patients may need soft restraints to prevent injury, facilitate intravenous access, and enhance sedation. Prolonged use of restraints with continued struggling may lead to rhabdomyolysis, hyperthermia, and metabolic acidosis.

The goal of therapy for the agitated alcohol withdrawal patient is sedation. Benzodiazepines, the cornerstone of therapy are sedative–hypnotics, like ethanol, and exert their pharmacologic effect via the GABA receptor (8). Benzodiazepines are usually effective in the treatment of alcohol withdrawal because they possess *cross-tolerance* with alcohol. Nevertheless, some patients require massive doses of intravenous benzodiazepines for adequate sedation. Patients "refractory" to benzodiazepines should be treated with a different GABA agonist, such as a barbiturate (e.g., phenobarbital). Patients with severe refractory alcohol withdrawal, unresponsive to benzodiazepines, may respond to a propofol infusion. Propofol is both a GABA agonist and an NMDA antagonist and is effective in several case reports to treat alcohol withdrawal. Patients who receive barbiturates or propofol are more likely to require airway protection, because of potential respiratory depression.

Symptom-triggered therapy refers to the administration of benzodiazepines when the patient's symptoms exceed a threshold of severity and is given until the patient's symptoms are adequately controlled. This is in contrast to a fixed-dose regimen of a set amount of benzodiazepine at regular intervals with a subsequent taper after the patient's symptoms are under control. The symptom-triggered method is a better technique and decreases the total amount of benzodiazepines administered, the duration of treatment, and the incidence of delirium tremens, as compared to the fixed-dose method (9,10).

Diazepam (Valium), chlordiazepoxide (Librium), and lorazepam (Ativan) are the most common agents for alcohol withdrawal and can also be used for sedative–hypnotic withdrawal. These agents are preferred over benzodiazepines with shorter half-lives because they

require less frequent dosing and allow gradual elimination of the drug over several days.

Long-acting benzodiazepines may be more effective than short-acting agents in preventing withdrawal seizures and can contribute to smoother withdrawal with fewer rebound symptoms (4). The active metabolites of diazepam and chlordiazepoxide prolong their therapeutic effect. In elderly patients and those with hepatic dysfunction, lorazepam may be preferred because it has no active metabolites. In other cases, lorazepam does not appear to offer any distinct advantage over diazepam or chlordiazepoxide (4). See Table 298.2 for dosing recommendations for various benzodiazepines.

TABLE 298.2
Pharmacologic Management of Ethanol Withdrawal

Ethanol or Sedative–Hypnotic Withdrawal
First choice: Diazepam
5-mg IV bolus every 5–15 min until sedated
May increase dose to 20 mg every 5–15 min in refractory cases
Total over 24-hr period may exceed 1,000 mg
If >300 mg given, may consider adding another GABA agent (e.g., barbiturate, propofol)
Do not exceed 5 mg/min
Second choice: Lorazepam
1–2 mg IV bolus every 5–15 min until sedated
Not as long acting as diazepam
Preferable in cases of hepatic failure or recurrent seizures
Third choice: phenobarbital
130 to 160 mg IV bolus
Can repeat every 15–20 minutes
Continue to sedation
Potential for more respiratory depression than benzodiazepines
Do not exceed 50 mg/min
Alternatives
Chlordiazepoxide, secobarbital

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In a patient who can tolerate oral medication and is in mild withdrawal, oral benzodiazepines may be sufficient. However,

intravenous dosing of benzodiazepines is faster, more precise and preferred for patients with more severe withdrawal. Agitation may preclude oral administration, and gastritis may impair drug absorption. Intramuscular lorazepam (but not diazepam or chlordiazepoxide) is absorbed predictably and is recommended when intravenous access is not readily obtained. Once symptoms are controlled, several days of oral treatment may be used for maintenance.

Patients who have abstinence seizures should be given standard supportive therapy and benzodiazepines to stop seizure activity. Phenytoin is not effective for treating alcohol withdrawal seizures and should not be given unless the patient has a known seizure focus and was previously taking this drug prior to presentation. Carbamazepine and valproic acid are mildly efficacious in certain settings but have not been studied in an ED setting or in patients with delirium tremens. Consequently, these anticonvulsants are not recommended for patients with significant signs and symptoms of alcohol withdrawal.

Historically, beta-adrenergic antagonists, clonidine, and antipsychotics (phenothiazines and butyrophenones) have been used for the treatment of alcohol withdrawal, but none of these agents exerts its primary effects through GABA. Though they may appear to control symptoms and improve vital signs, their efficacy in improving withdrawal outcomes is not demonstrated, and their routine use is discouraged.

CRITICAL INTERVENTIONS

- Treat alcohol withdrawal early with IV fluids and IV benzodiazepines. Treatment becomes increasingly more difficult as the disease progresses.
- Identify any precipitating illness. Concurrent infection is often the precipitant for ethanol abstinence and subsequent withdrawal.

DISPOSITION

Depending on the particular withdrawal syndrome, the reason for cessation of alcohol, and the severity of alcohol withdrawal signs and symptoms, the disposition of patients with alcohol withdrawal is extremely variable. As long as there are no critical medical conditions that will prevent the patient with mild alcohol tremulousness from resuming normal activities, patients may be safely discharged with treatment and referral to a detoxification program.

Patients with more severe signs and symptoms of alcohol withdrawal, including alcohol withdrawal seizures and alcoholic hallucinosis, will require hospital admission. Patients with delirium tremens will require admission to an intensive care unit for close cardiac and hemodynamic monitoring. Patients who are not adequately sedated with conventional doses of benzodiazepines may require propofol, necessitating intensive care unit admission for respiratory monitoring and subsequent endotracheal intubation, if necessary.

Common Pitfalls

- Overlooking alcohol withdrawal as a potential cause of altered sensorium and autonomic instability
- Failing to recognize and correct metabolic or treat infectious causes of illness in the alcoholic patient
- Using a fixed-dose schedule of benzodiazepines to treat ethanol withdrawal rather than titrating doses to symptoms

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CHAPTER 299 Ethylene Glycol

Thomas C. Arnold

Ethylene glycol (EG; 1,2-ethanediol) is a colorless, odorless, sweet-tasting, water-soluble liquid that has a wide variety of household and commercial uses (1). Because of its low freezing point (~13°C) and high boiling point (198°C), EG is commonly used as antifreeze–coolant. Automotive antifreeze contains about 95% EG and is the source of most EG poisonings. EG is also found in adhesives, brake and hydraulic fluids, cosmetics, de-icers, detergents, fire extinguishers, inks, lacquers, paints, pesticides, polishes, and some windshield-washer fluids.

In 2011, poison centers in the United States received reports of 6,277 single exposures to EG, including 18 fatalities. The majority of exposures occur unintentionally through misuse or by accident (2). Intentional ingestion with suicidal intent results in the majority (>75%) of fatalities but accounts for only 15% of EG exposures. In 2011, one fatality was attributed to unintentional exposure to EG (2). Widespread availability probably accounts for its ingestion by alcoholics seeking an ethanol substitute, while its interesting color and pleasant, bittersweet taste make it attractive to children.

Unmetabolized EG produces about the same degree of central nervous system (CNS) depression as ethanol. Other effects (anion gap metabolic acidosis, coma, seizures, cardiopulmonary dysfunction, and acute renal failure) result largely from accumulation of toxic metabolites, that is, glycolic and oxalic acids (1,3,4).

EG is absorbed rapidly from the gastrointestinal tract and distributed throughout total body water (0.6 L/kg). Peak blood

concentration occurs about 2 hours after ingestion (4). About 20% to 50% of EG is excreted unchanged in the urine (4). The remaining EG is metabolized in the liver to a variety of compounds with varying toxicities (eFig. 299.1). EG elimination is first order, with a half-life of 2.5 to 4.5 hours in patients with normal renal function and alcohol dehydrogenase activity (1,4–6).

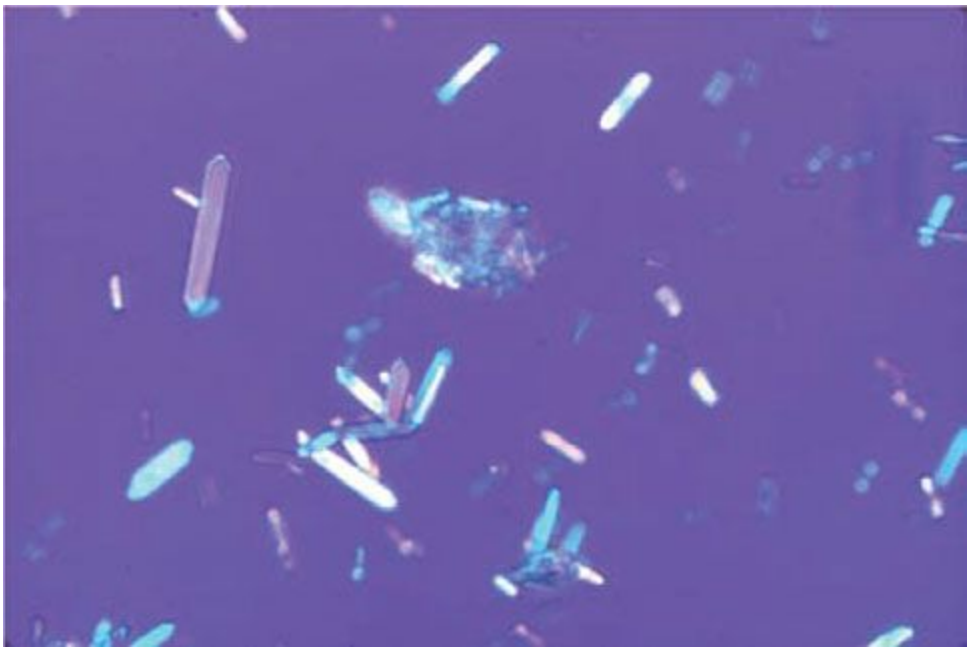
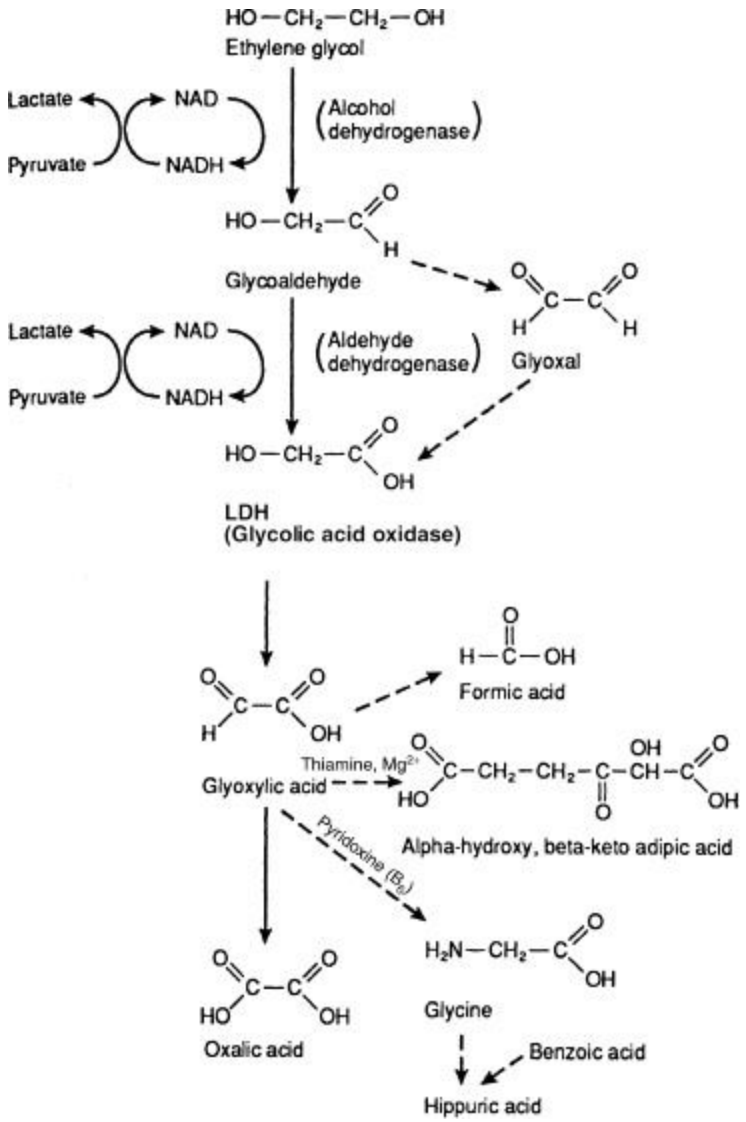


FIGURE 299.1 Calcium oxalate as needle-shaped monohydrate crystals. (From Tilley, DVM, Smith, DVM. *The 5-Minute Veterinary Consult: Canine and Feline*. 3 ed. Lippincott Williams & Wilkins; copyright 2004.)



eFIGURE 299.1 Metabolism of ethylene glycol. Solid lines, known pathways of metabolism; dashed lines, postulated pathways of metabolism.

The first step in the metabolism of EG is its oxidation to glycoaldehyde by alcohol dehydrogenase (ADH) (4). Because ADH has a much higher affinity for ethanol and fomepizole (a synthetic ADH inhibitor) than for EG, these substrates are preferentially bound over EG. Their presence inhibits the metabolism of EG sixfold, preventing the formation of toxic metabolites, which is the mechanism of their action as antidotes (1,3,4).

Once formed, glycoaldehyde is metabolized rapidly by aldehyde dehydrogenase to glycolic acid, which is further metabolized slowly by glycolic acid oxidase to glyoxylic acid (1,4). Because this latter step is rate limiting, glycolic acid tends to accumulate (1,3). The level of glycolic acid correlates with the increased anion gap, decreased arterial pH, development of renal injury, and mortality associated with advanced EG poisoning (3,4). Once formed, glyoxylic acid is oxidized rapidly to one of several metabolites. Its principal metabolite, oxalic acid, precipitates as calcium oxalate crystals in various organs and tissues (1,4).

The deposition of calcium oxalate monohydrate crystals is responsible for much of the end-organ injury that results from serious EG poisoning (e.g., nephrotoxicity, meningoencephalitis, and cerebral and pulmonary edema) (1,4). Accumulation of crystals within proximal renal tubules leads to physical blockage and compression of the tubular lumen, direct renal tubular cytotoxicity (cell membrane and oxidative cellular injury), and subsequent development of acute tubular necrosis and renal failure (4). Although some evidence suggests that glycoaldehyde and glyoxylic acid are also nephrotoxic, their contribution to renal tubular injury in EG poisoning is probably negligible because they are metabolized rapidly (1,4).

Significant systemic toxicity from EG occurs only after ingestion (1,4). Skin exposure can cause minor irritation, and direct eye contact can cause conjunctivitis, chemosis, and iridocyclitis. Because of the high boiling point of EG, there is no toxicity from vapor inhalation. The toxic and lethal doses of EG after acute ingestion vary. Because ingestion of just 0.1 mL/kg of pure EG can induce potentially toxic blood concentrations, the ingestion of even a mouthful of the liquid should be considered hazardous. Although the lethal oral dose is approximately 1.5 mL/kg, there is a poor correlation between the amount consumed and prognosis (4,5).

CLINICAL PRESENTATION

EG poisoning manifests in three distinct stages of CNS, cardiopulmonary, and renal involvement. Their onset, progression, and confluence vary widely (1,4). Thirty minutes to 12 hours after ingestion, CNS signs and symptoms predominate, starting with slurred speech, ataxia, nystagmus, and lethargy. The patient may appear intoxicated but instead of the breath odor of ethanol, a faint, sweet, or aromatic odor may be detected. Nausea, vomiting, and abdominal pain might also be present.

After a latent period of 3 to 12 hours, signs and symptoms develop from accumulated toxic metabolites. CNS depression progresses to stupor and coma. Hyperreflexia, tremor, tetany, cranial nerve abnormalities, and seizures (both focal and generalized) may occur. Severe CNS disturbances could reflect the development of cerebral edema and meningoencephalitis (4). In the late stages of poisoning, when most or all EG has been metabolized, measuring the serum glycolic acid level might be the only way to confirm the diagnosis.

Cardiopulmonary signs such as hypertension, tachycardia, dysrhythmias, and pulmonary edema develop 12 to 36 hours after the ingestion of EG. During this stage, compensatory tachypnea and Kussmaul respirations reflect a progressively worsening anion gap metabolic acidosis.

Urinalysis can provide additional evidence of EG poisoning. Proteinuria and microscopic hematuria are seen in more than 60% of cases (3–5). The presence of hematuria and oxaluria is not predictive of acute renal failure (5). Calcium oxalate crystalluria, although nonspecific, is present on admission in more than 40% of patients; this percentage increases with serial urinalysis and delayed presentation (3–5). Calcium oxalate is often excreted as needle-shaped monohydrate crystals (Fig. 299.1), which might be misidentified as hippuric or uric acid crystals (4). At higher urinary concentrations, calcium oxalate is also excreted in an envelope-shaped dihydrate form (Fig. 299.2) (4). The binding of calcium to oxalate may result in hypocalcemia, causing myoclonic jerks or tetanic contractions (1,4). Because fluorescein is added to many commercial antifreeze preparations, fluorescence of urine or gastric

contents with a Wood lamp supports EG poisoning early after ingestion. Fluorescence is insensitive and nonspecific, however, and cannot be relied on to make or exclude the diagnosis of EG poisoning.

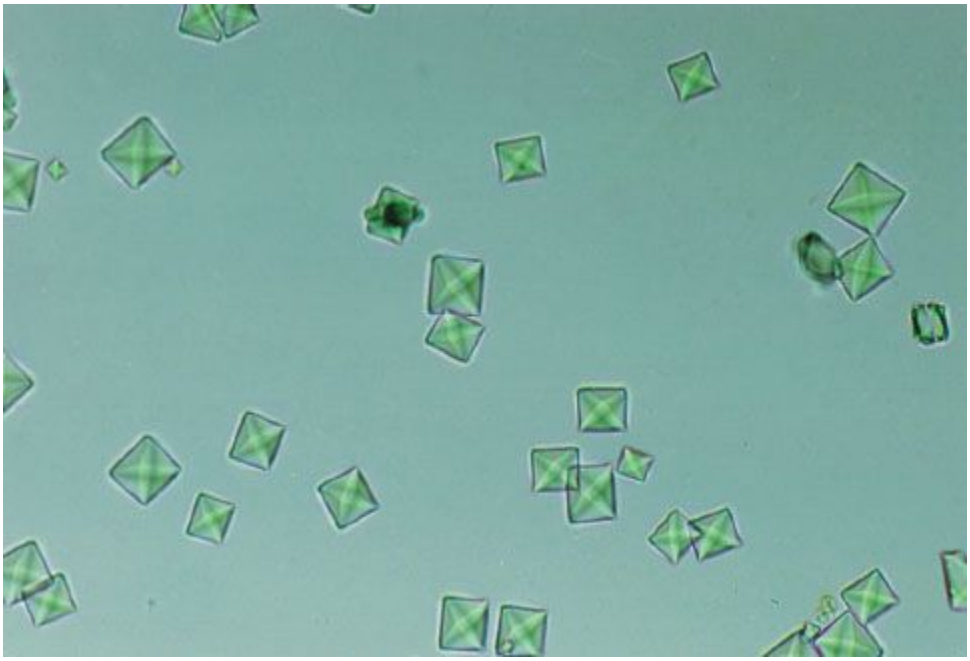


FIGURE 299.2 Calcium oxalate as envelope-shaped dihydrate crystals. (McClatchey KD, M.D., D.D.S. *Clinical Laboratory Medicine*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002.)

EG plasma concentrations do not correlate with mortality (5). Rapid diagnosis and treatment prevent EG bioactivation and lethality, regardless of the initial plasma EG concentration (7). Severity of illness is best predicted by the degree of anion and osmolal gap. Patients with anion gaps less than 20 and osmolal gaps less than 25 usually survive (7). Death results from cerebral edema and infarction, multiple organ failure, and irreversible shock (1,4). Even with treatment, the mortality rate is 5% to 17% (3).

Renal dysfunction (seen in nearly 70% of cases) is characterized by oliguria, proteinuria, and urine with a low-specific gravity and sodium content (acute tubular necrosis). Some patients complain of severe flank pain (1,4). Renal dysfunction may be noted as early as 9 hours after ingestion (3). The high frequency of renal injury may

be attributed to delayed presentation or delayed diagnosis and treatment (5). The degree of metabolic acidosis or glycolic acid accumulation at the initiation of treatment, rather than EG plasma concentration, correlates closely with the subsequent development of renal injury (3–5). In one retrospective study, an initial glycolic acid level >8 mmol/L, an anion gap >20 mmol/L, or an arterial pH <7.30 was highly predictive of acute renal failure (5). Conversely, acute renal insufficiency is unlikely to develop in patients who have an initial glycolic acid level <8 to 10 mmol/L, an arterial pH >7.30, or normal renal function upon initiation of appropriate treatment (3,5). Although most treated patients have a complete recovery, some may have protracted renal insufficiency requiring months of hemodialysis.

Cranial nerve deficits (usually VII nerve dysfunction), basal ganglia and brainstem infarction, parkinsonism, and cerebral edema are rare but possible consequences of EG poisoning. They can present as long as 3 weeks after acute poisoning (1,4,8).

DIFFERENTIAL DIAGNOSIS

EG intoxication can mimic a large variety of poisonings or disease states, depending on the amount ingested and the degree of its metabolism at presentation. Diagnostic clues include drunken behavior without the odor of ethanol, a delay between ingestion and significant illness, hyperventilation on physical examination, increased osmolal or anion gap, metabolic acidosis, calcium oxalate crystalluria, and hypocalcemia. The differential diagnosis includes alcoholic, diabetic, and starvation ketoacidosis; lactic acidosis; renal failure; methanol poisoning; and advanced, untreated acetaminophen or salicylate poisoning. If the history does not suggest lactic acidosis or ketoacidosis, a high osmolal gap with anion gap metabolic acidosis strongly points toward EG or methanol poisoning (4). In methanol intoxication, crystalluria is absent, and the patient might report visual disturbances or have abnormal results on eye examination. Although a large osmolal gap (particularly >25) suggests toxic alcohol poisoning, a small gap

(<10) cannot be used to exclude significant EG poisoning, particularly in the later stages of poisoning, when significant metabolism has already occurred (1,4,5). Disorders of inborn organic acid metabolism should be considered in the differential diagnosis of young children with an increased anion gap metabolic acidosis.

ED EVALUATION

The history should include the time of ingestion; the volume and concentration of the ingested product; and the onset, nature, and progression of symptoms. The intent of the ingestion, accidental versus intentional, should be ascertained, since intentional ingestions are often more serious. The ingestion of other substances, particularly ethanol, should be documented. Patients should be asked specifically about ethanol-like intoxication, shortness of breath, flank pain, and urinary dysfunction.

The physical examination should focus on neurologic status, cardiopulmonary function, and any abdominal and back tenderness. In children or unreliable adults, fluorescein staining of the mouth or clothes can provide a clue to the exposure.

Laboratory evaluation is critical and should include urinalysis (UA) (specify crystal analysis) and quantitative serum EG concentration by gas chromatography and mass spectrometry (GC/MS) to confirm the diagnosis. In early stages and where EG levels are not available, measuring serum osmolality along with serum electrolytes, blood urea nitrogen, creatinine, glucose, serum ethanol can determine an elevated osmolal gap which may be a clue to the diagnosis of EG poisoning (4,5). Because of its low molecular weight (62 g/mol), only high concentrations of EG increase the serum osmolality appreciably. This increase in osmolality elevates the osmolal gap, the difference between the serum osmolality measured by the freezing-point depression (but not the vapor pressure method) and the calculated osmolarity ([2 × sodium] + [glucose/18] + [blood urea nitrogen/2.8] + [serum ethanol concentration/4.25]). Note that ethanol is osmotically active (1

mOsm for each 4.25 mg/dL of serum ethanol) and must be subtracted (4,5,9). Normally, serum osmolality ranges from 280 to 300 mOsm/kg H_2O, with a normal osmolal gap of –2 ± 6 mOsm/kg. If EG analysis is not readily available, the serum level (milligrams per deciliter) can be estimated roughly by multiplying the osmolal gap by 6.2 (mg/dL per mOsm of EG). The osmolal gap is not precise enough to make a diagnosis, but a very large osmolal gap is strongly suggestive.

A decrease in the serum bicarbonate concentration and an increased anion gap metabolic acidosis may be seen as early as 3 hours after EG ingestion (1,3). The normal anion gap (serum sodium minus chloride and bicarbonate), representing unmeasured anions in the serum, is 12 ± 2 mEq/L. In EG poisoning, glycolic acid accounts for a large part of the unmeasured anions. The absence of metabolic acidosis is consistent with an early presentation, an insignificant ingestion, or the coingestion of ethanol, which blocks the metabolism of EG. Measuring blood gas, ketones, lactate can help determine other causes of acidosis.

Because many antifreeze products contain methanol or propylene glycol, serum concentrations of these agents should be ordered if the identity of the ingested substance cannot be confirmed. Occasionally, glycolic acid quantification by special GC/MS techniques is necessary for patients who present very late (e.g., with renal failure and no detectable EG) (3,5).

KEY TESTING

- Early presenting patients should have EG levels, UA, laboratories to determine osmolal gap and a baseline blood gas analysis.
- In addition, late presenting patients and those waiting for EG levels to return should have calcium, blood gas analysis, lactate, and ECG.

ED MANAGEMENT

Airway protection and respiratory and circulatory support, with cardiac and hemodynamic monitoring, should be instituted as

necessary. Intravenous fluids should be administered liberally at first to maintain adequate urine output; a large urine flow increases the excretion of EG in patients not in renal failure (4). If the patient intentionally ingested EG only shortly before presentation, gastric aspiration via a nasogastric tube should be performed immediately. Activated charcoal adsorbs EG but might be clinically ineffective because EG is absorbed rapidly and the capacity of charcoal to bind EG is exceeded when moderate amounts of EG are ingested. Activated charcoal is recommended if a coingestant is suspected. Most accidental exposures involving a single swallow or two will probably not benefit from gastric decontamination.

Specific treatment for EG poisoning consists of sodium bicarbonate to correct metabolic acidosis, calcium to correct symptomatic hypocalcemia, ethanol, or fomepizole to inhibit production of toxic metabolites, hemodialysis to remove EG and its toxic metabolites, and cofactors (e.g., magnesium, pyridoxine, and thiamine) to enhance endogenous clearance of toxic metabolites (1).

Correction of metabolic acidosis might require large amounts of intravenous sodium bicarbonate ($NaHCO_3$):

$$NaHCO_3 \text{ dose} = 0.7 \times \text{kg} \times (24 - \text{actual } [HCO_3^-])$$

where 0.7 is the volume of distribution of bicarbonate in acidemia, kg is the lean body weight, and 24 is the desired $[HCO_3^-]$. $NaHCO_3$ should be given in 1-mEq/kg increments (1,4). Increasing the serum pH increases the fraction of ionized acid metabolites, thereby minimizing their tissue redistribution and maximizing their renal clearance through ion trapping. The patient's acid–base status should be reevaluated frequently to assess the response to therapy. Hypocalcemia could be worsened by sodium bicarbonate administration (1,4).

Serum calcium levels should be monitored frequently. Symptomatic hypocalcemia (e.g., cardiac dysrhythmias, tetany, and seizures) should be treated with intravenous calcium chloride or gluconate (7 to 14 mEq for adults and 1 to 7 mEq for children). The 10% calcium chloride solution contains 1.4 mEq of calcium per

milliliter, and a 10% calcium gluconate solution contains 0.46 mEq/mL. Calcium is not recommended for patients with asymptomatic hypocalcemia, as its administration could increase calcium oxalate tissue precipitation and overall EG toxicity. Seizures should be treated with standard drugs (diazepam, lorazepam, or a barbiturate).

Traditionally, ethanol has been used to inhibit the alcohol-dehydrogenase–mediated metabolism of EG. Fomepizole (4-methylpyrazole, 4-MP; Antizol) is a potent, long-acting, competitive alcohol dehydrogenase inhibitor that is a safe, easy, and effective alternative to ethanol (1,3,4,6). Unlike ethanol, fomepizole is approved by the US Food and Drug Administration (FDA) for the treatment of EG and methanol poisoning. In humans and animals poisoned by EG, fomepizole attenuates and prevents metabolic acidosis and renal failure by halting the accumulation of glycolic and oxalic acids, respectively (1,3,5). Fomepizole has higher potency, longer duration of action, more predictable kinetics, and an easier dosing regimen than ethanol (1,3,5) and does not require frequent monitoring and adjustment of plasma concentrations. In addition, fomepizole does not produce the CNS depression, hypoglycemia, gastritis, pancreatitis, fluid overload, and habituation commonly associated with ethanol therapy (1,3,6,8). Fomepizole is generally safe in humans, although it has been associated with dizziness, eosinophilia, headache, nausea, rash, transient hepatic transaminase elevation, phlebitis, and seizures (1,3,6,8). The higher cost of fomepizole (~$1,000 US per 1.5-g vial) is balanced by greater patient safety and the lower costs of less patient monitoring and fomepizole has become preferred over ethanol in the United States. In 2011, poison centers received 2,053 reports of its use compared with 91 reports of ethanol use (2). Fomepizole has not been studied specifically in the children but one review of published literature suggests fomepizole is effective and well tolerated in children when given in the normal adult dosages (10). Fomepizole is labeled pregnancy category C by the FDA and therefore is recommended for use during pregnancy only when the benefit

outweighs the risk. It is contraindicated in patients who are allergic to pyrazole derivatives.

Both ethanol and fomepizole bind alcohol dehydrogenase preferentially over EG, which prevents the further metabolism of EG to its toxic metabolites so that EG can be eliminated by urinary excretion or hemodialysis. Indications for treatment with ethanol or fomepizole include a measured serum EG concentration >20 mg/dL; a documented history of significant recent EG ingestion when a serum EG concentration is not immediately available (particularly if the osmolal gap is elevated); or strong suspicion of EG ingestion based on abnormal clinical or laboratory findings (e.g., unexplained anion gap metabolic acidosis, elevated corrected osmolal gap [or both], or oxalate crystalluria) (1,3,4).

For fomepizole, a loading dose of 15 mg/kg IV should be followed by doses of 10 mg/kg IV every 12 hours thereafter (3). All doses are diluted in 100 mL of 5% dextrose in water or normal saline and administered by slow IV infusion over 30 minutes (2,8). Like ethanol, fomepizole is effective when orally administered but this route has not been fully studied or approved (1). Fomepizole is continued until the EG concentration falls below 20 mg/dL (3).

For ethanol therapy, the therapeutic goal is a serum ethanol concentration of at least 100 mg/dL, which is sufficient to prevent metabolism of EG even at high concentrations (4). IV administration is preferred, because it achieves a more rapid and constant serum concentration (1,4). Administration of an IV loading dose of 10 mL/kg of 10% ethanol (preferably in a glucose-containing solution, such as D_5W, to avoid hypoglycemia) over 30 to 60 minutes, followed by a maintenance infusion of 1.5 mL/kg/hr, generally produces a serum ethanol concentration of slightly >100 mg/dL (4). Alternatively, 5 mL/kg of 20% (40 proof) ethanol can be administered orally or via nasogastric tube to achieve the desired loading dose; the hourly maintenance oral dose is similar to that for IV administration (1.5 mL/kg/hr of 10% ethanol) (1,4). Mental status, serum ethanol and glucose concentrations should be

monitored and the dose of ethanol adjusted, as necessary, to maintain a therapeutic ethanol concentration.

Hemodialysis rapidly removes both EG and glycolic acid (4,5). Elimination half-lives are reduced to approximately 3 hours for each, compared with 19 and 10 hours, respectively, with alcohol dehydrogenase inhibitor therapy alone (1,3,6). Indications for hemodialysis include significant metabolic acidosis (arterial pH <7.30), renal insufficiency (serum creatinine >1.2 mg/dL), or deterioration in these parameters or clinical status despite conventional treatment (1,3–5).

Traditionally, hemodialysis has been recommended for patients with a serum EG concentration of 50 mg/dL or greater (4). However, this concentration does not define toxicity, predict prolonged elimination, or correlate with patient outcome. Recent evidence suggests that patients who present before the development of metabolic acidosis and renal impairment can be managed effectively and safely with fomepizole monotherapy (i.e., without hemodialysis) regardless of the initial EG concentration (1,3,5). In these patients, EG is excreted by the kidneys, with an approximate half-life of 18 hours (1,3,5,6). For patients who present with elevated serum creatinine, however, EG elimination half-life is prolonged to approximately 49 hours, and hemodialysis is recommended (3,6). These patients will also likely require hemodialysis based on the presence of a significant metabolic acidosis. Hemodialysis should be continued until acid–base and metabolic abnormalities are corrected and serum EG concentrations are below 50 mg/dL (3,4).

The infusion rate of ethanol should be increased to 3 mL/kg/hr during hemodialysis to compensate for increased clearance (1,4). Because fomepizole is also dialyzable, it should be administered by a continuous IV infusion of 1 to 1.5 mg/kg/hr or its dosing frequency increased to every 4 hours during hemodialysis (3). If hemodialysis is unavailable or technically difficult (e.g., in infants), peritoneal dialysis can be used, although this method is considerably less effective than hemodialysis.

Pyridoxine, thiamine, and magnesium are cofactors in the metabolism of EG to less toxic products (see eFig. 299.1). Their administration could preferentially shunt metabolism of glyoxylic acid away from oxalic acid. Both pyridoxine and thiamine are given intravenously in doses of 100 mg four times daily (4).

CRITICAL INTERVENTIONS

- Administer fomepizole or ethanol to patients with signs, symptoms, or laboratory evidence of EG poisoning.
- Administer IV sodium bicarbonate to patients with acidemia.
- Arrange hemodialysis for patients with EG poisoning that is severe or refractory to other treatment.

DISPOSITION

Patients with significant EG poisoning require admission to an intensive care unit. The need for hemodialysis should always be anticipated, and transfer to a facility with that capability should be considered if such treatment is unavailable in the initial treating hospital. Patients who have ingested only a small volume of EG accidentally and do not develop acidosis or have toxic levels of EG can be discharged.

Common Pitfalls

- Failure to consider EG as a cause of ethanol-like intoxication and increased anion gap metabolic acidosis.
- Failure to appreciate that a normal osmolal or anion gap does not exclude the presence of potentially toxic amounts of EG.
- Failure to observe and monitor all patients with known or suspected ethylene EG ingestion until an EG level can be obtained or until the time of expected toxicity has passed without incident.
- Failure to appreciate the importance of fully correcting acidemia.
- Failure to appreciate that ethanol and fomepizole are removed by hemodialysis and to increase their dosing accordingly during this procedure.

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CHAPTER 300 Methanol

Thomas C. Arnold

Methanol (methyl alcohol, “wood alcohol”) is a clear, colorless, highly flammable liquid at room temperature. It is less dense than water (0.81 g/mL) and has a faint odor resembling ethanol. Methanol is a widely used industrial solvent in the production of formaldehyde and methylated compounds. It is found in many commercial products such as gasoline, antifreeze, windshield washer fluid, copy machine fluid, canned heat (Sterno), stains, paint thinners, varnishes, and wood refinishing solvents. Poisoning easily occurs after the accidental or intentional ingestion of such products. In 2011, poison centers in the United States received reports of 1,711 methanol exposures, 9 of which resulted in death (1). Although most cases are isolated, epidemics of poisoning can occur when methanol is mistakenly substituted for ethanol or when it contaminates alcoholic beverages such as wine or moonshine whisky.

Methanol is absorbed within 30 to 60 minutes after ingestion and is water soluble. It can penetrate the skin to some degree and is slightly volatile. For these reasons, toxicity after extensive dermal contact and inhalation has been reported (2). The volume of distribution approximates total body water, at 0.6 L/Kg. The metabolism of methanol to formaldehyde by alcohol dehydrogenase follows zero-order kinetics and accounts for 90% of its elimination. Small amounts are also excreted in expired air and urine. Formaldehyde is rapidly metabolized to formic acid, which is responsible for the toxic effects of methanol (Fig. 300.1) (3). The metabolism of formate is dependent on folate stores. Primates have a

small folate reserve and are the only species that accumulates formate and susceptible to methanol toxicity (3).

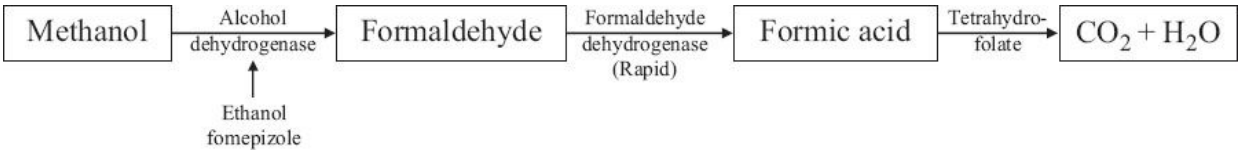

FIGURE 300.1 Methanol metabolism.

Early in poisoning, toxicity is caused by the central nervous system (CNS) depressant effect of methanol and metabolic acidosis caused by formic acid accumulation (3). Later, the toxicity is caused mainly by the histotoxic effects of accumulated formate, which inhibit mitochondrial respiration. This results in lactate production, worsening acidosis, and increased penetration of the blood–brain barrier by formate as it becomes protonated. The eye and basal ganglia are the primary targets for methanol's toxic effects; the reason is not known (3,4). The lethal dose of methanol is reported variably as 30 to 240 mL, with 1 g/kg (1 g = 1.2 mL) considered the best estimate (3). The minimum dose that causes permanent visual defects is unknown.

Ethanol and fomepizole bind to alcohol dehydrogenase with a higher affinity than methanol and hence block the production of toxic metabolites. Ethanol is metabolized by alcohol dehydrogenase, but fomepizole is not. When these antidotes are used, the elimination half-life of methanol increases from 24 hours to as long as 60 hours (3,5).

CLINICAL PRESENTATION

In most cases, 6 to 24 hours elapse from the time of ingestion to the emergence of symptoms. This period of time is required for a sufficient amount of formic acid to be produced by methanol metabolism. A latent period up to 90 hours has been reported when ethanol is coingested because ethanol competitively inhibits methanol metabolism by alcohol dehydrogenase (5).

Methanol itself has few direct effects. Mild ethanol-like CNS depression has been reported (3). Methanol is about half as potent as ethanol in this regard. Nausea, vomiting, and abdominal pain may develop shortly after ingestion of a concentrated methanol solution. During the early stages of poisoning, the diagnosis is confirmed by measuring the serum methanol level, but this laboratory process is usually not readily available or the results are not rapidly obtainable. Because of methanol's low molecular weight (32 g/mol), high serum concentrations can increase the serum osmolality. Therefore, the diagnosis can be suggested by an increased osmolal gap, that is, the difference between the measured osmolality and the calculated osmolality (2 × sodium [mEq/L] + blood urea nitrogen [mg/dL]/2.8 + glucose [mg/dL]/18 + ethanol [mg/dL]/4.25) (6). The "normal" range for the osmolal gap has been debated extensively and has been reported to vary from −10 to 20 mOsm (7). Although an osmolal gap above 20 indicates exogenous osmoles of some kind, an osmolal gap within the normal range does not exclude the possibility of a toxic methanol ingestion. The serum methanol level can be estimated (in mg/dL) by multiplying the excess osmolal gap by 2.6, the amount of methanol that increases the osmolality by 1 mOsm/kg H_2O. Because the molecular weight of methanol is lower than for ethylene glycol, the same volume causes a greater osmolal gap and is easier to detect. Shortly after ingestion, when the highest methanol levels and osmolal gap are present, metabolic acidosis can be absent because significant conversion to formate has not yet occurred. Severity of illness is best predicted by the degree of anion gap, osmolal gap, and acidosis. Patients with anion gaps less than 30, osmolal gaps below 49, and pH values greater than 7.22 usually survive (8).

Clinical features during the intermediate stage of poisoning include anorexia, headache, nausea, and vomiting, accompanied or followed by increasing hyperventilation as a result of progressive anion gap metabolic acidosis (3). The normal anion gap ([Na] − [Cl + HCO_3]) is 12 ± 2 mEq/L. Visual symptoms (blurred vision, decreased acuity, halo vision, tunnel vision, photophobia, and "snowfields") might precede or accompany the aforementioned symptoms. Objective

signs, such as dilated pupils that are partially reactive or nonreactive to light and funduscopic findings of optic disk hyperemia with blurring of the margins, occur later. During this intermediate stage, the diagnosis is confirmed by detecting methanol or formate in the serum; an elevated osmolal gap might or might not be present. Occasionally, patients present with abdominal pain from associated acute pancreatitis (3).

Without treatment, late effects of coma and respiratory and circulatory failure can ensue. In a few patients, methemoglobinemia develops from an interaction between formate and the ferric part of hemoglobin. In the late stages of methanol poisoning, when most or all of the methanol has been metabolized to formate, the anion gap is elevated, methanol might not be detectable so the osmolal gap is normal. In this situation, measurement of the serum formate concentration could be the only way to confirm the diagnosis. Toxic effects on the basal ganglia do not immediately produce detectable signs and symptoms, because they are masked by pronounced CNS depression. Survivors might later experience parkinsonism and polyneuropathy, with basal ganglion necrosis noted on computed tomography (CT) scan or magnetic resonance imaging (MRI) (9).

DIFFERENTIAL DIAGNOSIS

Other causes of metabolic acidosis and increased serum osmolality should be considered in the differential diagnosis (Fig. 300.2), particularly when the history is unclear and quantitative methanol and formate levels are not readily available. Increased anion and osmolal gaps also occur in ethylene glycol poisoning. Differentiating the two may be difficult, but the treatments are essentially the same. Visual complaints suggest methanol poisoning, whereas hypocalcemia, seizures, and urine oxalate crystals suggest ethylene glycol poisoning (3).

Anion gap	Osmolal gap	Both
Ketoacids	Diabetes	Ethylene glycol
Lactate	Ethanol	Methanol
Paraldehyde	Mannitol	
Salicylate	Other alcohols	
Uremia		

FIGURE 300.2 Causes of an increased anion and osmolal gaps.

ED EVALUATION

Important aspects of the history include the amount, concentration, if the original product was diluted, and time of methanol ingestion; the nature and onset of symptoms; and whether ethanol was coingested. The intent of the ingestion—accidental versus intentional—should be ascertained, since intentional ingestions are often more serious. Usually, accidental ingestions are of only a small amount and much less likely to be toxic than intentional ingestions. Patients should be questioned carefully about the presence or absence of visual complaints, gastrointestinal (GI) symptoms, and a feeling of intoxication. The physical examination should focus on vital signs (especially respiratory rate) and the patient's neurologic, visual, and cardiopulmonary status. Visual acuity and funduscopic findings should be documented.

The laboratory evaluation of early-presenting patients should include methanol level, and if not readily available, osmolality, ethanol, electrolytes, blood urea nitrogen, creatinine, glucose to calculate an osmolal gap. Quantitative serum methanol and/or formic acid levels should be determined by gas chromatography and mass spectrometry (GC/MS). If the diagnosis is based on the osmolal and anion gaps, osmometry must be performed by the freezing point depression technique, not by the vapor pressure technique, because

the latter does not detect the increased osmolality caused by volatile alcohols.

Blood gas analysis with serum lactate can detect the metabolic acidosis and should be repeated to assess the degree of acidosis if treatment is delayed. A chest radiograph and an electrocardiogram can be obtained if clinical toxicity is pronounced. A CT scan or MRI of the brain should be performed on patients with coma or persistent neurologic dysfunction.

KEY TESTING

The laboratory evaluation should include the following:

- Quantitative serum methanol and/or formic acid levels by GC/MS for all patients
- If methanol levels are delayed or if patients present late, add blood gas analysis, electrolytes, blood urea nitrogen, creatinine, glucose
- A chest radiograph and an electrocardiogram if clinical toxicity is pronounced

ED MANAGEMENT

General treatment measures include supportive care and GI decontamination. Immediate gastric aspiration via nasogastric tube may be helpful for intentional ingestions if performed within 1 hour after ingestion. Activated charcoal is probably of limited value because of limited binding (3).

Specific treatment of methanol poisoning includes intravenous (IV) sodium bicarbonate for metabolic acidosis, antidotal therapy with ethanol or fomepizole to inhibit methanol metabolism to formate, and hemodialysis to remove methanol and formate. Folinic acid (leucovorin), 1 mg/kg IV up to 50 mg every 4 hours, may be of value to increase the metabolism of formate (10). If folinic acid is unavailable, folic acid in the same dose can be used.

Metabolic acidosis should be treated aggressively with enough sodium bicarbonate ($NaHCO_3$) to fully correct acidemia:

$$NaHCO_3 \text{ dose} = 0.7 \times kg \times (24 - \text{actual } [HCO_3^-]),$$

where 0.7 is the volume of distribution of bicarbonate, 24 is the desired $[HCO_3^-]$, and kg represents the lean body weight.

$NaHCO_3$ should be given in 1 mEq/kg increments. As much as 400 to 600 mEq of $NaHCO_3$ could be required during the first few hours. Bicarbonate therapy decreases the amount of undissociated formic acid and CNS toxicity (3). Hence, metabolic acidosis from methanol poisoning should *always* be treated with bicarbonate. Frequent reassessment of acid–base and electrolyte status is prudent during treatment.

Alkali treatment must be accompanied by administration of ethanol or fomepizole to block further production of formic acid. If methanol poisoning is suspected and a level cannot readily be obtained, fomepizole or ethanol therapy should be started in any patient with an increased osmolal gap, acidosis, symptoms, or a potentially toxic ingestion suggested by the history. Antidotal treatment can be discontinued when the methanol level drops below 20 mg/dL, provided the acid–base status is normal and the patient is experiencing no complications.

Fomepizole (4-methylpyrazole; Antizol) is a safe alternative to ethanol (5,10). The loading dose of 15 mg/kg IV is followed by doses of 10 mg/kg IV every 12 hours. During hemodialysis, the dosing frequency should be increased to every 4 hours. Fomepizole is superior to ethanol as an antidote, because it does not carry the risk of respiratory depression, the need to monitor blood ethanol levels, or the requirement for an ICU setting for IV infusion; the only negative consideration is its cost.

Ethanol antidotal treatment, at a therapeutic blood ethanol level of at least 100 mg/dL is still effective. However, the ethanol level necessary to block methanol metabolism varies with the blood level of methanol because of competition for alcohol dehydrogenase. The molar ethanol concentration should be at least one-fourth of the molar methanol concentration (3).

An approximate blood ethanol level of 100 mg/dL can be achieved by giving a bolus dose of 0.6 mg/kg, followed by 66 to 154

mg/kg/hr intravenously or orally (the higher maintenance dose is for heavy drinkers). Mixing 50 mL of absolute ethanol with 500-mL isotonic glucose yields a 10% ethanol solution. With this solution, a bolus of 10 mL/kg (>0.5 hour), followed by 1.5 mL/kg/hr can be the initial dose. The maintenance infusion should be adjusted according to frequently measured ethanol levels. As a rule of thumb, the maintenance dose of ethanol should be doubled during hemodialysis. If this is not done, methanol metabolism can resume as ethanol is removed, thus allowing toxicity despite hemodialysis.

Hemodialysis efficiently removes methanol and formate and helps to correct the metabolic acidosis (3,5). The one absolute indication for hemodialysis is any visual impairment in a patient with metabolic acidosis or a detectable methanol level. Other indications include severe acidemia (particularly if the patient is unresponsive to bicarbonate and ethanol therapy), a blood methanol level above 50 mg/dL (because of the very slow elimination of methanol during antidotal therapy), renal insufficiency, or ingestion of more than 1 g/kg of methanol. With the use of fomepizole, most patients need dialysis only to shorten the duration of fomepizole treatment by removing unmetabolized methanol. However, in severe poisoned patients with pronounced acidemia and visual disturbances, hemodialysis should be performed to remove formate and methanol. Hemodialysis should be continued until the blood methanol level is below 20 mg/dL and acidemia is corrected. If methanol analyses are unavailable, hemodialysis should be continued for at least 8 hours or until the osmolal gap is normal (5,7). Peritoneal dialysis is not effective enough to be clinically useful.

CRITICAL INTERVENTIONS

- Administer ethanol or fomepizole to patients with signs, symptoms, or laboratory evidence of methanol poisoning
- Administer IV sodium bicarbonate to patients with acidemia
- Arrange hemodialysis for patients with methanol poisoning that is severe or refractory to other treatment

DISPOSITION

When the diagnosis of methanol poisoning is made or suspected, a nephrologist should be consulted, because many of these patients require hemodialysis, especially when admitted in a late stage. If hemodialysis is likely to be needed, the patient should be transferred to a facility with this capability. Bicarbonate and antidotal therapy should be given prior to and during transport.

If a methanol level is not immediately available, asymptomatic patients with known or suspected methanol ingestion and a normal anion and osmolal gap should be observed and reevaluated for clinical and acid–base status until the methanol level becomes known. Patients with signs, symptoms, or laboratory evidence of methanol intoxication should be admitted, usually to an ICU because of the frequency of monitoring required. They should also have an ophthalmologic evaluation for detection and management of ocular injury.

Common Pitfalls

- Failure to consider methanol poisoning in the differential diagnosis of metabolic acidosis of unknown origin
- Failure to consider the possibility of multiple victims when the source of methanol is unknown or is known to be contaminated ethanol
- Failure to appreciate that the absence of early symptoms, a normal anion gap, or a normal osmolal gap does not exclude a potentially serious methanol intoxication
- Failure to assess and document visual acuity
- Failure to observe and monitor patients with known or suspected methanol ingestion until a methanol level can be obtained or until the time of expected toxicity has passed without incident
- Failure to fully correct acidemia
- Failure to appreciate that ethanol and fomepizole are removed by hemodialysis and to adjust their dosing during this procedure accordingly

- Failure to have the visual function of methanol-poisoned patients assessed formally by an ophthalmologist

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CHAPTER 301

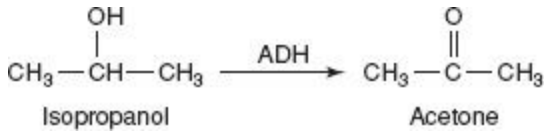
Isopropanol, Acetone, and Other Glycols

Jeffrey R. Suchard

Although ethylene glycol (Chapter 299) and methanol (Chapter 300) are potentially more dangerous, exposures to isopropanol and acetone occur more frequently and are more likely to be encountered in the emergency department (ED).

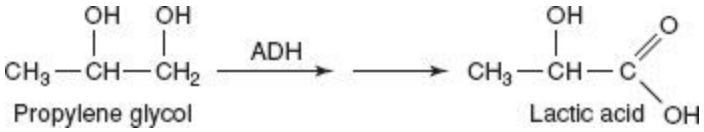
Isopropanol (2-propanol, isopropyl alcohol) is a disinfectant, solvent, cleaner, and deicing agent. Rubbing alcohol is the most common household source, typically containing 70% isopropanol by volume. Despite a slightly bitter taste and distinctive, pungent smell, isopropanol is the most commonly ingested nonbeverage alcohol. Other routes of exposure include inhalation and transdermal absorption, particularly among small children. Isopropanol is rapidly absorbed from the stomach; peak serum levels can be measured within 30 minutes (1,2). Clinical effects are evident within 0.5 to 1.5 hours (3). Isopropanol is a central nervous system (CNS) depressant about twice as potent as ethanol.

Isopropanol is primarily metabolized by alcohol dehydrogenase (ADH) to acetone (eFig. 301.1). Ketonemia and ketonuria caused by the presence of acetone occur rapidly after exposure to isopropanol (1). Unlike methanol and ethylene glycol, no organic acid metabolites are produced, and an elevated anion-gap metabolic acidosis is not expected. The serum half-life of isopropanol varies considerably, but is in the range of 2.5 to 6 hours.



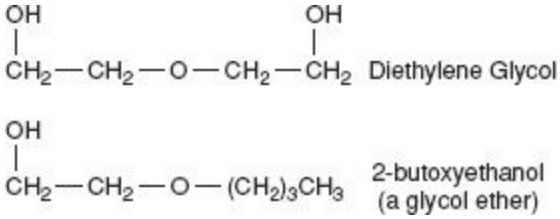
eFIGURE 301.1 Isopropanol metabolized to acetone.

Acetone (2-propanone, dimethyl ketone), a metabolite of isopropanol (4), is a solvent in industry and the home. Fingernail polish remover is a common cause of acetone exposures (5). Acetone is rapidly absorbed and then excreted unchanged (4). Reports of acetone's elimination half-life vary widely but range from 17 to 31 hours (4,5). Propylene glycol (1,2-propanediol [PG]) is a solvent and CNS depressant found in many foods, cosmetics, and intravenous medications. Roughly 50% of PG is excreted unchanged into the urine, and the remainder is metabolized via ADH and aldehyde dehydrogenase into lactic acid (eFig. 301.2).



eFIGURE 301.2 Propylene glycol metabolized to lactic acid.

Diethylene glycol (DG), another common solvent and CNS depressant, consists of two ethylene glycol molecules connected by an ether bond (eFig. 301.3). The strong ether bond is not metabolized in humans to release free ethylene glycol, but DG poisoning can still produce renal failure and neurologic toxicity. Epidemics of renal failure have occurred when DG has been used as an inappropriate substitute for glycerin in oral liquid medications (6).



eFIGURE 301.3 Other glycols.

Glycol ethers are compounds that consist of a glycol, usually ethylene glycol, connected to an alkyl group by an ether bond. Ethylene glycol-butyl-ether (2-butoxyethanol), a typical glycol ether, is shown in eFigure 301.3. Glycol ethers are used as industrial solvents, as glass and surface cleaners, and in automobile brake fluid.

CLINICAL PRESENTATION

Isopropanol poisoning is characterized by CNS depression, gastrointestinal effects, ketosis, and an elevated osmolal gap (OG) without metabolic acidosis. Two common scenarios are (a) chronic alcoholics seeking an alternative when deprived of ethanol; and (b) exploratory ingestions by children. It is difficult to correlate the degree of intoxication with serum isopropanol levels, probably because of cross-tolerance to isopropanol in alcoholics or lack of previous exposure to intoxicants among children. Complicating the issue is the ubiquitous presence of acetone, an isopropanol metabolite that is also a CNS intoxicant.

With a few exceptions, signs and symptoms of isopropanol and acetone intoxication are very similar to those of ethanol. The disinhibited phase that may be seen with early ethanol intoxication has not been reported with isopropanol, but the CNS depressant effects are otherwise the same. Patients ingesting isopropanol often have higher levels of acetone than isopropanol by the time of presentation. Because of its slower metabolism and the intoxicating effect of its acetone metabolite, the duration of isopropanol intoxication is longer than ethanol. Gastrointestinal effects are more common than with ethanol and include nausea, vomiting, abdominal pain, and hemorrhagic gastritis.

Acetone produces a characteristic fruity or ether-like odor in the breath. Serum acetone levels after isopropanol or acetone ingestion often greatly exceed those found in diabetic ketoacidosis, so this olfactory clue may be even more obvious than usual. Ketonemia and ketonuria occur rapidly after isopropanol or acetone poisoning (1).

Most cases of PG toxicity occur iatrogenically in hospitalized patients, particularly with high doses of intravenous benzodiazepines (7,8), but it can also result from ingestion of PG-containing household products such as cosmetics and automotive antifreezes (sold as safer alternatives to ethylene glycol). Signs and symptoms include CNS depression, hyperosmolality, lactic acidosis, and renal insufficiency.

DG and glycol ether poisoning may result in CNS depression, metabolic acidosis, renal failure, hepatitis, and pancreatitis. Glycol ethers can also cause hemolysis, hypotension, hypoglycemia, hematuria, and acute respiratory distress syndrome (9).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of isopropanol and acetone exposure includes any of the other CNS depressants, and other medical or surgical conditions that alter mental status, including intracranial trauma, CNS infection or tumors, hypoglycemia, and other severe metabolic derangements.

The primary exogenous substances in the differential diagnosis are other alcohols. Patients ingesting any of the short-chain alcohols typically present with a similar clinical picture of CNS depression and an elevated OG. Differentiating the early stages of intoxication with any of these agents may be difficult. Fortunately, the most commonly ingested alcohol is ethanol, which can be rapidly quantified by most clinical laboratories. Late-presenting patients might be differentiated by an anion-gap metabolic acidosis (methanol and ethylene glycol), renal insufficiency (ethylene glycol), visual symptoms (methanol), hyperlactatemia (PG), and the smell of acetone on the breath (isopropyl alcohol or acetone). Patients with ethanol-like CNS effects, an elevated OG, and a normal anion gap and who smell like acetone may presumptively be diagnosed with isopropanol or acetone toxicity pending laboratory confirmation. Concurrent ingestion of isopropanol and ethanol or another “toxic alcohol” is not uncommon (2).

Ketones from isopropanol or acetone ingestion may falsely elevate measurement of serum creatinine (10), and an elevated creatinine with a normal blood urea nitrogen (BUN) suggests this diagnosis. Renal insufficiency from ethylene glycol should occur in conjunction with an increased BUN and a significant anion-gap metabolic acidosis. Other causes of ketosis to consider include diabetic ketoacidosis and alcoholic ketoacidosis, both of which also elevate the OG, and starvation ketosis. Elevated serum acetone levels are found in patients with ketoacidosis, although these levels are usually lower than those seen with isopropanol or acetone ingestion.

Although fingernail-care product ingestion is a common and usually benign source of acetone exposure, care should be taken to confirm the history and product ingredients in such cases. The ingestion of artificial nail remover (as opposed to nail polish remover) containing acetonitrile, rather than acetone, has caused fatal cyanide toxicity.

PG-induced lactic acidosis, especially among hospitalized patients receiving IV medications with PG as a solvent, may be confused with many other serious causes of lactic acidosis, including hypoxia, hypotension, and sepsis that need to be excluded before ascribing the lactic acidosis to PG toxicity.

ED EVALUATION

The history should include identification of the substance(s) involved, concentration, route(s) of exposure, estimated volume ingested, and time elapsed since exposure. Any history of potential co-ingestants or trauma should be elicited. Early definitive product identification can help identify potential disasters, such as acetonitrile-containing nail-care products in children or methanol and ethylene glycol ingestion by chronic alcoholics deprived of ethanol. Physical examination should focus on the patient's mental status, airway, and vital signs.

Patients presenting with altered mental status should have a rapid glucose determination to rule out hypoglycemia. With serious intoxication, laboratory tests should include a quantitative level of

the substance involved (if available). Routine serum chemistries (to rule out anion-gap metabolic acidosis), an ethanol level, arterial blood gas, and measurement of serum and urinary ketones may also be helpful where the diagnosis is not clear by history. The close chemical structural relationship between ethanol, isopropanol, and acetone can cause analytical interference when employing breathalyzer ethanol tests and enzymatic ethanol assays using ADH.

The serum OG can be helpful as a screening tool for detecting exogenous low–molecular-weight alcohols or glycols. A serum osmolality measured by freezing-point depression exceeding the calculated osmolality (2[Na] + [BUN]/2.8 + [Glucose]/18 + [Ethanol]/4.2) suggests the presence of isopropanol, acetone, methanol, ethylene glycol, or PG. If the identity of the substance is known, its serum concentration in milligrams per deciliter can be roughly estimated by multiplying the OG by the substance's molecular weight and dividing by 10. The molecular weight of isopropanol is 60 g/mol, acetone is 58 g/mol, and PG is 76 g/mol. For example, if a patient with an acetone ingestion has an OG of 20, the estimated serum acetone concentration is (20 × 58)/10 = 116 mg/dL. Because the molecular weights of glycol ethers are higher than those of the other alcohols, toxic levels of glycol ethers often do not significantly elevate the OG.

KEY TESTING

- Chemistry panel, to calculate serum anion gap
- Serum osmolality and ethanol levels should be ordered along with the chemistry panel to calculate the serum OG
- Serum levels of isopropanol and acetone, if available in a clinically relevant timeframe

ED MANAGEMENT

Treatment of isopropanol or acetone toxicity is supportive, with most patients requiring only observation. Early-presenting patients should be observed for deterioration, as toxicity should manifest within the first few hours. Activated charcoal does not bind these

toxins well, and is not recommended unless the patient also recently ingested toxins that will adsorb to it. Patients not adequately protecting their airway should be intubated. Hypotension, if present, should be treated with intravenous saline and, if necessary, vasopressor agents.

Hemodialysis can greatly enhance isopropanol and acetone elimination. Hypotension refractory to treatment with intravenous saline is the primary indication for hemodialysis. Because acetone is not substantially more toxic than isopropanol, ethanol or fomepizole treatment to inhibit alcohol dehydrogenase is not useful. Patients with abdominal pain or heme-positive emesis may have a hemorrhagic gastritis and should be evaluated for gastrointestinal bleeding and anemia.

The treatment of severe toxicity such as renal failure and acidosis from DG, PG, or glycol ethers should include ethanol or fomepizole and hemodialysis, with similar doses and protocols as used with ethylene glycol (Chapter 299) or methanol (Chapter 300) toxicity (7,9).

CRITICAL INTERVENTIONS

- Support the airway and respiratory function in patients with CNS depression.
- Administer intravenous fluids and vasopressors for hypotension.
- Consider hemodialysis for profound CNS depression, refractory hypotension, metabolic acidosis, or renal failure.
- Administer ethanol or fomepizole to patients with severe DG, PG, and glycol ether poisoning.

DISPOSITION

Patients with minor exposures to isopropanol or acetone, such as pediatric non-intentional ingestions, will need only 2 or 3 hours of observation to ensure they do not develop CNS depression. Patients with mild symptoms can be observed as with ethanol intoxication. Patients with coma, hypotension, metabolic disturbances, or end-

organ toxicity should be admitted to an intensive care unit with poison center, toxicologist, and nephrologist consultation as needed.

Common Pitfalls

- Assuming that all isopropanol and acetone exposures are benign.
- Failure to monitor and re-evaluate both asymptomatic and intoxicated patients.
- Failure to appreciate that acetone and isopropanol affect breathalyzer measurement.
- Failure to appreciate that acetone causes falsely elevated serum creatinine levels and diagnosing renal failure when the BUN is normal.
- Failure to appreciate that DG, PG, and glycol ethers can cause toxicity similar to ethylene glycol.

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PART 3 • ANALGESICS

CHAPTER 302 Acetaminophen

Jeffrey Brent

Acetaminophen (N-acetyl-*p*-aminophenol, or APAP) is the most commonly used analgesic/antipyretic in the world. Given its widespread availability, poisoning with acetaminophen is common. Because many lay people underestimate its toxicity, suicide gestures may result in unintentional actual suicides. In 2012, nearly 150,000 potential APAP poisonings and almost 140 deaths as a result of acetaminophen alone and in combination with other agents were reported to US poison centers (1). In 2011, medical toxicologists personally treated over 900 cases of APAP toxicity (2). These figures represent only a fraction of the total number of incidents.

Acetaminophen itself has very little intrinsic toxicity. It is almost entirely metabolized in the liver by the pathways shown in Figure 302.1. About 94% of an ingested therapeutic dose of APAP is metabolized to the nontoxic glucuronide (52%) or sulfate (42%) conjugates, which are excreted in the urine. Of the remaining 6% of the dose, about half is excreted unchanged in the urine, and a similar amount undergoes oxidative metabolism primarily by the 2E1 isozyme of the hepatic P450 system (CYP2E1) to form a highly reactive intermediate, N-acetyl-*p*-benzoquinoneimine (NAPQI) (3). With therapeutic APAP dosing, the small amount of NAPQI produced is rapidly conjugated by glutathione and excreted as the mercapturate conjugate plus other minor metabolites, all of which are nontoxic.

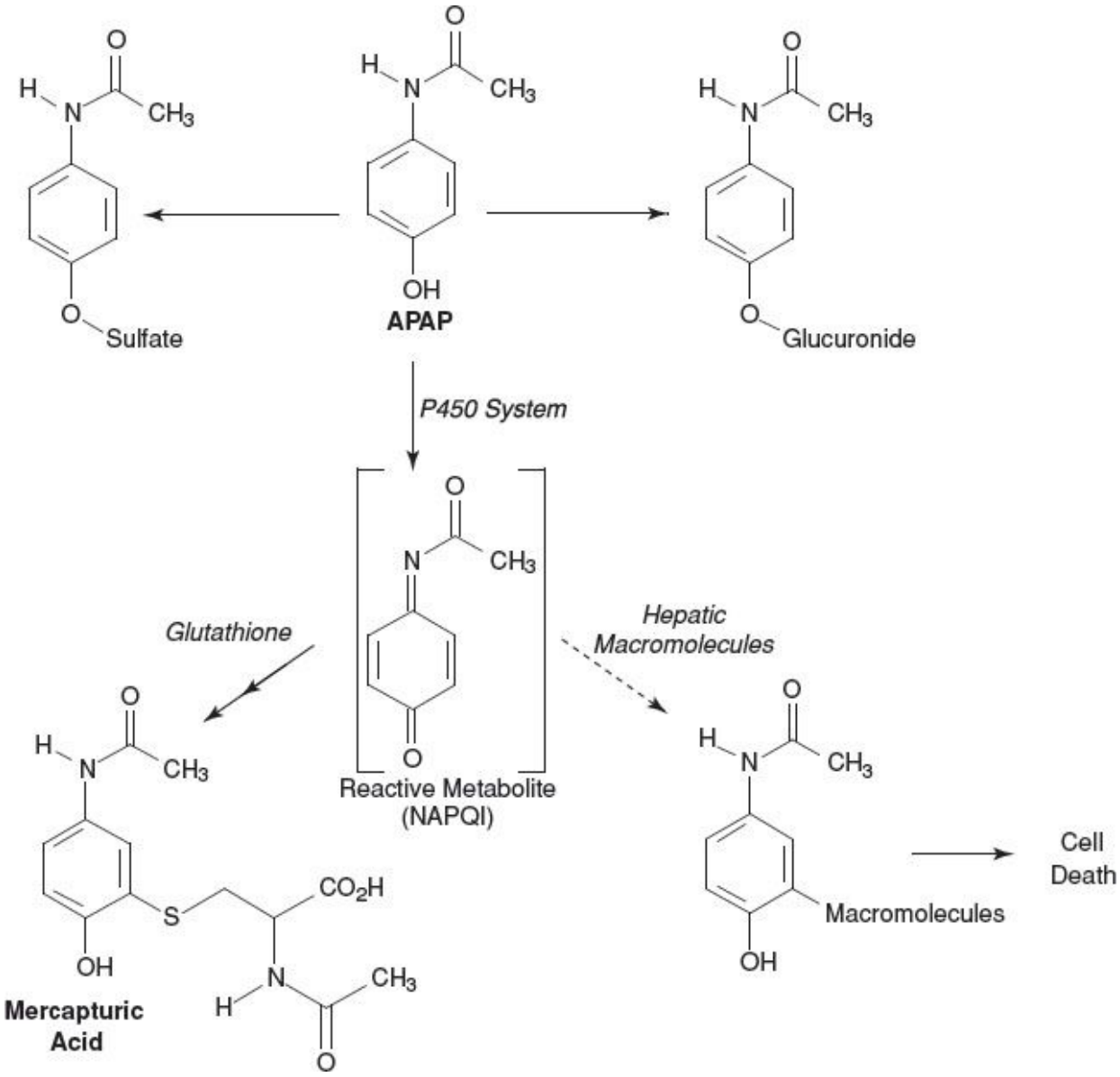

FIGURE 302.1 Metabolic pathways for acetaminophen metabolism.

In animal models, toxicity occurs when hepatic glutathione stores are depleted by about 70%, which renders the hepatocytes vulnerable to the effects of NAPQI (3). In the setting of inadequate glutathione stores, NAPQI is conjugated by hepatic macromolecules, which is generally thought to be the cause of hepatocyte death in APAP poisoning. Histologically, necrosis occurs at the highest concentrations of CYP2E1 in the centrilobular (zone III; perivenular) portions of the hepatic lobule (3).

Although the clinical picture of APAP overdose is predominantly one of hepatotoxicity, some patients also have nephrotoxicity. Rarely, and only anecdotally, renal damage has been reported to occur in the absence of substantial hepatotoxicity. The nephrotoxicity is most likely a result of renal APAP biotransformation to the toxic NAPQI metabolite by CYP2E1 in the kidney. Additionally, renal failure is an occasional concomitant complication of severe APAP-induced hepatotoxicity as a result of the hepatorenal syndrome.

CLINICAL PRESENTATION

Acetaminophen toxicity can be divided into four stages (Table 302.1). The first stage of APAP poisoning is a relatively subtle period characterized by nausea, vomiting, and general malaise. In this phase, APAP is being absorbed and metabolized, and glutathione stores are being consumed. Although hepatotoxicity is beginning, it is often not apparent clinically or in routine laboratory results. Phase I typically lasts <24 hours. The antidote N-acetylcysteine (NAC) is most effective during this early phase and is virtually 100% effective in preventing hepatotoxicity if initiated within 8 hours of ingestion.

TABLE 302.1
Stages in the Clinical Course of Acetaminophen Toxicity

Stage	Time after Ingestion	Characteristics
I	0.5–24 hrs	Anorexia, nausea, vomiting, malaise, pallor
II	24–48 hrs	Right upper quadrant abdominal pain and tenderness; elevated bilirubin, prothrombin time, hepatic enzymes; oliguria
III	72–96 hrs	Peak liver-function abnormalities; anorexia, nausea, vomiting, malaise may reappear
IV	4 d–2 wks	Resolution of hepatic dysfunction or fulminant hepatic failure

Modified from Linden CH, Rumack BH. Acetaminophen overdose. *Emerg Med Clin North Am.* 1984;2:103.

During the second phase, which usually starts late on the day of the ingestion, the gastrointestinal effects of phase I resolve, and plasma concentrations of APAP are low or nondetectable. (Serum and plasma APAP concentrations can be considered to be equivalent.) The hepatotoxic effect of the NAPQI, which has not been inactivated by glutathione, begins to cause hepatocellular destruction. The predominant clinical picture is of hepatotoxicity but, as toxicity evolves, some cholestatic features may occur. However, primary or prominent cholestatic injury is not caused by APAP.

Phase III of acetaminophen toxicity is the time of maximum hepatotoxicity. During this phase, transaminases will peak and then decline, but effects on coagulation may continue to increase. Patients who present in stage II or III may have right upper quadrant pain, nausea, vomiting, jaundice, bleeding, and encephalopathy. Associated with this is a progressive increase in bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels, and PT/INR. The magnitude of these liver-function abnormalities can be dramatic, with ALT and AST levels of 10,000 to 20,000 IU/L frequent. In most cases, these abnormalities peak in 48 to 96 hours (stage III) and gradually resolve.

In the final phase (IV), there will be either recovery or fulminant hepatic failure (FHF). Patients with severe untreated APAP toxicity exhibit a pattern of continued rising prothrombin time, bilirubin, and ammonia levels as the AST and ALT decline. This pattern signifies FHF. However, most patients, even those with severe hepatotoxicity, eventually recover, with normal livers. Patients who recover from APAP hepatotoxicity should not have residual liver abnormalities, and there is no reason for concern regarding future therapeutic APAP use.

A number of poisoning cases have a high anion-gap metabolic acidosis, thought to be a poor prognostic sign of liver failure. In addition, some cases may also be related to elevated levels of 5-oxoproline, also known as pyroglutamic acid, which is involved in glutathione metabolism. Most of these patients are women with chronic acetaminophen exposure, significant malnutrition, and other

chronic disease, most recover with supportive treatment. The significance of this entity remains unclear.

The relationship between the plasma concentration of APAP, the time after acute ingestion, and the potential for toxicity is described by the nomogram developed by Rumack and Matthew (Fig. 302.2) (3). The nomogram stratifies patients into risk categories of "probable" or "possible" hepatotoxicity. Toxicity is not generally expected in the "possible risk" area, which includes a 25% margin of safety to account for possible errors in establishing the time of ingestion. Possible risk is traditionally considered an indication for antidotal therapy in the United States, although some medical toxicologists and poison centers use the "probable toxicity" line starting at 200 μg/mL at 4 hours. There is considerable variation worldwide in the treatment thresholds used. Some countries use the "probable toxicity" line starting at 200 μg/mL at 4 hours. The UK has recently adopted the line starting at 100 μg/mL at 4 hours, although the empirical justification for using such a low threshold is weak. Denmark has abandoned the nomogram and simply treats all patients who give a history of APAP ingestion above therapeutic amounts. Use of low, or nonexistent, thresholds may subject patients to unnecessary hospitalizations and possible iatrogenic complications, more than doing any good.

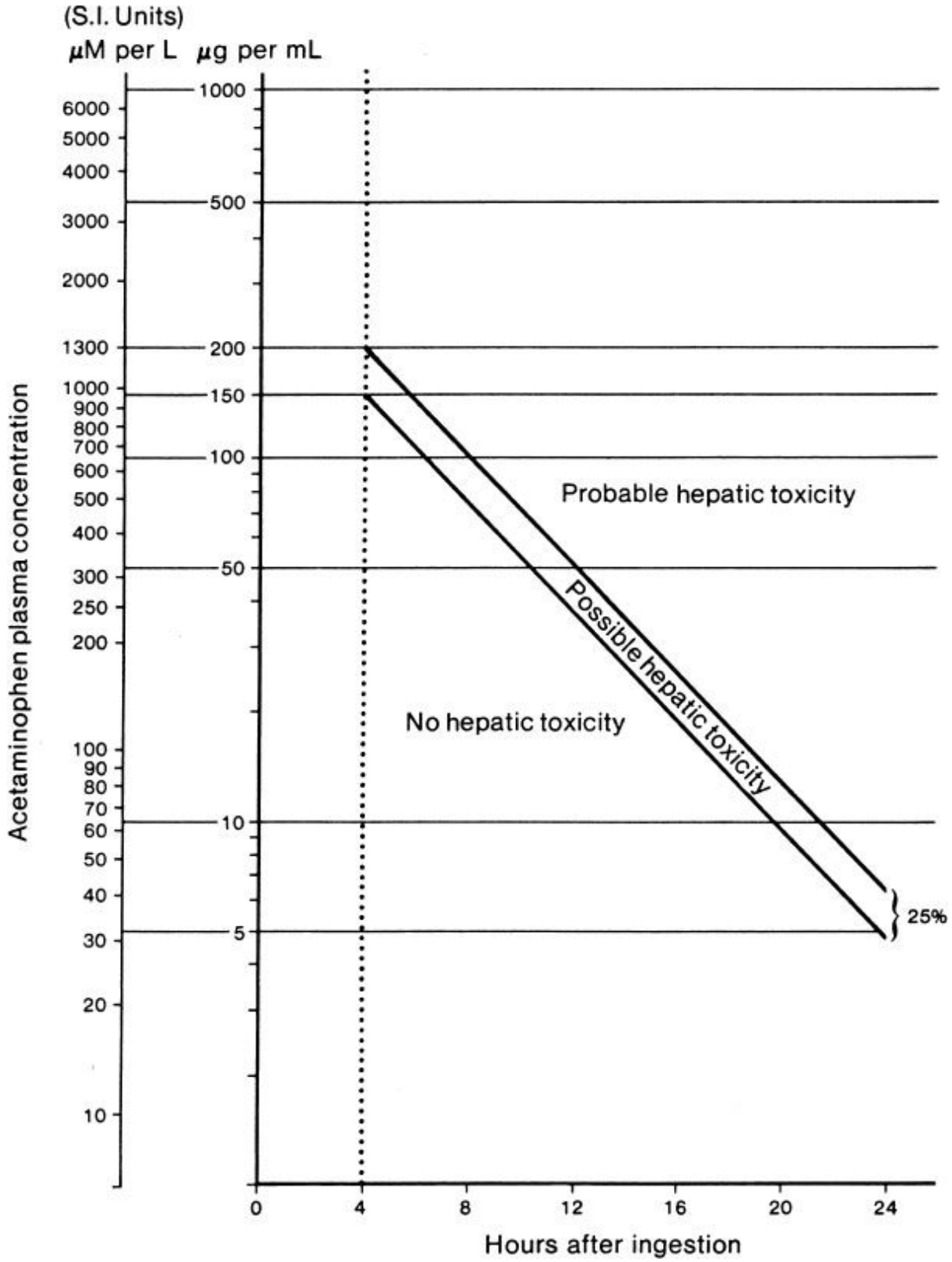

FIGURE 302.2 Rumack–Matthew nomogram for acetaminophen poisoning. Relation between plasma APAP levels and toxicity

correlated with time after exposure. (Reproduced with permission from Rumack BH. Acetaminophen overdose in children and adolescents. *Pediatr Clin North Am. 1986;33:691–701.)*

The nomogram begins at 4 hours after ingestion and extends to 24 hours. Early plasma APAP concentrations obtained before this time—during the absorption and distribution phases—are difficult to interpret, however, early APAP concentrations of <100 μg/mL suggest a lack of toxicity risk. Both nomogram lines have a slope equivalent to a 4-hour half-life, so by remembering that they begin at plasma concentrations of 150 and 200 μg/mL, the level at each subsequent 4-hour time can be calculated by halving the previous level.

The APAP nomogram is based only on initial plasma concentrations. Repeat levels offer no further useful information, can cause confusion and their utility has not been validated. Although this has been recommended for sustained-release APAP overdose, the value of this practice for determining risk of hepatotoxicity has not been validated. Based on the known volume of distribution of APAP of 0.9 to 1.0 L/kg, an ingestion of 10.5 g APAP in a 70-kg adult, or 150 mg/kg in a child, may produce plasma concentrations in the possible toxicity range.

The current nomogram is derived solely from adult cases. Children with toxic plasma levels after an acute overdose appear to be less susceptible to APAP toxicity than adults (4). Patients who have ingested a potentially toxic dose of APAP and have a history of anorexia or severe malnutrition may be more susceptible to APAP hepatotoxicity because of decreased glutathione stores. Patients with chronic liver disease tend to have glutathione stores maintained even as their content of CYP2E1 fall, hence they do not appear to be at a significant risk of toxicity with therapeutic dosing. Patients with a history of alcohol abuse also do not appear to be at an increased risk of toxicity at therapeutic doses unless they are severely malnourished in acute overdose. These patients can be evaluated using the standard nomogram.

DIFFERENTIAL DIAGNOSIS

In the earliest stage of APAP poisoning, the presumptive diagnosis is made by a history suggestive of overdose. Because there are no consistently reliable or pathognomonic signs or symptoms, the possibility of occult APAP poisoning must be considered when one is confronted with any overdose. The common practice of measuring APAP levels with every intentional ingestion increases the detection of any APAP in the plasma which must alert the clinician to the possibility of a toxic APAP ingestion, especially in the setting of elevated transaminases.

The patient in stage II, III, or IV of APAP toxicity presents a different diagnostic challenge. By this time, there may be little or no detectable APAP in the plasma, so the diagnosis depends heavily on the history and clinical suspicion.

The differential diagnosis of hepatic injury includes most commonly viral, autoimmune, ischemic, cholestatic or chemical etiologies. Virtually any drug can cause hepatotoxicity as an idiosyncratic reaction. The chemistry profiles typically seen with the different types of hepatitis are shown in Table 302.2. As shown in Figure 302.3, liver function test (LFT) results may not rise dramatically until a day after the ingestion, although LFT, PT/INR elevations are often seen within the first day (5).

TABLE 302.2
Laboratory Values in the Common Acute Hepatitides: Viral, Alcoholic, Acetaminophen

Hepatotoxin	Acute Viral Studies	AST (IU/L)	ALT (IU/L)
Viral	Usually positive	Hundreds to low thousands	Variable but less than AST
Alcohol	Negative	Usually <300 or 10× normal	Usually ALT/AST >2
APAP	Negative	May be very high	Much less than AST

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

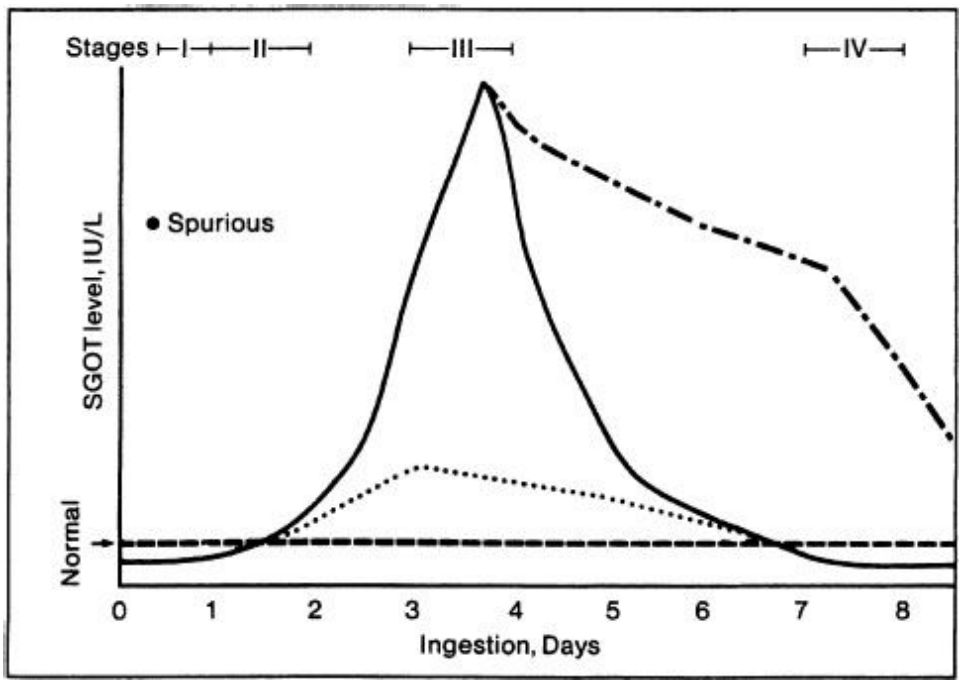

FIGURE 302.3 *Dotted line:* the course of those who received acetylcysteine. *Solid line:* those with natural a course. *Dotted-dashed line:* those with a severe course. (Reproduced with permission from Smilkstein MJ, Knapp GL, Kulig KW, et al. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study [1976 to 1985]. *N Engl J Med.* 1988;319:1557–1562.)

ED EVALUATION

The amount, formulation, and time(s) of APAP or other drug ingestion should be noted. Because of the many over-the-counter medications and prescription opioid combinations containing APAP, the patient may not even be aware of the amount ingested. The history should address risk factors such as anything affecting nutritional status (which might reduce hepatic GSH concentrations) such as chronic severe malnutrition or acute starvation, and the use, or misuse of opioid–APAP combinations. The physical examination should focus on the vital signs and assessment of cardiovascular, gastrointestinal, and neurologic function and hydration status. A plasma APAP concentration should be obtained and, for acute ingestions, compared to the nomogram. If the level is potentially

toxic, or the time of ingestion is unknown and APAP is present, baseline LFTs (AST, ALT, and total bilirubin levels and prothrombin time) and plasma creatinine concentration should be obtained. A normal presenting plasma ALT level has been shown to have an approximately 100% negative predictive value for significant liver injury in treated patients (6).

The Rumack–Mathew nomogram is based on single ingestions and cannot be applied to cases with a history of excessive APAP ingestion over more than a single point in time. Based on empiric observation, these patients can be evaluated for possible APAP-induced toxicity or risk of such toxicity if:

1. They are under 6 years of age and they have ingested either (a) 100 mg/kg or greater over a single 24-hour period or (b) 150 mg/kg or greater per 24-hour period for the preceding 48 hours or (c) 100 mg/kg or greater per 24-hour period for the preceding 72 hours.
2. Patients 6 years old or older and they have ingested either (a) at least 10 g or 200 mg/kg (whichever is less) over a single 24-hour period or (b) 6 g or 100 mg/kg (whichever is less) per day for the preceding 2 days.
3. Patients who are malnourished, fasting, or taking an agent known to induce CYP450 2E1 (e.g., isoniazid), who have ingested more than 4 g or 100 mg/kg (whichever is less) (7).

Patients presenting with a history of ingesting excess amounts of APAP over a period of time that meet the criteria outlined above should be treated with NAC if their plasma APAP concentration is $\leq$20 μg/mL or if there hepatic transaminases are elevated (unless these are known to be chronic). Treatment should be continued until the plasma APAP level is $<$15 μg/mL and transaminases are clearly falling.

Urinary organic acid screening may detect 5-oxopropline in patients with an unexpected high anion-gap metabolic acidosis. Future testing may rely on biomarkers: (1) microRNA-122 (which has high hepatic specificity), (2) high mobility group box-1 (a marker of apoptosis), and (3) keratin 18 (a marker of necrosis, or if measured as the caspase-cleaved molecule, it is a marker of

apoptosis) which have been shown to be highly sensitive for the prediction of hepatic injury and are elevated before transaminases rise (8).

KEY TESTING

- A plasma APAP concentration should be obtained on all overdoses, regardless of the patient's history of taking, or not taking, APAP
- LFTs and a plasma APAP concentration in patients who have been taking excessive therapeutic doses

ED MANAGEMENT

Advanced life-support measures should be provided if necessary (e.g., for coingested agents). Intravenous fluids may be required for patients with vomiting and dehydration. Treatment of acute APAP overdose is directed toward preventing absorption and administering NAC when indicated. The efficacy of activated charcoal (AC) for altering outcome is not known but there is evidence that early administration of a single dose of AC given within 2 hours after ingestion may decrease measured plasma APAP concentrations (9), the single metric relied on for the determination of the need for therapy in most cases (4). Beyond this time frame, there is no indication for the use of AC. Gastric lavage should not be used (10).

Patients with a potentially toxic plasma APAP concentration should receive NAC (3), which is metabolized to the amino acid cysteine, a precursor of glutathione. NAC also enhances APAP sulfation, potentially leaving less APAP available to the hepatic P450 system (see Fig. 302.1). NAC is almost 100% effective in preventing APAP toxicity if it is started within 8 hours of the ingestion, regardless of the plasma APAP concentration (3). Delay in starting therapy beyond this time results in a progressive diminution of its efficacy (3,11). If a plasma APAP concentration is unavailable within 8 hours after ingestion, a history (or suspicion) of APAP overdose is sufficient to warrant starting NAC therapy until the plasma APAP levels are known. If APAP is present and the time of ingestion is

unknown, or LFTs are abnormal as a possible result of APAP poisoning, NAC therapy should be instituted regardless of the APAP level.

Two protocols are now used for the treatment of APAP overdose (Table 302.3). For both, it is necessary to treat patients with NAC until plasma APAP concentrations are undetectable, transaminase levels are normal or falling, and PT/INR are normalizing. The duration of NAC therapy using these criteria is frequently <24 hours. In most cases, oral and intravenous routes of administration have equal efficacy (11).

TABLE 302.3
US FDA-Approved Protocols for N-Acetylcysteine Administration

Route of Administration	Loading Dose (mg/kg)	Subsequent Doses	Comments
Oral	140	70 mg/kg q4h	Although this is approved as a 72-hr protocol in most instances, it is stopped early; see text for suggested stopping criteria
Intravenous	150	50 mg/kg over 4 hrs, followed by 100 mg/kg over 16 hrs	Although this is approved as a 20-hr protocol, often it is stopped early; see text for suggested stopping criteria

Intravenous NAC was in widespread use even before its approval for use in 2004 and was also the standard therapy outside the United States. Although NAC given intravenously is easier to administer than the oral preparation, IV administration may be associated with anaphylactoid reactions (primarily itching and rash but also bronchospasm and hypotension). Anaphylactoid reactions are more common when NAC is administered by the IV route. These are generally self-limiting and generally not life-threatening. If serious reactions occur during IV therapy, further NAC treatment can be

given orally. However, if the reaction was minor, or if it is infeasible to use the oral route, it is very reasonable, and common, to continue with IV dosing at a slower infusion rate. The likelihood of such anaphylactoid reactions appears to be inversely proportional to the plasma APAP concentration and may be related to the rate of NAC infusion.

The major practical error with continuous IV infusion of NAC occurs when a patient receives the loading dose in the emergency department (ED) but the maintenance infusion is delayed for some period, often because the patient is being transferred to the ward. Although there is inadequate literature addressing this specific circumstance, based on NAC's 5.6 hour half-life, the author recommends that the entire IV loading dose be re-administered prior to starting the maintenance infusion if more than 5.5 hours has passed since the end of the loading dose.

Giving oral NAC can be challenging because it tastes and smells like rotten eggs and is poorly tolerated. NAC is available as the mucolytic agent Mucomyst® in a 10% or 20% solution. Before administration, it can be diluted to 5% in a soft drink to increase its palatability. It is also helpful to have the patient drink it through a straw from a closed container to prevent the unpleasant odor from causing gagging or emesis. Adding ice is helpful as it decreases the vapor pressure, and therefore the odor, of NAC. Emesis after NAC ingestion is common; the dose should be repeated in full if emesis occurs within an hour of the dose. Standard antiemetics such as metoclopramide (Reglan; 0.1 to 1.0 mg/kg), promethazine (Phenergan; 12.5 to 25 mg), or the 5HT3 antagonist dolasetron (Anzemet; 0.35 mg/kg up to 12.5 mg) may be given and repeated as necessary. Dolasetron may increase the QT interval and thus should be used with caution in patients with cardiac conduction abnormalities, hypokalemia, or hypomagnesemia. It may be best to avoid granisetron and ondansetron because of their association with hepatotoxicity. If emesis continues, IV instead of oral NAC administration can assure adequate and timely therapy.

Infants and small children are dosed with the same dose (in mg/kg) of NAC, however, it is administered in a smaller volume.

Weight-based dosing instructions are provided with the package insert. APAP crosses the placenta, so when a pregnant patient overdoses on APAP, fetal hepatotoxicity is possible. However, NAC also appears to cross the placenta. If spontaneous delivery occurs while the mother is being treated, NAC may be given to the newborn. However, the necessity for NAC administration to neonates has not been established because their immature P450 system may not produce significant quantities of NAPQI.

The management of patients with APAP-induced hepatic or renal failure consists of NAC and supportive care. Intravenous NAC is efficacious in patients with FHF (12). With a first pass effect, the liver may receive a greater dose of NAC when given orally, however, there are no clinical trials supporting the use of oral NAC in FHF. Patients who appear to have FHF may be candidates for transplantation. However, transplantation should not be done simply on the basis of elevated transaminases, because this does not necessarily portend a poor prognosis. The most commonly used transplantation criteria are given in Table 302.4.

TABLE 302.4
Transplantation Criteria for Patients with APAP-Induced Fulminant Hepatic Failure

Arterial pH <7.25–7.30 after adequate fluid resuscitation OR all of the following:
Prothrombin time of >100–180 sec, AND
Serum creatinine >3.4 mg/dL, AND
Grade III–IV encephalopathy

In contrast, low-risk patients can be treated safely in an ED-based observation unit. Patients can be classified as low risk if their ALT is normal and they do not have significant co-ingestants or comorbidities.

CRITICAL INTERVENTIONS

- Obtain a plasma APAP concentration on all patients with a known or suspected drug overdose or hepatotoxicity of unknown cause.

- Administer NAC if the APAP concentration is potentially toxic by the nomogram, if APAP is present and the time of an acute overdose is unknown, or if the APAP concentration is ≤ 10 μg/mL or hepatic transaminases are abnormal after chronic excessive dosing.
- Administer the initial dose of NAC within 8 hours of ingestion.

DISPOSITION

Any patient who has a potentially toxic APAP level by the nomogram requires treatment. Patients who present more than 24 hours after acute APAP ingestion or who have taken repeated supratherapeutic doses and have abnormal LFTs, or plasma APAP concentrations ≤ 20 μg/mL receive NAC therapy. All intentional overdose patients should undergo a psychiatric evaluation before discharge.

Common Pitfalls

- Failing to consider an occult APAP overdose in patients with intentional overdose, chronic pain, or unexplained elevation of hepatic transaminases.
- Starting the loading dose of the IV protocol in the ED without assuring the start of the maintenance doses as soon as the loading dose is completed.

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CHAPTER 303
Salicylates

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In ancient times, Hippocrates treated fever and pain with willow bark. Its active ingredient, salicin, would be extracted in 1829 to derive the salicylates (1). In 2011, American poison centers reported 39 deaths from ~30,000 cases involving salicylates (2); however, this is likely an underestimate of true salicylate exposure. There are many sources of salicylate in over-the-counter products and complementary medicine, making it highly accessible to the unwitting consumer (Table 303.1) (2,3). Additionally, salicylate poisoning is misdiagnosed and mistreated with considerable frequency. In-hospital mortality increases threefold if the diagnosis of salicylate poisoning is delayed and not made in the emergency department (1).

TABLE 303.1
Nonaspirin Sources of Salicylate

Formulation (Brand Name)	Percentage of Salicylate
Aspirin	75
Bismuth subsalicylate (Pepto-Bismol)	37
Choline and magnesium salicylate (Trilisate)	76
Choline salicylate (Arthropan)	56
Homomenthyl salicylate (sunscreen)	51
Magnesium salicylate (Doan, Magan)	90
Methyl salicylate (oil of wintergreen)	89
Salicylic acid (topical keratolytic)	100
Salicylsalicylic acid (Disalcid, Salsalate)	96
Sodium salicylate (Pabalate)	84

eTABLE 303.1
Elimination of a Single Dose of Salicylic Acid

Pathway	Product(s)	Percentage
Conjugation with glycine	Salicyluric acid	75[a]
Conjugation with glucuronic acid	Salicyl phenolic glucuronide	10[a]
	Salycylacyl glucuronide	5
Oxidation (hydroxylation)	Gentisic acid	1
Urinary excretion	Salicylic acid	10

[a]Saturable pathways.

Salicylates are classified into two groups: (1) phenolic esters (aspirin) and (2) carboxylic acid esters (methyl salicylate). The clinical presentations of overdose are similar though the absorption and potency differ. Aspirin is available in tablet, capsule, and suppository formulations, often over-the-counter and in combination with prescription anticholinergic, antihistamine, muscle-relaxing, and narcotic agents (2). The recommended analgesic, anti-inflammatory, and antipyretic dose is 10 to 15 mg/kg every 4 to 6 hours, not to exceed 80 mg/kg/d. Aspirin acts by irreversibly inhibiting cyclo-oxygenase (COX), also known as prostaglandin G/H synthase, which converts arachidonic acid to prostaglandins and thromboxanes. Analgesic, anti-inflammatory, and antipyretic effects result from inhibition of the COX-2 isoform, which is induced by a variety of inflammatory mediators and suppressed by glucocorticoids. Inhibition of prostacyclin synthesis and resulting accumulation of lipoxygenase causes increased alveolar membrane permeability and pulmonary edema (3). Gastric inflammation and ulceration, decreased renal blood flow, and glomerular filtration are mediated primarily by the COX-1 isoform, present in platelets, endothelium, gastric mucosa, and the kidney. Much lower dose (e.g., 80 mg/d) is needed to inhibit platelet aggregation (3), prolonging the bleeding time for up to 1.5 weeks. Prothrombin time may also be prolonged due to decreased synthesis of clotting factors VII, IX and X.

Aspirin is a weak acid (pK_a 3.5) and because it is mostly nonionized at gastric pH (4), absorption primarily occurs in the small intestine, where it is rapidly hydrolyzed by plasma esterases to

the active metabolite salicylic acid. Pharmacologic effects begin within 30 minutes of ingestion, peak in 1 to 2 hours, and last for about 4 hours. High therapeutic levels are achieved only with chronic dosing. Salicylic acid is extensively bound to serum proteins at low or therapeutic levels and has low protein binding at higher concentrations. High protein binding and predominance of the ionized form results in a small volume of distribution (0.2 L/kg). It is primarily eliminated by hepatic metabolism to inactive metabolites that are excreted in the urine, with a half-life of 2 to 3 hours (eTable 303.1). Salicylate readily crosses the placenta and enters breast milk, but fetal or infant elimination may be prolonged due to immature metabolism and clearance. Liver and renal failure patients have inefficient aspirin elimination as well.

Even though significant clinical and/or laboratory evidence of toxicity is not evident, salicylate levels may be quite high within the first 18 hours of an acute overdose. Conversely, minimally elevated or even therapeutic salicylate levels may be seen with severe poisoning after chronic overdose or late presentations of acute overdose (5). Delayed toxicity may result from pharmacobezoar formation or salicylate-induced pylorospasm. Hence, the severity of poisoning is based on clinical and metabolic findings, not on the salicylate level (1,5). Salicylate poisoning may occur with topical (skin or gum) application of methyl salicylate or salicylic acid, as well as in neonates exposed to therapeutic doses of aspirin and breast-fed infants.

The two main pathways of hepatic metabolism (conjugation; see eTable 303.1) become saturated when salicylate levels are elevated and elimination moves from first-order (proportional to the level) to zero-order (constant) kinetics (6). Hence, with chronic dosing, the salicylate “half-life” increases to 6 to 12 hours; small increases in dose causes proportionately greater increases in serum and tissue salicylate levels, facilitating chronic salicylate toxicity. For the same reason, the salicylate “half-life” may triple after a large acute overdose.

When hepatic metabolism becomes saturated, urinary excretion becomes the major route of salicylate elimination (6). The amount

of excreted salicylate depends on the balance between glomerular filtration of nonionized salicylate, active proximal tubular secretion of ionized salicylate, and passive distal tubular reabsorption of nonionized drug. Augmenting urine flow increases glomerular filtration and tubular secretion while decreasing reabsorption (1). Raising the urine pH decreases reabsorption by converting urinary salicylate to the ionized, nondiffusible form (ion trapping) (4). Raising the serum pH also increases the ionized fraction and limits tissue distribution. Alkaline diuresis increases the renal elimination of salicylate by a factor of 20 or more (1). Conversely, low urine output and pH, which may occur with fever, dehydration, and aciduria, decreases salicylate excretion.

The mechanisms underlying salicylate poisoning are complex and self-perpetuating. When salicylate concentrations exceed therapeutic levels, direct stimulation of the medullary chemoreceptor trigger zone and respiratory center causes vomiting and hyperventilation (respiratory alkalosis), respectively (1). Vomiting may occur shortly after salicylate ingestion as a consequence of direct gastric irritation, and increased carbon dioxide production may contribute to respiratory stimulation. These effects result in dehydration, not only from insensible fluid losses, but also from the bicarbonate diuresis that occurs as a compensatory response to hyperventilation-induced alkalemia (1). Because sodium and potassium are excreted with bicarbonate, there is depletion of these electrolytes (3). Alkalosis may also cause functional hypocalcemia (decreased ionized calcium) with cardiac irritability, tetany (7), and seizures.

As toxicity progresses, the accumulation of intracellular salicylate causes uncoupling of mitochondrial oxidative phosphorylation, inhibition of Krebs cycle enzymes (aminotransferases and dehydrogenases) and amino acid metabolism, and stimulated gluconeogenesis, glycolysis, and lipid metabolism (1,3). These derangements result in increased but ineffective metabolism, with increased body temperature, increased glucose, lipid, and oxygen consumption, and increased amino acid, carbon dioxide, glucose, ketoacid (acetoacetic and β-hydroxybutyric), and lactic and pyruvic acid production. The accumulation of these organic acids, with a

small additional contribution from salicylic acid and its metabolites, leads to an increased anion-gap metabolic acidosis (1). The associated diaphoresis, fever, and osmotic diuresis cause further electrolyte and fluid losses and consequent dehydration (6,7). The renal excretion of organic acids results in aciduria, preventing elimination.

When high salicylate levels are sustained, progressive metabolic derangements and increasing levels of organic acids may cause increased pulmonary capillary permeability, central nervous system (CNS) and respiratory depression, cerebral and pulmonary edema, cardiovascular collapse, and acute renal failure (acute tubular necrosis) (1,3,8,9).

CLINICAL PRESENTATION

Most aspirin toxicity presents after a (1) large acute overdose or (2) after multiple, often inadvertent chronic dosing errors. Mild salicylate poisoning is characterized by respiratory alkalosis (Table 303.2). It typically develops 3 to 8 hours after acute overdose but can occur days after chronic overdose (3). Levels approximate 40 to 80 mg/dL acutely but are lower in chronic poisoning and may be 20 to 30 mg/dL (4). Patients may have nausea, vomiting, abdominal pain, headache, hearing loss, tinnitus (may occur at therapeutic levels), tachypnea and/or hyperpnea, ataxia, dizziness, agitation, and lethargy (1). Mild to moderate dehydration is invariably present. Minor shifts in serum glucose, potassium, and sodium levels are common, but blood urea nitrogen (BUN), creatinine, sodium, and potassium levels often remain normal despite total body fluid and electrolyte deficits.

TABLE 303.2
Stages of Salicylate Poisoning

Stage/Severity	Plasma pH	Urine pH
Early/mild	>7.4	>6
Intermediate/moderate	≥7.4	<6
Late/severe	<7.4	<6

Moderate poisoning, usually associated with levels of 80 to 100 mg/dL acutely or 30 to 40 mg/dL in a chronic case (4), is characterized by metabolic acidosis with respiratory alkalosis, alkalemia, and "paradoxical" aciduria (see Table 303.2). It occurs 6 to 18 hours after an acute overdose and days after chronic overdose. Gastrointestinal (GI) effects persist, and dehydration and neurologic symptoms become more pronounced. Fever, asterixis, diaphoresis, deafness, pallor, confusion, slurred speech, disorientation, hallucinations, tachycardia, tachypnea, and mild or orthostatic hypotension may be present (1). Although patients may appear agitated and combative, it is important not to blunt their respiratory drive with sedative agents, as this could worsen their acidemia (9). Leukocytosis, thrombocytopenia, increased or decreased glucose and sodium levels, hypokalemia, hypocalcemia, and increased BUN, creatinine, ketone, and lactate levels may be seen on laboratory evaluation.

Severe acute salicylate poisoning, associated with levels >100 mg/dL acutely or >40 mg/d in a chronic overdose, is dangerous (4), and is characterized by an increased anion-gap metabolic acidosis, acidemia, and aciduria (see Table 303.2). It usually develops 12 to 24 hours after acute overdose and longer after chronic overdose. Hyperventilation (respiratory alkalosis) or hypoventilation (respiratory acidosis) and hypoxemia may be present. Other manifestations include coma, seizures, cerebral edema, papilledema, respiratory depression, hypothermia or hyperthermia, hypotension, pulmonary edema, congestive heart failure, dysrhythmias, and profound dehydration with oliguria (1,3). The chest radiograph may show noncardiogenic pulmonary edema, and brain CT scan may reveal cerebral edema. Electrocardiographic abnormalities may result from direct cardiotoxicity, electrolyte

abnormalities, or co-ingestants. Sinus tachycardia is common. Asystole is the most common cause of cardiac arrest, but ventricular tachycardia and ventricular fibrillation may also occur.

Pediatric poisonings tend to advance faster than those in adults, whereas adults are more prone to pulmonary complications (1). Morbidity is higher when the diagnosis is delayed and with chronic more than acute poisoning. Although the overall mortality is $<0.01\%$, fatality rates of 15% to 50% occur with severe poisoning. Some neurologic dysfunction may persist in those who recover from severe poisoning.

DIFFERENTIAL DIAGNOSIS

Increased anion-gap metabolic acidosis is seen in only 15% to 20% of adults with salicylate poisoning. Metabolic acidosis with respiratory alkalosis is seen in 50% to 61% of poisoned adults. Respiratory alkalosis is the sole acid–base disturbance in 20% to 25%, and a combined respiratory and metabolic acidosis is seen in 5%. Metabolic acidosis is more common and respiratory alkalosis is less common or absent in children, in patients with large acute ingestions, chronic intoxication, and delayed treatment.

Salicylate poisoning should be considered in any patient with an unexplained anion-gap acidosis. The diagnosis is initially missed in 25% to 60% of patients, particularly those chronically taking the drug. These patients are often elderly, take nonaspirin salicylates, and have underlying medical problems (3). Patients with chronic overdoses, classically present confused or unresponsive with increased temperature, dehydration, hypotension metabolic acidosis, and respiratory alkalosis. Often, these signs are mistaken for sepsis but signs and symptoms of salicylate poisoning have been mistakenly attributed to anxiety, cardiopulmonary disease, cerebrovascular disease, chronic obstructive pulmonary disease, dementia, encephalopathy, alcohol intoxication, ketoacidosis, withdrawal, viral encephalitis, meningitis, pancreatitis, psychiatric disorders, and sepsis (4). These patients require a thorough workup for other causes of altered mental status.

Salicylate poisoning in children may be indistinguishable from Reye syndrome. A low (subtherapeutic) cerebrospinal fluid salicylate level, high serum alanine, glutamine, and lysine levels, and fatty infiltration of the liver indicate Reye syndrome rather than salicylate poisoning. Salicylate poisoning may also be confused with inborn errors of metabolism as well.

Other causes of anion-gap metabolic acidosis include toxic alcohols, ketosis, and lactic acidosis associated with hypoxia, seizures, or shock. Salicylate poisoning may be ruled out in a patient who has persistently normal arterial blood gas (ABG) and serum electrolytes but is symptomatic many hours after an unknown overdose.

ED EVALUATION

The history should include the time(s), amount(s), and formulation of salicylate ingested. The physical examination should focus on vital signs, neurologic status, and cardiorespiratory function. Ensuring accurate measurement of the respiratory rate, temperature, and degree of dehydration is essential (1). Papilledema, peritoneal signs, and occult blood in vomitus and stool should be identified.

Aspirin products are frequently confused with acetaminophen and vice versa (2). Unless the product is available for identification or a third party confirms history, serum levels of both drugs should be obtained when the ingestion of either is reported, particularly in those with intentional overdose.

Because of delayed and prolonged absorption, if salicylate levels are elevated, they should be checked repeatedly until levels are declining. A nontoxic salicylate level soon after ingestion does not rule out a significant overdose, particularly with enteric-coated or sustained-release formulations (4). If the patient is symptomatic or the salicylate level is elevated, then testing should include ABG analysis, serum electrolytes, glucose, BUN, creatinine, and urinalysis. If acid–base abnormalities are present, further evaluation should include serum calcium, magnesium, ketone, and lactate levels, liver function tests, complete blood count, coagulation

profile, ECG, and chest radiograph (1,3). If levels continue to rise, repeat metabolic reevaluation is necessary.

KEY TESTING

- Serum salicylate
- Acetaminophen level for intentional ingestions
- Blood gas analysis
- Serum electrolytes
- Urinalysis and urine pH
- Electrocardiogram
- Chest radiography for possible pulmonary edema
- Additional tests: serum calcium, magnesium, lactate, liver enzymes, and head CT for decreased level of consciousness and possible cerebral edema

ED MANAGEMENT

Patients with salicylate poisoning may present after acute ingestion or have chronic exposure leading to more subtle presentations. In either case, advanced life-support measures should be instituted when indicated. When patients require endotracheal intubation, maintaining hyperventilation before, during, and afterwards is critical because losing the respiratory alkalosis worsens acidemia and enhances toxicity. Since artificial ventilation is associated with increased airway resistance and dead space, mechanical hyperventilation will be less effective than spontaneous hyperventilation (1,5). Therefore, sodium bicarbonate ($NaHCO_3$), 1 to 2 mEq/kg over 5 minutes, is suggested at the time of induction for patients with acidemia or a pCO_2 less than 20 mm Hg. ABGs should be checked after intubation and after sodium bicarbonate therapy.

Because CNS hypoglycemia may occur despite a normal serum glucose in patients with salicylate poisoning, D50 (50 mL) should be given to those with altered mental status, unless the glucose level is elevated (1). Seizures should be treated with benzodiazepines and barbiturates and supplemental glucose. It is also advisable to

administer $NaHCO_3$ (0.5 mEq/kg IV over 2 to 5 minutes) as acidemia worsens after a seizure. Patients who are unresponsive or postictal may have cerebral edema and may benefit from head elevation, hyperventilation, and possibly mannitol, furosemide, and dexamethasone. Diuretics should be used cautiously since patients often have hypovolemia.

The degree of dehydration is often underestimated. Volume deficits of 2, 4, and 6 L (20, 40, and 60 mL/kg in children) are typical with mild, moderate, and severe poisoning, respectively. IV fluid can be given as 5% dextrose solution with three 50-mL ampules of $NaHCO_3$ added to each liter (1). With hypernatremia, a more hypotonic solution should be used. The use of a dextrose-containing solution is important because of the potential for occult CNS hypoglycemia. Cerebral or pulmonary edema should be monitored closely in those with renal dysfunction. Monitoring urine output is helpful for assessing rehydration.

Central venous pressure monitoring or ultrasonography of inferior vena cava collapse may guide treatment for hypotension or oliguria, especially if there is evidence of heart failure or pulmonary edema. Congestive heart failure should be treated accordingly, but patients with noncardiac pulmonary edema should be treated with positive end-expiratory pressure rather than diuretics. Preventing increased acidemia by maintaining hyperventilation is critical in patients with compromised pulmonary function (1,5).

Hyperthermia should be treated with cooling blankets, ice packs, and evaporative methods. Acetaminophen and NSAIDs should be avoided. The presence of peritoneal signs necessitates surgical evaluation. Vitamin K should be given for coagulation abnormalities. Underlying metabolic derangements should be corrected. Insulin is not needed for nondiabetics with hyperglycemia and may be dangerous, particularly if there is coexisting hypokalemia. Hyperkalemia does not usually require specific therapy and will likely resolve with fluid administration and correction of acidosis. Paper-bag breathing or sedatives for the

treatment of agitation is not recommended because an increase in the pCO_2 can worsen concomitant acidemia.

ACUTE SALICYLATE POISONING CONSIDERATIONS

GI decontamination with single-dose activated charcoal is recommended for patients with accidental ingestions of >150 mg/kg and in all patients with intentional overdoses. Although early activated charcoal decontamination is ideal, late administration may still prevent absorption since salicylates can form concretions. If the amount ingested is known, the dose of activated charcoal is a 10:1 ratio (activated charcoal:salicylate) (5). For unknown ingested quantities, children may be given 10 to 25 g and adults may be given 50 to 100 g.

Multidose activated charcoal (MDAC) may not only decrease continued absorption, especially when salicylate levels continue to rise, but may also enhance elimination. Although not associated with a mortality benefit, MDAC may shorten the salicylate half-life after acute overdose and is recommended for those with a salicylate level >30 mg/dL, when metabolic pathways are saturated and toxicity is present (6). The optimal dosing and frequency for MDAC administration is controversial, though a reasonable approach is 50 g orally every 2 to 4 hours as long as the patient is hemodynamically stable with bowel sounds and the mental status to tolerate it (1).

Orogastric lavage may help decontaminate large salicylate ingestions, but the risks associated with this procedure are thought to usually outweigh the benefits (1,8). Whole-bowel irrigation is popular for patients with large ingestions of enteric-coated or sustained-release preparations (1), however its efficacy is unproven. Serial salicylate levels should be obtained to assess the efficacy of GI decontamination. Decontamination of the skin is warranted for exposure to topical salicylates (1).

Other methods of enhanced elimination include urinary alkalization and dialysis. Urinary alkalization may shorten the salicylate half-life to 6 to 12 hours (7) in acute overdose with

salicylate levels <70 mg/d by decreasing tubular salicylate reabsorption (7). Indications are the same as those for MDAC. The goal is a urine pH of ≤ 7.5 with a brisk (3 to 6 mL/kg/hr) urine output. Although counterintuitive, this is still indicated during early or mild intoxication, when the serum and urine pH are both alkaline, because respiratory alkalosis with compensatory renal bicarbonate and fluid excretion account for these findings. If left untreated, this can lead to dehydration and more severe metabolic acidosis later. Urinary alkalization is ineffective if hypokalemia is present, which is thought to occur when hydrogen ions shift into cells and potassium shifts out. Potassium supplementation is usually necessary because patients are commonly potassium-depleted, especially in the presence of acidemia (approximately 0.6 mEq/L for each 0.1 U decrease in pH). As a general guideline, 10 to 20 mEq of potassium will be necessary for each 50 mEq of $NaHCO_3$ administered. Acetazolamide should not be used because it can cause acidemia by increasing the ionized drug fraction and CNS salicylate levels (4).

Complications of $NaHCO_3$ administration include excessive alkalemia, hypocalcemia, hypokalemia, hypernatremia, and fluid overload with cerebral and pulmonary edema, particularly in the elderly and with severe poisoning (3). Cardiac monitoring, frequent evaluation of vital signs, mental status, cardiorespiratory function, urine output, and laboratory parameters (ABG analysis, serum calcium, and electrolytes) should be performed during and after such therapy. Relative contraindications for $NaHCO_3$ include oliguric renal failure, congestive heart failure, and cerebral or pulmonary edema. In these situations there should be a lower threshold for the initiation of hemodialysis; in fact, it is likely that hemodialysis is underutilized in salicylate poisoning (4,6,8).

Hemodialysis may shorten the salicylate half-life to 2 to 3 hours. Peritoneal dialysis, exchange transfusion, and other methods of extracorporeal removal are less effective and should be used only if hemodialysis is unavailable, contraindicated, or technically impossible (e.g., in infants or in patients with active or recent

bleeding complications) (4). Clinical indications for hemodialysis include confusion, disorientation, coma, seizures, cerebral or pulmonary edema, renal failure, and clinical or metabolic deterioration despite other therapies (6,8). Patients with serum salicylate levels greater than 100 mg/dL in acute overdose (5) may require hemodialysis regardless of symptoms. Acidemia and body temperature $>38^{\circ}C$ are associated with high mortality and should prompt consideration for hemodialysis. Toxicity that progresses or fails to improve with other treatment (e.g., those with comorbidities or limited reserve) should be considered for hemodialysis even if salicylate levels are not markedly elevated (1).

In contrast to the usual dialysis patient with chronic renal failure, those with salicylate poisoning are often hemodynamically compromised because of underestimated or undertreated dehydration and cardiac dysfunction. As such, they are prone to cardiovascular decompensation on initiation of hemodialysis (5). Hypotension is common and ventricular dysrhythmias are considered premorbid events. Priming the dialysis circuit with normal saline and administering a fluid bolus prior to and during dialysis are recommended as prophylactic measures, along with correction of volume deficits and metabolic abnormalities. The dialysate bath should contain bicarbonate (32 mEq/L) to treat and prevent acidemia and to enhance the removal of salicylate.

Clinical improvement with decreasing salicylate levels is the endpoint of therapy. Once the salicylate level has reached 30 mg/dL, first-order kinetics resume. In patients with very high levels or ongoing absorption from a gastric bezoar, levels may rise after an initial decline (8). Repeat levels ensure that toxicity does not recur after dialysis.

CHRONIC SALICYLATE POISONING CONSIDERATIONS

GI decontamination will not benefit the patient who presents with chronic salicylate exposure. The slower rise in serum salicylate level has allowed the drug to affect its target organ, the brain. Unlike acute intoxication where the tissue levels lag behind serum levels, in

chronic exposure the tissue level will be in equilibrium with serum levels so toxicity occurs with lower serum levels. Seizures are common with serum levels of 40 mg/dL. Urinary alkalization is of little benefit since serum salicylate concentrations are relatively low, urine levels are low, and many of these patients have pulmonary or cerebral edema that may preclude large doses of bicarbonate. Hemodialysis is much more important in these patients, as their mental status is a better marker of toxicity than their serum levels. Hemodialysis is warranted in chronically exposed patients with serum salicylate levels >60 mg/dL, regardless of symptomatology.

CRITICAL INTERVENTIONS

- Maintain hyperventilation during and after endotracheal intubation.
- In patients with acidemia, administer $NaHCO_3$ prior to intubation.
- Replace volume deficits with intravenous fluids containing dextrose and saline.
- Alkalinize the urine with intravenous $NaHCO_3$ and correct hypokalemia.
- Perform frequent clinical and laboratory reevaluation and obtain serial salicylate levels.
- Consider hemodialysis for patients with confusion, seizures, uncorrected acidosis, cerebral edema, pulmonary edema, acute level >100 mg/dL and chronic level >60 mg/dL, progressive deterioration despite other treatments or early evidence of volume overload.
- Give activated charcoal in large acute overdose.

DISPOSITION

Patients with only tinnitus and GI symptoms and easily corrected acidosis after acute overdose can often be treated in an observation setting if 1) the peak salicylate level is <60 mg/dL after aggressive treatment, and 2) the level is decreasing. Patients with chronic poisoning, higher levels, underlying medical problems, and

moderate or severe toxicity should be admitted to an intensive care unit. A nephrologist should be alerted about severe poisonings for hemodialysis. Patients with severe poisoning or moderate poisoning with high (or rising) salicylate levels should be transferred to a facility in which hemodialysis is available.

Common Pitfalls

- Failure to consider salicylate ingestion and obtain a salicylate level for unexplained acidemia, particularly with altered mental status.
- Failure to obtain salicylate and acetaminophen levels in those reporting overdose of either.
- Failure to obtain repeat salicylate levels to detect delayed absorption.
- Failure to suspect chronic salicylate poisoning in ill and/or elderly patients..
- Failure to monitor for complications of salicylate poisoning and its treatment.
- Overvigorous bicarbonate or saline contributing to pulmonary or cerebral edema.
- Basing treatment only on drug levels instead of clinical and laboratory findings.
- Failure to match pre-intubation and post-intubation tidal volume, resulting in severe acidemia.

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CHAPTER 304

Nonsteroidal Anti-Inflammatory Drugs

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of agents that have anti-inflammatory, analgesic, and antipyretic activity. There are a variety of NSAIDs, which can be classified by target specificity and structure (Table 304.1). With widespread use and over-the-counter availability, it is not surprising that NSAIDs constitute one of the most common medications encountered in intentional overdose. Three-fourths of these ingestions involve ibuprofen, the first nonsalicylate NSAID to be approved for over-the-counter use in the United States. Despite their frequency, most NSAID overdoses result in minimal symptoms, and death is rare. Major complications such as gastrointestinal (GI) bleeding during therapeutic use are a much greater health problem.

TABLE 304.1
Pharmacokinetics of NSAIDs after Therapeutic Doses

Drug	Brand Name	Time to Peak Level (hrs)	Half-life (hrs)	Maximum Daily Adult Dose (mg)
Nonselective COX inhibitors				
Acetic acids				
Diclofenac sodium	Voltaren	2–3	1.2–1.8	225
Diclofenac potassium	Cataflam	0.3–2.0	1.2–1.8	150
Etodolac[a]	Lodine	1–2	7.3	1,200
Indomethacin[a–c]	Indocin	1–2	4.5–6.0	200
Ketorolac[c]	Toradol	0.5–1.0	2.4–8.6	IM 120; PO 40
Nabumetone[d]	Relafen	2.5–4.0	22–30	2,000
Sulindac[e]	Clinoril	1–2	7.8	400
Tolmetin	Tolectin	0.5–1.0	1.1–1.5	2,000
Fenamic acids				
Mefenamic acid	Ponstel	1–3	2–4	1,000
Meclofenamate	Meclomen	0.5–2.0	2	400
Oxicams				
Meloxicam[f]	Mobicox	5–6	20	22.5
Piroxicam	Feldene	3–5	30–60	20
Propionic acids				
Fenoprofen	Nalfon	1–2	2–3	3,200
Flurbiprofen	Ansaid, etc.	1–2	3–4	200
Ibuprofen[b]	Motrin, Advil, Nuprin	0.5–2.0	1.8–2.5	3,200
Ketoprofen[a]	Orudis, etc.	0.5–2.0	1.5–4.0	300
Naproxen[a,b]	Naprosyn, Aleve	2–4	12–15	1,500
Naproxen sodium[a]	Anaprox	1–2	12–15	1,375
Oxaprozin	Daypro	3–5	42–50	1,800
Carprofen	Rimadyl			1,200
Pyrazolones				
Oxyphenbutazone	Oxalid			27–72
Phenylbutazone	Azolid, Butazolidin	1–4	50–100	600
Salicylates				
Acetylsalicylic acid	Aspirin, etc.	1–2	2–30	4,000
Diflunisal	Dolobid	1–2	5–20	1,500
Selective COX-2 inhibitors				
Celecoxib	Celebrex	2–4	11	400
Rofecoxib	Vioxx	2–3	17	50
Parecoxib	Dynastat	2 (IM)	8	IV/IM 40
Valdecoxib	Bextra	8		40
Etoricoxib	Arcoxia		22	120

[a]Available as a sustained-release product.
[b]Available as a liquid formulation.
[c]Also available as parenteral formulation.
[d]Prodrug metabolized to 6-methoxy-2-naphthylacetic acid.
[e]Prodrug metabolized to sulindac sulfide (half-life 16.4 hours).
[f]Preferential COX-2 inhibitor but selectivity lost at therapeutic doses.

The primary pharmacologic effects of NSAIDs result from the inhibition of cyclooxygenase (COX), the enzyme family involved in the initial step of prostaglandin (PG) synthesis. Two isoforms, termed COX-1 (constitutive) and COX-2 (inducible), have been identified. Because the anti-inflammatory properties of NSAIDs result primarily from COX-2 inhibition, NSAIDs with selective COX-2 inhibition were developed with the promise of fewer side effects (1), but some of these agents were subsequently withdrawn due to increased cardiovascular risk. In overdose, selectivity for COX-2 may be lost, and the acute toxicity resembles that of nonselective NSAIDs.

Inhibition of COX shunts arachidonic acid to leukotrienes, at times precipitating severe allergic reactions. The adverse GI effects of gastritis and ulceration result from the inhibition of PGD_2, PGE_2, and PGF_2, which maintain the gastric mucosal barrier, and direct irritation. Acute renal failure with salt and water retention is attributed to inhibition of PGI_2 and PGE_2, which have vasodilatory and natriuretic activity in the kidney (2). The cardiovascular toxicity of the selective COX-2 agents appears to result from decreased PGI_2 in the vascular endothelium (COX-2), coupled with minimal effects on platelet thromboxane A_2 (COX-1).

Most NSAIDs are rapidly and almost completely absorbed (3). They are weak acids with pK_a values ranging from 3.5 to 5.6 and have small volumes of distribution (0.08 to 0.4 L/kg) from extensive protein binding (celecoxib, at 6 L/kg, is an exception). Elimination is primarily via hepatic CYP2 C, with subsequent renal excretion of glucuronide conjugates. As much as 50% of ketorolac and 30% of indomethacin is excreted unchanged in the urine (3). Only small quantities ($<10\%$) of other NSAIDs are excreted unchanged in the urine, limiting the efficacy of urinary alkalinization in promoting elimination. Indomethacin, sulindac, etodolac, phenylbutazone, meloxicam, and piroxicam undergo enterohepatic recirculation. The renal clearance of naproxen and oxaprozin is increased at high plasma concentrations owing to saturation of protein binding. Phenylbutazone exhibits dose-dependent Michaelis–Menten elimination. Pharmacokinetic data are summarized in Table 304.1.

Except for pyrazolones and fenamic acids, NSAIDs seldom cause serious toxicity, even in large doses (4). There is inadequate information to determine the minimum toxic or lethal dose for most NSAIDs. In a series of ibuprofen overdoses, all children who ingested <100 mg/kg remained asymptomatic, whereas those who ingested >400 mg/kg were at risk of developing significant toxicity (5). In adults, the correlation between the amount ingested and subsequent development of symptoms was poor, with those ingesting between 6 and 54 g of ibuprofen at risk for potentially serious toxicity (6). In contrast, seizures have been reported with mefenamic acid ingestions

of as little as 2.5 g in a 12-year-old child (4). Phenylbutazone has caused death with as little as 2 g in a 1-year-old child and 2.5 g in an alcoholic adult (4,7).

CLINICAL PRESENTATION

Most patients remain asymptomatic or develop only mild GI or neurologic symptoms following acute overdose. Specific signs and symptoms are summarized in Table 304.2. Death is rare and usually results from secondary complications such as aspiration or sepsis. In the absence of acute renal failure or secondary complications, full recovery can be expected within 6 to 24 hours. The elderly are more likely to develop adverse effects with therapeutic doses and toxicity with overdoses.

TABLE 304.2
Signs and Symptoms of Nonsteroidal Anti-Inflammatory Drug Overdose

Gastrointestinal: nausea, vomiting, anorexia, abdominal pain, diarrhea, gastritis, GI bleeding, occasional hepatocellular injury, rare cholestasis
Neurologic: dizziness, nystagmus, diplopia, blurred vision, headache, tinnitus, restlessness, lethargy, ataxia, confusion, coma, muscle fasciculations, seizures
Respiratory: hyperventilation, respiratory depression with cyanosis, apnea, diaphoresis
Cardiovascular: hypotension, bradycardia, occasional tachycardia, rare cardiac arrest
Renal: sodium retention and edema, proteinuria, hematuria, acute oliguric or nonoliguric renal failure
Hematologic: decreased platelet aggregation, prolongation of prothrombin time and partial thromboplastin time
Other: occasional metabolic acidosis, rare electrolyte imbalance

In contrast, the pyrazolones and fenamic acids can cause severe toxicity. Phenylbutazone and its active metabolite oxyphenbutazone can cause coma, seizures, dysrhythmias, cardiogenic shock, respiratory alkalosis, and metabolic acidosis (4,8,9). Tinnitus, deafness, and a rash may be present. Hepatic necrosis, without other symptoms, may develop 24 hours after overdose. A red discoloration

of the urine caused by the metabolite rubazonic acid may be observed. Mefenamic acid can cause muscle twitching and tonic–clonic seizures within 12 hours of ingestion (4). Respiratory and cardiac arrest may follow seizures.

Propionic and acetic acid derivatives are associated with relatively low toxicity. Of these agents, fenoprofen appears to be the most toxic (4). Metabolic acidosis after ibuprofen overdose is probably caused by high levels of the acidic parent drug and metabolites (10). Indomethacin frequently causes headaches and tinnitus, even at therapeutic doses.

After piroxicam overdose, dizziness with blurred vision and brief coma are reported (4). Because of the long elimination half-life of piroxicam, overdose symptoms can be prolonged. Multisystem toxicity (with GI, neurologic, renal, hepatic, and hematopoietic effects) was noted in a 2-year-old child who ingested 100 mg of piroxicam (11). Prolonged toxicity should be anticipated after overdose of oxaprozin and nabumetone, which also have long half-lives. NSAID plasma levels are not routinely available and are not necessary for the treatment of acute ingestion (5).

DIFFERENTIAL DIAGNOSIS

The diagnosis of NSAID overdose is made on the basis of history and the exclusion of other etiologies. The possibility of acetaminophen, colchicine, and salicylate ingestion should be considered in patients with overdose of an unknown arthritis medication or analgesic.

The central nervous system (CNS) depression that occurs with NSAID overdose is usually mild; coma unresponsive to stimulation is uncommon. Deep coma, marked hypotension, and severe respiratory depression suggest the presence of other drugs. The high anion-gap metabolic acidosis caused by ibuprofen is relatively mild and short-lived compared with that caused by salicylates, ethylene glycol, and methanol (10).

ED EVALUATION

A detailed history including available medications may provide the only clue to NSAID overdose. The amount and time of ingestion and

the onset, nature, and progression of symptoms should be noted. The physical examination should include complete vital signs, oxygen saturation measurement, and assessment of mental status and cardiorespiratory function. Evaluation for occult GI bleeding should be considered for patients with abdominal pain.

Accidental ingestions of a nontoxic dose need no laboratory testing. For symptomatic patients, those with underlying kidney dysfunction, and the elderly, a urinalysis, blood urea nitrogen (BUN) and creatinine, electrolytes and glucose, and perhaps a complete blood count (CBC) should be obtained. Etodolac may cause a false-positive urine bilirubin and a false-positive urine ketone test on dipstick. Although the time of onset of renal failure is poorly defined, urinalysis, serum BUN, and creatinine may be useful in adults who ingest >6 g of ibuprofen (5). Arterial or venous blood gases should be monitored in patients with significant mental status changes or respiratory depression. After pyrazolone overdose, liver function tests should be obtained. As with other ingestions, serum acetaminophen and possibly salicylate concentrations should be measured in patients with intentional overdose. Toxicology screens of urine and blood rarely detect or correctly identify most NSAIDs other than salicylates and are not useful.

KEY TESTING

- There are no specific tests for NSAID overdose.
- Symptomatic patients, those with underlying kidney dysfunction, and the elderly may need a urinalysis, CBC, electrolytes with anion gap, BUN, creatinine, glucose.

ED MANAGEMENT

Management consists of supportive care. The rare severely ill patient may need mechanical ventilation, especially if respiratory acidosis is present. Hypotension can be managed with intravenous crystalloids. Vasopressors are seldom necessary. Benzodiazepines should be given for seizures. Sodium bicarbonate should be given to patients with significant metabolic acidosis. GI bleeding should be treated by

standard measures. Coagulopathy can be corrected by administering fresh-frozen plasma and vitamin K_1.

Activated charcoal should be considered in patients with recent intentional overdose of more than 10 therapeutic doses, and children who present within 4 hours of accidentally ingesting more than 5 adult doses (8). Fenamic acids or pyrazolones may cause serious toxicity with even a twofold overdose, and decontamination is appropriate for all these patients. Multiple-dose activated charcoal (MDAC) therapy has not been studied with most NSAIDs. Although the elimination half-life of therapeutic doses of phenylbutazone was decreased by 30% using MDAC (12), the effectiveness of this treatment is likely to be minimal, even for NSAIDs that undergo enterohepatic recirculation. Because most NSAIDs are highly protein-bound and rapidly metabolized, diuresis or dialysis is not useful, except perhaps for severe phenylbutazone poisoning.

CRITICAL INTERVENTIONS

- Establish intravenous access, initiate cardiac monitoring, and provide supportive care as clinically indicated.
- Consider other ingestions, including acetaminophen and salicylates, in patients with intentional overdose.

DISPOSITION

Most patients will be observed for 4 to 6 hours after ingestion or until minor symptoms resolve and then are discharged (5,8). After the ingestion of fenamic acids or pyrazolones, symptomatic patients should be monitored for at least 12 hours. Patients with coma, respiratory depression, seizures, or renal failure should be admitted to a medical intensive care unit.

Patients with an abnormal urinalysis or underlying renal dysfunction should have follow-up kidney function tests. A CBC and kidney and liver function tests should be repeated 24 to 48 hours after pyrazolone overdose. Follow-up liver function tests should be obtained in symptomatic piroxicam overdose patients.

Transfer would rarely be necessary. If acute renal failure develops, a nephrologist should be consulted. Intentional ingestions should be evaluated for ongoing suicidal risk.

Common Pitfalls

- Failure to consider other ingestions in patients with significant CNS depression, metabolic acidosis, or vital sign abnormalities.
- Failure to consider acetaminophen, salicylate, or colchicine ingestion in patients who overdose on an unknown arthritis medicine.
- Failure to appreciate that phenylbutazone and mefenamic acid can cause serious toxicity after overdose.

ACKNOWLEDGMENT

The author gratefully acknowledges the contributions of Paula L. Townsend as author of this chapter in previous editions.

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CHAPTER 305

Opioids

Jerry W. Snow and R. Brent Furbee

The term *opiate* applies to naturally occurring derivatives of opium. *Opioid* originally referred only to synthetic or semisynthetic compounds that exert effects through opioid receptors but increasingly, the term *opioid* applies to both groups. *Narcotic* is an outdated term to describe the effects, used before the mechanism was known. The opium poppy, *Papaver somniferum,* is the source of naturally occurring opioids. Opium contains morphine, codeine, and thebaine, from which natural and semisynthetic opioids are derived. Papaverine (a vasodilator) and noscapine (an antitussive) are nonanalgesics found in opium. The opioid antagonists, naloxone and naltrexone, are semisynthetic derivatives of thebaine.

Opioid prescription abuse is recognized as a growing epidemic. Increased use of opioids for treatment of chronic noncancer pain increased in the 1980s. "Chronic pain" is defined by the International Association for the Study of Pain as "pain that persists beyond normal tissue healing time, which is assumed to be three months" (1). Although it appears logical, the use of hydrocodone, oxycodone, methadone, and other opioids for chronic noncancer pain has increased dramatically despite the lack of evidence supporting its effectiveness. Several epidemiologic studies indicate an increase in methadone-related deaths in the United States. This may be associated with QT_c prolongation and resultant arrhythmias (1). Sales of opioid analgesics increased fourfold between 1999 and 2010, and between 1997 and 2007 the average amount of opioids distributed to persons in the United States jumped from 96 mg of

morphine equivalents/person to 700 mg/person, an increase of over 600% (2). Diversion is also a growing concern. A 2010 National Survey on Drug Use and Health (NSDUH) showed that an estimated 22.6 million, or 8.9% of Americans, aged 12 or older, were current or past month illicit drug users (3).

Since 2003, opioid analgesic deaths have been more than from cocaine and heroin combined (2) and now account for more deaths than suicide or motor vehicle accidents (3). Hydrocodone topped all opioid prescriptions with 136.7 million prescriptions in 2011. Factors that predict drug abuse, misuse, or aberrant drug behavior include personal or family history of drug or alcohol abuse, younger age, or presence of psychiatric conditions (1). Patients who are prescribed doses of $<$100-mg morphine equivalents/day account for nearly 80% of the at-risk population, but only 20% of prescription drug overdoses. Patients receiving high doses ($>$100 mg morphine equivalent/d) or those receiving prescriptions from multiple physicians accounted for about 20% of the at-risk population, but 80% of the overdoses (2). In West Virginia, and Ohio, 25% to 66% of deaths from pharmaceutical overdoses used opioids prescribed for someone else. Opioid analgesic misuse and death are highest among men, persons aged 20 to 64 years, non-Hispanic white, and poor and rural populations as well as patients with mental illness (2).

This “epidemic” is due, in part, to changing attitudes toward pain management. In the late 1990s, state medical boards began to curtail restrictions on laws controlling the prescribing of opioids for chronic noncancer pain. New pain management guidelines such as those by the Joint Commission on the Accreditation of Health Care Organizations (JCAHO) in 2000 recognizing the “right to pain relief” encouraged physicians to be more liberal in their prescribing of opioids. Manchikanti concluded in 2012 that, “It has been speculated that in the coming years, there will likely be an extensive “postmortem” on the massive opioid treatment movement and the escalating social crisis that has accompanied it. It is universally accepted that this massive treatment movement has led to huge collateral damage in terms of diversion, misuse, and abuse of opioids” (3).

MECHANISM OF ACTION

Opioids' clinical effects are the result of complex interactions with the three primary opioid receptor types (mu, delta, and kappa). Three additional receptor types, nociception/orphanin FQ, epsilon, and zeta, are not yet well characterized in humans. The sigma receptor has been reclassified because actions mediated via this receptor are not reversed by naloxone. The mu receptor mediates the majority of clinical effects and most supraspinal analgesic effects as well as sedation and respiratory depression. Delta and kappa receptors act primarily at the spinal cord level. Euphoria is mediated by mu receptors and dysphoria by kappa receptors. These receptors are found throughout the body including the periphery, pre- and postsynaptic sites in the spinal cord, and brain to form an ascending pain transmission system and a descending initiatory system that modulates spinal cord pain transmission (4).

Upon opioid binding, G proteins are activated and use a secondary messenger system involving cyclic AMP to have several effects that produce pain inhibition through (1) blockade of calcium channels, resulting in a decrease of presynaptic neurotransmitter release, and (2) opening potassium channels, producing hyperpolarization of postsynaptic neurons and a decrease in transmission of pain (4). Alpha-2 agonists such as clonidine have some effects similar to opioid receptor binding (see Chapter 322) (5).

Opioid antagonists competitively bind to each type of the opioid receptors and reverse the clinical effect of opioids as well as altering the configuration of the receptor to decrease the availability of receptor sites. Pure antagonists (naloxone, nalmefene, and naltrexone) avidly bind to all major opioid receptor subtypes.

CLINICAL PRESENTATION

The classic opioid toxidrome includes the triad of (1) CNS depression, (2) respiratory depression, and (3) miosis. However, opioids can present with a wide range of clinical findings and atypical presentations (Table 305.1). Opioids are used through

intravenous, intramuscular, intranasal, inhalational, oral, subcutaneous, intradermal, or transdermal routes. Unintentional poisoning in addicts/recreational users typically occurs in novice users, during binging, or when an experienced user obtains an unfamiliar supply of heroin and accidentally miscalculates the dose owing to differences in purity. Intentional suicidal overdose or attempted homicide is also common.

TABLE 305.1
Atypical Presentations of Opioid Poisoning

Agent	Prominent/Atypical Feature
Propoxyphene (Darvon)	Rapid, sudden onset of opioid effects
	Seizures, psychosis (unresponsive to naloxone)
	Hypotension
	Prolongation of PR, QRS, and ventricular tachycardia
	Delayed onset of membrane-depressant effects
	Low dose is life-threatening (11 mg/kg)
	Higher doses of naloxone needed to antagonize narcotic effects
Diphenoxylate (Lomotil)	Initial anticholinergic features
	Delayed onset of opioid effects
	Children at high risk for toxicity
Fentanyl	Chest wall rigidity
	Serotonin syndrome
Meperidine (Demerol)	Mydriasis
	Prolonged half-life of metabolite
	Seizures
	Increased muscle tone; serotonin syndrome
Methadone	QT_c prolongation, torsade de pointes
Pentazocine (Talwin)	Higher doses of naloxone needed to antagonize effects
Tramadol (Ultram)	Seizures unresponsive to naloxone
	Serotonin syndrome

Children usually present with unintentional exposure although iatrogenic poisonings and dosing errors do occur. Overdose in children characteristically has a delayed onset, unexpected severe

toxicity, and prolonged effects. Children may ingest pills or apply/ingest transdermal patches (that sometimes become stuck on the roof of the mouth). Elderly patients, particularly those on opioid therapy for chronic pain control, also represent a high-risk group for unintentional poisoning. Contributing factors include comorbidities, slower metabolism, decreased renal clearance and other age-related physiologic changes, and alterations in body composition.

The onset of symptoms is nearly immediate after injection, inhalation, and nasal insufflation. Although effects are usually noted within 30 minutes of ingestion, absorption can be erratic and delayed, particularly in children and with sustained-release formulations. Lomotil (diphenoxylate and atropine) is notorious for causing delayed toxicity, perhaps because both constituents can inhibit gastrointestinal motility. The effects of transdermal medications also begin about 30 minutes after application and can develop or progress after the patch is removed. Intravenous injection and oral ingestion of fentanyl patches delivers the entire drug content of the patch at one time rather than the ongoing absorption of small aliquots of fentanyl.

Respiratory

Respiratory depression is dose-dependent following exposure to opioids, leading to decreased respiratory rate and/or tidal volumes. The mechanism involves mu2 receptors that decrease sensitivity of the medulla respiratory center to hypercapnia. Opioids also suppress the hypoxic drive of ventilation. This combination is what eventually leads to apnea, although agonist–antagonists demonstrate a ceiling effect on respiratory depression.

Acute lung injury (ALI) from opioids has been reported since the 1880s and should be considered when hypoxia persists despite adequate respiration. Patients may develop hypoxia and pulmonary crackles within minutes or hours after regaining normal ventilation. There are several theories on the mechanism: (1) attempted inspiration against a closed glottis leading to negative intrathoracic pressure resulting in fluid shifting into to alveoli is a mechanical

mechanism. In addition, (2) similar to neurogenic pulmonary edema, a sympathetic vasoactive response from catecholamines on the myocardium produces cardiogenic pulmonary edema, and (3) some feel ALI is a result of hypoxia. No single mechanism can explain all cases of opioid-induced ALI at this time. In the past, naloxone was blamed as a cause of ALI, but ALI had been clearly documented prior to the development of naloxone and is seen in fatal overdoses that never receive this antidote. In addition, pulmonary edema may not be detectable until ventilation has been restored (6).

Another complication of opioid abuse is interstitial lung disease from the injection of insoluble binding agents in oral opioid tablets such as talc, cornstarch, or cellulose. The result is microscopic pulmonary emboli and inflammation progressing to interstitial fibrosis and pulmonary hypertension. Clinically, this presents as emphysema and chronic respiratory failure. Historically, the oral opioid most frequently cited in pulmonary talcosis is pentazocine, often used in conjunction with tripelennamine or methylphenidate known as Ts (for Talwin) and Blues (for the color of the other drug). It is also seen with methadone, meperidine, codeine, and oxycodone (7). Similarly, retinopathy may develop from the injection of oral medications (8).

Neurologic/CNS

All opioids can cause CNS depression, however other manifestations of opioid CNS toxicity include seizures in acute overdoes, most likely due to hypoxia. Seizures secondary to propoxyphene, tramadol, and meperidine toxicity are well described. Serotonin syndrome occurs when opioids with serotoninergic effects (meperidine, tramadol, and dextromethorphan) are used with monoamine oxidase inhibitors (MAOIs) or other serotonin agonists; however, similar symptoms occur with large doses of those opioids in the absence of other serotonergic drugs (Chapter 343, Serotonin Reuptake Inhibitors).

A severe, acute Parkinsonism has followed illicit use of a meperidine analog synthesized in a clandestine laboratory contaminated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Affected individuals were known as “frozen addicts.”

Miosis

The mechanism of miosis caused by opioids is controversial. But, stimulation of mu receptors in the Edginger–Westphal nucleus of CN III by morphine does produce miosis. Miosis alone is not pathognomonic for opioid overdose. Overdose with numerous other substances can produce miosis and CNS depression including clonidine, organophosphates, phenothiazines, sedative–hypnotics, anticonvulsants, olanzapine, and ethanol. In addition, normally reactive or mydriatic pupils can be seen with meperidine, propoxyphene, tramadol, and Lomotil poisoning. Numerous polysubstance ingestions or abuse may confound pupillary findings with a variety of results.

Cardiovascular

Opioids can produce mild hypotension through nonspecific histamine release. This is often orthostatic and may not be evident in the supine position. Antihistamines are effective in blocking these effects. Opioids may also produce bradycardia secondary to decreased CNS stimulation.

Propoxyphene is known to have sodium channel–blocking properties similar to class 1 A antidysrhythmics which can produce QRS widening. This can lead to wide complex tachycardias and negative contractility. Methadone and its derivative LAAM may inhibit delayed potassium rectifier currents, increasing the QT interval and the subsequent risk for developing torsade de pointes. Prolonged QT syndrome and torsade de pointes appear to be dose-dependent and are more likely with high-dose methadone.

Gastrointestinal

Nausea and vomiting are common with therapeutic use and overdose. These effects are the product of dopamine-receptor agonism at the chemoreceptor trigger zone in the medulla. Antiemetics can be effective in controlling these symptoms. Constipation secondary to decreased GI motility is very common and is mediated by mu receptors within the GI tract.

Other clinical findings

Sensorineural hearing loss has been reported with opioid exposure usually after high doses and chronic use although it has followed acute overdose. Onset is sudden and rapidly progresses to bilateral hearing loss. Vestibular symptoms are usually, but not always, absent. Hearing loss may resolve with abstinence from opioids. Cochlear implants are usually successful.

Urinary retention due to increased sphincter tone may also develop. Other complications include pressure necrosis, compartment syndrome with rhabdomyolysis, hypoglycemia, and hypothermia in patients who have been comatose.

Tolerance and Withdrawal

Tolerance may be innate (genetically determined) or acquired. Acquired forms include *pharmacokinetic tolerance* from repeat exposure leading to changes in metabolism or distribution. *Pharmacodynamic tolerance* refers to physiologic adaptation such as changes in receptor density. *Learned tolerance* connotes a reduction of drug effects due to learned compensatory mechanisms such as the *conditioned tolerance* that develops when environmental cues are consistently paired with the administration of the drug. Some opiate overdoses experienced by drug addicts may occur if the drug is taken under new circumstances, tolerance is reduced, and the drug's effect enhanced. Numerous studies have demonstrated that altering the context of drug administration increases the lethality of many drugs, including opioids (9).

Although physical dependence and behavioral addiction is not fully understood, the mu receptor is involved in both processes and

the dopamine pathway is thought to be involved in dependence. Long-term use of opioids can lead to tolerance and withdrawal. Tolerance is most pronounced with the euphoric, analgesic, and sedative effects of opioids. Respiratory tolerance has also been reported in large therapeutic doses, up to 1,000 mg/hr of IV morphine without respiratory depression (10).

CNS excitation, tachypnea, mydriasis, nausea, vomiting, diarrhea, abdominal pain, myalgias, insomnia, piloerection, yawning, lacrimation, rhinorrhea are all symptoms of opioid withdrawal. These occur when stopping use or when an antagonist is delivered. Patients may present with significant fluid and/or electrolyte abnormalities from GI symptoms. Long-term opioid use is associated with decreased levels of endogenous opioids. If exogenous opioid administration is suddenly stopped, the inadequate amount of endogenous opioids fails to provide adequate inhibition to adrenergic pathways resulting in overactivation. Unlike benzodiazepine, barbiturate, and alcohol withdrawal, opioid withdrawal is generally not life-threatening but can cause seizures in neonates. It is important to note that opioid withdrawal does not cause altered mental status.

ED EVALUATION

The history should include the type of opioid, co-intoxicants, and the amount, time, intent, and route of exposure. The physical examination should focus on assessing the airway and the adequacy of ventilation. After the patient has been stabilized, it is important to look for fentanyl patches. The exam should include the all skin surfaces, including axillae, perineum, scrotum, and oropharynx. All patches should be removed and the area cleaned with soap and water to prevent any continued absorption. All major muscle groups should be palpated to evaluate the firmness, swelling, and tenderness that might reveal concerns for compartment syndrome. Patients should have cardiac and oxygen saturation or end-tidal CO_2 monitoring. Patients with altered mental status should have blood glucose testing and intravenous access established. Electrolytes,

creatine kinase (CK), and urine myoglobin should be checked if patients are combative, agitated, or convulsing. A chest radiograph and ECG should be obtained for unstable vital signs, hypoxia, or an abnormal cardiopulmonary examination. Acetaminophen and aspirin, found in combination with opioids in many medications, should be excluded. Urine drug screens (UDSs) detect some opioids, but will not detect propoxyphene, meperidine, methadone, fentanyl and derivatives, buprenorphine, hydromorphone, or naloxone. Hydrocodone and oxycodone may be detected in high concentrations. Heroin will be picked up as morphine, its metabolite. To specifically determine heroin use, 6-monoacetyl morphine (6-MAM), an intermediate metabolite between heroin and morphine, should be obtained. False positives for opiates on a UDS may include poppy seeds, dextromethorphan, chlorpromazine, diphenoxylate, ephedra, and ciprofloxacin. If action such as notification of child protective services or police is going to be based on the results of a UDS, the results should be confirmed by a second method such as gas chromatography/mass spectrometry. In contrast, a lack of response to adequate doses of opioid antagonists virtually excludes this diagnosis. Although most opioid-induced CNS depression will be reversed with lower doses of naloxone, some opioids such as propoxyphene may require doses as high as 10 mg. A positive response to naloxone is usually diagnostic, but clonidine and valproate (and rarely benzodiazepines, ethanol, and chlorpromazine) have been reported to occasionally respond.

KEY TESTING

- No testing for simple cases that respond to naloxone
- Electrolytes, BUN, creatinine, creatine kinase if comatose for a long time
- ECG
- Chest x-ray in suspected ALI

ED MANAGEMENT

Supplemental oxygen and assisted ventilation should be provided, as necessary. With the expeditious use of opioid antagonists and temporary ventilation via a bag-valve-mask, endotracheal intubation can often be avoided. Although the relationship between carbon dioxide and ALI is not clear, adequately ventilating and oxygenating the patient may help prevent a catecholamine surge that could contribute to the development of pulmonary edema (6).

Naloxone is a competitive opioid receptor antagonist that reverses opioids' clinical effects indicated primarily for the treatment of respiratory depression and may be effective for opioid-induced seizures. It can be diagnostic in patients with altered mental status of unknown etiology. The application of four-point restraints is recommended before naloxone administration, as the patient may become uncooperative and combative with reversal of opioid intoxication. Suction equipment should be set up in advance, because vomiting may occur after naloxone administration.

The onset of action of naloxone is typically less than 2 minutes when administered IV. In suspected addicts, a low initial dose of naloxone (0.04 mg IV) should be administered to avoid precipitating a severe withdrawal reaction. If there is no response, the dose should be increased every 1 to 2 minutes with escalating doses (0.5, 2, 4, 10 mg) or until respiratory depression is reversed and the patient awakens. Because some opioid overdoses (e.g., propoxyphene and methadone) are relatively resistant to naloxone, up to 15 mg may be administered. However, if the clinical findings are not reversed after the 10 mg dose, it is very unlikely that the cause is opioid toxicity. If the patient is not a suspected addict, 0.4 to 2 mg of naloxone can be given as the initial bolus. The effective dose of naloxone depends on the amount to which the patient has been exposed, the affinity of the opioid for the receptor, the patient's weight, and the ability of the opioid to enter the CNS. Of the other two opioid antagonists, naltrexone has a slightly longer half-life and is used for abstinence maintenance. Nalmefene has a much longer half-life and is more expensive. The use of longer-acting antagonists mandates a much longer observation period after

reversal of opioid effects. For that reason, naloxone is considered the best choice for use in the emergency setting.

If intravenous access cannot be obtained, naloxone may be administered via the intramuscular, intranasal, subcutaneous, or endotracheal route, but not orally because of extensive first-pass effect. The time to response after intramuscular administration is about the same as the time required to place an intravenous line and administer the drug. However, intramuscular administration decreases the risk of needlestick injury, especially in an uncooperative patient or with veins sclerosed from injection drug use.

Naloxone's duration of action is 20 to 90 minutes, which is a much shorter time than that of many opioids, especially after oral overdose and with diphenoxylate and methadone. Repeat doses or a continuous naloxone drip of two-thirds of the initial dose of naloxone needed to reverse respiratory depression, given every hour, should maintain arousal. It may be necessary to give one-half of the original dose as an additional bolus 15 to 20 minutes after initiation of the drip. Patients that improve after a single dose of naloxone should be observed 4 to 6 hours prior to considering discharge. Patients with exposure to extended release preparations, or recurrent respiratory depression, or needing naloxone infusion warrant admission to an ICU.

A partial response to naloxone requires a careful search for other accompanying illnesses, injury, or intoxicants. Endotracheal intubation is necessary in patients with hypercarbia, hypoxia, or an inability to protect their airway. Seizures should be treated with intravenous benzodiazepines (diazepam or lorazepam) or phenobarbital. Ongoing seizures suggest a cause other than pure opioid poisoning.

Within 1 hour of ingestion, activated charcoal should be considered. However, outside of this time frame it offers no benefit and is not without risk (aspiration, impairing airway visualization). Following ingestion of a fentanyl patch, whole bowel irrigation (WBI) with polyethylene glycol have been suggested to help with

elimination; however, studies of WBI have failed to show a difference in clinical outcome.

Hypotension is usually not a prominent feature of pure opioid overdose, and should be managed with crystalloid fluid and an aggressive search for another cause. Antihistamines may be helpful to block hypotension from histamine release. Propoxyphene may need vasopressors such as norepinephrine. Arrhythmias due to propoxyphene are similar to those of the tricyclic antidepressants and may require sodium bicarbonate therapy (see Chapter 339). Naloxone will not reverse propoxyphene cardiotoxicity. Although naloxone only partially inhibits tramadol-mediated analgesia, it reverses respiratory depression and coma due to this agent. Magnesium with potassium replacement may be required for methadone-poisoning, especially a prolonged QT_c or torsade de pointes.

If hypoxia persists following naloxone, this may be a sign of ALI. Fortunately, most cases only require supportive care, but some patients may require positive pressure ventilation or orotracheal intubation for severe hypoxia; most cases resolve within 24 hours. These patients are typically not volume overloaded, therefore diuretics do not play a role in the treatment. Rhabdomyolysis should be treated aggressively with fluid resuscitation to help prevent renal injury. Antiemetics can be effective in controlling nausea and vomiting. If compartment syndrome is suspected, immediate consultation for fasciotomy should be obtained.

CRITICAL INTERVENTIONS

- Administer naloxone to patients with altered mental status and respiratory depression.
- Begin with small doses of naloxone in opioid addicts with unintentional poisoning to avoid withdrawal.
- Give large doses of naloxone to those with intentional overdose and to children with accidental ingestions.
- Admit all patients who require naloxone after oral overdose and all children with possible opioid ingestions.

DISPOSITION

Careful observation is required for any patient requiring naloxone. Patients with intravenous overdose can be observed for 6 hours for evidence of relapse or the development of noncardiac pulmonary edema. Complications, if they develop, are usually evident soon after presentation. In contrast, patients requiring naloxone after an oral overdose should be admitted to an intensive care unit with cardiac and respiratory monitoring (and suicide precautions, as needed). They should not be discharged until they are symptom-free (off naloxone) for 12 hours. Adults who are or become asymptomatic for 6 hours after an oral overdose may be discharged. Children, especially those under age of 3, should be admitted for 12 to 24 hours, even if ingestion cannot be confirmed. Psychiatric or social work follow-up must be arranged for all intentional or pediatric poisonings. Asymptomatic patients who have been treated with narcotic antagonists should be monitored.

The appropriate disposal of transdermal fentanyl patches is an important matter. Historically, practices were to throw them in the trash or discard them in sharp disposal containers. However, secondary to residual fentanyl in a patch after delivery, witnessed drug wastage is now recommended. For ED disposal, the recommendation is drug wastage requiring co-signatures after cutting up the patch and flushing it down the toilet. For outpatient use, an exchange program of used patches for new patches may be helpful.

Common Pitfalls

- Failure to consider opioid overdose in patients who present with altered mental status, including seizures or combativeness, and CNS depression.
- Failure to apply restraints, thereby risking injury to staff, before giving naloxone to suspected addicts.
- Failure to evaluate for pulmonary complications, aspiration, and concomitant traumatic and medical illness.

- Failure to examine thoroughly for medication patches (e.g., fentanyl).

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CHAPTER 306

Complications of Injection Drug Use

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Although precise data are not available, the Centers for Disease Control and Prevention (CDC) estimated in 2002 that approximately 1.2 million people in the United States actively used nonprescribed drugs by intravenous, subcutaneous, and other routes of injection and in 2008 approximately 4 million had self-injected drugs at least once (1). Injection drug use (IDU) brings with it the risk of complications directly related to the local or systemic effects of the substances injected, the use of nonsterile methods of injection, and other aspects of injection practices as well as the risk of death from overdose (Table 306.1). The lifestyle associated with drug use also increases the risk of trauma and numerous infections including HIV, hepatitis, tuberculosis, and sexually transmitted diseases.

TABLE 306.1
Medical Complications of Injection Drug Use by Organ System

- Cutaneous
  - Needle foreign body
  - Abscess
  - Necrotizing fasciitis
  - Gas gangrene
  - Cellulitis
- Vascular
  - Septic phlebitis
  - Thrombophlebitis
  - Pseudoaneurysm
  - Infected hematoma
  - Intra-arterial injection
- Musculoskeletal
  - Vertebral osteomyelitis
  - Septic arthritis
  - Compartment syndrome
  - Pyomyositis
- Pulmonary
  - Pneumothorax
  - Hemothorax
  - Talcosis
  - Septic pulmonary embolus
  - Pneumonia
- Neurologic
  - Peripheral nervous system
    - Puncture injuries
    - Compression injuries
    - Plexitis/plexopathy
  - Central nervous system
    - Infections
    - Meningitis
    - Abscesses: cerebral, epidural, spinal
    - Mycotic aneurysm
    - Transient ischemic attacks
    - Mucormycosis
    - Stroke
- Internal organs
  - Heart
    - Endocarditis
    - Myocardial infarction, ischemia
  - Liver
    - Hepatitis
    - Spleen
    - Abscess
  - Kidney
    - Nephrotic syndrome
    - Glomerulonephritis
    - Abscess
    - Infarct
  - Intestine
    - Mesenteric ischemia, infarction
- General, other
  - Cotton fever
  - Septicemia
  - HIV infection
  - Tetanus
  - Wound botulism
  - Endophthalmitis
  - Amyloidosis
  - Malaria

Complications from unsafe injection methods are the most common reason IDU patients present to the emergency department (ED). Soft tissue infections such as abscesses and cellulitis often occur in IDU patients at the site of injection. IDU has been identified as an important risk factor for community acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) especially of the USA 300 clonal group and is the predominant cause of purulent soft tissue infections (2). Observational studies have reported that IDU is associated with an increase in nasal carriage and wound colonization with CA-MRSA as compared to healthy or other control populations and cohort studies have demonstrated a significant increase in the prevalence of MRSA among those who use injection drugs over time (3,4). In addition to *S. aureus* and *Streptococci,* infections with gram-negative bacteria or oral anaerobes are also observed in IDU patients, related to nonsterile methods of preparation of the drugs.

Uncommon medical diseases, including wound botulism and tetanus, continue to be reported among patients using injection drugs. In 2005, all 28 reported cases of wound botulism in the United States were associated with IDU. Injection drug users are also at risk for more serious deep soft tissue infections, including necrotizing fasciitis (see Chapter 180), myositis, and pyomyositis. Broken needles at the site of intravenous injection are usually an incidental finding noted on radiograph. Such retained needle fragments rarely embolize centrally. However, serious complications such as pericarditis with pericardial effusion secondary to central migration have been reported.

Vascular complications related to IDU include unintentional intra-arterial injection, with resultant vasospasm or thrombosis and limb ischemia; venous and arterial pseudoaneurysm formation; development of an infected hematoma; and venous thrombosis and septic thrombophlebitis. IDU is a major risk factor for deep vein thrombosis, especially among those who have injected in the femoral veins.

Mycotic aneurysms involving central arteries such as the hepatic, mesenteric, cerebral, and pulmonary arteries and large vessel

occlusive emboli may occur in the context of endocarditis (see Chapter 88). Mycotic aneurysms involving the brachial, subclavian, axillary, and femoral arteries may develop after local injections. The bacteriology of both arterial and venous mycotic aneurysm is polymicrobial in up to 40% of cases. *S. aureus,* frequently β-lactam–resistant, is often cultured from the wound or blood. Anaerobic organisms have been reported in up to 20% of some series.

Injection into the supraclavicular fossa to access the jugular, subclavian, or brachiocephalic veins, known as "pocket shooting," often leads to pneumothorax, hemothorax, hydropneumothorax, or pyopneumothorax. In prior studies, moderate to large pneumothoraces and tension pneumothorax have been common findings.

Injection of solubilized tablets and capsules can lead to pulmonary dysfunction from injected particulate matter that deposit in the lung. Tablets are usually crushed, dissolved in water or other liquid, sometimes heated, and injected directly or through cotton filters. Talc fillers in tablets and other foreign materials induce granulomas in and around the arterioles and capillaries of the lung and deposit in retinal vessels; this condition is referred to as "talcosis." Both restrictive and obstructive pulmonary dysfunction can be seen along with pulmonary hypertension and cor pulmonale. Autopsy studies have suggested that this disorder, although confirmed histologically, is often not clinically recognized (5).

Osteomyelitis and septic arthritis secondary to IDU may result from direct contamination or hematogenous spread. Hematogenous pyogenic spinal infections from IDU include spondylodiscitis, discitis, vertebral osteomyelitis, and epidural abscess. Vertebral osteomyelitis is the most common form of skeletal infection in IDU patients, especially involving cervical sites compared to the lumbar and thoracic spine, which are more common in those who do not use injection drugs (6). Patients with osteomyelitis are more likely to have polymicrobial infections, infections due to gram-negative organisms, and anaerobic infections compared to those with septic arthritis (7).

The axial fibrocartilaginous joints including the sacroiliac, sternoclavicular, costochondral, hip, and pubic symphysis synchondroses are the most frequent sites of septic arthritis in IDU patients, although other joints, including the knees, hips, and shoulders, may be involved. *Pseudomonas aeruginosa* and *Serratia marcescens* often cause osteoarticular infections, but *S. aureus* is the most likely organism associated with IDU. *Eikenella corrodens* associated with "needle licking" causes septic arthritis in a subgroup of patient with IDU.

IDU patients are at increased risk of central nervous system (CNS) infections, including fungal and bacterial meningitis, cerebritis, and spinal epidural, and brain abscesses. Indolent CNS aspergillosis, cerebral mucormycosis, and anterior spinal artery syndrome with resultant paraplegia have been reported. A syndrome of cerebral mucormycosis is well described in IDU patients who are seronegative for the human immunodeficiency virus (HIV). Fungal endophthalmitis, caused by such organisms as Aspergillus and Fusarium, have been described in patients with IDU as the only identified risk factor for these rare infections. Peripheral nerve injuries may result from needle-induced trauma, extrinsic compression, and direct toxic or hypersensitivity reactions to injected materials.

Systemic infections may result from exposure to skin contaminants, contaminated apparatus, contaminated injection mixture, and blood-borne pathogens transmitted by the practice of needle sharing. Approximately 10% of new cases of acquired immunodeficiency syndrome (AIDS), and 50% of new hepatitis C cases are associated with IDU. In addition, HIV-infected patients on antiretroviral therapy who are active IDUs have increased morbidity and mortality compared to their non-IDU counterparts despite equal access to antiretroviral therapy. Infection with the HTLV virus (types I and II) is associated with IDU (8).

Hepatitis GB virus type C, an important cause of fulminant non–A-E hepatitis, is also more common in IDU patients. A number of uncommon infections have also been described, including disseminated candidiasis attributed to the use of lemon juice in the

preparation of brown heroin for injection, malaria (both falciparum and vivax), endophthalmitis, and tick-borne relapsing fever.

CLINICAL PRESENTATION

Patients with superficial abscesses often have localized pain, redness, and swelling at a previous injection site. Fever, cellulitis, and systemic complaints may also be present. Potential infection with MRSA should be presumed in all patients presenting with abscesses purulent cellulitis.

Tetanus presents as increased muscle tone, spasm, or trismus. Patients with wound botulism usually present with neurologic complaints such as cranial palsies or descending symmetric paralysis. Atypical signs, including asymmetric or unilateral cranial nerve weakness and peripheral motor weakness, may be present. Atypical presentations and false-positive edrophonium tests have caused patients to be misdiagnosed with Eaton–Lambert syndrome or myasthenia gravis, resulting in prolonged delays in appropriate therapy (9).

Deep soft tissue infections can have a subtle initial presentation but can rapidly progress to limb- and life-threatening illness. Myositis and pyomyositis may present initially with only mild erythema of the overlying skin but rapidly develop pain, significant edema, and crepitus. Sometimes a brown discoloration of the skin or purplish blebs develop. When the infection has progressed enough to cause marked cutaneous changes, the patient will frequently develop septic shock.

Broken needle fragments at injection sites may be asymptomatic or cause localized pain, as a result of the needle itself or of infectious complications. Patients may present with concerns about the risks of a retained needle fragment. They may also be unaware of its presence or fail to mention it unless asked.

Inadvertent intra-arterial injection causes immediate severe pain, hyperemia, numbness, weakness, distal swelling, cyanosis, and motor deficit and, often, sensory abnormalities. Distal ischemia may progress to gangrene, myonecrosis, and associated complications.

Injecting crushed oral medications into the lower extremity appears to be associated with more severe complications.

Venous pseudoaneurysms are most commonly noted in the groin and may present bilaterally. Pain, swelling, and purulent drainage may be noted. Some patients may appear clinically septic, with minimal localized complaints. In these patients, either pulmonary complaints or symptoms referable to sites of metastatic septic involvement may be more prominent.

Any mass over a vascular structure may actually be a pseudoaneurysm and should be approached with caution. Arterial mycotic aneurysms usually present as an indurated mass with local pain, and swelling. The mass may not be pulsatile, but a bruit is often heard over the swelling. Fever and leukocytosis are common, but bleeding, although occasionally massive, is usually intermittent, minor, or absent. Claudication, paresthesias, or compression neuropathy can occur. Signs and symptoms of distal embolic phenomenon, including cutaneous purpura, may be present and may precede systemic manifestations.

IDU patients with infective endocarditis usually have fever, but a new heart murmur, Roth spots, Osler nodes, Janeway lesions, splinter hemorrhages, or embolic phenomena are rare. The history and physical examination have a poor sensitivity and specificity for detecting infective endocarditis. The mortality rate in patients with IDU, HIV infection, and endocarditis is associated with the degree of immunosuppression as reflected by CD4 counts.

Patients with pneumothorax typically present with a history of recent neck injection, dyspnea, and pleuritic chest pain. Particulate-induced pulmonary dysfunction frequently presents as progressive dyspnea. Chest radiography can show a micronodular pattern which progress over time to show large homogenous opacities, usually in the perihilar regions and upper lobes. Chest computed tomography (CT) scans have demonstrated fine micronodular changes, perihilar conglomerate masses, ground glass attenuation, and emphysema, especially of the lower lobes, among patients who inject solubilized oral medications. Retinoscopy by an ophthalmologist can identify talc deposits (small, whitish, glistening dots) and may have a higher

diagnostic yield than either routine chest x-ray or pulmonary function tests.

Skeletal infections often present as localized pain and tenderness. IDU patients commonly develop septic arthritis and osteomyelitis at sites rarely seen in the general population, including the sternum, sacroiliac joints, and pubic symphysis. Almost 20% of patients with vertebral osteomyelitis related to IDU have had pain for more than 3 months at the time of diagnosis. Fever is usually absent or low grade. Neurologic signs and symptoms occur infrequently (<15%) and are usually transient. Patients with septic arthritis associated with IDU are similar in presentation to other patients with septic arthritis, except for the prominence of fibrocartilaginous joint involvement. Local signs of inflammation and fever, leukocytosis, and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually noted. Asymptomatic HIV infection has been reported prevalent among patients with septic arthritis.

A patient with fungal endophthalmitis usually presents with decreased vision, photophobia, and ocular pain, which develop slowly. The infection may occur in one or both eyes. White vitreal exudates may be seen on funduscopic examination. Bacterial endophthalmitis has a similar but more rapidly progressing presentation.

Patients with cerebral mucormycosis usually have headache, fever, and rapidly developing cranial nerve and motor deficits. Basal ganglia lesions on CT scan should suggest this diagnosis. Cotton fever may cause dyspnea, palpitations, headache, and rigors.

Patients who inject drugs are also at risk for systemic drug or drug contaminant toxicity (see Chapters 305, 310, 345, and 348), withdrawal syndromes (see Chapter 351), and CNS infections (see Chapter 278).

DIFFERENTIAL DIAGNOSIS

The most important requirement for developing an appropriate differential diagnosis is obtaining the history of IDU. Because patients often do not fit the stereotypes of end-stage IVDU, the

physician may miss this possibility. It may be necessary to consider the possibility of IDU, even if denied by the patient. In such cases, a urine screening test for drugs of abuse may be helpful.

Unless the history of IDU is routinely obtained or considered, conditions such as vertebral osteomyelitis and epidural abscess may not be considered in the differential diagnosis of complaints such as back pain. Consider botulism, endocarditis, or intracranial abscesses and mycotic aneurysms in the IDU patient presenting with stroke symptoms. What appears to be an abscess in an IDU may actually be a pseudoaneurysm, and a simple incision and drainage might have disastrous consequences. The IDU patient who develops a fever or flu-like symptoms is much more likely to have an infection requiring hospital admission than a non-IDU patient who presents with similar complaints. Infective endocarditis should be in the differential diagnosis of all IDU patients with fever, even if another source of fever is found. Studies from the 1980s and 1990s of patients with IDU with fever demonstrated that a small proportion of patients had major illnesses such as bacterial endocarditis that were not clinically apparent on initial evaluation. Although an acute but self-limited pyrogenic reaction induced by intravenous injection of foreign material from cotton balls used to filter injected solution is a common cause of fever, the history, physical examination, and routine laboratory testing cannot reliably differentiate “cotton fever” or other minor conditions from more serious causes of fever.

ED EVALUATION

The possibility of IDU, recent or remote, should be included in the standard “screening history.” A nonthreatening question such as, “Do you smoke cigarettes, or use alcohol or other drugs?” should be routinely asked of all patients. Depending on the clinical concern, it may be appropriate to ask patients about more specific questions about drug use including drug injected, amount, needle sharing, skin preparation (alcohol wipes), and whether they have a history of hepatitis, endocarditis, HIV, pain at injection sites, recent fever, and nonprescribed antibiotic self-treatment. Because many IDU patients

will not reveal their drug use, track marks or a positive urine toxicology screen may be the only clue to the diagnosis.

The physical examination of a patient with recognized IDU should include a careful review of vital signs, particularly an accurate temperature. Examination of the skin for signs of endocarditis, jaundice, infection at injection sites, and markers of HIV infection, such as oral thrush, should be performed in addition to a complaint-oriented examination. Evidence of opiate withdrawal, such as diaphoresis, lacrimation, yawning, pupillary dilation, and piloerection, should also be sought.

Routine laboratory tests are of limited use. Drug screens provide little information that will affect decisions, except possibly to suggest drug use when it is denied. Although the complete blood count and markers of inflammation (ESR, CRP) lack sufficient sensitivity and specificity to guide disposition decisions, if infection is suspected or diagnosed, a very high or low white blood cell count might prompt admission, even for a simple abscess. Point of care HIV testing that is increasingly available in EDs and can aid triage, treatment, and referral decisions.

Ultrasonography may identify occult abscesses that require drainage that otherwise would be missed on physical examination alone. Cutaneous abscesses with associated systemic complaints should be cultured. A radiograph or ultrasound should be considered in patients with cutaneous complaints of pain and tenderness at injection sites to exclude retained needle foreign bodies and to identify gas-forming infections. Surgical consultation should be considered for abscesses that could involve deeper tissue based upon their location or appearance. Deltoid abscesses have increased potential for deeper and more serious infections in IDU patients and are five times more likely to be drained and explored in the operating room compared to abscesses in other locations (10).

Suspected deep soft tissue infections such as myositis, pyomyositis, or necrotizing fasciitis can be evaluated with magnetic resonance imaging (MRI). However, given the rapid progression of these conditions, MRI should not delay surgical exploration for a definitive diagnosis in cases when there is high clinical suspicion.

Ultrasound may identify a perivascular abscess and color flow Doppler can readily identify nonvisceral mycotic aneurysms. Other imaging modalities such as CT or MR angiography or arteriography may be necessary to confirm the diagnosis.

Patients with suspected endocarditis should have three sets of blood cultures, a chest radiograph, and cardiac ultrasonography. A point of care transthoracic ultrasound performed as part of the ED evaluation can identify vegetations or valvular complications in patients with suspected endocarditis (it is specific, but not sensitive). Pocket shooters and those with respiratory complaints should have a chest radiograph and measurement of oxygen saturation. When they become available, advances in rapid diagnostic methods such as real time polymerase chain reaction (PCR) tests to detect bacteremia may better identify which febrile patients to admit.

Patients with joint pain and effusion should have two sets of blood cultures and aspiration, Gram stain, and culture of affected joints. Septic synchondroses may be safely aspirated in the ED and should be evaluated similarly. Diagnostic criteria for prosthetic joints infection differ (see Chapter 150). Two sets of blood cultures and an MRI should be obtained for suspected vertebral osteomyelitis or epidural abscess. An elevated ESR and CRP are not specific for osteomyelitis or septic arthritis and have limited utility for risk stratification or as triage tools. Using a normal ESR and CRP to triage IDU patients with back or neck pain who are at risk for an epidural abscess has not been validated in well-designed prospective studies. MRI is the modality of choice for detection of vertebral osteomyelitis and can be diagnostic for infected joints involving the axial skeleton and pelvis in uncertain cases. An MRI can also be normal in the early stages of an epidural infection. Given that history, physical examination, and all other diagnostic testing lack significant sensitivity and specificity, an MRI should be considered on all IDU patients presenting with axial skeletal pain. Laboratory studies can supplement the clinical evaluation.

Patients with complaints that suggest a CNS process (headache, weakness, ataxia) require a detailed neurologic examination, CNS

imaging with CT scan or MRI, and a lumbar puncture to identify cerebrovascular complications of IDU use, opportunistic CNS infections, or malignancy (whether related or unrelated to HIV infection). Patients with complaints of visual loss should have a complete eye examination, usually dilation with indirect funduscopy. In patients with fever, three sets of blood cultures, chest radiograph, urinalysis, and urine culture should be obtained.

KEY TESTING

- Febrile IDU should have testing appropriate for targeted source of infection
- Skin/soft tissue—consider bedside ultrasound and x-ray
- Musculoskeletal complications (osteomyelitis, epidural abscess, pyomyositis)
  MRI, blood cultures, routine laboratory studies
- Fever without evident source such as bacteremia, endocarditis should have blood cultures, ESR, CRP, possible point of care transcutaneous cardiac ultrasound to evaluate for vegetations
- Suspected CNS infection
  - Neuroimaging (CT angiography, MR angiography) with suspected cerebral mycotic aneurysm, (bacterial, fungal)
- Wound tetanus, botulism: have no diagnostic tests in the ED; the diagnosis is clinical.
- HIV testing if available or not recently performed

ED MANAGEMENT

Patients with IDU-related infections should be given tetanus prophylaxis as indicated. Localized cutaneous abscesses without vascular involvement may be managed with routine incision and drainage or loop drainage. If there is a possibility of vascular involvement, ultrasound or, needle aspiration should be done prior to drainage. Patients with localized infections involving the neck, groin, or vascular structures and those with suspected deep soft tissue infections such as myositis or pyomyositis should be evaluated by a surgeon. Although antibiotics and hospitalization are

not routinely required for cutaneous abscesses that have been drained, patients with HIV infection, neutropenia, vascular involvement, deep space infections, or possible sepsis should be admitted and given parenteral antibiotics. Extensive extremity infections, especially those found in the deltoid area, should be explored in the operating room, as inadequate drainage may prolong hospitalization. Ultrasound-guided regional nerve blocks or procedural sedation may be required for large abscesses.

Small uncomplicated abscesses without significant overlying cellulitis require only incision and drainage or placement of a loop. The addition of antibiotics is not shown to improve cure rate or outcome. Antibiotic treatment is advised for patients with abscesses that are complicated, have significant overlying edema, or are associated with systemic effects. Antibiotic choice should be guided by local antibiotic resistance and susceptibility patterns. The increasing prevalence of MRSA should be considered when choosing empiric antibiotic therapy. For inpatient therapy, vancomycin (Vancomycin 15 mg/kg IV q12h) can be used. For oral therapy, use trimethoprim–sulfamethoxazole (160/800 mg PO q12h) or double dosage to treat MRSA or severe MRSA infection, doxycycline (100 mg PO q12h), clindamycin (Clindamycin 300 to 450 mg PO q6 to 8h), though in many areas MRSA resistance to clindamycin is greater than 50% or linezolid (600 mg PO q12h), though its high cost may preclude widespread use. An antipseudomonal regimen including an aminoglycoside (APAG) such as gentamicin (traditional dosing 1 to 2 mg/kg IV q8 to 24h with the frequency depending on renal function, and high dose 5 to 7 mg/kg IV q24h) combined with an agent such as ceftazidime (2 g IV q8h) or cefepime (1 to 2 g IV q12h) should also be given if enteric organisms or *Pseudomonas* has been identified as part of the local “IDU” flora. Patients with gas-forming or necrotizing infections require *immediate* operative intervention and combination broad-spectrum antibiotic therapy that may include clindamycin (600 to 900 mg IV q8h), high-dose penicillin G (3 to 4 mU IV q4h, or vancomycin to treat MRSA and an APAG, and consideration of such adjunctive therapy as intravenous immunoglobulin and hyperbaric oxygen therapy. Such antibiotics as

piperacillin/tazobactam EI (3.375 g IV q8h) or imipenem (1 g IV q6 to 8h) can also be considered. Infectious disease consultation may be considered to aid in antibiotic selection and adjunctive therapy for such complex soft tissue infections as necrotizing fasciitis or myonecrosis associated with *Clostridium* (see Chapter 180). Early administration of antitoxin is important in patients with wound botulism (9). On March 22, 2013, the FDA approved the first botulism antitoxin that can neutralize all seven known botulinum nerve toxin serotypes. Heptavalent antitoxin (toxins A through G) is available at the CDC (770−488−7100 (24/7)). Early infectious disease consultation should be considered.

When associated with infection or vascular injury, needle fragments require urgent removal. Patients who have retained needle foreign bodies but do not have these complications may be given appropriate discharge instructions and referral to a surgeon for elective removal. In general, emergency physicians should not attempt to remove fractured needle fragments. Even if they are palpable, finding them may be difficult, important neurovascular structures may be injured, and migration may occur despite the use of a proximal tourniquet.

Patients with signs and symptoms of intra-arterial injection require aggressive management because of the potential for limb ischemia. Treatment should include antibiotics and anticoagulation with heparin. Consultation with a general or vascular surgeon is essential. Measurement of extremity compartment pressures should also be considered. A variety of off-label treatments have been described in case reports, including IV dextran 40 (20 mL/hr) and dexamethasone (4 mg q6h) or the intra-arterial injection of a vasodilator such as papaverine (40 to 60 mg), phentolamine (2 mg), iloprost, a prostacyclin analogue, and intra-arterial thrombolysis. Given the potential morbidity, appropriate infectious disease consultation should be considered.

Patients with pseudoaneurysms require blood cultures, preoperative laboratory testing including blood typing, and consultation with a general or vascular surgeon for excision and possible distal revascularization. Hospitalization is usually

indicated. An endovascular approach can be considered for some mycotic aneurysms by some specialists. Hemorrhage control with direct pressure may be required. Local drainage should not be attempted in the ED, as life-threatening hemorrhage may result.

Many experts continue to recommend admitting *all* IDU patients with fever as ruling out endocarditis and bacteremia remains problematic in the ED. Although one clinical trial conducted in 1996 suggested that oral antibiotics might be an acceptable alternative to intravenous therapy when intravenous access is very difficult or high risk in febrile drug users with possible endocarditis (e.g., "rule out endocarditis") this approach has not been studied in patients with MRSA infection. Advances using ultrasound to successfully obtain peripheral intravenous access in patients with difficult access have the reduced the risk and necessity of placing central lines in patients who are admitted to exclude bacterial endocarditis. Pulmonary dysfunction from other causes is treated by supportive measures.

Vertebral osteomyelitis and septic arthritis should be treated with vancomycin and an APAG. Ultrasound-guided arthorcentesis has become a well-accepted procedure performed by emergency physicians. Consultation with an orthopedic surgeon should be obtained. Spinal epidural abscess should be managed with urgent surgical drainage and empiric antibiotic therapy with both vancomycin and a third- or fourth-generation cephalosporin such as cefepime or ceftazidime until culture results become available (11).

Emergency physicians can consider hyperbaric oxygen therapy for some complications of IDU. Hyperbaric therapy has been reported as an adjunct to limb-threatening vascular injection, necrotizing infections, and complicated wound management.

Patients with cotton fever require only supportive care. This illness usually resolves within 12 to 24 hours. However, given the possibility that a serious medical condition is the etiology of fever, inpatient observation is recommended until the patient is well and the results of blood cultures are known.

CRITICAL INTERVENTIONS

- Consult an appropriate specialist for IDU patients with complicated infections, deep soft tissue infections, symptomatic retained needle fragments, limb ischemia, or masses in the neck or groin, or with vertebral osteomyelitis, septic arthritis, or visual complaints.
- Consider admitting all IDU patients for IV antibiotics until endocarditis and bacteremia can be excluded.
- Consider IDU in patients with multiple unusual infections.

DISPOSITION

Patients with cutaneous abscesses who are otherwise asymptomatic and healthy may be discharged with appropriate instructions and referral for follow-up in 24 to 48 hours. Patients with retained needle foreign bodies can be referred for elective surgery on an outpatient basis unless there are signs of infection. The ability of a patient to comply with outpatient therapy and follow-up should be considered. Most patients with other infectious complications require admission. Concomitant HIV infection should lower the threshold for admission.

Patients should be educated about practices that have been shown to reduce the morbidity and mortality from IDU. They should be referred for substance abuse treatment and, if available, to needle exchange; hepatitis, influenza, and pneumococcal vaccination programs; and for HIV, hepatitis, and sexually transmitted disease screening. Innovative efforts have combined screening for substance use, motivational interviewing, and linkage to drug abuse treatment. Patients can be referred to acupuncture, detoxification, needle exchange programs, outpatient buprenorphine providers, and other resources. Patients who continue to use injection drugs benefit from education about prevention practices, such as antiseptic skin preparation prior to injection, the use of bleach for cleaning needles and syringes, and the use of condoms. Programs that combine medical care with public health services have reduced ED visits by 40%, surgical admissions by 43%, and operating room procedures by 71% (7).

Common Pitfalls

- Failure to ask about IDU in all patients, including adolescents and older adults.
- Failure to consider the possibility of undiagnosed HIV infection.
- Labeling patients with IDU as "drug seekers" or allowing a judgmental attitude to interfere with a careful medical evaluation.
- Failure to appreciate that IDU patients with back pain as a result of vertebral infection may provide a history of minor trauma and have a normal neurologic examination.
- Attributing fever in an IDU to a trivial illness or to cotton fever.
- Attempting to drain a soft tissue mass in proximity to a major blood vessel.
- Failure to consider the possibility of arterial injection, compartment syndrome, deep-space infection, or nerve injury in patients with limb complaints.
- Failure to appreciate that extensive abscesses cannot be adequately drained in the ED.

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PART 4 • ANTICONVULSANTS AND SEDATIVE-HYPNOTICS

CHAPTER 307

Barbiturates

Samuel J. Stellpflug and Carson R. Harris

Barbiturates are central nervous system (CNS) depressants used as anxiolytics and hypnotics, for the induction of anesthesia, and as anticonvulsants. They act by enhancing γ-aminobutyric acid (GABA) inhibition in excitable tissues mainly in the CNS, but also to a lesser extent in skeletal muscle, smooth muscle, and heart. Barbiturates bind to the $GABA_A$ receptor complex, augment the chloride current and also increase the duration of channel opening, hyperpolarizing the cells and thereby inhibiting depolarization. This enhances the activity of GABA, potentially acting synergistically with other GABA-active agents. That being said, especially in high doses, barbiturates can stimulate $GABA_A$ receptors directly even in the absence of GABA. In addition, phenobarbital also decreases the paroxysmal firing of nerve cells by an unknown mechanism along with GABA stimulation. Barbiturates are divided into four distinct categories based on their duration of action: (1) ultrashort-acting, (2) short-acting, (3) intermediate-acting, and (4) long-acting barbiturates (Table 307.1).

TABLE 307.1
Barbiturate Kinetic Data

Drug	Usual Adult Dose (mg)	Onset (hr)	Peak (hr)	Duration (hr)	Half-Life (hr)	Percentage Protein Binding	Volume of Distribution (L/kg)
Ultrashort-Acting							
Thiopental	50–75	<0.1	<0.1	<0.5	3–11	72–86	1.4–6.7
Methohexital	50–120	<0.2	<0.2	<0.5	1–4	83	1–2.6
Short-Acting							
Pentobarbital	50–200	0.25	0.5–2	>3–4	15–50	45–70	0.5–1
Secobarbital	100–200	0.25	1–6	>3–4	19–34	45–70	1.5–1.9
Intermediate-Acting							
Amobarbital	65–200	<1	2	>4–6	10–40	59	0.9–1.4
Aprobarbital	40–160	<1	12	>4–6	14–34	20	—
Butabarbital	100–200	<1	0.5–1.5	>4–6	66–140	26	—
Butalbital	100–200	—	2	—	61	—	—
Long-Acting							
Mephobarbital	50–100	0.5–2	—	>6–12	10–70	40–60	2.6
Phenobarbital	100–320	<0.1	0.5–2	>6–12	80–120	20–50	0.5–0.9
Primidone	300–1,000	—	—	—	3.3–12	20–30	0.4–1

The ultrashort-acting barbiturates (thiopental, methohexitol) are highly lipophilic, rapidly entering the CNS, and thus their primary use is anesthesia induction. Overdose of this group of barbiturates is typically iatrogenic as these agents are available only as intravenous formulations.

Short-acting barbiturates (pentobarbital, secobarbital) were extensively prescribed in the 1960s and 1970s as sedative–hypnotics. In the late 1970s, nearly 70% of all suicides by drug ingestion involved barbiturates (1). Their use markedly declined over the subsequent decades with the introduction of newer and safer sedative–hypnotics and anticonvulsants. Short-acting barbiturates have a lower therapeutic margin than the benzodiazepines, more frequent development of tolerance, and a greater potential for abuse. Moreover, drug–drug interactions are numerous, with more than 150 drugs and herbal interactions.

Intermediate-acting barbiturates (amobarbital, aprobarbital, butabarbital, butalbital) are most commonly found in combination analgesic medications (Fiorinal, Fioricet, etc.) containing butalbital to treat tension–vascular headaches. Amobarbital and butabarbital have been replaced by benzodiazepines, and the use of sodium amobarbital as “truth serum” has allegedly long been abandoned.

Long-acting barbiturates (phenobarbital and primidone) are still used to treat epilepsy. They have lower lipid solubility than short-acting barbiturates, causing them to accumulate more slowly in tissue and to have peak effects that are delayed for several hours.

Onset of symptoms usually occurs within 1 to 2 hours, and the peak effect may occur more than 10 hours after ingestion (2).

Pharmacokinetic data are summarized in Table 307.1. Barbiturates are well absorbed from the intestinal tract, except for mephobarbital, which is about 50% absorbed. The onset of action varies from 10 to 60 minutes depending on the agent and formulation. Food in the stomach decreases the rate of absorption but not the total amount absorbed. In overdose, the onset and peak of symptoms may be delayed. Ultrashort-acting barbiturates are administered intravenously, with initial effect seen within 1 minute and duration of effect of 10 to 30 minutes. Short-acting barbiturates are almost entirely metabolized in the liver to inactive metabolites that are excreted in the urine as glucuronides. However, liver metabolism of barbital, phenobarbital, primidone, and phenylethylmalonamide is limited because of lower lipid–water partition coefficients; so urinary excretion accounts for 95%, 25% to 35%, 15% to 42%, and 95% of the elimination of these agents, respectively. Phenobarbital undergoes enterohepatic recirculation, which contributes to its long half-life.

Barbiturates induce cytochrome P450 isozymes, including CYP2C9, CYP2C19, CYP2C8, and CYP3A4, thus enhancing elimination of other drugs metabolized by these enzymes. Although phenobarbital is a strong inducer of cytochrome P450, it does not induce its own metabolism and appears to have a longer half-life with chronic use (2). Barbiturates also induce δ-aminolevulinic acid (ALA) synthetase, leading to increase production of δ-ALA, a precursor of porphobilinogen. This may precipitate attacks of acute intermittent porphyria and porphyria variegata in susceptible individuals; thus porphyria, although uncommon, is a contraindication to barbiturate use.

CLINICAL PRESENTATION

Significant ingestions are now rare but still life-threatening and typically present with depressed level of consciousness ranging from lethargy to deep coma. Patients may also have respiratory depression, which is responsible for most deaths. With the short and

intermediate-acting barbiturates, symptoms usually begin within 1 hour of ingestion, and peak effects are seen within 4 to 6 hours. Patients with chronic lung disease and sleep apnea are more susceptible to severe respiratory depression, even at therapeutic doses. Other clinical findings in overdose include hypothermia, sluggish pupillary light reflex, nystagmus, and diminished bowel sounds. Bullous skin lesions, occasionally referred to as “coma blisters,” may appear on shoulders, hands, buttocks, and knees, where the body weight has caused pressure ischemia to the skin. About 40% of patients with severe toxicity also develop aspiration pneumonia (3). Cardiovascular collapse may manifest with bradycardia or tachycardia, hypotension, and shock. Drug-induced venous dilatation with consequent pooling of blood and reduction in effective vascular volume can lead to shock. Prolonged coma increases the risk for hypothermia, venous thromboembolism, rhabdomyolysis, and acute tubular necrosis secondary to shock. The acid–base abnormality, especially in a severe overdose, is likely to be a mixed respiratory and metabolic acidosis from hypoventilation and lactate. Coingested ethanol, benzodiazepines, and barbiturates have synergistic effects, and there is increased risk even when lesser amounts are ingested. Withdrawal symptoms occur when the drug is discontinued after chronic use of barbiturates leads to tolerance. Tolerance can develop with prolonged use and abuse, leading to a progressive increase in doses needed to achieve the desired effect. The withdrawal state is similar to ethanol withdrawal.

Laboratory abnormalities include hypoglycemia, electrolyte disturbances, and alterations in acid–base and fluid balance. The creatine phosphokinase (CPK) may be elevated if the patient has been comatose and immobile for a prolonged period. A chest radiograph may show aspiration pneumonia or pulmonary edema. The electrocardiogram (ECG) is usually normal but in severe toxicity may show bradycardia or tachycardia. The electroencephalogram (EEG) shows diffuse slowing during barbiturate-induced coma.

The amount of drug required to produce toxic symptoms can vary significantly depending on patient tolerance (4). The therapeutic doses for common barbiturates are given in Table 307.1. For

nonaddicted patients, the toxic dose for short-acting barbiturates is about 3 to 6 g (5 to 8 mg/kg in pediatrics) and for phenobarbital is about 6 to 9 g (8 mg/kg in pediatrics). Patients with physical dependence on barbiturates may tolerate higher doses. Geriatric patients may be much more sensitive to drug effects and can present with significant findings at lower doses. This may be attributed to decreased enzyme activity in the elderly and the higher likelihood of drug interactions and comorbidities in this population (5).

DIFFERENTIAL DIAGNOSIS

Other sedative–hypnotic agents, opiates, or alcohol intoxication should be included in the differential. Similar presentations may be encountered with γ-hydroxybutyrate, clonidine, skeletal muscle relaxants, and imidazoline decongestants (e.g., oxymetazoline). An overdose of psychiatric medications such as cyclic antidepressants, trazodone, phenothiazines, and antipsychotics also cause sedation and respiratory depression. Carbon monoxide poisoning, head trauma, CNS infections, sepsis, hypoglycemia, electrolyte abnormalities, and hypothermia may present similarly to barbiturate overdose and must be considered.

ED EVALUATION

The initial history is not always obtainable or reliable but, when possible, one should attempt to identify the drug ingested, the approximate amount ingested, the time of ingestion, and the reason for the ingestion (i.e., accidental or intentional). The physical examination should focus on the vital signs, including rectal temperature and oxygen saturation, and the degree of CNS depression. Other findings on examination may point to unsuspected trauma or other conditions in the differential. Absence of bowel sounds suggests ileus; suprapubic percussion or bedside ultrasound may detect a distended bladder.

After initial stabilization, physical examination, bedside fingerstick glucose and basic metabolic panel (electrolytes, blood urea nitrogen, creatinine) should be ordered. Testing is generally not helpful in the diagnosis but can detect other condition and may help general

supportive care. These include breath or blood alcohol concentration, and an acetaminophen concentration should be considered, as with most ingestions, and especially since it is contained in some preparations of barbiturate combination products. A salicylate concentration, and an ECG are reasonable, however will not be diagnostic of barbiturate ingestion. A complete blood count is almost always quite unhelpful. A total CPK concentration is reasonable, especially if there is concern for prolonged patient down time. With signs of acid–base imbalance blood gas analysis (venous if patient is well perfused, arterial if the patient has hemodynamic compromise) can help in the analysis. Chest radiography may reveal normal findings, however pulmonary edema and signs of aspiration are common. As with other causes of altered mental status, head computed tomography and lumbar puncture for testing is sometimes necessary to rule out causes other than ingestion. In the case of prolonged ED stay time, EEG can be obtained in the nonresponsive patient, but should not be used to rule out barbiturate overdose, as the EEG can reflect brain death in this setting.

Barbiturate-specific testing does not impact decision making in the emergency department (ED). Clinical signs of barbiturate overdose should dictate management rather than relying on serum or urine concentrations. Rapid urine immunoassay testing (“drug screen”) for qualitative presence of barbiturates is relatively reliable for exposure (more reliable than other drug classes tested by urine immunoassays), but is not particularly helpful because the exposure could have been hours or days prior to arrival and may not have anything to do with the clinical presentation. There can be an argument for never ordering rapid urine immunoassay screens in the workup of overdoses. Blood concentrations are not available at many facilities, and plasma concentrations may not accurately reflect brain concentrations, as tissue solubility changes with fluctuation in pH. However, quantitative testing can be done with more advanced techniques on serum and urine with chromatography combined with mass spectrometry, and this should be considered in cases where child abuse, elder abuse, and drug-facilitated sexual assault are

concerns. This may also prove beneficial in cases of clinical brain death without another reasonable cause.

KEY TESTING

- There are no specific tests for typical cases.
- Qualitative barbiturates levels may be helpful to document in cases of child abuse, elder abuse, date rape, and falsely presumed brain death.

ED MANAGEMENT

The treatment of barbiturate toxicity is primarily supportive. Patients with depressed respirations and altered mental status require airway management and intubation to support breathing and protect the airway. Blood pressure should be supported initially with intravenous crystalloid, administering 10 to 20 mL/kg boluses barring preventive comorbidities, and with close monitoring of response. The core temperature should be checked and rewarming instituted if needed. Management decisions should be based on the patient's clinical condition rather than on blood drug levels.

For serious phenobarbital overdose, multidose activated charcoal (MDAC) leads to more rapid recovery and a significant reduction in elimination half-life (6,7). The usual dose is 1 g/kg, followed in 2 to 4 hours by 0.5 g/kg in aqueous solution and alternating for 24 hours. Sorbitol-based charcoal has fallen out of favor and aqueous-based charcoal should be used.

Barbiturates are weak acids, and theoretically increasing the urine pH increases the fraction of ionized drug in the urine and thus decreases the amount of nonionized drug available for passive tubular reabsorption. This is most well established for phenobarbital and not well for other barbiturates; urine alkalinization can increase the renal clearance of phenobarbital up to 10-fold and can shorten the half-life by one-half to two-thirds (8). The best evidence for urinary alkalinization even in the context of phenobarbital is inferior to MDAC. There are no data to support the use of urine alkalinization for overdose with short- and intermediate-acting barbiturates (8).

Urine alkalinization is contraindicated in patients with renal insufficiency and cerebral or pulmonary edema.

Hemodialysis may be used in life-threatening barbiturate overdose (9). Early notification of the nephrology service can expedite initiation of treatment. Both charcoal hemoperfusion and high-flux hemodialysis enhance the elimination of all barbiturates. High-efficiency hemodialysis with a high blood flow rate may be superior to hemoperfusion which is also difficult to accomplish and has more inherent complications than dialysis (10). As these procedures have some risk, their use should be reserved for patients with pulmonary edema, cerebral edema, or shock unresponsive to supportive measures.

CRITICAL INTERVENTIONS

- Provide appropriate airway management with supplemental oxygen.
- Treat hypotension with intravenous fluids, and vasopressors if necessary.
- Administer MDAC, especially for phenobarbital poisoning.
- Consider early hemodialysis for severe overdoses, especially phenobarbital ingestions.

DISPOSITION

Nephrology consultation should be obtained when hemodialysis is being considered. Awake patients who have ingested short-acting barbiturates and whose symptoms are mild and are not progressing may be observed for 4 to 6 hours and then evaluated for psychiatric admission or discharged. For patients who have ingested long-acting barbiturates, the observation period should be based on both barbiturate levels *and* clinical symptoms. If quantitative serum concentrations are available (as with phenobarbital), serial concentrations can be obtained and the patient observed until concentrations peak and are decreasing, although this should likely be done during inpatient stays rather than in the ED. Patients with abnormal vital signs or significant CNS depression should be

admitted to an intensive care unit. Patients who require intensive care or extracorporeal elimination may need to be transferred if necessary. Advanced life-support measures to stabilize the patient and activated charcoal given prior to transfer. Suicide evaluation is indicated for all suspected suicide attempts when the patient is alert enough to be interviewed.

Common Pitfalls

- Failure to check for hypoglycemia as a cause of altered mental status.
- Failure to protect the airway in a somnolent patient.
- Failure to repeat MDAC and failure to check bowel sounds.
- Failure to consider barbiturate withdrawal in patient with seizures.

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CHAPTER 308

Benzodiazepines

Samuel J. Stellpflug and Carson R. Harris

There are many different benzodiazepines (BZDs) marketed in the United States (Table 308.1) and these are widely used as anxiolytics, muscle relaxants, and anticonvulsants. Although BZD abuse and overdose is very common, life-threatening toxicity and fatalities are comparatively rare (1). That being said, BZDs are used for panic disorder and anxiety, conditions that may increase the risk of overdose (2). In addition, BZDs increase the risk of falling, particularly in the elderly and other physically at risk populations.

TABLE 308.1
Benzodiazepines Dosage and Kinetics

Agent	Dosage Oral (Adult mg/d, Child mg/kg/24 hr)	Peak Plasma Concentration (hrs)	Half-Life (hrs)	Major Active Metabolites ($t_{1/2}$ hrs)	PB (%)	Vd L/kg
Alprazolam (Xanax)	0.75–4 (1) 0.25, 0.5, 1 tabs	0.7–1.6	6–26	Yes	68–80	0.7–1
Chlordiazepoxide (Librium)	15–100 (25) 0.5 mg/kg/24 h 5, 10, 25 mg tabs	2–4 Total 2–5 d[c]	5–30	Desmethyl CPZ demoxepam, desmethyl DZP (0–100)	95	0.3
Chlorzepate (Tranxene)	15–60 (15) 3.75, 7.5, 15 mg tabs	1–2.5[a] Total 2–4 d[c]	1.1–2.9	Desmethyl DZP (50–100) Elimination	NA	0.1–0.8
Clonazepam (Klonopin)	1.5–20 (2) 0.1–0.2 mg/kg/24 hr 0.5, 1, 2 tabs	1–4	18–50 2–3 d[c]	Desmethyl DZP (50–100)	74–80	3.2
Diazepam (Valium)	6–40 (10)[d] 0.12–0.8 mg/kg/24 hr 2, 5, 10, 15 mg tabs	1–2 Total 2–4 d[c]	14–100	Desmethyl DZP (50–100) Oxazepam (active)	98	0.9–1.1
Estazolam (Prosom)	1–2 mg 1, 2 mg tabs	1–2	12–15	1-oxo-estazolam	NA	NA
Flunitrazepam (Rohypnol)	1–2	<1	24	7-Aminoflu-nitrazepam (23) N-desmethyl flunitrazepam (31)	NA	NA
Flurazepam (Dalmane)	15–60 (30) 15, 30 tabs	0.5–2	1.6–5.3 2–4 d[c]	desalkyl FZP (50–100)	NA	1–1.3
Halazepam (Paxipam)	60–160 (40) 20, 40 mg tabs	1–3 Total 2–4 d[c]	1.6–5.3	3-Hydroxy desmethyl DZP (50–100)	NA	3.4
Lorazepam (16) (Ativan)	2–6 (2) 0.05–0.2 mg/kg/dose 0.5, 1.2 tabs	2–5 IV	10–20	None	85–95	NA
Midazolam (Versed)	5–30 (7.5–15) PO >6 yr syrup 0.25–1 mg/kg	20–50 min 3–5 min after IV dose	1.2–12.3	α_1-hydroxy	97	0.8–1.7
Nitrazepam (Mogadon)	5–10 (10)	2	24–29	No data Not currently available	NA	NA
Oxazepam (Serax)	30–120 (30) 10, 15, 30 tabs	1–2	8–25	None Elimination	97	0.6–2
Prazepam (Centrax)	20–60 (10) 5, 10 mg tabs	6 Total 2–4 d[c]	0.6–2	3-Hydroxy desmethyl DZP	NA	9–19
Quazepam (Doral)	15 7.5, 10 mg	2	39	N-desalkyl-2-oxoquazepam	95	NA
Temazepam (Restoril)	15–30 (20) 15, 30 tabs	2–3	10–20	None	96	0.7–1.5
Triazolam (Halcion)	0.125–0.5 (0.5) for debilitated or elderly, max dose 0.25 mg 0.125, 0.25, 0.5 mg 2–5	0.5–1.5	2–5	None	90	0.8–1.3
Zaleplon (Sonata)[b]	5–20 mg 5, 10 mg tabs	1	1	5-oxo-zaleplon	60	1.4
Zolpidem (Ambien)[a]	5–20 mg 5, 10 mg tabs	1–2	1.5–2.5	3 inactive	92	0.54

IV, intravenous; PB, protein binding; Vd, volume distribution
[a]not a benzodiazepine chemically but an imidazopyridine, which is selective benzodiazepine-1 receptor agonist.
[b]Not abenzodiazepine but a pyrazolopyrimidine derivative which is a $GABA_A$ benzodiazepine receptor agonist
[c]Half-lives include active metabolites.
[d]Average dose in parentheses.
Note: Half-lives vary; some include the metabolites half-life.

BZDs potentiate the inhibitory action of GABA by enhancing channel flow after binding nonselectively at BZD receptor sites that contain the $GABA_A$ α_1 subunit (3). BZDs enhance chloride ion permeability, rendering postsynaptic sites less excitable. Several BZD receptor sites have been identified in the CNS that modulate anxiolytic, hypnotic, neuroleptic, and anticonvulsant properties (3).

Receptor antagonists, such as flumazenil, competitively inhibit BZD effects.

Gastrointestinal (GI) absorption is rapid and complete for most BZDs, but absorption by the intramuscular route can be erratic and delayed. After oral administration, the rate of GI absorption, rather than lipophilicity, determines the onset of action. Diazepam, alprazolam, and triazolam are the most rapidly absorbed oral agents; prazepam is the slowest. Peak concentrations occur in 1 to 3 hours; ethanol enhances absorption and may cause the peak concentration to occur closer to 1 hour. In general the BZDs are highly protein-bound (85% to 99%).

After a single dose the more lipophilic BZDs, such as diazepam and midazolam, have a shorter duration of CNS action than less lipid soluble BZDs, such as lorazepam and chlordiazepoxide. Increasing lipophilicity enhances drug distribution out of blood and brain into inactive peripheral storage sites (adipose tissue), but after multiple doses, lipophilicity prolongs elimination. BZDs are primarily eliminated through hepatic metabolism. The two principal pathways involve either hepatic microsomal oxidation (*N*-dealkylation or aliphatic hydroxylation) or glucuronide conjugation (eFig. 308.1). BZD are substrates for cytochrome P450 (CYP) 2C19 and CYP 3A4 hepatic enzymes. CYP 3A4 is inducible by a variety of drugs, including rifampin, phenobarbital, and phenytoin (4). Elimination half-life can be increased by microsomal enzyme inhibitors, especially with midazolam. Examples of inhibitors include clotrimazole, erythromycin, estrogens, isoniazid, and ketoconazole (4). The elimination half-life is prolonged in elderly men because of unknown mechanisms, in obese patients because of an increased volume of distribution (Vd) and in patients with hepatic dysfunction because of impaired metabolism. Pharmacokinetic parameters and duration of action are summarized in Table 308.1.

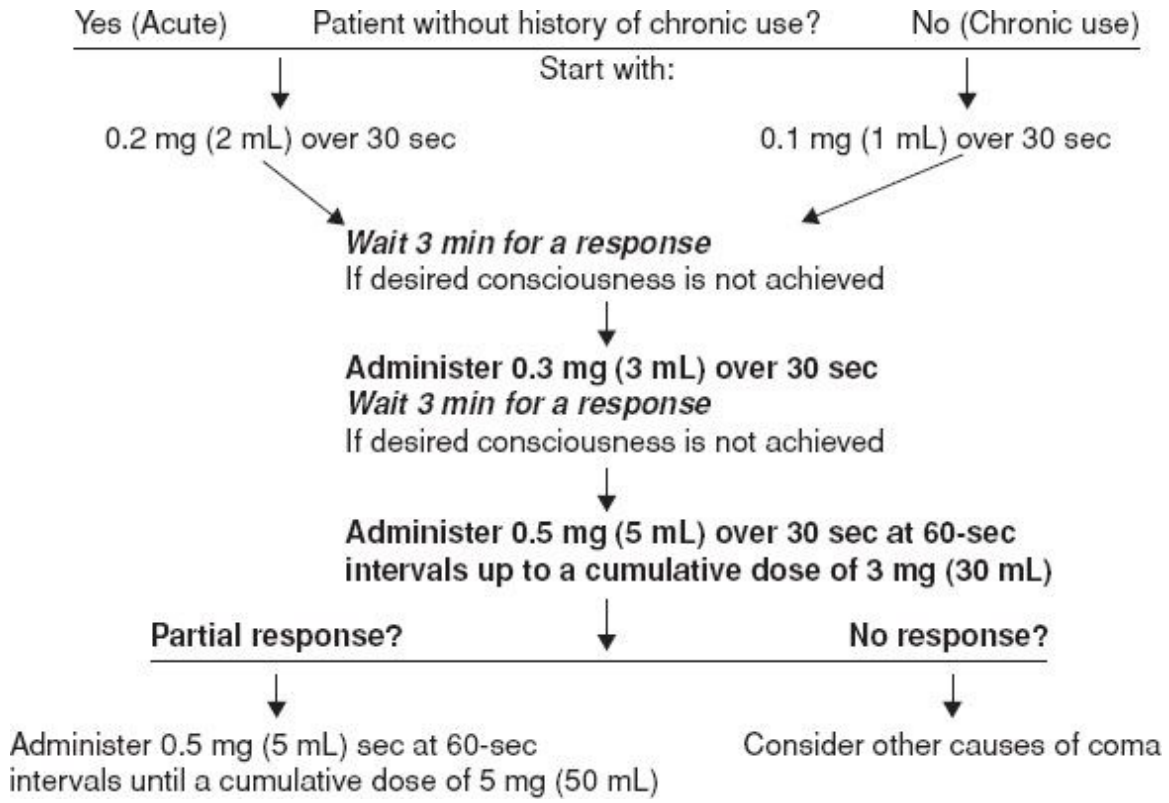
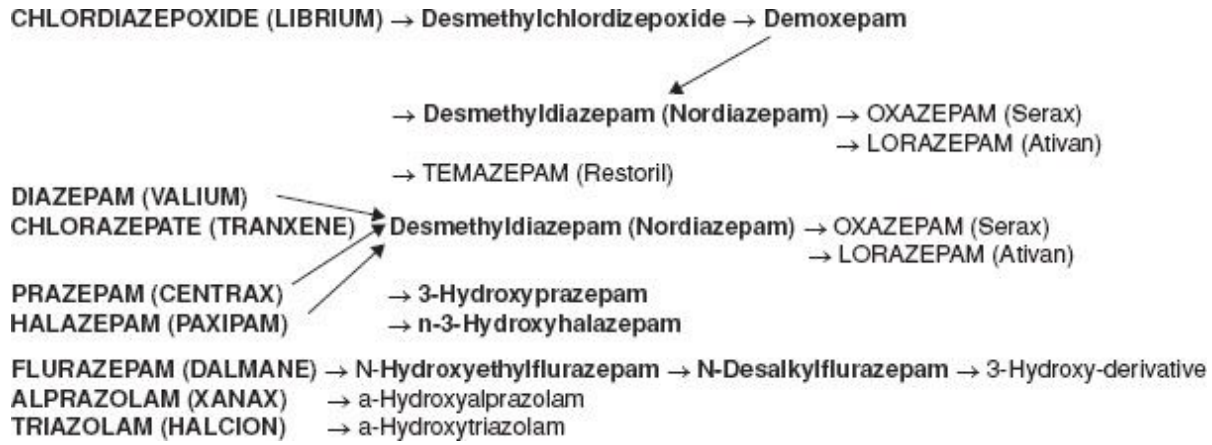


FIGURE 308.1 Flumazenil dosing for acute benzodiazepine exposure.



eFIGURE 308.1 Metabolism of benzodiazepines. Compounds in upper-case bold have active metabolites. Compounds in upper-case nonbold are active drugs without active metabolites. Compounds in lower-case bold are active metabolites. Compounds in lower-case nonbold are not clinically significant active metabolites.

A specific lethal dose for BZDs has not been established, as BZD-associated deaths most often occur in combination with other CNS depressants, such as ethanol. Rapid intravenous administration may result in apnea and hypotension. The propylene glycol vehicle used in parenteral BZD formulations may cause cardiovascular toxicity and may also lead to elevated anion gap metabolic acidosis.

Flunitrazepam (Rohypnol), known on the street as “roofies,” “Mexican valium,” “parachute,” and “roach 2,” is a BZD with a fast plasma peak sold by prescription in many countries. Flunitrazepam is sold illegally in the United States and abused as a “date rape” drug because of the antegrade amnesia it causes (3). The drug readily mixes with alcohol-containing beverages, although the manufacturer (Roche) has produced tablets that will break down into small particles and turn the beverage blue. It is touted as a remedy for the depression that often follows a stimulant high, hence the street name “parachute.” The onset of effects is within 0.5 to 2 hours, peak effect is <2 hours after oral ingestion, the duration of action is 8 hours or more after a 2-mg dose, and an elimination half-life is 20 to 30 hours (5). Flunitrazepam can be identified in urine from 4 to 30 days after ingestion, although routine drug screening immunoassays does not detect flunitrazepam. Your local laboratory may refer you to a national laboratories (such as NMS 800-522-6671) that can do forensic testing for “date rape” drugs. Quantitative drug levels are not useful or emergency department (ED) management but may confirm a diagnosis. Tolerance, drug coingestion, active metabolites, and distant tissue binding sites result in poor correlation between blood concentrations and clinical effects.

Newer “Z drugs” have replaced some BZD use because of their supposed lower side effects (6). Zolpidem (Ambien) is a non-BZD, imidazopyridine sedative–hypnotic drug. Imidazopyridines are thought to interact with the same GABA receptor/chloride channel complex as the BZDs by high affinity with the “central-type” BZD receptors. Zolpidem is approved only for short-term treatment of insomnia. It is rapidly absorbed from the GI tract, with a Vd of 0.54 L/Kg, 92.5% protein binding, and serum peak concentrations being reached in 1 to 2 hours. It is metabolized in the liver and has a half-

life of 2.5 hours, but is prolonged in the elderly (6). Like the BZDs, zolpidem overdose does not typically produce severe respiratory depression unless other agents are coingested. Although zolpidem produces some psychomotor and memory impairment over the first few hours after administration, it has few next-day effects (including effects on daytime well-being and morning coordination). Caution should be exercised in patients with obstructive sleep apnea. Adverse effects include headache, nausea, diarrhea, miosis, and next-day drowsiness. Confusion in the elderly can occur at doses of more than 20 mg. Zolpidem can cause withdrawal and tolerance (7).

Zaleplon (Sonata) is another non-BZD used for the short-term treatment of insomnia, which appears to cause less tolerance than triazolam, is less likely to potentiate the effects of ethanol, and is unlikely to produce amnestic effects. Zaleplon is rapidly absorbed and undergoes extensive presystemic metabolism. The compound has a plasma half-life of approximately 1 hour and is metabolized primarily via the aldehyde oxidase system. Because CYP3A4 may also contribute to metabolism (8), CYP inhibitors or inducers may affect zaleplon or the other drugs. The abuse potential of zaleplon (at doses above the therapeutic dose range) is similar to that seen with triazolam. Rebound insomnia and other withdrawal effects have not been demonstrated with zaleplon, and the drug is well tolerated in both young and elderly patients. These characteristics may be clinically advantageous for patients who should not receive BZDs (8) (see Chapter 310, Other Sedative-hypnotic Agents).

CLINICAL PRESENTATION

Manifestations of BZD poisoning include ataxia, lateral nystagmus, hypotonia, drowsiness, slurred speech, and coma (9). Even when BZDs are given in large doses, a deep coma causing cardiorespiratory depression and loss of deep tendon reflexes is rare. The ultrashort-acting agents and temazepam are important exceptions and are more dangerous.

Paradoxical excitement, including hallucinations, hostility, and seizures, have been reported with BZD overdose. Triazolam can produce delirium and psychosis. The elderly and very young children

are more susceptible to the CNS depressant action of BZDs. The toxic dose of flunitrazepam for a child is 0.1 mg/kg and is approximately 10 times as potent as diazepam. Most patients with acute BZD poisoning, however, recover without sequelae within 24 hours. Patients with pre-existing medical conditions such as hepatic disease may be more susceptible to toxicity.

A spectrum of affective disorders (psychosis, agitation, confusion, hallucinations, and delirium) and motor dysfunction (tremors, restlessness, myoclonic jerks, and seizures) may develop on withdrawal from diazepam when taken in daily doses of 60 to 300 mg. Seizures are rare and most commonly develop 7 to 8 days after withdrawal (range, 2 to 12 days). Withdrawal symptoms develop in an average of 3 to 4 days after discontinuation (range, 1 to 11 days), peak in 5 to 6 days, and resolve by 4 weeks, but minor symptoms may persist for months. Earlier onset and peak and shorter duration of withdrawal may be seen with shorter-acting agents (see Chapter 351).

DIFFERENTIAL DIAGNOSIS

The presence of deep coma, apnea or significant respiratory depression, hypotension, multiple organ involvement, or a prolonged time for recovery should prompt a search for coingestants (ethanol, other alcohols, other sedatives, narcotics, sympatholytics, cholinergics) or another cause (e.g., CNS lesions, trauma, infection, or metabolic disturbances). There is a long differential for decreased level of consciousness (see Chapter 11).

ED EVALUATION

The history should include the time and intent of all agents ingested and the amount and duration of chronic daily BZD documented, if possible. The physical examination should focus on vital signs, level of consciousness, cardiorespiratory function, and the ability of the patient to protect the airway.

Except for measurement of oxygen saturation, routine laboratory tests are not necessary in the verbally responsive patient. Unresponsive patients need appropriate testing for supportive care

such as a complete blood count, metabolic profiles, urinalysis, and blood gas analysis (venous if well perfused, arterial if hemodynamically compromised). Serum and urine testing for BZD is not helpful for clinical management but may confirm the presence of the drug to document in child abuse, elder abuse, sexual assault, and falsely presumed brain death. Most urine toxicology testing using immunoassay screening techniques have many false negatives since they detect only BZDs that are metabolized to desmethyldiazepam or oxazepam. In addition, most BZDs are not detected by thin-layer chromatography of the urine as a result of low drug concentrations.

KEY TESTING

- There is no special testing for BZD poisoning. Testing should be done as part of usual supportive care.
- Serum acetaminophen and other tests may rule out other exposures.

ED MANAGEMENT

Advanced life-support measures should be instituted as necessary. Massive overdoses of BZDs may have severe effects but most patients do well with simply good supportive care (9). Supportive therapy is usually all that is necessary when a BZD is the sole agent involved. Activated charcoal should be considered for patients within 1 hour of ingestion, although the evidence supporting this practice is lacking. Forced diuresis and hemodialysis are ineffective in enhancing BZD elimination because of high protein binding and volume of distribution. In uncomplicated cases, full recovery can be expected within 12 to 24 hours.

Flumazenil (Romazicon) is a specific competitive BZD receptor antagonist that reverses BZD-induced CNS depression. It also appears to reverse the sedative effects of zolpidem and endogenous BZD receptor agonists associated with hepatic encephalopathy. It does not antagonize other portions of the GABA receptor (e.g., barbiturate, ethanol, and general anesthetic binding sites) and does not change the bioavailability, plasma concentration, or elimination half-life of

BZDs. Most important, it may not reverse BZD-induced hypoventilation (10). Airway protection and mechanical ventilation are definitive treatment for respiratory distress or failure. In overdoses, flumazenil is best reserved for patients with pure, acute BZD overdose who are verbally unresponsive and have no history of seizures or long-term BZD use, as reversal may precipitate acute withdrawal. The use of flumazenil as a diagnostic and therapeutic tool in general patients with coma of uncertain etiology is not recommended.

In intravenous doses of 0.1 to 0.2 mg, flumazenil is partially antagonistic. In doses of 0.4 to 1 mg, onset of action and reversal of the CNS effects are evident within 1 to 2 minutes. An 80% response occurs within 3 minutes, and the peak effect is within 6 to 10 minutes. Duration and degree of reversal is related to the dose and the plasma concentration of BZD. Because flumazenil has a shorter duration of action than most BZDs, a 1-mg bolus usually lasts about 60 minutes but can last as long as 6 hours (10). The suggested treatment protocol for using flumazenil in patients with known or suspected BZD overdose is shown in Figure 308.1. It may be repeated in boluses of 0.1 mg or administered as an infusion of 0.1 to 0.5 mg/hr if necessary.

Patients who respond to flumazenil should be monitored for recurrence of sedation. Furthermore, because flumazenil may not reverse hypoventilation, patients who awaken may need to be reminded to breath (i.e., “take a deep breath”), and the adequacy of ventilation must be frequently reassessed. Emergence reactions after flumazenil administration (e.g., anxiety, agitation, confusion) can occur, particularly when flumazenil is given rapidly or in higher doses.

Flumazenil has no significant intrinsic pharmacologic activity. It has been reported to cause withdrawal and seizures in BZD-dependent patients, and it should be used in such patients with caution with lower than recommended doses and slower administration if the benefits are felt to outweigh the risks. Seizures have also been reported after flumazenil in patients intoxicated with cyclic antidepressants, cocaine, or isoniazid and in those with CNS

trauma. Flumazenil should not be given to patients taking BZDs as an anticonvulsant. A flumazenil-related dystonic reaction has also been reported. Naloxone, physostigmine, and stimulants such as aminophylline or theophylline are not indicated in the treatment of BZD poisoning.

Stopping the use of BZDs in any patient who has been maintained on these drugs longer than 6 weeks should be accomplished gradually over a minimum of 3 weeks and up to 2 to 3 months BZD withdrawal is managed with oral diazepam (10 to 60 mg) for several days, followed by tapering the dose by 10% daily, usually over several weeks with close follow-up.

CRITICAL INTERVENTIONS

- Protect the airway and provide ventilatory support with CNS depression.
- Titrate the dose of flumazenil to the desired effect, beginning with low doses and waiting at least 3 minutes for a response before administering incremental doses, particularly in patients with chronic BZD use.
- Most cases of BZD poisoning alone require only ED observation.

DISPOSITION

Patients with mild clinical toxicity (lethargic or asleep but who respond to verbal stimuli) can be observed in the ED until they recover. Psychiatric evaluation should be performed unless the exposure is accidental. Outpatient referral and follow-up are indicated for patients who have evidence of chronic abuse, dependence, or psychological problems such as depression and do not require inpatient therapy.

Patients who respond only to painful stimulation, regardless of whether flumazenil is given, probably require 12 or more hours of monitoring and treatment. If ED observation is not possible, these patients should be admitted to a closely monitored setting. Transfer is rare and indicated only if the initial facility lacks the equipment or personnel for caring for intubated patients.

Common Pitfalls

- Failure to consider coingestants or other causes of CNS dysfunction in patients with severe CNS depression.
- Failure to appreciate that most urine screening tests do not detect all BZDs.
- Failure to appreciate that flumazenil can precipitate seizures in patients with chronic BZD use, history of seizures, or the coingestion of drugs known to cause seizures.
- Failure to appreciate that recurrent toxicity can develop after flumazenil administration and that continued observation is necessary.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Matthew W. Morgan, Thomas R. Carraccio, Howard C. Mofenson, and Robin B. McFee to this chapter in previous editions.

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CHAPTER 309

Gamma Hydroxybutyrate

Stephen W. Smith

Gamma hydroxybutyrate (GHB) is a central nervous system (CNS) depressant and drug of abuse that is also present endogenously, at trace levels, in the brain and peripheral tissues. GHB occurs as a metabolite and precursor of the neuroinhibitory transmitter, gamma aminobutyric acid (GABA) and is proposed to be a neuromodulator. Initially used in France in 1960 as an anesthetic, popular use of GHB for purported anabolic effects began in the 1980s, followed by recreational use for euphoric, soporific, stimulant, and sexual effects. Use of GHB analogs (or precursors), gamma butyrolactone (GBL) and 1,4 butanediol (BD) began in the late 1990s in the form of GBL- and BD-containing "dietary supplements" (subsequently removed from the market). Both GBL and BD are industrial chemicals that, when ingested, are rapidly metabolized to GHB, with the same toxic and recreational effects (1). Unless specifically noted, references to GHB in this chapter refer to GHB and analogs.

Abuse of GHB, GBL, and BD continue. GHB is available through street supplies and is easily manufactured in home kitchens using "recipes" and ingredients readily available on the Internet. GBL and BD remain available as industrial chemicals and in cleaning products and solvents, including GBL-containing acetone-free nail polish removers. Product concentrations vary widely and are often unknown to users (2,3).

CLINICAL PRESENTATION

Acute GHB Toxicity

Although there is significant variability of GHB effects, the characteristic presentation of acute GHB toxicity is dose-related CNS depression, manifested as somnolence, lethargy, hypothermia, bradycardia, respiratory depression, coma, and death (1,2,4). The onset of coma may be rapid and abrupt, with Glasgow Coma Scale (GCS) scores of 3; symptoms typically resolve within several hours. Biphasic stimulant-sedative effects of GHB have been documented (5) and stimulant effects such as psychomotor agitation are commonly seen in acute toxicity cases, even in the absence of stimulant co-intoxicants. Agitation may occur before coma, in rapid alternation with somnolence or coma, in response to interventions such as intubation, as emergence delirium, or in the form of self-injurious behaviors (4,6). Urinary and fecal incontinence may occur, as well as nausea and vomiting, the incidence of which may be increased with alcohol co-ingestion. Myoclonus and/or seizure-like effects may occur and, far less frequently, true seizures. Ophthalmologic effects include blurred or distorted vision, loss of peripheral vision, disconjugate gaze, and nystagmus. Although controlled study has shown pupillary dilation with GHB administration, pupillary reactions in GHB toxicity cases are variable, likely due to effects of co-intoxicants. Rare cases of cardiac arrhythmias and atrial fibrillation have been reported. Additional effects include ataxia, sudden loss of muscle control, dizziness, confusion, headache, and amnesia (1,2,5,7).

The onset of GHB toxicity is rapid, typically 15 to 20 minutes post ingestion. The steep dose-effect of GHB results in characteristically abrupt onset and clearing of effects. Clinical effects typically peak approximately 30 to 60 minutes post ingestion. Duration of effects is dose-dependent, typically from 2 to 4 hours in nonintubated patients with no co-intoxicants (4,7).

GHB-associated fatalities have been reported, due to GHB intoxication and associated trauma, with and without co-intoxicants. In a series of 226 GHB-associated fatalities, 213 resulted from cardiopulmonary arrest and 13 resulted from motor vehicle collisions, drownings, and smoke inhalation; 34% occurred with no co-intoxicants (3).

The risks of GHB use and toxicity are increased by its steep dose response, abrupt onset, interindividual variability of effects, availability in diverse forms and concentrations, the common misperception that it is a "sleep it off" drug, and frequent use with co-intoxicants. Co-ingestion with alcohol or other CNS depressants may potentiate respiratory depressant effects (1–4).

GHB Dependence and Withdrawal

Chronic GHB use can result in the development of dependence and withdrawal. GHB-dependent individuals use multiple doses daily, some around-the-clock. Onset of withdrawal symptoms is rapid, generally within 1 to 6 hours of the last dose. GHB withdrawal presents with tremor, anxiety, agitation, diaphoresis, and insomnia. Symptoms may progress rapidly (within 24 hours) to hallucinations, delusions, and delirium (2,8,9).

In contrast with the severe autonomic disturbance documented for ethanol and sedative–hypnotic withdrawal, tachycardia and hypertension may be transient and mild, even in severe GHB withdrawal with profound delirium (8,9). Severe and refractory agitation increases the risk of hyperthermia, rhabdomyolysis, and DIC. Severe withdrawal may result in intensive care unit (ICU) stays of up to 15 days and result in death (8). Insomnia, depression, anxiety, and cognitive deficits may persist for weeks to months after detoxification and relapse is common. Because of frequent and chronic dosing, GHB-dependent users are also at risk of overdose and trauma resulting from motor vehicle collisions and falls. Co-dependency of GHB and other drugs is common (2,8,9).

GHB-Facilitated Sexual Assault

GHB is used to facilitate sexual assault due to its rapid onset, its disinhibitory and amnestic effects, its absence from routine hospital toxicology screens, and its rapid clearance from blood (4 to 6 hours) and urine (6 to 12 hours), leaving only CO_2 and H_2O as metabolites. Victims typically present late, beyond the window of detection for targeted testing; thus, false-negative testing is the rule. Amnesia

may or may not be associated with loss of consciousness, and victims may or may not remember the assault or assailant. GHB use should be suspected in patients presenting with unexplained lapses in memory of events, sudden onset of intoxication disproportionate to ethanol consumption or recorded ethanol level, missing or disheveled clothing, uncharacteristic behaviors, and symptoms consistent with GHB toxicity including sedation, agitation, and coma (10).

DIFFERENTIAL DIAGNOSIS

Important indicators of GHB intoxication are abrupt onset and clearing of effects and characteristic presentations of coma with psychomotor agitation. The differential diagnosis can be divided into two categories: (a) obtundation, stupor, and coma (see Chapter 11 for detailed discussion of the wide differential of altered mental status); and (b) psychomotor agitation which has many causes including ethanol, sympathomimetic drugs of abuse (PCP, amphetamines, methamphetamines), cocaine, or hallucinogens. Psychiatric disorders and withdrawal from ethanol or other sedative–hypnotic drugs must be considered.

The differential diagnosis of GHB withdrawal includes other withdrawal syndromes, head injury, CNS infection, anticholinergic or sympathomimetic poisoning, seizures, pheochromocytoma, serotonin syndrome, neuroleptic malignant syndrome, thyroid storm, and functional psychosis.

ED EVALUATION

Because GHB is not detected on routine hospital toxicology screens, the diagnosis of GHB toxicity must be made clinically. The ED history should focus on details of the onset and course of altered mental status, specifically: (a) rapid and abrupt onset of altered mental status and coma, particularly when known to be disproportionate to the amount of alcohol or drugs consumed; (b) periods of psychomotor agitation occurring prior to onset of coma, agitation in rapid alternation with somnolence or coma (2- to 3-

minute cycles), agitation in response to interventions such as intubation, emergence delirium after coma, and self-injurious behaviors; and (c) rapid and abrupt clearing of effects. Dance clubs, raves, parties, and bars are common venues for use of GHB and other "club drugs," alone or in combination. Physicians should also question patients regarding past medical and psychiatric history and regular medications. GHB withdrawal is also diagnosed by history; physicians should question patients regarding chronic use, time of last dose, and onset of withdrawal symptoms.

Physical examination should include assessment of vital signs, cardiopulmonary function, and neurologic status. Assessment and frequent monitoring of respiratory status (airway patency and protection, adequacy of ventilation) is of primary concern, particularly in coma. Pulse oximetry is recommended. Arterial blood gases may detect hypoventilation.

Testing is usually not helpful in GHB intoxication or withdrawal. Blood ethanol and drug screens and blood urea nitrogen (BUN), creatinine, electrolytes, fingerstick glucose, and urinalysis are usually unnecessary but may be helpful in specific circumstances.

With GHB withdrawal, electrolytes, BUN, Cr, glucose, complete blood count with differential, coagulation studies, transaminases and liver function tests, creatine phosphokinase (CPK), urine drug screen, and drug levels (i.e., anticonvulsants, antidepressants) may help to detect complications from ongoing GHB use.

GHB is not detected on routine hospital toxicology screening. Confirmation is by targeted analysis with gas chromatography/mass spectrometry, which requires approximately 1 week and thus does not help ED management. For forensic evidence in cases of suspected GHB-facilitated sexual assault, because of its rapid clearance, 100 mL of first-catch urine should be collected and refrigerated. If a blood specimen is necessary, 10 to 30 mL should be obtained in a gray top tube (with sodium fluoride and potassium oxalate) and refrigerated. Established chain of custody procedures should be followed.

KEY TESTING

- There is no confirmatory ED test for GHB.
- Testing should concentrate on detecting complications.
- Forensic testing relies on sending a first-catch urine sample with chain of custody.

ED MANAGEMENT

Management of acute GHB toxicity is supportive. Airway protection, adequate oxygenation, and prevention of aspiration are the goals. Frequent monitoring is necessary, and intubation and mechanical ventilation may be indicated. Sedation may be necessary for agitation. Because many patients recover rapidly and spontaneously, a conservative approach to intubation is appropriate; however, the low frequency of reported intubation complications must be weighed against the potentially lethal risk of respiratory depression. Rapid-sequence intubation using succinylcholine is recommended; otherwise, intubation attempts of an apparently comatose patient may trigger agitation. Bradycardia is typically asymptomatic, but the use of atropine may be necessary. The few reported cases of atrial fibrillation have resolved spontaneously.

Physical and/or chemical restraints may be needed for control of agitation. Benzodiazepines such as lorazepam (1 to 3 mg IV or IM) or butyrophenones such as droperidol (2.5 to 5 mg IV or IM) or haloperidol (5 to 10 mg IM) may be administered.

Though myoclonic movements have been well documented, seizures are rare. Although causality is not apparent, in the absence of definitive data, benzodiazepines such as lorazepam 2 to 4 mg IV or midazolam 2 to 4 mg IV can be employed for seizures. CPK levels, cardiac enzymes, and urine myoglobin may be indicated to monitor for rhabdomyolysis.

Gastric lavage and activated charcoal are not indicated, because of GHB's rapid absorption. There are no proven antidotes or reversal agents for acute GHB intoxication. Naloxone should be considered only in cases of suspected co-ingestion of opioids (7).

GHB withdrawal requires aggressive supportive care and is very similar to management of severe delirium tremens. Agitation and

delirium must be controlled and efforts made to prevent hyperthermia, rhabdomyolysis, renal failure, injury, and other complications. Long-acting sedatives such as diazepam (10 mg IV per dose, and titrated to restfulness) are recommended. Propofol may be used for intubated patients, starting with an IV infusion of 5 μg/kg/min (0.3 mg/kg/hr) for 5 to 10 minutes until sedation is achieved, and maintaining infusion rates of 5 to 50 μg/kg/min. Barbiturates such as pentobarbital (100- to 200-mg IV increments) or phenobarbital (250-mg IV increments), titrated for symptom control, may also be utilized (6). Close monitoring and continuous pulse oximetry are critical after administration of sedative agents described earlier, and intubation and mechanical ventilation are frequently necessary.

CRITICAL INTERVENTIONS

- For acute GHB toxicity:
  - Intubation and mechanical ventilation for airway protection
  - Treat agitation with benzodiazepines and/or antipsychotics such as butyrophenones (droperidol or haloperidol) or newer antipsychotics such as olanzapine
  - Monitor for rapid development of GHB withdrawal
  - Question for history of known or suspected GHB use
- For GHB withdrawal:
  - Adequate sedation
- For suspected GHB-facilitated sexual assault:
  - Symptomatic treatment and appropriate specimen collection in accordance with chain of custody procedures

DISPOSITION

The majority of cases of acute GHB toxicity resolve spontaneously without complications within 2 to 6 hours. After close observation, patients may often be discharged from the ED when clinically stable and mental status has fully normalized. For coma requiring intubation and mechanical ventilation, admission to the ICU may be necessary; however, as with patients managed in the ED, recovery in

the ICU may be rapid and abrupt, and patients may self-extubate. Complications such as aspiration or associated trauma may also necessitate ICU admission. Signs of GHB withdrawal can develop rapidly after the patient wakes up. This may begin in the ED or in the ICU in patients who have presented with acute toxicity. Counsel patients regarding the potentially lethal risks of GHB. For habitual users, referral for substance abuse counseling and treatment is critical.

Common Pitfalls

- Assuming that a negative toxicology screen rules out GHB; GHB is not included on standard hospital toxicology screens.
- Confusing the diagnosis of GHB intoxication with other drugs: Agitation resulting from GHB toxicity, in particular may be mistakenly attributed to stimulants such as methamphetamine, cocaine, PCP, etc.
- Missing GHB-facilitated sexual assault in patients presenting with altered mental status or unexplained memory loss.
- Failure to note early signs of GHB withdrawal after awakening from acute toxicity.

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of Deborah L. Zvosec, PhD to the content of this chapter.

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CHAPTER 310

Muscle Relaxants and Other Sedative–Hypnotic Agents

Benjamin S. Orozco and Samuel J. Stellpflug

Muscle relaxants refer to drugs used to mitigate muscular spasm through various mechanisms. Sedating medications have been used for muscular spasm and muscle relaxants are often sedating; consequently, there is substantial overlap in therapeutic and toxic effects between muscle relaxants and sedative hypnotics. Muscle relaxants used to treat muscle spasms and spasticity include baclofen, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, carisoprodol, methocarbamol, orphenadrine, and tizanidine. The nonbarbiturate, nonbenzodiazepine sedative–hypnotic agents used for the relief of anxiety and as sleeping aids include buspirone, chloral hydrate, eszopiclone, meprobamate, ramelteon, zaleplon, zolpidem, and zopiclone. Ethchlorvynol, glutethimide, and methaqualone are no longer available in the United States. See elsewhere for a discussion of other sedative hypnotics such as barbiturates and benzodiazepines (Chapters 307 and 308, respectively) and sleep aids such as diphenhydramine or sodium oxybate (GHB) and related compounds (Chapters 344 and 309, respectively).

Most sedative–hypnotics and muscle relaxants are metabolized in the liver. Several undergo oxidation by cytochrome p450 enzymes, making drug interactions a concern. Pharmacokinetic data for these agents are summarized in Table 310.1. A list of important drug

metabolizing enzyme substrates is summarized in the content Table 310.2.

TABLE 310.2
Drug Metabolizing Enzymes

Drug	Cytochrome Substrate	Inducer/Inhibitor
Buspirone	CYP 3A4	
Eszopiclone	CYP 3A4 (major), 2E1 (minor)	
Carisoprodol	CYP 2C19	
Chloral hydrate	CYP 2E1	
Chlorzoxazone	CYP 2E1	
Cyclobenzaprine	CYP 1A2, 2D6, 3A3/4	
Orphenadrine	CYP2B6, 2D6, 3A3/4	CYP 2B6 inhibitor
Ramelteon	CYP 1A2 (major), 3A4/2C family (minor)	
Tizanidine	CYP 1A2	
Zaleplon	CYP 3A3/4 (minor)	
Zolpidem	CYP 3A3/4	

CLINICAL PRESENTATION

The majority of sedative hypnotic agents are well absorbed, and onset of effect occurs within 30 minutes to 1 hour after ingestion, sooner for zaleplon. Orphenadrine and cyclobenzaprine may have delayed onset of action, likely as a result of anticholinergic properties.

Grouping drugs with similar mechanisms or toxicities helps with a conceptual understanding of the poisonings though several agents have unique or unexpected toxicities. In overdose, central nervous system (CNS) depression with respiratory depression is expected, and this effect may be accentuated by co-ingesting alcohol or other CNS depressants. Respiratory failure and apnea are a potential with any sedating medication, but the older sedative–hypnotic agents (e.g., chloral hydrate, meprobamate, and carisoprodol) have a lower safety margin than benzodiazepines and newer nonbenzodiazepine sedative–hypnotic agents, such as buspirone, eszopiclone, ramelteon,

zaleplon, zolpidem, and zopiclone. Respiratory arrest due to one of these newer agents is uncommon without co-ingestants.

The sedative hypnotics and muscle relaxants with γ-aminobutyrate (GABA) potentiation will cause CNS and respiratory depression in overdose. This includes meprobamate, chloral hydrate, carisoprodol, zolpidem, zolpidem, zaleplon, zopiclone, eszopilcone, and baclofen. All of these agents can be abused and when used long term at high doses, there is risk of withdrawal complicated by seizures or a delirium tremens-like syndrome.

Meprobamate and chloral hydrate potentiate GABA activity and cause CNS depression. Meprobamate, a drug first used in the 1940s, has anxiolytic, anticonvulsant, and skeletal muscle relaxant properties. In addition, overdose of meprobamate may cause myocardial depression and hypotension. Prolonged toxicity may occur secondary to pharmacobezoar formation (1). Chloral hydrate is one of the oldest known hypnotics and is still used for procedural sedation in children. Chloral hydrate is metabolized by alcohol dehydrogenase to trichloroethanol, and a portion is subsequently oxidized to trichloroacetic acid. Toxicity results from the parent drug and metabolites. The half-life of its active metabolite, trichloroethanol, is 8 hours at therapeutic doses but may be prolonged to 12 to 35 hours after overdose. The combination of alcohol and chloral hydrate (“Mickey Finn”) is particularly potent; these agents not only have additive CNS depressant effects but also inhibit each other’s metabolism. In overdose chloral hydrate may present with coma, miosis, and hypotension. This presentation could be confused with tizanidine or similar agents discussed below. Chloral hydrate is also a gastrointestinal irritant and frequently causes nausea and vomiting. Hemorrhagic gastritis and gastric necrosis occur rarely. As a halogenated hydrocarbon, it can also cause hepatic injury, renal failure, and cardiotoxicity. It reduces myocardial contractility, shortens the refractory period, sensitizes the myocardium to circulating catecholamines, and precipitates dysrhythmias (see Chapter 331).

The nonbenzodiazepine sleep aids are short-acting drugs that potentiate the GABA chloride channel via the benzodiazepine

receptor complex (zolpidem, zaleplon) and possibly at other sites (zopiclone, eszopiclone). A review of eszopiclone, zolpidem, and zaleplon ingestions found drowsiness as the most common clinical effect. Tachycardia and slurred speech were noted in 5% to 10% with zolpidem and zaleplon. Agitation and irritability occurred in 5% of eszopiclone exposures. The patients who took zolpidem and zaleplon had mild CNS effects, including dizziness, slurred speech, and lethargy. Few patients had nausea, vomiting, or abdominal discomfort. Deep sedation is rare barring co-ingestant (2,3).

Baclofen, a muscle relaxant used for chronic spasticity, interacts with the GABA B type receptor may cause profound CNS depression with loss of cranial nerve reflexes. Moreover, it is utilized orally and/or in intrathecal pumps and may paradoxically cause refractory seizures in overdose and in withdrawal. Autonomic disturbances (e.g., bradycardia or tachycardia, hypotension, or hypertension) or dysrythmias occur less frequently. Pupillary response is inconsistent with mydriasis and miosis both reported. Serum concentrations do not correlate with toxicity. Elimination of baclofen is unpredictable after overdose where coma may be consistent with its 3- to 8-hour half-life or quite prolonged. In a series of adolescents with acute baclofen toxicity, mechanical ventilation was required for up to 60 hours after ingestion (4).

Cyclobenzaprine and orphenadrine have anticholinergic properties in overdose though muscle-relaxing effects are due to sedation. The anticholinergic effects may cause confusion, agitation, and hallucinations, which may also occur after therapeutic doses. These agents may precipitate seizures in overdose. Orphenadrine is structurally similar to diphenhydramine and may also cause QRS prolongation and ventricular tachycardia due to sodium channel blockade. Although cyclobenzaprine is structurally similar to amitriptyline, serious cardiovascular effects were not noted in a series of 209 isolated cyclobenzaprine ingestions. This may be due to less toxicity and lower dosage formulation of cyclobenzaprine in contrast to amitriptyline (5).

Tizanidine, a centrally acting α-2 adrenergic agonist similar to clonidine and guanfacine, may be used to treat tension headaches

and trigeminal neuralgia in addition to muscular spasticity. Overdose produces hypotension and relative bradycardia accompanied by miosis, which may be confused with opioid poisoning. Effects generally resolve in less than 24 hours.

Buspirone, a sedative–hypnotic, antianxiety agent, is a partial agonist at the serotonin 1A (5-HT1A) receptor. Its exact mechanism is not known, although it does not interact with the benzodiazepine–GABA receptor complex. Seizures have been described 36 hours after the ingestion of 420 mg of buspirone (6). Serotonin syndrome (see Chapter 343) may occur in patients concurrently taking buspirone and a selective serotonin reuptake inhibitor, trazodone, or St. John's wort.

Dantrolene, a skeletal muscle calcium channel antagonist, is used for malignant hyperthermia, neuroleptic malignant syndrome, and chronic spasticity, but chronic use can cause hepatotoxicity limiting widespread use. There are no published cases of dantrolene poisoning.

Ramelteon is a selective melatonin receptor agonist approved for the treatment of insomnia. It is metabolized in the liver to the major metabolite M-II, which is active and has weak affinity for the serotonin 5-HT_{2B} receptor. Possible serotonin syndrome was associated with ingestion of 30 8-mg ramelteon tablets in a woman on escitalopram (7), but no serious toxicity was observed by a poison center over 5 years ($N = 222$). Lethargy/drowsiness was by far the most common effect (5).

Many of the other muscle relaxants (carisoprodol, chlorzoxazone, ethchlorvyol, glutethimide, metaxalone, methaqualone, and methocarbamol) are muscle relaxants primarily via sedation and cause varying degrees of CNS depression in overdose. Coma may be prolonged in severe ethchlorvynol and glutethimide overdose. Glutethimide also has anticholinergic properties and may cause alternating periods of coma and agitation. Methaqualone commonly causes muscle hyperactivity, including hyperreflexia, twitching, and clonus, in addition to CNS depression. Hypotension and respiratory depression occur infrequently. Carisoprodol, which is metabolized to meprobamate, is the most abused of the muscle relaxants and has

been a Drug Enforcement Administration Schedule IV drug since 2012. Most of the sedative hypnotics including meprobamate are also Schedule IV. In overdose, carisoprodol may present with tremor, myoclonus, muscle rigidity and less often, tachycardia, and hypertension (8). Abrupt discontinuation may result in withdrawal.

DIFFERENTIAL DIAGNOSIS

Poisoning by alcohols, anticonvulsants, barbiturates, benzodiazepines, β-blockers, calcium channel blockers, centrally acting antihypertensives, cyclic antidepressants, opioids, and skeletal muscle relaxants can all cause similar signs and symptoms. Hypotension out of proportion to the degree of CNS depression suggests meprobamate, a cardiovascular agent, or a cyclic antidepressant. Cyclic coma suggests glutethimide, GHB ingestion or formation of a gastric pharmacobezoar. CNS infection and trauma, hypoglycemia, hypernatremia, hypercalcemia, and hypermagnesemia should also be considered. Ingestion of plants, mushrooms, and many different nonprescription and prescription medications can all cause anticholinergic symptoms.

ED EVALUATION

The history should include the time and amount of drug(s) ingested, the time and the nature of symptoms, and medical history, including the pattern and extent of muscle relaxant or sedative–hypnotic use. The physical examination focuses on vital signs, level of consciousness, and cardiopulmonary status.

Symptomatic patients may have baseline laboratory testing as needed for general care. Serum glucose concentration with decreased level of consciousness, electrolytes, blood urea nitrogen (BUN), creatinine, and an electrocardiogram may be useful. Chest radiography or blood gas measurements may be helpful if aspiration or pulmonary edema is suspected and markers of hepatotoxicity if a hepatotoxin has been ingested (chloral hydrate). Patients with deep coma, pressure sores, or seizures should be evaluated for rhabdomyolysis by serum creatine phosphokinase and urinalysis. Drugs-of-abuse immunoassays will not detect these agents, and will

likely be more misleading than helpful. For example, cyclobenzaprine may cause a false positive for tricyclic antidepressants. Comprehensive urine toxicology tests may confirm presence of some agents but does not guide emergency department management. Quantitative serum level testing is not clinically useful.

KEY TESTING

- Complete set of vitals and continuous waveform pulse oximetry
- Blood glucose if decreased conciousness
- EKG to evaluate intervals (QRS and QTc) prolongation
- Serum chemistries, BUN, creatinine in symptomatic patients

ED MANAGEMENT

Therapy involves stabilization and support of vital signs and early decontamination with activated charcoal if mental status permits. Most patients recover with good supportive measures alone. If a patient starts to deteriorate after apparent recovery or is deteriorating despite good supportive care, a pharmacobezoar should be suspected. In rare cases endoscopy may be necessary to remove the bezoar (1). If hypotension fails to respond to fluids or if the patient is already fluid-overloaded, a trial of peripherally acting vasopressors such as norepinephrine or phenylephrine is preferable for vasodilatory shock. Partial or full cardiopulmonary bypass or intra-aortic balloon pump therapy should be considered for hemodynamically unstable patients who fail to respond to vasopressors and inotropic agents. Barring hypoxic injury, full recovery can be expected once the drug is eliminated.

Patients with methaqualone poisoning may require pharmacologic paralysis for control of neuromuscular hyperactivity. Flumazenil, the benzodiazepine antagonist, has reversed CNS depression from zolpidem, zaleplon, zopiclone, baclofen, carisoprodol, chloral hydrate, and meprobamate (9,10). Routine use of flumazenil in the management of overdoses due to these agents requires some thought, as detailed in the discussion of its role in treatment of benzodiazepine toxicity (see Chapter 308). Sodium bicarbonate

should be the first line of treatment for dysrhythmias or conduction disturbances associated with orphenadrine. Physostigmine may be useful to control severe anticholinergic effects associated with orphenadrine and cyclobenzaprine (see Chapter 344). There is no specific antidote for baclofen toxicity.

The anticholinergic properties of cyclobenzaprine, glutethimide, and orphenadrine may slow absorption and lead to delayed gastric emptying, so activated charcoal may be used hours after ingestion depending on the mental status of the patient. Fluids should be given with caution in treating the hypotensive effects of meprobamate, because its myocardial depressant properties increase the risk of pulmonary edema. The use of extracorporeal elimination may be useful in the treatment of life-threatening meprobamate overdoses unresponsive to supportive measures.

Ventricular dysrhythmias from chloral hydrate are often refractory to treatment. Lidocaine, magnesium for torsades de pointes, β-blockers, and overdrive pacing have been used with success. Excess stimulation or manipulation of the patient, as well as catecholamine pressor agents, should be avoided to decrease the risk of precipitating dysrhythmias. Hemodialysis may be considered in cases of profound hypotension and unstable dysrhythmias.

CRITICAL INTERVENTIONS

- Establish intravenous access, cardiac monitoring, and maintain airway patency and respirations with endotracheal intubation and mechanical ventilation if necessary.
- Administer norepinephrine or phenylephrine for hypotension refractory to IV crystalloids.
- Administer intravenous sodium bicarbonate if QRS prolongation is present.
- Consider the use of flumazenil in selected cases when seizure is low risk to reverse toxicity from zolpidem, zaleplon, zopiclone, ezopiclone and possibly others.
- Consider cardiopulmonary bypass, intra-aortic balloon pump, and hemodialysis in severe poisoning refractory to standard therapy.

DISPOSITION

Patients with mild symptoms may be observed in the emergency department until asymptomatic, depending on the duration of action (Table 310.1) of the offending agent(s). Patients with moderate or severe symptoms require intensive care admission for close monitoring, and supportive care is necessary. Patients with unstable vital signs should be transferred to a facility that is capable of intensive care for poisoning victims. Advanced life-support equipment and staff should accompany the patient during transfer.

TABLE 310.1
Data for Nonbarbiturate, Nonbenzodiazepine Sedative–Hypnotic Agents and Muscle Relaxants

	Half-Life (hr)	Protein Binding (%)	Vd (L/kg)	Renal Elimination (%)	Active Metabolite	Therapeutic Blood Level (μg/mL)	Toxic Blood Level (μg/mL)	Lethal Blood Level (μg/mL)
Baclofen	4–34	30	0.8–2.4	85–90	NA	0.1–0.4	0.5–15	6–17
Buspirone	2	95	6	1	Pyrimidinyl piperazine	0.5–3.0	NA	NA
Carisoprodol	8	NA	NA	Trace	Meprobamate	2.5–4	30	110
Chloral hydrate	8–35[a]	40[a]	0.6	0	TCE	10	100	250
Chlorzoxazone	1.1	NA	0.4	<1	NA	9–30	NA	NA
Cyclobenzaprine	18	93	NA	1	NA	0.03	0.03–0.35	0.6–0.5.3
Eszopiclone	6	52–59	NA	<10	(S)-N-desmethylzopiclone	NA	NA	NA
Ethchlorvynol	1–3/10–25[b]	35–50	3–4	10	None	6–8	20	100
Glutethimide	10–12	35–59	>TBW	<1	4-HEPG	4	5–120	10–100
Meprobamate	6–16	20	0.75	10–12	None	10	60–120	140–400
Metaxalone	9	NA	NA	0	NA	0.9	NA	19–39
Methaqualone	10–40	70–90	2.4–6.4	<1	None	2	2–16	5–40
Methocarbamol	0.9–2	46–50	NA	10–15	NA	20–40	NA	257–525
Orphenadrine	14–20	20	4.3–7.8	8	Nororphenadrine	0.1–0.4	3.1	6–37
Ramelteon	1–2.6	70	74[c]	<0.1	M-II	NA	NA	NA
Tizanidine	2–4	30	2.4	<2	None	0.004–0.015	NA	NA
Zaleplon	1	60	1.4	<1	None	0.015–0.05	NA	NA
Zolpidem	2	92	0.54	<1	None	0.06–0.12	0.1–0.7	1.6–7.7

Vd, volume of distribution; Renal, percentage eliminated unchanged; TBW, total body water; 4-HEPG, 4-hydroxy-2-ethyl-2-phenylglutarimide; TCE, trichloroethanol; NA, data not available.
[a]Data for TCE.
[b]Distribution of $t_{1/2}$ of 1 to 3 hours, with elimination $t_{1/2}$ of 10 to 25 hours.
[c]Volume of distribution provided as total volume and not per body weight.

Common Pitfalls

- Failure to consider pharmacobezoar and continuing drug absorption in patients with progressive, prolonged, or cyclic coma (especially with glutethimide and meprobamate).
- Failure to identify that meprobamate induced hypotension may precede CNS depression.

- Failure to appreciate that baclofen, buspirone, methaqualone, carisoprodol, and agents with anticholinergic properties such as cyclobenzaprine, glutethimide, and orphenadrine can cause neuromuscular hyperactivity or seizures in addition to CNS depression.
- Failure to monitor for pulmonary edema during fluid resuscitation.
- Failure to anticipate and treat withdrawal syndromes in chronically dependent patients.
- Failure to appreciate that chloral hydrate-induced ventricular dysrhythmias are exacerbated by catecholamines and may respond to β-blocker therapy.

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of E. Martin Caravati and Barbara Insley Crouch as authors of this chapter in previous editions.

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CHAPTER 311

Phenytoin

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Phenytoin is one of the most commonly utilized anticonvulsants and has been commercially available in the United States since 1938. Initially known as diphenylhydantoin, phenytoin was first synthesized by Heinrich Blitz in 1908 (1). In 1938, Merritt and Putnam described the anticonvulsant properties of phenytoin, making it one of the earliest known anti-epileptics after the bromide salts and phenobarbital. Today, phenytoin remains in use for the treatment of tonic–clonic seizures, for the treatment of partial complex seizures, in the setting of traumatic brain injury, and in the setting of neurosurgical procedures. Although phenytoin has also been used with varying success for trigeminal neuralgia and neuropathic pain, it appears to be less effective for toxin-induced or alcohol withdrawal seizures (2).

Phenytoin is available in many forms, including extended- and immediate-release capsules, chewable tablets, suspension, and phenytoin sodium injection solution. The injection solution contains a 40% propylene glycol and 10% ethanol diluent which is adjusted to a pH of 12 using sodium hydroxide. Infusion-related cardiotoxicity and local tissue injury from extravasation and intramuscular (IM) injection are caused by the propylene glycol–containing alkaline diluent. Fosphenytoin is a phosphate ester prodrug of phenytoin approved for use in 1996. Fosphenytoin has a pH of 8.6 to 9.0, is more water soluble, lacks the propylene glycol diluent, and allows for both intravenous (IV) and IM administration. To avoid potential conversion errors, fosphenytoin is dosed using phenytoin equivalents (PE), where 1.5 mg fosphenytoin is equal to 1.0 mg phenytoin.

Therapeutic phenytoin plasma levels (10 to 20 μg/mL) can usually be achieved with an IV loading dose of 15 to 20 mg/kg of phenytoin or PE units of fosphenytoin. Because of propylene glycol cardiotoxicity, IV phenytoin should not be infused at a rate in excess of 50 mg/min (0.5 to 1.0 mg/kg/min in neonates and children). Fosphenytoin can be administered at a maximum rate of 150 PE units/min in adults or 3 PE units/kg/min in children. The adult maintenance dose of phenytoin is typically 4 to 6 mg/kg/d in divided doses.

In therapeutic oral use, peak plasma concentrations occur in 1.5 to 3 hours, with extended-release formulations producing peak levels at 4 to 12 hours (1). Oral overdoses may have erratic, incomplete, markedly delayed, and prolonged absorption (3). As with other drugs, ingested quantity, chronic therapy, co-ingestants, gut motility, and bezoar formation all influence toxicokinetics.

Fosphenytoin is converted to phenytoin by phosphatases in the blood and liver with a conversion half-life of approximately 15 minutes. Although peak serum levels of IV administered phenytoin are obtained at the end of the infusion, phenytoin levels should not be monitored following fosphenytoin infusion until conversion is complete at approximately 2 hours afterward (3). IM fosphenytoin is well absorbed and produces more sustained, albeit lower, blood levels when compared to IV therapy.

Phenytoin rapidly diffuses into tissues, particularly the central nervous system (CNS) and CNS levels equilibrate with the plasma compartment within 10 minutes of IV infusion (1). Phenytoin is 90% protein bound, primarily to albumin. Because only the 10% of free drug is active, altered plasma protein binding or decreased plasma protein concentrations as may occur with malnutrition or cirrhosis may reduce the threshold for toxicity. The apparent volume of distribution ranges from 0.4 to 0.6 L/kg in adults and is probably increased in overdose.

Phenytoin is metabolized by hepatic microsomal enzymes, primarily CYP2C9, resulting in the production of the inactive 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (*p*-HPPH) metabolite. Phenytoin also undergoes enterohepatic recirculation. Cytochrome-P450–

mediated drug interactions can result in significant changes in phenytoin levels and result in toxicity (Table 311.1). The metabolism of phenytoin is a saturable process. At concentrations <10 μg/mL, there is first-order metabolism, with a fixed proportion being metabolized per unit of time and an approximate half-life of 6 to 24 hours (1). At concentrations in the high therapeutic range, the metabolic pathways become saturated, resulting in zero-order kinetics where a fixed amount of drug is metabolized per unit of time, and the "apparent half-life" increases as the concentration increases. This saturation most likely accounts for the wide range of "apparent half-lives" (7 to 60 hours) reported with therapeutic use and the prolonged elimination observed after overdose (4).

TABLE 311.1
Factors Influencing Phenytoin Kinetics

Pharmacokinetic Effects	Condition or Concomitant Drug Use	Pharmacologic Effect
Decreased protein binding	Acidosis	Increased risk for phenytoin toxicity
	Age (neonates)	
	Uremia	Higher free fraction of circulating phenytoin
	Hepatitis	
	Hypoalbuminemia	
	Valproic acid	
	Nonsteroidal anti-inflammatory agents	
Decreased clearance	Metabolic inhibitors (e.g., amiodarone, SSRIs [fluoxetine])	Increased risk for phenytoin toxicity
	Tamoxifen, isoniazid, disulfiram, ticlopidine	Accumulation of phenytoin during chronic dosing caused by prolonged half-life
	Genetic deficiency of liver enzyme system (CYP2C9 and CYP2C19 polymorphisms)	
Increased clearance	Hepatic enzyme inducers (e.g., phenobarbital, carbamazepine)	Loss of efficacy with risk for breakthrough seizures
	Ciprofloxacin, ethanol	Shortened half-life results in less accumulation during chronic dosing
	Pregnancy	

The mechanisms of the therapeutic and toxic effects of phenytoin are not fully understood. Phenytoin's anticonvulsant effects most likely arise from inhibition of neuronal high-frequency firing by reducing the ability of Na^+ channels to recover from inactivation. This use-dependent effect is caused by preferential binding to the inactivated state of the Na^+ channel.

Phenytoin toxicity occurs in a number of settings. Acute overdose can result from deliberate or unintentional oral ingestion, generally of >20 mg/kg. Exposure to phenytoin may also occur from the adulteration of illicit drugs, such as crack cocaine, and from the use

of imported medications containing undisclosed anticonvulsants. In such cases, nystagmus, ataxia, and vomiting may provide valuable clues to suggest phenytoin poisoning. Acute overdose also follows the iatrogenic infusion of excessive doses of phenytoin or fosphenytoin. Errors in prescribing or administering, as well as changes in dosing or formulation, may lead to inadvertent toxicity during chronic oral therapy.

Given the central role of cytochrome P450 enzymes in metabolizing phenytoin, a number of drugs (Table 311.1) can cause toxicity by altering the clearance of phenytoin. Amiodarone, cimetidine, cotrimoxazole, disulfiram, fluconazole, metronidazole, and various antidepressants can decrease clearance of phenytoin. In contrast, medications that induce the cytochrome-P450 system, such as alcohol, barbiturates, carbamazepine, theophylline, and rifampin, can increase the clearance of phenytoin. Failure to adjust maintenance doses of phenytoin downward when stopping therapy with a cytochrome-P450 inducer may cause phenytoin intoxication.

CLINICAL PRESENTATION

The predominant signs and symptoms of acute or chronic oral phenytoin overdose are related to CNS dysfunction. Effects such as nystagmus, nausea, vomiting, tremor, ataxia, diplopia, and dysarthria often reflect cerebellar and vestibular impairment; toxicity usually correlates with increasing plasma concentrations. Although some patients may tolerate and therapeutically require phenytoin levels >20 μg/mL, patients with underlying brain disease may become toxic at only slightly elevated drug levels. Although nystagmus is common as concentrations rise >20 μg/mL, the absence of nystagmus does not rule out toxicity. Horizontal, vertical, bidirectional, or alternating nystagmus can be noted with significant poisoning, but may disappear as CNS depression and depth of coma increase (4). At levels >30 μg/mL, ataxia, slurred speech, and tremor are common. As levels rise to >40 μg/mL, confusion, lethargy, and stupor may occur. Although progressive CNS depression is typical, fluctuating agitation and lethargy have also been described. With levels >50 μg/mL, marked CNS depression and

coma predominate; profound CNS depression is associated with hyporeflexia and depression of cranial nerve reflexes. Infrequently encountered CNS findings include choreo-athetosis, ballismus, opisthotonus, and dystonias (5). Focal neurological deficits may occur in patients with prior hypoxic or ischemic brain injury. Rare "paradoxical" seizures have been noted with phenytoin levels >30 to 50 μg/mL, typically in the setting of a pre-existing seizure disorder. In the setting of acute overdose, seizures should prompt a search for co-ingestants or physiologic derangements.

Cardiovascular toxicity is not a clinical concern following oral overdose (6), but is the major toxicity seen with rapid administration of IV phenytoin. Hypotension, apnea, bradycardia, asystole, and ventricular dysrhythmias occur at rates in excess of 50 mg/min (rates as low as 25 mg/min have been recommended for patients >50 years of age). Associated electrocardiographic (ECG) changes may include ST segment and T wave changes, as well as atrioventricular blocks. Although the propylene glycol diluent in phenytoin injection solution is believed to be the primary mediator of cardiovascular toxicity, there may be other mechanisms. Bradyasystolic arrest has occurred in infants following several-fold overdoses of IV fosphenytoin, which does not contain propylene glycol. Although the cardiotoxicity associated with IV phenytoin is usually transient and expected to dissipate after the infusion is stopped, the potential for sudden life-threatening toxicity is greatest within this setting.

Extravasation of phenytoin can cause skin and soft-tissue necrosis, compartment syndrome, gangrene, and may lead to limb loss. "Purple glove syndrome," which consists of progressive limb edema, bluish discoloration, pain, and blistering, may follow IV administration of phenytoin on a delayed basis, even in the absence of evidence of extravasation. Risk factors for "purple glove syndrome" include advanced age, use of large repeated doses, small gauge IV catheter use, and use of the same infusion site for multiple doses (7). This syndrome has not been reported with fosphenytoin.

An idiosyncratic anticonvulsant hypersensitivity syndrome may develop in patients taking phenytoin, typically developing weeks to months after the initiation of therapy. This syndrome often produces

multisystem involvement and may present with fever, rash, hepatitis, eosinophilia, blood dyscrasias, pneumonitis, myositis, vasculitis, and/or nephritis. Anticonvulsant hypersensitivity syndrome is thought to occur from the generation of toxic arene metabolites of aromatic anticonvulsants (carbamazepine, phenobarbital, and phenytoin) and is potentially life-threatening (8). Additional adverse effects of phenytoin include Stevens–Johnson syndrome, toxic epidermal necrolysis, and drug-induced lupus.

Death is rare after acute oral overdoses of phenytoin. Most fatalities involve co-ingestants or respiratory failure and its associated complications, and many of the deaths reported in the medical literature predate modern intensive care and supportive care (5). Fatal cases are usually associated with phenytoin levels in excess of 120 μg/mL (3).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of phenytoin intoxication includes other illnesses that can produce the typical constellation of nystagmus, ataxia, dysarthria, and mental status changes. Other anticonvulsants can produce similar signs and symptoms and are often utilized by patients with epilepsy. Similarly, an overdose of sedative-hypnotic agents, ethanol, muscle relaxants, or psychiatric medications such as lithium, cyclic antidepressants, or the SSRIs can produce a comparable clinical presentation. CNS pathology, particularly cerebellar infarction, hemorrhage, or neoplasm, should also be considered. Other diagnostic considerations include hypoglycemia, Wernicke encephalopathy, extrapyramidal disorders, seizure disorders, and postictal states.

ED EVALUATION

The time and quantity of ingestion should be the primary focus, but a history of seizure disorder and other medication use should also be sought. The examination should focus on the neurological system. The clinician should note the presence or absence of altered mentation, nystagmus, slurred speech, and ataxia.

Serum glucose and an ECG should be obtained in patients with an altered mental status or when there may be a co-ingestion of other substances. ECG screening may provide additional information when ingestion of psychotropic or cardioactive agents is being entertained. If the patient has a known seizure disorder but is taking unknown medications, phenytoin, phenobarbital, carbamazepine, and valproic acid are commonly prescribed medications for which blood levels can be measured. If medications are known, levels of the specific agents should be ordered. When levels are positive and the patient is either unreliable or may have attempted suicide, serial levels can establish a peak and declining trend. These levels should be clinically correlated with the patient's condition. Serum albumin level may be helpful in patients with nephrotic syndrome, malnutrition, or liver failure or who are otherwise at risk since hypoalbuminemic patients may exhibit toxicity at normal or minimally elevated phenytoin levels. Acetaminophen and salicylate levels are typically obtained in suicidal overdoses, as these agents are common co-ingestants. Routine laboratory studies and a pregnancy test in females of childbearing age may help for general supportive care.

KEY TESTING

- Blood glucose if altered mental status
- Serum phenytoin level(s)
- Serum albumin level in at-risk patients
- ECG in symptomatic patients

ED MANAGEMENT

Patients who develop hypotension or bradycardia during IV infusion should have the drip immediately discontinued. The drip rate and concentration should be checked. When vital signs are normalized, a slower infusion rate can then be continued with cardiac monitoring.

For oral overdose, the patient's airway, breathing, and circulation (ABCs) should be monitored and stabilized appropriately. Oral phenytoin overdose is rarely fatal with attentive supportive care, and cardiovascular toxicity is unlikely. An initial ECG should be obtained

to establish normal intervals, and cardiac monitoring should be initiated if there are any abnormalities. If there is significant ataxia or nystagmus or gait abnormalities, the patient should be protected from falls and should have frequent neurological reevaluations.

A single dose of activated charcoal is a reasonable method for gastric decontamination following oral exposure in patients without significantly depressed mentation. The use of multiple doses of charcoal, although of theoretical value, remains of unclear clinical utility (9). If the patient has an underlying seizure disorder, phenytoin should be administered to avoid allowing the phenytoin level to decreasing to less than the therapeutic range.

Although extracorporeal removal of phenytoin is rarely necessary given the efficacy of standard supportive care measures, high-flux hemodialysis may provide significant drug removal in selected cases of severe poisoning (10).

CRITICAL INTERVENTIONS

- Establish a peak and declining trend by following serial phenytoin levels in all potentially significant exposures.
- When loading phenytoin IV, the patient should have continuous cardiac monitoring, and extravasation must be avoided.
- Infusions should be stopped if there is evidence of bradycardia or hypotension.

DISPOSITION

Patients with no or minimal toxicity after a suicidal ingestion and a therapeutic peak phenytoin concentration can be cleared for psychiatric evaluation. Patients with elevated peak phenytoin levels and moderate to severe symptoms, such as ataxia, tremor, confusion, or stupor, require hospitalization. Patients admitted after oral phenytoin overdose can be admitted to nontelemetry settings (6), but should go to a setting where fall precautions can be instituted and frequent neurological checks can be performed. Only rare severely intoxicated patients will require an intensive care setting.

Nonsuicidal patients with mild symptoms and a reliable family support system can be discharged home with instructions to prevent falls. The family should also be counseled on holding doses for the next day or two as appropriate. More seriously intoxicated patients should be admitted to the hospital as above for supportive treatment.

Common Pitfalls

- Exceeding phenytoin IV infusion rates of 25 to 50 mg/min, causing hypotension and/or bradycardia.
- Causing phenytoin toxicity by not checking a drug level prior to giving a loading dose.
- Admitting all oral phenytoin overdoses to a telemetry setting. Cardiac toxicity is extremely rare, and this is generally not necessary.
- Failing to consider phenytoin toxicity and proceeding with imaging evaluation for other acute neurological conditions.
- Failing to recognize the anticonvulsant hypersensitivity syndrome.
- Failing to recognize the purple glove syndrome.

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CHAPTER 312 Valproic Acid

Patrick M. Lank and Sean M. Bryant

Originally synthesized from a chemical found in valerian root, valproic acid has been in clinical use as an antiepileptic drug for over 45 years. Initially prescribed for a broad range of seizures, including absence, partial, and generalized tonic–clonic, valproic acid has also been used for the treatment of mania in bipolar disorder, migraine headaches, and neuropathic pain (1). Given valproic acid's multiple indications, particularly for psychiatric disorders, it is commonly encountered in both intentional and unintentional overdoses (2). In 2011, 8,052 toxic exposures to valproic acid were reported to US poison centers (more than carbamazepine and phenytoin combined) and were associated with more than 20 poison-related deaths in the same year (2).

Valproic acid is a simple branched chain carboxylic acid that is structurally dissimilar to other anticonvulsants. Antiepileptic effects of valproic acid come from various mechanisms including 1) increasing γ-aminobutyric acid (GABA) activity, 2) decreasing NMDA receptor–mediated glutamate activity, and 3) inhibiting voltage-gated sodium channels (3). Mechanisms related to valproic acid's newer uses as a mood stabilizer and adjunctive agent in pain syndromes are complex and yet to be defined (4).

Valproic acid (Depakene) is available as a syrup, capsule, and intravenous formulation (Depacon). Divalproex sodium (Depakote) is a 1:1 ratio of valproic acid and sodium valproate. It is packaged as a sprinkle, delayed- or extended-release capsule. Oral bioavailability is near 100%, and peak concentrations are reached within 6 hours for therapeutic dosing. In overdose, especially with

delayed- or extended-release formulations, initial levels may be undetectable, and peak levels are extended out as far as 18 hours or longer (4). The volume of distribution is small, and the drug is rapidly distributed throughout the body. Protein binding is significant, though this decreases in overdose. The half-life at therapeutic levels is 8 to 17 hours, but after overdose, it may be as long as 19 to 20 hours (5).

The bulk of valproic acid is metabolized by hepatic glucuronidation, and then its metabolites are largely excreted in the urine. Through multiple direct and indirect mechanisms, valproic acid interferes with the normal mitochondrial function in the urea cycle, leading to accumulation of ammonia. Carnitine is a required co-factor for the metabolism of ammonia as part of the urea cycle, but the use of valproic acid has been associated with carnitine depletion (6). This mechanism of carnitine depletion-related hyperammonemia is the physiologic basis for the potential use of supplemental carnitine in valproate-associated hyperammonemia.

CLINICAL PRESENTATION

Slow absorption delays the onset of symptoms. Central nervous system depression including coma is the predominant finding in severe valproic acid toxicity (7). Valproic acid toxicity may also cause nausea, vomiting, pancreatitis, hepatitis (although rare after acute ingestion), hemodynamic instability, and cerebral edema. Metabolic effects are seen with more severe toxicity and may include hypernatremia and lactic acidosis with an anion gap.

ED EVALUATION

Because valproic acid overdose primarily manifests as central nervous system depression, the airway must be carefully assessed. After completion of the primary survey and appropriate interventions, a detailed history should include whether the ingestion was accidental or intentional, the potential for co-ingestants, other medications the patient has had access to, time of ingestion, and apparent acute versus chronic ingestion. Physical

examination should focus on mental status. History provided by paramedics, friends, family, and old medical records is often helpful in the patient with altered mental status.

Serum valproic acid concentrations between 50 and 100 μg/mL are considered therapeutic, but the exact range depends on the laboratory-specific range. Although higher levels do not correlate exactly with clinical findings, some generalizations can be made. Levels <450 μg/mL are associated with less serious toxicity, and those >850 μg/mL are associated with critical illness including coma (7). This leaves a wide range of concentrations correlating with variable clinical effects, though it is clear that patients with levels between 450 and 850 μg/mL may also be critically ill. Slow absorption and late peak serum concentration of valproic acid mandates serial testing regardless of the presence or absence of symptoms.

DIFFERENTIAL DIAGNOSIS

The list of agents that can cause altered mental status is extensive (see Chapter 11, "Altered Mental Status and Coma"). Valproic acid intoxication can mimic most other central nervous system depressant drugs. Postictal states, metabolic derangements, central nervous system lesions, trauma, infection, hypoglycemia, and hypoxia may present similarly. Ammonia may be elevated in liver disease. The key to arriving at the correct diagnosis is a good history, exclusion of alternate etiologies, and serial serum valproic acid concentrations.

KEY TESTING

- CBC, chemistry (with anion-gap calculation), lactic acid
- Valproic acid concentration
- Ammonia level
- Liver function tests and lipase

ED MANAGEMENT

Aggressive supportive care and strict attention to airway and breathing is critical, with intubation and ventilation for airway compromise or respiratory depression. Prior to definitive airway management, naloxone and bedside glucose testing are appropriate in the undifferentiated comatose patient but not helpful for valproic acid.

Early decontamination may prevent absorption and subsequent toxicity, however an intact airway and mental status are required for this. For larger overdoses, activated charcoal is the preferred mode of decontamination, as it readily adsorbs valproic acid. Appropriate initial dosing of activated charcoal is in a 10:1 ratio to amount of drug ingested (e.g., 50 g of activated charcoal should be given for a 5 g ingestion), as tolerated, up to 100 g initially. Repeat dosing may be indicated if continued absorption is occurring.

Enhanced elimination with hemodialysis may result in lowering of drug levels, especially in cases where the valproic acid concentration is excessive (>850 mg/L). Hemodialysis should particularly be considered when there is renal insufficiency, significant electrolyte disturbance, or acid–base derangement (7).

L-carnitine has been used to hasten resolution of coma in patients with valproic acid–associated hyperammonemia (8). Although use of L-carnitine for valproic acid–associated hyperammonemia in the overdose setting has limited evidence, it is safe, has minimal side effects, and is a reasonable adjunct to therapy. Dosing recommendations vary, but 100 mg/kg intravenously (up to 6 g) over 30 minutes, followed by 15 mg/kg every 4 hours, is appropriate. The end point is clinical improvement or 3 days of therapy.

CRITICAL INTERVENTIONS

- Airway management for severely poisoned patients with depressed mental status
- For patients with overdose: electrolyte panel, liver function panel, ammonia level
- Monitor anion gap and lactate in critically ill patients

- *Serial valproic acid concentrations* in all patients with acute overdose
- Hemodialysis for renal failure
- l-carnitine for elevated ammonia

DISPOSITION

All patients with evidence of mental status decline or respiratory insufficiency warrant an intensive care unit admission with continuous cardiac monitoring and airway assessment. In suicidal patients, clearance for psychiatric admission should wait until a downward trend in valproic acid concentration is confirmed. Both therapeutic and subtherapeutic concentrations have been reported to steadily rise, with concurrent signs of significant poisoning after acute overdose (9). Patients should not be discharged until serum levels are falling based on serial levels, are in the therapeutic range, and the patient is asymptomatic.

Common Pitfalls

- Failure to detect a delayed rise of valproic acid levels. Serial levels are required.
- Failure to consider delayed onset of toxicity.
- Premature medical clearance.
- Failure to work up patients completely for alternate etiologies of abnormal mental status.

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CHAPTER 313 Carbamazepine

Marco L.A. Sivilotti

Carbamazepine (CBZ) is used for the management of epilepsy, trigeminal neuralgia, chronic pain syndromes, and affective disorders. Its main actions are to reduce the permeability of neuronal membranes to sodium and potassium ions and to block norepinephrine reuptake. CBZ also has anticholinergic effects and is structurally related to the tricyclic antidepressants. Despite the structural resemblance between CBZ and imipramine, there is only partial overlap of their toxicities after overdose. Notably, CBZ has a much greater therapeutic index and is much safer.

CBZ is available in 100- and 200-mg immediate-release tablets, in 100- to 400-mg controlled-release tablets and capsules, and as a 100-mg/5-mL suspension. Oxcarbazepine, a newer, chemically related anticonvulsant, is discussed in Chapter 314. Although CBZ is almost completely absorbed, the rate of absorption can be erratic. Peak concentrations, usually found 4 to 8 hours after therapeutic dosing or liquid suspension ingestions, may be delayed 24 to 72 hours after massive ingestions of tablets and up to 106 hours with controlled-release preparations (1–3). At therapeutic concentrations (8 to 12 μg/mL), CBZ is 75% bound to plasma proteins, with a volume of distribution of 0.8 to 1.2 L/kg (adult). CBZ is predominantly metabolized by hepatic CYP 3A3 and 3A4 to CBZ-10,11 epoxide (CBZ-E), which in turn is metabolized and excreted in both urine and bile. CBZ-E is pharmacologically active, possessing anticonvulsant properties and adding to the toxic effect in overdose. Concentrations of CBZ-E are usually about 20% of those of CBZ.

CBZ induces its own metabolism. Consequently, patients naive to CBZ eliminate it with a half-life of 20 to 65 hours, much more slowly than chronic users (8 to 17 hours). The half-life of CBZ-E is 5 to 7 hours (4). Other anticonvulsants, such as phenobarbital, phenytoin, valproic acid, and felbamate, may further increase the metabolism of CBZ by heteroinduction. CBZ metabolism is inhibited by erythromycin, propoxyphene, isoniazid, calcium channel blockers, cimetidine, fluvoxamine, lamotrigine, ketoconazole, and other CYP 3A3 and 3A4 inhibitors, which can result in toxicity despite therapeutic CBZ dosing. After an overdose, even among patients on chronic therapy, serum CBZ concentrations fall slowly due to saturation of the rate-limiting epoxidation and ongoing gastrointestinal absorption.

In an adult patient not regularly taking CBZ, significant toxicity can be expected after ingestion of 20 to 30 mg/kg and life-threatening effects after 140 mg/kg. Ingestions of >20 g have resulted in death (5). Neurologically intact survival has been reported after an ingestion of 60 g of controlled-release CBZ (2) and after an ingestion of 34 g leading to prolonged asystole with 50 minutes of external chest compressions (1).

CLINICAL PRESENTATION

The clinical manifestations of CBZ toxicity involve four main areas: 1) central nervous system (CNS), 2) ocular, 3) cardiac, and 4) motor. Although a sequential progression is classically described, individual patients may present at any stage and at times progress rapidly to profound coma and cardiac instability (6). Initial CNS symptoms include restlessness, confusion, excitation, and aggression. Dizziness, ataxia, nystagmus, diplopia, nausea, and vomiting are often present. As toxicity progresses, drowsiness, coma, and respiratory depression may occur, often after several hours (2,5). Hypotension, global hypokinesia, and cardiac rhythm disturbances may be seen in severe poisoning (1,3,6). Loss of P waves, premature ventricular beats, QRS prolongation, and complete atrioventricular block have been described (3), as have

bradycardia, Adams–Stokes syncope, and ventricular standstill (1). Prolongation of the age-adjusted QRS interval is common in children (3). Severely poisoned patients may have fixed and dilated pupils and disconjugate gaze (1).

Abnormal motor findings include tremor, choreoathetoid movements, and hemiballismus. Reflexes may initially be hyperactive with clonus. Seizures can occur, usually in patients with an underlying seizure disorder (7). The electroencephalogram may show occipital δ activity (usually suggestive of a brainstem disorder) (3). In the deeply comatose patient, adynamic ileus, hypothermia, and pulmonary edema may be present (2). Complications include aspiration, resistant status epilepticus, and the sequelae of hypoxia and seizures (1,5). Hyponatremia may result from an antidiuretic effect in either acute or chronic overdoses. Acute intoxication may result in hypokalemia.

Confusion, lethargy, and ataxia are usually associated with peak plasma CBZ concentrations of about 20 μg/mL. Coma, hypotension, dysrhythmias, seizures, and death often occur with peak plasma concentrations, which may occur hours or days after ingestion, above 40 μg/mL (3,5,7). Initial drug levels correlate only weakly with clinical course and are imperfect prognosticators of outcome (2,4). Because of the long half-life after overdose and continued absorption over many hours, the clinical course is typically prolonged (1–3). Severely poisoned patients may require more than a week to make a full recovery. Cyclic coma, in which partial recovery is followed by a relapse into a coma, can occur as gastrointestinal absorption resumes after ileus resolves (7).

DIFFERENTIAL DIAGNOSIS

Mild poisoning may resemble hypoglycemia, neurologic disease, serotonin syndrome, or intoxication by ethanol. In severe poisoning, the clinical picture may mimic overdose with cyclic antidepressants, anticholinergic agents, or other anticonvulsants. Other physiologic depressants, coexistent trauma, and co-ingestions should also be considered. A prolonged postictal state in a patient with a history of

seizures should raise suspicion for poisoning with CBZ or another new anticonvulsant.

ED EVALUATION

A directed history should be obtained from the patient, prehospital care providers, or available friends and family members. Recent dosing changes or newly prescribed medications that may inhibit CBZ metabolism (e.g., erythromycin, propoxyphene, isoniazid, calcium channel blockers, cimetidine, fluvoxamine, lamotrigine, ketoconazole) should be identified. The physical examination should include a full set of vital signs; pupil position, size, and reactivity; bowel sounds; and a neurologic examination focused on level and content of consciousness, responsiveness to stimuli, reflexes, motor tone, and cerebellar function. A 12-lead electrocardiogram (ECG), cardiac monitoring, and serum electrolyte and glucose determinations are indicated in symptomatic patients. Urine toxicology testing is generally not useful; computed tomography scanning of the head may be helpful in cases of diagnostic uncertainty. CBZ can cause a falsely positive urine drug screen for tricyclic antidepressants due to the structural similarity.

Frequent measurements of serum CBZ concentrations are helpful to detect continued absorption in patients with acute overdose. Serial levels should be followed until the patient is asymptomatic and levels have clearly peaked and fallen into the therapeutic range of 4 to 12 μg/mL. Rebound in CBZ levels coinciding with clinical deterioration is well described. Serum CBZ and CBZ-E concentrations can be separately determined by high-performance liquid chromatography. Immunologic assays used in most centers cannot distinguish between CBZ-E and the parent compound, but quantification of CBZ-E is not necessary for clinical care of the patient (2,4).

KEY TESTING

- ECG for QRS prolongation

- Continuous cardiac monitoring if symptomatic or conduction abnormality
- Serial serum CBZ concentrations

ED MANAGEMENT

As always, airway has the highest priority since most deaths from CBZ overdose are from complications such as pulmonary aspiration and respiratory depression. Level of consciousness and vital signs should be monitored. Hypotension should be managed with intravenous fluids and, if necessary, invasive monitoring and pressors such as norepinephrine. Central venous pressure monitoring is recommended in such patients to avoid fluid overload, which can result from CBZ antidiuretic effect. Wide-complex cardiac dysrhythmias should be treated with hypertonic sodium bicarbonate as described for cyclic antidepressants (see Chapter 339). Aggressive resuscitation efforts, including prolonged chest compressions and extracorporeal circulatory support, have been used successfully for severe cardiogenic shock (1,3).

Activated charcoal (AC) is recommended for all symptomatic patients regardless of time after ingestion, and for others with significant recent ingestions by history. Multiple-dose activated charcoal (MDAC) therapy enhances the elimination of both CBZ and CBZ-E and should be instituted for patients with significant symptoms or CBZ levels above 20 μg/mL (8). MDAC should be continued until levels have fallen into the therapeutic range or lower for patients not dependent on the anticonvulsant properties of CBZ. Ileus after massive overdose may preclude or complicate MDAC (1,2).

Forced diuresis, peritoneal dialysis, and continuous renal replacement therapies are of limited value in CBZ poisoning (1). CBZ and CBZ-E are both filtered efficiently by high-flux hemodialysis (9,10), but only a relatively small proportion of the body burden is removed. Although charcoal hemoperfusion also clears CBZ from the blood (1,2), this modality is not available in most centers. Extracorporeal removal should only be considered for

patients with significant dysrhythmias, hypotension, or prolonged coma and extremely elevated CBZ levels despite MDAC.

CRITICAL INTERVENTIONS

- Obtain serial serum CBZ concentrations until values clearly peak and then fall into the therapeutic range.
- Check for other drugs that affect CBZ metabolism.
- Administer MDAC in patients with significant symptoms or CBZ concentrations above 20 μg/mL.

DISPOSITION

Patients who are symptomatic or who have a CBZ level >15 μg/mL should be admitted. Those with moderate or severe clinical toxicity, rising drug levels, or an abnormal ECG should be treated in an intensive care unit. Patients with intentional overdose should be evaluated for suicide risk.

Common Pitfalls

- Failure to appreciate that CBZ absorption is slow and erratic and that peak levels may not occur until many hours or days after acute overdose.
- Failure to appreciate that although CBZ is an anticonvulsant, overdose can cause or exacerbate seizures.
- Failure to appreciate that CBZ is structurally similar to cyclic antidepressants and can cause similar CNS and cardiovascular toxicity.
- Failure to appreciate that AC and MDAC may be useful, even many hours after ingestion.
- Failure to appreciate that CBZ has active metabolites and that toxicity may take days to resolve.

ACKNOWLEDGMENT

The author gratefully acknowledges the contributions of Andrew J. W. Heath to this chapter in previous editions.

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CHAPTER 314

Newer Anticonvulsants

Zhanna Livshits

Epilepsy is a common neurologic disorder affecting approximately 2.3 million Americans, with an individual lifetime incidence of approximately 3% (1). Prior to 1993, anticonvulsant medications (now commonly referred to as the "older" or "traditional" agents) were limited to phenobarbital, phenytoin, carbamazepine, valproic acid, ethosuximide, and primidone. Although studies show similar efficacy among these agents, their use is often limited by adverse effects, unpredictable pharmacokinetics, and drug–drug interactions (2). The "newer" (second-generation) anticonvulsants appear to be well tolerated, with broader spectrums of actions against a number of different seizure types than the older drugs, fewer serious adverse effects, and fewer drug–drug interactions (Table 314.1). These newer anticonvulsants are involved in overdose with growing frequency. Patients with epilepsy have a 10-fold greater suicide rate (11.5%) than the general population (1.1% to 1.2%) (3), and each of the anticonvulsants discussed in this chapter carries an FDA warning of an increase in suicidal thoughts and behavior in patients taking these medications. This is compounded by off-label use including for chronic pain syndromes and psychiatric disorders.

TABLE 314.1
Anticonvulsants Introduced in the United States Since 1993

Drug	Indications	Dosage Range	Pharmacokinetics	Drug Interactions	Amenability for Hemodialysis	Toxic Dose	Serious Effects, Reported
Felbamate (Felbatol) Chemical class: dicarbamate	Adults: **refractory** partial seizures with/without generalization Pediatrics: **refractory** Lennox–Gastaut syndrome, partial and generalized seizures	Adults (>14 yrs): 1,200–3,600 mg/d Pediatrics: (2–14 yrs): 15–45 mg/kg/d Dose adjustment with renal impairment	Oral bioavailability: 90% $t_{1/2}$: 20–23 hrs V_d: 0.7–1.0 L/kg Protein binding: 20–25% Metabolism: hepatic Excretion: 90% renally, 40–50% unchanged	Increases concentration of phenytoin, phenobarbital, and valproate; Decreases carbamazepine Felbamate clearance is increased by carbamazepine and phenytoin and decreased by valproate	Not established as effective means of elimination	Not established in humans	Aplastic anemia Hepatic failure Crystalluria and renal failure
Gabapentin (Neurontin) Chemical class: GABA analog	Adults: partial seizures with secondary generalization and postherpetic neuralgia, off-label for pain syndromes, e.g., diabetic neuropathy Pediatrics: partial seizures	Adults (>12 yrs): 900–3,600 mg/d divided into tid dosing Pediatrics: (3–12 yrs): 10–40 mg/kg/d Dose adjustment with renal impairment	Oral bioavailability: 27–60% $t_{1/2}$: 5–7 hrs V_d: 0.8–1.3 L/kg Protein binding: <3% Metabolism: not metabolized Excretion: 75–80%	Hydrocodone and morphine decrease gabapentin clearance	Dialyzable; consider in severely renal-impaired patients if benefits of procedure outweigh risks	Not established in humans	Altered mental status, coma, respiratory depression, myoclonus is more common with renal impairment
Lamotrigine (Lamictal) Chemical class: phenyltriazine	Adults: bipolar disorder, partial and generalized seizures, Lennox–Gastaut syndrome Pediatrics: Lennox–Gastaut syndrome, partial and generalized seizures	Adults: 25–500 mg/d Pediatrics: 0.15–15 mg/kg/d Dose adjustment with renal and severe hepatic impairment	Oral bioavailability: 98% $t_{1/2}$: 12–62 hrs V_d: 0.9–1.3 L/kg Protein binding: 55% Metabolism: extensively hepatic; Excretion: 98% renal	Acetaminophen, carbamazepine, oral contraceptives, phenobarbital, and phenytoin enhance lamotrigine clearance; Valproate decreases lamotrigine clearance	May be amenable to hemodialysis (HD); however, not established as effective means of elimination	Overdoses up to 15 g have been reported to result in fatalities	Lethargy, ataxia, nystagmus, encephalopathy, coma, seizures; conduction disturbances with PR and QRS prolongation; rash with therapeutic dosing or chronic overdose
Levetiracetam (Keppra) Chemical class: pyrrolidine derivative	Adults: partial, myoclonic and generalized seizures Pediatrics (4–16 yrs): myoclonic seizure (>12 yrs), partial and generalized seizure	Adults: 1,000–3,000 mg/d Pediatrics: 20–60 mg/kg/d (maximum dose: 3,000 mg/d) Dose adjustment with renal impairment	Oral bioavailability: 100% $t_{1/2}$: 6–8 hrs V_d: 0.7 L/kg Protein binding: <10% Metabolism: enzymatic hydrolysis Excretion: 95% in urine (66% unchanged drug and 24% inactive metabolite)	Does not induce hepatic enzymes	Approximately 50% removal by 4 hrs HD	Not established in humans	Altered mental status, behavioral changes (aggression, psychosis)
Oxcarbazepine (Trileptal) Chemical class: iminostilbene derivative	Adult: partial seizures Pediatrics (4–16 yrs): partial seizures	Adults: 600–2,400 mg/d Pediatrics: 8–10 mg/kg/d maximum dosing depends on patient's weight Dose adjustment with renal and severe hepatic impairment	Oral bioavailability: >95% $t_{1/2}$: oxcarbazepine 2 hrs; MHD (active metabolite) 9–11 hrs; V_d: oxcarbazepine 3–15 L/kg, MHD, 0.7 L/kg Protein binding: 40% Metabolism: extensively hepatic Excretion: 95% in urine	Inhibits the metabolism of phenobarbital and phenytoin Carbamazepine, phenytoin, and phenobarbital increase oxcarbazepine clearance May decrease oral contraceptive efficacy	Not established as effective means of elimination	Not established in humans	Lethargy, nausea, dizziness, ataxia, seizures, hyponatremia, bradycardia, hypotension, rash
Pregabalin (Lyrica) Chemical class: GABA analog	Adults: partial seizures, postherpetic neuralgia, diabetic neuropathy, neuropathic pain with spinal cord injury, fibromyalgia Pediatrics: not established	Adults: 150–600 mg/d Pediatrics: Not established Dose adjustment with renal impairment	Oral bioavailability: >90% $t_{1/2}$: 5–6 hrs V_d: 0.5 L/kg Protein binding: none Metabolism: hepatic negligible Excretion: 90–99% unchanged in urine	Does not induce hepatic enzymes	Amenable to HD; approximately 50% is removed within 4 hrs HD	Not established in humans	Lethargy, somnolence, coma, myoclonus
Tiagabine (Gabitril) Chemical class: nipecotic acid derivative	Adults: partial seizures Pediatrics (>12 yrs): partial seizures	Adults: 4–56 mg/d Pediatrics: >12 yrs, 4–32 mg/d (not approved <12 yrs) Dose adjustment with renal and hepatic impairment	Oral bioavailability: >90% $t_{1/2}$: 7–9 hrs V_d: 0.8–2.1 L/kg Protein-binding: 96% Metabolism: extensive hepatic Excretion: fecal 63%, renal 25%	Carbamazepine, phenobarbital, and phenytoin, increase tiagabine clearance	Not dialyzable	Not established in humans	Lethargy, coma, seizures with/without status epilepticus, agitation, myoclonus

Drug	Indications	Dosage Range	Pharmacokinetics	Drug Interactions	Amenability for Hemodialysis	Toxic Dose	Serious Effects, Reported
Topiramate (Topamax) Chemical class: sulfamate-substituted monosaccharide	Adults: partial and generalized seizures, Lennox–Gastaut syndrome, migraine prophylaxis Pediatrics: Lennox–Gastaut, partial seizures, generalized seizures	Adults: 25–400 mg/d Pediatrics: 1–3 mg/kg/d to 5–9 mg/kg/d Dose adjustment with hepatic impairment	Oral bioavailability: 75–80% $t_{1/2}$: 21 hrs V_d: 0.6–0.8 L/kg Protein binding: 15–41% Metabolism: hepatic, small extent Excretion: 70%, most unchanged in urine	Phenytoin and carbamazepine increase topiramate clearance Contraindicated with carbonic anhydrase inhibitors May decrease oral contraceptive efficacy	Amenable to HD	Not established in humans	Lethargy, dizziness, ataxia, oligohidrosis and hyperthermia, acute angle closure glaucoma, non-anion-gap metabolic acidosis
Vigabatrin (Sabril) Chemical class: GABA derivative	Adults and Pediatrics: refractory complex partial seizures, infantile spasms	Adults: 1–3 g/d Pediatrics: (10–16 yrs): 500 mg/d increase in dose is weight-based; Pediatrics: (1 mo–2 yrs): 50–150 mg/kg/d Dose adjustment with renal and severe hepatic impairment	Oral bioavailability: 50–65% $t_{1/2}$: 5.7 hrs for infants; 9.5 hrs for children, 10.5 hrs for adults V_d: 1.1 L/kg Protein binding: none Metabolism: hepatic, minimal Excretion: 95% renal	Decreases phenytoin plasma concentration	Dialyzable; warrants risk/benefit analysis following overdose	Not established in humans	Fatigue, dizziness, coma, psychosis, vision loss
Zonisamide (Zonegran) Chemical class: sulfonamide	Adults: partial seizures Pediatrics (>16 yrs): safety and effectiveness not established	Adults and pediatrics (>16 yrs): 100–400 mg/d divided into bid dosing Dose adjustment with renal and severe hepatic impairment	Oral bioavailability: >90% $t_{1/2}$: 63 hrs V_d: 1.45 L/kg Protein binding: 40%; extensively bound to erythrocytes Metabolism: hepatic Excretion: 62% renal, 3% fecal	Carbamazepine and phenytoin increase zonisamide clearance	Unknown	Not established in humans	Lethargy, coma, seizures, respiratory depression, bradycardia, hypotension, aplastic anemia, oligohidrosis and hyperthermia, nephrolithiasis, SJS/TEN Avoid in sulfa allergy

$t_{1/2}$, serum half-life; V_d, volume of distribution.
Table adapted from individual medication package inserts.

Although better tolerated than the older agents, overdose may be associated with significant morbidity and mortality. US poison centers reported 32,882 cases of exposures to these "newer anticonvulsants" in 2012, an increase from 22,182 cases in 2005 (4). Of these, 142 were classified as having a major outcome (defined as life-threatening or resulting in significant residual disability or disfigurement), and there were 4 deaths (4).

The newer anticonvulsants, each with its unique mechanism of action and pharmacologic profile, are FDA-approved as adjunctive treatment of partial seizures in adults (2). Felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, and vigabatrin are also used to treat partial seizures in children (5).

Felbamate (Felbatol), the first of the second-generation anticonvulsants, is used only in refractory cases of partial and generalized seizures, because of associated high morbidity and mortality from aplastic anemia and hepatic failure. The exact anticonvulsant mechanism is unknown but may entail neuronal sodium-channel blockade, calcium-channel blockade, as well as

glutamate antagonism at *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/kainate receptors (6).

Gabapentin (Neurontin) is commonly prescribed for seizures and postherpetic neuralgia, although off-label uses comprise more than 80% of prescriptions (6). Its mechanism of anticonvulsant action remains unknown but is thought to involve a unique receptor in the brain (5,6). Although it is a structural analog of the neurotransmitter γ-aminobutyric acid (GABA), gabapentin neither interacts with GABA receptors nor modulates GABA metabolism.

Lamotrigine (Lamictal) is a phenyltriazine derivative structurally unrelated to other currently available anticonvulsants. Its exact mechanism of action is unknown. Studies suggest that lamotrigine's antiepileptic effect results from stabilization of neuronal membranes through the inhibition of voltage-dependent sodium channels and, to a lesser extent, calcium channels (5,6).

The exact mechanism of action of levetiracetam (Keppra), a pyrrolidine analog, is also unknown, but antagonism of *N*-type calcium channels and presence of a unique binding site, the synaptic vesicle protein SV2 A, have been suggested (5).

Oxcarbazepine (Trileptal), an iminostilbene derivative, is a keto-derivative of carbamazepine. Oxcarbazepine is a prodrug with a pharmacologically active 10-monohydroxy metabolite (MHD). Although the exact mechanism is unknown, oxcarbazepine may exert its anticonvulsive effects via blockade of voltage-sensitive sodium channels, enhanced potassium conductance, and modulation of high-voltage calcium channels (5,6).

Pregabalin (Lyrica), like gabapentin, is a structural analog of GABA but does not bind to the GABA receptor and does not modulate neuronal GABA activity. Pregabalin and gabapentin are pharmacologically indistinguishable. Modulation of calcium influx through voltage-gated neuronal calcium channels is the proposed mechanism of both anticonvulsive and nociceptive action (5).

Tiagabine (Gabitril) is a potent and selective inhibitor of the GABA transporter. It prevents GABA uptake in neuronal and glial cells, resulting in elevated GABA concentrations in the synaptic cleft (5,6).

Topiramate (Topamax) is structurally similar to the carbonic anhydrase inhibitor acetazolamide. Topiramate's anticonvulsant effects are due to several mechanisms, including inhibition of voltage-sensitive sodium and calcium currents, potentiation of GABA activity, and blockade of AMPA/kainate type glutamate receptors (5,6).

Vigabatrin (Sabril) is a synthetic GABA derivative that irreversibly inhibits GABA transaminase, thus inhibiting GABA metabolism and increasing central nervous system (CNS) GABA concentration (5).

Zonisamide (Zonigran) is a sulfonamide with a broad spectrum of anticonvulsant activity. Although the exact mechanism of action is unknown, in vitro analysis demonstrates blockade of voltage-sensitive sodium channels, calcium currents through T-type calcium channels, and enhancement of both dopaminergic and serotonergic neurotransmission (5).

CLINICAL PRESENTATION

Although the chemistry and pharmacology of each of the new anticonvulsants is unique, CNS effects usually predominate following overdose. Common symptoms include dizziness and lethargy.

Adverse effects may be seen in both therapeutic dosing and overdose. Most of the anticonvulsants discussed in this chapter are well tolerated following overdose and respond to supportive care. The unique clinical characteristics of each drug are discussed below.

Common effects following felbamate overdose include somnolence, ataxia, vomiting, and tachycardia. Documented fatalities from hepatic failure from aplastic anemia have occurred with therapeutic use. Acute renal failure and crystalluria are reported following overdose (7).

Isolated gabapentin overdose in otherwise healthy patients generally causes only mild toxicity. In a case series of 20 exposures to gabapentin ranging from 50 to 35,000 mg, drowsiness, dizziness, nausea and vomiting, tachycardia, and hypotension were the most common effects reported in symptomatic patients (8). Toxicity is more pronounced in patients with renal impairment. Altered mental

status and myoclonus have been described in patients with renal failure (5).

Lamotrigine overdose typically leads to neurologic and cardiac effects. The most common symptoms include lethargy and ataxia. Coma and seizures and QRS interval prolongation are the most consequential effects. PR and QT interval abnormalities have been reported. Patients taking lamotrigine therapeutically may develop a rash with progression to Stevens–Johnson syndrome (SJS) and toxic epidermal necrolytsis (TEN) (5). A few patients may develop drug reaction, eosinophilia, and hypersensitivity syndrome (DRESS), with rash, eosinophilia, and inflammatory organ changes.

Levetiracetam overdose is well tolerated, with few adverse effects. Transient alteration of consciousness, coordination problems, and behavioral abnormalities such as aggression and psychosis may be seen. Only one case report in an adult describes obtundation with respiratory depression following ingestion of 30 g (9).

Common clinical effects following oxcarbazepine overdose include fatigue, dizziness, ataxia, and nausea. The more serious effects include lethargy, coma, paradoxical seizures, bradycardia, hypotension, and hyponatremia (5). A drug rash progressing to SJS and TEN has been reported with therapeutic dosing (5).

Lethargy, somnolence, and coma are the most consequential effects following pregabalin toxicity (10). Myoclonus may be seen in patients with renal impairment (5).

Tiagabine toxicity is commonly associated with fatigue, dizziness, ataxia, and lethargy. Coma and agitation may be seen following overdose. Paradoxical seizures, both convulsive and nonconvulsive status epilepticus, have been described in postmarketing analysis of patients taking tiagabine therapeutically (5).

Topiramate toxicity causes sedation, word-finding difficulties, dizziness, and ataxia. Oligohidrosis and subsequent hyperthermia may be seen and are more common in children. Acute angle closure glaucoma, coma, and non–anion-gap hyperchloremic metabolic acidosis are the more serious effects with both therapeutic dosing and overdose (5).

Vigabatrin side effects commonly manifest as fatigue and dizziness. Coma may ensue following overdose. Psychotic behavior has been reported with therapeutic use as well as following overdose. Bilateral concentric visual field defects and progression to vision loss is the most consequential effect of therapeutic dosing.

Zonisamide toxicity causes sedation, ataxia, and nausea. The most important adverse effects seen in therapeutic dosing include SJS and TEN, aplastic anemia, oligohidrosis, and subsequent hyperthermia in the pediatric population, as well as nephrolithiasis. There are several reports of psychotic reactions after initiating zonisamide that resolve after discontinuation of the drug. Coma, seizures, respiratory depression, hypotension, and bradycardia are described following overdose (5). Cross-reactivity can occur in patients with sulfonamide allergy.

It should be noted that overdoses with the anticonvulsants can be complicated by co-ingestants. The potential for complications increases with more agents, including dose-dependent adverse effects, idiosyncratic reactions, drug–drug interactions, and long-term effects.

DIFFERENTIAL DIAGNOSIS

Numerous agents can cause CNS depression. These include the traditional anticonvulsants (carbamazepine, phenobarbital, phenytoin, and valproic acid), antidepressants, antipsychotics, antihistamines, alcohol, β-blockers, muscle relaxants, opioids, sedative–hypnotics, and many other agents. Medical causes such as stroke, trauma, intracranial hemorrhage, infection, electrolyte abnormalities, and cardiac dysrhythmia should be considered and differentiated from drug-induced effects.

ED EVALUATION

History includes the time of ingestion and type and amount of drug(s) taken, any treatment in the field, the onset and nature of symptoms, existing medical or psychiatric problems, and current drug therapy, particularly if the patient is on multiple medications for epilepsy. A rapid glucose concentration and vital signs, including

temperature, cardiac monitoring, and pulse oximetry, should be obtained.

Physical examination should focus on vital signs, cardiopulmonary status, and neurologic assessment. Skin assessment is important in lamotrigine, oxcarbazepine, and zonisamide exposure. Eye evaluation should be performed for visual complaints with topiramate and/or vigabatrin exposure. Seizure precautions should be instituted. Patients should be assessed for depression or suicide risk and those with intentional overdose require close observation while undergoing medical evaluation. Screening ECG for evaluation of PR, QRS, and QT intervals is important following lamotrigine exposure. Complete blood count (CBC) screens for aplastic anemia from felbamate and zonisamide. Basic metabolic panel (BMP) detects hyponatremia from oxcarbazepine exposure and hyperchloremia seen with topiramate-induced metabolic acidosis, and evaluates the renal function. Urinalysis may detect hematuria seen with nephrolithiasis from zonisamide and crystalluria following felbamate exposure. Liver function tests are necessary to screen for hepatotoxicity following felbamate exposure. Arterial blood gas is helpful in evaluating for topiramate-induced metabolic acidosis and seizure-induced lactic acidosis. EEG is instrumental in evaluation of nonconvulsive status. Patients with intentional overdose warrant an acetaminophen and salicylate concentration. Additional tests, such as CT head, may be warranted in evaluation of a patient with undifferentiated altered mental status or signs of trauma. Serum concentrations of anticonvulsants are not helpful in management of overdose.

KEY TESTING

- Specific drug levels are not helpful
- ECG, electrolytes, CBC, blood gases, EEG are necessary for certain anticonvulsants
- Additional tests may be useful for supportive care and to rule out other conditions

ED MANAGEMENT

Symptom-based supportive therapy is the cornerstone of managing second-generation anticonvulsant overdoses. Stopping the medication is the first step. Respiratory depression may warrant endotracheal intubation. Hypotension is usually responsive to intravenous crystalloids but may necessitate vasopressors, particularly in the presence of co-ingestants.

Intravenous sodium bicarbonate may be given for lamotrigine-induced QRS interval prolongation of >100 milliseconds. If a rapid bolus of 1 to 2 mEq/kg decreases the QRS duration, an infusion of sodium bicarbonate solution (150 mEq mixed in 1 L of D_5W) should be given.

Benzodiazepines are the first-line treatment for seizures, followed by phenobarbital and propofol for refractory cases or status epilepticus. First- or second-generation anticonvulsants have no role in anticonvulsant-induced seizures.

A single dose of oral activated charcoal may be considered in an awake patient shortly after a large ingestion. Gastric lavage is likely to be of more risk than benefit. Whole bowel irrigation may be considered for significant ingestions of extended-release preparations.

Hyperthermia, although rare, warrants rapid cooling with ice bath for goal temperature of <102 F within 20 minutes. Oxcarbazepine-induced hyponatremia should be treated with slow sodium repletion. In patients with intact mental status and absence of seizures, normal saline should be administered, followed by repeat lab testing. Patients with significant hyponatremia with either mental status changes or seizures may warrant hypertonic saline therapy. (See Chapter 210, “Disorders of Sodium”).

Topiramate-induced acute angle closure glaucoma should be treated rapidly.

Stopping topiramate usually alleviates the associated non–anion-gap hyperchloremic metabolic acidosis. The benefit of hemodialysis in overdose of second-generation anticonvulsants is unclear but may be considered for severe acid–base and electrolyte disturbances. Experience with intravenous lipid emulsion therapy (ILE) is limited

to case reports of lamotrigine overdose and cannot be routinely advised.

Discontinuing the medication is adequate for a drug reaction rash but patients with SJS or TEN may need admission to the burn unit. Patients with suspected DRESS syndrome require close observation, prompt discontinuation of the drug, and methylprednisolone therapy.

Consultations from neurology for continuous EEG monitoring may be helpful for status epilepticus and nonconvulsive status, from ophthalmology for visual changes following topiramate and vigabatrin exposures, from psychiatry for suicidal ideations or attempts, and with the Poison Control Center (1-800-222-1222) for new developments in management.

CRITICAL INTERVENTIONS

- Provide airway protection and respiratory support as clinically indicated.
- Administer intravenous fluids for hypotension.
- Administer intravenous sodium bicarbonate for prolonged QRS interval.
- Administer benzodiazepines as a first-line agent for seizures.
- Consider EEG monitoring in patients with persistent altered mental status.
- Hyponatremia should be corrected slowly with either normal saline in asymptomatic patients, or hypertonic saline in patients with altered mental status or seizures.
- SJS or TEN may warrant transfer to the burn unit for aggressive wound care.
- Consider contacting the Poison Control Center (1-800-222-1222) for the most recent developments in management.

DISPOSITION

Patients who remain completely asymptomatic after an observation period of 8 hours, or mild hyponatremia that corrects after normal saline may be medically cleared, unless a co-ingestant requires

further management. Patients with CNS or respiratory depression, status epilepticus, hemodynamic instability, or cardiac conduction disturbances should be admitted to an intensive care unit. Patients with an isolated seizure, renal insufficiency, or DRESS syndrome without hemodynamic instability may be observed on a medical floor. Evidence of TEN or SJS should prompt consultation with a burn unit. Consultation with the patient's physician is warranted if medication is discontinued. Patients and their families should be educated in cases where an unintentional exposure occurred to prevent re-exposure.

Common Pitfalls

- Failure to consider that, although rare, significant CNS depression can occur after overdose with second-generation anticonvulsants.
- Failure to assess for suicide risk, given the increased risk both with a diagnosis of epilepsy and with therapeutic use of second-generation anticonvulsants.
- Failure to consider that tiagabine may cause both convulsive and nonconvulsive status epilepticus.
- Failure to consider that cardiac conduction disturbances occur after lamotrigine overdose.
- Failure to recognize oxcarbazepine-induced hyponatremia.
- Failure to consider SJS and TEN following exposure to zonisamide, lamotrigine, and oxcarbazepine.
- Failure to appreciate topiramate-associated acute angle closure glaucoma and vigabatrin-associated vision loss.
- Failure to appreciate aplastic anemia as a complication of felbamate and zonisamide therapy.
- Failure to consider hyperthermia from oligohidrosis in pediatric patients with exposure to topiramate and zonisamide.
- Failure to consider the risks of medical comorbidities, drug interactions, and adverse effects.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Walter H. Mullen, Jenny J. Lu, and Mark B. Mycyk to this chapter in previous editions.

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PART 5 • ANTI-INFECTIVE AGENTS AND BIOCIDES

CHAPTER 315

Antimalarial Drugs

Suzanne M. Shepherd, Thomas Grosheider, and William H. Shoff

Malaria is one of the most important infectious diseases worldwide. Approximately 200 to 500 million new cases, and as many as 0.6 to 2.7 million deaths, occur each year in the 3 billion exposed. Malaria was eradicated in the United States (1947 to 1951), but 1,500 new cases annually, including 10% of cases of severe malaria with an increased risk of death, reported to the Centers for Disease Control (CDC) are associated with returning travelers and immigrants (see Chapter 193, " Parasitic Disease").

A higher risk of adverse drug reactions is tolerated in the treatment of malaria, with its high mortality if not expeditiously managed (1), and so the therapeutic ratios of some antimalarials are narrow and toxicity is likely when recommended dosing is exceeded. Patients at increased risk of developing severe adverse events are those at the extremes of age, HIV-positive, and G6PD deficient (2). Table 315.1 summarizes current common malaria chemoprophylaxis and treatment options in the United States.

TABLE 315.1
Common Chemoprophylaxis and Treatment of Malaria in the United States

Drug	Usage	Prophylaxis	Treatment	Safe in Pregnancy	Contraindications
Chloroquine (Aralen)	Sensitive, *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malaria*	(+)	(+)	(+)	Hepatic disease, persons with visual changes
Hydroxychloroquine sulfate (Plaquenil)	Chloroquine-sensitive *P. falciparum* and non-*falciparum* species	(+)	(+)	(+)	Hepatic disease, persons with visual changes
Mefloquine (Lariam)	Chloroquine-resistant *P. falciparum* and *P. vivax*	(+)	(+)	(+)	Seizure disorders, conduction disturbance, or history of significant psychiatric disease
Clindamycin (Cleocin)	Chloroquine-resistant *P. vivax* (in combination with quinine–quinidine)	(–)	(+)	(+)	Can be used with children <8 yrs
Doxycycline (Vibramycin)	Chloroquine-resistant *P. falciparum* and *P. vivax* (in combination with quinine–quinidine)	(+)	(+)	(–)	Lactating females and children, in patient <8 yrs, should be taken with food
Atovaquone/proguanil (Malarone)	Chloroquine-resistant *P. falciparum* and probably chloroquine-resistant non-*falciparum* species	(+)	(+)	(–)	Severe renal failure (CrCl <30 mL/min), should be taken with food
Primaquine (Palum)	Prolonged exposure to *P. vivax* or *P. ovale*	(+)	(+)	(–)	G6PD deficiency (can cause hemolysis), should be taken with food
Tetracycline	Chloroquine-resistant *P. falciparum* and *P. vivax* (in combination with quinine–quinidine)	(+)	(+)	(–)	Lactating females and children <8 yrs, should be taken with meals
Quinidine IV only (combine with doxycycline, clindamycin, or tetracycline)	Chloroquine-sensitive *P. falciparum* and non-*falciparium* species when parenteral drug needed	(+)	(+)	(–)	Conduction disorders, history of blackwater fever, thrombocytopenia, optic neuritis
Artemether (artemether/lumefantrine; Coartem)	Chloroquine-sensitive *P. falciparum*	(–)	(+)	(+)	Designated by FDA as orphan drug in United States: 2007
Artesunate	Chloroquine-sensitive *P. falciparum*	(–)	(+)	(+)	Designated by FDA as orphan drug in United States: 2007 Limited availability

Adapted from Griffith KS, Lewis LS, Mali S, et al. Treatment of malaria in the United States: A systematic review. *JAMA*. 2007;297:2264–2277; John CC. Drug treatment of malaria in children. *Pediatr Infect Dis J*. 2003;22:649–651.

Drug resistance has forced the use of new and fixed combinations of drug therapy. Older antimalarials are being used less frequently with less accidental or purposeful overdosing. Data on many of the newer drugs are less available, particularly in combination overdoses (3). Antimalarial agents currently in use in the United States include quinoline derivatives, dihydrofolate reductase inhibitors, antibacterials, artemisinin derivatives, and ubiquinone analogs (Table 315.2). Most antimalarial poisonings are the result of accidental childhood exposures or intentional adolescent and adult suicide attempts.

TABLE 315.2
Classification of Antimalarials

Quinoline Derivatives
Chloroquine
Hydroxychloroquine
Mefloquine
Quinidine
Quinine

Amino-4-quinolines
Amodiaquine

Amino-8-quinolines
Primaquine

Ubiquinone Analog–α-hydroxy-1,4-naphthoquinone
Atovaquone
(Atovaquone/proguanil [Malarone])

Pyrimethamine
(Pyrimethamine/dapsone [Maloprim])
(Pyrimethamine/sulfadoxine [Fansidar])
Sulfonamides

Antibacterials
Clindamycin
Doxycycline
Tetracycline

Artemisinin Derivates (Qinghaosu)
Artemether artesunate

Chloroquine, quinine, quinidine, amodiaquine, halofantrine, hydroxychloroquine, mefloquine, and primaquine are quinoline derivatives that cause severe toxicity in overdoses (1,4). The antimalarial quinine is an alkaloid derived from the bark of the Cinchona tree. Quinine has a black box warning in the United States due to hematologic toxicity. Quinoline derivatives carry an undeserved reputation as abortifacients (1). Both quinine and quinidine have been associated with immune thrombocytopenia caused by antibodies that bind only when the drug is present (5).

Chloroquine is usually well tolerated in prophylaxis and treatment doses. Mild side effects, including nausea and headache, may occur. Certain populations infected with malaria, such as Africans with G6PD and certain hemoglobin genotypes, may experience generalized pruritis via a nonallergic interaction. Chloroquine may worsen psoriasis and is rarely associated with psychosis and seizures. Acute chloroquine toxicity is usually seen when higher parenteral doses are administered too rapidly. Acute adverse reactions may

include central nervous system (CNS) and cardiovascular toxicity. Due to these side effects, chloroquine is contraindicated in those with a seizure disorder or generalized psoriasis.

Quinine is associated with (1) cinchonism, (2) hypotension, and (3) hypoglycemia. It has local anesthetic and irritant effects, some skeletal muscle-blocking action, vasodilatory effect due to its α-blocking activity, and acts centrally to cause emesis. Chloroquine and hydroxychloroquine share these effects and also act as respiratory depressants. Quinoline derivatives share several cardiac effects, causing negative cardiac inotropism, slowing depolarization and conduction, increasing action potential duration, and in overdose, lengthening the effective refractory period (widening QRS and QTc intervals) (1,3). Chloroquine in supratherapeutic levels causes direct arterial vasodilation. Nitric oxide and histamine release may mediate hypotension and postural hypotension. Case reports link both chloroquine and quinine to fatal cardiomyopathies (6). Chloroquine and hydroxychloroquine use may cause hypokalemia.

Oral quinine and chloroquine are rapidly absorbed in the small intestine, with 80% to 90% bioavailability and peak levels occurring 1 to 3 hours after ingestion. The apparent volume of distribution (VD) is 1.6 to 1.8 L/kg for quinine and 116 to 285 L/kg for chloroquine, with plasma protein binding of 89% and 55%, respectively. Due to high chloroquine tissue binding, brain concentration may be four times that of plasma, and may precipitate seizures (7). The VD for hydroxychloroquine is about 63 L/kg (8). Dose-related gastrointestinal (GI), CNS, and cardiovascular toxicity may result from excessive intravenous (IV) infusion or from accumulation following oral administration. Severe hypotension may develop if the drug is injected too rapidly. The toxic effects of quinoline derivatives are caused by their cardiac, cytotoxic, and irritant properties.

Ocular toxicity develops in 17% to 42% of patients with quinine poisoning and appears to be caused by a direct toxic effect on the photoreceptor and ganglion cell layers of the retina and can lead to blindness (9). The central 10% of the visual field is the initial site of toxicity. Cumulative dosing >800 g, age >70, and plasma

concentration of quinine >15 mg/L during overdose appear to be major risk factors for ocular toxicity. The risk of ocular toxicity is higher in dosing of quinolone derivatives used to treat rheumatologic disorders.

Chloroquine has a narrow margin of safety, with toxicity occurring at doses as low as 1.0 to 1.5 g, or 20 mg/kg. Doses >2 g in adults are almost always associated with toxic effects, and doses >5 g are usually lethal. Toxicity correlates with plasma quinine and chloroquine concentrations, and blood chloroquine levels >3 μg/mL are usually toxic. Death is likely if the level is >8 μg/mL. Chloroquine and hydroxychloroquine poisonings are associated with high fatality rates but are rare in the United States.

The toxic dose of quinine in adults ranges from 1.8 to 4.0 g. A single dose of quinine >3 g can cause serious and potentially fatal toxicity in adults, including CNS signs and seizures. Much smaller doses may be lethal in children. The therapeutic range of quinine is 5 to 15 μg/mL. Quinine levels as low as 2 μg/mL are associated with mild, reversible hearing loss. More toxic effects are seen with levels of 6 to 15 μg/mL. Cardiac arrhythmias, irreversible blindness, and death are reported with levels >15 μg/mL. Survival has occurred with levels as high as 23.5 μg/mL, but concentrations >13 μg/mL at 5 hours and 6 μg/mL at 20 hours predict severe toxicity.

Even therapeutic doses of primaquine can cause hemolytic anemia, including fatal hemolysis, in individual who are G6PD deficient. Methemoglobinemia can occur in those receiving therapeutic dosing, and can be severe in individuals with a congenital deficiency of NAD methemoglobin reductase. Rarely, usually with primaquine overdose, agranulocytosis or granulocytopenia, arrhythmia, hypertension, and CNS toxicity may occur. Hydroxychloroquine plasma concentration from 0.6 to 9.9 μg/mL is associated with severe toxicity. Amodiaquine has a similar mechanism of action as chloroquine and can cause hepatitis and agranulocytosis.

Mefloquine, also commonly used as chemoprophylaxis, may have cardiac depressant activity, and marked GI or CNS adverse effects, such as severe nausea, psychosis, odd vivid dreams, and seizures. Severe neuropsychiatric reactions requiring hospitalization, including

hallucinations and seizures, is reported in 1:15,000 to 20,000 of those taking mefloquine for chemoprophylaxis with more adverse reactions at higher treatment doses (1). Oral absorption is rapid, and half-life of 9 to 13 days follows hepatic biotransformation.

Pyrimethamine alone rarely causes toxicity, except for decreased hematopoiesis or skin rash. Excessive doses or overdose can cause megaloblastic anemia, similar to folate deficiency, hepatitis, serum sickness reactions, and severe to fatal skin reactions, such as erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis.

Atovaquone's, (a unique napthoquinone), most common reactions are maculopapular rash, fever, headache, apthous ulceration, and GI side effects including vomiting, abdominal pain, and diarrhea. Elevated transaminases and rare cases of hepatitis have been reported with the use of atovaquone–proguanil. Hepatic metabolism is the major path of elimination of proguanil, with 40% of the drug eliminated renally. The half-life of proguanil is 12 to 21 hours.

Artemisinin and its antimalarial derivatives artesunate and artemether are well-tolerated in both adults and children. IV artemether has been available in the United States since 2007 via an investigational new drug protocol through the CDC. Coartem, a fixed combination of artemether and lumefantrine, was FDA approved in 2009. Sesquiterpene alkaloids have been associated with allergic dermatoses and liver toxicity. Adverse effects of artemether and artemisinin derivatives include bradycardia, dizziness, rash, and fever. In combination with lumefantrine (Coartem), side effects also include abdominal pain, anorexia, nausea, vomiting, diarrhea, and headache. Human poisonings are rare, with the potential for GI, liver, cardiac, and CNS toxicity (10). Dizziness and GI disturbances are seen when the drugs are used orally. Toxicity occurs with long-term exposure rather than short-term peak concentrations (11).

CLINICAL PRESENTATION

Cinchonism is the most common early feature of quinine overdose, usually occurring within 4 hours of ingestion but as early as 2 hours and as late as 8 to 12 hours. Cinchonism can be seen with acute or

chronic poisoning and is noted in about 75% of patients. Mild cinchonism, including tinnitus, visual disturbances, high-tone deafness, headache, dysphoria, postural hypotension, nausea and vomiting, occurs frequently and resolves soon after the drug is stopped (1,6).

Cardiac toxicity after quinine is typically mild and dose related, producing sinus tachycardia and minor electrocardiographic (ECG) changes. However, ventricular arrhythmias, including torsades de pointes, significant conduction disturbances, and complete atrioventricular dissociation have been reported (1). ECG abnormalities include prolonged PR and QT intervals, ST- and T-wave changes, U waves, bundle-branch blocks, and QRS interval widening. Mefloquine has no effect on the QT interval. QT interval prolongation following artemether–lumafantrine use is similar or less than that with chloroquine, mefloquine, or combined artesunate and mefloquine, and significantly less than with quinine or quinidine (1). With massive exposures, convulsions, coma, respiratory depression, adult respiratory distress syndrome, and cardiac arrest may occur.

The incidence of early retinopathy in patients not monitored regularly is 10% for chloroquine, 3% to 4% for hydroxychloroquine, and 0.5% for advanced retinopathy (1,9). Visual disturbances can be delayed for 6 to 24 hours after ingestion and may present with progressive blurring of vision or sudden blindness. Dilated pupils that become fixed before vision loss occurs have been reported. Peripheral visual-field defects, color misperceptions, diplopia, and poor dark adaptation can precede the development of total blindness or can be transient. The fundus is usually normal at the onset of visual defects, but retinal arteriole constriction, macular edema, and a cherry-red macular spot can develop within hours, evolving into optic atrophy (1,9). Laboratory findings include hypoglycemia, hypokalemia, slight elevation of muscle enzymes, and thrombocytopenia. Hypoglycemia is quite common, and may occur as a result of quinine-induced insulin secretion. Quinine seldom induces abortion but is associated with fetal abnormalities and maternal deaths. Hydroxychloroquine should be used very carefully during pregnant individuals with malaria (12).

In contrast, chloroquine toxicity presents differently with a rapid onset of symptoms, severe cardiovascular effects, greater respiratory depression, marked hypokalemia, and milder and transient ocular and auditory toxicity. Cardiovascular collapse is common within 2 hours in serious overdoses and is a result of marked myocardial depression and ventricular dysrhythmias. Toxicity can be predicted by a prolonged QRS interval and hypokalemia, probably from intracellular shifts. Toxic effects are usually short-lived, despite persistently high plasma levels of the drug. Seizures may occur within a few hours after overdose, or be delayed to several weeks.

Other quinoline derivatives, such as primaquine, do not have severe cardiovascular toxicities but are associated with GI distress, hemolytic anemia, and methemoglobinemia.

Mefloquine overdoses produce neuropsychiatric manifestations including headache, dizziness, vertigo, seizures, affective disorder, paranoia, hallucinations, anxiety, sleep disturbances, suicidal ideation, and hearing loss. Nausea, vomiting, diarrhea, abdominal pain, and transient elevations in transaminase levels may be seen in a posthepatic syndrome caused by mefloquine-induced liver damage, coupled in some with thyroid inhibition. Because of the prolonged half-life, these adverse events can persist for weeks.

Myopathy is rare, but reported with the use of higher doses of quinolone antimalarials. Risk is increased with advanced age, underlying renal disease, diabetes, hypothyroidism, and liver disease. Patients may complain of painful or painless muscle weakness. Deep tendon reflexes and sensation may also be decreased. Creatine kinase (CK), aldolase, myoglobin, lactate dehydrogenase, aspartate aminotransferase, as well as phosphorus and potassium may be elevated, with CK the most sensitive but not specific (1).

Of the dihydrofolate reductase inhibitors, pyrimethamine is the most toxic and may cause ataxia, seizures, coma, blindness, and deafness and folate deficiency with megaloblastic anemia. Proguanil, another dihydrofolate reductase inhibitor, is one of the safest antimalarial drugs. GI distress with vomiting, diarrhea, and abdominal pain coupled with headaches, nausea, and hematuria has been reported with ingestions of 1 g or more. Therapeutic doses of

proguanil are associated with mouth ulcerations, GI distress, rash, and anemia.

Dapsone, another dihydrofolate reductase inhibitor, may cause acute methemoglobinemia and hemolytic anemia. A series of five HIV-positive patients developed methemoglobinemia while on primaquine and dapsone.

Massive doxycycline overdoses have resulted in precipitation of calcium and hypocalcemic death in animals. In humans, precipitation of calcium can lead to staining of teeth in children younger than 8 years. Doxycycline has been associated with Sweet syndrome, which is characterized by nonpruritic, painful, reddish nodules on the head, neck, chest, or upper limbs usually with fever, general malaise, and leukocytosis. Photosensitization is common. Benign intracranial hypertension, transient liver injury with transaminase elevation, GI upset, and esophageal ulcerations have also been reported with doxycycline.

Atovaquone, a novel hydroxynaphthoquinone, has produced minimal effects with overdoses up to 31.5 g. Methemoglobinemia has also been reported in a co-ingestion of atovaquone and dapsone.

DIFFERENTIAL DIAGNOSIS

Overdose with chloroquine and quinine can be confused with cerebral malaria. Quinoline derivative toxicity may resemble other agents that cause visual, auditory, or cardiac effects. Methanol, ergot derivatives, and heavy metals (e.g., lead and mercury) are in the differential diagnosis of visual disturbances. Unlike the quinolones, methanol is usually associated with a marked anion-gap acidosis and osmolal gap. Manifestations of cinchonism are similar to those of salicylate toxicity, but the latter also causes an elevated anion gap, and acid–base imbalances. Visual blurring may be seen with acute salicylate toxicity, but not visual loss. Quinidine, an isomer of quinine, causes similar cardiac effects but no visual deficits. Many drugs, such as the cyclic antidepressants, can cause similar cardiovascular and ECG effects, but these are not linked to auditory or visual changes. In patients with unexplained thrombocytopenia,

drug-induced (e.g., quinine, quinidine) immune-mediated causes should be considered.

ED EVALUATION

In the overdose or toxic patient who presents with visual, auditory, neuropsychiatric, and CV symptoms of unknown cause, a history of recent travel or the use or availability of antimalarial agents is suggestive. Attempted abortion by quinine should be suspected in a pregnant patient with these complaints. Physical examination and evaluation of the vital signs, cardiac rhythm and inotropy, auditory and visual acuity, pupillary size and reactivity, funduscopic findings, visual-field testing, and a neurologic examination, including cerebellar status, are important. An ECG should be obtained. Laboratory studies include rapid serum glucose assessment and monitoring, and blood levels of quinine, quinidine, salicylate, electrolytes, lactate, liver transaminases, blood urea nitrogen, CK, and a complete blood count. Myoglobin may be helpful in those with muscle weakness. Methemoglobin levels and hemolysis evaluation may be warranted for some agents. If available, electroretinograms and visual-evoked response testing may detect signs of retinal damage in quinine overdose.

KEY TESTING

- Rapid fingerstick serum glucose
- Basic metabolic and liver panel
- ECG and continuous cardiac monitoring
- Chromatography of drug levels if available

ED MANAGEMENT

A suspected ingestion of antimalarials requires immediate attention to the vital signs, cardiac monitoring, and potentially activated charcoal administration, depending on the time from ingestion. Prevention of absorption is most effective in the first hour and, if done early, may reduce peak plasma levels. The half-life in healthy volunteers taking a therapeutic dose of quinine was reduced by 50%

and, in overdoses, was shortened from more than 24 hours to 8 hours by repeated doses of activated charcoal. However, clinical outcome improvement has not been documented. Activated charcoal administration may be problematic because of the rapid onset of hypoglycemia, CNS depression, and seizures, particularly with chloroquine or quinine overdose.

Hypotension usually responds to IV fluids but may require a vasopressor (e.g., epinephrine, dopamine, or norepinephrine) and inotropes (e.g., dobutamine) (1). Hypotension, ventricular dysrhythmias, and cardiac conduction abnormalities often respond to serum alkalization to a pH of 7.5 with sodium bicarbonate administration, hyperventilation, or a combination of these. Lidocaine has been used, but may potentiate dysrhythmias and seizures. Class 1A and 1C antidysrhythmics, such as procainamide, disopyramide, and flecainide, should be avoided as they will potentiate quinine cardiotoxicity. Torsade de pointes is treated with IV magnesium, isoproterenol, or overdrive pacing. Serum potassium should be monitored, however overcorrection must be avoided as it will exacerbate the cardiac effects of chloroquine.

Benzodiazepines, combined with mechanical ventilation, and epinephrine have been helpful in the chloroquine-overdosed patient. High doses of diazepam (0.5 to 3 mg/kg IV) may counteract the hemodynamic and ECG changes associated with chloroquine toxicity. Other sedating and anticonvulsant agents, such as barbiturates, have been suggested but may risk exacerbation of the hypotension seen in severe chloroquine toxicity. Because the cardiac toxicity is similar to that seen with hyperkalemia, potassium replacement is not advised unless hypokalemia is severe.

Despite its theoretical potential for enhanced quinoline derivative elimination, acidification of the urine is unproven and may increase toxicity. Resin and charcoal hemoperfusion, hemodialysis, peritoneal dialysis, plasmapheresis, and exchange transfusion are ineffective because of protein binding and high volumes of distribution. Methylene blue should be given for methemoglobinemia (see Chapter 335).

Attempts at reversal of retinal arteriolar vasospasm by stellate ganglion block, anterior chamber paracentesis, retrobulbar injections, and systemic nitrate vasodilators are not effective and can produce significant complications. Hyperbaric oxygen (HBO) therapy has been promoted on the premise that retinal hypoxia secondary to arteriolar vasoconstriction contributes to visual loss. However, the reported benefit may represent natural recovery.

Recovery from quinoline overdose is usually gradual and complete, but visual defects from quinine may not completely resolve.

CRITICAL INTERVENTIONS

- Establish IV access, cardiac monitoring, and obtain an ECG and fingerstick glucose level.
- Protect the airway and assist ventilation in patients with seizures or CNS depression.
- Administer IV benzodiazepines and sodium bicarbonate as warranted to patients with severe chloroquine toxicity.
- Administer IV pressor to patients unresponsive to IV fluids.

DISPOSITION

Patients suspected of ingesting a toxic amount of a quinoline derivative should be observed for 6 to 8 hours. Symptomatic patients and any with cardiac conduction abnormalities should be admitted to an intensive care unit. An ophthalmologist should be consulted in patients with visual symptoms. Those with hearing deficit may need referral for audiology testing.

Common Pitfalls

- Failure to obtain a history of travel to a malarial area and/or antimalarial use or access, in patients with auditory, visual, cardiac, and neuropsychiatric abnormalities of unknown cause.
- Failure to appreciate that hypoglycemia and rapid neurologic and CV deterioration can occur after chloroquine overdose.
- Failure to appreciate that benzodiazepines can prevent dysrhythmias and seizures in patients with chloroquine overdose.

- Failure to consider multiple-dose activated charcoal therapy.
- Failure to appreciate that potassium replacement can exacerbate chloroquine-induced cardiac toxicity.

ACKNOWLEDGMENTS

Special thanks to Timothy E. Albertson, Kathy A. Marquardt, and Judith A. Alsop, who contributed to this chapter in previous editions.

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CHAPTER 316

Herbicides

Victor Tuckler

Herbicides are chemicals used to control unwanted vegetation. Most herbicides are applied as water-based sprays and are usually safe to use in agriculture. Synthetic organic herbicides can be sprayed using helicopters or airplanes. Herbicidal toxicity occurs by inhibiting cell division, photosynthesis, respiration, or amino acid production. Herbicides can mimic natural auxin hormones, which regulate plant growth, and cause deformities in new growth. There are several classes that pose a potential health hazard. This chapter focuses on three classes: (1) bipyridyls (paraquat, diquat); (2) chlorophenoxy acids (2,4-D, 2,4,5-T, Agent Orange); and (3) organic phosphorus compounds (glyphosate, glufosinate).

BIPYRIDYLS (PARAQUAT, DIQUAT)

Chemically paraquat (1,1′-dimethyl-4,4′-bipyridilium) and diquat (1,1′-ethylene-2,2′-dipyridilium) are classified as bipyridyl compounds. Paraquat is a rapidly acting, nonselective herbicide that is relatively inexpensive. It is used as a desiccant, defoliant, and plant growth regulator, classified by the Environmental Protection Agency as “restricted use,” which means it can only be applied by licensed individuals. Dermal or spray exposure generally causes only limited, localized injury but accidental or deliberate ingestions have a high mortality rate. The toxic effects of smoking paraquat-contaminated marijuana are either very rare or nonexistent and do not result in lung damage because the paraquat is pyrolyzed to dipyridyl during smoking which presents little toxic hazard.

Paraquat is a blue-green solution to avoid accidental confusion with other chemicals, with concentrations from 20% to 40% with dilutions of 0.1% to 0.5% typically made for formulations used in the field.

The LD50 for paraquat in humans is approximately 3 to 5 mg/kg, which translates into 10 to 15 mL of a 20% solution. Common brand names include Herbaxone, Gramoxone, Gramonol, Gramixel, Preglone, and Weedol. Diquat is available as Aquacide, Reglone, Reglox, and Weedtrim.

Paraquat is rapidly absorbed after ingestion. About 1% to 5% of paraquat is absorbed from the gastrointestinal (GI) tract. Peak concentrations are achieved within 2 hours. Dermal absorption through intact skin is minimal. Mucous membrane and ocular exposures may cause minimal systemic absorption, but local tissue damage may be significant. Inhalation of paraquat spray is unlikely to cause any systemic toxicity.

After absorption, paraquat is distributed to all major organ systems but it selectively accumulates in the lungs at concentrations 10 to 15 times greater than plasma levels. Peak lung concentrations are achieved 4 to 5 days after ingestion. Paraquat is actively taken up by type 1 and type 2 pneumocytes, the principal target organ for toxicity. The primary mechanism is through the generation of free radicals with oxidative damage to lung tissue. Oxygen potentiates paraquat-induced pulmonary fibrosis.

Paraquat is enzymatically reduced to an unstable free radical and then is reoxidized to produce a superoxide radical, causing lipid peroxidation, mitochondrial dysfunction, necrosis, and apoptosis. Free radical scavengers such as glutathione are rapidly overwhelmed. Over a period of hours to days, this mechanism leads to multiorgan failure. The organs most affected are the lungs, heart, kidneys, and liver. Aveolar epithelial destruction, pulmonary hemorrhage, and congestion progressing to obliterative fibrosis can occur in paraquat toxicity. The brain is usually not affected since paraquat does not readily cross the blood–brain barrier. Paraquat is not metabolized. Renal excretion is the major route of elimination for paraquat, occurring within the first 12 to 24 hours. However,

20% to 30% that may remain tissue-bound is excreted over 2 to 3 weeks. Damage to the proximal renal tubule can occur.

Diquat is a dibromide monohydrate salt related to paraquat with liquid concentrations from 15% to 25% and with dilutions of up to 0.23% for field use. It is a nonselective contact herbicide, desiccant, and plant growth regulator used as a general herbicide for control of broadleaf and grassy weeds in terrestrial noncrop and aquatic areas. It is also used as a desiccant in seed crops and potatoes. Diquat appears to involve mechanisms and clinical manifestations similar to those of paraquat but much less likely to cause pulmonary injury (1).

CHLOROPHENOXY ACIDS (2,4-D, 2,4,5-T, AGENT ORANGE)

Chlorophenoxy acid herbicides act as plant hormones (auxins) to limit the growth of broadleaf and woody vegetation. Chlorophenoxy acid herbicides include 2,4-D (2,4-dichlorophenoxyacetic acid), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and 4-chloro-2-methyl-phenoxypropionic acid. Both 2,4-D and 2,4,5-T were used as defoliants in the Vietnam War, and referred to as Agent Orange, named for the orange stripes painted on the 55-gallon drums in which it was stored. Agent Orange was a 50:50 mixture of 2,4-D and 2,4,5-T but was contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, or dioxin), which is known to be carcinogenic and teratogenic in animals (suspected in humans). Only 2,4-D is currently available for general use in the United States. Brand names include Aqua-Kleen, Chloroxine, Esterom, Salvo, Weedar, Weed-B-Gone, and Weedone.

The GI absorption of chlorophenoxy acids is slow; peak blood levels may not occur for 12 hours or longer. 2,4-D has an apparent volume of distribution (Vd) of about 0.1 L/kg, with the highest concentrations found in the blood and heart. Elimination occurs primarily by renal excretion of unchanged 2,4-D, with a half-life of about 12 hours after low doses but longer after overdose and with renal failure.

Toxicity may involve interference with cell membrane lipid structure and function; formation of acetyl-Co-A analogs and choline esters with disruption of metabolic pathways and neurotransmission; and uncoupling of oxidative phosphorylation. Myotonia and rhabdomyolysis may result from increased activity of skeletal muscle mitochondrial enzymes. Serious poisoning almost always occur after suicidal ingestion of concentrated solutions. 2,4-D doses of 50 mg/kg produce mild toxicity, those of 100 mg/kg cause severe poisoning, and those of 250 mg/kg or more may be fatal. Pulmonary absorption from inhalation is possible, but unlikely to cause systemic toxicity. Although skin absorption is low, chronic dermal exposure may result in systemic toxicity.

ORGANIC PHOSPHORUS COMPOUNDS (GLYPHOSATE, GLUFOSINATE)

Glyphosate and glufosinate are phosphorylated glutamic acid analogs that inhibit plant enzymes involved in amino acid metabolism. Glyphosate (N-phosphonomethyl glycine) is sold in commercial preparations that also contain a surfactant, polyoxyethyleneamine (POEA), and is sold in the United States under the brand names Glifonox, Glycel, Rodeo, Rondo, and Roundup. Glufosinate (2-amono4-hydroxymethylphosphonyl butanoic acid) is marketed as Basta, Challenge, Finale, Hayabusa, and Ignite. These herbicides have limited oral and poor dermal absorption, undergo negligible metabolism, and are eliminated by urinary excretion. Glyphosate has a Vd of about 0.3 L/kg and a half-life of 2 to 3 hours. Glufosinate has a larger Vd (about 1.4 L/kg) and longer half-life (about 10 hours) which is increased in renal failure.

Although ingestion of commercial formulations clearly causes poisoning, and uncoupling of oxidative phosphorylation has been suggested as a mechanism, it appears that POEA, a nonionic surfactant with cationic (corrosive) effects, is actually responsible for GI, cardiovascular (CV), and pulmonary toxicity. Glyphosate and the accompanying surfactant (POEA) are also corrosive contact toxicants. Ingestion, aspiration, or prolonged cutaneous contact can

result in skin and mucous membrane irritation, edema, and ulceration.

Neurotoxic effects of glufosinate may be from stimulation of excitatory N-methyl-D-aspartate receptors or inhibition of glutamine acid decarboxylase and consequent decreased synthesis of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), whereas CV toxicity appears to be as a result of the POEA component. In adults, the ingestion of 50 to 100 mL of an undiluted organic phosphorus herbicide–surfactant formulation is likely to cause mild poisoning, 100 to 200 mL may result in moderate to severe poisoning, and 200 to 300 mL or more is potentially fatal.

CLINICAL PRESENTATION

Paraquat

The toxicity of paraquat and diquat depends on the dose and primarily the concentration involved. Tachycardia and hypotension may occur as a result of the fluid loss due to GI caustic burns and hemorrhage. Tachypnea develops in patients who develop pulmonary injury. Oropharyngeal burns may result from ingesting paraquat or diquat. Mucosal edema of the tongue and oropharynx may also develop. The GI tract is also a site of initial injury to mucosal surfaces following ingestion. Severe corrosive corneal injury may result from eye exposure. Conjunctivitis and corneal scarring may occur after exposure.

Upper respiratory tract exposure may result in mucosal injury and epistaxis. Inhalation may lead to cough, dyspnea, chest pain, and pulmonary edema. Pulmonary toxicity represents the most lethal manifestation of toxicity from paraquat.

Acute pulmonary edema and early lung damage may occur within a few hours of severe acute exposures, and may progress despite treatment. The delayed toxic damage of pulmonary fibrosis most commonly occurs 7 to 14 days after ingestion and respiratory symptoms may persist for several weeks after inhalational exposure. Dermal caustic effects include local skin irritation and ulceration of epithelial surfaces. Concentrated solutions may cause dermal burns

that enhance absorption. Systemic toxicity due to dermal exposure through intact skin is uncommon. Local skin damage can cause a contact dermatitis. Prolonged contact will produce erythema, blistering, abrasion, and ulceration. CV effects occur from necrosis of the myocardium. Patients may develop hypotension due to fluid losses and cardiac dysrhythmias. Myocarditis and skeletal muscular necrosis can occur after ingestion.

Diquat and paraquat can produce GI symptoms such as nausea, vomiting, abdominal pain, and diarrhea. The toxicity is manifested by swelling, edema and painful ulceration of the mouth, pharynx, esophagus, stomach, and intestine. Corrosive injuries to the esophagus and stomach such as hemorrhage and perforations may occur. Hepatic failure due to centrilobular hepatocellular necrosis may occur 24 to 48 hours postingestion. Renal failure may occur postingestion due to acute tubular necrosis. Cerebral edema, lethargy, and coma occur in severe cases with either paraquat or diquat. Pontine purpura and brainstem infarct have occurred with diquat.

Diquat

Diquat is structurally similar to paraquat but is less toxic. Diquat is toxic to the kidneys and is much less likely to cause respiratory failure than paraquat, and it has not caused pulmonary fibrosis. Symptoms begin with GI effects similar to paraquat, but diquat does not produce pulmonary fibrosis. Local corrosive toxicity can occur after oral, dermal, inhalational, eye exposure to diquat-containing formulations. Burning in the mouth and painful ulcerations are common after diquat ingestion.

Chlorophenoxy Acid

The ingestion of concentrated chlorophenoxy acid herbicides may cause a burning sensation in the pharynx, chest, and abdomen. Vomiting occurs early and may be persistent. Agitation, confusion, headache, dizziness, lethargy, coma, and seizures may develop within a few hours after exposure. Cyanosis, flushed skin, and

diaphoresis have been reported. Pupils tend to be small but reactive. Opisthotonus, myoclonus, fasciculations, and muscle tenderness have been described. In severe cases, progressive tachycardia, hypotension, and hyperthermia may ensue. Early death may be from ventricular fibrillation. Eye, skin, and respiratory tract irritation may follow exposure by these routes.

Laboratory abnormalities include an increased anion-gap metabolic acidosis, hypoxia, hyperkalemia, hypocalcemia, leukocytosis, elevated creatine kinase, mildly elevated hepatic enzyme levels, and renal function disturbances. The ECG may show flat or inverted T waves. Although pulmonary edema and aspiration have been reported, the chest radiograph usually is normal. Nerve conduction and electromyographic studies may show evidence of peripheral neuropathy and myopathy.

In mild to moderate chlorophenoxy acid intoxication, recovery occurs within 2 to 3 days; in severe cases, it may take longer than 1 week. Coma and acidemia are poor prognostic signs. Neuritis and myopathy with limb pain, paresthesias, twitching, tenderness, and weakness may be delayed in onset and persist for several months.

Organic Phosphorus Compounds

Ingestion of concentrated solutions of organic phosphorus herbicides can cause acute GI and pulmonary injury, delayed CV toxicity, and secondary hepatic and renal dysfunction. Inhaled glyphosate can produce respiratory irritation. The respiratory irritation can cause a burning pain, rhinorrhea, upper airway edema, coughing, stridor, or laryngospasm; and the aspiration of ingested glyphosate can cause noncardiogenic pulmonary edema.

Glufosinate also causes neurologic toxicity, which can be delayed (4 to 36 hours after ingestion) in onset and progressive over 24 to 48 hours. Neurologic findings include ataxia, confusion, disconjugate gaze, nystagmus, tremors, central nervous system (CNS) depression ranging from drowsiness to coma with central hypoventilation and apnea, and seizures. Generalized seizures, invariably preceded by coma, are typically recurrent, and can last

for several days. Complications include hyperthermia, acidosis, and rhabdomyolysis.

Signs and symptoms of caustic injury to GI, pulmonary, CV, hepatic, and renal systems are similar to those described for bipyridyl and chlorophenoxy acid herbicides. Hypovolemic shock may result from GI fluid losses and sequestration. Cardiogenic shock can occur subsequently. Severe GI injury, respiratory failure, and cardiogenic shock are associated with a fatal outcome. Patients with coma or seizures can have prolonged amnesia, encephapathy, and myopathy with recovery taking weeks. Exposure to organophosphorus–surfactant herbicides that have been diluted for use may still cause eye, skin, and mucosal irritation, but systemic toxicity is unlikely.

DIFFERENTIAL DIAGNOSIS

The initial presentation may resemble that of other corrosive exposure. Caustic injury to mucosa and oropharyngeal membranes may be mistaken for diphtheria or ingestion of caustic agents. The rapid progression of multiorgan failure following serious paraquat ingestion may resemble sepsis, cardiogenic shock, or severe salicylate toxicity. Pulmonary fibrosis occurring may resemble silicosis, asbestosis, and sarcoidosis. The rapid progression of severe pulmonary fibrosis is highly characteristic of paraquat ingestion. Diquat is more likely to cause acute renal failure and paralytic ileus.

Acute corrosive exposures have been mistaken initially for HIV-related infections such as oral candidiasis and *Pneumocystis jiroveci* pneumonia (2).

Except with glufosinate, the CNS depression caused by herbicides is not associated with respiratory depression. Severe 2,4-D and glufosinate poisoning patients may present with coma, seizures, tachycardia, hypotension, fever, rhabdomyolysis, and metabolic acidosis. This presentation may be confused with septic shock, diabetic ketoacidosis, severe stimulant poisoning, and intoxications by methanol, ethylene glycol, and salicylates. Other uncouplers of oxidative phosphorylation, such as the dinitrocresol and

dinitrophenol herbicides and the pentachlorophenol fungicides, may produce similar presentations. Cresylic and phenolic herbicides may stain the skin yellow and cause dark-colored urine.

ED EVALUATION

The history should include the concentration, amount, and route of herbicide exposure. Determining whether the product was diluted prior to exposure and estimating the exposure time and dose are important prognosticators. Vital signs should include measurement of the oxygen saturation.

The physical examination should include inspection of exposed surfaces for evidence of corrosive injury. After irrigation, patients with eye exposures should have fluorescein and slit-lamp examinations. Patients with GI signs and symptoms should also have an ECG, chest radiograph, arterial blood gas analysis, pulmonary function tests, complete blood count, electrolytes, BUN, creatinine, glucose, amylase, liver function tests, cardiac enzymes, lactic acid, and urinalysis. Paraquat may cause hypokalemia, which indicates a poor prognosis. In a retrospective study, a lactate concentration above 4.4 mmol/L (40 mg/dL) in paraquat poisoning is associated with a fatal outcome (3). Chest radiograph may be normal initially but will become abnormal after time with paraquat ingestions. Toxicology screening tests are not helpful because herbicides are not detected by the methods used. The detection and quantitation of herbicides usually requires sending a blood specimen to a reference laboratory. Although results can confirm exposure, they will not be immediately available and, except for paraquat, they have no prognostic value and will not help with making treatment decisions.

Quantitative paraquat levels are predictive of prognosis. Plasma levels >2 mg/L at 4 hours and >0.1 mg/L at 24 hours usually indicate a fatal outcome (4). Arrangements for a quantitative paraquat level can be made by calling Zeneca Ag Products (24-hour emergency line 800-327-8633). A qualitative urine test detects paraquat concentrations >1 g/mL and confirms exposure but is not prognostic. It may be performed by adding 1 mL of a 1% solution of

sodium dithionite in 2 N sodium hydroxide to 10 mL of urine. A blue color indicates the presence of paraquat.

KEY TESTING

- Most patients will need electrolytes, myoglobin, blood gases, lactate, renal and liver function tests.
- Patients with paraquat exposures need pulse oximetry, and serial chest x-rays; paraquat levels can be sent out to assist in prognosis.

ED MANAGEMENT

Initial treatment for herbicide exposure should focus on decontamination and supportive care. There is no specific antidote for herbicide poisoning. Supportive care with appropriate airway management is vital. ED management of the patient with acute paraquat poisoning should avoid oxygen therapy unless there is confirmed hypoxia. Oxygen may exacerbate the oxygen-mediated cellular damage induced by the superoxide radical. The treatment of diquat poisoning is generally the same as that for paraquat poisoning.

Decontamination is paramount and healthcare workers need to protect themselves. Personnel involved in decontamination must wear appropriate personal protective equipment, including gloves, masks, gowns, and goggles, to protect their airways, skin, and eyes. All clothing is removed. Contaminated skin and eyes should be flushed with copious amounts of water for at least 15 minutes.

Gastric decontamination procedures have not been shown to alter poisoning morbidity or mortality.

Gastric lavage is not recommended routinely because of the possibility of increasing the risk of iatrogenic perforation in corrosive injuries.

Activated charcoal has been shown to be successful with some herbicide ingestions and can be useful if it can be given prior to the distribution of the majority of the herbicide. Activated charcoal can reduce the amount absorbed if given within 60 minutes, but there is

inadequate evidence to determine if it is effective later than this. The potential benefit of charcoal should be weighed against any risk for aspiration. The exception is in poisoning by paraquat, which is well adsorbed by activated charcoal, Fuller's earth, and food. Many experts recommend that because serious paraquat poisoning is catastrophic and irreversible, and has no effective antidote, all such patients be given 1 gm/kg of activated charcoal in water, even with late presentation. However, endoscopy will be difficult, and more likely to be indeterminate, after oral activated-charcoal administration.

In severe cases, endotracheal intubation may be required. The airway is at risk due to the corrosive action of concentrated glyphosate and paraquat solutions. When intubating patients with chlorophenoxy acid poisoning, a nondepolarizing neuromuscular blocker (e.g., rocuronium) may be preferable to succinylcholine because the neuromuscular effects of succinylcholine are similar to those caused by these herbicides.

Endoscopy is recommended for those with evidence of corrosive injury to the airway or upper GI tract. The presence of gastric or esophageal ulcers indicates a poor prognosis. Benzodiazepines, muscle relaxants, or therapeutic paralysis should be used for agitation, fasciculations, myoclonus, or muscle rigidity, particularly those with hyperthermia or rhabdomyolysis. Propofol, which has antioxidant activity, should be considered for intubated patients with paraquat poisoning. Active external cooling measures may be necessary with hyperthermia. Avoid the use of salicylates, which also cause uncoupling of oxidative phosphorylation.

Supportive care should include monitoring for and treatment of hepatic, renal, cardiac, and pulmonary dysfunction and fluid and electrolyte abnormalities. With the exception of paraquat poisoning, standard therapies are employed. Because oxygen increases the pulmonary toxicity of paraquat, concentrations $>21\%$ should be used only when the pO_2 falls below 50 mm Hg. Positive end-expiratory pressure may improve arterial oxygenation.

Urinary alkalinization may be helpful, but evidence to support this practice is limited (5). Sodium bicarbonate can be used to correct acidemia and enhance herbicide elimination in patients with chlorophenoxy acid poisoning (6). Chlorophenoxy acids have pK_a values between 1.9 and 4.8, and increasing the pH increases the ionized fraction and traps these compounds in the blood and urine, thereby preventing their tissue distribution and enhancing their renal excretion. Sodium bicarbonate should be given as a bolus to correct acidemia and as a constant infusion to alkalinize the urine. Alkaline diuresis decreases the half-life of 2,4-D by about 50%. Urine pH must be increased to 8.0 to enhance excretion significantly.

Extracorporeal elimination therapies are indicated for patients with severe paraquat, diquat, and chlorophenoxy acid poisoning or potentially lethal ingestions and progressive clinical toxicity. Charcoal or resin hemoperfusion are the procedure of choice for bipyridyls, although hemodialysis is preferred for chlorophenoxy acids. Early, prolonged hemoperfusion appears to be useful in removing paraquat and limiting systemic toxicity when started within 10 hours of ingestion (15 to 20 hours in the presence of renal failure) and performed 8 hours daily or continuously for 2 to 3 weeks. Hemodialysis and continuous arteriovenous hemofiltration also enhance the elimination of paraquat and may be useful if hemoperfusion is unavailable. Data are limited regarding the use of hemoperfusion in diquat poisoning.

Free radical scavengers and antioxidants have been used in an attempt to prevent pulmonary fibrosis paraquat poisoning, but their efficacy remains unproven (7). Given the lethality of this condition, however, the following treatments should be considered: corticosteroids, cyclophosphamide N-acetylcysteine, and vitamin E. S-carboxymethylcysteine (Loviscol) has been used when N-acetylcysteine is unavailable. Lung transplantation may be considered. Nitric oxide inhalation and extracorporeal membrane oxygenation might be useful as interim measures. The National Pesticide Telecommunications Network provides a 24-hour-a-day

consultation services (800-858-7378) and the regional poison center (1-800-222-1222) may provide additional guidance.

CRITICAL INTERVENTIONS

- Identify the herbicide and estimate the dose and concentration.
- Perform aggressive decontamination with activated charcoal for paraquat.
- Correct acidosis.
- Consider hemodialysis for renal insufficiency.

DISPOSITION

Inpatient management is warranted for all patients after herbicide ingestion. Dermal burns from paraquat should be admitted. Unless the exposure is minor and the severity of poisoning is mild, transfer to a tertiary care center and admission to an intensive care unit are advised.

Discharge from the hospital should occur in asymptomatic patients if toxic effects do not develop within a few days of exposure.

Common Pitfalls

- Underestimation of the potential toxicity of herbicides, particularly with intentional ingestions of concentrated solutions.
- Failure to appreciate that although concentrated herbicide formulations are highly toxic, the likelihood of serious toxicity is greatly diminished once they have been diluted for use.
- Failure to appreciate that prolonged observation is necessary to rule out toxicity in patients with ingestions of dilute herbicide and with significant skin exposures to paraquat.
- Failure to evaluate symptomatic patients for multisystem organ dysfunction, including metabolic disturbances and rhabdomyolysis.
- Failure to appreciate that the pulmonary toxicity of paraquat is potentiated by oxygen and that if supplemental oxygen is

needed, the lowest possible concentration should be administered.
- Failure to appreciate that extracorporeal removal can enhance the elimination of paraquat, diquat, and chlorophenoxy acid herbicides.

ACKNOWLEDGMENTS

The author acknowledges Dr. Christopher H. Linden and Dr. William J. Lewander, who contributed to earlier versions of this topic review.

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CHAPTER 317 Isoniazid

Alan D. Woolf

Isoniazid (isonicotinic acid hydrazide, INH), a derivative of vitamin B_3 (nicotinamide), has been used for the prophylaxis and treatment of tuberculosis (TB) since 1952. INH is a prodrug that becomes bactericidal when complexed with NADH intracellularly and activated into reactive species by catalase-peroxidase (KatG). The complex interferes with the synthesis of mycolic acid, a necessary cell wall constituent in *Mycobacterium tuberculosis*. Generation of nitric oxide may also contribute to isoniazid's antimycobactericidal activity (1).

With the resurgence of TB has come an increasing incidence in INH poisoning. There were 249 INH poisonings reported to US poison control centers in 2011, with more than 45% severe enough to require treatment in a health care facility (2). The incidence of self-poisoning is greatest among those adult populations with a high prevalence of both tuberculosis and depression (e.g., Native Americans, immigrant populations). INH is rapidly absorbed from the small intestine, within 30 to 60 minutes after ingestion. Recommended therapeutic doses in children are 8 to 12 mg/kg (maximum, 300 mg) daily, given orally or by intramuscular (IM) injection (3). Peak INH serum levels (therapeutic range, 5 to 8 μg/mL) are reached within 1 to 2 hours. The drug is minimally bound to plasma proteins and has a small apparent volume of distribution (0.6 L/kg). INH can be detected in such diverse bodily fluids as saliva, cerebrospinal fluid (CSF), and breast milk. Up to 36% of the drug may be excreted unchanged in urine (4).

Metabolism by acetylation in the liver yields inactive metabolites that are predominantly excreted in the urine. People with normal renal function excrete 50% to 80% of a therapeutic dose of INH within 24 hours.

There is great genetic variability in the metabolism of INH. Between 45% and 75% of Caucasians are “slow acetylators” and have a mean serum INH half-life of about 5 hours. By contrast, 95% of Inuits are “fast acetylators” and have an average serum half-life of 80 minutes. These differences are therapeutically important: slow acetylators can achieve sustained bactericidal drug levels on every-other-day dosage regimens, whereas fast acetylators have inadequate levels unless they receive the drug daily (4). INH can increase the clinical effects of warfarin, carbamazepine, phenytoin, cyclosporine, and theophylline by interfering with their metabolism. It may decrease the antifungal actions of ketoconazole and itraconazole.

Several mechanisms are responsible for the toxic effects of INH. With both acute poisoning and chronic therapy, INH hydrazone analogs arise spontaneously (especially in slow acetylators) and form rapidly excreted complexes with pyridoxine, leading to a pyridoxine deficiency. INH hydrazones also inhibit pyridoxine kinase, thereby decreasing the conversion of pyridoxine to its active cofactor form, pyridoxal phosphate. In acute overdoses, INH inhibits the pyridoxal 5-phosphate–dependent enzyme, glutamic acid decarboxylase (GAD), which decreases the conversion of glutamic acid to γ-aminobutyric acid (GABA). The decrease in GABA, an inhibitory neurotransmitter, causes seizures. Pyridoxine deficiency itself causes brain excitability and seizures.

INH is structurally similar to nicotinic acid, substituting for it in the synthesis of nicotinamide adenine dinucleotide (NAD), to produce an inactive coenzyme. Inhibition of NAD-dependent Krebs cycle enzymes may result in hyperglycemia, and inhibition of NAD-mediated conversion of lactate to pyruvate worsens the profound lactic acidosis that typically accompanies seizures.

During chronic INH therapy, patients who are malnourished, pregnant, alcoholic, elderly, diabetic, or uremic may be at

particularly high risk for pyridoxine deficiency (5), which can lead to peripheral neuropathies, anemia, and a lowered seizure threshold. Pyridoxine depletion can also inhibit the activity of pyridoxine-dependent decarboxylases and transaminases (leading to decreased catecholamine synthesis), cytochrome P450 enzymes (leading to decreased drug metabolism), histaminase, and monoamine oxidase (MAO). Pyridoxine given as a supplement at 10 mg/d can avoid this deficiency.

CLINICAL PRESENTATION

Seizures may be seen after acute overdoses of INH as low as 35 mg/kg in adults. Severe toxicity occurs with ingestions of 5 to 7 g (80 to 150 mg/kg); but death has occurred after the ingestion of as little as 3 g. Although ingestions of >12 g in an adult have a high fatality rate, survival has been reported after the ingestion of as much as 25 g. Poisoning is associated with an INH serum concentration >30 μg/mL, although such laboratory assays for INH are not routinely available.

The initial symptoms of acute poisoning may occur as soon as 30 to 120 minutes after ingestion, and include nausea, vomiting, slurred speech, blurred vision, and disorientation. Anticholinergic signs (e.g., mydriasis, tachycardia, and urinary retention) and hyperreflexia or areflexia may also be prominent. In severe poisonings, seizures appear abruptly and precede the development of a profound metabolic acidosis and coma, the triad that forms the classic clinical picture. Patients with INH-induced seizures and severe acidosis can have full recovery after receiving pyridoxine. A 2-year-old girl who ingested 2 g of INH suffered status epilepticus and an arterial pH of 6.86, but survived without sequelae (6).

Multiple seizures over a short time are the hallmark of INH poisoning. Other symptoms and signs include confusion or irritability, hallucinations, stupor, ataxia, garbled speech, hyperpyrexia, nausea and vomiting, and respiratory depression. Laboratory findings include lactic acidosis, ketosis, hyperglycemia, an increased anion gap, hyper- or hypokalemia, peripheral blood

leukocytosis, CSF pleocytosis, and renal defects (e.g., glycosuria, keotnuria, albuminuria, and oliguria). An elevated creatine phosphokinase (CPK-MM fraction) level as a result of rhabdomyolysis may precede myoglobinuria and renal failure. In one series of INH poisoning, 60% had an elevated CPK-MM level, which correlates both with the dose of INH ingested and the frequency of seizures (7). An electroencephalogram (EEG) often demonstrates diffuse slowing or paroxysmal electrical activity compatible with subclinical seizures. The clinical course of the untreated patient with a massive INH overdose is often unremitting seizures, resulting in death from acidosis and cardiovascular and respiratory collapse. Survivors may suffer from persistent neuropsychological sequelae, including personality changes, poor memory, learning problems, and/or motor skills deficits (8).

Hepatotoxicity, with elevated liver enzyme levels, is relatively common among patients taking INH chronically. Such hepatotoxicity appears transient in most cases, even with continued use of the drug. Patients rarely develop acute liver necrosis, liver failure, and death. One study found 0.5% of patients treated with INH for 12 months were hospitalized for a hepatic event and estimated a rate of 0.1 cases of severe hepatitis per 100 person-years of INH use, with an increased risk among patients older than 65 years (9). Concomitant use of rifampin and INH in TB prophylaxis may increase the risk of an adverse hepatic event. A meta-analysis of 38 studies found that drug-metabolizing enzyme polymorphisms, including slow N-acetyl-transferase (NAT2), glutathione S-transferase (GSTM1), and CYP 2E*1 A, increased the risk of susceptibility to liver injury (10).

Toxic effects of chronic INH use also include euphoria, tinnitus, ataxia, impaired memory, encephalopathy, and optic neuritis. Progressive lethargy, garbled speech, confusion, and coma were described in a man who mistakenly took 1,200 mg of INH daily for 6 weeks (5).

Allergic manifestations, such as rashes, eosinophilia, vasculitis, arthralgias, and a positive antinuclear antibody test, have also been described. By inhibiting P450 series cytochromes, INH can interfere

with drug clearance and increase the toxicity of other drugs such as phenytoin, carbamazepine, theophylline, and warfarin. INH action as a weak monoamine oxidase inhibitor (MAOI) may result in symptoms (e.g., headache, flushing, nausea, vomiting, palpitations) in patients consuming foods containing tyramine or histamine (see Chapter 342). Hematologic abnormalities such as neutropenia, thrombocytopenia, sideroblastic anemia, pure red cell aplasia, and autoimmune hemolytic anemia have also been described in association with exposure to INH.

Patients with underlying hepatic disease or impaired renal function do not metabolize INH well, have a prolonged serum half-life, and are at greater risk for toxicity. Those with a preexisting seizure disorder are at higher risk for neurotoxic effects.

DIFFERENTIAL DIAGNOSIS

INH overdose should be strongly considered in the patient who presents with (1) seizures refractory to conventional anticonvulsants, and (2) a high anion-gap metabolic acidosis, especially in the context of depression, suicidal ideation, TB, and with access to INH. A diagnostic clue to INH poisoning is the prompt termination of seizure activity after the administration of IV pyridoxine.

Agents that can cause a clinical picture similar to that of INH overdose include salicylates, cyanide, carbon monoxide, other hydrazines (e.g., monomethylhydrazine-containing mushrooms), anticholinergics, and sympathomimetics. Other pharmacologic causes of status epilepticus include baclofen, carbamazepine, dimenhydrinate, and theophylline. Neurotoxins such as pesticides, camphor, lead, mercury, narcotics, strychnine, and tricyclic antidepressants should also be considered. Other medical conditions, such as bacterial meningitis with sepsis, diabetic ketoacidosis, uremia, other metabolic disorders, meningoencephalitis, and head trauma, should also be included in the differential of patients presenting with seizures, coma, and acidosis.

ED EVALUATION

The time, dose, and intent of ingestion; the time of onset, nature, and severity of symptoms; prehospital care; and medical and psychiatric history should be noted. The physical examination should focus on vital signs and neurologic status, including assessment for hyperreflexia, focal neurologic deficits, abnormal thought processes, and central nervous system (CNS) depression. Laboratory evaluation should include serum electrolytes, rapid bedside glucose, blood urea nitrogen, creatinine, and arterial pH, and blood gases. In severe or chronic cases, creatine kinase and liver function tests should be obtained. A chest radiograph can detect aspiration, and an electroencephalogram (EEG) may be helpful in patients with persistent coma.

KEY TESTING

- Arterial blood gases and lactic acid to detect metabolic acidosis with seizure
- Bedside blood glucose for coma or seizures
- Myoglobin and renal function tests for suspected rhabdomyolysis
- Complete blood count and electrolytes for general supportive care
- Liver function tests for suspected hepatitis in chronic users
- Head CT or MRI if other etiologies for seizures and coma are suspected

ED MANAGEMENT

Advanced life-support measures should be instituted as necessary. Pyridoxine (vitamin B_6) is the specific antidote for seizures. It should be given in gram-for-gram equivalency to the estimated total amount of INH ingested. If the total ingested dose of INH is unknown, 5 g of pyridoxine hydrochloride (IV injection solution available at a concentration of 100 mg/mL) can be given empirically by slow intravenous push (maximum 0.5 g/min), and repeated in 20 minutes if there is no clinical response. Typically, the seizures abate and the patient's level of consciousness slowly

improves. Diazepam (5 to 10 mg IV, preferably in a second IV site) may be used as an adjunct to control seizures and additional pyridoxine is sometimes necessary for the resolution of INH-induced coma.

The use of adequate doses of diazepam and pyridoxine has essentially eliminated the need for other treatment of INH overdose. Multiple large doses of pyridoxine should be avoided because chronic pyridoxine overdosing can cause a peripheral sensory neuropathy. Some commercially prepared IV pyridoxine may contain two different preservatives: chlorobutanol, which may cause mild sedation in high doses, and parabens, which has been implicated in hypersensitivity reactions.

Although severe metabolic acidosis should be treated with IV sodium bicarbonate, large doses are usually unnecessary, because the acidosis is mostly due to seizures and resolves shortly after seizures have been controlled. Diuresis is not of benefit. After stabilization, activated charcoal should be given in early-presenting, acute-overdose patients to prevent further absorption of INH or other co-ingestants.

CRITICAL INTERVENTIONS

- Administer IV pyridoxine hydrochloride (gram for gram of INH ingested), along with benzodiazepines, for INH-induced seizures
- Follow blood gas values and administer IV sodium bicarbonate to patients with severe acidemia, especially those with persistent seizures

DISPOSITION

Asymptomatic or mildly symptomatic patients can be observed in the emergency department for 6 hours before discharge, with suicidal evaluation as needed.

Moderately or severely symptomatic patients should be admitted to an intensive care unit. Patients with refractory seizures, severe respiratory depression, or renal failure should be transferred to a

hospital with intensive care capabilities if they are not locally available.

Common Pitfalls

- Failure to consider INH poisoning in patients with seizures refractory to conventional anticonvulsants and a high anion-gap metabolic acidosis.
- Failure to appreciate that asymptomatic patients may rapidly deteriorate.
- Failure to give pyridoxine early after a known overdose.
- Administration of excessive doses of sodium bicarbonate for the treatment of metabolic acidosis, which spontaneously resolves when convulsions cease.

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CHAPTER 318 Organophosphate and Carbamate Insecticides

Christopher P. Holstege

Organophosphates (OPs) and carbamates are acetylcholinesterase (AChE) inhibitors which are generally encountered in emergency medicine following (1) pesticide poisoning and when (2) considered as a possible chemical weapon of mass casualties (see Chapter 350). World health statistics estimate that over 3 million serious pesticide poisonings occur worldwide, and such poisonings are the leading cause of suicide fatalities in the world (1). Thousands of patients exposed to OP- or carbamate-containing pesticides were reported to American poison centers in 2011 (2). Although exposures to these pesticides may be less common in urban regions, all emergency physicians must be familiar with treatment regimens because AChE inhibitors are also used as pharmaceuticals (e.g., topical malathion for the treatment of head lice; echothiophate, a long-acting topical miotic used to treat glaucoma; pyridostigmine and neostigmine, used for myasthenia gravis; and rivastigmine, galantamine, and donepezil for treatment of Alzheimer disease) and as chemical warfare agents (e.g., nerve agents soman, sarin, tabun, and VX).

Acetylcholine is a neurotransmitter found throughout the nervous system, including the central nervous system, the sympathetic and parasympathetic autonomic ganglia, the postganglionic parasympathetic nervous system, and at the skeletal muscle motor end plate (Fig. 318.1). Acetylcholine binds to and activates muscarinic and nicotinic receptors. Activating muscarinic receptors stimulates or inhibits cellular function at visceral smooth muscle,

cardiac muscle, and secretory glands. Nicotinic receptors are located at postsynaptic membranes in autonomic ganglia and at skeletal muscle motor end plates. The enzyme AChE regulates acetylcholine's activity within the synaptic cleft. As acetylcholine binds to AChE active site, the enzyme rapidly hydrolyzes acetylcholine to choline and acetic acid. These hydrolyzed products rapidly dissociate from AChE so that the enzyme is free to metabolize another molecule. OPs and carbamates inhibit AChE by binding at the enzyme's active site, the inhibited enzyme is unable to inactivate acetylcholine. As a result, excessive acetylcholine stimulation occurs. Carbamates form an unstable complex which spontaneously hydrolyzes within 24 to 48 hours, regenerating AChE and limiting the duration of toxicity. OPs differ from carbamates in that OPs undergo a second step: a portion of the bound OP is then cleaved producing a stable, covalent bond between the OP and AChE. This process is called *aging*. The time it takes for aging to occur depends upon the OP. AChE reactivaters, such as pralidoxime chloride, can remove the OP before aging occurs, and can restore enzyme function. However, once this aged covalent bond forms, AChE cannot be reactivated and activity is not restored until new enzyme is synthesized.

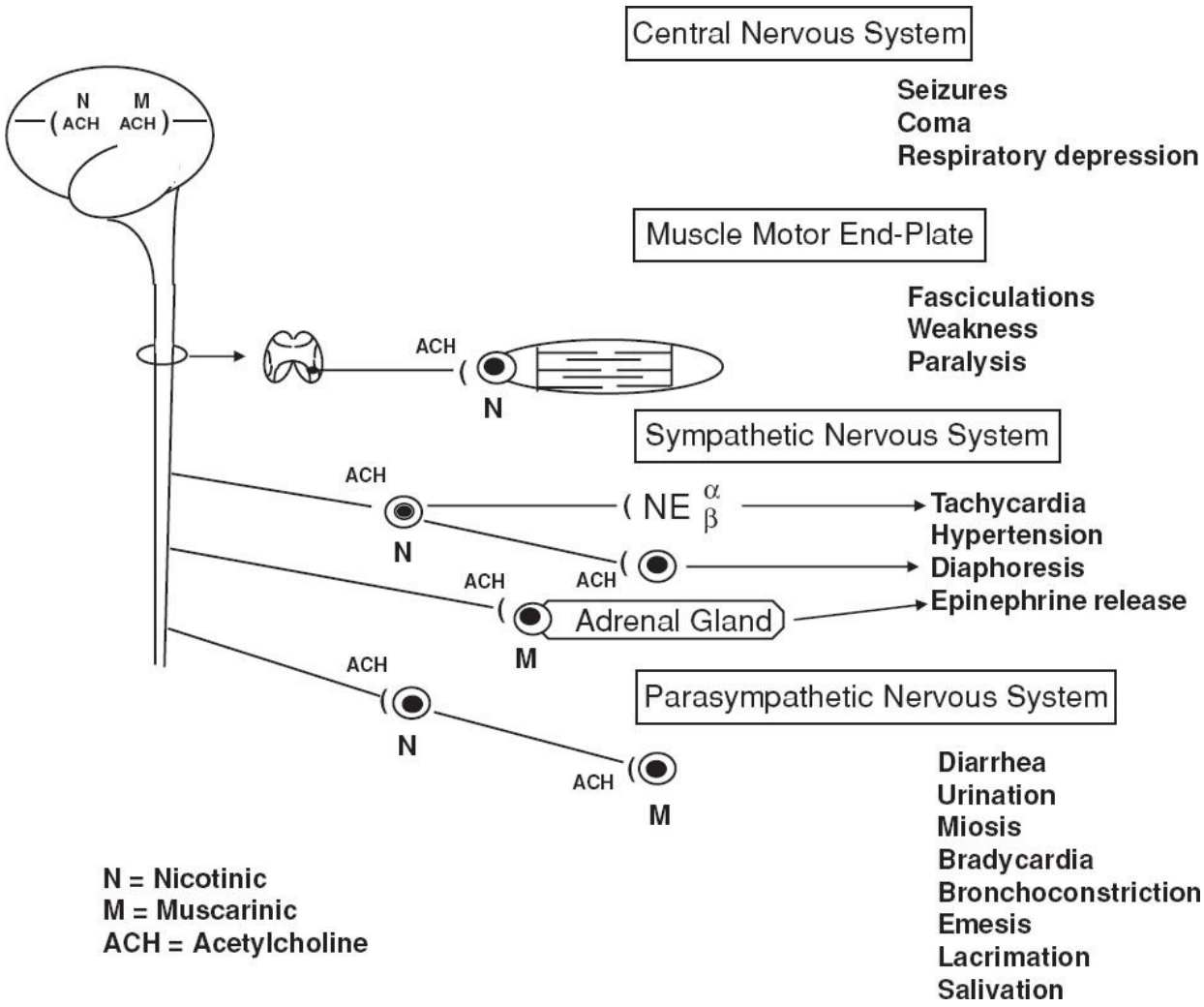

FIGURE 318.1 Clinical effects seen in organophosphate and carbamate poisoning caused by access of acetylcholine (Ach) in the central, autonomic, and peripheral nervous systems. M, muscarinic; N, nicotinic; NE, norepinephrine.

CLINICAL PRESENTATION

Acute Toxicity

The onset, severity, and clinical effects of OP and carbamate poisoning vary widely (Table 318.1) (3). Human exposures may occur inadvertently via inhalation or skin contact during pesticide application or via intentional ingestion. The type of agent, the dose, and the route of exposure are factors in determining the clinical effects. Depending on these variables, the progression of the signs

and symptoms can range from a gradual intoxication to cardiopulmonary collapse, seizures, and death within minutes.

TABLE 318.1
Signs and Symptoms of Acute Organophosphate and Carbamate Poisoning

Muscarinic Manifestations
Ophthalmic
Conjunctival injection, lacrimation, miosis, blurred vision, diminished visual acuity, ocular pain
Respiratory
Rhinorrhea, stridor, wheezing, cough, excessive sputum, chest tightness, dyspnea, apnea
Cardiovascular
Bradydysrhythmias, hypotension
Dermal
Flushing, diaphoresis, cyanosis
Gastrointestinal
Nausea, vomiting, salivation, diarrhea, abdominal cramping, tenesmus, fecal incontinence
Genitourinary
Frequency, urgency, incontinence
Nicotinic Manifestations
Cardiovascular
Tachydysrhythmias, hypertension
Striated Muscle
Fasciculations, twitching, cramping, weakness, paralysis
Central Nervous System Manifestations
Anxiety, restlessness, depression, confusion, ataxia, tremors, convulsions, coma, areflexia

Respiratory

The respiratory system effects of these agents tend to be dramatic and are often the major factor leading to the death of the victim. The development of respiratory failure is typically a triad of increased airway resistance, neuromuscular failure, and depression of the central respiratory centers. Weakness of the muscles of the tongue and pharynx can lead to upper airway obstruction. Laryngeal muscle

paralysis may occur resulting in vocal cord dysfunction and subsequent stridor. OP and carbamate can result in profuse watery nasal discharge, nasal hyperemia, and marked salivation. The lower respiratory tract may develop bronchorrhea and bronchoconstriction resulting in a prolonged expiratory phase, cough, and wheezing. As systemic absorption occurs, respiratory muscle weakness ensues and secretions cannot be cleared. Induced central respiratory center failure may contribute to the demise of the patient if intubation and ventilation is not initiated.

Central Nervous System

Cholinergic receptors are found throughout the central nervous system. Because of the widespread presence of these receptors, these agents can produce a large variation in neurological signs and symptoms. Headache, vertigo, paresthesias, anxiety, insomnia, depression, excessive dreaming, and emotional liability have all been reported following exposure. Centrally mediated respiratory failure can occur resulting in apnea. OP and carbamate are associated with seizure initiation, status epilepticus, seizure-related brain damage (SRBD), and subsequent death. Based on current evidence, the pathophysiologic progression of AChE inhibitor–induced seizures can be divided into three phases: (1) an early cholinergic phase that lasts from the time of exposure to approximately 5 minutes after seizure onset; (2) a transitional phase of progressively mixed cholinergic/noncholinergic modulation that begins more than 5 minutes after seizure onset and lasts until approximately 40 minutes; and finally (3) a predominantly noncholinergic phase beginning in approximately 40 minutes. These three phases are due to the cholinergic-induced seizure activity itself recruiting other excitatory neurotransmitter system (i.e., NMDA) that can eventually maintain the seizures independent of the initial cholinergic drive. The activation of NMDA ionic channels may lead to massive calcium fluxes into the postsynaptic cells resulting in cell degeneration and contributing to the profound SRBD.

Cardiovascular

The cardiovascular effects from OP and carbamate poisoning are variable and caused by either direct cholinergic effects at the heart or nicotinic effects at the autonomic ganglia. In addition, tachycardia and ventricular dysrhythmias are seen secondary to the hypoxia from respiratory failure. Cardiotoxicity resulting from AChE inhibitors has been divided into three phases. Initially, a period of intense sympathetic activity results in sinus tachydysrhythmias with or without hypertension. Patients may subsequently develop bradydysrhythmias, prolongation of the PR interval, atrioventricular blocks, and hypotension as parasympathetic tone predominates. The third phase occurs with QT prolongation and possible progression to polymorphous ventricular tachycardia (torsades de pointes). These phases can occur at any time in the poisoned victim and do not necessarily follow a specific progression.

Musculoskeletal

Somatic muscular activity is initiated at nicotinic receptors at motor end plates. With early or minimal exposure to these agents, symptoms may be vague and consist of muscular weakness and difficulty with ambulation. With increasing exposure, these agents resemble succinylcholine causing muscular fasciculations and subsequent paralysis. This is especially problematic as this paralysis may mask seizure activity.

Eye

These agents may rapidly penetrate the conjunctiva and stimulate muscarinic receptors resulting in lacrimation and miosis. Miosis can develop immediately after vapor exposure or after direct ocular contact with liquid. Following dermal absorption, miosis can be absent or delayed after other systemic signs and symptoms.

Dermal

The dermal sweat glands are innervated by sympathetic muscarinic receptors. When these receptors are stimulated, profuse sweating occurs.

Gastrointestinal and Genitourinary

Muscarinic receptor stimulation results in profuse watery salivation, nausea, vomiting, abdominal cramps, tenesmus, uncontrolled defecation, and involuntary urination.

Intermediate Syndrome

Intermediate syndrome was first described in 1987 and refers to the delayed development of muscle weakness without fasciculations or cholinergic features that occurs in OP-poisoned patients 24 to 96 hours after the acute poisoning. Patients who develop intermediate syndrome initially present with the classic cholinergic signs and symptoms of OP poisoning and have improvement following atropine and pralidoxime therapy. Relapse beginning approximately 48 hours later results in muscle weakness, cranial nerve palsies, and areflexia (4). The patient's mentation is not affected. These patients may progress to respiratory distress and paralysis lasting up to 2 weeks. Atropine and pralidoxime therapy are ineffective. The treatment of this syndrome is primarily supportive with intubation and ventilation as needed.

Delayed Peripheral Neuropathy

OP-induced delayed neuropathy (OPIDN) is associated with patients who developed significant OP toxicity and may occur 1 to 3 weeks following the initial poisoning (5). Typically, the patient will initially complain of weakness of the lower extremities, progressing to the upper extremities, ataxia, and potentially paralysis. Mild cases may recover over the ensuing months, whereas more severe cases will have persistent symptoms. OPIDN is partially caused by OP binding to neuropathy target esterase (NTE), an axonal membrane-bound target enzyme. Treatment of OPIDN is supportive and recovery may be incomplete.

Chronic Toxicity

Farmworkers who apply OPs and carbamate pesticides are at risk for ongoing low-level poisoning. These patients may present with no acute history of exposure and more subtle signs and symptoms. Symptoms may include blurred vision from miosis, and weakness as

well as the nausea, vomiting diarrhea, diaphoresis seen with acute exposure but in a more subdued or chronic course.

DIFFERENTIAL DIAGNOSIS

Similar cholinergic manifestations can be seen in patients poisoned with direct-acting cholinergic agonists such as bethanechol. Opioid and clonidine poisoning should be considered in patients who present with altered mental status and bradycardia, without other obvious signs of cholinergic toxicity. Lethargy and prominent sialorrhea or salivation may occur with certain antipsychotic agents, such as clozapine. Patients with nicotine poisoning as a result of ingestion of tobacco products or harvesting wet tobacco may have similar findings, including vomiting, diarrhea, fasciculations, weakness, altered mental status, and autonomic instability.

ED EVALUATION

The history should document the amount, time, and route of exposure and the identity of the agent involved if known. A regional poison center can assist in product identification and characterization of anticipated toxicity. Continuous cardiac monitoring and pulse oximetry are crucial because of potential tachy- and bradydysrhythmias, QT prolongation, torsade de pointes, and respiratory failure due to secretions and paralysis. The physical examination should focus on the vital signs and assessment of cardiopulmonary and neuromuscular function, especially motor strength and respiratory effort. Cholinergic signs, particularly respiratory tract secretions, should be noted. Blood gas analysis and forced vital capacity (FVC) will help quantify respiratory dysfunction. An ECG, chest radiograph, and routine blood workup, including complete blood count (CBC), electrolytes, blood urea nitrogen, creatinine, glucose, creatine phosphokinase, amylase, and liver function tests, should be obtained on symptomatic patients.

The diagnosis may be confirmed by documenting decreased plasma or red blood cell (RBC) cholinesterase activity. RBC cholinesterase activity is more specific, but plasma (pseudo) cholinesterase activity tests are less expensive and more widely

available. Although results are usually unavailable in a clinically relevant time frame, they can be helpful in cases in which the diagnosis is uncertain and in the evaluation of workers who apply pesticides with occupational exposures. Specimens should be obtained prior to the administration of pralidoxime, because this antidote can increase measured enzyme activity. Interpretation of results may be difficult as a result of the variability in baseline values, which are subject to a variety of factors.

KEY TESTING

- Pulse oximetry, FVC, blood gas, and chest radiograph to assess respiratory function
- ECG, CBC, serum electrolytes, renal and liver function should be obtained on symptomatic patients
- Plasma and RBC cholinesterase to confirm diagnosis in chronic exposure and to document the extent of poisoning

ED MANAGEMENT

The skin plays a protective role against the invasion of most chemicals. However, many of these agents rapidly penetrate this barrier. Patient decontamination is a fundamental aspect of the management to both terminate toxin exposure and prevent secondary contamination of staff. Decontamination begins with clothing removal and copious water irrigation. Staff should be protected with appropriate gowns, gloves, and masks (see Chapter 350).

Lifesaving treatment of severe poisoning should initially focus on a patent airway, adequate ventilation, and aggressive atropine administration. Early endotracheal intubation is crucial in the critically ill patient. If rapid sequence intubation is performed, succinylcholine should be avoided because it is metabolized by AChE and subsequent neuromuscular blockade would be prolonged (6). A nondepolarizing alternative such as rocuronium would be preferred. Initial attempts at ventilation may be difficult due to induced bronchoconstriction. Copious secretions in the upper and lower

airways must be suctioned. Intravenous access should be obtained immediately. Aggressive atropine use will improve ventilation by drying secretions and decreasing airways resistance. Because of a demonstrated dissociation between motor convulsant activity, or lack thereof, and EEG activity, continuous EEG monitoring should be performed.

Atropine is the initial drug of choice in the symptomatic victim (7). Atropine acts as a muscarinic receptor antagonist and blocks neuroeffector sites on smooth muscle, cardiac muscle, secretory gland cells, peripheral ganglia, and in the central nervous system. Atropine is therefore useful in alleviating bronchoconstriction and bronchorrhea, relieving tenesmus, abdominal cramps, nausea and vomiting, resolving bradydysrhythmias, and halting seizure activity. If IV access is not available, atropine can also be given by the intramuscular, or endotracheal, route. The dose varies with the type of exposure. For the mildly and moderately symptomatic patient, 2.0 mg for adults and 0.02 mg/kg for children (minimum of 0.1 mg) is administered every 5 minutes. In the severely poisoned patient, dosage will need to be given more rapidly and increased to very large amounts up to 40 mg or more in 24 hours. Tachycardia is an effect of poisoning and is not a contraindication to atropine administration. Drying of the respiratory secretions and resolution of bronchoconstriction are the therapeutic end points used to determine the appropriate dose of atropine. If bag-assisted ventilation is difficult or secretions continue, then the atropine dose must be increased. Atropine has no effect on the nicotinic receptors, autonomic ganglia, and the neuromuscular junction. Therefore, muscle weakness, fasciculations, tremors, and paralysis are not an indication for further atropine dosing. It does have a partial effect on the central nervous system and is helpful in resolving seizures. Miosis is a poor clinical sign to follow for guiding repeat doses of atropine. If the resolution of miosis is used as the end point of atropine dosing, an anticholinergic syndrome can develop.

Pralidoxime chloride (2-PAMCL, Protopam Chloride) reactivates AChE by removing the OP from the AChE leaving the regenerated enzyme able to once again metabolize acetylcholine. This

reactivation is clinically most apparent at the skeletal neuromuscular junctions, which is not improved with atropine with less activity at muscarinic sites. Pralidoxime must therefore be administered concurrently with adequate atropine doses. If pralidoxime is delayed, the process of aging will permanently bond the OP to the AChE active site and prevent pralidoxime from regenerating the AChE active site; therefore, the earlier the administration of pralidoxime, the greater the clinical effect. The recommended dose of pralidoxime is 1.0 g for adults or 15 to 25 mg/kg for children by intravenous route. Slow administration over 15 to 30 minutes can minimize side effects, which include hypertension, headache, blurred vision, epigastric discomfort, nausea, and vomiting. In order to achieve a steady state blood level of pralidoxime following loading, it has been recently recommended that a continuous IV infusion is safe and effective (8). Because carbamate poisoning does not induce aging and resolves spontaneously much quicker than OP poisoning, the use of pralidoxime for carbamates remains controversial. Pralidoxime use is probably not harmful for these patients and should be used if there is any doubt as to the pesticide involved.

OP and carbamate poisoning is associated with seizure initiation, status epilepticus, SRBD, and subsequent death. Effective and rapid management of seizures is critical. All centrally acting anticholinergic agents (i.e., atropine and scopolamine) can block onset or terminate seizures if given before or within 5 minutes of seizure onset, but are ineffective alone if treatment is delayed more than 40 minutes after seizure onset. Benzodiazepines (i.e., diazepam, midazolam, lorazepam) are effective in treating OP and carbamate agent–induced seizures. The combination of a benzodiazepine and an anticholinergic agent should be used to terminate seizures (9).

CRITICAL INTERVENTIONS

- Monitor oxygen saturation and evaluate airway patency.
- Monitor the cardiac rhythm and obtain an ECG.
- Administer atropine to patients with increased secretions and bronchospasm.

- Quickly work to stop associated seizures by giving atropine and benzodiazepines.
- Administer pralidoxime early to patients following symptomatic OP or unknown poisoning.

DISPOSITION

Patients with an unintentional exposure who remain asymptomatic after at least 6 hours of observation may be discharged to home with a family member. Those requiring treatment with atropine or pralidoxime and those with evolving toxicity should be admitted to an intensive care unit (ICU) for close observation and monitoring. Prophylactic intubation prior to initiating transport may be advisable in patients with borderline respiratory status.

Common Pitfalls

- Failure to decontaminate the skin of patients with dermal exposures.
- Failure to take appropriate precautions to prevent secondary exposure to healthcare workers.
- Failure to give atropine to patients with tachycardia who have excessive respiratory tract secretions or bronchospasm.
- Failure to appreciate that atropine should be titrated to drying of secretions rather than to heart rate or pupil size in doses that may exceed standard ACLS recommendations.
- Failure to treat symptomatic OP poisoned patients with pralidoxime to prevent "aging."
- Failure to appreciate that highly fat-soluble OPs may cause delayed, prolonged, or recurrent toxicity.

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CHAPTER 319

Nicotine, Neonicotinioids, Pyrethrins, and Organochlorine Pesticides

William K. Chiang and Richard Y. Wang

Nicotine, the primary alkaloid of tobacco, is a naturally occurring pesticide obtained from *Nicotiana tabacum, N. rustica,* and other plants. It is also used in gum, nasal inhalers, and transdermal patches to aid in the cessation of smoking. Nicotine binds to nicotinic cholinergic (acetylcholine) receptors in the sympathetic and parasympathetic ganglion cells, neuromuscular junction, adrenal medulla, and the central nervous system (CNS). An initial transitory stimulation of nicotinic receptors is followed by a more persistent depression and paralysis as a result of desensitization (1). Clinical symptoms may reflect receptor stimulation, depression, or both.

Absorption occurs through intact skin, the gastrointestinal tract, and the respiratory tree. Nicotine has a pK_a of 8.5 and is not well absorbed in the acid milieu of the stomach but alkalinization markedly increases absorption. The volume of distribution is approximately 1 L/kg. Protein binding is 20%. Once absorbed, 80% to 90% of the chemical is detoxified into cotinine by the liver, and 20% is excreted unchanged by the kidneys. The elimination half-life is 0.8 hours in smokers and 1.3 hours in nonsmokers. Elimination is complete in about 16 hours.

Tobacco leaves contain 1% to 6% nicotine; a cigarette contains 15 to 20 mg of nicotine, with one-fourth remaining in the butt; snuff contains 4.6 to 15 mg of nicotine per gram of moist material; chewing tobacco contains 2.5 mg of nicotine per gram of dry material; a cigar contains 15 to 20 mg of nicotine. Nicotine gum contains 2 mg of nicotine buffered to a pH of 8.5 to enhance absorption. Transdermal nicotine patches release 7 to 21 mg of nicotine per day. However, the total nicotine content may range from 8.3 to 114 mg per patch. Nicotine nasal spray contains 10 mg of nicotine per milliliter. Electronic cigarette liquid refills may now be the most concentrated and potentially toxic nicotine products available. The nicotine concentration can be as high as 36 mg/mL, with bottle sizes exceeding 100 mL.

The toxic dose of nicotine varies. As little as 4 mg can cause symptoms; 40 to 60 mg is potentially fatal in an adult. In a small child, 1 mg of nicotine may cause symptoms (2). Ingestion of one cigarette, three cigarette butts, one cigar butt, or any amount of nicotine chewing gum or patch should be considered potentially toxic in a child.

Neonicotinoids, the only new major class of insecticides developed in the past four decades, are used for crop protection from piercing-sucking insects and for flea control in cats and dogs, and are available as a general insecticide for home use. Neonicotinoids are currently among the most widely used insecticides in the world. Neonicotinioids can be applied to seeds or soil; they are taken up by the plant and may offer protection from these insects for up to 40 days. Similar to nicotine, neonicotinoids act at the postsynaptic nicotinic receptors, where prolonged activation leads to desensitization and inactivation of the receptors, causing insect paralysis and death. Neonicotinoids are highly selective for insect nicotinic receptors (100 to 1,000 times more than vertebrates); making them relatively safe in human and animal exposures (3).

There are seven compounds available currently: acetamiprid, clothianidin, dinotefuran, imidacloprid, nitenpyram, thiacloprid, and thiamethoxam. Imidacloprid is the most commonly used compound. Because of concerns for their impacts on honey bee

population, on April 29, 2013, the European Union enacted a 2-year ban on the use of imidacloprid, clothianidin, and thiamethoxam on flowering plants until further scientific evidence is available. Neonicotinoids may also be toxic to birds and invertebrates.

Pyrethrins are naturally occurring insecticides extracted from chrysanthemum flowers; they are esters of pyrethric and chrysanthemic acid. *Pyrethroids* (e.g., permethrin, deltamethrin) are synthetic pyrethrins that are more stable (resist photolysis) in the natural environment and more potent against insects than pyrethrins. They can be separated into two classes based on their chemical structures: type II agents contain a cyano group at the alpha carbon (e.g., deltamethrin), and type I agents do not (e.g., permethrin).

Pyrethrins and pyrethroids are widely used as insect sprays because of their rapid incapacitating (knock-down) effects on insects. Most are formulated in petroleum distillates for spray applications. Synergists such as piperonyl butoxide, *N*-octyl-bicycloheptene dicarbonimide, and sesame oil derivatives are commonly added to inhibit the metabolism of pyrethrins and thus increase their efficiency. Pyrethrins and pyrethroids are also used to treat head lice and scabies and as insect repellents.

In insects, pyrethrins and pyrethroids rapidly cause death by paralyzing the nervous system. They inactivate sodium channels in nerve axons by binding and prolonging the open state. Other potential mechanisms of toxicity include the inhibition of adenosine triphosphatases and direct effects on membrane integrity. Type II pyrethroids also antagonize inhibitory chloride channels and alter calcium-ion transit, but this contribution to clinical toxicity is unclear (4). Because type II pyrethroids cause a longer opening of the sodium channels, they are generally more toxic than type I agents.

These compounds are rapidly degraded and are popular because they leave almost no residual in the environment. They are considered less toxic to mammals than any other major class of insecticides. Human toxicity is limited by a large first-pass effect by the liver, poor bioavailability, and rapid metabolic breakdown by

ester hydrolysis, followed by hepatic oxidation. Furthermore, the diversity of the α-subunits of the sodium channels in humans makes them less susceptible to pyrethroid toxicity than insects. Ingestion of amounts up to 5 mg/kg is unlikely to cause significant toxicity. The toxic oral dose is estimated to be >100 to 1,000 mg/kg, with a lethal dose estimated to be 10 to 100 g. Synergists also have low human toxicity.

Organochlorine pesticides are low-molecular-weight, fat-soluble aliphatic, aromatic, and complex hydrocarbons that contain chlorine (Table 319.1). The US Environmental Protection Agency canceled the use of many of these pesticides in the 1970s and 1980s because they persist in human tissue and the environment. In the years that followed this action, the remaining organochlorine pesticides were no longer registered for use or will be phased out by 2016 in the United States, although some of these insecticides can be available in other countries. An exception is heptachlor, which is still available as a second-line agent in the control of fire ants. *Lindane* (γ-hexachlorocyclohexane) is still available as a second-line agent in the control of human scabies. Enteral absorption of *organochlorines* is efficient and increased in the presence of animal or vegetable fat. To a lesser extent, they are absorbed across pulmonary membranes, but only 10% or less of a dermally applied dose (e.g., lindane) is absorbed. Different compounds exhibit different tissue-storage and hepatic elimination rates. Many (e.g., chlordane, dieldrin, and heptachlor) can induce hepatic enzymes.

TABLE 319.1
Chlorinated Hydrocarbon Insecticides

Insecticide	Brand/Trade Name
Aldrin	Aldrex, Aldrite, Drinox
Chlorobenzilate	Acaraben, Folbex, Kop-Mite
Chlordane	1068, Belt, Chlor Kill, Niran
Chlordecone	Depone, Tat Ant Trap
DDT	Anofex, Dinocide, Pentech
Dieldrin	Albit, Dorytox, Octalox
Endosulfan	Thiodan, Phaser, Thionex
Endrin	Agrine, Endrex, Hexadrin
Heptachlor	Velaicol, 53-CS-17
Lindane	Agrocide, Isotox, Kwell
Methoxychlor	DMDT, Marlate, Moxie
Mirex	Dechlorane, Ferriamide
Toxaphene	Alltox, Camphoclor, Motox

These compounds are excreted in the feces and can be found in breast milk. They are slowly cleared from the body because of their limited hepatic metabolism and preferential storage in the adipose tissue, which is poorly perfused by blood. It may require many months to years to eliminate mirex, chlordecone, DDT, and β-hexachlorocyclohexane; weeks to months for aldrin, dieldrin, heptachlor, and hexachlorobenzene; and hours to several days for endrin, chlordane, toxaphene, endosulfan, methoxychlor, and chlorobenzilate. Since the ban of these pesticides, the residual concentration of these organochlorines in Americans, especially in adipose tissue, has been decreasing.

Toxicity is due primarily to interference with the axonal transmission of nerve impulses. *Organochlorines* interfere with the normal flow of sodium and potassium ions across the axon membrane as nerve impulses pass. Unlike organophosphate insecticides, they do not depress cholinesterase enzymes. The acute toxic potential of organochlorines varies with the different compounds and their rates and routes of absorption. The products with the highest risk for toxicity include endrin, dieldrin, aldrin, chlordane, and toxaphene (5). Those with intermediate risk include chlordecone, endosulfan, heptachlor, mirex, and DDT. The products with the lowest risk for toxicity are methoxychlor, perthan, kelthane, chlorobenzilate, and hexachlorobenzene. Lindane is potentially toxic after multiple applications to the skin (6). Dermal

and inhalational exposures occur in workers who spray organochlorine pesticides or re-enter fields too soon after spraying. Oral exposure may result from eating or drinking contaminated food or water (7). The estimated oral lethal dose in adults is 3 to 7 g for aldrin, 6 g for chlordane (< 2 g can cause stupor and seizures), 1 to 5 g for dieldrin, and 10 to 30 g for lindane (as little as 1.6 g can cause seizures in children) (5).

CLINICAL PRESENTATION

Poisoning from *nicotine* can occur from (1) exposure to nicotine sulfate insecticides; (2) percutaneous absorption of nicotine in tobacco harvesters who pick and brush up against wet tobacco leaves (green tobacco sickness); (3) ingestion of tobacco products, such as cigarettes, snuff, chewing tobacco, and cigars; chewing or ingestion of nicotine chewing gum; and (4) improper use or ingestion of nicotine patches. Infants and young children are most susceptible to nicotine poisoning because of their small body size and the lack of tolerance. Similarly, tobacco harvesters are more likely to be symptomatic when they have the lowest nicotine tolerance, at the beginning of the harvesting season and workweek. Nonsmokers, lack of work experience, wet conditions, and the lack of protective clothing are risk factors for green tobacco sickness (8). Many nonsmoking tobacco harvesters resort to tobacco chewing as a means to develop nicotine tolerance. Overall, nicotine-related fatalities are rare because of its decreasing use as a pesticide.

Onset of toxicity is rapid and can be seen within 15 minutes of exposure. Initial signs and symptoms include nausea, vomiting, salivation, bronchorrhea, abdominal pain, and diarrhea from parasympathetic stimulation and tachycardia, hypertension, and diaphoresis as result of sympathetic and adrenal stimulation. Early CNS effects include dizziness, headache, confusion, agitation, incoordination, and seizures. Muscular fasciculations may result from neuromuscular junction stimulation.

As symptoms progress, hypotonia, muscle paralysis, respiratory failure, coma, bradycardia, and hypotension may ensue. Because of

both stimulatory and inhibitory effects on multiple systems, the signs and symptoms vary by the time, dose, and route of exposure. In severe cases, such as oral nicotine pesticide poisoning, the progression from stimulation to inhibition of the various systems may be rapid (2).

In mild nicotine poisoning, symptoms can last for several hours. In severe cases, clinical toxicity can endure for 18 to 24 hours or more. Severe cases involve seizures and coma within 30 minutes, with respiratory arrest and death within 1 hour or less, especially with concentrated nicotine products. Patients who survive the first 4 hours usually recover fully. Radiographic and electrocardiographic (ECG) findings are nonspecific. Nicotine can be detected in the urine by chromatographic drug assays.

The clinical presentations of *neonicotinoid* toxicity are similar to those of nicotine toxicity. Vomiting, oral ulcers, diaphoresis, bronchorrhea, mydriasis, bradycardia, tachycardia, and lethargy are common. In severe cases, the symptoms may progress to coma, hypotension, and respiratory failure. Oral mucosal corrosion may be secondary from the solvent carrier. The overall mortality reported for neonicotinoid poisoning is less than 3%, which is similar to that of pyrethroids but much lower than organophosphates and carbamates (9).

Direct toxicity from *pyrethrins* and *pyrethroids* is uncommon. When they occur, adverse effects are usually as a result of allergic hypersensitivity and include bronchospasm, vasomotor rhinitis, contact dermatitis, and, rarely anaphylaxis (10). After inhalation, the most common presentation is a stuffy nose with clear discharge and a “scratchy” throat. In rare cases, sudden bronchospasm, swelling of the laryngeal mucosa, and shock (anaphylaxis) can occur. Patients allergic to ragweed have a higher risk of developing allergic reactions to pyrethrins. Natural *pyrethrins* are more likely than synthetic *pyrethroids* to cause these reactions.

Direct dermal exposure to pyrethrins can produce a contact dermatitis consisting of redness, blisters, burning, stinging, and numbness. Transient paresthesia is related to the direct effects on cutaneous nerve endings and more commonly associated with type

II pyrethroids. Ocular exposure to hydrocarbon propellants can cause eye irritation and corneal abrasions. Large exposures to type II pyrethroids can cause tremors, salivation, paresthesia, ataxia, choreoathetosis, and seizures. Similar exposure to type I agents can result in tremors, agitation, and hyperthermia.

The onset of symptoms after exposure to *organochlorine* insecticides may vary from minutes to hours, depending on the route and method of exposure and the physicochemical properties of the agent (7). Nausea, vomiting, and diarrhea can occur as soon as 45 minutes after acute ingestion. Initial CNS effects include apprehension, headache, dizziness, tremors, ataxia, and disorientation. Stupor, coma, and seizures with respiratory depression may be seen in severe cases. Dysrhythmias may result from increased myocardial sensitivity to catecholamines.

Aspiration of formulations containing a petroleum distillate can result in a chemical pneumonitis. CNS toxicity, including seizures, can also occur in children after prolonged or excessive topical *lindane* exposures during the treatment of lice or scabies (6). In severe cases, potential complications include lactic acidosis, rhabdomyolysis, and disseminated intravascular coagulation.

Chronic exposure to *organochlorines* in workers can cause neurologic manifestations, including paresthesia, tremors, opsoclonus, and seizures. Extensive or prolonged dermal contact can result in skin irritation in the occupational setting. Chronic ingestion of hexachlorobenzene has been associated with cutaneous porphyria.

DIFFERENTIAL DIAGNOSIS

Without a history of exposure, there are no pathognomonic signs of nicotine and neonicotinoid poisoning. It could be confused with acetylcholinesterase inhibitor poisoning, such as OP or carbamate insecticides, and carbamate drugs (edrophonium, physostigmine). In nicotine and neonicotinoid poisoning, however, there is no depression of the red blood cell cholinesterase.

Direct-acting cholinomimetic agents such as bethanechol, carbachol, methacholine, and pilocarpine can also produce cholinergic effects similar to those of nicotine. However, because these agents have minimal effects on nicotinic receptors (except for carbachol), they produce minimal or no sympathetic or muscular symptoms. Central and peripheral sympatholytics (α-adrenergic and β-adrenergic receptor blockers, clonidine, guanabenz, topical decongestant imidazoline derivatives, and calcium blockers) can mimic the later stages of nicotine poisoning. These agents will not produce any muscarinic symptoms or neuromuscular weakness. Tree tobacco (*Nicotiana glauca*), native to the temperate regions of America, contains the alkaloid anabasine, an isomer of nicotine that can cause similar symptoms. Other substances to consider are the insect-repellent diethyltoluamide, Veratrum and sabadilla plants, Clitocybe and Inocybe mushrooms, and poison hemlock (*Conium maculatum*).

Pyrethrins and pyrethroids should be included in the differential diagnosis of patients who present with an apparent hypersensitivity reaction of the skin or respiratory system when exposed to flora, insecticides, or insect bites. Because almost all of the insecticides containing these compounds are in a hydrocarbon base, the risk of hydrocarbon pneumonitis must be considered in humans ingesting these products.

Acute organochlorine insecticide poisoning must be distinguished from any condition that produces “gastroenteritis” with an altered mental status, especially ataxia, tremors, and seizures. CNS disease, drug withdrawal, stimulant intoxication (e.g., from sympathomimetics, xanthenes, anticholinergics, hallucinogens, and isoniazid), and infectious etiologies should be considered.

ED EVALUATION

The history should document the time, agent, dose, route, intent, and duration of exposure and the nature and course of symptoms. The physical examination should pay particular attention to cardiovascular, respiratory, and neurologic function. Patients with

vital sign abnormalities should have an ECG. Symptomatic patients should have cardiac and oxygen saturation monitoring. Chest radiographs, oxygen saturation measurement or arterial blood gas analysis, and pulmonary function tests can assess respiratory function and possible aspiration in patients with wheezing, dyspnea, cough, and fever. Blood chemistries and hematologic analysis should be obtained based on clinical severity.

No specific laboratory tests are diagnostic. The presence of nicotine in the urine of a nonsmoker is supportive. Plasma nicotine levels are not useful. Organochlorine insecticides can be measured in the serum by using gas chromatography/mass spectrometry, but levels are not useful for clinical management. However, in a patient with a suspicious exposure for DDT, a high DDT to DDE ratio confirms that the exposure was recent.

KEY TESTING

- There are no specific laboratory tests.
- ECG and CXR should be obtained in symptomatic patients.
- Pesticide levels can be obtained but do not aid clinical management.

ED MANAGEMENT

GI, skin, and eye decontamination should be performed. Activated charcoal (AC) is the preferred method for early GI decontamination. Pyrethrins and pyrethroids are lipophilic, so milk, cream, or substances that contain animal or vegetable fats should not be administered. Except for recent ingestion (<1 hour) of large quantities of a nicotine or neonicotinoid pesticides, gastric aspiration or lavage would not likely provide additional benefit. Seizures and coma can occur rapidly, and emesis increases the risk of aspiration. If present, all transdermal patches should be removed.

Exposed skin areas should be washed with soap and water. Exposed eyes should be irrigated with copious amounts of water for 15 minutes. Powder contaminating the skin should first be

vacuumed off. Contaminated clothing should be removed, and the skin, hair, and nails scrubbed.

The patient should be closely monitored for the first few hours after exposure. Supportive care, including oxygen, endotracheal intubation, and assisted ventilation, should be instituted as necessary. Intravenous access and cardiac monitoring are indicated for all but mild intoxications. Seizures should be treated with intravenous benzodiazepines such as diazepam (for adults, 5 to 10 mg initially, repeated every 5 to 10 minutes as necessary, up to 30 mg; for children, 0.25 to 0.4 mg/kg per dose) or lorazepam (0.05 to 0.1 mg/kg, which may be repeated twice every 15 minutes as necessary). If seizures cannot be controlled with diazepam or lorazepam, a barbiturate (such as phenobarbital or pentobarbital) or propofol may be given. Phenytoin is not likely to be effective and may actually increase the incidence of seizures in organochlorine poisoning.

Excess parasympathetic stimulation (e.g., marked bronchial secretions) from nicotine and type II pyrethroids can be controlled by atropine (adults, 0.5 to 1 mg intravenously, repeated every 5 minutes as necessary; children, 0.01 to 0.02 mg/kg intravenously). Oxygen and ventilation may be necessary. Hypotension should be treated with intravenous fluids; dopamine or norepinephrine may be added. Mecamylamine (Inversine), an older antihypertensive agent, is a specific nicotine antagonist but is available only in tablets, and is not practical in a patient who is vomiting, seizing, or hypotensive.

Anaphylaxis should be treated as usual (see Chapter 175). The management of hydrocarbon aspiration is supportive (see Chapter 331). Respiratory distress as a result of bronchospasm is managed with inhaled bronchodilators and humidified oxygen. Parenteral administration of adrenergic amines (e.g., epinephrine) is not recommended in organochlorine insecticide poisoning because myocardial irritability may be enhanced. Contact dermatitis may be treated with topical corticosteroids.

Because organochlorine compounds have an extensive enterohepatic recirculation, multiple-dose activated charcoal (MDAC) is recommended to enhance their elimination. Multiple

doses of cholestyramine resin are also effective but is less well tolerated than charcoal. Extracorporeal procedures are not effective in enhancing organochlorine elimination. MDAC, hemodialysis, and hemoperfusion have not been evaluated in nicotine, neonicotinoid, and pyrethrin poisoning.

CRITICAL INTERVENTIONS

- Establish IV access and institute cardiac monitoring.
- Secure the airway and assist ventilation as necessary in patients with neurotoxicity.
- Decontaminate dermal exposures with clothing removal and soap with copious water.
- Administer benzodiazepines and, if necessary, barbiturates and propofol for seizures.
- Administer atropine to treat excess parasympathetic stimulation.
- Treat hypersensitivity reactions to pyrethrins or pyrethroids similarly as in any other allergic reaction.
- Administer MDAC for organochlorine insecticide ingestions.

DISPOSITION

Patients who remain or become asymptomatic after a 6-hour period of observation after an acute exposure may be discharged with appropriate follow-up. Patients with mild allergic reactions can be discharged after treatment. Chronic organochlorine insecticide exposures can generally be treated as outpatients. All others should be admitted to the hospital, observed, and treated supportively. Because the cardiorespiratory system requires monitoring, intensive care unit admission is advised. If such facilities are unavailable, the patient should be transferred with advanced life-support measures and anticonvulsants available. If necessary, consultation can be obtained from a regional poison center (1-800-222-1222) or the National Pesticide Telecommunications Network (1-800-858-7378). If the exposure occurred at the workplace, the proper health agency should be notified to prevent further occurrences.

Common Pitfalls

- Failure to discover a nicotine patch unintentionally stuck to the skin of an infant or toddler with altered mental status who was not completely undressed.
- Failure to properly decontaminate patients with dermal exposures.
- Failure to diagnose and treat respiratory failure, the primary cause of death in nicotine and neonicotinoid poisoning.
- Failure to appreciate that antacids for GI symptoms may increase the absorption of ingested nicotine.
- Failure to consider the possibility of aspiration (hydrocarbon) pneumonitis in patients with respiratory symptoms after ingestion.
- Mistaking organochlorine insecticides for OP insecticides (and vice versa), resulting in incorrect treatment.

The findings and conclusions in this chapter are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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CHAPTER 320 Rodenticides

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Rodenticides, "rat poisons," are a large, disparate group of chemical compounds; their only commonality is that they are utilized to kill rats, mice, squirrels, and other small animals. They have varied mechanisms of action, toxicities, and times of onset. Fortunately, medically significant, unintentional rodenticide exposures are uncommon in the United States due to legislation regulating their sale and use. Most exposures are in children, especially those younger than 6 years old, accidental, involve an oral anticoagulant, and result in minimal or no toxicity. Adults with intentional ingestions, however, often develop significant morbidity and mortality.

Oral anticoagulants are the most commonly used rodenticides in the United States (1). Toxicity results from inhibition of the cyclic regeneration of vitamin K, a cofactor required for the activation of coagulation factors II, VII, IX, and X. Although vitamin K depletion occurs almost immediately, no anticoagulant effect is seen until the activity of at least one clotting factor is diminished to below 25% of normal (2). Because factor VII has the shortest half-life among the clotting factors affected ($t_{½}$ = 5 hours), at least three half-lives (15 hours) are usually required before any toxicity is manifested.

Conventional anticoagulant rodenticides contain low concentrations of warfarin (0.025% to 0.05% or 100 to 200 mg in a pound of bait). These products were designed to kill rodents who ingest this bait daily over a period of several weeks. Their widespread use resulted in rodents' becoming resistant to their effects. Thus, higher-potency agents (superwarfarins) were

developed. These cause prolonged coagulopathy with ingestions of even smaller doses.

Other less commonly utilized rodenticides include arsenic compounds, organophosphates (OP), red squill, sodium monofluoroacetate, strychnine, tetramine, thallium, vacor, cholecalciferol, yellow phosphorus, and zinc phosphide. Arsenic compounds, used more commonly in the past, were a leading cause of rodenticide-related deaths in the 1950s and 1960s. Professional exterminators may still have access to arsenicals, depending on local laws. Arsenic causes rapid onset of toxicity by combining with and inhibiting sulfhydryl-containing enzymes (see Chapter 326).

Cholinesterase inhibitors include OP and carbamate compounds, which are used primarily as insecticides (see Chapter 318). Although they are not sanctioned for use as rodenticides in the United States, foreign manufacturers may use them for this purpose, and the probability of these products reaching the United States continues as international travel and immigration continues to increase. A case series from the New York Poison Control Center of 35 patients with exposure to "Tres Pasitos" identified aldicarb, an extremely potent carbamate-type cholinesterase inhibitor that is not licensed for rodenticide use in this country. It highlights an ongoing epidemic of acute poisoning, primarily in Dominican descendants living in New York City, following illicit sale of undocumented compounds, and its availability poses a substantial public health threat (3).

Red squill is a cardiac glycoside derived from the plant *Urginea maritima.* Its toxicity relates to its ability to block sodium–potassium-ATPase similar to digoxin. This toxin is poorly absorbed in humans because of its potent emetic effects. In rodents, however, whose vomiting mechanism is less well developed, the toxin is fairly effective.

Sodium monofluoroacetate (SMFA) is a white, odorless, tasteless, water-soluble salt typically available as a powder. Once absorbed, SMFA (and the closely related compound fluoroacetamide) rapidly enters the Krebs cycle, in which it is converted to fluorocitric acid, which inhibits the Krebs cycle, blocking aerobic metabolism (4).

Strychnine, a natural alkaloid derived from the native Indian tree *Strychnos nux-vomica,* has been used as a rodenticide since the 1600s. It is a potent neurotoxin that acts by competitively inhibiting glycine at postsynaptic receptors. Because glycine is the predominant inhibitory neurotransmitter in the spinal cord, its inhibition results in muscular rigidity and hyperexcitability (5).

Tetramine is not sanctioned for use as a rodenticide in the United States. However, it is utilized for this purpose in mainland China with sporadic cases reported in the United States and Hong Kong. Tetramine is an extremely potent picrotoxin-like agent that blocks γ-aminobutyric acid receptors in the brain causing prolonged convulsions leading to multi-organ failure and imminent death (6).

Thallium is an odorless, tasteless, highly toxic heavy metal. Although it can penetrate intact skin, it is more readily absorbed when ingested. Thallium, like arsenic, binds to and inhibits sulfhydryl-containing enzymes. Unlike arsenic, however, it preferentially affects mitochondria (7).

When first introduced, *Vacor* was thought to have no human toxicity. After numerous cases of severe poisoning occurred, it was voluntarily withdrawn from the market in 1979. Vacor is selectively toxic to pancreatic β-islet cells, producing a chemically induced form of insulin-dependent diabetes mellitus. The exact mechanism for the islet cell destruction is unclear, but it may be as a result of Vacor's ability to deplete β-islet cells of nicotinamide adenine dinucleotide (NAD) (8).

CLINICAL PRESENTATION

The majority of oral anticoagulant exposures involve unintentional ingestions in children younger than 6 years of age. Acute, single, unintentional ingestions of conventional anticoagulants are unlikely to cause toxicity because of their low warfarin concentrations. Similarly, children who unintentionally ingest superwarfarins in a single dose are unlikely to develop toxicity. In contrast, adults with intentional ingestions or children with repeated ingestions often develop a coagulopathy within 24 or, at the latest, 48 hours. If this goes untreated, bleeding complications may develop. The most

common sites of bleeding are the gastrointestinal (GI) and genitourinary tracts (1).

The other rodenticide agents are much less common and their clinical presentations are listed in Table 320.1.

TABLE 320.1
Rodenticide by Unique Identifier, Clinical Presentation, and Time of Symptom Onset

Rodenticide	Unique Identifier	Clinical Presentation	Onset
Arsenic	Garlic-like odor in breath	Severe vomiting, bloody diarrhea, dehydration, ventricular dysrhythmias, CNS and CV depression, CV collapse, late-onset neuropathies (see Chapter 326)	Early
Cholinesterase inhibitors	Cholinergic syndrome	Oral, dermal, or inhalation route of exposure. Salivation, lacrimation, defecation, urination, vomiting, GI cramping and/or pain, mental status change, seizures, muscle fasciculations, or weakness (see Chapter 318)	Early
Red squill	Similar to cardiac glycoside such as digoxin	Myocardial irritation, dysrhythmias, hyperkalemia, GI symptoms, blurred vision (see Chapter 325)	Early
SMFA toxicity	Severe lactic acidosis	Ingestion is most common exposure route in severe poisoning; initial symptoms: nausea and apprehension, followed by lactic acidosis, pulmonary edema, coma, hypokalemia, hypocalcemia, seizures, dysrhythmias; poor prognosis with early-onset acidosis and secondary renal insufficiency (4)	Early
Strychnine	Risus sardonicus (facial spasms), mistaken for having "seizures"	Decorticate posturing, opisthotonos, "seizure" with normal mental status; prolonged muscle spasm leads to hyperthermia, rhabdomyolysis, lactic acidosis, and death often from respiratory dysfunction; similar presentation to tetanus (5)	Early
Tetramine	Rapid onset seizures	Status epilepticus, high fatality rate, residual neurological injury in survivors (6)	Early
Thallium	12 to 24 hours delay in onset, extremely painful extremity paresthesias	Initially, GI symptoms predominate; in severe cases, dysrhythmias develop +/– death; survival characterized by period of alopecia and neurological findings (neuropathies, paresis, ataxia, choreiform movements, optic nerve atrophy) (7)	Early or late
Vacor	Severe diabetic ketoacidosis (DKA), odor of peanuts	Rapid loss of glucose control (destroys pancreatic beta cells), acute pancreatitis, autonomic instability, peripheral paresthesias, esophageal or GI perforation; survivors characterized as brittle insulin-dependent diabetics, often with accelerated microvascular diabetic disease (8)	Late
α-Naphthylthiourea	Acute lung injury	Hypothermia, pulmonary edema	Early
Barium	Neuromuscular blockage	GI symptoms, headache, long QTc, cardiac and pulmonary failure	Early
Bromethalin	Focal motor seizures	Muscle tremors, ataxia, myoclonic jerks	Early
Yellow phosphorus	Skin and GI burns	Dysrhythmias, coma, seizure, cardiac arrest	Early
Oral anticoagulants	Hemorrhage	Elevated INR, death from hemorrhage (1,9)	Late
Cholecalciferol	Hypercalcemia	Lethargy, renal failure, weakness	Late

DIFFERENTIAL DIAGNOSIS

Exposure to an unknown rodenticide is common. In such cases, it is useful to classify rodenticides clinically, based on their time of onset and symptoms (see Table 320.1). When the time of symptom onset and the nature of the symptoms are considered, a presumptive diagnosis can be established. Patients exposed to rodenticides with a rapid onset of action can be expected to manifest symptoms within 6 hours of ingestion. Those with exposure to rodenticides that have a delayed onset typically manifest symptoms beginning 12 hours or more after ingestion.

When symptoms are rapid in onset, cholinergic findings suggest OP poisoning; muscular hyperactivity suggests strychnine; seizures, coma, and metabolic acidosis suggest SMFA or tetramine; severe GI symptoms suggest arsenic; hyperglycemia suggests Vacor; and GI symptoms with cardiac dysrhythmias suggest red squill.

Lack of symptoms during the first 6 hours after exposure to an unknown rodenticide suggests either a nontoxic exposure to a rapidly acting agent or a potentially toxic exposure to a rodenticide with a delayed onset of toxicity (e.g., an oral anticoagulant or thallium). The most common cause of delayed symptoms from rodenticide poisoning is superwarfarin anticoagulants.

An additional diagnostic clue for suspected rodenticide exposure is odor. Arsenic and yellow phosphorus smell like garlic. Vacor smells like peanuts, and patients with Vacor-induced diabetic ketoacidosis (DKA) may have the fruity odor of ketones on their breath.

ED EVALUATION

Patient history is critical and must include the amount ingested, the time of ingestion, and the identity of the product involved. The most useful piece of information is the precise name and manufacturer of the ingested product.

A family member should be asked to return to home and try to get this information if the product is not brought along with the patient. The actual container or list of active ingredients is preferred over the commercial name, because many commercial names have been used for several products with different active ingredients. If product identity is unavailable, clinical manifestations may suggest the offending agent (see Table 320.1, Unique Identifiers).

While the diagnostic evaluation is proceeding, consideration and institution of therapy must occur simultaneously, as many of these poisons cause rapid and potentially fatal toxicity. The initial assessment should address the airway, breathing, and circulation. Strychnine may cause respiratory failure secondary to tonic muscle contractions and inability to ventilate. Toxicity from several of the other rodenticides can evolve rapidly to produce CV collapse.

Vital signs should be obtained immediately and reassessed frequently. Life-threatening hyperthermia may occur as a result of increased muscle activity with strychnine poisoning. Clinical clues include specific odors associated with the different toxins and the quality and amount of emesis or diarrhea. Signs of bleeding in the GI or genitourinary tract may indicate oral anticoagulant exposure, although these findings would be delayed in onset.

Laboratory testing should be based on the history and physical exam, identity of product ingested, and unique identifying aspects of clinical manifestation, when present. Blood chemistries and a complete blood count are rarely useful in the absence of clinical findings. A low serum bicarbonate concentration might be found in symptomatic patients with SMFA, strychnine, tetramine, or Vacor exposures. An elevated serum glucose level, especially in association with a metabolic acidosis, suggests Vacor-induced DKA. A prothrombin time/international ratio (PT or INR) should be obtained in patients with remote (>24 hours) or repeated anticoagulant ingestions. If obtained shortly after a single ingestion, the PT/INR should be normal, and measurement is not helpful. In chronic anticoagulant exposures or in patients who present with active bleeding several days after exposure, an elevated PT/INR may be diagnostic.

The need for radiographic assessment should be guided by the toxin involved. Exposure to agents that produce pulmonary toxicity mandates a chest radiograph. Abdominal radiography may help detect opacities in the gut in recent ingestions of the metal toxins (arsenic or thallium). If a sample of an unidentified rodenticide is obtained, taking a radiograph of it may help determine its heavy-metal content (7).

KEY TESTING

- Testing is based on the compound
- PT/INR is not necessary after a single acute anticoagulant ingestion
- PT/INR is helpful several days after anticoagulant ingestion or in patients with bleeding

ED MANAGEMENT

Treatment begins with stabilization of vital signs; advanced life-support measures are instituted, as appropriate. Once the patient is stable, gastric decontamination should be considered for recent ingestions. For the asymptomatic patient who has ingested an unknown rodenticide, activated charcoal is the preferred method. Orogastric lavage may be used in any patient giving a history of recent ingestion (within 2 to 4 hours) of a highly toxic rodenticide such as arsenic, superwarfarin anticoagulants, SMFA, strychnine, tetramine, thallium, or Vacor. Although little data exist on the efficacy of orogastric lavage, this intervention seems justified given the severe potential toxicity and lack of effective antidotes for most of the compounds in this group. Activated charcoal should be given after lavage.

Management of asymptomatic patients with unknown ingestions involves daily follow-up with PT/INR testing to see whether anticoagulant toxicity has manifested. A normal PT/INR at 48 hours after ingestion excludes significant anticoagulant toxicity (9). Prophylactic treatment with vitamin K_1 is not recommended when there is a normal PT/INR. It is important to note that vitamin K_1 will not prevent toxicity, which might last for a month, and thus only delays detection (9).

The treatment of *tetramine* poisoning is entirely supportive. Management of *arsenic* poisoning also includes chelation therapy (see Chapter 326) and that for cholinesterase inhibitor poisoning also includes atropine and pralidoxime (see Chapter 318). *Red squill* poisoning is treated the same as cardiac glycoside toxicity from other causes; digoxin-specific Fab fragments can be used (see Chapter 325).

Coagulopathy from *superwarfarins* without significant bleeding is treated with vitamin K_1. It is important to note that not all vitamin K preparations are effective; phytonadione (AquaMephyton, vitamin K_1) is the only antidote recommended for this purpose. The dose and the duration of treatment vary with the type and amount of

anticoagulant ingested and the patient's rate of toxin metabolism. Obtaining serial levels of the toxin to determine its elimination curve may help predict the duration of treatment; however, in practice, treatment is continued until the coagulopathy is corrected. Doses of up to 100 mg/d of vitamin K_1 for as long as 10 months have been necessary for superwarfarin poisoning (9). In patients with life-threatening bleeding, fresh-frozen plasma, recombinant activated factor VII, and/or plasminogen complex concentrates should be administered. Little data are available comparing efficacy of these different agents. Use of one agent over another or in combination should be made on a case by case basis (10).

Suggested antidotal treatments for *SMFA* toxicity include glycerol monoacetate or ethanol, although neither approach has been well studied. Glycerol monoacetate is thought to work by bypassing the site of blockage in the Krebs cycle. Ethanol may inhibit the conversion of *SMFA* to fluorocitrate and allow for excretion of the nontoxic parent compound (4). Given the relative safety of ethanol administration and the severe toxicity of SMFA, treatment with ethanol appears warranted.

Treatment of muscle overactivity, the main problem that leads to the life-threatening complications in *strychnine* poisoning, includes high doses of benzodiazepines and, if necessary, neuromuscular paralysis. If the patient is hyperthermic, aggressive rapid cooling (see Chapter 360, "Heat-Related Illness") is critical.

Patients with *thallium* poisoning should be treated with prussian blue (ferric ferrocyanide) (7) and multiple-dose activated charcoal, with the addition of either hemodialysis or hemoperfusion in life-threatening cases. Prussian blue is given at a dose of 250 mg/kg/d with a cathartic in divided doses.

Niacinamide (nicotinamide) is an effective antidote for *Vacor* in experimental animals. In these studies the earlier the antidote was given after exposure, the better the outcome. Niacin is not an effective substitute. Niacinamide (500 mg initially, followed by 100 to 200 mg every 4 hours for 2 days) is recommended for all patients with Vacor ingestion. Because an intravenous formulation is not

available, it should be given orally. Patients who develop DKA are managed like other diabetic patients.

CRITICAL INTERVENTIONS

- Positively identify the rodenticide's active ingredients
- Arrange for a 48-hour follow-up PT/INR for asymptomatic superwarfarin or unknown rodenticide exposures

DISPOSITION

For symptomatic patients exposed to a highly toxic rodenticide such as arsenic, superwarfarin anticoagulants, sodium monofluoracetate, strychnine, tetramine, thallium, or Vacor, hospital admission to a monitored setting is warranted. Because of the relative rarity of these exposures, consultation with a medical toxicologist or a regional poison center is recommended early in the presentation.

Patients with unintentional exposures who remain asymptomatic after 6 hours of observation can be discharged. For patients exposed to superwarfarin or long-acting oral anticoagulants, follow-up coagulation studies are needed at 48 hours after ingestion. These studies may be performed in the outpatient setting for patients with unintentional ingestions, provided there is adequate family and social support. All other patients, including those with intentional ingestions, are best managed as inpatients.

Common Pitfalls

- Failure to obtain a sample or container to identify the ingested agent.
- Misidentification of the rodenticide because an identical or similar brand name or market name is used for more than one agent.
- Failure to consider ingestion of an agent with delayed onset of action in a patient with an unknown rodenticide exposure who remains asymptomatic after a period of observation.
- Using the wrong type of vitamin K to treat oral anticoagulant toxicity.
- Beginning vitamin K treatment when the PT/INR is normal.

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PART 6 • CARDIOVASCULAR DRUGS

CHAPTER 321

Antidysrhythmic Drugs and Local Anesthetics

S. Rutherfoord Rose and Paul E. Stromberg

This chapter focuses on Vaughan–Williams class I and class III antidysrhythmic agents (Table 321.1) and local anesthetics, whose mechanism and toxic effects are similar to that of lidocaine. Other antidysrhythmics are discussed elsewhere. See Chapter 323 (Vaughan–Williams class II) and Chapter 324 (Vaughan–Williams class IV).

TABLE 321.1
Classification of Antidysrhythmic Drugs

Class	Actions	Examples
I	Sodium channel inhibition	
A	Increased APD	Quinidine, disopyramide, procainamide
	Increased ERP	
	Slowed conduction	
B	Little/no decrease in APD	Lidocaine, tocainide, phenytoin, mexiletine
	Increased ERP in diseased tissue	
	May increase conduction velocity	
C	Variable effect on APD	Encainide, flecainide, propafenone
	Small increase in ERP	
	Markedly slowed conduction	
II	β-Adrenergic blockade	Atenolol, metoprolol, propranolol, acebutolol, bisoprolol, sotalol
III	Prolonged repolarization	Amiodarone, dronedarone, bretylium, dofetilide, ibutilide, sotalol, *N*-acetylprocainamide
IV	Calcium channel inhibition	Diltiazem, nifedipine, verapamil, bepridil

APD, action potential duration; ERP, effective refractory period.

Class I antidysrhythmics decrease the influx of sodium through fast channels in myocardial cell membranes during depolarization (phase zero of the action potential), thereby slowing the rate of rise of the action potential (V_{max}) in myocardial cells. This action results in decreased conduction velocity and increased QRS duration. Class I drugs are further divided into A, B, and C subclasses based on their respective rates of dissociation from fast sodium channels. Class IC agents dissociate slowly and therefore produce the greatest degree of QRS prolongation, even at therapeutic doses. Class IB drugs, including lidocaine, quickly dissociate from binding sites and produce no QRS prolongation at therapeutic concentrations. Class IA drugs have intermediate dissociation constants and cause mild QRS prolongation with therapeutic dosing.

Class IA drugs also have variable α-adrenergic–blocking effects, and disopyramide has relatively potent negative inotropic and anticholinergic effects. Propafenone has relatively weak β-adrenergic activity, which may be clinically important in patients on

high doses or in the approximately 7% of patients who poorly metabolize propafenone to an active metabolite, which has class IC–like properties.

Amiodarone, dronedarone, sotalol, dofetilide, and ibutilide are examples of class III drugs, which prolong repolarization and the refractory period in all cardiac tissue by blocking outward potassium channels. Because amiodarone has vasodilating and weak β-adrenergic–blocking properties, intravenous (IV) administration results in pharmacologic effects consistent with all four Vaughan–Williams classes. Dronedarone is a synthetic analog of amiodarone, available for oral use primarily in the treatment of atrial fibrillation, that lacks the thyroid and pulmonary toxicities of amiodarone (1). Like amiodarone, dronedarone exhibits electrophysiologic properties of all four Vaughan–Williams classes. Sotalol is a nonselective β-adrenergic blocker that also prolongs the refractory period throughout the conduction system, including bypass tracts. Dofetilide prolongs the action potential duration and effective refractory period without affecting conduction velocity. Dofetilide is available only to hospitals and physicians who have received appropriate dosing and treatment education, as the risk of inducing dysrhythmias is significant. Dofetilide toxicity can be minimized by paying careful attention to pretreatment QT intervals and renal function. Ibutilide is structurally related to sotalol but does not affect β-adrenergic receptors. Ibutilide activates slow sodium channels at low doses, in addition to blocking delayed rectifier potassium channels in higher doses. Class IA drugs are used to treat a wide variety of dysrhythmias of both ventricular and supraventricular origin, including re-entry tachycardias and Wolff–Parkinson–White syndrome. The efficacy of these drugs in preventing re-entry dysrhythmias is probably the result of a change from unidirectional to bidirectional block resulting from slowed conduction. Class IC drugs have very narrow therapeutic windows and are primarily used for maintenance of sinus rhythm in patients with atrial fibrillation. The Cardiac Arrhythmia Suppression Trial demonstrated increased mortality in patients given encainide or flecainide after myocardial infarction, and these IC drugs are

typically reserved for treatment of refractory supraventricular tachycardias. The class III drugs have become more prominent as initial therapy for both ventricular and supraventricular rhythm disturbances.

Compared with other cardiovascular (CV) drugs (e.g., β-blockers or calcium channel blockers), overdose with antidysrhythmic drugs is rare. Most overdoses occur in adults and are accidental. Adverse effects are common, however, occurring in 20% to 50% of patients on chronic therapy.

These drugs are well absorbed orally, and peak plasma levels following ingestion of immediate-release dosage forms usually occur within 1 to 3 hours, except with amiodarone (typically 4 to 6 hours, but up to 12 hours) and disopyramide (as a result of its anticholinergic effects). Metabolites of quinidine, encainide, propafenone, amiodarone, and dronedarone are not monitored clinically but have varying degrees of pharmacologic activity and probably contribute to overall effects. The principal metabolite of procainamide, *N*-acetylprocainamide (NAPA), prolongs repolarization (resembling Class III drugs) but is not approved for use in the United States. Amiodarone is unique in that it has a very prolonged elimination half-life (50 days); serum levels may continue to rise for a month after starting therapy.

The toxic effects of antidysrhythmics result from exaggerated therapeutic activity. Dose-dependent delays in conduction lead to variable degrees of atrioventricular block and, eventually, asystole. High drug levels also result in myocardial depression (classes IA, IC, and III) and peripheral vasodilatation (classes IA and III), which can result in profound hypotension. Central nervous system (CNS) effects appear to be independent of cardiac effects unless shock is present.

There is insufficient data to determine the minimum toxic doses for most antidysrhythmic drugs. For class IA drugs, toxicity may be expected after acute ingestions of 1 g or more. Ingestions >2.5 to 3.0 g may result in serious toxicity but survival has occurred with acute doses of up to 20 g and peak serum levels of 21.4 μg/mL (quinidine) and 77 μg/mL (procainamide). However, 2 g of

disopyramide resulted in cardiopulmonary arrest in a 16-year-old girl, and fatalities have been reported following estimated doses as low as 3.6 to 6.8 g in adults and 600 mg in a child, and serum levels of 8.3 μg/mL.

Class IC drugs appear to be more toxic than class IA drugs. Severe toxicity has occurred in a 6-month-old child who ingested a single 25-mg encainide tablet. Seizures, hypotension, bradycardia, and coma have occurred following ingestion of 3.0 to 3.5 g of encainide. Ingestion of 1.8 g of flecainide was fatal in an 18 year old, and 1.5 g has produced seizures and polymorphous ventricular tachycardia (VT). An acute overdose of 1.8 g (133 mg/kg) of propafenone in a 2-year-old child resulted in hypotension, seizures, and a prolonged QT interval. Ingestion of 8.1 g of propafenone caused seizures, coma, hypotension, and prolonged QRS interval in an adult with a propafenone serum level of 3.2 μg/mL. An overall mortality of 22.5% was reported in a retrospective review of patients with propafenone, flecainide, ajmaline, and prajmaline toxicity (2). About half of these patients became nauseated within 30 minutes of ingestion, and severe cardiac toxicity (atrioventricular block, bradycardia, pulseless electrical activity, asystole) occurred within 30 to 120 minutes after ingestion.

There is much less information about the acute toxicity of class III drugs. Amiodarone doses of 2.6 to 8.0 g have produced mild bradycardia, prolonged QT interval, and a brief episode of nonsustained VT, all with a delayed onset of 12 to 48 hours. There is limited data on dronedarone overdose, but bradycardia, QT prolongation, and heart failure can occur, even with therapeutic dosing. Sotalol toxicity may result in QT prolongation and cardiac dysrhythmias.

Excessive dosing or impaired excretion of these compounds frequently leads to toxic levels during chronic therapy. Clinical toxicity at a relatively lower serum concentration may be expected during chronic therapy as a result of prior saturation of tissue stores and the likelihood of pre-existing cardiac disease.

Local anesthetics decrease neuronal permeability to sodium ions (a similar mechanism to the cardiac antidysrhythmics), which

prevents transmembrane depolarization and subsequent propagation of the action potential. Lidocaine is a group II (amide-type) local anesthetic, and the most commonly used local anesthetic. Other group II anesthetics include bupivacaine, ropivacaine, mepivacaine, prilocaine, dibucaine, and etidocaine. A common mnemonic device notes that the local anesthetics with two letter "*i*"s in the generic name are all in the amide class.

Group I local anesthetics contain esters rather than amides and include cocaine, tetracaine, procaine (Novocaine), proparacaine, and benzocaine. Patients with a reported allergy to a local anesthetic are typically allergic to all agents of the same group (amide or ester) but may be safely given an anesthetic from the other group.

Lidocaine is well absorbed through mucous membranes and sufficient gastrointestinal (GI) tract absorption may result in toxic serum levels. Peak plasma concentrations are reached within 2 minutes of IV administration, within 10 minutes of endotracheal administration, and within 30 to 60 minutes of ingestion. Following IV injection, lidocaine is rapidly distributed to well-perfused tissues (brain and heart), with subsequent slower distribution to less well-perfused tissues such as skeletal muscle and fat. The initial distribution serum half-life is approximately 10 minutes. The peak serum concentration, which depends on the rate of administration, then rapidly declines. Because of this biphasic pattern of distribution, an infusion is required to maintain therapeutic serum concentrations following IV bolus for an antidysrhythmic effect. A standard IV dosing regimen is 1.0 to 1.4 mg/kg, followed in 10 minutes by an additional bolus of 0.7 mg/kg and a maintenance infusion of 1 to 4 mg/min (20 to 50 μg/kg/min for children).

Lidocaine and other amide class anesthetics undergo extensive liver metabolism, primarily via glucuronidation, though metabolites do not contribute significantly to clinical or toxic effects. The plasma elimination half-life of lidocaine ranges from 1.5 to 2.0 hours, and the elimination half-lives of metabolites are 3 and 5 hours, respectively. Only 5% to 10% of the parent drug is excreted unchanged into the urine. High concentrations of lidocaine

metabolites may produce toxic effects even when serum lidocaine concentrations are low. The risk of lidocaine toxicity is increased in patients with hepatic dysfunction, congestive heart failure, and shock as a result of alterations of metabolism, hepatic blood flow, and volume of distribution. Because of changes in the volume of distribution, lidocaine serum levels may be 30% higher in patients with congestive heart failure.

CLINICAL PRESENTATION

The onset of symptoms following acute oral antidysrhythmic overdose usually occurs within 4 hours and often occurs within 1 to 2 hours. However, drug absorption may continue for many hours following the ingestion of massive amounts, sustained-release preparations, or agents with anticholinergic effects. Delayed onset of toxicity is characteristic of amiodarone overdose.

Extracardiac manifestations of acute toxicity include dizziness, visual disturbances, psychosis, anticholinergic symptoms (disopyramide), hypoglycemia (disopyramide), hyperglycemia (encainide), hypokalemia, and hypersensitivity reactions (e.g., fever, rash, urticaria). Thrombocytopenia and a lupus-like syndrome (arthralgias, fever, myocarditis) with antinuclear antibodies have been well documented during chronic quinidine and procainamide therapy. Chronic amiodarone use is associated with numerous adverse effects, including corneal microdeposits, photosensitivity, hepatic dysfunction, myopathy, pulmonary fibrosis, hypo- or hyperthyroidism, and peripheral neuropathies. Dronedarone is considered less toxic than amiodarone, though adverse effects include nausea, vomiting, diarrhea, rash, and photosensitivity.

Hypotension, bradycardia, CNS depression, seizures, metabolic acidosis, and CV collapse can occur in severe poisoning. Seizures appear to be more prevalent with class IC drugs. Clinical effects associated with quinidine include seizures, immune-mediated hemolytic anemia, syncope, and cinchonism. Syncope is caused primarily by torsade de pointes but may also be associated with adrenergic blockade (orthostasis) or, rarely, idiosyncratic reactions.

Cinchonism (see Chapter 315) is associated with chronic therapy and does not appear to be dose-related. Procainamide and quinidine predictably produce hypotension if given too rapidly by IV infusion. Death can result from refractory dysrhythmias or CV collapse.

Disturbances in cardiac conduction and rhythm are the electrocardiographic (ECG) hallmarks of antidysrhythmic-agent poisoning. Excessive prolongation of the QT interval is almost always present in severe poisoning. With class IA and IC agents, this is from prolongation of the QRS interval, whereas with class III agents, it is caused by QT prolongation. In general, an increase of the QRS or QT interval by 25% is considered therapeutic, and widening by 50% or more suggests toxicity. The PR interval may also be prolonged, if there is sinus activity. Conduction disturbances and myocardial depression contribute to a host of supraventricular and ventricular dysrhythmias, including sinus bradycardia, atrioventricular dissociation, VT or fibrillation, slow idioventricular rhythm, and asystole. Torsades de pointes is a triggered (early after depolarization) polymorphous VT resulting from excessive QT prolongation, most commonly associated with class IA and class III drugs (e.g., quinidine, amiodarone, dofetilide, ibutilide).

All antidysrhythmic drugs can aggravate existing dysrhythmias or induce new ones in patients being treated for supraventricular or ventricular dysrhythmias (i.e., antidysrhythmics may be proarrhythmic) (3). The incidence of proarrhythmia is estimated at 5% to 20% and most often occurs with initiation of therapy or a dosage increase (4). Dysrhythmias should always be suspected in patients on antidysrhythmic drugs who present with syncope.

The correlation of serum levels with clinical effects depends on previous exposure to the drug, the presence of heart disease, and the degree of absorption, metabolite formation, and elimination. In general, serum levels exceeding 7, 8, and 15 μg/mL for quinidine, disopyramide, and procainamide, respectively, should be considered toxic. Lower levels may result in toxicity in patients who ingest other CV agents. Patients on chronic therapy who take an acute overdose appear to be at greater risk for severe intoxication.

Lidocaine toxicity involves the CNS and the CV system and can result from all routes of administration, but most frequently occurs during IV infusion. CNS effects have been reported in up to 47% of patients receiving IV lidocaine. Initial symptoms, such as lightheadedness, dizziness, drowsiness, and euphoria, may occur at therapeutic concentrations. At higher concentrations, more serious symptoms include confusion, hearing loss, dysarthria, visual disturbances, ataxia, agitation, and muscle twitching, which may lead to seizures and coma. Seizures may be prolonged. CV toxicity is rare and usually occurs from rapidly administered IV infusions. When serum concentrations are >11 μg/mL, the refractory period is decreased, automaticity and myocardial contractility are depressed, and hypotension and bradycardia ensue. Conduction abnormalities include sinus bradycardia, atrioventricular block, complete heart block, and sinus arrest. Conduction defects are more common in patients with preexisting bundle-branch abnormalities.

Mucosal lidocaine absorption bypasses hepatic first-pass metabolism, making lidocaine more bioavailable than by intestinal absorption. Seizures have occurred in children following mucosal application of 2% to 4% viscous lidocaine. Therefore, topical or oral lidocaine for the treatment of painful oral lesions in children should be used cautiously, if at all.

Seizures have also occurred following lidocaine infiltration. During laceration repair, the total dose for infiltration of lidocaine without epinephrine should not exceed 4.5 mg/kg, or 7.0 mg/kg of lidocaine with epinephrine. The standard 1% lidocaine solutions contain 10 mg/mL of lidocaine; thus, the maximal volumes used for local infiltration in a 70-kg adult patient are roughly 30 mL without epinephrine and 50 mL with epinephrine. Fortunately, most wounds repaired in the emergency department (ED) only require small volumes of anesthetic.

The neurologic and cardiac toxicities of other local anesthetics are similar to that of lidocaine. For example, patients referred to the ED from dental offices often have CNS toxic effects as a result of injection of procaine or other local anesthetics for dental procedures. Several local anesthetics, particularly benzocaine, have

also been reported to cause methemoglobinemia (see Chapter 335). Benzocaine is found in over-the-counter infant teething gels and adult oral anesthetics and is also used as a topical anesthetic to aid in endotracheal or gastric intubation and various endoscopic procedures.

DIFFERENTIAL DIAGNOSIS

Similar bradyarrhythmias may be caused by β-blockers, calcium antagonists, cholinergic agents (carbamate and organophosphate insecticides), digitalis, clonidine, lithium, and cyclic antidepressants. QRS and QT interval prolongation may result from poisoning with antihistamines, phenothiazines, cyclic antidepressants, lithium, hypermagnesemia, and hyperkalemia. Ventricular tachyarrhythmias may occur with sympathomimetics.

Stimulants, hypoglycemia, hypoxia, and metabolic disturbances should be considered in the differential diagnosis of patients with CNS manifestations. Patients presenting with apprehension, anxiety, or other neurologic symptoms after very recent dental work, medical procedures on the upper aerodigestive tract, or wound repair would strongly suggest the possibility of local anesthetic toxicity. Methemoglobinemia should be considered in a patient who becomes cyanotic and is responding poorly to oxygen therapy after exposure to local anesthetics.

ED EVALUATION

The history should include the exact product, strength (immediate or sustained release), the amount ingested, the time ingested, and treatment before arrival. Any history of CV disease should be elucidated. Mechanisms for chronic toxicity, such as excessive dosing, exacerbation of congestive heart failure, or change in renal function, should be investigated.

The physical examination should focus on vital signs, with attention to CV stability and respiratory and neurologic status. An ECG should be obtained as soon as possible to check for conduction delays and dysrhythmias. In most patients with local anesthetic

toxicity, an extensive metabolic workup will not be necessary. Patients suspected of having toxicity from antidysrhythmic drugs are often taking these agents therapeutically and often have significant underlying disease. For them, laboratory evaluation should include a blood-glucose level; electrolyte analysis; blood urea nitrogen, creatinine, and magnesium measurement; liver-function tests; and appropriate serum drug levels, if available. Chest radiography and blood-gas analysis are added for patients with depressed levels of consciousness or serious dysrhythmias. If suspected, venous or arterial blood should be sent for a methemoglobin level.

KEY TESTING

- ECG for all patients with antidysrhythmic poisoning
- Poisoned patients need serum electrolytes measured, renal- and hepatic-function tests
- Serum drug levels (if available) can be helpful

ED MANAGEMENT

Advanced life-support measures should be instituted as necessary. All patients suspected of antidysrhythmic drug toxicity should have IV access, continuous cardiac monitoring, and pulse oximetry. Unstable patients need close hemodynamic monitoring, supplemental oxygen, and airway management as indicated clinically. Acid–base, electrolyte, and magnesium derangements should be corrected. Potassium should be replaced cautiously, because hypokalemia may protect against cardiotoxicity from quinidine (and possibly other agents). Seizures are treated with standard doses of IV benzodiazepines and barbiturates.

Hypotension is initially treated cautiously with IV normal saline. Infusions of sodium bicarbonate can reverse hypotension associated with class IA and IC drugs. Hypotension refractory to volume expansion may require the use of direct-acting vasopressors or inotropes (epinephrine, norepinephrine, dopamine), aortic balloon counterpulsation, or cardiopulmonary-bypass (CPB) pump support.

Sodium bicarbonate (2 mEq/kg IV bolus) should be given to patients with hypotension, prolonged QRS intervals, premature ventricular contractions (PVCs), and monomorphic VT if class I antiarrhythmic toxicity is suspected. Sodium bicarbonate has beneficial effects by increasing the serum sodium level to help offset the sodium channel blockade, by increasing serum-protein binding (e.g., decreasing free drug) in a more alkalotic serum, and by driving drugs off the sodium channels. Symptomatic bradycardia or atrioventricular dissociation will probably require ventricular pacing if there is inadequate response to atropine and sodium bicarbonate. Successful pacemaker capture may require concomitant epinephrine therapy.

After sodium bicarbonate, lidocaine is the drug of choice for ventricular ectopy (except, of course, for patients with lidocaine toxicity). Other antidysrhythmic drugs in the same class are contraindicated for treatment of dysrhythmias. Torsade de pointes usually responds to isoproterenol infusion (1 to 6 μg/min) and atrial or ventricular overdrive pacing; a heart rate of 150 beats/min is usually required. IV magnesium sulfate (1 to 4 g in several minutes to 1 hour, depending on the hemodynamic stability) may also be effective.

Recent animal studies and human case reports suggest that intravenous lipid emulsion (ILE) may be effective and potentially life-saving in patients with refractory cardiotoxicity associated with local anesthetics (5). Most evidence exists for bupivacaine toxicity, though there are case reports of success following overdose of other local anesthetics including lidocaine. Although the optimal dose remains undefined, a 1.5-mL/kg bolus infusion of 20% lipid emulsion followed by 0.25 mL/kg/min for 30 to 60 minutes is generally recommended. An additional bolus can be considered for continued asystole, though total doses exceeding 10 mL/kg are not recommended. The mechanism of action of ILE is unclear but possibilities include (1) providing an intravascular “lipid sink” to pull drug from receptors, (2) providing an energy source for cardiac myocytes, or (3) activation of calcium and potassium channels by fatty acids (6). Patients in cardiac arrest have been successfully

resuscitated following treatment with ILE. Patients with anesthetic-induced symptomatic methemoglobinemia can be treated with methylene blue (as described in Chapter 335).

Once the patient has been stabilized, activated charcoal should be given to decontaminate the GI tract in awake patients with recent ingestions. Patients whose vital signs can be supported during endogenous drug elimination usually recover fully. Efforts to enhance elimination of these compounds have had variable success. Patients should be adequately hydrated to maintain renal perfusion. In the presence of renal failure, hemodialysis can increase the clearance of NAPA fourfold and that of procainamide twofold.

CRITICAL INTERVENTIONS

- Establish IV access, initiate cardiac monitoring:
- 12-lead ECG in patients with potential toxicity from antidysrhythmic agents or local anesthetics.
- Administer sodium bicarbonate to patients with hypotension, prolonged QRS interval, PVCs, and monomorphic VT as a result of class I antiarrhythmic poisoning.
- Administer magnesium sulfate IV, and induce sinus tachycardia with isoproterenol or overdrive pacing in patients with torsade de pointes.
- Consider intravenous lipid therapy for CV collapse due to local anesthetic toxicity.

DISPOSITION

Patients with local anesthetic exposures can be discharged once free of neurologic and cardiac toxic effects, often within just a few hours. Those with persistent CNS symptoms or an abnormal ECG should be admitted to a monitored setting.

Patients who remain asymptomatic and have a normal ECG, 6 hours following antidysrhythmic agent ingestions can usually be safely discharged. A 12-hour observation period is recommended if a sustained-release preparation is involved. Patients with amiodarone overdose should be admitted for prolonged observation.

Patients who are symptomatic or exhibit ECG evidence of cardiotoxicity from either acute or chronic intoxication need admission to a monitored bed. Those patients with CV instability should be admitted to an intensive care unit. Patients with severe toxicity should be admitted to a facility with cardiopulmonary bypass and aortic balloon counterpulsation capabilities. Patients with an intentional overdose should undergo psychiatric evaluation before discharge.

Common Pitfalls

- Failure to appreciate that severe toxicity can result from therapeutic doses of antidysrhythmic agents.
- Failure to consider the possibility of drug-induced dysrhythmias as a cause of syncope and weakness in patients taking antidysrhythmic agents.
- Failure to appreciate that drug-induced dysrhythmias may resemble the ones for which the drug was prescribed; thus, drug levels should be checked before further drug treatment.
- Failure to check the dose and concentration of local anesthetic solutions and to adhere to recommended dosing guidelines.
- Failure to use cardiac monitoring on patients receiving IV regional local anesthetics and large doses of local anesthetics by infiltration.
- Failure to appreciate that local anesthetics can cause both CNS excitation and depression.
- Failure to warn patients and parents of children that multiple doses of oral viscous lidocaine can be toxic and that the preparation should not be swallowed.

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CHAPTER 322

Centrally Acting Antihypertensive Agents

Susan E. Farrell

The centrally acting antihypertensive agents include the first-generation agents: clonidine, guanabenz, guanfacine, methyldopa, and reserpine; and the second-generation agents: moxonidine and rilmenidine. All of these agents reduce blood pressure through their central inhibition of sympathetic tone mediated by their agonist activity at α_2-adrenergic and I_1-imidazoline receptors in the nucleus tractus solitarii of the rostral ventrolateral medulla. The ultimate effect of their actions at these central vasomotor centers is a reduction of catecholamine concentrations and diminished autonomic sympathetic outflow from the central nervous system (1–3).

The first-generation agents are associated with a greater number of adverse effects due to their activity at both the α_2-adrenergic and the I_1-imidazoline receptors. In contrast, moxonidine and rilmenidine are selective for the I_1-imidazoline receptor, which limits their adverse effects. These findings suggest that the centrally mediated antihypertensive effects of these drugs are likely at the I_1-imidazoline receptor, in cooperation with some activity at the α_2-adrenergic.

Clonidine, the prototypical first-generation centrally acting antihypertensive agent, is an imidazoline derivative first synthesized in 1962 as a topical nasal decongestant. Clonidine is available in oral formulations, combination preparations, a transdermal patch,

and as intravenous solution. It is a component of multidrug antihypertensive therapy in patients with comorbidities such as diabetes mellitus or acute renal failure, in patients with sympathetically driven forms of hypertension, and for the treatment of perioperative hypertension. Clonidine has also been used as adjunctive therapy for heart failure and chronic pain syndromes, in migraine prophylaxis, in treatment of posttraumatic stress disorders, and for menopausal flushing (2). Clonidine is used to ameliorate the symptoms of alcohol, narcotic, nicotine, and γ-hydroxybutyrate (GHB) withdrawal and has increasingly become second-line therapy for attention-deficit hyperactivity disorders and Tourette syndrome (4).

Reports of fatal toxicity as a result of clonidine overdose are rare. A 7-year retrospective study of >10,000 pediatric clonidine poisoning exposures found major effects in only 2% of the children, including 23 cases of respiratory arrest and 1 fatality (4). However, the incidence of clonidine exposure and potential toxicity is increasing in children, associated with a greater prevalence of its use for pediatric behavioral problems (4–6).

Moxonidine and rilmenidine are structural analogs of clonidine, but more selective in their effect; available in other countries but not yet in the United States. In addition to their antihypertensive effects, these agents may also be beneficial in the management of metabolic syndrome (7). Both agents have long durations of action (up to 24 hours), and dose adjustment is necessary in renal insufficiency. These drugs are contraindicated in patients who are taking monoamine oxidase inhibitors (2). Moxonidine is contraindicated in the setting of sick-sinus syndrome, bradydysrhythmias, and renal failure; and rilmenidine is contraindicated in severe depression and renal failure. There are no reports of overdose of these agents.

CLINICAL PRESENTATION

Signs and symptoms of toxicity of the centrally acting antihypertensive agents are similar, usually occur within 30 to 60

minutes after ingestion, and consist of bradycardia, respiratory depression, lethargy, coma, and miosis. Hypotension, hypothermia, and hyporeflexia are common signs of serious toxicity and may sometimes be delayed by several hours.

In adults, significant clinical toxicity can occur after the ingestion of 1 to 2 mg of clonidine. Children may develop serious toxicity after the ingestion of a single adult therapeutic dose of clonidine (0.1 to 0.3 mg) (8). Toxicity does not always correlate well with the amount ingested, and a specific lethal dose has not been determined.

Intermittent apnea, responsive to physical or auditory stimuli, has been noted in children, and respiratory failure requiring mechanical ventilation has been reported. Clonidine interacts with other CNS depressants, and the concomitant ingestion of these substances can aggravate CNS depression and contribute to coma.

Hypertension and hypertensive crisis have been reported in the initial phase of clonidine or methyldopa overdose. This elevation of blood pressure resolves spontaneously and is quickly and precipitously followed by hypotension.

Adverse effects of maintenance therapy with clonidine, and most of the first-generation centrally acting antihypertensives, is due to their agonist activity at central α_2-adrenergic receptors, and include sedation and dry mouth, orthostatic hypotension, fatigue, constipation, sexual dysfunction, and dizziness. These adverse effects can be prominent in elderly patients. A positive direct Coombs test develops in 10% to 20% of patients taking methyldopa, but hemolysis is seldom a clinical problem. Hypersensitivity hepatitis occurs in 6% of patients using methyldopa (2). Alternative antihypertensive agents may be safer options in patients with sinus node or atrioventricular conduction abnormalities. Skin reactions including erythema, vesiculation, and induration have been associated with transdermal patch application.

The clonidine withdrawal syndrome is characterized by symptoms consistent with excessive sympathetic autonomic activity including rebound hypertension, tachycardia, tremulousness, insomnia,

anxiety, sweating, and palpitations (2,9). Withdrawal can occur after the abrupt cessation of chronic clonidine therapy, especially after doses of >1.0 mg/d (2). A case report of abrupt clonidine withdrawal in an elderly female was associated with accelerated hypertension, tachycardia, and myocardial infarction within 24 hours (9).

The incidence of adverse effects due to moxonidine and rilmenidine is less, presumably because of their greater selectivity for I_1-imidazoline receptors compared with α_2-adrenergic receptors (7).

DIFFERENTIAL DIAGNOSIS

The presenting symptoms of poisoning with the centrally acting antihypertensive agents may be clinically indistinguishable from toxicity caused by other α_2-adrenergic and imidazoline-receptor agonists such as brimonidine, naphazoline, oxymetazoline, tetrahydrozoline, and xylometazoline, common components of topical ophthalmic or nasal-decongestant preparations.

Because of the constellation of miosis, altered mental status, and respiratory depression, toxicity is often confused with that of opioid overdose. Centrally acting antihypertensive-agent toxicity may also resemble that caused by overdose of sedative–hypnotics, β-adrenergic antagonists, calcium channel blockers, and digitalis. Hypoglycemia, sepsis, hypothermia, cerebrovascular accident, and head trauma should also be considered in the differential diagnosis.

ED EVALUATION

The evaluation of patients with known or suspected centrally acting antihypertensive-agent overdose includes continuous assessment of airway maintenance, ventilation, and cardiovascular status, including continuous electrocardiographic monitoring for bradycardia, and an evaluation to rule out concomitant trauma or nondrug-related medical abnormalities.

The diagnosis of poisoning is based on the history and clinical findings. There are no specific laboratory or clinical tests of

diagnostic value. These agents are not detected on routine drugs of abuse screens. Quantitative drug levels are unavailable in the acute clinical setting and are of no value in management. Radiographic imaging, routine laboratory tests, and toxicologic analysis are useful only to rule out or confirm concomitant pathology.

KEY TESTING

- Electrocardiogram: to evaluate bradycardia and conduction abnormalities
- Fingerstick or bedside glucose testing: to evaluate for hypoglycemia

ED MANAGEMENT

Prehospital care is supportive and consists of continuous electrocardiographic monitoring and maintenance of intravenous access. The routine administration of naloxone and evaluation or treatment for hypoglycemia are appropriate in symptomatic patients. Activated charcoal is the preferred method of gastrointestinal decontamination with early and large ingestions. In the case of clonidine transdermal patch ingestion, there may be a role for whole-bowel irrigation.

Treatment of centrally acting antihypertensive-agent overdose is primarily supportive and symptomatic. Respiratory depression and periodic apnea may require tracheal intubation and assisted ventilation. Bradycardia usually reverses with intravenous atropine, repeated if necessary, based on heart rate and blood pressure response. Hypotension usually responds to crystalloid infusion. Occasionally, vasopressors may be required and dopamine, epinephrine, and cardiac pacing are of theoretical benefit, but their use in clonidine poisoning has not been described. In the unusual case in which early, transient hypertension occurs, aggressive antihypertensive treatment should be avoided because of the potential for subsequent serious and prolonged hypotension (10). Elevated blood pressure usually requires only observation, although occasionally a short-acting titratable antihypertensive such as

nitroprusside may be warranted. Hypothermia and coma are treated with supportive care. Clinical recovery is usually noted within 24 to 48 hours. Hemodialysis, charcoal hemoperfusion, and forced diuresis are of no proven value. Because clonidine is excreted unchanged in the urine, adequate urine output should be assured.

There are no proven antidotes for centrally acting antihypertensive-agent overdose. Naloxone has been used to reverse lethargy and respiratory depression associated with these agents, but the response is inconsistent. Naloxone's use is acceptable as a therapeutic trial in patients with depressed mental status. The optimal dose of naloxone in this setting is unknown, but doses similar to those used for opioid poisoning have been suggested. Patients who are administered naloxone should be closely observed for hemodynamic deterioration and recurrent respiratory depression.

The acute symptoms of clonidine withdrawal have been treated with labetolol for control of elevated blood pressure and diazepam for tremor and agitation (9). The clonidine withdrawal syndrome is best treated by the reinstitution of clonidine therapy and tapering of the dose over 5 to 10 days. This approach can be used in the treatment of withdrawal from other similar agents.

CRITICAL INTERVENTIONS

- Establish intravenous access, and institute continuous respiratory and cardiac monitoring in patients with acute overdose or acute withdrawal.
- Keep advanced life-support airway equipment and cardiovascular drugs readily available.

DISPOSITION

Patients who remain asymptomatic 6 hours after ingestion and who have normal vital signs may be discharged from the emergency department with appropriate psychiatric or social service follow-up. Symptomatic patients require admission to a medical unit capable of continuous cardiac and respiratory monitoring. There is no known

cyclical nature to clonidine overdose, and improvement is not followed by relapse. Patients may be safely transferred to another facility with advanced life-support measures during transport.

Common Pitfalls

- Failure to appreciate that clonidine poisoning may result in severe CNS, respiratory, and cardiovascular depression.
- Misdiagnosis of clonidine poisoning as narcotic overdose because of the constellation of miosis, altered mental status, and respiratory depression.
- Overly aggressive treatment of early, transient hypertension, especially with long-acting agents.
- Reliance on unproved antidotes rather than supportive care in the treatment of toxicity.
- Failure to consider the possibility of child abuse or attempted homicide in children with overdose and to address psychiatric issues in patients with suicide attempts.

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CHAPTER 323 Beta Blockers

Fermin Barrueto, Jr.

β-Blockers competitively block β-adrenergic receptors, part of the sympathetic nervous system with three main subtypes (β_1, β_2, and β_3) that regulate physiology in various locations in the body (Table 323.1). Their blockade decreases the intracellular concentration of cyclic adenosine monophosphate (cAMP), a secondary messenger that mediates the cellular effects of β-stimulation.

TABLE 323.1

	Anatomic Location	Effect of Receptor Agonism
β_1	Heart	Increase inotropy and chronotropy
	Eye	Increase aqueous humor production
	Kidney	Increase renin secretion
β_2	Smooth muscle	Relaxation around bronchi and vasculature
	Skeletal muscle	Glycogenolysis, K^+ uptake
	Liver	Glycogenolysis and gluconeogenesis
β_3	Adipose	Lipolysis

The clinical effects of β-blockers vary with regard to β-receptor selectivity, α-receptor blocking activity, lipophilicity, intrinsic sympathomimetic (β-receptor agonist) activity, and membrane-stabilizing activity (MSA) (Table 323.2). β_1-Selectivity is preferred for cardiovascular therapy to avoid the detrimental effects of β_2-blockade, such as bronchoconstriction. Labetalol and carvedilol are β-blockers that also antagonize α-adrenergic receptors, although not as prominently as β-receptors. These medications may exacerbate

hypotension as a result of vasodilation. β-Blockers with MSA inhibit fast sodium channels, which can lead to QRS prolongation and ventricular dysrhythmias. In overdose, selective activity is often lost, and most β-blockers have similar toxicologic effects.

TABLE 323.2

	Receptor Selectivity	Lipophilicity	Intrinsic Sympathomimetic Activity	Membrane-Stabilizing Activity
Acebutolol	β_1	Low	+	++
Atenolol	β_1	Low	–	–
Betaxolol	β_1	Low	–	++
Bisoprolol	β_1	Low	–	–
Carteolol	β_1,β_2	Low	+	–
Carvedilol	α_1,β_1,β_2	High	–	–
Esmolol	β_1	Low	–	–
Labetalol	α_1,β_1,β_2	Mod	–	+
Metoprolol	β_1	Mod	–	+
Nadolol	β_1,β_2	Low	–	–
Nebivolol	β_1	Low	–	–
Oxprenolol	β_1,β_2	High	+	++
Pindolol	β_1,β_2	Mod	+	+
Propranolol	β_1,β_2	High	–	++
Sotalol	β_1,β_2	Low	–	–
Timolol	β_1,β_2	Mod	–	–

β-Blockers also vary with respect to protein binding, volume of distribution, route of elimination, and half-life (Table 323.3). They are generally well absorbed after ingestion, with peak levels and effects occurring 1 to 2 hours after a therapeutic dose. Because their duration of action is relatively short (6 hours or less), extended-release formulations were developed, to allow for less frequent dosing.

TABLE 323.3
Pharmacokinetics of α-Blockers

Agent	Dose (mg)[a]	Absorption (%)	First-Pass Metabolism	Protein Binding (%)	Distribution (L/kg)	Volume of Elimination	Route of Half-Life (hrs)
Acebutolol	200–400	70	Yes	25	2.3	Renal	6
Atenolol	50–100	50	No	15	0.7	Renal	6–9
Betaxolol	10–40	100	Yes	50	6.1	Hepatic	14–22
Bisoprolol	5–40	90	No	30–36	2.7–3.1	Hepatic	11
Carvedilol	2.5–10	>90	Yes	98	1.6	Hepatic	7–10
Carteolol	3.125–25	80	No	23–30	4	Renal	6
Esmolol	IV only	NA	NA	55	3.4	Serum esterase	0.15
Labetalol	200–400	>90	Yes	50	10.0	Hepatic	3–4
Metoprolol	50–400	>90	Yes	12	5.5	Hepatic	3–4
Nadolol	40–320	30	No	30	2.1	Renal	14–24
Nebivolol	1.25–40	Unknown	Yes	High	10	Hepatic	12
Penbutolol	20–80	100	No	80–98	32–42	Hepatic	5
Pindolol	2.5–30	>90	No	57	2.0	Renal	5–12
Propranolol	20–120	>90	Yes	93	3.6	Hepatic	3–6
Sotalol	80–480	70	No	0	0.23	Renal	5–12
Timolol	20–60	>90	No	10	1.5	Renal	4–5

[a]Single oral adult dose.

CLINICAL PRESENTATION

Most accidental β-blocker overdoses are relatively minor and do not result in significant toxicity, particularly in children (1,2). Large doses or the combination of a β-blocker with a calcium channel blocker can result in significant morbidity and mortality (2).

Bradycardia and hypotension are the most common effects after overdose (1). Nausea and vomiting can occur. Hypoperfusion can lead to lethargy, decreased mental status, stroke, myocardial infarction, mesenteric ischemia, renal insufficiency, with pale and clammy skin.

Highly lipophilic agents and those with MSA can affect the CNS directly to cause altered mental status despite a normal blood pressure. Delirium, coma, and seizures may occur in severe poisoning.

If the SA node is affected, sinus bradycardia may progress to sinus pauses or arrest. Negative inotropic effects add to cardiotoxicity, particularly with β-blockers that have MSA (3). β-Blockers that have MSA can cause delayed depolarization with QRS prolongation and ventricular tachyarrhythmias (3,4). Sotalol is unique in that it also blocks delayed rectifier potassium channels, which results in delayed repolarization with QT prolongation, and can cause torsade de pointes (polymorphic) ventricular tachycardia and other lethal ventricular dysrhythmias (5).

In overdose, all β-blockers can cause β_2-antagonism that leads to bronchospasm. This scenario may be more prominent and dangerous in patients with asthma or chronic obstructive pulmonary disease (1). Hypoglycemia and hyperkalemia are common, although they are usually mild and not clinically significant (1). Hypoglycemia may be more common in children.

DIFFERENTIAL DIAGNOSIS

Diseases that cause bradycardia include sick sinus syndrome, inferior wall myocardial infarction, hypothermia, and carotid sinus hypersensitivity. Other drugs that can cause bradycardia include calcium channel blockers, cardiac glycosides, cholinergic agents, α_2-agonists, opioids, and sedative–hypnotics.

Like β-blockers, diltiazem and verapamil have strong negative inotropic and chronotropic effects. Dihydropyridine calcium channel blockers (e.g., nifedipine, nimodipine, and amlodipine) typically cause reflex tachycardia in response to vasodilation and hypotension. Unlike β-blocker overdose, the mental status is often normal and calcium channel blockers cause hyperglycemia rather than hypoglycemia. Cardiac glycoside (e.g., digoxin) poisoning usually does not cause hypotension until a nonperfusing dysrhythmia occurs. Additionally, cardiac glycoside overdose produces characteristic ECG patterns.

Cholinergic agents (e.g., organophosphorus insecticides) cause diarrhea, lacrimation, urination, miosis, and vomiting along with bradycardia, bronchorrhea, and bronchoconstriction. Overdose with opioids, sedative hypnotics, and α_2-agonists may lead to mild bradycardia and hypotension associated with a depressed mental status, but cardiac conduction disturbances are rare.

ED EVALUATION

The history should include the time and amount of drug(s) taken, treatment in the field (if any), the time of onset and nature of symptoms, known medical or psychiatric problems, and current drug therapy. Determining whether the β-blocker is a sustained-release

preparation or if there were any co-ingestants with cardiovascular effects is particularly important.

The physical examination should focus on the vital signs, cardiopulmonary system, and neurologic status. Continuous cardiac monitoring and a 12-lead ECG may reveal AV nodal dysfunction with PR interval prolongation and AV block (4). A fingerstick or serum glucose concentration should be obtained, particularly with an abnormal mental status. Blood gases, chemistry panel to check for hypokalemia, complete blood count, acetaminophen level, toxicology testing, and chest radiograph (CXR) should be obtained when clinically indicated.

KEY TESTING

- ECG (which may be repeated) in patients with changes in heart rate, intervals, or dysrhythmia
- Glucose and potassium should be monitored in symptomatic patients
- Complete blood count, chemistries, CXR, and other laboratory testing as needed for supportive care

ED MANAGEMENT

Advanced cardiac life-support measures should be instituted as needed. Activated charcoal should be considered if ingestion occurred within 1 hour. If a sustained-release preparation has been ingested, activated charcoal can still be considered even later than an hour after ingestion.

Patients with bradycardia with normal blood pressure need only close monitoring. For bradycardic and hypotensive patients, a stepwise approach is recommended in which interventions, each employed to a maximal degree, are successively applied and the hemodynamic response assessed. In severely poisoned patients, multiple therapies must be instituted and maintained simultaneously. Hypotension can initially be treated with intravenous fluids. If bradycardia is also present, atropine, 1 mg intravenously (0.02 mg/kg; minimum dose, 0.1 mg in children), repeated in 5 minutes as

necessary, can be given but is frequently ineffective in β-blocker overdose.

Glucagon (5 mg intravenously over 5 minutes; 50 to 100 μg/kg in children) may be effective for hypotension, even in the absence of bradycardia. If there is no effect after 10 to 15 minutes, the dose should be repeated. Patients who respond should be given an infusion of glucagon at a rate of 1 to 5 mg/hr (50 μg/kg/hr in children). Glucagon bypasses the β-blockade by activating a G-protein bound to adenylate cyclase and also activating the cascade indirectly to increase intracellular cAMP (Fig. 323.1). Because glucagon often causes vomiting, prophylactic anti-emetics may be useful. Although there are no human controlled trials, animal studies show that glucagon has a positive chronotropic effect in β-blocker overdose but a minimal effect on mean arterial pressure (6).

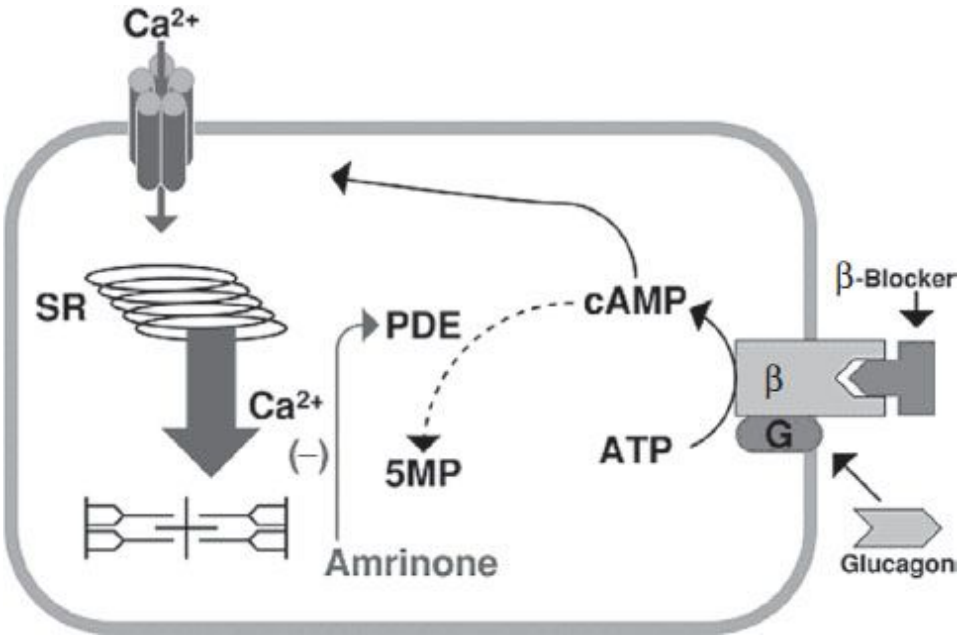

FIGURE 323.1 The effects of amrinone and glucagon on cAMP. Extracellular Ca^{2+} influx will cause the SR (sarcoplasmic reticulum) to release Ca^{2+} exponentially to bind the excitation–contraction apparatus, made of actin and myosin filaments. cAMP increases intracellular Ca^{2+} and is created by an adenylate cyclase that is part of the β-receptor and broken down by PDE (phosphodiesterase). Glucagon can activate the G protein, bypass the β-receptor if

blocked, and increase cAMP. Amrinone inhibits PDE, thus also increasing cAMP. (FIGURE by Walter Barrueto.)

Intravenous calcium assists with inotropy in animals (7) and in reversing hypotension in humans (8,9). The dose is the same as for calcium channel blocker poisoning (see Chapter 324). Vasopressors are often necessary. There is no human data to show which pressor is more efficacious than another, so dobutamine, epinephrine, and dopamine have all been used, but the required dose is often much higher than what is traditionally used (1). Invasive cardiac monitoring or echocardiography can help to identify the agent that brings the best response and to titrate to the desired effect.

If the patient requires vasopressors, hyperinsulinemia–euglycemia (insulin and glucose) therapy has been anecdotally effective (10,11). The same protocol as in calcium channel blocker poisoning (see Chapter 324) should be used. In canine propranolol poisoning, this therapy was superior to glucagon and epinephrine (12). Hyperinsulinemia–euglycemia therapy may work by maximizing myocardial glucose utilization, augmentating cytosolic calcium concentrations, or possibly through a direct inotropic effect (12). The response may be delayed 15 to 60 minutes, so other therapies must be continued.

A phosphodiesterase inhibitor such as amrinone is of theoretical benefit but has propensity to cause vasodilation, is difficult to titrate, and often does not improve the bradycardia seen in β-blocker exposure (see Fig. 323.1) (6). This treatment is controversial and not recommended. If a lipophilic β-blocker is involved or if the patient is hemodynamically unstable or critical, one can consider using 1.5 mL/kg of 20% lipid emulsion as a single bolus with an option to repeat the bolus. This has been effective with local anesthetics and overdoses involving lipophilic drugs like verapamil and propranolol (13).

Should pharmacologic therapy be ineffective, intravenous cardiac pacing can be used to treat bradycardia; however, it is likely that there will be little improvement in cardiac output, and difficulty with capture is common. Some authors have reported a decrease in blood

pressure, which may be caused by loss of atrial contraction and/or impaired ventricular relaxation. Intra-aortic balloon pump counterpulsation and partial or complete cardiac bypass pump support have been used in severe poisoning (14). Hemodialysis has been used with apparent success for atenolol and sotalol overdose; charcoal hemoperfusion might be effective for water-soluble β-blockers that have a low volume of distribution like atenolol and acebutolol (15,16). Patients who might benefit most from extracorporeal elimination measures are already hypotensive, making these procedures technically difficult and potentially hazardous. Continuous veno-venous hemodialysis is another alternative, but has never been studied.

In patients with sotalol poisoning, hypokalemia and hypomagnesemia should be corrected. The treatment of recurrent torsade de pointes includes overdrive pacing and magnesium infusion (5). Bradycardia and hypotension are treated the same as with other β-blockers.

CRITICAL INTERVENTIONS

- Treat with intravenous fluids for hypotension.
- If hypotension and bradycardia persist, use glucagon, calcium, and high-dose pressors.
- Hyperinsulinemia–euglycemia therapy should be considered if the patient remains unstable.
- Consider transvenous pacing, intra-aortic balloon pump, or extracorporeal circulatory support measures for patients who have not responded to other treatment modalities.
- Certain β-blockers (e.g., atenolol, sotalol) are amenable to hemodialysis or hemoperfusion.

DISPOSITION

Patients with β-blocker ingestions who remain or become asymptomatic 6 hours after ingestion can be discharged or medically cleared for a psychiatric disposition (2,3). If sotalol or a sustained-release preparation is ingested, a 12- to 24-hour observation period

is recommended since sotalol has produced symptoms, QT prolongation, and other dysrhythmias up to 20 hours from the time of ingestion (5). With extended-release preparations, prolonged and erratic absorption may result in delayed toxicity. Patients with abnormal vital signs, mental status, or ECG findings require continuous cardiac monitoring and frequent vital signs. This usually requires admission to an intensive care unit. The hospital's supply of glucagon should be ascertained, as many pharmacies are not prepared to administer the large doses required to treat β-blocker exposures. Transfer of the patient to a tertiary care facility should be considered in cases of severe poisoning where intra-aortic balloon pump or other advanced therapies are available. Psychiatric consultation should be obtained for patients with intentional ingestions prior to discharge. Education in poison prevention, particularly in children, should also be provided prior to discharge.

Common Pitfalls

- Failure to determine whether the drug ingested was an immediate- or extended-release formulation, potentially leading to undertreatment and inappropriate disposition.
- Failure to check a fingerstick blood glucose, as β-blockers can cause hypoglycemia.
- Failure to appreciate that β-blockers with MSA can cause delayed depolarization, cardiac conduction disturbances (QRS prolongation), and ventricular tachyarrhythmias.
- Failure to anticipate seizures with lipophilic β-blockers such as propranolol.
- Failure to appreciate that sotalol blocks potassium channels, causing a prolonged QT interval and torsade de pointes, and has late presenting symptoms.
- Failure to plan for severe poisonings that are likely to require invasive monitoring, multiple pharmacologic treatments, and mechanical hemodynamic support.

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of Linda Kesselring and Christopher H. Linden to previous editions of this chapter.

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CHAPTER 324 Calcium Channel Antagonists

Matthew D. Sztajnkrycer

Calcium is critical for cellular function, involved in diverse processes including myocyte excitation–contraction coupling, intracellular second-messenger signaling, release of neurotransmitters and hormones, and initiation and propagation of the action potential. Intracellular calcium is largely sequestered within the sarcoplasmic reticulum and released through direct receptor activation or through second-messenger–mediated systems. Calcium channels are found in the membranes of many cells, including vascular smooth muscle, the myocardium, and the specialized pacemaker and conducting fibers of the heart. Three general classes of calcium channel have been identified, based on mechanism of activation: (1) voltage-operated calcium channels (VOCCs), (2) receptor-operated calcium channels, and (3) second-messenger–operated calcium channels.

Calcium channel antagonists (CCAs) are a structurally diverse group of drugs used in the treatment of supraventricular tachyarrhythmias, hypertension, angina, heart failure, and subarachnoid hemorrhage and in the prevention of migraine headaches. Eleven CCAs are currently approved by the US Food and Drug Administration for use in the United States (Table 324.1); verapamil and amlodipine possess pediatric FDA approval. All act by depressing the activation, inactivation, and recovery of the L-type VOCC, and are thus classified as class IV antiarrhythmics. Cardiovascular (CV) responses to therapeutic doses vary considerably (see **Tables 324.1** and **324.2**).

TABLE 324.1
Therapeutic Doses of Calcium Channel Blockers

Drug	Trade Name	Usual Dose	Therapeutic Range
Verapamil	Calan, Isoptin, Verelan		
Oral		80–160 mg tid	15–100 ng/mL
Intravenous		5–10 mg	
Diltiazem	Cardizem, Dilacor	30–90 mg qid	30–130 ng/mL
Nifedipine	Adalat, Procardia	10–40 mg tid	25–100 ng/mL
Nicardipine	Cardene	20–40 mg qid	28–50 ng/mL
Nimodipine	Nimotop	60 mg q4h	7–96 ng/mL
Felodipine	Plendil	5–20 mg qd	0.7–8.0 ng/mL
Isradipine	DynaCirc	2.5–10.0 mg bid	2–8 mg/mL
Nisoldipine	Sular	20–40 mg qd	
Amlodipine	Norvasc	2.5–10.0 mg qd	5–15 mg/mL
Clevidipine	Cleviprex	Initial dose 1–2 mg/hr; maintenance 4–6 mg/hr	
Bepridil	Vascor (no longer available in US)	200–400 mg qd	

TABLE 324.2
Cardiovascular Response to Drug Therapy

	Verapamil	Diltiazem	Nifedipine and Other Dihydrophyridines	Bepridil
Heart rate (sinoatrial node)	⇑ or ⇓	⇓	⇑	⇓
Atrioventricular nodal conduction	⇓⇓	⇓	⇑	⇓
Smooth-muscle tone	⇓⇓	⇓	⇓⇓⇓	⇓
Blood pressure	⇓	⇓	⇓⇓	⇓
Contractility (in vivo)	⇓⇓	⇓	⇑ or ⇓	⇓

CCAs are well absorbed after oral administration. With immediate-release preparations, effects are noted within 2 to 3 hours of oral administration. Effects of sustained-release preparations may be delayed 6 to 8 hours and are reported as long as 15 hours after ingestion. CCAs are 80% to 98% protein-bound, have a moderate

volume of distribution (1.4 to 4.3 L/kg), are extensively metabolized by the liver, and are excreted in the urine and bile. Verapamil, diltiazem, and bepridil have active metabolites.

The CCA toxicology experience is based primarily on four agents: Verapamil, diltiazem, nifedipine, and amlodipine. Nicardipine, felodipine, nisoldipine, isradipine, and nimodipine are members of the same class as nifedipine and amlodipine (dihydropyridines) and have similar toxicity. Clevidipine, approved in 2008, is an intravenous short-acting dihydropyridine. Bepridil is a unique agent, with sodium and potassium channel antagonism in addition to CCA effects. Toxic CV effects of CCAs are in large part an exaggeration of their therapeutic effects. However, with overdose, the drug-specific effects noted in Table 324.1 are often lost (1). Though peripheral vascular resistance is always decreased, cardiac output may be normal, increased, or decreased. As only nimodipine penetrates the blood–brain barrier, central nervous system (CNS) effects are essentially due to hypoperfusion. Both hypoperfusion and impaired carbohydrate metabolism may lead to acidosis and ketosis. Impaired calcium-dependent insulin release and peripheral insulin resistance may cause hyperglycemia (2). This combination may lead to a diabetic ketoacidosis-like picture.

CCAs are considered so toxic that “one pill can kill” in the pediatric population. Death has been reported in a child after ingestion of a single tablet of nifedipine. The elderly are susceptible to toxicity at lower doses (3). Toxicity can also be seen when taken in therapeutic doses with other myocardial depressants, such as β-adrenergic antagonists and quinidine-like agents.

CLINICAL PRESENTATION

Signs and symptoms of toxicity include hypotension and bradycardia, but reflex tachycardia has been reported, especially with dihydropyridine ingestion. Inadequate perfusion may result in myocardial, cerebral, renal, and bowel ischemia or infarction. In severe cases, coma, seizures, and respiratory distress associated with cardiogenic and noncardiogenic pulmonary edema are described.

Toxic effects typically last 24 to 36 hours but may be longer with bepridil, amlodipine, and sustained-release preparations.

DIFFERENTIAL DIAGNOSIS

Myocardial infarction and overdose of β-adrenergic antagonists, cardiac glycosides, clonidine, guanabenz, imidazolines, angiotensin converting enzyme inhibitors, cholinergic agents (nicotine, organophosphate and carbamate insecticides, and agents to treat myasthenia gravis), tricyclic antidepressants (TCAs), alpha-methyldopa, and veratrum alkaloids may present similarly to those with CCA ingestion.

β-Adrenergic blocking agents are more likely to cause hypoglycemia, and CCAs are more likely to cause hyperglycemia. With cholinergic agents, salivation, nausea, vomiting, diarrhea, and weakness dominate the presentation. TCA toxicity infrequently presents with heart block and bradycardia. Although both TCA and CCA ingestions may result in prolonged QRS complexes (the latter as a result of ventricular escape rhythms), TCA-intoxicated patients often manifest evidence of antimuscarinic toxidrome and CNS depression in normotensive or hypertensive patients (see Chapter 339, “Cyclic Antidepressants”).

ED EVALUATION

The history should include time of ingestion and identification of other substances ingested or available to the patient. Physical examination should focus on cardiopulmonary and CNS status. Continuous peripheral and pulmonary artery pressure monitoring may be necessary in patients with hemodynamic compromise.

Laboratory abnormalities are nonspecific and may include metabolic acidosis and hyperglycemia. Serum drug levels are not readily available and are not useful in the management of these patients. The electrocardiogram (ECG) often shows decreased rate and first-, second-, or even third-degree AV block and may have changes indicative of ischemia or infarction (Fig. 324.1) (3). QT-prolongation and torsades de pointes may be noted with bepridil ingestion. Chest radiography may show pulmonary edema.

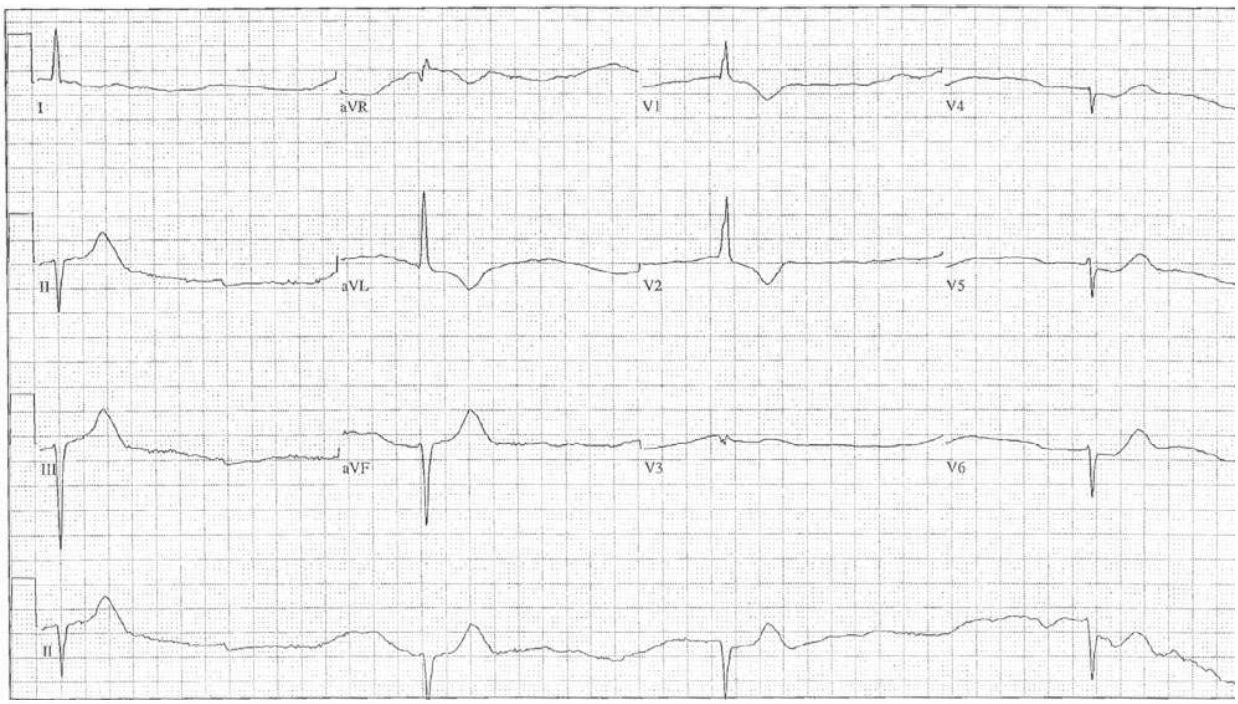

FIGURE 324.1 Initial electrocardiogram of a patient presenting after sustained-release verapamil ingestion. Findings include complete heart block with severe bradycardia and repolarization abnormalities.

KEY TESTING

- ECG and cardiac monitoring
- CXR for pulmonary edema
- No drug levels are useful; routine laboratory studies might be helpful for general supportive care

ED MANAGEMENT

Supportive care, activated charcoal, and advanced life-support measures should be initiated as necessary. Intravenous access should be established in all patients. Whole-bowel irrigation (WBI) is recommended for ingestions of sustained-release preparations, especially in patients presenting early. Smooth muscle relaxation may result in an ileus, limiting the utility of WBI. Mild hypotension may respond to a fluid challenge with 1 to 2 L of saline solution (10 to 20 mL/kg in children). When bradycardia, with or without AV

block, is also present, atropine (1.0 mg IV, 0.02 mg/kg in children) can be tried. Response is infrequent but may be improved after calcium administration (3). Patients with hypotension and concomitant symptomatic bradycardia or conduction defects should receive either calcium chloride (1 g IV slow push; 10 to 20 mg/kg in children) or calcium gluconate (3 g IV slow push; 30 to 60 mg/kg in children). This dose may be repeated every 5 to 15 minutes up to three times in patients who show incomplete, transient, or absent response (4). Calcium chloride extravasation can result in severe tissue damage, so limit calcium chloride use to central venous administration whenever possible. Owing to the short-lived effects of intravenous calcium, a continuous infusion at a rate of 0.2 to 0.4 cc/kg/hr (10% calcium chloride) or 0.6 to 1.2 cc/kg/hr (10% calcium gluconate) may be used to support heart rate and blood pressure in patients who respond to an initial bolus (5). Although calcium is frequently ineffective, proponents argue that this is a result of inadequate dosing. Doubling of serum calcium concentration was associated with significant hemodynamic improvement in both animal models and human cases. An ionized calcium concentration of 2 mmol/L has been suggested as a target level (6).

No single pressor agent has been consistently effective. Dopamine, dobutamine, norepinephrine, isoproterenol, alone or in combination, have been used with mixed success. Glucagon may also be of benefit for hypotension, but it should not be used until the effects of traditional pressors are optimized. Acidemia must be corrected, as it impairs the function of L-type VOCCs, enhances the toxic effects of some agents (e.g., verapamil), and decreases the efficacy of calcium. A swine model of verapamil toxicity demonstrated improved myocardial contractility and cardiac output with sodium bicarbonate administration (7).

The pharmacologic management of patients who fail to respond to these therapies remains controversial. Although strong evidence-based data are lacking, most toxicologists advocate the early, aggressive use of hyperinsulinemia-euglycemia (HIE) therapy in patients who show an inadequate response after initial fluid

resuscitation, atropine, and calcium administration. Insulin, used as part of HIE therapy, improves hemodynamics and survival and has reversed catecholamine-unresponsive shock in both animals and in case reports (5,8,9). Insulin has positive inotropic effects in conditions of myocardial stress without increasing myocardial oxygenation demand. During myocardial stress, the metabolism of myocardial cells is shifted away from fatty acid oxidation, toward carbohydrate dependence, improving the efficiency of energy biomechanics. In cases of severe CCA toxicity, hyperglycemia is frequently noted. The etiology is multifactorial, reflecting both impaired insulin release and peripheral resistance (2). The net result is that the CCA-intoxicated myocardium is further impaired secondary to limited cellular glucose uptake at a time of glucose dependence and subsequent transition back to less-desirable fatty acid metabolism. HIE is believed to reverse this impaired energy utilization state and improve myocardial glucose utilization. HIE also likely increases intracellular calcium concentrations, although this may cause only a small improvement. The failure of catecholamines and glucagon, despite initial transient improvement, may reflect catecholamine-induced increased myocardial oxygen demand and promotion of fatty acid metabolism and ketosis (5).

Although studied dosages have varied, a reasonable approach to HIE therapy is an initial intravenous bolus of 1 IU/kg regular insulin, followed by an infusion of 1 to 10 IU/kg/hr, titrated to clinical effect (systolic BP $>$90 mm Hg, HR $>$50/min) (8,9). Patients with serum glucose levels $<$200 mg/dL should receive one 50-mL ampule of 50% dextrose (0.25 g/kg in children) followed by frequent glucose measurements and supplemental glucose as required. Owing to potential insulin–mediated effects on serum potassium, patients with serum potassium concentrations $<$2.5 mEq/L should receive 40 mEq of potassium (1 mEq/kg in children; maximum, 20 to 40 mEq/dose) as an oral supplement or IV potassium, 10 to 20 mEq (0.10 to 0.30 mEq/kg in children) administered over the course of 1 hour. Serum glucose and potassium concentrations should be regularly monitored during HIE therapy, and for up to 24 hours following discontinuation.

More recently, the successful use of intravenous fat emulsion (IFE) has been reported in the management of CCA intoxication (10), especially for the more lipophilic agent verapamil. It has been suggested that IFE works at least in part by sequestering lipophilic agents, thereby decreasing distribution to target tissues and redistributing the toxic agent from the tissue into the IFE lipid medium. While controversial in the setting of CCA toxicity, current IFE dosage recommendations for the management of local anesthetic toxicity are a 1.5 mL/kg bolus of 20% IFE followed by an infusion of 0.25 to 0.50 mL/kg/min 20% IFE until hemodynamic stability. IFE use has been associated with fat emboli syndrome and is contraindicated in the setting of acute myocardial infarction, known disorders of fatty acid metabolism and egg allergy. Concern also exists for the potential of IFE as a nonspecific sequestering agent to sequester concomitantly administered antidotes.

Hemodynamically significant bradycardia or heart block unresponsive to medical therapy may require pacemaker placement. Electrical capture occurs in only 50% of patients (Fig. 324.2) (3). Heart rate was improved more than blood pressure. In hypotensive patients unresponsive to pharmacologic therapies, intra-aortic balloon counterpulsation and cardiopulmonary bypass have been successfully employed. The specific role of enhanced elimination, other than through gastrointestinal decontamination, has not been clearly defined. Based upon pharmacokinetic properties, conventional extracorporeal elimination would be expected to be of limited effectiveness. Several reports have documented the successful use of albumin dialysis with the Molecular Adsorbents Recirculating System (MARS) (1). Full recovery can be expected unless prolonged shock has resulted in irreversible end-organ damage.

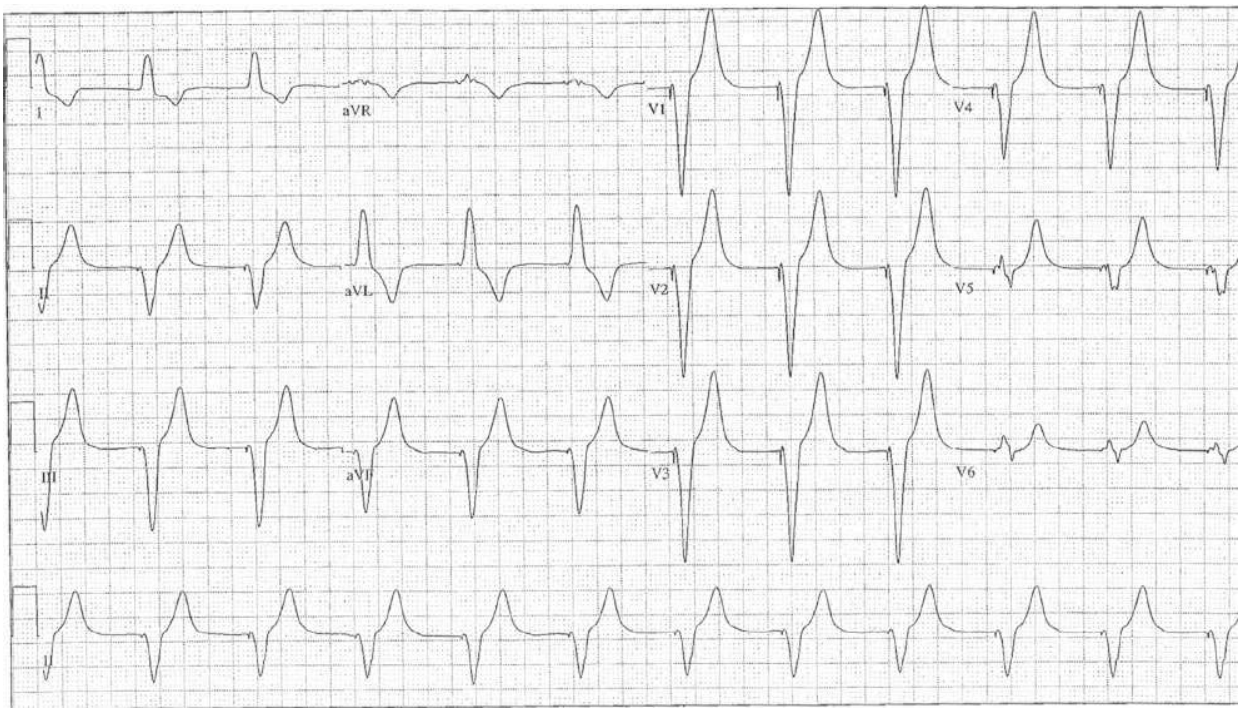

FIGURE 324.2 Follow-up electrocardiogram after emergent transvenous pacemaker placement. Note that electrical capture occurs in only 50% of patients and that blood pressure may not improve despite increased heart rate.

CRITICAL INTERVENTIONS

- Admit or observe asymptomatic patients with overdoses of sustained preparations for an extended period of time.
- Administer IV fluids, calcium, and atropine for hypotension and bradycardia.
- Initiate HIE therapy for hypotension unresponsive to fluids and calcium.
- Consider the use of IFE, especially in toxicity caused by more lipophilic agents.
- High doses of calcium may be needed for a clinical response.
- Owing to lack of consistently effective therapeutic interventions, early aggressive gastrointestinal decontamination is recommended.

DISPOSITION

Asymptomatic patients should be observed for 4 to 6 hours after ingestion of standard formulations and 18 to 24 hours after ingestion of sustained-release ones. Those who remain asymptomatic may be discharged or referred for psychiatric evaluation. Symptomatic patients should be admitted to an intensive care unit. Transfer may be necessary if an intensive care unit bed is unavailable and should be arranged as soon as the ingestion is recognized, because CV performance may rapidly deteriorate. The patient should be transferred in an advanced life-support unit with an adequate supply of CV drugs on hand. A regional poison center or a toxicologist should be consulted if the physician is unfamiliar with the management of CCA overdose.

Common Pitfalls

- Failure to consider CCA poisoning in patients with hypotension, bradycardia, or AV block, particularly when hyperglycemia is present.
- Failure to appreciate that ingestion of a single pill may be lethal in a toddler.
- Failure to consider whole-bowel irrigation and multiple-dose charcoal for patients with overdoses of sustained preparations.
- Failure to initiate aggressive HIE therapy in a timely manner.

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CHAPTER 325

Cardiac Glycosides

John S. Kashani

Cardiac glycosides (CGs) are a closely related group of chemicals having a common effect on the myocardium. CGs are found in a variety of plants, including oleander, foxglove, red squill, and lily of the valley, and in the skin, salivary glands, and venom glands of *Bufo* genus toads (Table 325.1). CGs have also been found in some herbal preparations, sometimes as an unintentional ingredient resulting from the misidentification of plants (1). The term *digitalis* is often used as a generic term referring to any substance containing CGs. Digoxin (Lanoxin, Digoxin, Digitek) is the only approved CG in the United States and is used for congestive heart failure, atrial fibrillation, atrial flutter, and paroxysmal atrial tachycardia. CGs are also being investigated as antineoplastic agents for the treatment of various cancers (2).

TABLE 325.1
Sources of Cardiac Glycosides

Genus and Species	Common Name	Part Used
Digitalis purpurea	Purple foxglove	Leaf
Digitalis lanata	Grecian foxglove	Leaf
Strophanthus kombé		Seed
Strophanthus gratis		Seed
Urginea maritima (squill)	Sea onion	Bulb
Nerium oleander	Oleander	All parts
Thevetia neriifolia	Yellow oleander	All parts
Convallaria majalis	Lily of the valley	All parts
Bufo sp	Toad	Skin

CGs inhibit the sodium potassium adenosine triphosphatase (ATPase) membrane pump in cardiac cells. Normally, depolarization follows the opening of the fast sodium channels. The rise in the intracellular potential opens voltage-gated calcium channels, causing the influx of calcium. The rise in intracellular calcium causes further calcium release from the sarcoplasmic reticulum, producing contraction. In the presence of CGs, the sodium potassium ATPase is inhibited, causing an increase in intracellular sodium which disrupts the sodium calcium counterexchange, raising intracellular calcium levels. The increase in intracellular calcium promotes interaction between actin and myosin, resulting in an increased inotropic effect. In addition to the inotropic effects, CGs increase automaticity, shorten the time for repolarization of the atria and ventricles, slow conduction through the sinoatrial (SA) and atrioventricular (AV) node, and increase vagal parasympathetic tone.

The therapeutic daily dose of digoxin ranges from about 0.005 mg/kg in premature infants to as much as 0.75 mg in adults. Digoxin is 40% to 90% intestinally absorbed, with an onset of action from 1.5 to 6 hours. The actual volume of distribution ranges from 4 to 7 L/kg in adults and 10 to 16 L/kg in children. Digoxin is 25% protein-bound, predominantly renally eliminated with a half-life upward of 1.6 days. Dosing adjustment is based on creatinine clearance, and with a decrease in the dose and frequency for renal failure patients. Therapeutic serum digoxin levels are 0.5 to 2.0 ng/mL but a serum concentration $>$2.0 ng/mL measured at least 6 hours postingestion may indicate CG toxicity. High blood levels occur early after ingestion, before the drug has had time to distribute to tissues. After an acute ingestion, before distribution occurs, a level will only verify that ingestion has occurred but does not predict the degree of clinical toxicity (3).

Ingestion of oleander or Bufo toxins can result in a false-positive digoxin level as a result of the partial cross-reactivity in the assay, but the measured digoxin levels do not correlate with toxicity. Other nondigoxin CGs may or may not cross react with digoxin immunoassays. A source of false-positive digoxin levels are

substances called endogenous digoxin-like steroidal substances (EDLS). These substances may be present in patients with renal insufficiency, hepatic disease, hypertension, agonal states, pregnancy, cor pulmonale, myocardial infarction, mucocutaneous lymph node syndrome, subarachnoid hemorrhage, or congestive heart failure and in both premature and full-term infants (4). Levels are usually low but have occasionally been measured >2.0 ng/mL.

Electrocardiogram (ECG) changes occur frequently but it is important to understand that, in the absence of significant dysrhythmias, ECG changes only indicate the presence of digoxin and do not correlate with toxicity. The "digitalis effect" refers to four typical ECG findings which can be seen at therapeutic levels. The earliest finding includes T-wave abnormalities, with inversion or elevation that may mimic acute ischemia or pericarditis. Peaking of the terminal of the T wave may occur. The second finding is a shortened QT interval. The third finding is scooping or sagging of the ST segment with concomitant ST-segment depression (more pronounced in the lateral leads). Finally, there may be an increase in the U-wave amplitude.

Digoxin toxicity is the result of exaggerated therapeutic effects. Ectopy results from increased automaticity. Bradycardia and AV blocks result from depressed cardiac conduction. Ventricular tachycardia (VT) in the setting of CG toxicity has a 50% mortality rate. Risk factors associated with a poor prognosis include advanced age, heart disease, male sex, high-degree AV block, and hyperkalemia (5). The coadministration of P-glycoprotein inhibitors may result in an increased digoxin level and toxicity (6). Many other factors are known to contribute or predispose to toxicity (Table 325.2).

TABLE 325.2
Conditions Contributing to Digoxin Toxicity

Advanced age
Renal impairment
Hypoxia
Myocardial ischemia
Hypothyroidism
Hypokalemia
Hypomagnesemia
Hypercalcemia

CLINICAL PRESENTATION

Toxicity in the acute or chronic setting present differently. Acute toxicity occurs most often in a younger population as an accidental or intentional ingestion. In healthy adults, single acute doses of <5 mg of digoxin seldom cause toxicity. Chronic toxicity usually occurs in the elderly. Because of the narrow therapeutic range of digoxin, toxicity can occur with only two to three times the therapeutic dose in patients on chronic therapy.

Patients with acute digoxin toxicity will often present with nausea and vomiting. Chronic toxicity is more likely to present with central nervous system (CNS) findings, including confusion, lethargy, depression, fatigue, headache, paresthesias, weakness, scotomata, and disturbances of color vision, especially xanthopsia (yellow vision).

Virtually any dysrhythmia may develop as a result of toxicity, although rapid atrial fibrillation or atrial flutter is rare (see Table 325.3). PVCs, either unifocal or multifocal, are most common. The three classically described dysrhythmias include (1) paroxysmal atrial tachycardia with block (considered to be pathognomonic of digitalis toxicity), (2) junctional (AV-nodal) tachycardia, and (3) VT. The presence of any tachydysrhythmia with block (e.g., paroxysmal atrial tachycardia with block, atrial fibrillation with a regular ventricular response as a result of AV block with a junctional escape rhythm) is highly suggestive of CG toxicity. Any slowing of the ventricular response to atrial fibrillation in a patient on digoxin may suggest toxicity. AV-conduction blocks from first degree to third degree may occur, although Mobitz type II is rare. Sinus

bradycardia, from increased vagal tone, and other bradydysrhythmias are common. Hypotension suggests a hemodynamically significant dysrhythmia, loss of vasomotor regulation, or the presence of coingestant(s).

TABLE 325.3
Common Digitalis-Induced Dysrhythmias

Bradyarrhythmias	Tachyarrhythmias
Sinus exit block or sinus arrest	Atrial tachycardia with block
Sinus bradycardia	Junctional tachycardia
Atrioventricular nodal block first degree; second-degree type 1; third degree	Ventricular premature beats ventricular tachycardia especially bidirectional
	Ventricular fibrillation

After acute overdose, the most common ECG abnormalities are sinus bradycardia and varying degrees of AV block; ventricular dysrhythmias are less frequently seen. Chronic intoxication is more commonly associated with ventricular dysrhythmias, atrial tachycardia, and junctional tachycardia. Hyperkalemia is common after acute overdose whereas hypokalemia, probably related to concurrent diuretic use, is more common in chronic poisoning.

DIFFERENTIAL DIAGNOSIS

Intoxications that can cause CG-like bradydysrhythmias include those from class 1B antidysrhythmics, baclofen, β-adrenergic blockers, calcium channel antagonists, cholinergic agonists, cholinesterase inhibitors, clonidine, guanabenz, ingested imidazoline decongestants, and nicotine. CG-like tachydysrhythmias can be caused by poisoning with class 1A, class IC, and class III antidysrhythmics, antihistamines, baclofen, cyclic antidepressants, fluoride, heavy metals, local anesthetics, meperidine, neuroleptics, propoxyphene, quinine and related antimalarials, and sympathomimetics. Plants causing similar cardiotoxicity include *Phoradendron tomentosum* (American mistletoe), *Remijia* sp, *Rhododendron* sp, *Schoenocaulon officinalis* (sabadilla), *Stylophorum*

diphyllun, Veratrum sp (e.g., American hellebore), and *Zanthoxylum brachycanthum.* Worsening cardiomyopathy, congestive heart failure, CNS hemorrhage/ischemia, electrolyte abnormalities, myocardial ischemia/infarction, myocarditis, pericarditis, pheochromocytoma, pre-excitation syndromes, and thyroid dysfunction should also be considered in the differential diagnosis of CG-like cardiotoxicity.

Intoxications that can cause CG-like visual disturbances include carbon disulfide, ergot alkaloids, ethambutol, heavy metals, methanol, quinine and antimalarials, salicylates, and tamoxifen. The differential diagnosis of visual disturbances includes diseases such as cataracts, cerebrovascular disease, corneal disease, diabetes, glaucoma, macular degeneration, migraine, optic neuritis, retinal detachment, vasculitis, and vitreous hemorrhage.

ED EVALUATION

The history should include the amount, route, duration, and intent of exposure. Because CGs may be present in herbal supplements, the medication history should include herbal supplement use. The patient should be specifically examined for signs consistent with congestive heart failure and decreased peripheral perfusion. The patient should be placed on continuous cardiac monitoring, and a 12-lead ECG should be obtained. Routine laboratory studies include serum electrolytes, calcium, magnesium, blood urea nitrogen, and serum creatinine. Digoxin levels and potassium levels can be checked every 3 to 4 hours after an acute ingestion. A chest radiograph should be obtained in patients with cardiac dysrhythmias, hypotension, underlying cardiac disease, or hypoxia.

KEY TESTING

- ECG should be done quickly.
- Serum digoxin and potassium levels should be checked and followed until stable.
- An elevated creatinine slows digitalis excretion and may increase length of toxicity.
- Other routine laboratories consistent with supportive care.

ED MANAGEMENT

Advanced cardiac life support (ACLS) measures should be instituted as necessary. Intubation should be considered in patients with an altered mental status. Acid–base abnormalities, hypoxia, fluid, and electrolyte imbalances should be corrected. Although hypokalemia can exacerbate digoxin toxicity, caution is advised when replacing potassium in patients with renal failure. It is traditionally taught that the administration of (IV) calcium in the setting of digoxin toxicity can lead to potentially fatal dysrhythmias. There is no objective human evidence to support this concept, and calcium has been administered in patients with hyperkalemia and digoxin toxicity without complication (7). However, hyperkalemia in the setting of acute digoxin responds well to Digibind and as such, it should be considered a first-line agent. IV sodium bicarbonate, inhaled β-adrenergic agonists, insulin, and glucose can be used to treat hyperkalemia in the setting of hyperkalemia and digoxin toxicity. Because hyperkalemia reflects transmembrane shifts, and not total body overload, exchange resins that deplete potassium are of no benefit. Digoxin Fab antibody fragments correct the hyperkalemia from acute CG poisoning.

While activated charcoal decreases drug absorption, there are no well-designed human studies that show actual clinical benefit when activated charcoal is administered to a poisoned patient. The position of the American Academy of Clinical Toxicology is that activated charcoal should not be routinely used in the treatment of poisoned patients, but it may have a benefit if given within 1 hour of a drug that is known to be adsorbed to activated charcoal (8). Antidigoxin Fab antibody fragments should be used for hemodynamic compromise, life-threatening bradydysrhythmias and tachydysrhythmias and for hyperkalemia (serum potassium $\leq$5.5 mEq/L) after an acute overdose (5). Although an elevated serum-digoxin level confirms an overdose, it should not guide the use of Fab fragments and there is no known benefit of prophylactic administration of Fab fragments.

Digoxin Fab fragments are prepared by immunizing sheep, purifying their antibodies, and cleaving off the Fc fragments with papain. Those patients with a history of allergy to sheep or papaya may be at risk for an allergic reaction. The two antibody preparations commercially available, Digibind (Glaxo Wellcome) and DigiFab (Protherics Inc.), are virtually identical therapeutically. Antibody fragments possess a greater affinity for digoxin than sodium potassium ATPase and lower the extracellular unbound digoxin concentration. Further equilibration of receptor-bound digoxin with the extracellular fluid leads to a rapid release of digoxin from its receptor sites. The drug-antibody complex is renally excreted, with a half-life of 16 hours in normal renal function and up to 4 days in patients with renal failure.

If the quantity of digoxin ingested is known, the dose (in vials) of DigiBind or DigiFab can be calculated. The ingested dose in milligrams is divided by 0.6 mg/vial. Each vial of DigiBind contains 38 mg of Fab fragments, which will bind 0.5 mg of digoxin, although each vial of DigiFab contains 40 mg of Fab fragments. A typical dose for acute overdose is 5 to 10 vials. In chronic toxicity, the body load in milligrams can be estimated by multiplying the steady state serum concentration of digoxin by 5.6 times the patient's weight in kilograms divided by 1,000. The usual dose of Fab fragments in the setting of chronic toxicity is one to two vials. Digoxin Fab antibody fragments are given IV over 30 minutes unless the patient is in cardiac arrest, when it should be given as a bolus. Resolution of the digoxin-induced dysrhythmias and hyperkalemia are usually noted within 30 minutes of Fab-fragment administration, but it may take several hours for a maximal effect. The only proven beneficial treatment for symptomatic yellow oleander poisoning is digoxin-specific antibody fragments (9). In the setting of CG toxicity secondary to oleander or bufo toxins, larger doses of Fab fragments may be required, because of weak cross-reactivity.

Because serum digoxin assays measure both protein-bound and unbound drug, the serum digoxin level will rise after administration of antidigoxin Fab fragments as the drug is pulled from the tissues and is sequestered with the antibody in the serum. Free digoxin

levels, measured by equilibrium dialysis or ultrafiltration, will be low if the proper amount of Fab-fragment drug is given. A rebound rise in serum digoxin levels within 24 hours of antibody administration is seen in patients with normal renal function and may be seen in up to 8 days in patients with renal failure. This rise is presumably as a result of metabolic degradation of the antigen-antibody complex. Recurrent clinical toxicity is rare.

Other treatment may be necessary if digoxin Fab fragments are unavailable, while waiting for an effect, and when antibody therapy is unsuccessful. Atropine (0.5 mg IV) can be given for bradydysrhythmias. Since Fab fragments are more effective and safer, pacing should not delay antibody therapy. Irritation by the pacing wire in a digoxin-poisoned heart can precipitate ventricular tachydysrhythmias. Therapy for CG-induced ventricular tachydysrhythmias may include IV phenytoin (25 mg/min until a desired effect or a total of 15 mg/kg has been given), lidocaine (1 mg/kg), and magnesium sulfate (2 to 3 g IV in 1 minute). Refractory cardiac tachydysrhythmias induced by digoxin may respond to magnesium infusions (10). Pulseless rhythms require defibrillation or cardioversion. Cardioversion may precipitate ventricular fibrillation. If possible, medical management should be used initially. When cardioversion is necessary, initial settings should be at reduced power settings (5 to 10 J).

CRITICAL INTERVENTIONS

- Administer digoxin Fab antibody fragments for hemodynamically compromising or potential lethal dysrhythmias and for hyperkalemia (K $>$5.5 mEq/L) after acute overdose.
- Avoid using calcium and exchange resins to treat hyperkalemia.
- Begin with low power settings when cardioverting digoxin-induced tachydysrhythmias.

DISPOSITION

Intensive care unit admission is advised for patients with acute symptoms or who have elevated digoxin levels and dysrhythmias.

Chronically poisoned patients that are hemodynamically stable and do not require active treatment may be observed on a telemetry unit. If Fab fragments or pacemaker therapy is not available, the patient should be transferred by ACLS personnel to the nearest facility that has these modalities or the Fab fragments can be transported to the hospital. Poison centers and hospital pharmacies are often aware of the institutions with Fab fragments.

Common Pitfalls

- Failure to consider plant products such as herbals or teas in the differential diagnosis of CG-like cardiotoxicity.
- Failure to appreciate that toxicity is delayed up to 8 hours after acute ingestion.
- Failure to appreciate that digoxin assays may not yield a measurable digoxin level with ingestions of CGs from plants or Bufo toads.
- Failure to appreciate the differences between acute and chronic CG poisoning.
- Failure to appreciate that pacemaker wires can irritate the CG poisoned myocardium and precipitate ventricular tachydysrhythmias.

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PART 7 • CHEMICALS, GASES, AND METALS

CHAPTER 326

Arsenic and Mercury

Beth A. Baker

Arsenic has been used as a poison throughout history. Potential sources of arsenic exposure include intentional poisoning, contaminated drinking water, rock and volcanic eruptions, arsine gas, gallium arsenide used in the computer and semiconductor industries, smelting of metals, and arsenic-containing wood preservatives. Elevated levels of arsenic are found in drinking water in many parts of the world; the largest arsenic water contamination event occurred in Bangladesh and West Bengal, India. Arsenic is found in the earth's crust primarily as inorganic arsenic and is a contaminant of a variety of metal ores. Seafood or shellfish may contain organic arsenic, which is considered to be nontoxic. The average dietary intake of arsenic is about 2 to 92 μg/d (4).

Arsenic is tasteless, odorless, and readily absorbed by the gastrointestinal (GI) tract and inhalation but is poorly absorbed through the skin. An ingestion of 100 to 200 mg of arsenic is potentially fatal. Arsenic exists as either the less toxic pentavalent (arsensate or As^{+5}), or the more toxic trivalent (arsenite or As^{+3}) form. The organic arsenic present in seafood is considered nontoxic and is cleared from the body within days. Arsenic trioxide is used to treat promyelocytic leukemia. Arsenic is an intracellular toxin that impairs cellular respiration by inhibiting more than 200 enzymes throughout the body (including the sulfhydryl group containing enzymes) and may substitute for phosphates in high-energy compounds. Arsenic is a known human carcinogen and is linked to increased rates of skin, lung, and other cancers.

Mercury is a protoplasmic poison that binds to sulfhydryl groups. It exists in three forms that each have a different toxicity: (a) elemental, (b) inorganic, and (c) organic. Elemental mercury is a mobile liquid at room temperature. Elemental mercury is poorly absorbed through intact skin or via ingestion (<1%) but readily volatilized and well absorbed via inhalation (50% to 80% absorbed) (6). The half-life of mercury in blood after a single exposure is approximately 3 days (6). Mercury is primarily excreted in the urine, and the urine half-life is 30 to 90 days (3). Inorganic mercury is primarily absorbed via the GI tract and is corrosive. Inorganic mercury does not enter the central nervous system (CNS) as well as elemental or organic mercury. Mercury is naturally present in the environment, but most of the atmospheric inorganic mercury is from manmade sources such as smelting, coal combustion, and incineration. Inorganic mercury is primarily excreted by the kidneys, but organic mercury is primarily excreted in feces. Atmospheric mercury if deposited in water may be transformed or methylated by microorganisms from inorganic to organic or toxic methylmercury. Mercury-contaminated fish is a concern throughout the world. Organic mercury or methylmercury bioaccumulates in the food chain. Large, predatory fish such as shark, swordfish, king mackerel, and tilefish have higher mercury levels than small fish (10). However, it is also found in shellfish and is well absorbed via the GI tract. Methylmercury is the type of organic mercury most commonly found in nature and bioaccumulates up the food chain. Organic mercury is well absorbed via ingestion. Some organic mercury compounds such as dimethylmercury are extremely toxic and are well absorbed through intact skin.

Mercury exposure may occur through dental amalgams, although most experts believe amalgams do not cause significant health effects. Mercury is also found in food or grain treated with mercury-containing fungicides, disc batteries, thimerosal (preservative that contains ethyl mercury), mercury thermometers, and dyes. Mercury is used in batteries, switches, and scientific equipment and as a chemical intermediate, fungicide, or catalyst. Though the American Academy of Pediatrics asked that thimerosal be removed from

childhood vaccines in 1998 because of concerns about autism, there is no proven causal association found between autism and thimerosal-containing vaccines, and many vaccines since 2001 contain no thimerosal (5).

CLINICAL PRESENTATION

Acute arsenic ingestion causes GI symptoms such as nausea, vomiting, abdominal pain, and "rice water" diarrhea within 10 minutes to several hours after exposure. Patients may also develop shock and pulmonary edema owing to capillary leakage, toxic hepatitis, rhabdomyolysis, GI ulcerative lesions, acute tubular necrosis, delirium seizures, coma, and death (5). Arsenic toxicity may cause cardiovascular instability, hypotension, intravascular volume depletion, myocardial dysfunction, a prolonged QT interval, and dysrhythmias.

Subacute or chronic symptoms from arsenic poisoning include anemia, leukopenia, aplastic anemia, and peripheral neuropathy. Arsenic-induced skin changes may include hyperpigmentation, hypopigmentation, hyperkeratosis, Bowen disease, squamous cell cancers, basal cell cancers, or Blackfoot disease (a form of arsenic-induced peripheral vascular disease resulting in gangrene). Mees lines (transverse white lines in the nails) occur in a minority of arsenic toxic patients. Neurologic problems caused by arsenic toxicity include peripheral neuropathies, fatigue, CNS depression, tremulousness, ataxia, and incoordination. Arsine gas is a colorless, nonirritating gas that causes a triad of abdominal pain, hematuria, and jaundice owing to massive hemolysis.

Subacute or chronic poisoning may present with CNS symptoms, skin changes, and GI or renal dysfunction. Symptoms include tremors, gingivitis, stomatitis, cheilitis, rash, headaches, choreoathetosis, weight loss, fatigue, and erethism, a syndrome that includes shyness, anxiety, emotional lability, irritability, and delirium.

Elemental mercury inhalation can cause symptoms within hours; these include cough, chills, fever, nausea, vomiting, diarrhea,

interstitial pneumonitis, bronchitis, and eventually lung fibrosis. Elemental mercury in the GI tract is unlikely to be absorbed and does not typically cause systemic effects unless it becomes trapped in the gut or if there is GI perforation (3). Intravenous or subcutaneous injection of mercury may result in abscess or granuloma formation at the injection site and systemic symptoms (Fig. 326.1) (1,8).

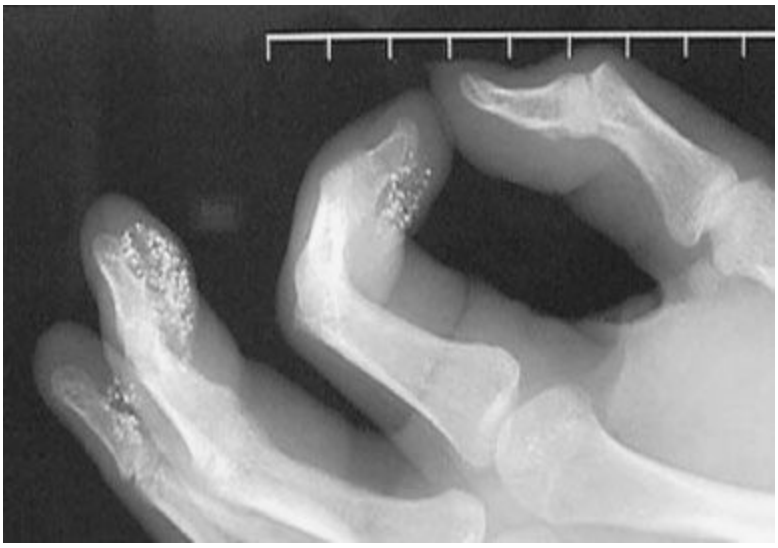

FIGURE 326.1 Multiple subcutaneous mercury deposits that were injected by patient.

Inorganic mercury salts such as those in mercury disc batteries, if ingested, causes irritant or caustic GI irritation, bloody diarrhea, abdominal pain, darkened and discolored oral mucosa, necrosis of the GI tract, hematochezia, hematemesis, circulatory collapse, acute tubular necrosis, and death. One to 4 g of mercuric chloride may be fatal in adults (11). Mercuric stomatitis, gingivitis, loosening of the teeth, jaw necrosis, and acute renal failure may occur. Inorganic arsenic causes skin and mucous membrane irritation.

Ingestion of organic or alkyl mercury causes primarily CNS symptoms such as paresthesias, tremor, ataxia, dysarthria, dementia, and tunnel vision. Acrodynia or pinks disease was originally reported in children and results in erythema and induration of the palms and soles along with systemic symptoms.

Maternal organic mercury exposure may cause cerebral palsy, mental retardation, blindness, seizures, cataracts, hearing loss, and CNS abnormalities in the fetus. Organic mercury crosses the placenta and is secreted in breast milk. The US Environmental Protection Agency and the Food and Drug Administration recommend pregnant women, women who might become pregnant, nursing mothers, and young children to not eat shark, swordfish, king mackerel, or tilefish, but they can eat up to 12 ounces (two average meals) a week of a variety of fish and shellfish that are lower in mercury (such as shrimp, canned light tuna, salmon) and check local advisories about the safety of fish caught by family or friends (10). Local fish may be tainted from nearby coal plants or incinerators.

DIFFERENTIAL DIAGNOSIS

Arsenic and mercury poisoning may present with GI symptoms and neurologic symptoms. Similar symptoms may occur with other heavy metals such as iron, lead, and thallium, and other toxins such as botulism, viral or bacterial infections, mushrooms, and other toxic agents such as organophosphates, ricin, lithium, alcohol, theophylline, antimetabolites, and colchicine.

Infectious gastroenteritis mimics the GI symptoms, but neurologic symptoms and long-lasting unexplained symptoms warrant suspicion.

ED EVALUATION

The initial evaluation should identify specific symptoms and the route of exposure and specific chemical or product that the patient was exposed to. Physical examination should include vital signs, cardiovascular, respiratory, and neurologic evaluations. The mouth and oral mucosa may show corrosive injury. Elemental mercury inhalation and acute arsenic poisoning may cause acute respiratory distress, and a chest x-ray is therefore appropriate. Abdominal x-ray may identify retained mercury or arsenic densities or ingested disc batteries. Electrocardiograph (ECG) monitoring to detect prolonged

QT and arrhythmias is appropriate for significant arsenic toxicity. Additional studies may be needed, including complete blood count (arsenic, arsine gas), arterial blood gas or oxygen saturation (elemental mercury, arsenic), serum electrolytes, blood urea nitrogen, Cr, glucose, liver function tests, and creatine kinase (CK) (severe mercury or arsenic poisoning).

Arsenic levels may be measured in blood, urine, hair, or nails. Blood arsenic is cleared within hours and is of little value. Urinary arsenic is the most reliable indicator of recent inorganic arsenic exposure. Twenty-four-hour urine arsenic is most commonly used but, if necessary, a spot urine arsenic corrected for creatinine concentration can be collected in the emergency department (ED) prior to chelation. Normal urine arsenic levels may vary from laboratory to laboratory but are usually <50 μg/L or <50 μg/g creatinine (2). Organic arsenic from seafood or shellfish ingestion may cause an elevated urine arsenic level for several days up to 2,000 μg/L, but it is relatively nontoxic and is rapidly cleared from the body. If organic arsenic is suspected, the laboratory can speciate the arsenic to determine whether the elevated level is due to organic or the more toxic inorganic arsenic. Urine arsenic elimination has three phases: First-phase half-life is 2 days (65% of dose), second-phase half-life is 10 days (30% of dose), and third-phase half-life is 40 days (4% of dose) (9). Arsenic levels may also be assessed in hair or nails, which may better reflect chronic arsenic toxicity. Hair levels, however, may reflect external contamination from water, sweat, or airborne arsenic and not internal contamination.

Typically whole blood mercury level is <10 μg/dL, but only a level >25 μg/dL requires treatment. Normal 24-hour urine mercury level is <20 μg/dL; levels >150 μg/dL require treatment. Urine mercury may correlate with inorganic mercury toxicity but may not be as useful for methylmercury or organic mercury toxicity. A blood mercury level is recommended for methylmercury or organic mercury toxicity. Elevated urine or blood mercury levels may occur after seafood or fish consumption. Mercury may also be measured in hair, but organic mercury is not detected in hair.

KEY TESTING

Arsenic

- EKG if acute cardiac symptoms
- Spot urine arsenic or 24-hour urine arsenic
- CBC, Hb in arsine gas
- Abdominal x-ray if ingested, CXR if respiratory symptoms

Mercury

- Abdominal x-ray if ingested, CXR if respiratory symptoms
- Blood mercury (better for organic mercury)
- Spot urine mercury or 24-hour urine mercury

ED MANAGEMENT

Acute arsenic or mercury poisoning may be life-threatening, and advanced life-support measures may be required. The primary treatment for arsenic and mercury toxicity is supportive care and removal of the patient from further exposure. Urine arsenic levels or blood or urine mercury levels can be collected in the ED, but results are not available for several days. Aggressive intravenous fluid resuscitation may be needed with large ingestions of arsenic or inorganic mercury salts or arsine gas exposure. With arsenic, it is important to maintain potassium, magnesium, and calcium concentrations within normal ranges and to avoid use of drugs that would prolong the QT interval.

Acute inhalation of mercury vapor may result in life-threatening respiratory failure, and ventilatory support may be needed. Patients exposed to arsine gas should have dermal decontamination. Both arsenic and mercury adsorb poorly to activated charcoal. Whole-bowel irrigation can be helpful if abdominal x-rays show persistent radiopaque material in the GI tract (8).

If there are concerns about corrosive lesions or ulcers after inorganic mercury ingestion, upper GI endoscopy should be considered before lavage and whole-bowel irrigation are performed. Inorganic mercury salt ingestion may result in severe gastroenteritis with third-spacing and cardiovascular collapse. As the most likely cause of death after ingestion of inorganic mercury salts is renal

failure, aggressive fluid therapy to maintain renal perfusion may be helpful. Arsenic and mercury levels will usually fall to normal range within several weeks to months if the patient is removed from further exposure (7). Chelation therapy is recommended only for patients with significant symptoms or extremely high arsenic or mercury levels (4,8). Patients who are severely ill with known or high suspicion of acute arsenic or mercury poisoning can be chelated after a spot urine arsenic or spot urine mercury or blood mercury is collected. Dimercaprol or British anti-Lewisite (BAL) can be given as a 3- to 5-mg/kg IM injection every 4 to 6 hours for severely arsenic-poisoned patients, but there is evidence from animal studies that BAL may shift arsenic or mercury into the brain (2). Patients with significant symptoms from inorganic mercury poisoning can be treated with BAL—5 mg/kg/dose every 4 hours IM for 48 hours, then 2.5 mg/kg every 6 hours for 48 hours, then 2.5 mg/kg every 12 hours for 7 days (8).

DMSA, or 2, 3-dimercaptosuccinic acid, is a more effective derivative of BAL that is an oral chelator if the patient can tolerate oral medication. Oral DMSA is the preferred chelator for organic mercury poisoning and for mercury poisoning if the patient has normal renal function and is not severely ill (8). BAL may be contraindicated with methylmercury (7). The usual dose for DMSA is 10 mg/kg tid for 5 days, then bid for 14 days. Use of DMSA is off-label as DMSA is approved by the FDA only for treatment of lead poisoning or mercury poisoning in children. DMPS has been shown to effectively chelate arsenic or mercury but is not approved for clinical use by the FDA. Chelation with intramuscular BAL is appropriate for patients with significant GI toxicity who are unable to take oral meds and may be started if there is a high level of clinical suspicion even before the blood or urine levels are available. BAL and DMSA are both renally excreted and should be used with caution in patients with renal impairment. Chelating agents should be used in pregnancy only if a patient is extremely ill.

Patients who have injected elemental mercury subcutaneously or IV should have x-rays of the affected sites (1). Large amounts of retained subcutaneous mercury should be surgically removed to

prevent granulomas and skin necrosis (1,8). Hemolysis due to arsine gas exposure may respond to exchange transfusions or blood transfusions and does not respond to BAL chelation.

For spills of elemental mercury, appropriate clean-up measures include use of a high efficiency particulate air filter vacuum cleaner and a decontamination kit instead of sweeping. Usually the health department is notified to coordinate the clean-up.

CRITICAL INTERVENTIONS

- Diagnosis of arsenic poisoning is based on appropriate symptoms and elevated urine arsenic level.
- Diagnosis of mercury poisoning depends on appropriate symptoms and elevated blood or urine mercury level.
- Supportive care is appropriate such as IV fluids.
- Obtain blood mercury or urine mercury or urine arsenic level.
- Administer BAL or DMSA chelation for severe symptoms.
- If radiopaque material is present in the GI tract after a recent ingestion, whole-bowel irrigation may be appropriate.
- Avoid medication that will prolong the QT interval in arsenic poisoning.

DISPOSITION

Patients with significant symptoms from arsenic or mercury poisoning should be admitted to the hospital. Patients with moderate toxicity should be observed for 6 to 8 hours in the ED prior to discharge, particularly with acute arsenic ingestion (ECG monitoring), elemental mercury inhalation and arsine gas inhalation. Most patients with mild to moderate toxicity can be treated as outpatients and should have a follow-up visit set up 2 to 3 days after the ED visit. A psychiatric evaluation prior to discharge is appropriate for patients with intentional exposures or ingestions.

Common Pitfalls

- Failure to identify exposure source and preventing future exposure.

- Inappropriate use of chelating agents in patients with mild toxicity who are asymptomatic.
- Failure to identify QT prolongation and arrhythmias in toxicity or delayed pulmonary edema in severe inorganic arsenic poisoning, or hemolysis and renal failure after arsine gas exposure.
- Failure to identify pulmonary effects from elemental mercury inhalation or severe neurologic and multisystem effects of organic mercury.

ACKNOWLEDGMENT

The author gratefully acknowledges the contributions of Jay L Schauben to the content of this chapter.

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CHAPTER 327

Carbon Monoxide

Heather Long

Carbon monoxide (CO) is a colorless, odorless gas produced by the incomplete combustion of any carbon-containing material. CO is a leading cause of poisoning worldwide, with an estimated 50,000 emergency department (ED) visits annually in the United States for CO exposure (1). Common sources include fires (see Chapter 337), automobile exhaust and faulty home-heating systems (see Table 327.1). Non–fire-related CO poisoning peaks in winter months due to increased use of heating systems, alternative heat sources and practices such as warming up automobiles in attached garages. CO poisoning due to improper placement of generators and indoor use of charcoal grills and camp stoves often follows natural disasters. In the wake of Hurricane Sandy in 2012, more than 260 cases of CO poisoning were reported to poison centers (2). In 2007, CDC surveillance found there were 21,304 ED visits with confirmed cases and 439 deaths due to non–fire-related CO poisoning (3,4).

TABLE 327.1
Sources of Carbon Monoxide Poisoning

Fires/smoke inhalation
Automobile exhaust
Faulty home furnaces
Fuel-powered generators, space heaters, tools, etc.
Charcoal grills
Gas kitchen stoves
Camp stoves/lanterns
Boat motors
Propane-powered forklifts
Ice resurfacing machines
Wood pellet storage
Hookah pipes

CO causes tissue hypoxia, binding hemoglobin with an affinity approximately 250 times greater than that of oxygen. Thus, even at low CO levels, significant saturation of hemoglobin-binding sites with CO may decrease the oxygen-carrying capacity of the blood. In addition, CO binding to hemoglobin alters the shape of the oxygen–hemoglobin dissociation curve, effectively shifting it to the left, and further decreasing the intracellular oxygen concentrations. However, issue hypoxia from decreased oxygen delivery does not fully explain the observed toxicity from CO. Direct binding of CO to intracellular proteins appears to trigger an immune and inflammatory-mediated ischemic reperfusion injury to the brain characterized by generation of reactive oxygen species, lipid peroxidation, and apoptosis (1,5). Hypotension, thought due to myocardial depression as well as the vasodilatory effects of CO, appears to be a prerequisite for this ischemic reperfusion injury to the brain.

The toxic dose of CO depends on the rate of ventilation, the underlying health of the victim, and the presence of other toxins. Equilibrium is reached more rapidly in people who perform vigorous physical activity. As little as 0.1% CO (1,000 ppm) may produce potentially fatal 50% saturation of hemoglobin at equilibrium, although this might require several hours of exposure. The exposure limit in the workplace is 25 ppm as an 8-hour time-weighted average. The level considered immediately dangerous to

life or health is 1,200 ppm. People with underlying pulmonary or cardiovascular (CV) disease may not be able to tolerate hypoxia produced by even mild or moderate CO levels.

CO is rapidly absorbed from the lungs and carried in the blood as carboxyhemoglobin (COHgb). After removal from exposure, COHgb has an apparent half-life in room air of about 4 to 5 hours (6). Half-life drops to 1 to 2 hours at 100% oxygen at ambient pressure and to about 20 to 40 minutes with hyperbaric oxygen (HBO) at 2.5 atm. Methylene chloride is a paint stripper that can be inhaled ingested or absorbed through the skin. Because it is metabolized to CO by cytochrome P450 in the liver, the production of CO is ongoing which increases the apparent half-life of COHgb following methylene chloride exposure to at least 12 to 14 hours.

CLINICAL PRESENTATION

The signs and symptoms of CO poisoning are highly variable and non-specific but primarily involve the brain and the heart, the organs most sensitive to CO poisoning. Headache is the most common complaint followed by dizziness, nausea, vomiting, and fatigue. With more significant CO exposures, confusion, syncope, shortness of breath, tachycardia, tachypnea, and chest pain may occur. Severe poisoning may cause coma, seizures, hypotension, cardiac dysrhythmias, and death. Patients may present with focal neural deficits resembling stroke. Sensorineuronal hearing loss and cortical blindness are reported.

Although the severity of intoxication usually parallels the COHgb concentration, there are reports of patients with severe intoxication with prolonged exposure at relatively low levels and of patients with high levels after a short exposure but minimal symptoms.

In a large case series, myocardial injury developed in 20% of 250 CO-poisoned patients. Predictors of myocardial injury are male sex, an initial GCS <14 and CO exposure ≤ 2 hours (3). Myocardial manifestations include ischemia, ST and non-ST elevation myocardial infarction, thromboembolic events, and dysrhythmias

including atrial fibrillation, ventricular fibrillation, Brugada pattern changes and QT prolongation.

Other acute manifestations of CO poisoning include acute kidney injury and retinal hemorrhage. A cherry-red coloration of the skin, mucous membranes, and venous blood on rare occasion may occur from the bright red color of the COHgb complex. However, its presence or absence cannot be considered diagnostic; it is more likely to be noted at autopsy than in patients who survive. Arterial blood gas analysis and serum electrolytes often reveal metabolic acidosis caused by tissue hypoxia–ischemia. The arterial PaO_2 and the calculated oxygen saturation are usually normal because dissolved oxygen in the serum is not affected by CO. The oxygen saturation measured directly by co-oximetry is less than that calculated from the PO_2 by an amount roughly equal to the percent COHgb, but typically the oxygen saturation measured by pulse oximetry is falsely normal (7).

A myriad of persistent or delayed neurologic and neuropsychiatric sequelae may develop following CO poisoning. Deficits range from subtle alterations in personality, memory deficits, headaches and difficulty concentrating to blindness, deafness, parkinsonian features, dementia, and permanent vegetative state. Deficits may be permanent or improve with time. Delayed neurologic sequelae are associated with neurologic symptoms including syncope and coma at time of presentation, but mild CO poisoning does not exclude its development.

DIFFERENTIAL DIAGNOSIS

Influenza-like illness is the most common misdiagnosis and not surprising given the overlap in symptoms, peak incidence in winter months and the ability to affect multiple household members simultaneously. Other causes of coma and altered mental status should be sought, such as hypoglycemia, head trauma, stroke, meningitis, and drug or alcohol intoxication. Almost half the patients with intentional CO poisoning ingest other potential toxins including alcohol (8). In addition to CO poisoning, other toxic gases

should be considered in any patient with smoke inhalation. Cyanide, hydrogen sulfide, agents that cause methemoglobinemia, and other toxins may produce symptoms and signs of systemic hypoxia that are similar to those of CO (6).

ED EVALUATION

A high index of suspicion is key to the diagnosis of CO poisoning. Think CO in all patients who present with headache and especially in those who present with confusion or altered mental status and who are by default, poor historians. Think CO in winter and following large power outages. High-risk history includes smoke inhalation, household members with similar symptoms, found in car with engine running or adjacent house, use of fuel-powered tools, generators, pool, and space heaters, etc. especially in poorly ventilated areas and riding in motor boats, houseboats, and beds of pick-up trucks.

Immediate evaluation in the ED should include rapid neurologic assessment and determination of the COHgb level. COHgb is measured in the laboratory by a co-oximeter and may be performed on either a venous or arterial blood gas sample. Normal COHgb levels range from 3% to 5% in nonsmokers and up to 10% in smokers. Fingertip pulse co-oximeters are devices that measure COHgb noninvasively. Agreement between pulse co-oximeters and laboratory-measured COHgb levels is variable, and CO may be undetectable by pulse co-oximetry in the setting of hypoxemia (9). Pulse co-oximetry may be useful as a rapid screening test in the field or in the ED but cannot be used as a substitute for laboratory-measured COHgb in guiding the management decisions of an individual patient.

Depending on severity, further diagnostic tests may be indicated including blood gas analysis, lactate concentration, metabolic profile, creatine phosphokinase, troponin, ECG, and chest radiography. An elevated lactate level in the context of smoke inhalation can suggest concomitant cyanide poisoning. Check fingerstick glucose in all patients who present with altered mental

status. Unsuspected acetaminophen may be detected by measuring a serum level in cases of intentional CO poisoning; additional serum and urine ethanol and drug testing should be used as suspected. Potential injuries sustained in the setting of trauma should guide ordering of additional studies.

Lesions in the basal ganglia, the area of the brain most susceptible to CO, may be evident on CT scan within 12 hours of significant CO exposure. MRI is better than CT at detecting these lesions and diffusion tensor imaging in particular, may be useful in predicting severity and outcome (6).

KEY TESTING

- COHgb level from venous or arterial blood sample
- Evaluate for anion gap metabolic acidosis in severely poisoned patients
- Send lactate in severely poisoned patients

ED MANAGEMENT

Oxygen is first-line treatment for anyone with suspicion of CO exposure until confirmatory COHgb level is attained and should be provided through a nonrebreather mask with an oxygen reservoir bag or an endotracheal tube. Oxygen should be administered to waiting room patients prior to further triage and registration and continued until symptoms are resolved and COHgb is less than 5%. Advanced life-support measures and cervical spine precautions should be instituted as needed. The only decontamination needed is removing the victim from the toxic environment with the exception of exposure to the paint stripper methylene chloride. Treat hypotension with IV crystalloid and vasopressors and potential myocardial ischemia with cardiac monitoring, serial ECGs and treatment per standard chest pain protocols. Consider hydroxocobalamin for critically ill smoke inhalation victims with CN poisoning (see Chapter 313). Because acidosis may facilitate oxygen delivery to the tissues by moving the oxygen–hemoglobin dissociation curve to the right, mild-to-moderate metabolic acidosis

(i.e., serum pH 7.2 to 7.3) should not be treated with sodium bicarbonate.

HBO, 100% oxygen provided under pressures >1 atm, should be considered in all cases of significant CO poisoning. It reduces the half-life of COHgb to about 20 minutes, but more importantly, may prevent CO-induced postischemic reperfusion injury and reduce the risk of persistent/delayed neurologic and neuropsychiatric sequelae. Animal studies show a mechanism of action and convincing data that HBO modulates CO-induced vascular injury and improves CV status and neurologic outcome (1,5). Clinical studies, most with marked methodologic flaws, have found mixed results. The one large, prospective, double-blind randomized controlled trial found treatment with HBO conferred a small but statistically significant benefit in neurologic outcome (7).

Controversy remains about which patients should receive HBO treatment. Most hospitals do not have ready access to a hyperbaric chamber so treatment requires a transfer and all the inherent risks of transporting patients. Ideally, only those patients thought to be at greatest risk for persistent/delayed neurologic sequelae would be referred for potential HBO, but those criteria have not been prospectively validated. See Table 327.2 for suggested indications for HBO. COHgb levels do not predict clinical outcome, but most experts recommend HBO for patients with high levels, generally ≤25%. Aside from the risks, cost and inconvenience of transport, the most common side effect of HBO is barotrauma to the middle ear which can be prevented by myringotomy.

TABLE 327.2
Indications for Potential Hyperbaric Oxygen Therapy

Syncope
Prolonged exposure (>24 hrs)
Age ≥36 yrs
Abnormal cerebellar function
Seizure
Coma
Altered mental status
COHgb level >25%

Pregnant women and children pose a special problem in CO poisoning. The maternal COHgb level does not predict fetal outcome, but the maternal clinical presentation does. Severe CO poisoning in the mother is associated with CNS damage and fetal demise while pregnant women with mild poisoning have good outcomes (10). Fetal hemoglobin may not have a greater affinity for CO as was previously thought, but CO does take longer to be eliminated in the fetus. COHgb levels may be difficult to interpret in infants as CO levels are naturally higher in infants than in older children and adults and may be even higher in the setting of jaundice. In addition, the co-oximeter may give a falsely elevated COHgb in the presence of fetal hemoglobin. Children are thought to be at increased risk of CO poisoning because of their higher metabolic rate and to become symptomatic at lower COHgb levels than adults. Prolonged oxygen therapy and a lower threshold for HBO are often recommended for pregnant women and children, although, once again, studies are lacking.

The prognosis after severe CO poisoning is unpredictable but grim. While survival of awake patients is high, as many as 40% of victims have permanent neurologic injury. Patients with an abnormal computed tomography, single-photon emission computed tomography scan, or magnetic resonance imaging scan on admission appear to be at higher risk for permanent sequelae (6).

CRITICAL INTERVENTIONS

- Administer oxygen at 10 to 15 L/min by nonrebreather mask with an oxygen reservoir bag or 100% by endotracheal tube to

all patients with possible CO poisoning.
- Consider HBO therapy for patients with a history of loss of consciousness or syncope, cerebellar findings, seizure, coma, prolonged exposure times, COHgb levels 25% or higher, age over 36 and for pregnant women and children.

DISPOSITION

Patients with mild CO poisoning should be treated with 100% oxygen until symptoms resolve and COHgb is less than 5%. Patients with loss of consciousness, seizures, or evidence of MI or ischemia should be admitted to the hospital; severely poisoned patients will require intensive care admission. Many authorities would also admit any patient with a CO-hemoglobin level >25%, regardless of symptoms.

HBO treatment may be indicated for some patients (Table 327.2) and a poison center or medical toxicologist may be able to assist. A critical care nurse or paramedic should accompany the potentially unstable patient during transport to an HBO facility. Once the acute episode of poisoning has resolved, patients should be referred for follow-up neuropsychiatric evaluation. Those discharged from the ED should be instructed to return to the ED if any neurologic symptoms develop.

Patients who are discharged after unintentional poisoning should have a safe environment to avoid repeat exposure. This may require the fire department to measure ambient levels or a stay in a temporary shelter until a home or other setting can be cleared of CO.

Common Pitfalls

- Failure to consider the diagnosis of CO poisoning in patients presenting with headache, altered mental status, and influenza-like illness, particularly in cold climates or seasons.
- Failure to consider the ingestion of alcohol or other drugs in patients with suicidal exposure to CO.

- Failure to appreciate that the arterial blood gas PaO_2, calculated oxygen saturation, and pulse oximetry oxygen saturation are usually normal despite severe CO poisoning.
- Failure to appreciate that the severity of poisoning depends on the duration of exposure and that carboxyhemoglobin levels may not correlate with the severity of poisoning.
- Failure to warn patients about the possibility of delayed neurologic toxicity and to return if symptoms develop.

ACKNOWLEDGMENT

The author gratefully acknowledges the contributions of Kent R. Olsen to the content of this chapter.

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CHAPTER 328

Corrosives and Chemical Burns

Larissa I. Velez

Most corrosive injuries involve acids or alkalis. Other corrosives damage tissues by various mechanisms, including oxidation, reduction, vesication, desiccation, metabolic inhibition, or cellular poisoning. Fluoride and hydrofluoric acid are discussed in Chapter 330, and chemical warfare agents (including the blistering agents) are discussed in Chapter 350. This chapter focuses on the damaging effects of acids and alkali.

Acids (pH <7) are proton donors that dissociate into conjugate bases and free hydrogen ions (H^+) in solution. Alkalis (pH >7) accept protons, resulting in the formation of conjugate acids and free hydroxide ions (OH^-). In general, substances with a pH <3 or >11 have the most potential to cause significant corrosive injury, as they produce more free ions (Table 328.1). Acids denature proteins and cause coagulation necrosis. The formation of a firm coagulum or eschar often limits the penetration of injury. Alkalis cause liquefaction necrosis, which dissolves proteins and saponifies fats. The injured tissues slough, allowing for deeper injury when compared to acids.

TABLE 328.1
Approximate pH of Some Common Solutions

Solution	pH
1.0 M HCl	0
Battery acid (1% solution)	1.4
Acid toilet cleaner (1%)	2.0
Citrus juices	1.8–4
Wines	2.8–3.8
Black coffee	5.0
Rainwater	6.5
Water (25°C)	7.0
Bleach (1% solution)	9.5–10.2
Automatic dishwasher detergents	10.4–13
Laundry detergents	11.6–12.6
Ammonia cleaners (<10%)	11.9–12.4
Alkaline drain cleaners	13.3–14
1.0 M NaOH	14
Saturated ammonia solution	15

The extent, location, and severity of gastrointestinal (GI) injury depend on the physical state of the corrosive or chemical agent, the pH and concentration of the agent, the amount ingested, the duration of tissue contact, the presence of food in the stomach, and the tonicity of the pyloric sphincter. Solid particles dissolve on contact with body fluids, producing highly concentrated solutions, which may result in severe localized damage. Solids and viscous solutions tend to adhere to tissues and frequently result in proximal rather than distal involvement. Larger amounts, which are common with intentional ingestions, have a higher potential for severe injury. However, acids usually have a strong odor and result in immediate pain and smooth muscle spasm, which may limit the amount ingested. Alkalis are often odorless and do not cause immediate pain after contact. In addition, sloughing of tissue after liquefactive necrosis results in deeper penetration of alkalis. Because of these characteristics, alkali ingestions usually involve larger volumes and result in more severe injury. In general, longer contact times with a corrosive substance results in greater injury. Finally, the presence of food in the stomach is somewhat protective. Systemic toxicity sometimes accompanies severe GI injuries and is

usually secondary to tissue inflammation, necrosis, perforation, acidosis, and infection. Fluid and electrolyte shifts can accompany extensive burns and result in hypovolemic shock. Some corrosives also cause systemic toxicity when absorbed.

The subsequent injury and repair processes are similar for both acids and alkali. There is bacterial invasion after 24 to 48 hours, an inflammatory response, and development of granulation tissue. Because collagen deposition may not begin until the second week, tensile strength of the healing tissue is low during the first 3 weeks (1). Scar retraction begins in the third week, commonly continuing for months, and may result in stricture formation. Finally, mucosal repair can take weeks to months.

Ocular damage is most severe following alkali burns as a result of early disruption of the corneal epithelium and rapid tissue penetration. As with ingestions, the overall severity of alkali burns is generally more than that seen with acids.

Chemical burns caused by corrosives differ in several important ways from thermal burns. First, the initial severity of the injury may be underestimated because tissue penetration of the chemical may be deeper than anticipated by visual inspection. In addition, tissue penetration and damage may continue for hours to days. Furthermore, absorption of the chemical may result in systemic toxicity. As with ingestions, the severity of the dermal injury is dependent on several factors, including the specific mechanism of toxicity and concentration of the agent, duration of exposure, surface area exposed, thickness of the skin involved, and depth of penetration. Patient factors such as age, pre-existing conditions of the skin, and concurrent illnesses also affect the severity of the injury.

CLINICAL PRESENTATION

Sites commonly affected by corrosive ingestion are the oropharynx, esophagus, and stomach, although injury may occur as far as the proximal jejunum (2,3). Injury to other organs, including the heart, liver, and pancreas, has been reported, but is rare (4,5).

Patients usually present with oral, throat, chest, or abdominal pain. Dysphagia, drooling, and vomiting are common. Children may refuse to drink, cry excessively, or be unable to swallow their secretions. Stridor, hoarseness, hematemesis, and melena occur less frequently (6). Tachypnea can occur from aspiration of the corrosive with resultant pneumonitis or as a compensation for a metabolic acidosis. The metabolic acidosis may reflect tissue necrosis or the systemic absorption of ingested acids.

On inspection, superficial burns of the oropharynx are often covered with a pale membrane, and deeper burns are black, hemorrhagic, or friable but the presence or absence of burns in the oropharynx does not reliably predict more distal injuries (3,6). Full-thickness injuries to the esophagus or stomach are at risk of perforation and fistula formation into the trachea, mediastinum, or peritoneum (3). Mediastinitis can present with chest pain, respiratory distress, fever, subcutaneous emphysema, pleural rub, and Hamman sign (an audible crunch with each heart beat). Chest radiographic findings of mediastinitis may include mediastinal widening, pleural effusion (usually left-sided), pneumomediastinum, and pneumothorax.

The abdominal examination is an unreliable indicator of the severity of the injury, but frank peritonitis is an ominous sign. Peritonitis may result from viscous perforation or the extension of severe gastric burns to surrounding abdominal organs. Patients with peritonitis may have marked third-spacing of fluids, resulting in abdominal distention and hypotension. Abdominal compartment syndrome, or intra-abdominal hypertension, has been reported.

The late presentations after a corrosive ingestion include dysphagia, nausea, and vomiting as a result of the formation of strictures. Esophageal strictures develop in up to 70% of patients with deep esophageal ulcers and in nearly all patients with areas of necrosis (3). Ulceration superficial to the muscularis mucosa layer does not lead to stricture formation. Half of all esophageal strictures develop during the initial hospitalization, and 80% are evident within 2 months. Esophageal carcinoma, a late sequela of alkali

ingestion, has been diagnosed after a latency period of about 40 years (1) but is only rarely reported with acid burns.

Ocular injury most commonly results from splash exposures at home or in the work environment. Injuries have also been reported after airbag deployment, where sodium hydroxide is produced (7,8). The severity of these injuries ranges from transient irritation to severe disabling ocular damage and blindness. Manifestations include immediate eye pain, photophobia, blepharospasm, lacrimation, conjunctival injection or hemorrhage, and decreased visual acuity. The pupils may be nonreactive as a result of severe iritis. Intraocular pressure rises with damage to the trabecular meshwork, resulting in new glaucoma. With more significant involvement, chemosis and corneal edema, opacification, sloughing, ulceration, and necrosis occur. Destruction of blood vessels may result in a very white sclera indicative of corneal ischemia which along with corneal opacification are both ominous signs. If penetration is deep enough, retinal damage occurs. Ultimately, inflammation leads to fibrosis, synechiae, and cataract formation.

Dermal exposure usually results in immediate pain at the affected site, but the onset of pain can sometimes be delayed for several hours, especially with hydrofluoric acid (see Chapter 330). Petroleum distillates, weak sodium hydroxide solutions, and wet cement, which is an alkali, typically do not produce burns unless allowed to remain in contact with the skin for prolonged periods. Such exposures may initially appear trivial but can progress to full-thickness burns. Chemical burns rarely blister, and the affected skin is usually dark, insensate, and firmly attached regardless of the burn depth. With time, the skin hardens and cracks, exposing the underlying dermis or subcutaneous tissue. Healing of chemical burns usually takes longer than for thermal burns.

DIFFERENTIAL DIAGNOSIS

With ingestions, it is important to determine the coingestion of other agents. If shock or altered mental status is present soon after ingestion, other causes than caustics should be sought. The ingestion

of heavy metals and hydrocarbons can cause symptoms similar to a caustic ingestion. Allergic reactions may also present with some of the features of corrosive ingestion, specifically if the hypopharynx or larynx is involved. Infections such as epiglottitis, croup, retropharyngeal abscess, and mucosal ulceration as a result of herpesvirus or coxsackievirus should be considered in children.

The differential diagnosis of corrosive injury to the eye includes traumatic corneal abrasion or ulceration, corneal foreign bodies, allergic reactions, infectious processes such as viral or bacterial conjunctivitis, iritis, iridocyclitis, acute narrow-angle glaucoma, and exposure to fumes, vapors, and other sensitizing agents.

Considerations in the differential diagnosis of chemical dermal injuries include thermal burns, radiation burns (including sunburns and from welding), mechanical irritation or trauma, allergic reactions and drug eruptions (such as Stevens–Johnson syndrome or toxic epidermal necrolysis), contact dermatitis, infections, and bacterial toxin-mediated conditions such as staphylococcal scalded skin syndrome or toxic shock syndrome.

ED EVALUATION

The identity, concentration, and amount of chemical or product involved and the time and circumstances of exposure should be determined as soon as feasible. Product labels, when available, should be examined for ingredients and signal words. The signal words “caution,” “warning,” and “danger” identify a product as a weak irritant (to eyes, nose, and throat), strong irritant (to skin and mucous membranes), or corrosive (capable of causing permanent or fatal tissue damage), respectively. If a sample is available, measure its pH. A pH meter is more accurate than pH paper (e.g., pHydrion paper, which is also used for testing amniotic fluid) but is not generally available. A regional poison-control center can assist with identifying the product and for advice on evaluation and management of the exposure. However, none of these should delay the patient evaluation and management.

In patients with corrosive ingestion, attention should initially be directed to airway patency, because obstruction may develop with progressive mucosal edema. In the absence of stridor or respiratory distress indicating the need for immediate endotracheal intubation, patients with a hoarse voice or respiratory symptoms should have the upper airway assessed by direct fiberoptic laryngoscopy. Patients suspected of having a significant corrosive injury should also have an electrocardiogram, blood-gas analysis, complete blood count, type and crossmatch, prothrombin time, electrolyte, glucose, liver-function, and renal-function tests. Radiologic studies should include an upright chest radiograph if the patient has respiratory symptoms and abdominal films if perforation is suspected.

Endoscopy of the upper GI tract is the gold standard for the diagnosis of corrosive injury (9). Endoscopy should be performed in all symptomatic patients. A complete lack of symptoms or signs suggests that significant injuries are absent and that endoscopy is not necessary (6). Nevertheless, endoscopy should be considered for asymptomatic patients who have intentionally ingested a strong acid or alkali or if the history is unreliable. Endoscopy is optimally performed 12 to 24 hours after exposure (3). If undertaken earlier, the full extent of injury may not be apparent; if performed later, the risk of perforation may be increased (2).

Esophageal and gastric burns are graded in a similar fashion as dermal burns. Grade 1 burns just have erythema of the mucosa (3). Grade 2 burns have partial-thickness submucosal lesions, ulceration, and exudates. Some authors consider 2 a burns as noncircumferential, and 2b as near circumferential. Grade 3 burns are deep, full-thickness burns with ulcers and necrosis into the periesophageal tissues (6). Third-degree burns have an 85% incidence of stricture development. Overall, the best predictor for the development of strictures is the severity of the initial injury. Endoscopic ultrasound has been used to measure injury to the muscularis layer. Injury to the muscularis layer has also been shown to correlate with late stricture formation (10). Contrast esophagography is less sensitive than endoscopy in assessing burn injury, although it is useful for detecting perforation. A water-

soluble contrast agent (gastrografin) must be used whenever perforation is suspected. Cine-esophagogram can detect esophageal motility disorders and gastroesophageal reflux, which also predict stricture formation. CT scan has also been used for detection of stomach perforation. A grading scale for caustic burns on CT scan can be used (10).

With symptomatic ocular exposures, decontamination must always precede the formal evaluation of the eye. A complete eye examination including measurement of visual acuity, conjunctival pH, and a slit-lamp examination should follow the decontamination. If injury to the anterior chamber is suspected, the intraocular pressure should be measured. However, this last step must be avoided if there is a concern for ocular globe disruption.

The assessment of dermal injuries is similar to that for thermal burns. Location, size, color, texture, and neurovascular status should be noted. If the affected area is >5% of total body surface area or if systemic toxicity is possible, a more thorough physical examination and laboratory testing can be performed to assess for systemic involvement.

KEY TESTING

- Early endoscopy for all symptomatic caustic ingestions, regardless of oral findings
- Direct fiberoptic laryngoscopy for hoarseness, stridor, or respiratory symptoms
- Chest and abdominal radiographs, and esophagogram with low–molecular-weight contrast, for possible esophageal or gastric perforation
- Laboratories for supportive care include CBC, chemistries, and coagulation studies
- Conjunctival pH testing after eye irrigation

ED MANAGEMENT

Any patient with evidence of significant upper airway obstruction such as severe respiratory distress, stridor, or inability to speak

should undergo immediate endotracheal intubation. Delay in securing a definitive airway will only result in further development of airway edema and increase the difficulty with endotracheal intubation. This, however, is a rare event (10).

The efficacy of GI decontamination is limited. However, the mouth should be rinsed liberally with water in patients with oral burns. Because emesis re-exposes the esophagus to the corrosive agent and increases the risk of aspiration, antiemetics should be given to patients with persistent nausea or vomiting. A nasogastric tube for stomach emptying may be considered in recent, large-volume ingestions. Activated charcoal should be avoided since it obscures the endoscopist's view, and most corrosives are not significantly adsorbed by charcoal. Dilution of gastric contents with oral fluids within minutes of ingestion may be beneficial, although the current evidence is inconclusive (10). If dilution is to be used, it should be within minutes of exposure in patients with a normal airway and mental status, without significant nausea, vomiting, or pain, and who are able to speak and cooperate. The amount swallowed should be limited to 5 mL/kg to avoid inducing emesis.

Although corticosteroids reduce the incidence and severity of esophageal strictures in animal studies, their value in humans is controversial. In human trials in which steroids were not given until up to 24 hours after exposure, there are conflicting conclusions as well as points of general agreement. Patients with first-degree esophageal burns do not require steroids, because strictures do not develop in this group. Steroids do not appear to alter the development of esophageal strictures in patients with extensive areas of deep ulceration or necrosis (grade 3 burns) and may actually increase the rate of complications such as infection, hemorrhage, or perforation. For patients between these two extremes, whose injuries consist of circumferential or extensive superficial ulceration or small areas of deep ulceration or necrosis, steroids are of potential benefit. The most recent pooled analysis of the available data did not show a statistically significant benefit of steroids for second-degree burns (11). An earlier systematic review of published cases also failed to show benefit in second-degree burns

(12). The decision to use steroids is based on the grading of the burns, which highlights the importance of early endoscopic evaluation.

Concomitant penicillin, ampicillin, or clindamycin are recommended whenever steroids are being used. Although they are of no proven benefit in promoting healing or reducing complications, antacids, sucralfate, H_2 blockers, proton pump inhibitors, and analgesics (ibuprofen) can provide symptomatic relief (2,10). Oral medications and feedings should be withheld until after endoscopy, and then should be given only to patients with injuries limited to mucosal inflammation or small areas of superficial ulceration. These patients may be given oral fluids when they are able to swallow their own secretions. Those patients with more severe injuries should receive intravenous fluids and nothing by mouth.

Surgical exploration is indicated if perforation is confirmed by radiographs or endoscopy, when there is persistent hypotension, or in the presence of abdominal rigidity. Surgical exploration has also been recommended in patients who are at high risk of perforation, sepsis, necrosis, or hemorrhage. Because endoscopy cannot fully evaluate the depth of the burns (e.g., the status of the serosal surface), exploration has also been proposed for patients with grade 2 or 3 burns to overcome this limitation. In one study, a serum pH <7.22 and a base excess more than –12.0 were predictors of severe injury requiring an emergency salvage operation (10).

Immediate copious irrigation is the single most important intervention in the management of eye exposures (13). The severity of ocular damage at the time of presentation is a good predictor of the ultimate outcome, as are timeliness and adequacy of irrigation. Ideally, irrigation will have been performed immediately at the time of exposure in the home or workplace and continued en route to the hospital. The patient can use a running faucet or hold his or her breath while blinking while *the face is in a pan of water*. If the patient has significant pain, irrigation must again be performed in the emergency department (ED). Acceptable irrigation solutions

include tap water, normal saline, Ringer lactate, or D_5W. Commercially available irrigation solutions (Previn, Diphoterine) are also acceptable, but the irrigation should not be delayed while these solutions are obtained irrigation will be aided greatly with topical anesthetic solution, eyelid retractors, intravenous analgesics, or sedatives. The eyelids should be everted, and any particulate matter should be removed with a cotton swab. Continuous irrigation of the eye is made easier with use of a scleral lens with inflow channel (Morgan Therapeutic Lens), or one can simply irrigate manually with intravenous tubing connected to irrigation solution. Initially the eye should be irrigated with 1 L and for at least 20 minutes. For highly corrosive substances, especially alkali exposures, irrigation should continue for at least an hour.

After irrigation, the pH of the inferior cul-de-sac should be tested with litmus or pH paper. If a neutral pH of 7 to 8 has not yet been achieved, continued irrigation is warranted. Once a neutral conjunctival pH is achieved, the pH should be rechecked every 30 minutes for 2 hours, because corrosive material may be slowly released from corneal tissue for several hours. A subsequent change in pH indicates the need for further irrigation.

Standard treatment for corneal injuries includes topical antibiotics, steroids, cycloplegics, and mydriatics. If intraocular pressure is elevated, topical timolol maleate and oral acetazolamide may be required. Tetanus prophylaxis and analgesics should be administered if needed.

Initial management of dermal injuries is also directed at rapid decontamination with copious water irrigation of the skin surface with water for most exposures. Ideally, irrigation will have been initiated immediately at the scene and continued en route to the hospital (14). Delayed decontamination can result in increased tissue damage and deeper penetration of the offending agent. In industrial accidents, rescuers should wear appropriate protective gear such as gloves, gowns, masks, and eye shields. All contaminated clothing, footwear, jewelry, and contact lenses should be removed from the victim. Immediate irrigation with water should

never be delayed to search for an alternative irrigation solution. Irrigation should continue for at least 20 minutes. A longer period of irrigation lasting up to several hours is required for alkalis and other serious exposures. Gently brush away particulate material before irrigation is started. Adherent materials may be removed by gentle scrubbing with soapy water while avoiding abrasions. Appropriate analgesia and tetanus prophylaxis should be provided, and wounds should be treated with topical antibiotic cream and protective dressings.

Irrigation should not be performed for burns caused by elemental forms of alkali metals such as sodium, potassium, lithium, cesium, and rubidium. These elements react with water to form hydroxides, strong bases that will significantly increase tissue damage. Furthermore, ignition or explosion occurs when water contacts pure magnesium, sulfur, strontium, titanium, uranium, yttrium, zinc, and zirconium. These two groups of substances should be covered with mineral oil to isolate them from water. Any solid particles that are removed from the victim must be stored in mineral oil to prevent further reactivity. These specific caustic agents are not commonly available and are thus seldom encountered. Patients with such exposures may come to the ED with Material Safety Data Sheets (MSDS) from their workplace. These data sheets can provide specific information about the agent.

CRITICAL INTERVENTIONS

- Evaluate the airway in patients with ingestions or facial-skin exposures, and intubate patients with respiratory distress, stridor, or inability to speak.
- Begin irrigation immediately, and continue for at least 20 minutes in symptomatic patients with eye and skin exposures.
- Consult a gastroenterologist for the endoscopy of patients with GI symptoms or suicidal corrosive ingestion.
- Consult a surgeon for patients with evidence of perforation, endoscopic evidence of severe GI injury, peritoneal signs, hypotension, or metabolic acidosis after corrosive ingestion.

- Consult an ophthalmologist for patients who have evidence of corneal injury or persistent pain after eye exposure.
- Consult a regional burn center for patients with significant dermal injury.

DISPOSITION

Exposed patients who are asymptomatic or become asymptomatic after oral rinsing and dilution may be discharged from the ED after an observation period (1). It is generally agreed that patients who are asymptomatic after unintentional ingestions will have normal endoscopies (6). For patients with more significant exposures, endoscopy should be arranged, with transfer to an appropriate facility if necessary. Suspected suicidal ingestions should have a psychiatric evaluation and the possibility of nonaccidental injury should be considered in all pediatric cases (1). Patients with no visible injury on endoscopy and those with injuries limited to mucosal inflammation or small areas of superficial ulceration may be medically discharged as long as they are able to tolerate oral fluids (15). Patients with persistent symptoms or inconclusive findings at endoscopy should be admitted for observation. If symptoms persist, endoscopy should be repeated.

Patients with mild chemical conjunctivitis can be referred to an ophthalmologist for follow-up the next day. Immediate ophthalmology consultation should be obtained for those with evidence of corneal injury or persistent pain. Patients with significant eye injuries should be admitted to the hospital for further irrigation, for assessment of injury progression and the need for surgical intervention, and to ensure initial compliance with the medical regimen.

Consultation with a general surgeon, plastic surgeon, or regional burn center is recommended for patients with significant dermal injuries. Patients with minor injuries may be discharged, if the patient is reliable and follow-up the next day can be arranged. Patients with systemic toxicity; second- or third-degree burns; extensive first-degree burns (>5% of body surface area); burns to

the face, eyes, ears, perineum, hands and feet; and high-risk patients such as those with significant pre-existing illness, the elderly, and psychiatric or otherwise noncompliant patients should be admitted (16).

Common Pitfalls

- Inducing vomiting by giving excessive amounts of oral fluid for dilution.
- Giving activated charcoal, which is not indicated for acid or alkali ingestion, and which will obscure endoscopic evaluation.
- Assuming that the absence of oropharyngeal burns precludes the presence of significant GI injury in symptomatic patients.
- Failing to continue eye irrigation long enough, as determined by conjunctival pH testing.
- Underestimating the severity of dermal exposures and failing to provide adequate decontamination.

ACKNOWLEDGMENT

The author acknowledges the contributions of Collin S. Goto in previous editions of this chapter.

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CHAPTER 329
Cyanide

Heather Long

Acute cyanide (CN) poisoning is a rare and potentially fatal but treatable condition. Potential sources of CN include smoke inhalation, ingestion of CN salts and cyanogenic compounds, occupational exposures, and iatrogenic exposures (see Table 329.1). Hydrogen cyanide (HCN) gas for chemical warfare dates to the time of Napoleon III and was used again during World Wars I and II and in concentration camps during World War II. Both HCN and CN salts remain chemical terrorism threats. Most CN deaths arise from intentional suicides, particularly among those with occupational access, for example, chemists, jewelers (1). A recent case series describes intentional self-poisoning and suicide with cyanide-containing jewelry and metal cleaners purchased at Southeast Asian ethnic markets among the US Hmong communities (2). The contribution of HCN to smoke-inhalation injury among fire victims is increasingly recognized (see Chapter 337).

TABLE 329.1
Sources of Cyanide

Fires and smoke inhalation: Combustion of wool, silk, rubber, polyurethane, and nitrocellulose releases CN

Occupational exposures: Industrial processes that require CN reagents include electroplating, metal refining, fumigation, and photography

Cyanogenic compounds: Acetonitrile (found in artificial-nail remover); CN is released after ingestion and metabolism by the cytochrome P-450 system

Cyanogenic foods: Pits of the *Prunus* species (apricot, bitter almond, cherry, peach) contain the cyanogen amygdalin. Cassava (tuber consumed in many developing countries) contains two cyanogenic compounds

Iatrogenic: Sodium nitroprusside contains five molecules of CN. If given at high dose or for long duration, it may overwhelm body's stores of thiosulfate and cause CN poisoning

CN toxicity depends on the dose, the route of exposure, and the form of CN. CN toxicity may occur following inhalation, ingestion, and parenteral or dermal exposure, with inhalation and ingestion accounting for most significant toxicity reported. Inorganic CN exists either as a gas or a salt. HCN is a gas at standard temperature and pressure. HCN may be immediately lethal at an air concentration of 270 ppm, and exposures to >110 ppm for >30 minutes are potentially lethal. CN salts such as potassium cyanide (KCN) generate HCN on exposure to acid. The HCN may then be inhaled or, if the salt is ingested, absorbed into the bloodstream. The lethal oral dose of KCN is 200 mg, with death in approximately 20 minutes. Toxicity following ingestion of cyanogenic compounds, for example, acetonitrile, may be delayed several hours while the parent compound is metabolized to yield CN.

At the cellular level, CN produces hypoxia by complexing with the ferric iron of mitochondrial cytochrome oxidase a_3 of the electron-transport chain, blocking oxidative phosphorylation and formation of adenosine triphosphate (ATP). Anaerobic metabolism prevails, and lactic acid accumulates. Central nervous system (CNS) toxicity arises from the decrease in oxygen utilization as well as oxidant-stress–induced lipid peroxidation and the cell death triggered by increased release of excitatory neurotransmitters (3,4).

CLINICAL PRESENTATION

Inhalation of high concentrations of HCN may cause sudden loss of consciousness after only a few breaths. With ingestion of alkaline CN salts (calcium CN, KCN, sodium CN), life-threatening symptoms may occur in 15 minutes to 1 hour. In fatal cases, rapid progression to coma, seizures, dysrhythmias, intractable hypotension, apnea, and death is common.

Onset of symptoms may be delayed after exposure to cyanogens such as laetrile and cyanogenic glycosides from plant sources (up to 1.5 hours) or aliphatic nitrile compounds such as acetonitrile in artificial glue-on-nail removers (up to 6 to 12 hours) (5,6). Systemic poisoning may occur after dermal HCN exposure.

Tissues with the greatest oxygen demand (myocardium and brain) are most profoundly and rapidly affected by CN. Initial CNS and cardiovascular (CV) stimulation is followed by depression. Initial signs and symptoms of CNS stimulation include giddiness, headache, and anxiety followed by confusion, seizure, and coma. The initial CV response may be characterized by a brief period of hypertension and bradycardia followed by hypotension and a reflex tachycardia. Ultimately there is hypotension and bradycardia and cardiac arrest.

Early in the clinical presentation, there may be CNS-mediated hyperpnea that is later followed by bradypnea. Both cardiogenic and noncardiogenic pulmonary edema (more correctly termed *acute lung injury*) are reported at autopsy. Gastrointestinal symptoms including nausea, vomiting, and abdominal pain may follow ingestion of CN salts and cyanogenic compounds.

Classically, CN poisoning is associated with a cherry-red skin color resulting from the inability of tissues to extract oxygen from the blood and the resulting increased oxygen saturation of venous hemoglobin. CN itself does not cause cyanosis; however, patients with apnea and circulatory collapse may exhibit cyanosis. The smell of bitter almonds with CN poisoning is sporadically present, and even when present, only 60% of people are able to detect it.

Sodium nitroprusside treatment may cause iatrogenic CN poisoning within hours to days, typically in patients with renal failure. Manifestations include altered mental status and metabolic acidosis, particularly in the setting of tachyphylaxis to nitroprusside

therapy. CN poisoning in this setting can be prevented by the concomitant administration of hydroxocobalamin or sodium thiosulfate.

DIFFERENTIAL DIAGNOSIS

Early symptoms may be confused with anxiety or hyperventilation, which are common after nontoxic exposures. Rapid development of more serious clinical signs differentiates these benign conditions and nontoxic CN exposures from significant CN poisoning. Hydrogen sulfide and sodium azide poisoning may cause similar findings, and diabetic decompensation has been initially suspected in patients who were later found to have ingested CN.

The following laboratory values may suggest the diagnosis when no history is available: Plasma lactate level >8 mmol/L and elevated anion gap metabolic acidosis. Decreased tissue oxygen extraction from the blood results in a relatively normal pO_2 in ventilating patients and an elevated peripheral venous pO_2 (>40 mm Hg) or decreased arteriovenous O_2 saturation difference (central venous or mixed pulmonary artery O_2 saturation >70% with a relatively normal co-oximeter–measured arterial O_2 saturation). Hydrogen sulfide and sodium azide can also cause a similar pattern of oxygen saturation. Patients exposed to hydrogen sulfide may have the odor of sulfur or “rotten eggs” on the body or clothes or in a freshly drawn tube of blood.

ED EVALUATION

Whenever possible, the history should include the specific compound involved, route of exposure, any decontamination measures already undertaken, possible dose, time since ingestion or exposure, and any pre-existing allergies or chronic medical conditions. Initial physical examination should focus on vital signs (monitored frequently and serially) and the respiratory system, CV system, and CNS. The cardiac rhythm should be continuously monitored.

Determination of serum electrolytes (with calculation of the anion gap), blood glucose levels, pulse oximetry, arterial blood gas analysis, chest radiography, and 12-lead electrocardiography should be done initially and monitored frequently if clinical signs or symptoms of CN poisoning are present. Whole blood CN levels can be measured, but results usually take hours or days to obtain and thus cannot be used to guide emergent diagnosis or treatment. They are useful only to document exposure. A more practical test is the plasma lactate concentration. In the right clinical setting, a lactate concentration >8 mmol/L that is refractory to ventilation, oxygenation, and perfusion is a marker of CN toxicity (7).

KEY TESTING

- Electrolytes and blood gas for anion gap acidosis
- EKG for cardiac ischemia and dysrhythmias
- Elevated serum lactate refractory to treatment suggests CN

ED MANAGEMENT

First priority is the rapid, safe removal of victims from the scene by those with adequate training and protection. Start with airway management, 100% supplemental oxygen, cardiac monitoring, at least one large-bore intravenous line, and intravenous fluids if hypotension is present. Rescuers must not enter areas of potential HCN gas exposure without a self-contained, positive-pressure breathing apparatus. Mouth-to-mouth resuscitation should be avoided, if possible. If it is unavoidable, rescuers must be careful not to inhale the victim's expired air. Exposed skin (particularly open wounds) and eyes should be decontaminated by copiously flushing with water. Contaminated clothing should be removed and isolated.

On arrival to the emergency department (ED), care again begins with the ABCs (airway, breathing, circulation), with the particular caveat that the significantly CN-poisoned patient may deteriorate rapidly. Pulse oximetry or arterial blood gases should be monitored, and metabolic acidosis should be corrected with adequate ventilation and sodium bicarbonate if appropriate. Pulse oximetry

may be unreliable following administration of methemoglobin-inducing nitrite antidotes, and co-oximetry may be unreliable following administration of hydroxocobalamin. Once CN poisoning is suspected, either by history or by clinical presentation, specific antidotal therapy should be initiated. First-line therapy for CN is hydroxocobalamin (Cyanokit). Alternative antidotes for CN poisoning include sodium nitrite and sodium thiosulfate or sodium thiosulfate alone.

The Cyanokit contains two 2.5-g vials of hydroxocobalamin. Hydroxocobalamin binds directly with CN to rapidly form nontoxic cyanocobalamin (vitamin B_{12}), which is subsequently excreted in the urine. In addition, hydroxocobalamin has been shown to raise blood pressure, potentially advantageous in treatment of the patient with CV collapse (8). The main side effect of hydroxocobalamin is a clinically insignificant reddish-brown skin discoloration that resolves spontaneously. It also causes red discoloration of the urine and blood, potentially interfering with some colorimetric laboratory studies so if there is time, tubes of blood should be gathered for subsequent laboratory analysis prior to administration of hydroxocobalamin. The adult dose is 5 g of hydroxocobalamin reconstituted in 100 mL 0.9% sodium chloride and given intravenously over 15 minutes; the pediatric dose is 70 mg/kg. A second dose may be repeated over 15 minutes to 2 hours for severe poisoning. Metabolism of cyanogenic glycosides or aliphatic nitrile compounds to CN cause prolonged poisoning, requiring multiple antidote doses.

The Cyanide Antidote Kit, in use for decades in the United States, has been discontinued but a kit containing sodium nitrite 3% solution and sodium thiosulfate 25% solution is still available. The adult dose of sodium nitrite is one 10-mL ampule (300 mg) of the 3% solution administered intravenously. The pediatric dose ranges from 0.12 to 0.33 mL/kg (3.6 to 9.9 mg/kg). **Sodium nitrite is a potent vasodilator; rapid administration may result in severe hypotension,** which can be avoided by giving the sodium nitrite in 50 to 100 mL of D_5W slowly intravenously over 5 minutes. Start the

infusion slowly, with frequent blood pressure monitoring, and then increase to the most rapid infusion without causing hypotension. Sodium thiosulfate 25% solution is also administered intravenously and is supplied in a 50-mL vial (Adult dose: One entire vial. Pediatric dose: 1.65 mL/kg up to 50-mL maximum). A second half dose of sodium nitrite and sodium thiosulfate may be given after 30 minutes if there is an incomplete clinical response. Repeated doses or a continuous infusion (1 g/hr) of sodium thiosulfate (without further sodium nitrite) should be considered if there is ongoing metabolism to CN following ingestion of a cyanogenic compound.

In addition to its vasodilatory effects, sodium nitrite induces formation of methemoglobin, which binds CN to form cyanohemoglobin as part of the detoxification process. Methemoglobin levels should be monitored, especially if multiple doses of sodium nitrite are required, and should be kept to $<30\%$ of total hemoglobin. When oxygen transport is already compromised, as in a smoke-inhalation patient with concomitant carbon monoxide poisoning, this induction of methemoglobinemia further impairs cellular hypoxia (see Chapter 319). This situation can be avoided by using hydroxocobalamin, but if it is not available, a reasonable approach in the critically ill smoke-inhalation patient with suspected CO and CN poisoning, is to administer only the sodium thiosulfate without the sodium nitrite. Sodium thiosulfate indirectly metabolizes CN by catalyzing the body's own conversion of CN to sodium thiocyanate.

Because activated charcoal has decreased mortality in experimental CN poisoning (9) and 1 g may bind as much as 35 mg of CN, consider giving 1 g/kg activated charcoal in patients who have ingested CN.

Extracorporeal elimination procedures such as hemodialysis and hemoperfusion have no place in the treatment of acute CN poisoning. Hyperbaric oxygen therapy has not lowered CN concentrations in fire victims with concomitant carbon monoxide poisoning (10).

CRITICAL INTERVENTIONS

- Suspect CN poisoning in patients with rapid development of unexplained coma, seizures, elevated plasma lactate, elevated anion gap metabolic acidosis, and intractable hypotension.
- Suspect CN poisoning in comatose and critically ill patients with smoke inhalation.
- Administer hydroxocobalamin intravenously (adult dose: 5 g) to comatose or persistently acidotic or seizing patients with possible CN exposure.

DISPOSITION

Asymptomatic CN-exposed patients should be observed in a controlled setting for 4 to 6 hours. Following ingestion of cyanogenic compounds or foods, the observation period should be extended to 12 hours. Mildly symptomatic patients can be observed in the ED until symptoms resolve. Those requiring antidote administration should be admitted to an intensive care unit for a minimum of 24 hours or until all symptoms have resolved.

Survivors of acute CN poisoning have developed parkinsonian-like states or more subtle neuropsychiatric deficits (11). Outpatient follow-up should be arranged for patients with significant acute toxicity to screen for these sequelae.

If transfer is necessary, the most rapid means available should be used with personnel who can initiate intravenous access, perform endotracheal intubation and mechanical ventilation, and administer specific antidotes, sodium bicarbonate, anticonvulsants, and anti-arrhythmic medications.

Common Pitfalls

- Failure to stock an in-date CN antidote in the ED or other readily available location.
- Failure to consider the diagnosis of CN poisoning in patients with smoke inhalation, sudden-onset coma, CV collapse, or lactic acidosis of unknown etiology.
- Waiting for laboratory confirmation before antidote administration in unstable patients.

- Using sodium nitrite with concomitant carbon monoxide poisoning in a smoke-inhalation patient.

ACKNOWLEDGMENT

The author gratefully acknowledges the contributions of Alan Hall, to the content of this chapter.

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CHAPTER 330

Fluoride and Hydrofluoric Acid

Kennon Heard

Fluoride, the most electronegative anion, binds strongly to divalent serum cations such as calcium and magnesium. In the body, this precipitates as fluoride salts, resulting in hypocalcemia and hypomagnesemia. Fluoride inactivates enzymes required for cellular metabolism and may activate intracellular second messengers. Fluoride also interferes with Na+/K+-ATPase and activates calcium-dependent potassium channels in cell membranes, causing potassium to enter into the extracellular space, with potential hyperkalemia. Hypocalcemia, hypomagnesemia, and hyperkalemia contribute to cardiac dysrhythmias. Hypocalcemia also inhibits calcium-dependent clotting factors and can cause coagulopathy.

Although fluoride is found in many household dental products (e.g., toothpaste), exposure to these products rarely results in serious effects (1). However, ingestion of prescription dental products may result in serious toxicity. Sodium fluoride has been used as a pesticide. Ammonium fluoride and ammonium bifluoride are been used as wheel cleaners, and have caused several cases of severe accidental poisoning.

As a relatively weak acid (pKa = 3.8), hydrofluoric acid (HF) damages tissue primarily through the strong electronegative effect of the fluoride ion. HF is found in products used for glass etching, grout cleaners, and silicon chip manufacturing. It is also used in household and commercial rust removal products. The effect is determined by the concentration of HF in the product. Low-

concentration exposures may not cause an initial caustic injury but can still cause significant tissue damage and pain. High-concentration exposures found in commercial products may cause life-threatening systemic poisoning and classic caustic injury.

CLINICAL PRESENTATION

Dermal HF exposures are the most commonly encountered fluoride exposure in the emergency department (ED). Exposure to other fluoride cleaning products (e.g., ammonium bifluoride) may cause similar effects. The major manifestation of these exposures is pain. At low concentrations (<20% HF), symptoms may be delayed more than 24 hours (2). With lower-concentration exposures, dermal findings range from normal appearing skin to full-thickness burns. In one series of low-concentration exposures, just over half of the patients had erythema and swelling, 5% developed blisters, but 23% had normal appearing skin (2). Burns from high concentrations (>50% HF) may appear similar to other caustic injuries. Exposure of more than 1% of the total body surface area (TBSA) to a 50% HF product may result in systemic poisoning. Ocular exposures to low-concentration products may result in eye pain and corneal injury, and animal models suggest that exposure to concentrations >20% will cause immediate corneal edema and opacification.

Patients with HF ingestions may have deceptively minimal or no findings suggestive of caustic exposure. Fatal fluoride intoxication following ingestion has been reported without significant gastrointestinal (GI) symptoms (3). When present, GI symptoms include abdominal pain, vomiting, and hematemesis (3). Effects after HF inhalation may range from mild pulmonary irritation to hemorrhagic pulmonary edema and delayed multisystem organ failure. Systemic absorption of fluoride may occur after inhalational exposure. Manifestations of systemic fluoride poisoning include headache, paresthesias, visual complaints, and signs of hypocalcemia such as carpal-pedal spasm, positive Chvostek sign and Trousseau sign, hyperreflexia, tetany, and prolongation of the QT interval on the electrocardiogram. Hypocalcemia is often severe

(serum calcium level <5 mg/dL). Metabolic acidosis, hypomagnesemia, hyperkalemia, and coagulopathy can also occur. Coma, seizures, shock, dysrhythmias, and death may occur in severe cases. Lethal dysrhythmias include refractory ventricular tachycardia and ventricular fibrillation.

DIFFERENTIAL DIAGNOSIS

HF acid exposure should be strongly considered when a patient presents following a dermal exposure with severe pain and minimal dermal findings. Other diseases with similar findings would include other chemical burns, Raynaud syndrome, local ischemia, or sensory neuropathy. Systemic fluoride poisoning should be considered for the patient who presents with cardiovascular (CV) instability and hypocalcemia. Other potential causes of this presentation would include acute hypoparathyroidism, hyperphosphatemia or poisoning from sodium ethylenediaminetetraacetic acid.

ED EVALUATION

Important factors in the history include the route of exposure, the strength and concentration of the product involved, the use of protective equipment, and whether decontamination was performed. Signs and symptoms and their time of onset with respect to exposure should be noted. The physical examination should initially focus on the site of exposure. Patients with facial burns should have conjunctival pH determined and a full eye examination performed after any needed irrigation. Patients with limited (<5% body surface area) dermal exposures to low (<10%) concentration HF products do not require any laboratory testing or monitoring. Patients with more extensive dermal exposures, dermal exposure to higher (>20%) concentration products, or ingestion of HF products should have an electrocardiogram and serum calcium determinations. Cardiac monitoring for prolongation of the QT interval is recommended, although the diagnostic accuracy of the QT interval for predicting toxicity is not known.

Patients with hypocalcemia should have a complete blood count, serum electrolytes, magnesium, blood urea nitrogen, and creatinine. Chest radiographs are indicated for symptomatic patients with inhalational exposure.

KEY TESTING

- Rapidly determine serum calcium in patients with large- or high-concentration dermal exposures and in patients who have ingested nondental fluoride products
- Cardiac monitoring for hypocalcemia, QT prolongation, and potential dysrhythmias
- Serum magnesium

ED MANAGEMENT

The first step with dermal exposure is immediate (ideally at the scene of exposure) irrigation with water. In a series of more than 400 dermal exposures (most involving 40% HF) treated with immediate water irrigation, no patient developed deep tissue necrosis, and all recovered within days (4). Irrigation should be performed for a minimum of 20 minutes. If symptoms have not resolved, irrigation should be continued. Hexafluorine, a proprietary product that binds fluoride much more effectively than calcium, has been advocated, but it offers no clear advantage over irrigation with water.

Patients who have continued pain despite irrigation or who present several hours after the exposure should be treated in a stepwise fashion. Topical calcium is the standard first-line therapy. One effective way to deliver the calcium is to mix 10% calcium chloride with methylcellulose to form a gel with a final calcium concentration of 2.3% to 2.5%. If methylcellulose is not available, a water-based lubricant (e.g., KY jelly) may be used. The mixture is then applied topically to the affected area. Exposures involving the digits can be treated by having the patient wear a tight-fitting glove filled with the gel. The glove is worn for at least 30 minutes after the pain resolves. Fingernail removal is not advocated, and patients

with exposure that involves the nail beds are best treated with regional perfusion (see further). Patients who have pain relief may be discharged and apply the gel every 4 to 6 hours or sooner if needed, for the next 24 hours (5).

Patients who have continued pain despite topical calcium therapy should be treated with calcium injection or regional perfusion. Local subcutaneous injection of calcium gluconate is best suited for areas in which the tissue can expand to accommodate the fluid (e.g., trunk, scalp, proximal extremities, face). The dose is 0.5 cc of 10% calcium gluconate per cm^2 of involved skin. Calcium chloride should not be used, as it may cause tissue injury. The injection is performed with a small (27 g or smaller) needle. Successful treatment results in immediate improvement in symptoms (6). Use of a local anesthetic is not recommended as relief of pain is used to monitor of the effectiveness of therapy. Patients may be discharged with topical calcium gel therapy.

Often, the tissue on the hand, fingers, and foot cannot comfortably accommodate the volume of fluid during these injections. These areas are best treated by regional perfusion. This may be accomplished by either direct arterial injection or using intravenous injection with Bier technique. Arterial perfusion requires placing an arterial catheter. After confirming intra-arterial placement by either waveform or arteriography, 100 cc of a 2.5% calcium gluconate solution is infused over 60 minutes with a pump (7). An alternative to arterial infusion is regional venous calcium infusion using a Bier block. With this technique, an IV catheter is placed in the hand or foot, and the extremity is exsanguinated by elevation (with or without application of an elastic bandage). A pneumatic tourniquet is applied proximal to the IV site and the burn and inflated to 100 mm Hg above systolic blood pressure. Once the tourniquet is inflated, 10 cc of a 10% calcium gluconate diluted with 40 cc of saline is infused into the catheter in the affected extremity. After 15 to 25 minutes, the tourniquet is deflated slowly over 5 minutes (8). Most patients will require parenteral analgesia to tolerate the tourniquet.

Ocular exposures should be treated with immediate water irrigation. As with any caustic exposure to the eye, the ocular pH should be monitored. There is no evidence that irrigation with calcium or magnesium-containing solutions offers any advantage, and any delay that occurs while these solutions are obtained is likely to be detrimental. Although animal models suggest that severe injury is possible, reported cases have gone on to good recovery. One report suggested that calcium gluconate drops may be a useful adjunctive therapy after decontamination, but this is not routinely recommended.

Nebulized calcium gluconate (2.5%) has been used for inhalational exposures, but the evidence for this intervention is anecdotal and limited, so it cannot be considered standard.

Systemic fluoride poisoning may occur after exposure to many fluoride-containing products. The management of systemic fluoride poisoning does not vary depending on the type of fluoride or the route of exposure. Patients with ingestions of fluoride-containing products should rinse their mouth and drink 50 to 100 cc of water to dilute the caustic effects. Charcoal does not adsorb fluoride and should not be administered. Oral administration of calcium-containing solution is of unproven value. One animal model found a survival benefit but only when the ratio of calcium to fluoride exceeded a 1:1 equivalent ratio (9). This would translate to more than 3 g of calcium chloride for each gram of fluoride ingested. Accidental exposures to most nonprescription dental products that contain fluoride do not result in serious toxicity although patients may develop GI symptoms. Patients with small (suspect <30 cc ingested), accidental exposures to low-concentration HF products or dental sodium fluoride products almost always do well (3). Asymptomatic patients with small ingestions (e.g., a sip) should have venous access obtained and be placed on a cardiac monitor. Baseline calcium measurements should be obtained immediately. If the serum calcium is below the normal range, it is reasonable to administer 1 g of calcium gluconate over 30 minutes and then immediately repeat the calcium level. Persistent hypocalcemia suggests a significant exposure, and the patient should be treated as

if there were a deliberate exposure. Patients with deliberate ingestions or accidental ingestions suspected to involve more than 30 cc of low-concentration HF products or sodium fluoride may benefit from prophylactic treatment with intravenous calcium. Animal models suggest that such treatment improves survival. The author recommends that any patient who presents after deliberate ingestion of an HF product should be treated with prophylactic calcium gluconate (at a rate of 3 g/hr) after baseline serum calcium is measured. Calcium chloride may be used, but it must be given through a well-functioning line, as extravasation may cause extensive tissue injury. If the initial serum calcium is normal, the infusion may be stopped, but serum calcium levels should be measured every 30 minutes for at least 3 hours and, if calcium levels are decreasing, the infusion should be restarted.

Patients who develop hypocalcemia or any CV effects must be treated very aggressively. Survival after cardiac arrest from fluoride poisoning has always been associated with very aggressive calcium therapy. One patient suffered cardiac arrest and survived after the administration of more than 110 mEq of calcium chloride (approximately 9 g) during a resuscitation (10). Although only suggestive, this case suggests that early administration may prevent CV collapse. Patients who have or develop hypocalcemia, hyperkalemia, cardiac dysrhythmias, hypotension, coma, or seizures should have central venous access, and the calcium infusion should be changed from calcium gluconate to calcium chloride (which contains three times as much calcium per gram) and continued at the same rate using the central venous access. The serum calcium should be measured every 30 minutes and, if hypocalcemia persists, the calcium infusion rate should be doubled. Fluids should be administered for hypotension. Cardiac dysrhythmias and hyperkalemia may not respond to usual therapies. Magnesium and potassium levels should also be monitored, and magnesium should be administered to maintain a normal serum level. Sodium bicarbonate boluses and a sodium bicarbonate infusion have been used to alkalinize critically ill patients to a serum pH of 7.45 to

7.50, but although systemic alkalosis has improved survival in animal models, alkalinization is likely to worsen hypocalcemia.

DISPOSITION

Patients who present with dermal exposures that have no symptoms after irrigation may be discharged with instructions to return or begin topical calcium therapy if pain develops. Similarly, patients who present with pain and respond well to topical or intradermal therapy in the ED may be discharged with topical therapy every 4 to 6 hours and a 24-hour follow-up. If visible burns are noted, a burn or hand surgeon should be consulted. Patients who require regional infusions are likely to require repeat therapy and should be admitted for 24-hour observation. Intra-arterial administration is an indication for intensive care unit admission (primarily for monitoring of the arterial line).

Patients who have no symptoms and a normal examination after irrigation for ocular exposures may be discharged with next day follow-up. An ophthalmologist should be consulted for patients with persistent symptoms or an abnormal ocular examination emergently. Patients with ingestions of HF products who have no symptoms and normal serum calcium levels after 6 hours may be discharged or referred for psychiatric evaluation. Those who require intravenous calcium should be admitted to an intensive care unit for ongoing monitoring and treatment.

CRITICAL INTERVENTIONS

- Immediately irrigate dermal or ocular exposures with water or saline.
- Topical calcium chloride in a gel can relieve many patients.
- Administer s.c. calcium gluconate, followed by regional, intravenous, or intra-arterial calcium gluconate infusion, for patients who have skin findings or persistent pain after dermal exposure.
- Institute cardiac rhythm (and QT interval) monitoring and give prophylactic IV calcium gluconate to patients with intentional

ingestions or large dermal, inhalational, or oral exposure.
- Administer IV calcium chloride through a central line to patients with hypocalcemia or QT interval prolongation.

Common Pitfalls

- Failure to appreciate that patients with dermal HF injury may have pain without abnormal skin findings.
- Failure to appreciate that systemic fluoride poisoning after ingestion may occur in the absence of GI symptoms.
- Failure to appreciate that severe systemic fluoride poisoning may result from large dermal and inhalational exposures.
- Failure to appreciate that large doses of calcium and magnesium may be required in patients with systemic fluoride poisoning.

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CHAPTER 331 Hydrocarbons

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Hydrocarbon is a term that covers a wide number of solvents and chemicals. Many are distilled petroleum products. Examples include: gasoline, mineral spirits, toluene, benzene, and xylene. They are commonly used as fuel, solvents, and carriers for other chemicals. Hydrocarbons are hydrophobic because of their high carbon and hydrogen content and tend to have an oily texture, but their more important properties include viscosity and volatility. More viscous substances are thicker; less viscous hydrocarbons are thinner and spread easily so that a small amount can cover a large surface, such as with furniture polish. Highly volatile chemicals become a gas easily and are prone to explosion (see Section IV), but also to inhalation, aspiration, and lung injury. Halogenated hydrocarbons contain fluorine, chlorine, bromine, or iodine, are typically excellent solvents (e.g. carbon tetrachloride or trichloroethylene found in dry cleaning fluids and refrigerants), but can cause liver disease with chronic exposure. As a solvent or carrier for other chemicals, metal-containing hydrocarbons such as leaded gasoline can cause additional toxicity.

Patients generally present in one of the four scenarios: (1) the toddler with a small accidental ingestion; (2) recreational inhalation for euphoria; (3) accidental ingestion of a small amount; or (4) intentional ingestion of a large amount by an adult. The degree of exposure and subsequent effects and symptoms vary depending on the volatility and viscosity, whether the exposure is inhaled, ingested, aspirated, or in contact with the skin, the presence of other additives, the degree of exposure, and the dose.

CLINICAL PRESENTATION

Neurologic: Hydrocarbons that are abused for euphoric effects via the respiratory route of exposure (e.g., toluene) are called inhalants. Organic solvents are readily accessible, as they are present in many household products. These products are frequently a mixture of solvents; however, toluene (in glue, lacquer, spray paint, etc.) is the substance that seems to have the highest abuse potential (1).

Misuse of volatile substances is popular among teenagers, owing to their wide availability and rapid effects. Of the 719,000 people (aged 12 or older) with first-time use of inhalants in 2011, about 67% were under 18 years of age (2). Of eighth graders surveyed in 2012, 11.8% had ever tried inhalants, 6.2% had used inhalants within the past year, and 2.7% had used within the past month (3). The abuse of inhalants may be predictive of future polysubstance abuse (1).

The chemical properties of the hydrocarbon determine its effect. Highly volatile compounds are more likely to be absorbed after inhalation. Those that are very lipophilic cross the blood–brain barrier more readily, and are more likely to result in central nervous system (CNS) effects. They also remain in the CNS longer, resulting in symptom duration that may persist after the exposure ends (1).

Acute hydrocarbon inhalation causes an initial euphoria that occurs within minutes of exposure. This can be followed by progressively worsening CNS depression, including: agitated delirium, hallucinations, ataxia, seizure, coma, and death. Associated signs can include nystagmus, hyporeflexia, tremor, and dysarthria. Some compounds are more likely than others to cause seizures, and camphor is particularly well known to cause rapidly occurring seizures. Overall, excitatory effects occur at lower doses, with sedating effects at higher doses. The exact mechanism of toxicity for each individual compound is not clear; however, toluene appears to cause both GABA-A stimulation and NMDA inhibition and may have effects at other receptors as well (1,4). Death by asphyxia can occur from airway occlusion by the plastic bags used in “bagging.” Impaired judgment from the acute intoxication can result in trauma or drowning, resulting in injury or death.

The long-term use of inhalants can result in progressive cognitive impairment. These symptoms, when associated with brain magnetic resonance imaging (MRI) changes, are termed leukoencephalopathy. Much of the literature on leukoencephalopathy in the setting of inhalant abuse is regarding toluene. Toluene abuse may also cause cerebellar and pyramidal tract dysfunction, and has been associated with cranial nerve deficits (including optic atrophy, tinnitus, and hearing loss) (5). Symptoms progress with continued use. Some authors have reported improvement after cessation of use, whereas others have observed persistent effects (6).

Toluene affects white matter to a greater degree than gray matter, which may be due to the high lipid content of the myelin that defines white matter. MRI changes with chronic toluene abuse include white matter lesions in 46%, ex-vacuo ventricular dilation in 27%, and hypointensity of the thalamus in 20%. The presence of white matter lesions and thalamic hypointensity were associated with greater than 4 years of abuse (7). Diffuse atrophy results in enlargement of the sulci and ventricles (see Fig. 331.1A,B) (6).

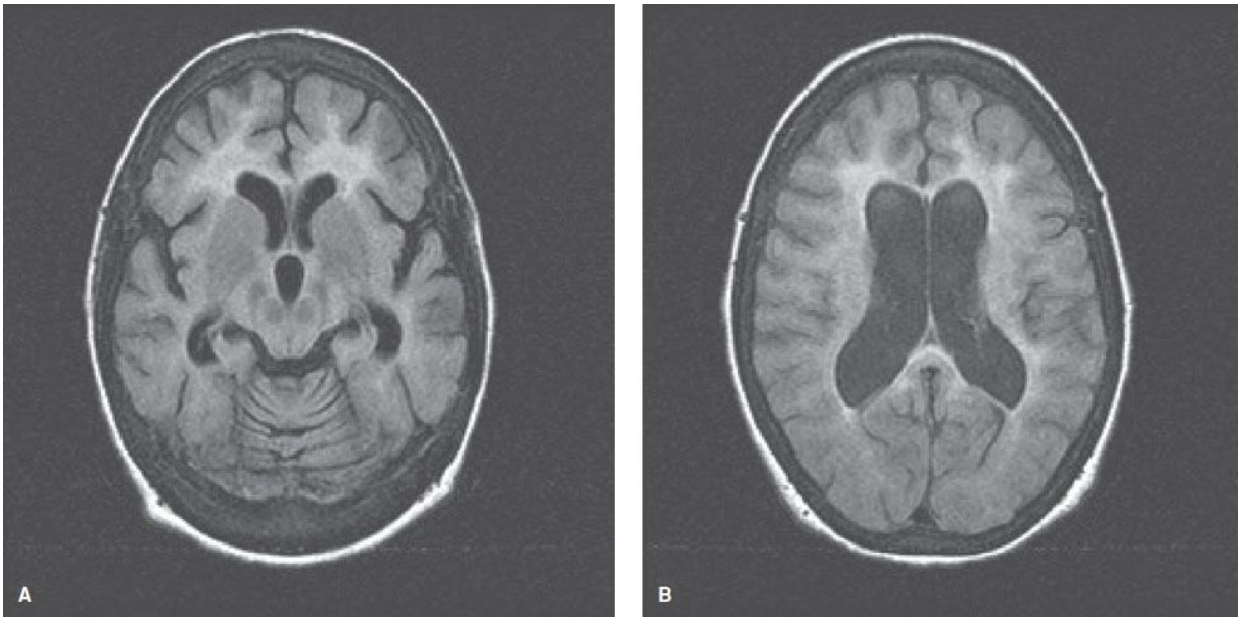

FIGURE 331.1 A, B: Toluene leukoencephalopathy. Axial FLAIR MRI of 27-year-old woman with history of chronic toluene abuse resulting in white matter changes and diffuse atrophy.

Neuropsychiatric testing of chronic toluene abusers reveals deficits in learning, memory, processing, attention, psychomotor tasks, and executive function. Compared to users of other drugs such as alcohol and cocaine, those who abused solvents had more impairment in both memory and executive function. These effects of chronic toluene use likely contribute to the higher risk of future polysubstance abuse, criminal behavior, and chronic psychiatric disease (6).

Ingestion of hydrocarbons rarely causes lethargy, seizures, coma, or other nervous system toxicity, but does present a risk of pneumonitis from aspiration.

Cardiac: Malignant arrhythmia (most commonly ventricular fibrillation) resulting in death is termed “Sudden sniffing death syndrome.” This scenario occurs in patients with a high concentration of hydrocarbon vapors, who are then suddenly excited or frightened. Dysrhythmias are more likely to occur with halogenated hydrocarbon (halocarbon) abuse. Experimental evidence shows that halocarbons induce arrhythmia by reducing gap junction conductance, hyperpolarizing cardiac cells (via blockade of potassium channels), inhibiting sodium channels, and altering calcium channel activity (8). These changes leave the heart vulnerable to catecholamine-induced after-depolarization and re-entrant arrhythmias (4).

Renal/Metabolic: Toluene intoxication causes renal tubular acidosis. Patients may present with generalized weakness, due to severe hypokalemia. There may also be muscle weakness and pain from rhabdomyolysis. Some patients report abdominal pain and vomiting.

Pulmonary: Aspiration pneumonitis is associated with high rates of morbidity and mortality. This occurs most often after an ingestion of a hydrocarbon by a toddler but also occurs after purposefully inhaling solvents, or trying to siphon gasoline. Hydrocarbons with high volatility and low viscosity pose the greatest risk for aspiration, as they can flow easily and penetrate deep into the distal airways. Examples of these substances are kerosene, mineral seal oil, lamp oil, gasoline, lighter fluid, and turpentine. Vomiting increases the risk of

development of pneumonitis, although aspiration can occur in the absence of vomiting. Symptoms of pneumonitis generally appear within 2 to 6 hours after aspiration, and include shortness of breath, fever, vomiting, and cough. More severe cases will present with grunting, wheezing, or cyanosis. Some patients will also have CNS symptoms secondary to hypoxia, independent of direct effects from the hydrocarbon (9).

Miscellaneous: Prolonged dermal contact with hydrocarbons can result in skin damage, ranging in severity from minor irritation to severe chemical burns. A rash surrounding the nose and mouth of chronic inhalant abusers is called “glue sniffer’s” or “huffer’s” rash and is secondary to a severe drying of the skin that may also allow secondary bacterial infection. Chronic dermal exposure to hydrocarbons, common at a worksite, may also result in a defatting injury. Patients who drink hydrocarbons may develop mucosal irritation, presenting as abdominal pain, nausea, and vomiting.

DIFFERENTIAL DIAGNOSIS

Intoxication from inhalant abuse can present similarly to the effects of GABA agonists (e.g., ethanol, benzodiazepines, GHB), anticholinergics, or opiates. The altered mentation is nonspecific and can be mistaken for trauma, meningoencephalitis, or systemic infection. Tachydysrhythmias and reentrant arrhythmias can occur with coronary artery disease, cardiomyopathy, electrolyte abnormalities, hypoxia, and numerous other drug and chemical exposures.

The differential of metabolic acidosis is broad, but includes methanol, ethylene glycol, salicylates, and iron poisoning. Hypokalemia can be from inadequate intake, excessive gastrointestinal loss, diuretic use, mineralocorticoid excess, or intracellular shift. Weakness from electrolyte disturbances can be mistaken for Guillain–Barré syndrome.

The respiratory symptoms of hydrocarbon aspiration can mimic reactive airway disease, pulmonary infection, or pulmonary embolism. Many other mucosal irritants produce the same

symptoms. Pulmonary infiltrates, fever, and leukocytosis secondary to aspiration of hydrocarbons may mimic an infectious process.

ED EVALUATION

After initial stabilization, a history should be obtained that includes the exact substances involved, route of exposure, and time course of ingestion. Hydrocarbon products which are ingested may contain additional toxins, such as heavy metals, pesticides, and camphor (see Chapters 318 and 326).

Symptomatic patients should be kept on a cardiac monitor. Soon after inhaled exposure, toluene is metabolized and hippuric acid forms to cause an increased anion gap acidosis. Patients can later have a normal anion gap metabolic acidosis, characterized by hyperchloremia, hypokalemia, and a high urine pH (10). Hypophosphatemia is frequently reported. Rhabdomyolysis may be present. Acute renal failure and hepatic impairment are rare complications. Patients with mild decreased level of consciousness will need observation, but patients with severe coma may need to be assessed for trauma and other causes of altered mental status.

When ingestion has occurred, the history should assess the risk of aspiration by noting manifestations such as cough, gagging, vomiting, or dyspnea. Continuous oxygen saturation monitoring should be considered to detect hypoxia. A chest x-ray should be taken for symptomatic patients, but since the findings on x-ray can be delayed, asymptomatic patients may be imaged after 6 hours to identify late infiltrates. The infiltrates seen with aspiration pneumonitis are usually interstitial and are generally bilateral (see Fig. 331.2). Hydrocarbon aspiration causes lung irritation and loss of surfactant, and can result in lipoid pneumonia (9). Leukocytosis is often present but is not necessarily indicative of an infectious process. A blood gas should be considered for those with respiratory distress.

FIGURE 331.2 Hydrocarbon-induced aspiration pneumonitis in a child.

KEY TESTING

- For inhalation, EKG and monitoring, BMP, urinalysis, calcium, magnesium, phosphorus
- For ingestion, CXR for possible aspiration; imaging if suspected head trauma
- For supportive care, CBC, BMP, LFT, CPK for suspected rhabdomyolysis

ED MANAGEMENT

For patients exposed to vapors, contaminated clothing should be removed and bagged, ideally before the patient enters the emergency department (ED). Affected skin should be cleaned gently with soap and water. Supportive care should be initiated, with special attention given to the neurologic, cardiac, and pulmonary organ systems. Patients may be at risk for dysrhythmia and sudden sniffing death.

For patients with altered mental status after inhalant abuse, most care is symptomatic and supportive. If seizure or agitation occurs, benzodiazepines should be used. Patients should be assessed for chemical dependency, and providers should recommend abstinence from further use.

After hydrocarbon ingestion, gastric decontamination is generally contraindicated, especially in cases where the hydrocarbon has a low viscosity and high volatility, as the risk of aspiration during decontamination is high. The presence of an endotracheal tube does not necessarily prevent aspiration. Emesis should also be avoided for the same reason. In rare cases, gastric decontamination may be considered, with either a nasogastric tube or activated charcoal. Not all hydrocarbons adsorb to activated charcoal but charcoal may be beneficial for a hydrocarbon solution containing dangerous additives, or for hydrocarbons with low risk of aspiration but high risk of systemic toxicity (e.g., carbon tetrachloride, methylene chloride, methylene bromide, trichloroethylene).

Airway stabilization should be the primary concern when managing a potential hydrocarbon aspiration. Supplemental oxygen may be required. For patients with inadequate oxygenation, severe respiratory distress, or alteration in consciousness, early intubation should be initiated. Positive end-expiratory pressure may be required to maintain oxygenation. For patients with wheezing or suspected bronchospasm, bronchodilators may be helpful. Steroids are not indicated. Antibiotics are not indicated as routine prophylaxis, and should not be used without clear and objective signs of infection, keeping in mind that infection is unlikely in the early stages of aspiration pneumonitis. No large-scale studies have been performed to show the most beneficial interventions for patients who have difficulty maintaining adequate oxygenation despite intubation. Case reports suggest use of surfactants, high-frequency jet ventilation, extracorporeal membrane oxygenation, or partial liquid ventilation.

Patients presenting with dysrhythmias should generally be treated with established cardiac guidelines. Catecholamines or sympathomimetics should be avoided so as to prevent ventricular fibrillation. Beta blockers are felt to be protective, and should be

considered in patients with dysrhythmias following acute hydrocarbon inhalant abuse.

Patients with renal tubular acidosis from toluene inhalation will need IV fluids and correction of electrolyte abnormalities and acid–base imbalance. They are likely to need potassium replacement. Those with rhabdomyolysis will need aggressive fluid support and alkalinization.

CRITICAL INTERVENTIONS

- Comprehensive laboratory workup for those with chronic inhalational exposure
- Cardiac monitoring and avoidance of catecholamines for those with inhalational exposure
- Assess those with intentional inhalation for chemical dependency
- Obtain chest x-ray in those with potential for hydrocarbon aspiration

DISPOSITION

Patients with sinus tachycardia after inhaling a hydrocarbon should be observed or admitted to a telemetry unit until the heart rate normalizes. Patients who have had a malignant arrhythmia should be admitted to an intensive care unit (ICU).

Patients with severe electrolyte abnormalities and anyone with weakness should be admitted to telemetry for electrolyte correction. Mild electrolyte changes generally resolve with cessation of abuse of toluene and some can be managed at home.

Patients who remain asymptomatic after aspiration and have a negative chest x-ray after 6 hours of observation may be released from the ED. Symptomatic patients who remain stable should be admitted to the hospital for observation. Indications for ICU admission include respiratory distress, altered mentation, or increasing oxygen requirement.

Common Pitfalls

- Failing to avoid catecholamine exposure in patients who have inhaled hydrocarbons.
- Failing to prevent emesis in those with hydrocarbon ingestion.
- Failing to recognize the potential severity of aspiration and the time lag of radiographic changes.

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CHAPTER 332

Hydrogen Sulfide

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Hydrogen sulfide (H_2S) is a colorless, highly lipophilic, irritant gas that is a potent inhibitor of the cytochrome oxidase system. Sources of naturally occurring H_2S include volcanoes, sulfur springs, mines ("stink damp"), and natural gas deposits ("sour gas") (1). More than 70 occupations have been identified with potential for H_2S exposure (1,2). The term *sewer gas* refers to the production of H_2S through anaerobic decomposition of sulfur-containing proteins, found in sewage and manure. After carbon monoxide poisoning, H_2S is the second leading cause of occupational toxin-related deaths. The predominant source of occupational exposure is oil and gas exploration (3). More recently, H_2S has been utilized as a means of chemical suicide, placing first responders at risk (4).

The odor threshold for H_2S ranges between 0.02 and 0.13 ppm (5). By 20 to 30 ppm, H_2S demonstrates a characteristic odor of rotten eggs. Olfactory fatigue, the point when the nose acclimatizes to the odor, occurs at levels of 100 to 150 ppm, although olfactory paralysis occurs rapidly at higher levels. Loss of ability to perceive the noxious odor may be incorrectly interpreted as dissipation of the gas, resulting in prolonged exposure to elevated levels. Levels greater than 300 ppm are considered immediately dangerous to life and health. Levels as high as 1,000 ppm occur in manure slurry tanks, resulting in the immediate deaths of farm workers and rescuers (5,6).

After absorption, H_2S is widely distributed throughout the body. Similar to cyanide, H_2S forms complexes with ferric ion–containing metalloenzymes, including cytochrome-aa_3, thereby inhibiting oxidative phosphorylation and causing cellular asphyxia. Although H_2S is a more potent inhibitor of cytochrome-aa_3 than cyanide, cyanide has a 200-fold greater binding affinity. As a result, cytochrome-aa_3 inhibition by H_2S is more readily reversible than cyanide (1).

CLINICAL PRESENTATION

Exposure to H_2S can cause both local irritant or systemic effects. Keratoconjunctivitis was first described in petroleum industry workers, at levels of 50 to 100 ppm. Symptoms include eye pain, burning, lacrimation, and mucopurulent drainage (5). Blurred vision and colored halos around lights ("gas eyes") have been attributed to corneal edema and inflammation. Corneal ulceration occurs with severe exposure (5).

Prolonged exposure to H_2S at concentrations as low as 50 ppm causes respiratory mucosal irritation and inflammation. The upper and lower respiratory tracts are equally affected resulting in pharyngitis, rhinitis, bronchitis, and pneumonitis. Symptoms include sore throat, nasal congestion and drainage, hoarseness, cough with occasional bloody sputum, and shortness of breath. Symptoms are more severe with longer duration of exposure. Pulmonary edema occurs after prolonged exposure to concentrations >250 ppm and occurs more rapidly at levels of 300 to 500 ppm (7). Autopsy findings have noted hemorrhagic pulmonary edema and scattered pleural petechial hemorrhages. In contrast to cyanide and carbon monoxide poisoning, cyanosis is frequently described in H_2S intoxication (8). The exact etiology remains unclear.

Systemic effects of H_2S exposure are predominantly from central nervous system (CNS) dysfunction. At lower concentrations, CNS effects of H_2S intoxication are nonspecific and reflect progressive cellular hypoxia. Signs and symptoms include headache, anxiety,

dizziness, ataxia, confusion, vertigo, seizures, lethargy, and coma. With acute, high-level exposure, CNS effects predominate over the delayed local irritant and inflammatory effects. Levels >200 ppm are associated with CNS depression, and levels between 700 and 900 ppm are associated with rapid loss of consciousness ("knock-down") and respiratory paralysis. Seventy-five percent of occupational exposures have loss of consciousness at the site of exposure (7).

DIFFERENTIAL DIAGNOSIS

H_2S exposure is suspected from the rapid loss of consciousness (knock-down), and the odor of rotten eggs, which can off-gas from clothing, blood, exhaled air, and gastric secretions (9). Blackened copper and silver coins or jewelry after exposure to H_2S is another clue. The differential diagnosis includes other cellular asphyxiants (e.g., cyanide, carbon monoxide, sodium azide), simple asphyxiants (e.g., methane, carbon dioxide, helium, nitrogen), pulmonary irritants (e.g., ammonia, nitrogen dioxide), and acquired dyshemoglobinemias (e.g., methemoglobinemia). Other causes of a rotten egg odor include mercaptans, disulfiram, and sulfur dioxide. Other knock-down agents include carbon disulfide, organophosphates, acetylene, and carbonyl sulfide (2).

Other etiologies of syncope and collapse must be considered, including cardiovascular, neurologic, thromboembolic, and hypoglycemic causes. Concomitant occult traumatic injury must always be considered (7,9). In one review, 27% of H_2S intoxicated patients had associated trauma. The differential diagnosis of dermal irritation includes contact dermatitis, photosensitivity reactions, trauma, infection, and vasculitis.

ED EVALUATION

Despite loss of consciousness at the scene, patients may be asymptomatic or minimally symptomatic on arrival at the emergency department (ED) (1,7,9). Initial history is directed toward confirming H_2S exposure and the severity of symptoms prior

to arrival. Important historical information includes location and actions preceding symptom onset, duration of exposure, time course of any alterations in level of consciousness, and any unusual odors noted. The possibility of coexistent trauma should also be addressed.

After evaluation of vital signs, the physical examination should focus on assessment for irritant (ocular, dermal, mucous membrane, pulmonary) and systemic (cardiovascular and neurologic) effects. A thorough neurologic examination, including mental status testing and neuropsychiatric screening batteries, if available, should evaluate for subtle neurologic dysfunction.

No tests are available to confirm the diagnosis of H_2S poisoning (2). Patients with limited irritant symptoms, normal vital signs, and normal physical examinations require no laboratory assessment. Patients with systemic toxicity should have a chest radiograph, electrocardiogram, and arterial blood gas analysis for evaluation of oxygenation and acid–base status. Anion gap metabolic acidosis and elevated serum lactate levels reflect the underlying cellular asphyxia. Occasionally, oxygen saturation gaps attributed to sulfhemoglobin may occur. Routine hematology and chemistry profiles may assess the general condition. Patients with prolonged loss of consciousness, persistent alteration in level of consciousness, or focal neurologic deficits may require radiologic imaging to evaluate for cerebral ischemic insult and trauma.

KEY TESTING

- Most patients do not need any testing.
- Evaluation of systemic symptoms includes CXR, ECG, ABG.

ED MANAGEMENT

Initial management involves removing the patient from the source of exposure. Survivors frequently improve simply with this intervention (3,7). Rescuers should not attempt to enter the environment of exposure without wearing self-contained breathing apparatus. Nearly one-fourth of occupational deaths are the result of rescue attempts (1,2,7,8). ED decontamination should include

removal of grossly contaminated clothing and cleansing with soap and water to limit local irritant effects. Ocular irrigation and the removal of contact lenses may be needed to decontaminate eye exposure.

Supportive care is the mainstay of treatment for systemic toxicity, with specific attention to advanced life-support, and management of altered mental status, pulmonary edema, hypotension, acidosis, and concomitant trauma. Supplemental oxygen (100%) enhances oxygen delivery and increase endogenous sulfide metabolism (10).

Specific data regarding antidotal therapy remain sparse and controversial. Similarities with cyanide intoxication led to the use of sodium nitrite in severe H_2S intoxication. Anecdotal reports and pretreatment animal models have demonstrated improvement with nitrite therapy (2); however, no convincing evidence exists that nitrite actually improves patient outcome or changes clinical course. In vitro time-course studies indicate that nitrite must be administered within minutes of exposure to be effective (3). In addition, the induction of methemoglobinemia by nitrites may further impair oxygen transport and worsen the clinical situation. Nitrite therapy remains recommended for patients with severe H_2S intoxication who do not rapidly improve on removal from the source, and the nitrite should be administered within 1 hour of exposure. The dose of sodium nitrite is identical to that used for cyanide (see Chapter 329). Sodium thiosulfate is not recommended. Improvement with hyperbaric oxygen (HBO) therapy has been reported, even in nitrite-refractory H_2S poisoning (2,10). HBO should be considered for severely intoxicated patients with persistent neurologic abnormalities, especially those patients unresponsive to supportive care or nitrite therapy.

CRITICAL INTERVENTIONS

- Rapid extrication of the victim from the source.
- Aggressive supportive care is the mainstay of therapy.
- Search for concomitant trauma.
- Consider sodium nitrite or HBO in severely intoxicated patients.

DISPOSITION

Patients presenting after a minor H_2S exposure may be discharged after a 4- to 6-hour observation period. Patients with toxicity limited to dermal or ocular irritation may be managed as outpatients. Patients with significant exposure (including loss of consciousness) or local airway irritation should be monitored for at least 24 hours. Patients with abnormal vital signs and cardiopulmonary and neurologic examinations should be admitted to an intensive care unit. Patients with initial loss of consciousness should be followed up within 1 week for examination for delayed neuropsychiatric sequelae. Transfer of severely intoxicated patients should be considered if intensive care or nitrite therapy is indicated but unavailable.

Common Pitfalls

- Failure of the prehospital rescuer to wear self-contained breathing apparatus and becoming an additional victim.
- Failure to consider H_2S poisoning in healthy patients who suddenly collapse at work.
- Failure to appreciate that lack of an odor does not imply safety.
- Failure to perform a scene search for other victims when an index case is found.
- Failure to anticipate delayed pulmonary injury in the minimally symptomatic patient.

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CHAPTER 333

Iron

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Although iron poisoning occurs in all age groups, it has been a leading cause of accidental poisoning death from pharmaceutical agents among young children. Household sources of iron are common and readily available for impulsive ingestions. Parents' iron supplements are often found in homes with toddlers; many of these preparations resemble candy, and some are even candy-coated. Chewable multivitamins with iron are specifically designed to appeal to young children. A dramatic decline in pediatric iron overdose deaths followed the 1997 Food and Drug administration (FDA) mandate that iron supplements be packaged in blister packs. This was combined with warning labels and public educational campaigns. After a long legal battle with pharmaceutical companies, the FDA rescinded this requirement in 2003. Fortunately, there has not been a significant rebound in the number of pediatric iron overdose deaths since 2003.

The amount of iron in each preparation varies, and toxicity after acute ingestion depends on the amount of elemental iron ingested (Table 333.1). In general, the ingestion of more than 20 mg of elemental iron per kilogram of body weight produces significant gastroenteritis; doses above the 40- to 60-mg/kg range are potentially fatal. Although confirmatory studies are lacking, children's chewable multiple vitamins with iron rarely cause severe iron poisoning and are less toxic than expected on the basis of elemental iron ingested per body weight (1). Some poison centers observe asymptomatic or only mildly symptomatic children at home after ingesting such preparations, even when the estimated ingestion

exceeds 20 mg/kg of elemental iron. In addition, newer nonionic iron formulations like carbonyl iron and iron polysaccharide have not been observed to cause significant toxicity in children.

TABLE 333.1
Common Iron Compounds and their Percent Elemental Iron Content

Common Iron Compounds and their Percent Elemental Iron Content	
Compound	**Percent Elemental Iron by Weight**
Ferrous sulfate	20
Ferrous fumarate	33
Ferrous gluconate	12

The human body cannot excrete iron so homeostasis relies on gastrointestinal (GI) absorption of iron, which is increased or decreased depending to the body's needs. Normally, about 10% of ingested iron, mainly in the ferrous (Fe^{2+}) state, is absorbed each day from the small intestine. Because free, unbound iron is toxic to tissue, the body has several mechanisms to keep iron bound to proteins or other macromolecules. After absorption, iron changes to the ferric (Fe^{3+}) state and is stored in the intestinal mucosa complexed to ferritin. Transport to other tissues occurs with iron bound to transferrin. The total amount of iron that transferrin can bind is termed the total iron-binding capacity (TIBC). Normal serum iron concentrations vary from 50 to 150 μg/dL, although normal TIBCs can range from 300 to 450 μg/dL. Because the TIBC is far in excess of the iron concentration, there is no circulating unbound iron under normal circumstances.

Excessive iron is corrosive to the GI tract, resulting in gastroenteritis, with the potential for hemorrhage, hypovolemia, and perforation. If enough iron is absorbed, systemic and metabolic consequences of iron poisoning develop. Iron accumulates mainly in the liver after overdose but can have toxic effects in almost any organ. Iron is concentrated in mitochondria, wherein it disrupts

oxidative phosphorylation and catalyzes the formation of oxygen-free radicals, leading to lipid peroxidation and cell death. Toxic amounts of iron also produce venodilation and increase capillary permeability. The metabolic acidosis seen in iron poisoning is from hypovolemia, tissue hypoperfusion, a shift to anaerobic metabolism as mitochondrial function is impaired, and the hydration of the ferric ion with generation of hydrogen ions:

$$[Fe^{3+} + 3H_2O \rightarrow Fe(OH)_3 + 3H^+]$$

Even before the onset of hepatic dysfunction, coagulopathy may occur from iron's inhibition of serine proteases, such as thrombin, and other coagulation factors. Isolated liver damage may occur, but multiple organ system failure is typical in severe iron poisonings (2).

CLINICAL PRESENTATION

Clinical effects of iron poisoning are usually considered in stages (2). However, patients present at different times after ingestion, the time frame for staging is imprecise, and it can be difficult to distinguish between stages because of rapid progression and overlapping signs, symptoms, and laboratory manifestations. Patients can die in any stage of iron poisoning but for different reasons.

The first stage develops within the first few hours after ingestion, as a result of the direct corrosive effects of iron on the GI tract, and is characterized by abdominal pain, vomiting, and diarrhea. Diarrhea may be the only manifestation in patients who ingest multiple vitamins with iron, particularly preparations intended for children. Hematemesis or melena may occur if there is significant GI bleeding. Patients with serious toxicity develop lethargy, shock, and metabolic acidosis as a result of hypovolemia, anemia, and tissue hypoperfusion. Serum iron concentrations may be normal or elevated.

With the second stage, GI symptoms resolve despite continued absorption of iron and increasing tissue iron burden. This stage may last until about 24 hours after ingestion. Patients may appear

clinically improved, but this can be falsely reassuring. Laboratory studies are likely to show elevated serum iron levels and a progressive metabolic acidosis.

In the third stage, systemic iron poisoning becomes clinically evident. This may occur early in patients with severe poisoning (bypassing stage 2). Toxic amounts of iron have now moved from blood into tissues, disrupting cellular metabolism, causing third-spacing of fluids and producing venous pooling of blood. Shock and metabolic acidosis in this stage can result from hypovolemia, anemia, hepatic dysfunction, impaired oxidative phosphorylation, heart failure, and renal failure. Fulminant hepatic failure with hypoglycemia, hyperammonemia, and coagulopathy may occur, although significant hepatic injury is unusual if peak serum iron levels remain below 500 μg/dL.

The fourth stage is an unusual occurrence several weeks after the acute toxicity has resolved, characterized by gastric outlet obstruction or small-bowel obstruction, which can develop as a result of scarring produced by iron's corrosive effects.

Elevated serum iron levels obtained near their peak, at 4 to 6 hours after ingestion, confirm the diagnosis of iron poisoning and may predict severity. A serum iron level drawn early after ingestion may be misleadingly low if absorption is still occurring. A normal serum iron level may occur in seriously ill patients many hours after ingestion after the iron has been distributed from the serum to the tissues, where it produces systemic toxicity. Therefore, a normal serum iron concentration obtained too early or too late after ingestion does not exclude iron poisoning.

Although sometimes elevated, the white blood cell count ($>$15 k/mm^3) and serum glucose concentrations ($>$150 mg/dL) are not of sufficient sensitivity to assess the severity of acute iron poisoning (3). The "deferoxamine challenge" test, in which the presence of vin rosé–colored urine after giving a dose of deferoxamine was considered an indication for chelation therapy, is no longer recommended because it is unreliable (4). An abdominal radiograph may demonstrate radiopaque tablets in the GI tract, a finding often present in patients who develop serious poisoning. However, a

normal radiograph does not exclude a significant ingestion. Even when iron tablets are noted initially, they are usually no longer visible at 24 hours.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of patients presenting with GI symptoms includes infectious gastroenteritis, medical and surgical intra-abdominal conditions, or sepsis that may cause vomiting, diarrhea, acidosis, and shock. Acute iron poisoning is not typically accompanied by fever unless a complication such as aspiration or bowel infarction develops. Iron poisoning can mimic intussusception with an ill-appearing toddler with occult fecal blood. Other toxicologic etiologies with a similar presentation include poisoning by acetaminophen, salicylate, hepatotoxic mushrooms, arsenic, caffeine and theophylline, caustics, copper salts, and mercurial salts.

ED EVALUATION

The history should include the time and the nature, severity, time of onset, and progression of symptoms. The physician should specifically ask about abdominal pain, vomiting, and diarrhea and the presence of blood. The amount of elemental iron ingested, in milligrams per kilogram, should be calculated from the amount of ingestion, and the identity of the iron preparation (see Table 333.1). The physical examination should focus on vital signs, overall appearance, and the abdomen.

Patients who have had only one or two episodes of vomiting or diarrhea and are subsequently asymptomatic should have a complete blood count (CBC) and measurement of serum electrolytes, glucose, blood urea nitrogen, creatinine, iron levels, and an abdominal radiograph. Those with abdominal pain or persistent GI symptoms, evidence of hypovolemia, or lethargy should also have liver function studies, serum lactate, prothrombin time, partial thromboplastin time, and blood gas analysis. Because measure of the TIBC is inaccurate in the setting of iron overload it is not helpful in the evaluation of iron toxicity (5).

KEY TESTING

- Obtain a CBC, serum electrolytes, glucose, blood urea nitrogen, creatinine, a serum iron concentration, and abdominal radiograph in patients who ingest >20 mg/kg of elemental iron OR are symptomatic.
- Consider serial iron concentrations in patients with significant symptoms until iron levels peak.
- Obtain liver function studies, serum lactate, prothrombin time, partial thromboplastin time, and blood gas analysis in patients with significant GI symptoms, hypotension, or lethargy.

ED MANAGEMENT

Activated charcoal does not effectively bind iron. Gastric lavage has not been shown to be of clinical benefit, possibly because most iron tablets are too large to evacuate. Simulated overdose studies suggest that oral magnesium oxide (milk of magnesia, 60 mL/g of elemental iron ingested) (6) or a slurry of charcoal mixed with deferoxamine (7) can reduce iron absorption, but the utility of such treatments in actual overdose patients is unknown.

Patients who remain completely asymptomatic (including absence of lethargy) for 6 hours after ingestion and have a normal physical examination do not require treatment.

Those who ingested >20 mg/kg of elemental iron but are seen within 6 hours might benefit from whole-bowel irrigation. Radiography demonstrating numerous tablets suggests that serum iron concentrations will rise and whole-bowel irrigation with a polyethylene glycol-electrolyte solution has been used with good results, although controlled studies are lacking (8). The empiric adult dose starts at 2 L/hr and pediatric dosing at 20 mL/kg/hr and adjust as tolerated until clear rectal effluents.

If the serum iron concentration in an asymptomatic patient is <350 μg/dL and a repeat serum iron level shows no rise in the iron level, the patient can be safely discharged. Patients who have had only one or two episodes of emesis or diarrheal stool but who have remained asymptomatic for several hours and have a normal

physical examination, abdominal films, and laboratory evaluation do not require further treatment.

Patients with more than two episodes of emesis or diarrhea or evidence of hypovolemia or exhibit lethargy require treatment with fluids and chelation therapy with deferoxamine mesylate. Typically, chelation is also recommended in patients with a serum iron concentration greater than 500 μg/dL at 4 to 6 hours postingestion. In patients with significant symptoms, treatment should not be delayed to wait for results of a serum iron determination, because the therapy is indicated regardless of the serum iron concentration. Iron ingestion can raise the serum iron level above the normal range, and an elevated iron level alone does not constitute an indication for deferoxamine or admission in the absence of clinical signs of toxicity.

With rare exceptions, all symptomatic patients are hypovolemic. IV fluid challenges of 20 mL/kg of normal saline or lactated Ringer's are given to restore fluid volume and ensure a normal urine output. Patients commonly require maintenance infusions at twice normal rates to keep up with GI losses and third-spacing.

Deferoxamine mesylate can remove iron from tissues and nontransferrin-bound iron from plasma. Deferoxamine binds to iron to form ferrioxamine, which is excreted in the urine over days to weeks. Ferrioxamine occasionally imparts a vin rosé color to the urine, but this color change is inconsistent and should not be used to determine the need for additional treatment (2,4). Deferoxamine mesylate can be mixed in any crystalloid and should be continuously infused intravenously at 15 mg/kg/hr. Higher infusion rates can be tried in severe cases but are sometimes associated with hypotension (presumably from histamine release); this is rare with infusion rates below 45 mg/kg/hr, and resolves with slowing the infusion. Intramuscular deferoxamine is not recommended.

Many statements in the manufacturer's package insert for deferoxamine do not reflect currently accepted treatment practices. Deferoxamine is not contraindicated for the treatment of acute iron poisoning in pregnancy. Animal data and human experience strongly suggest that neither toxic amounts of maternally ingested

iron nor deferoxamine or ferrioxamine cross into the fetal circulation (9). Fetal death results from maternal demise, and a pregnant woman should be treated in the same way as any other patient. At 15 mg/kg/hr, many patients receive well in excess of 6 g deferoxamine mesylate each day, which is safe for the short-term treatment of iron poisoning.

Deferoxamine causes serum iron concentrations to be falsely low (10), which should not be a cause for stopping chelation therapy. Intravenous deferoxamine should be continued until clinical toxicity has resolved, serum iron levels are normal or low, and vin rosé–colored urine (if ever present) disappears (2). Most patients require 12 to 24 hours of deferoxamine infusion, but occasional patients with very large overdoses require more prolonged therapy. Use of hemodialysis in addition to a deferoxamine infusion after massive overdose has been reported but experience is limited. The use of prochlorperazine (Compazine) and deferoxamine together has produced coma in humans and this drug combination should be avoided.

CRITICAL INTERVENTIONS

- Administer intravenous normal saline and deferoxamine to patients with significant GI symptoms, hypotension, lethargy, and/or a 4- to 6-hour postingestion serum iron level greater than 500 μg/dL.
- Consider whole-bowel irrigation when radiopaque tablets are seen on radiographs.

DISPOSITION

Patients who remain completely asymptomatic or those with a normal physical examination, normal abdominal radiograph, and laboratory evaluation and only one or two episodes of emesis or diarrhea and then remain asymptomatic 6 hours after ingestion can be discharged.

Patients with mild symptoms should have repeat laboratory studies demonstrating no rise in the serum iron level and no

evidence of metabolic acidosis before being cleared for discharge. Symptomatic patients should be admitted. The level of monitoring and treatment required usually necessitates admission to an intensive care unit. If serum iron levels or deferoxamine chelation therapy is not available, the patients should be transferred to a facility in which such services are available.

Common Pitfalls

- Failing to administer adequate amounts of IV fluids.
- Waiting for the serum iron level before administering deferoxamine to a symptomatic patient.
- Using the TIBC for evaluation and treatment decisions.
- Sending patients home during the second stage of poisoning because they appear clinically improved.
- Assuming that a normal iron level, serum glucose, white blood cell count, deferoxamine challenge, and abdominal x-ray exclude significant iron poisoning.
- Giving prochlorperazine (Compazine) and deferoxamine together.
- Failing to appreciate that deferoxamine may falsely lower serum iron concentration.

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CHAPTER 334

Lead

Steven M. Marcus

While public health efforts have successfully decreased the incidence of significantly elevated blood lead levels it is important to be aware of the possibility of exposure and to rule it out when symptoms and signs either suggest it or are so confusing that a definitive diagnosis cannot be made (3). Populations that might be considered at greatest risk are those occupationally exposed to sources of lead and the immigrant population that may have been exposed before immigrating or may have brought their source of lead with them in the process (5). The other population of importance is those individuals with retained metallic foreign bodies, such as veterans who may carry significant caches of lead bullets and other fragments in their muscle masses.

CLINICAL PRESENTATION

Patients with lead poisoning may present with nonspecific symptoms as headache, fatigue, malaise, abdominal pain, constipation, and vomiting. The abdominal pain is usually colicky and not responsive to standard analgesics. There may be complaints of peripheral paresthesias or hypoesthesias and occasional frank neurologic symptoms (e.g., wrist or ankle drop). The classic wrist drop more common in the dominant arm was seen in painters. Muscle weakness may also be noted. Depression and other affective disorders as well as erectile dysfunction have been reported in lead-poisoned adults (4). Hyperactivity, delayed development, or loss of

recently acquired skills may be seen in children with coma and seizures in severe cases.

Physical examination is generally unrevealing, although the blood pressure may be elevated. Occasionally, in adults with poor dental care, there may be a lead line, a dark bluish black discoloration of the gingiva at the dental border. This finding is rarely present in children or in adults with good dental hygiene. If increased intracranial pressure accompanies lead encephalopathy, examination of the optic fundi may show papilledema. Cardiac dysrhythmias such as premature ventricular contractions are reported.

An abdominal radiograph may detect radiopaque foreign bodies in patients with pica or accidental lead ingestion. In developing children, long-bone radiographs may show an increased density of metaphyseal growth plates as a result of disordered calcium deposition resulting in “lead lines.” This finding may persist into later childhood or adolescence but is rarely present in adults.

The laboratory usually reveals a hypochromic microcytic anemia. Lead may produce a nonautoimmune hemolytic anemia with increased red cell fragility and an elevated reticulocyte count. Basophilic stippling and eosinophilia are less often noted. Proteinuria, glycosuria, a Fanconi syndrome (with aminoaciduria and renal tubular acidosis), and increased blood urea nitrogen and creatinine levels may be seen in patients with lead nephropathy. Because lead reduces the excretion of uric acid, adults with lead toxicity are at risk to develop gout.

Although generally not available on an emergency basis, the definitive diagnosis of lead poisoning depends on the measurement of whole-blood lead which often also guides treatment. Lead levels as low as 5 μg/dL have been reported to produce biochemical abnormalities and, in children, may be associated with decreased intelligence and neurobehavioral problems (1,2). Lead levels above 10 μg/dL in children and above 40 μg/dL in adults are currently considered to be evidence of increased lead absorption serious enough to warrant intervention.

DIFFERENTIAL DIAGNOSIS

Lead poisoning can be called the great imposter, as the symptoms and signs are often obscure and resemble a host of medical and psychiatric illnesses and patients with risk factors for lead exposure should be evaluated. Lead poisoning shares symptoms with other heavy metal poisonings. The peripheral neuropathy from lead, more often seen in adults than children, tends to be more motor than sensory. Unlike arsenic, the peripheral neuropathy from lead is associated with decreased sensitivity; with arsenic, there are painful paresthesias. The "hallmark" of thallium poisoning is burning paresthesias and hair loss. Both lead and mercury poisoning are characterized by personality changes. Mercury intoxication is characterized by "erythrism" and rapid changes in affect, with outbursts of anger alternating with happiness. Lead poisoning is more often accompanied by depressive disorders.

ED EVALUATION

Patients who present to the emergency department (ED) with multisystem complaints, particularly chronic abdominal symptoms that have not responded to standard conservative therapy, should be suspected of having lead poisoning. The patient's occupation, hobbies, use of herbal or other folk remedies, or living conditions may suggest exposure to lead. Subtle changes in bowel habits, behavior, mood, and cognitive function and headaches, weakness, and paresthesias are nonspecific but provide supporting clues.

In addition to vital signs and a general physical examination, a detailed neurologic examination should be performed, including assessment for papilledema and gingival pigmentation. If recent lead ingestion is suspected, an abdominal radiograph showing a radiopaque object in the intestinal lumen may be helpful. In children, long-bone radiographs (knee and wrist) may reveal thickening of the growth plate from growth arrest and suggest chronic lead exposure. The laboratory evaluation should include a complete blood count, whole-blood lead, and free erythrocyte protoporphyrin (FEP) levels, serum blood urea nitrogen and

creatinine levels, and a urinalysis. Care must be taken to use lead-free collection techniques when measuring lead levels.

Unless a patient is symptomatic with a high suspicion of lead poisoning, blood lead levels should be confirmed before initiating treatment. Conversely, a patient presenting with symptoms and signs consistent with lead poisoning and a history suggestive of lead exposure should begin therapy immediately, to avoid any delay which may have serious effects on survival.

In some cases, a patient is referred to the ED with a known exposure or a known elevated blood level of lead. These patients need a baseline assessment and a decision whether chelation is necessary. When children are brought to the ED because parents are concerned about a possible exposure to lead contaminated toys, a blood level can be obtained and referral made for further management. If an acute ingestion is suspected, a plain film can be obtained to identify the need for whole-bowel irrigation.

KEY TESTING

- Blood lead level: use lead-free blood collection tubes
- Complete blood count
- If evidence of anemia workup to include, reticulocyte count, bilirubin direct and total, serum haptoglobin ferritin
- Basic metabolic profile with electrolytes, renal and hepatic functions, uric acid, and serum osmolarity

ED MANAGEMENT

It is increasingly unlikely to see a child, or adult, with acute, symptomatic lead poisoning. More likely, the physician is confronted with a child and his/her parent bearing a note stating the child's blood lead level. Since the primary treatment of lead poisoning is separation from the source of lead, unless the source is obvious, the most likely action will be to facilitate the individual's admission and environmental intervention.

Critical cases of acute poisoning with cerebral edema should be treated by hyperventilation, elevation of the head, and restriction of

fluids. Seizures should be controlled with pharmacologic agents such as benzodiazepines and barbiturates. In patients with acute encephalopathy (with or without coma or seizures), chelation therapy should be initiated before obtaining confirmatory laboratory data, because the long-term outcome is related to the length of time the vital organs are exposed to elevated lead levels. Although there is little science to prove efficacy or any alteration in outcome, whole-bowel irrigation may be considered if there is radiopaque material in the intestine, but decontamination should not delay parenteral chelation therapy in a symptomatic patient. Because there is controversy that oral chelation may increase absorption of lead, it should not be done in asymptomatic patients if there is lead within the proximal intestinal lumen (lead in the sigmoid colon or rectum is considered unabsorbable and not a risk).

Although there are no randomized clinical trials reporting the use of chelation, the standard of care since the late 1960s, is to treat all children with elevated lead levels that might cause neurologic damage. That range has varied over time depending on prevailing data. Currently, the FDA licensed indication for oral chelation therapy with succimer is for children with lead levels >45 μg/dL. Although not FDA licensed specifically, chelation is often recommended for adults with blood lead levels >80 μg/dL, and for patients with lower levels who have evidence of lead-associated symptoms or signs.

Dimercaprol (British Anti-Lewisite [BAL]) crosses the blood–brain barrier and forms a tight bond with lead; in patients with lead encephalopathy, it is the initial therapy of choice. An oil-based solution of dimercaprol is given intramuscularly in a usual dose of 3 to 5 mg/kg every 4 to 6 hours. BAL is suspended in peanut oil, so for patients with a history of peanut allergy, a test dose of BAL is **not** recommended since anaphylaxis could occur even with a test dose. Alternative treatment would then be recommended. Dimercaprol is painful when injected, and foul-smelling. Sterile abscesses may occur at the site of dimercaprol injection, and febrile responses are common. Many patients complain of lightheadedness and a terrible taste in their mouth.

Calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$, also known as calcium disodium versenate) is water-soluble and can be given IM or IV. The lead-EDTA bond is very strong and stable at a physiologic pH. However, in acid urine, the bond is less stable, and there is the potential for release of free lead into the renal tubule and subsequent renal tubular damage. The main side effects of EDTA are phlebitis (with concentrations >0.5 mg/mL) and potential renal toxicity. IV administration is preferred because IM injections are extremely irritating and produce elevations of creatine phosphokinase. If the intramuscular route is used, pain is decreased with procaine or lidocaine, usually added to produce a 0.5% concentration of the local anesthetic.

$CaNa_2EDTA$ dose of 50 mg/kg/d may be given as a continuous IV drip. At a concentration of 0.5 mg/mL, a large amount of fluid must be infused. However, if the patient can tolerate the fluid load, the incidence of side effects, particularly renal dysfunction, may be decreased. IM $CaNa_2EDTA$ is given in divided doses every 4 to 24 hours. Because the use of $CaNa_2EDTA$ alone may liberate bone lead and transiently raise brain lead levels and increase symptoms, it is advisable to start with an initial dose of dimercaprol in symptomatic patients and those with high blood lead levels (>55 μg/dL in children and 100 μg/dL in adults).

Oral chelation with dimercaptosuccinic acid or succimer (Chemet) may be indicated for children with lead levels above 45 μg/dL and is as effective in clearing lead as the combination of dimercaprol and EDTA. The side-effect spectrum is minimal, with a small incidence of skin rash, transaminase elevations, and GI discomfort. Although not officially licensed for adults, it has been used because of its effectiveness, combined with its low order of toxicity. The published dosage in children is safe in adults—10 mg/kg/dose every 8 hours for 5 days, followed by 10 mg/kg/dose every 12 hours for an additional 14 days. Patients should be monitored for toxicity with weekly blood counts, chemistry profiles, and urinalysis. The presence of ketones in the urine may be used as a measure of compliance, because it is a very common accompaniment of

successful treatment. A mild rash or mild transaminitis is usually not a reason to abandon therapy but requires more frequent observation. It is important to ensure that no further exposure to lead occur while on oral chelation. There is no data demonstrating any long-term improvement in children treated with succimer, and a controlled, randomized clinical trial study funded by the National Institute for Environmental Health Sciences treating children with blood lead levels between 25 and 45 μg/dL, showed that, beyond 6 months, there is not a difference between the blood lead levels in those chelated and those given placebo and no significant effect on cognitive development (6).

Another oral chelator, *d*-penicillamine, a derivative of penicillin, is given orally at a dosage of 30 mg/kg/d, with the average adult dose of about 1.0 to 1.5 g/d. It is usually used only for adults with mild or no symptoms but high lead levels. Side effects include diarrhea, renal toxicity, leukopenia and, occasionally, a rash. Penicillamine is less effective than dimercaprol or $CaNa_2EDTA$.

If renal toxicity develops as a result of antidotal therapy, fluid input should be increased to dilute the lead content of the urine. Alkalinization of the urine may also be helpful.

Chelation therapy should be continued until the lead level drops below 20 μg/dL in children and 40 μg/dL in adults. Maximum lead excretion occurs during the first 3 days of chelation therapy and falls off rapidly. After 5 days of therapy, it is unlikely that there will be further significant lead excretion without a rest period to allow lead to redistribute from tissue compartments to the blood. Hence, chelation therapy is usually limited to a 5-day course of parenteral drug, followed by a treatment-free interval of 2 to 7 days. Oral succimer therapy is usually discontinued after 19 total days of therapy. Additional courses of therapy are indicated if symptoms persist or blood lead levels remain elevated. Repeat lead levels should be monitored, initially, at least weekly. Reinstitution of therapy depends on the “rebound” in lead level. Children with lead levels below 20 μg/dL and adults with levels below 40 μg/dL do not need chelation but should be managed by preventing further

exposure by environmental and educational interventions. Follow-up evaluation and periodic monitoring are required.

The vast majority of lead-poisoned patients survive although the final neurologic outcome may not be known for many weeks or months after treatment. Patients with cerebral edema have a poor prognosis.

CRITICAL INTERVENTIONS

- Consult a poison center or lead-poisoning expert for management advice in patients with suspected or confirmed lead poisoning.
- Admit patients with lead encephalopathy and administer dimercaprol (BAL) IM followed by IV calcium disodium EDTA (calcium disodium versenate).
- Obtain blood lead levels in children with suspected exposure and arrange for close follow-up.
- Use special lead-free blood collection tubes and technique to collect specimens.

DISPOSITION

All patients with evidence of encephalopathy should be admitted. Although chelation with $CaNa_2EDTA$, penicillamine, and succimer can be done on an outpatient basis, it is advisable to admit all patients who are symptomatic. Since separation from source of lead is paramount in treating the lead-poisoned patient, admission may be the safest approach, even in the asymptomatic patient. Because blood lead levels are not immediately available at the time of initial evaluation, patients who are not acutely ill can be discharged and admitted later if blood lead confirms the suspected diagnosis.

For patients admitted for chelation the following can be considered a good guideline for discharge.

1. Blood lead levels dropped by a minimum of 50% or to <25 μg/dL.
2. Source of lead exposure documented and reexposure risk eliminated.

3. Patient/family has possession of appropriate chelating medication as needed.
4. Chelator can be administered correctly, if a child then an appropriate caregiver demonstrates the ability to administer the drug.
5. Weekly follow-up arranged to insure follow-up at least until blood lead level has stabilized < 25 μg/dL.

Further exposure to lead must be prevented with environmental and occupational investigations to determine the most likely source of lead so that it can be eliminated. Involvement of the public health department, primarily for a child with lead poisoning, is imperative. Many states have active divisions of occupational and environmental health that may be helpful in the long-term treatment of patients.

Although chelation therapy is not difficult, some of the nuances are appreciated only after treating many patients so it may be helpful to consult an experienced toxicologist or a regional poison control center.

All patients should be seen within 2 weeks of chelation therapy for repeat lead and FEP levels, because lead will be mobilized from storage sites, and blood levels will rebound after treatment. However, without continued exposure to lead, it is rare for the lead level at 2 weeks after therapy to equal or exceed the initial level.

Common Pitfalls

- Failure to consider the diagnosis of lead poisoning in patients with cognitive dysfunction, neurologic symptoms, and GI complaints.
- Failure to appreciate that elevated lead levels without coincidental elevations in FEP may be seen with recent exposures and to treat the patient with an extremely high lead level regardless of the FEP level.
- Failure to appreciate that lead poisoning is a reportable illness in many states.
- Failure to identify the source of lead and to prevent reexposure.

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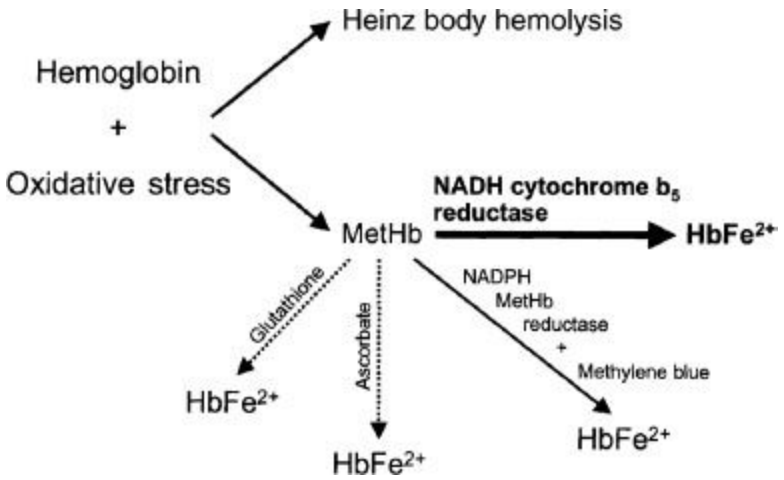
CHAPTER 335 Methemoglobinemia

David A. Tanen

Normal hemoglobin (oxyhemoglobin and deoxyhemoglobin) contains four heme groups, each with a ferrous (Fe^{2+}) ion capable of binding oxygen. Oxidative stress within the red cell produces methemoglobinemia when the iron in reduced hemoglobin is oxidized to the ferric state (Fe^{3+}). Under normal conditions, methemoglobin levels are <1% to 2% of total heme pigments. Higher fractions are termed *methemoglobinemia.* Oxidative stress within the red cell can also lead to the denaturation of red cell proteins (Heinz bodies), splenic sequestration of damaged erythrocytes (bite cells), and hemolysis.

Hemoglobin is slowly oxidized to methemoglobin under normal conditions, but the erythrocyte can catalyze the reduction of methemoglobin back to reduced hemoglobin (eFig. 335.1) by the enzyme variously known as NADH-dependent methemoglobin reductase or NADH cytochrome-b_5 reductase.



eFIGURE 335.1 Pathways of hemoglobin oxidation and methemoglobin reduction.

In normal people, enzymatic reduction of methemoglobin occurs at a rate 200- to 300-fold greater than its spontaneous formation. However, congenital deficiencies in NADH cytochrome-b_5 reductase or in cytochrome-b_5 itself can cause methemoglobinemia or can greatly predispose a person to developing methemoglobinemia. Neonates are at increased risk for developing methemoglobinemia after metabolic acidosis or oxidant stress (e.g., drugs, toxins, sepsis) because they have lower levels of NADH cytochrome-b_5 reductase and cytochrome-b_5 until they reach 4 months of age (1,2).

A second enzyme, nicotinamide adenine dinucleotide phosphate (NADPH) methemoglobin reductase, can facilitate the reduction of methemoglobin, but there is no cofactor for this enzyme. It has no role in maintaining methemoglobin levels at normal concentrations, however, exogenously administered methylene blue acts as an intermediate and greatly increases the activity of this enzyme.

People with depressed levels of erythrocytic NADPH (e.g., glucose-6-phosphate dehydrogenase [G6PD] deficiency) or a congenital lack of the NADPH-dependent reducing enzyme do not normally suffer from and are not predisposed to developing methemoglobinemia. However, if these patients who are functionally G6PD deficient do develop methemoglobinemia, treatment with methylene blue would be ineffective and may even trigger massive hemolysis (3).

Exposure to a variety of agents may result in acquired methemoglobinemia (Table 335.1). Not all of the compounds are direct oxidants, so in some cases, their metabolites or oxidizing intermediates (e.g., free radicals) are responsible for producing the methemoglobin. Although infrequently encountered, the most common therapeutic agents that cause methemoglobinemia are local anesthetics, which may be injected or applied topically (e.g., infant teething gels and benzocaine sprays), metoclopramide (Reglan),

phenazopyridine (Pyridium), and diaminodiphenylsulfone (Dapsone) (4,5).

TABLE 335.1
Some Methemoglobin-Producing Agents

Acetanilide	Food Additives	Phenacetin
Amyl nitrite	Hydrazines	Phenols
Aniline dyes	Hydroxylamine	Phenylazopyridine
Arsine	Inks	Prilocaine
Benzocaine	Lidocaine	Primaquine
Bismuth sulfate	Local anesthetics	Pyridine
Chlorates	Methylene blue	Quinones
Chromates	Metoclopramide	Riluzole
Cyclophosphamide	Mushrooms	Shoe dye or polish
Dapsone	Naphthalene	Sulfonamides
Dinitrophenol	Nitrates	Sulfones
Dinitrotoluene	Nitrites	Toluidine
EMLA	Nitrobenzene	Trinitrotoluene
Flutamide	Nitroglycerin	

Many environmental exposures can lead to the induction of methemoglobinemia. Aniline and related aromatic amines are some of the most common, along with exposure to nitrates that are converted to nitrites by bacteria in the gastrointestinal (GI) tract. Fatal cases of methemoglobinemia have been reported in infants who ingested well water high in nitrites. The recreational use of inhalable nitrites that are used as sexual enhancers, such as isobutyl nitrite has also caused methemoglobinemia (6).

Compared to red oxyhemoglobin, methemoglobin may possess a characteristic “chocolate brown color.” Typically, cyanosis requires 5 g/dL blood of reduced (ferrous) hemoglobin. However, in methemoglobinemia, only 1.5 g/dL of ferric heme is needed for noticeable discoloration. Therefore, cyanosis may be seen in nonanemic patients with 10% to 20% methemoglobin. Methemoglobin cannot transport oxygen and results in a functional anemia. The presence of ferric heme groups impairs the unloading

of oxygen by oxygenated (ferrous) heme, producing a leftward shift in the oxyhemoglobin dissociation curve. The physiologic consequences of methemoglobinemia are secondary to decreased tissue oxygenation. Metabolic acidosis develops secondary to functional hypoxia.

CLINICAL PRESENTATION

Nonanemic patients with 10% to 20% methemoglobinemia usually present with unexplained cyanosis and no other symptoms. Headache, dyspnea on exertion, tachypnea, tachycardia, and mild hypertension usually are not noted until the methemoglobin levels reach 15% to 35%. Higher fractions can result in confusion, coma, seizures, apnea, ventricular dysrhythmias, bradyarrhythmias, hypotension, and lactic acidosis. Death is frequently seen with methemoglobin fractions above 70%.

Patients with underlying cardiovascular or cerebrovascular disease are more susceptible to the effects of hypoxia. Those with pre-existing anemia or with concomitant Heinz body hemolytic anemia suffer greater toxicity at a given methemoglobin level, because the remaining functional hemoglobin concentration is lower. Also, cyanosis may not be apparent in the anemic patient because a greater percentage of methemoglobin would be needed to reach the 1.5 g/dL threshold of cyanosis as compared to the nonanemic patient. Hence, anemic patients can suffer from significant methemoglobinemia without exhibiting cyanosis.

The cyanosis of methemoglobinemia is refractory to oxygen. The arterial $PO_{2,}$ which measures dissolved oxygen in plasma, is actually normal or elevated and can be measured accurately by a co-oximeter. Pulse oximetry measurements, however, are inaccurate in the presence of methemoglobin, which falsely lowers the oxygen saturation reading. Metabolic acidosis may be present in severe cases. Venous blood may have a brown hue. A low hemoglobin, bite cells on peripheral blood smear, Heinz bodies with this stain, and increased serum haptoglobin and pink plasma from hemoglobinemia occur in severe cases of hemolysis. The electrocardiogram (ECG)

may reveal signs of tissue hypoxia such as tachycardia, bradycardia, ventricular dysrhythmias, and myocardial ischemia.

DIFFERENTIAL DIAGNOSIS

Unlike cyanosis from hypoxia, the cyanosis of methemoglobinemia is accompanied by a normal PO_2 on blood gas analysis which does not increase with supplemental oxygen. Arterial blood gas reveals a normal percentage of oxyhemoglobin (percentage saturation) because most blood gas instruments do not directly measure oxyhemoglobin fractions but, rather, calculate what the percentage hemoglobin saturation should be based on the dissolved oxygen tension. These calculations assume the absence of methemoglobin, carboxyhemoglobin, and sulfhemoglobin and assume there is no shift in the dissociation curve from changes in erythrocytic 2,3-diphosphoglycerate concentrations (5). A co-oximeter is required to directly measure and report the true percentage saturation, the total hemoglobin concentration, and percentages of oxyhemoglobin, methemoglobin, and carboxyhemoglobin. Sulfhemoglobin is usually recognized as methemoglobin by these instruments. The difference between the percentage of theoretical hemoglobin saturation calculated by the blood gas analyzer and the actual saturation measured by the co-oximeter is called the *oxygen saturation gap.* A large oxygen saturation gap in arterial blood is almost always as a result of carboxyhemoglobin or methemoglobin. To interpret blood gas reports accurately, the emergency physician must know whether reported percentage saturations on arterial blood gas samples are determined by co-oximetry.

Most traditional pulse oximeters (e.g., ear or finger oximeters) measure only oxyhemoglobin and deoxyhemoglobin and cannot account for methemoglobin or carboxyhemoglobin. As methemoglobin rises, the pulse oximetry reading approaches 84%. Therefore, a pulse oximeter can report a falsely low hemoglobin oxygen saturation in the presence of methemoglobinemia or carboxyhemoglobinemia (7). Recently, noninvasive pulse oximetry units have been developed that can also measure methemoglobin

and carboxyhemoglobin thereby enabling the clinician to rapidly identify these conditions (8).

A peculiar and poorly characterized cyanosis may also be seen in some cases of hydrogen sulfide. Sulfhemoglobinemia, a rare cause of cyanosis, causes noticeable discoloration at only 0.5 g/dL blood and can produce a saturation gap with a normal arterial PO_2. Most co-oximeters measure sulfhemoglobin as methemoglobin. Fortunately, sulfhemoglobin is rarely (if ever) severe enough to cause life-threatening symptoms. Generalized bluish discoloration from excessive administration of methylene blue may also be confused with cyanosis (4). Other unusual causes of blue skin coloring mistaken for cyanosis include dye from tight wet clothing that leaches onto the skin.

ED EVALUATION

A careful history should be taken from the patient and family regarding medications, occupational exposures to chemicals, family history of methemoglobinemia, recreational drug use and, in the case of children, any substances in the house that could have been ingested. The physical examination should focus on vital signs, skin color, and any evidence of cerebral or myocardial hypoxia. At the bedside, a drop of the patient's blood can be placed on filter paper and allowed to dry. Blood that appears obviously brown, predicts a level of at least 15% methemoglobin, assuming a normal total hemoglobin concentration. A formal color chart for comparison has been developed to reliably predict the methemoglobin concentration (9).

KEY TESTING

- If available, specialized noninvasive pulse oximetry can assess the degree of methemoglobinemia at the bedside.
- Venous blood for co-oximetry for determination of the methemoglobin fraction.
- Bedside color comparison of brown versus red blood.

- Complete blood count, especially hemoglobin to guide methylene blue dosage.
- Serum electrolytes, blood urea nitrogen, creatinine, and glucose do not routinely assist in the diagnosis but can identify comorbidities.
- Electrocardiogram for suspicion of hypoxic cardiac stress.
- Heinz body preparation, haptoglobin, plasma-free hemoglobin concentrations. and urinalysis if hemolysis is suspected.

ED MANAGEMENT

Patients with methemoglobinemia should be placed on oxygen to maximize the oxygen delivery of the residual normal hemoglobin and oxygen dissolved in the plasma. Intravenous access should be established, and the patient should be placed on a cardiac monitor.

Most patients with mild methemoglobinemia (<30%) are blue but asymptomatic and do not require treatment (1,2). Once exposure to the offending agent is terminated, methemoglobin levels usually return to normal within 12 to 36 hours. Patients with symptoms unrelieved by oxygen, with methemoglobin fractions above 30%, ECG changes, or a metabolic acidosis should receive antidotal therapy with methylene blue, provided there is no history of G6PD deficiency. Methylene blue is available as a 1% solution (10 mg/mL) and should be given intravenously over 3 to 5 minutes at an initial dose of 2 mg/kg (0.2 mL/kg of a 1% solution) (1,2). A dramatic response with resolution of cyanosis usually occurs within 15 minutes. If the patient is seriously symptomatic and no response is noted within 15 minutes or if the patient remains moderately symptomatic after 15 to 30 minutes, repeat doses of 1 mg/kg (0.1 mL/kg of 1% solution) can be given. If methemoglobin levels are readily available, they should be performed before repeat doses of methylene blue are given, because large doses of methylene blue themselves might cause oxidation if given too rapidly and produce methemoglobinemia and can cause discoloration of skin. The total dose of methylene blue during the first 2 to 3 hours should not exceed 5 to 7 mg/kg (1,2). Patients with anemia and lower total

hemoglobin should receive correspondingly lower doses of methylene blue.

Adverse effects of methylene blue include dysuria, substernal chest pain, and anxiety. Urine frequently turns blue and then green as the drug is excreted. Single doses of methylene blue as low as 5 mg/kg has been shown to induce methemoglobinemia in animals (3).

Methylene blue is contraindicated in patients with G6PD deficiency. These patients have low erythrocytic NADPH concentrations, making augmentation of the NADPH-dependent, methemoglobin-reducing enzyme by methylene blue impossible. More important, methylene blue may trigger massive hemolysis in such patients, further compromising oxygen delivery to tissues (3). About 15% of African American males are thought to be deficient in G6PD; men and women of Mediterranean ancestry also have an increased incidence of this enzyme deficiency.

As soon as time allows, GI and skin decontamination should be performed to limit continued absorption after acute dermal exposures to chemicals or after intentional ingestions of toxic agents. Dermal decontamination can be performed with a triple wash (water rinse, soap scrub, water rinse). If the drug or chemical causing methemoglobinemia cannot be readily eliminated from the body (e.g., dapsone), methemoglobinemia may continually recur for hours or days despite successful initial treatment with methylene blue. In this instance, serial measurements of methemoglobin levels are required, and a constant intravenous infusion of methylene blue at a rate of 0.1 mg/kg/hr has been used to maintain methemoglobin concentrations at a safe level (4). Repeated oral doses of activated charcoal may also enhance the elimination of dapsone. High-dose IV cimetidine has been shown to decrease dapsone-induced methemoglobin production. Renal failure is a relative contraindication to using a constant infusion or frequently repeated doses of methylene blue, because the drug is primarily renally excreted.

Treatment with hyperbaric oxygen (HBO) or exchange transfusions should be considered for patients with G6PD deficiency

or for those who do not respond satisfactorily to methylene blue. HBO can provide enough dissolved oxygen to support life in the presence of severe methemoglobinemia.

Symptomatic hemolytic anemia may require blood transfusions. Because massive hemolysis may cause hyperkalemia and acute renal failure, efforts should be made to maintain a good rate of urine flow.

Ascorbic acid also reduces methemoglobin to hemoglobin (nonenzymatically). A dose of 0.5 to 1.0 g ascorbic acid every 6 hours may be given intravenously or orally in conjunction with methylene blue. However, ascorbic acid works too slowly to be useful in the treatment of acute, acquired methemoglobinemia (1). Although *N*-acetylcysteine has been proposed as a possible adjunct, it did not reduce elevated methemoglobin levels in a human model of methemoglobinemia (10).

CRITICAL INTERVENTIONS

- Administer 100% oxygen to patients with suspected or diagnosed methemoglobinemia.
- Measure methemoglobin levels.
- Obtain Heinz body blood stain, serum haptoglobin, and plasma-free hemoglobin concentration in patients with a low hemoglobin.
- Administer methylene blue to patients with signs of cardiac ischemia, dyspnea, metabolic acidosis, or methemoglobin levels $>30\%$.

DISPOSITION

Patients with methemoglobinemia should be admitted after emergency department (ED) evaluation and management. Patients are best managed at a facility in which methemoglobin concentrations can be measured easily and quickly. If transfer is necessary, advanced life-support services and a supply of methylene blue should be available enroute. In the case of an accidental or intentional poisoning, the physician must evaluate and treat other

toxic effects of methemoglobin-producing agents. All patients who receive methylene blue should be observed for recurrence of symptomatic methemoglobinemia and for adverse effects such as hemolysis.

An asymptomatic and otherwise healthy patient who has been cyanotic for several days does not require admission if the total hemoglobin concentration is normal, the methemoglobin level is below 20%, exposure to the offending agent is terminated, and reliable follow-up is available. Methemoglobin concentrations will return to normal in these patients as the offending drug is cleared from the body. A conservative approach would be to admit all young children and elderly patients for observation, serial methemoglobin concentrations and, when indicated, serial ECGs.

Any patient who unexpectedly develops methemoglobinemia should be referred to a hematologist for evaluation of possible NADH cytochrome-b5 reductase deficiency. Any patient with methemoglobinemia that is unresponsive to treatment with methylene blue should be evaluated, after full recovery, for G6PD deficiency and the much less common, NADPH methemoglobin reductase deficiency.

Common Pitfalls

- Failure to consider the diagnosis of methemoglobinemia in patients with cyanosis unresponsive to oxygen.
- Failure to appreciate that a normal arterial PO_2 and a normal oxygen saturation calculated from arterial blood gases does not rule out methemoglobinemia.
- Failure to appreciate that resolution of cyanosis in a patient with methemoglobinemia may be as a result of accompanying hemolysis, with actual worsening of oxygen delivery to tissues.
- Failure to appreciate that methylene blue is contraindicated in patients with G6PD deficiency.

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CHAPTER 336

Irritant Gases and Other Toxic Inhalants

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Toxic inhalants can be (1) simple asphyxiants, nontoxic gases which displace oxygen in the atmosphere (not discussed in this book), (2) systemic asphyxiants (see Chapters 327, 329, and 332) or (3) irritant gases, discussed in this chapter, and (4) gases with other systemic effects, also discussed in this chapter. Irritant gases can cause injury anywhere from the oral mucosa to the pulmonary parenchyma and internal organs. The deposition and absorption of a gas or vapor in the respiratory tract are primarily governed by its water solubility. Highly water-soluble airway irritants such as chlorine and hydrochloric acid are quickly absorbed in the upper airways and usually cause mucous membrane and upper airway irritation. In contrast, less water-soluble chemicals such as phosgene tend to reach the lower airways and alveolar membrane, causing bronchospasm and delayed pulmonary edema (1). In addition, specific agents are responsible for clinically significant systemic toxicity and hypersensitivity responses with which the emergency physician should be familiar.

CLINICAL PRESENTATION

Inhalants with Immediate-Onset Symptoms

Agents that are intermediately or highly water-soluble generally produce immediate symptoms of mucous membrane irritation. The most commonly encountered agents in this category are chlorine

gas, chloramines, and ammonia. Less commonly encountered agents include sulfur dioxide (SO_2), formaldehyde, and chloropicrin.

Chlorine, a gas with intermediate water solubility, became infamous as a chemical warfare agent in World War I. It is heavy, dense, and greenish yellow in color. Exposure to chlorine gas may occur in several different settings. Industrially, it is used for water purification, as well as in textile and paper bleaching processes (2). Mixing an acid (typically found in toilet bowl cleaners) with bleach liberates chlorine gas in household exposures, which occurs fairly frequently (3). Finally, exposure to concentrated chlorine gas often occurs from accidents and malfunctions in pool chlorination systems (4).

Chlorine-induced injury results from its reaction with water on mucous membranes and the respiratory tract, forming hydrochloric acid (HCl), and hypochlorous acid (HOCl), which cause to tissue injury. Furthermore, HOCl degrades to HCl and oxygen-free radicals, which leads to oxidative cellular damage (2).

The clinical effects of chlorine gas exposure depend upon the concentration and duration of exposure. Individuals with brief low-dose household exposure most commonly complain of cough followed by shortness of breath and throat irritation. In the vast majority of patients symptoms resolve within about six hours (3). As the concentration and duration of exposure increase, the degree of mucous membrane and airway injury increases, which ultimately can lead to acute lung injury, adult respiratory distress syndrome, and even death with massive exposures (2).

Chloramines are produced when bleach is mixed with ammonia. Upon contact with mucous membranes and the respiratory tract, they degrade to ammonia, HOCl, and oxygen-free radicals, which cause an injury pattern similar to chlorine gas. Although acute lung injury has occurred with household exposures, the vast majority of patients experience resolution of their symptoms within several hours from exposure (5,6).

Ammonia is a highly water-soluble gas that has a characteristic pungent odor. It is used as a component of agricultural fertilizer, in

the manufacturing of plastics and explosives, and as a refrigerant and cleaning agent. Upon contact with water, it forms ammonium hydroxide, which causes a rapid and severe upper airway injury. Ammonia's strong odor and the rapid mucous membrane irritation it causes usually prevent ongoing exposure and further injury. However, individuals exposed to highly concentrated gas or those with prolonged exposure may develop lower respiratory tract injury and severe acute lung injury.

Sulfur dioxide (SO_2) is another highly water-soluble gas that has many industrial and occupational uses. It is a by-product in the smelting and oil refinery industries. It is also used as a preservative for fruits and vegetables, as a disinfectant in wineries and breweries, and as a bleaching agent in the textile and paper industries. In the presence of water, SO_2 is readily converted to sulfurous acid (H_2SO_3), which is largely responsible for producing the mucosal injury. Due to its characteristic pungent "burning match" odor, potential victims tend to remove themselves from exposure before severe injury can develop, and effects are therefore most often limited to upper airway and mucous membrane irritation. Higher concentrations, however, have been shown to cause morphologic changes consistent with acute lung injury, and, indeed, individuals with large or prolonged exposure can develop acute pulmonary edema and die within hours of exposure (7).

Pure formaldehyde is a gas at room temperature. The majority of formaldehyde produced in the United States is used for plastics and resin manufacturing. It is highly water-soluble and extremely irritating, primarily to upper respiratory mucous membranes.

Chloropicrin is a fumigant that has been used for cereals and grains. Because it is a highly potent irritant and lacrimator, it is also added to structural fumigants as a warning agent. It causes mainly mucous membrane irritation, but lung injury may occur with a high dose or prolonged exposure.

Inhalants with Delayed-Onset Symptoms

In contrast to the agents with high and intermediate water solubility, gases with low water solubility tend not to cause immediate mucous membrane irritation. This lack of symptoms may lead to prolonged exposure. Once poorly water-soluble gases are inhaled into the alveoli, their dissolution into the epithelial fluid occurs slowly over several hours, producing a delayed-onset pulmonary edema. Two important gases in this category are phosgene (carbonyl chloride) and nitrogen dioxide (NO_2).

Phosgene is a colorless gas with a smell often described as that of freshly mown hay. It was used as a chemical warfare agent in World War I and was estimated to cause more than 80% of all poisonous gas fatalities. Today, phosgene is used as an intermediate in the production of isocyanates, polyurethanes, pharmaceuticals, dyestuffs, and carbamate pesticides. In addition, it is formed upon the combustion of chlorinated organic compounds (8).

Phosgene causes injury by two mechanisms: acylation and hydrolysis to hydrochloric acid. As phosgene acylates sulfhydryl, hydroxyl, and amino groups, it disrupts the cell membrane and various cellular enzymes which ultimately lead to pulmonary cellular death. Second, upon contact with water, phosgene is slowly hydrolyzed to hydrochloric acid (HCl), which directly causes mucosal and pulmonary injury.

Unless there is a large exposure to concentrated gas, phosgene produces little to no immediate mucous membrane irritation. Although pulmonary injury may occur within an hour of exposure, the development of clinical symptoms may be delayed for 15 to 30 hours. The chest x-ray may appear normal or show only very subtle changes initially, but frank pulmonary edema may develop over 24 hours (8).

Nitrogen dioxide (NO_2) is a reddish-brown gas with a pungent odor and may be encountered in several different scenarios. NO_2 can form in grain silos as “silo gas” when the silage nitrates are fermented into nitrites, which subsequently combine with organic acids to form nitrous acid. Nitrous acid decomposes to water and other nitrogen oxides, which cause silo-filler’s disease (9). Another

source of exposure is through the exhaust of propane-powered ice cleaning machines in poorly ventilated ice skating rinks. Finally, nitrogen oxides may be generated by welding and as a by-product of the combustion of nitrocellulose, which is a major component of radiographic film.

Although NO_2 can directly oxidize cell membranes, it also forms reactive nitrogen species, particularly perioxynitrite ($ONOO^-$). These reactive species cause inflammation and damage to bronchiolar and alveolar type I and II epithelial cells. In addition to generating reactive nitrogen species, NO_2 forms nitric acid upon contact with respiratory tract water, which further contributes to pulmonary injury (10). Due to its poor water solubility, NO_2 often causes little or no immediate mucous membrane irritation. The result is a relatively asymptomatic patient with a normal chest x-ray, who may go on to develop pulmonary edema and clinical symptoms within 24 hours of exposure; at extremely high concentration, however, it can still cause sudden loss of consciousness.

Miscellaneous Irritants

Isocyanates are used in the production of urethane foams for insulation, packaging, and the sealing of electrical equipment. They are also used in many paints and finishes. Of the isocyanates, methyl isocyanate (MIC) is the most potent respiratory tract irritant, and its inadvertent release in 1984 in Bhopal, India, was responsible for more than 2,000 deaths. Today, MIC has largely been replaced by methylene diphenyl diisocyanate (MDI) and toluene diisocyanate (TDI). MDI is relatively safe because of its low volatility. However, TDI is volatile and can be easily inhaled to produce acute irritation of the mucous membranes and respiratory tract. It can also cause sensitization leading to the development of occupational asthma.

Pulmonary Inhalants with Systemic Toxicity

Arsine gas (AsH_3, arsenous hydride) is colorless gas with a garlic odor, generated when arsenic-containing materials contact water or acid (11). Common industrial processes that result in arsine formation include metal refining, smelting, and computer and fiberoptic chip manufacture. Arsine is generally a nonirritating gas, and exposures <0.5 ppm may not be readily apparent (12). Signs and symptoms may develop within 2 to 24 hours of exposure and include: nausea, vomiting, abdominal pain, diarrhea, dizziness, and weakness (12). The most feared complication of arsine exposure is intravascular hemolysis, evidenced by "black" urine, jaundice, and acute renal failure secondary to both direct arsine toxicity and heme pigment-associated tubular necrosis. The classic presentation of arsine poisoning is the clinical triad of jaundice, abdominal pain, and hematuria. Other reported signs and symptoms include pulmonary edema, skin "bronzing," myalgias, and delayed-onset peripheral neuropathy (13). Arsine-induced hemolysis may be related to disruption of red blood cell membrane ion gradients causing membrane instability and also direct heme release (12). Blood or spot urine arsenic measurements can aid in the initial diagnosis and can be followed up during treatment. Removal of the arsine hemoglobin complex and red blood cell fragments via early plasma exchange transfusion has been associated with clinical improvement and reduction in blood and urine arsenic levels. With the use of hybrid blood purification therapy (plasma exchange and continuous venovenous hemofiltration), 10 of 11 patients survived severe, acute arsine toxicity; however, there was no control group (11). Chelation therapy, as used for arsenic, has not been effective in arsine poisoning.

Ethylene oxide is a colorless gas with an ether-like odor commonly used as a sterilizing agent in hospitals. Mucosal irritation, dermal burns, nausea, vomiting, chest tightness, cough, dyspnea, loss of consciousness, and seizures have all been reported after acute ethylene oxide exposure. After chronic exposure, ethylene oxide has been associated with contact dermatitis and peripheral neuropathy (14). It has also been associated with a possible increased risk for

miscarriage and cancer. Treatment is removal from the source and supportive.

Phosphine gas (PH_3) is generated from the contact of aluminum phosphide and water. Aluminum phosphide is a solid fumigant pesticide used to preserve grain. Unintentional exposure occurs from inhalation of or dermal exposure to phosphine generated from fumigated grains. Lemoine et al. (15) recently reported a rare and unfortunate case of inhalation with two fatalities after an entire family was accidentally poisoned when aluminum phosphide pellets were used as a rodenticide outside the home. Intentional phosphine poisoning, by ingestion of solid aluminum phosphide tablets, or "Rice tablets", that react with gastrointestinal mucosa to form phosphine, is a common form of suicide in countries such as India (16). Signs and symptoms include initial severe vomiting followed by coma, seizures, metabolic acidosis, hypotension, and cardiovascular collapse. Other reported clinical manifestations include: cardiac arrhythmias, pulmonary edema, acute respiratory distress syndrome, hemolysis, methemoglobinemia, disseminated intravascular coagulation, acute tubular necrosis, hepatitis, and pancreatitis. Survivors of ingestion may develop esophageal strictures. A characteristic fishy or garlic odor is commonly described with phosphine exposure to air and may be a helpful clue to diagnosis. Although "off gassing" of phosphine from patients' vomitus or expired breath and causing toxicity in rescuers has been reported, "spontaneous ignition" has been reported Phosphine toxicity is believed to occur from free radical oxidant damage and inhibition of mitochondrial cytochrome c oxidase (16). Treatment is immediate removal from the source of exposure, including contaminated clothing, and skin washing with water in cases of dermal exposure and immediate cardiopulmonary resuscitation. There is no antidote for phosphine poisoning. Elevated blood and tissue phosphine levels have been reported after exposure (17). A bedside test using silver nitrate-impregnated paper on breath or heated gastric contents may provide a more rapid diagnosis. Treatment with immediate gastric lavage after ingestion, oral

coconut oil, magnesium, trimetazidine and, recently, gastric ventilation, have all been reported, but none has been validated. Sodium bicarbonate should be given to correct metabolic acidosis. Mortality has been reported as high as 60% (16). Recently, a prospective, randomized, controlled study of adding N-acetylcysteine (NAC) to supportive care demonstrated reduced biomarkers of oxidative stress, a decreased need for intubation, shorter length of ICU stay, and lower mortality rates in those who received NAC compared to controls (18).

Methyl bromide is a halogenated hydrocarbon used until the 1950s as a fire extinguisher but now employed primarily as a fumigant. It is a colorless and odorless gas even at high concentrations and is readily absorbed by the lungs and skin. Acute exposure is associated with early gastrointestinal upset, dizziness, and headache, which can be followed by progressive neurologic deterioration, including coma, myoclonus, seizures, and status epilepticus. Myocardial sensitization and ventricular arrhythmias have been reported. Pulmonary edema and both liver and renal insufficiency have also been associated with methyl bromide toxicity. Peripheral neuropathy and persistent psychiatric disturbances have been reported after large exposures (19). The mechanisms of methyl bromide toxicity may include (1) methylation of sulfur-containing enzymes similar to other metals, (2) glutathione depletion, and (3) free radical formation (19). Plasma bromide levels can help confirm exposure but may not predict toxicity. More immediate diagnostic clues are a falsely elevated serum chloride and low anion gap (19). Treatment is removal from the source and supportive care, with aggressive control of seizures with benzodiazepines. Catecholamines should be avoided in the presence of ventricular arrhythmias. Chelation, N-acetylcysteine, and hemodialysis are potential treatments.

Ethylene dibromide (1,2-dibromomethane) is a colorless liquid with a chloroform odor sold in 3-mL ampules. It was common fumigant in the United States until 1984, when its use was restricted; however, it is still used in countries such as India where it remains a common source of poisoning. Toxicity has been

reported with ingestion, inhalation, and dermal exposure; death has been reported with ingestion of as little as half an ampule (20). Clinical signs and symptoms include initial gastrointestinal and pulmonary disturbances, progressing to metabolic acidosis, liver and renal failure, and cardiovascular collapse (20). There is no antidote, and treatment is supportive. Favorable outcomes are associated with arrival to the hospital within six hours after exposure and normal hemodynamics at presentation.

Sulfuryl fluoride (Vikane) is a colorless, odorless fumigant used with the warning agent chloropicrin. Mucous membrane irritation and pulmonary edema occur with exposure to the warning lacrimator, chloropicrin. Hypocalcemia, hyperkalemia, metabolic acidosis, seizures, and ventricular arrhythmias occur with systemic fluoride toxicity. Treatment includes removal from the source, control of seizures, sodium bicarbonate for metabolic acidosis, and aggressive electrolyte supplementation.

Polymer fume fever is self-limited manifestation of exposure to polytetrafluoroethylene (Teflon) pyrolysis products. Typically, heating of contaminated products, such as cigarettes or hairspray, causes inhalation of pyrolyzed fluorinated polymer fumes and development of fever, cough, and dyspnea, but a normal chest radiograph. Rarely, pulmonary consolidation can occur with prolonged exposure or higher temperatures, Resolution occurs over 24 to 48 hours and is treated supportively with bronchodilators, antipyretics, adequate ventilation, and education on avoiding future exposure (21).

Metal fume fever (“Monday morning fever,” “Galvanizers poisoning,” “smelter’s chill”) is a self-limited respiratory illness secondary to metal oxide fume exposure, typically zinc. Similar to polymer fume fever, patients present with abrupt onset of fever, cough, dyspnea, myalgia, headache, and metallic taste within 48 hours of exposure with a similar duration. Chest radiographs are typically normal, and treatment is supportive. Metal levels are not elevated. Transient tolerance to oxide fumes is thought to occur, thus causing “Monday morning fever” with improvement over the weekend and recurrent symptoms upon re-exposure at the beginning

of the next work week (22). Repeated episodes should prompt the clinician to address proper workplace protective measures.

DIFFERENTIAL DIAGNOSIS

Similar clinical presentations may be caused by more common cardiac, allergic, infectious, or intrinsic lung diseases so these poisonings are easy to overlook if a history of exposure is not obtained. Entities such as metal or polymer fume fever resemble influenza-like illness, but are generally very rapid in onset and resolve relatively quickly compared to infectious diseases. As highly water-soluble gases generally cause acute mucous membrane and upper airway irritation, prompt symptom resolution after removal from the exposure can help distinguish inhalant toxicity from other causes. Less water-soluble agents may cause delayed pulmonary toxicity and may mimic other causes of noncardiogenic pulmonary edema, such as opioid or salicylate poisoning. Unusual toxicities, such as arsine-induced hemolysis, could present similarly to other causes of intravascular hemolysis such as paroxysmal nocturnal hemoglobinuria. A detailed history from the patient, scene responders, family, or coworkers is extremely helpful in differentiating an occupational exposure from an intrinsic medical cause. Unique odors may potentially be helpful, especially in cases of phosgene, phosphine, or arsine poisoning, for example.

ED EVALUATION

Signs and symptoms after a highly water-soluble gas exposure are sudden and easily noted, and correlated to a chemical exposure, but symptoms from other inhaled exposures may be nonspecific, delayed, progressive, and unexpected, making the diagnosis difficult to suspect. An accurate exposure history and review of medical history are paramount.

The emergency department (ED) evaluation includes germane medical history and details of the presenting illness, such as the nature, timing, and severity of symptoms and antecedent recreational or occupational activity. Also, if several patients present

with similar complaints, a common exposure to an irritant gas may be involved. The Material Safety Data Sheet (MSDS) for chemicals at the worksite should always be requested from worksites and carefully reviewed.

Vital sign abnormalities should be noted, especially decreased oxygen saturation, tachypnea, or fever. The physical examination should focus on any mucous membrane or skin involvement and abnormal cardiopulmonary findings. A peak flow measurement can monitor bronchospasm and a chest radiograph should be performed in patients with significant respiratory distress or hypoxemia, especially when pulmonary edema is suspected. Routine laboratory testing is generally not needed unless it is to exclude other disorders. However, in cases of suspected arsine toxicity, diagnostic testing should include urine or blood arsenic levels, complete blood count, renal function, indirect bilirubin, haptoglobin, lactate dehydrogenase, and urinalysis. Serum chemistries and ECG should be included in cases of sulfuryl fluoride exposure. Likewise, for phosphine and bromide, appropriate blood samples may help confirm exposure. A falsely elevated serum chloride and low anion gap may provide evidence of bromide exposure. Also, a bedside silver nitrate paper test on breath or gastric contents can help to quickly diagnose phosphine exposure.

KEY TESTING

- Peak flow measurement and CXR as needed for symptoms
- Routine laboratories are generally not helpful
- Test for hemolysis after arsine poisoning

ED MANAGEMENT

Removal from the exposure, rapid decontamination, and supportive care are the mainstays of prehospital treatment. A rescuer should never enter an area in which a toxic inhalant is potentially present without having adequate protection such as the self-contained breathing apparatus used by fire-fighters. Along with the provision of supplemental oxygen, thorough flushing of irritated surfaces with

water may be required. For inhalation only, without liquid condensation, no decontamination is necessary. If liquid toxin is on clothing or skin, simple decontamination maneuvers include removal and containment of contaminated clothing and washing of skin with soap and water.

Respiratory therapy is primarily supportive and should include humidified oxygen, bronchodilators for clinical evidence of bronchospasm, and either noninvasive ventilation or endotracheal intubation with positive end-expiratory pressure (PEEP) as clinically indicated for more severe lung injury or pulmonary edema. In pigs exposed to chlorine gas, inhaled budesonide and intravenous betamethasone improved oxygenation, pulmonary vascular resistance, and airway pressures but because of a lack of controlled clinical trials and unclear indications for their use in humans, their use cannot be recommended as routine management (23). Corticosteroid administration may be considered in severe cases of lung injury or based on local practice patterns. Sodium bicarbonate nebulization for chlorine gas inhalation is also controversial. Although case reports suggest a possible benefit, prospective study of individuals with chlorine gas inhalation has failed to demonstrate a clinically significant benefit.

Exchange transfusion may be needed for arsine-induced hemolysis. Sodium bicarbonate administration and NAC therapy should be considered for patients with phosphine toxicity to correct metabolic acidosis and oxidant stress, respectively. Supportive therapies may be needed, such as benzodiazepines or barbiturates for seizures, and hemodialysis for renal failure. Aggressive electrolyte and acid base management may be needed in patients exposed to sulfuryl fluoride. Identification of the sources of and reasons for exposure, especially in industrial settings, is critical during ED evaluation to limit potential future poisoning.

CRITICAL INTERVENTIONS

- Measure oxygen saturation in all patients with irritant gas exposure.

- Administer oxygen and bronchodilators to patients with cough, dyspnea, or wheezing; consider corticosteroid therapy in those with severe or persistent symptoms.
- Use PEEP or intubate to provide and controlled ventilation in patients with pulmonary edema or severe respiratory distress that is unresponsive to supportive care.
- For arsine toxicity, consider early institution of plasma exchange.

DISPOSITION

The decision to admit or discharge depends primarily on the severity and progression of clinical and laboratory manifestations. Patients exposed to agents that do not cause delayed pulmonary edema and who are or become asymptomatic after six hours of ED observation and treatment may be discharged, with follow-up as necessary. Those with moderate, severe, or worsening symptoms, hypoxemia, or pulmonary edema should be admitted to the appropriate hospital unit. If delayed toxicity is possible, patients who have even minimal initial symptoms should be admitted and observed for 24 hours. When possible, the MSDS should be reviewed, and the regional poison center and medical toxicologist should be consulted to help guide treatment and disposition. Patients who are discharged should be instructed to return if symptoms recur or worsen. Discharged patients should also be advised to avoid circumstances that resulted in exposure.

Common Pitfalls

- Failure to adequately decontaminate patients and to use proper protective equipment for patients with volatile liquid and gas exposure.
- Decontaminating patients who have had isolated gas exposure without risk of secondary contamination.
- Failure to take an adequate environmental or occupational exposure history.
- Failure to consider the possibility of delayed or systemic poisoning after gas exposure.

- Failure to obtain the most information possible from MSDS, regional poison center, the manufacturer, and other sources for further information regarding specific agent.
- Failure to instruct patients to avoid circumstances that led to exposure.

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CHAPTER 337
Smoke Inhalation

Heather Long

Smoke inhalation is the number one cause of death from fire and is the most common cause of acute inhalation injury seen in the emergency department (ED). Furthermore, burn patients with smoke inhalation have much greater morbidity and mortality, with increased rates of pneumonia, infection, sepsis, and increased length of hospital stay. The overall mortality rate from burns averages 13.9% but, among those with concomitant smoke inhalation injury, mortality rises to 27.6% (1).

Smoke is a mixture of heated air, gases, fumes, aerosols, vapors, and solid and liquid particles in suspension. Smoke toxicity depends on the composition of the fuel, the availability of oxygen, the completeness of combustion, and the heat intensity. Even within the same building, smoke composition can vary considerably with duration of the fire and location. Toxic combustion products (TCPs) from naturally occurring materials and synthetic polymers in the modern environment contribute to smoke toxicity (Table 337.1).

TABLE 337.1
Toxic Products of Combustion

Product of Combustion	Common Sources
Acids/aldehydes	Cellulose acetate (film), cotton, paper polystyrene, polyvinyl acetate, wood
Acrolein	Acrilan (carpet), acrylic, celluloid, cellulosics, polyolefins
Ammonia	Nylon, resins (melamine, phenolic), silk, wood
Carbon monoxide/dioxide	All organic material
Chlorine/hydrochloric acid/ phosgene	Chlorinated acrylics and hydrocarbons (fire extinguishers and retardants)
Cyanide/hydrogen cyanide	Acrylonitriles, nylon, paper, polyurethane, nitrocellulose (film), resins, silk, wool
Halogen acids and gases (Br, F)	Halogenated hydrocarbons, films, resins, flame retardants, and extinguishers
Isocyanates	Polyurethane
Nitrogen oxides	Celluloid, cellulose nitrate fabrics, paper, petroleum products, wood
Styrene	Polystyrene
Sulfur oxides/hydrogen sulfide	Hair, hides, meat, petroleum products, rubber, wool

TCPs like other inhaled toxins (Chapter 336, “Inhaled Toxins”) are categorized as simple asphyxiants, chemical asphyxiants, or irritant toxins (Table 337.2). Simple asphyxiants displace oxygen from the ambient environment causing suffocation but they generally have no inherent toxicity. The process of combustion itself depletes oxygen from the environment as well.

TABLE 337.2
Toxic Combustion Products

Simple Asphyxiants	Chemical Asphyxiants	Irritants
Carbon dioxide	Carbon monoxide	Highly water-soluble
Helium	Hydrogen cyanide	Acrolein
Methane	Hydrogen sulfide	Ammonia
Natural gas	Oxides of nitrogen	Formaldehyde
Nitrogen		Hydrogen chloride
Noble gases		Sulfur dioxide
Oxygen-deprived environment		Intermediate water solubility
		Chlorine
Propane		Isocyanates
		Poorly water-soluble
		Oxides of nitrogen
		Phosgene

Chemical asphyxiants inhibit cellular respiration by inhibiting mitochondrial electron transport or by impairing oxygen delivery. Agents inhibiting mitochondrial electron transport include carbon monoxide (Chapter 327), hydrogen cyanide (Chapter 329), and hydrogen sulfide (Chapter 332). Carbon monoxide and oxides of nitrogen, by inducing carboxyhemoglobin (COHgb) formation or methemoglobinemia (see Chapter 335), respectively, impair oxygen transport and delivery to tissues.

Carbon monoxide, produced by the incomplete combustion of any carbon-containing compound such as wood, charcoal, and propane, is still the major toxicant in modern fires. However, COHgb fractions in smoke inhalation deaths are often $<50\%$. An oxygen-poor environment combined with even sub-lethal levels of carbon monoxide significantly reduces the time to death. Blood ethanol concentrations correlate strongly with the COHgb fraction, suggesting that ethanol intoxication impairs the ability to recognize and escape danger, consequently prolonging smoke exposure.

Cyanide is produced from the combustion of nitrogen-containing products such as wool, silk, nylon, plastics, polyurethane, nitrocellulose, and synthetic rubber. Cyanide is present in appreciable amounts in air samples from fires and in blood from fire victims and is thought to have an additive, even synergistic effect,

on smoke toxicity. Cyanide levels >0.1 mg/L are considered abnormal.

Combustion of nitrogen-containing materials generates oxides of nitrogen. These oxides are capable of inducing methemoglobinemia and may also directly oxidize cells of the respiratory tract or generate free radicals that induce delayed damage to the respiratory epithelium. Methemoglobinemia is rarely reported in smoke inhalation victims. Combustion of nitrocellulose, a major component of radiographic film, caused 125 deaths as a result of cyanide and nitrogen dioxide poisoning in the 1929 fire in the Cleveland Clinic radiology department (2).

Irritant toxins are a varied group of chemically reactive compounds that ultimately exert their toxic effects through damage to the respiratory tract. Mechanisms of injury vary with the different agents. The lipid-soluble acrolein penetrates cell membranes and denatures proteins and nucleic acids. Ammonia, hydrogen chloride, and sulfur dioxide react with the moisture of respiratory mucosa to yield ammonium hydroxide, hydrochloric acid, and sulfurous acid, respectively. Chlorine and phosgene generate free radicals, mediating oxidative stress on cellular membranes.

Inhalation of soot and aerosols results in enhanced delivery of irritant gases to the respiratory tract. As soot deposits, adsorbed gases are able to react with the moist mucosal surface. Size of the soot particle determines where it is deposited; particles of 1 to 3 microns are able to reach the alveoli. Particles generated from building fires predominately range from 3 to 5 microns and affect the bronchioles.

Direct heat injury from smoke is confined to the upper airway because of its marked ability to dissipate heat. Because steam has 4,000 times the heat-carrying capacity of hot air, steam inhalation may be rapidly fatal as a result of laryngeal and glottic edema, thermal tracheitis, and hemorrhagic edema of the bronchial mucosa.

Smoke inhalation injury is a product of the inherent toxicity of the TCPs, the victim's minute ventilation, and the duration of exposure. Duration of exposure may be prolonged by anxiety; confusion; impaired visibility as a result of darkness, tearing, smoke,

and physical obstacles; respiratory distress and altered cognition from TCP exposure; a low ambient oxygen concentration; and impaired awareness and mobility from drug and alcohol intoxication, physical handicaps, or extremes of age.

Inhaled particles and toxic gases damage mucosal cells and alveoli, triggering release of inflammatory mediators. Chemotaxins actuate diffuse protein-rich exudate formation. Increased vascular permeability results in interstitial edema. There is increased airway resistance, decreased lung compliance, and bronchoconstriction; acute lung injury may ensue 12 to 24 hours after injury with lung injury scores typically reaching their nadir 72 hours following initial insult. Severity of inhalation injury correlates with alveolar neutrophilia, enhanced production of inflammatory mediators, elevated COHgb, prolonged mechanical ventilation and intensive care unit (ICU), and hospital length of stay (3).

Among firefighters, the type of respirator used influences the risk of smoke inhalation. Atmosphere purifying respirators (APRs) protect against some inhaled particles but not heated gases or CO; oxygen-supplying, self-contained breathing apparatus (SCBA) is the only NIOSH-approved respirator for firefighting. If oxygen is supplied via a demand valve requiring negative inspiratory pressure, smoke inhalation may occur if the mask does not fit tightly. With continuous positive-pressure devices, smoke inhalation will not occur unless the oxygen supply, which typically lasts 20 to 30 minutes, runs out. If either type of mask is removed during clean-up activities after the flames are extinguished, smoke inhalation may still occur. Wildfire fighters do not typically wear oxygen masks or APRs and may be at special risk for inhalation injury.

Smoke inhalation injuries pose significant potential for mass casualties. A train hauling hydrochloric acid, hydrofluoric acid, and acetic acid derailed in Baltimore in July 2001, causing a fire that burned for 5 days and sent hundreds of people to local EDs (4). In November 2000, 155 people died, most of them from smoke inhalation, after a fire broke out in a cable car traveling through a tunnel in Austria. In the 1990 Happy Land Social Club fire in New York City, all 87 deaths were due to smoke inhalation (5).

CLINICAL PRESENTATION

Respiratory signs and symptoms are the primary clinical manifestations of smoke inhalation toxicity. Clinical effects range from transient respiratory tract irritation to severe upper airway compromise and respiratory failure. Cough is often the first symptom. Other initial responses include increased mucous secretion and sneezing. Upper airway involvement results in hoarseness and stridor. Injury to the lower respiratory tract results in crackles and/or wheezing. Breath sounds may be inaudible in cases of severe bronchospasm. Important signs of potential inhalation injury include cough, dyspnea, hoarseness, soot in the oral cavity, singed nasal hair, edema of the posterior pharynx, burns to the face, and any major burn to the body.

Smoke inhalation may cause systemic manifestations as well. Examination of the eye may reveal the irritant effects of increased tearing, conjunctival injection, and blepharospasm. Progressive airway compromise and toxicity from agents with systemic effects, notably carbon monoxide, will produce signs and symptoms of hypoxia—tachycardia, tachypnea, dizziness, headache, nausea and vomiting, chest pain, and deteriorating mental status manifesting as agitation, confusion and ultimately seizures, coma, and death.

Laboratory evaluation may detect hypoxemia, metabolic acidosis, and elevated lactate levels, COHgb, and methemoglobin fractions. The electrocardiogram (ECG) may detect dysrhythmias or evidence of myocardial ischemia or infarction.

DIFFERENTIAL DIAGNOSIS

Patients with smoke inhalation are usually easily identified by history but may have concomitant dermal burns, traumatic injuries, or drug or alcohol intoxication and may be victims of arson, attempted murder, or attempted suicide. For patients presenting with coma and shock, hypoglycemia, intracranial hemorrhage and diffuse brain injury, spinal cord injuries, hypovolemia, myocardial injury, carbon monoxide poisoning, cyanide poisoning,

methemoglobinemia, alcohol intoxication, and drug overdose must also be considered.

ED EVALUATION

Significant smoke inhalation injuries may be delayed after exposure. History of entrapment, fire within an enclosed space, and altered consciousness at the scene should raise the suspicion of inhalation injury. Key risk factors associated with inhalation injury are in Table 337.3. The history should address the nature of burning material, presence of steam, evidence of trauma or suicidality and, for rescuers presenting as patients, the type of mask used.

TABLE 337.3
Risk Factors Associated with Inhalation Injury

Initial Exposure	Symptoms	Signs
Entrapment	Cough	Soot in the oral cavity
Fire in an enclosed space	Shortness of breath	Singed nasal hair
Loss of consciousness at the scene	Hoarseness	Pharyngeal edema
Facial or neck burns; any major burn		
		Stridor
		Crackles/wheezing
		Altered mental status

Examination begins with obtaining vital signs and oxygen saturation, however, transcutaneous pulse oximetry overestimates the true oxygen saturation in the presence of COHgb and methemoglobin. Co-oximetry directly measures an accurate oxygen saturation even in the presence of dyshemoglobinemias. A trauma survey with attention to signs associated with increased risk of smoke inhalation including facial burns, singed facial hair, soot in the nasal passages and airway, and burns involving extensive body surface area (>15%) should follow. The eyes in comatose patients or those with eye complaints should be examined with fluorescein staining to detect corneal burns and lacerations. Other causes of

altered mental status including drug and ethanol intoxication should be considered. Repeat examinations should focus on respiratory status and alterations in mental status. Lung injury scores typically worsen, reaching their nadir about 72 hours after the initial smoke inhalation.

COHgb and methemoglobin should be measured by co-oximetry. An elevated COHgb fraction in a fire victim is an indicator of significant exposure to combustion products and is associated with a markedly increased risk of smoke inhalation injury and toxicity. However, a low or undetectable COHgb concentration does not rule out the possibility of developing even severe inhalation injury.

Whole-blood cyanide levels are not timely but a plasma lactate concentration >8 mmol/L refractory to adequate ventilation, oxygenation, and perfusion is a surrogate marker of cyanide toxicity in the setting of smoke inhalation (6). Methemoglobin should be determined in symptomatic patients, particularly with cyanosis that does not improve with supplementary oxygen (Chapters 329 and 335).

Blood gas measurements should be obtained to assess arterial oxygenation, alveolar ventilation, and the presence of metabolic acidosis. Initially, the blood gas of even a significantly injured patient may be normal; serial measurements are recommended.

An ECG and a chest radiograph are recommended in symptomatic patients, especially in those with pre-existing cardiovascular or pulmonary disease. Chest radiographs may appear normal early in the course of smoke inhalation and therefore lack sensitivity as indicators of inhalation injury. Early findings, if present, are subtle: perivascular cuffing, bronchial wall thickening, and subglottic edema (7). Serial chest radiographs, however, may be very useful in monitoring disease progression. Common complications that do not typically manifest radiographically until more than 24 hours after the initial insult include acute lung injury/acute respiratory distress syndrome, aspiration, volume overload, and infection.

Fiberoptic bronchoscopy is considered the gold standard for diagnosis and evaluation of inhalation injury. Chest CT scan at time of hospital admission appears to complement bronchoscopy in

predicting severity of inhalation injury. Bronchial wall thickening measured by CT correlates with subsequent development of pneumonia and other markers of severity including ICU stay and ventilator requirement (8).

KEY TESTING

- Obtain a COHgb level, chest x-ray, and ECG in all patients with signs of smoke inhalation and/or cardiopulmonary symptoms
- Obtain a lactate level to evaluate for potential cyanide toxicity in seriously ill patients
- Obtain a methemoglobin level in patients with cyanosis and/or other signs including tachycardia, tachypnea, and altered mental status
- Consider early bronchoscopy in admitted patients
- Consider testing for ethanol and other drugs for altered mental status

ED MANAGEMENT

Prehospital directives include the rapid, safe removal of victims from the scene by those with adequate training and protection. Basic and advanced life-support measures are instituted as indicated, including cervical spine immobilization with trauma. Supplemental oxygen is indicated for all patients. Whether a patient should be transported to a burn center, trauma center, or hyperbaric facility is determined by local practice guidelines. Intravenous access and cardiac monitoring may be established en route.

On arrival to the ED, upper airway patency must be determined immediately. Airway compromise may be present initially, rapidly ensue, or develop insidiously over the next few hours. Failure to appreciate the potential for rapid decline in airway status is the major pitfall in managing the smoke inhalation patient. The factors that best correlate with the need for intubation and edema of either the true or false vocal cords are soot in the oral cavity, facial burns, and/or body burns (9). Early endotracheal intubation, performed in a controlled setting before edema makes it impossible, may be life-

saving and should be undertaken when these risks are present. In the patient with the edematous or difficult airway, fiberoptic laryngoscopy, flexible intubation guides, intubation laryngeal masks, retrograde intubation, transtracheal jet ventilation, and ultimately cricothyroidotomy may be necessary for establishing tracheal intubation. Aggressive rehydration of the burn victim may also cause airway edema requiring early intubation.

Early consultation for fiberoptic bronchoscopy should be considered if there is suspicion of inhalation injury. It may also assist in clearing debris from the respiratory tract and permits fiberoptically assisted intubation if required.

β_2-Adrenergic agonists may be useful in improving airflow. Corticosteroids are not indicated with smoke inhalation injury as they are associated with increased incidence of bacterial pneumonia and mortality and are not associated with improved pulmonary function (10). Prophylactic antibiotics also have no demonstrated benefit in the treatment of inhalation injury. Fever and leukocytosis that develop 2 days or more after the injury do suggest infection, and empiric antibiotic treatment that covers *Staphylococcus aureus* and gram-negative organisms should be instituted until culture results become available. Progressive respiratory failure and the development of pneumonitis, acute lung injury/adult respiratory distress syndrome, or other complications may require mechanical ventilation, continuous positive airway pressure, positive end-expiratory pressure, and frequent suctioning of pulmonary secretions.

Trauma-related injuries as a result of falls or explosions and burns must be managed concurrently with inhalation injury. Perform a fingerstick glucose or administer dextrose in the patient with altered mental status and coma and consider naloxone for possible opiate intoxication.

Treat suspected carbon monoxide poisoning with 100% oxygen via nonrebreather mask or endotracheal tube until confirmatory COHgb level is obtained. Consider referral for hyperbaric oxygen therapy (see Chapter 327). Suspect cyanide poisoning in patients

with coma and hypotension and treat with an antidote (see Chapter 329). Hydroxocobalamin (Cyanokit) does not induce methemoglobinemia and may be safely administered to the smoke inhalation patient with suspected cyanide toxicity. The other commercially available antidote kit contains sodium nitrite 3% solution and sodium thiosulfate 25% solution. Sodium nitrite is a potent vasodilator and may cause hypotension. It can also induce methemoglobinemia. When oxygen transport is already compromised, as in a patient with concomitant carbon monoxide poisoning, further impairment by the inducement of methemoglobinemia may exacerbate cellular hypoxia. If hydroxocobalamin is unavailable, a reasonable approach in the smoke inhalation patient with suspected cyanide toxicity, particularly the seriously ill patient with a lactate level >8 mmol/L refractory to resuscitation, is to administer 12.5 g of sodium thiosulfate (50 mL of a 25% solution for adults; pediatric dose, 1.65 mL/kg).

Symptomatic methemoglobinemia and/or concentrations >20% to 30% should be treated with methylene blue (see Chapter 335).

CRITICAL INTERVENTIONS

- Perform early endotracheal intubation in patients with oropharyngeal burns or edema, soot in the oral cavity, full-thickness circumferential neck burns, stridor, coma, or hypoxemia or respiratory distress unresponsive to oxygen administration.
- Administer 100% oxygen to patients with significant smoke exposure or respiratory symptoms.

DISPOSITION

Indications for admission for observation and further treatment are listed in Table 337.4. Severity of illness and the presence of concomitant burns or traumatic injuries should guide the decision to admit to an ICU, telemetry unit, or floor bed. Patients with carbon monoxide poisoning may require transfer for HBO therapy (see

Chapter 327), and those with significant surface burns or physical injuries may require transfer to a burn or trauma center. Advanced life-support capability should be available during transfer.

TABLE 337.4
Indications for Admission after Smoke Inhalation

Facial or nasal burns
Persistent respiratory symptoms (including cough and chest tightness)
Crackles or wheezing on auscultation
Altered mental status
History of loss of consciousness
Abnormal ABG, CXR, or ECG
History of chronic cardiopulmonary disease

ABG, arterial blood gas; CXR, chest x-ray; ECG, electrocardiogram.

Patients in good health who are asymptomatic (on arrival or after a short period of oxygen therapy) and have a normal physical examination including pulse oximetry, blood gas analysis (while breathing room air), ECG, chest radiograph, and COHgb level may be discharged. These patients should be observed for at least 3 or 4 hours before discharge, and they should be instructed to return immediately if any respiratory symptoms develop. Scheduled follow-up at 24 hours may be prudent.

Common Pitfalls

- Failure to anticipate deterioration despite an initially normal initial physical examination, laboratory evaluation, and chest radiograph and failure to frequently reevaluate the respiratory status.
- Failure to evaluate and treat for coexisting carbon monoxide poisoning, drug or alcohol intoxication, traumatic injuries, and psychiatric problems.
- Failure to give oxygen to all patients (including those with chronic obstructive pulmonary disease).

- Failure to fluid-resuscitate patients with trauma or surface burns for fear of exacerbating the edema of inhalation injury.
- Failure to recognize the potential hazards of inappropriate corticosteroid and antibiotic administration.

ACKNOWLEDGMENT

The author gratefully acknowledges the contributions of Christopher H. Linden to the content of this chapter.

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PART 8 • PSYCHOTHERAPEUTIC AGENTS

CHAPTER 338 Antipsychotic Agents

Landen Rentmeester and Richard F. Clark

Antipsychotic agents encompass a class of pharmaceuticals originally designed to treat the psychotic features of mental illnesses such as schizophrenia, schizoaffective disorder or acute psychosis but have also been found useful to treat nausea, agitation, hiccoughs, and tics. These medications, especially the older typical antipsychotics, have also been called "neuroleptics" or "major tranquilizers." Antipsychotics are generally divided into the "typical" and "atypical" agents. The "typical" agents were the first antipsychotics to be developed, and were effective in treating hallucinations, agitation, delusions, and behavioral disturbances, the "positive" symptoms of schizophrenia. These older medications are also associated with the development of motor disturbances collectively known as the extrapyramidal syndrome (EPS). The newer "atypical" antipsychotic medications were developed to minimize extrapyramidal effects but were also found to be more effective in treating the "negative" symptoms of schizophrenia, such as alogia, avolition, flattened affect, and social withdrawal (1).

Butyrophenones (e.g., haloperidol), dephenylbutylpiperidines (e.g., pimozide), and phenothiazines (e.g., thioridazine) are the three major classes of the typical antipsychotics, whereas the benzamides (e.g., metoclopramide), diazepines (e.g., olanzapine), indoles (e.g., risperidone), and quinolinones (e.g., aripiprazole) are the four major classes of atypical antipsychotics. The antipsychotic action of each of these medications is thought to be due to blockade of excessive dopamine–mediated neurotransmission in the central nervous system (CNS) (2). Antipsychotic medications also have pharmacologic

effects outside of the dopaminergic pathways, blocking alpha-adrenergic (α_1), histaminergic (H_1), muscarinic (M_1), and serotonergic (5-HT_{2A}) receptors (3).

The atypical agents have lower and more selective (mesolimbic) D_2 potency and higher M_1 and/or 5-HT_{2A} antagonist activity than the typical agents (3). Although higher doses are required for antipsychotic effect, they are less likely to cause acute dystonia and tardive dyskinesia and have minimal or no effect on prolactin secretion. Only clozapine, olanzapine, and quetiapine have significant antimuscarinic activity. Atypical antipsychotics cause EPS less frequently than the older agents; whereas lurasidone may be more likely to promote extrapyramidal symptoms than other atypical agents (4). For unclear reasons, all atypical antipsychotics can cause hyperglycemia and an FDA black box warning recommends that diabetics and those at risk for diabetes (e.g., obese patients and those with a family history of diabetes) be monitored for this complication at the start of therapy. Atypical antipsychotics, especially olanzapine and clozapine, seem to put patients at risk for "metabolic syndrome," a constellation of weight gain, insulin resistance, glucose intolerance, and hyperlipidemia (3). Among the first-generation antipsychotics agents, chlorpromazine is most frequently associated with weight gain (4).

Most antipsychotics are much more potent H_1 blockers than diphenhydramine. Antimuscarinic (M_1) potency correlates directly with sedation and inversely with the incidence of EPS. Chlorpromazine, chlorprothixene, and thioridazine have potent sedative effects, whereas haloperidol, zotepine, and chlorpromazine are commonly associated with EPS (4).

Hypotension and miosis are often seen with both therapeutic dosing and overdose of both typical and atypical antipsychotics, a result of peripheral α-adrenergic blockade. Hypotensive effects are primarily orthostatic and systolic in nature. Concomitant therapy with either β-receptor agonists (e.g., epinephrine) or β-receptor blockers (e.g., propranolol) may result in severe hypotension. All the antipsychotics, particularly chlorpromazine, clozapine, and loxapine

lower the seizure threshold and can induce epileptiform encephalogram (EEG) discharge patterns at therapeutic dosages and in overdose, probably because of inhibition of γ-aminobutyric acid (GABA) receptors, norepinephrine reuptake, or antimuscarinic effects.

Antipsychotics also have dose-related effects on cellular membrane ion channels (3). Phenothiazines (particularly chlorpromazine, thioridazine and its metabolite mesoridazine) block sodium channels, which in overdose may cause local anesthetic or quinidine-like (class Ia) effects and result in dysrhythmias, myocardial depression, and delayed depolarization with conduction disturbances, especially QRS prolongation. QRS prolongation is most often seen with quetiapine but is rarely an isolated finding with atypical agents (3). Droperidol, haloperidol, sertindole (Serlect), thioridazine, most atypical antipsychotics, and most other antipsychotics also block potassium channels, resulting in delayed repolarization with QT interval prolongation. Higher IV doses of the atypical agents such as ziprasidone may also cause this effect. Electrocardiogram (ECG) changes such as prolonged PR and QT intervals, ST-segment depression, T-wave abnormalities (biphasic, blunting, inversion, notching, widening), and increased U waves occur with both therapeutic and excessive doses (3,6). Reports of QT prolongation leading to torsades de pointes (polymorphic ventricular tachycardia), ventricular tachycardia (VT), and death prompted a controversial box warning for IV droperidol in 2001 and IV haloperidol in 2007 that an ECG be obtained prior to its use, that it not be given to those with QT prolongation ($>$440 ms in males and 450 ms in females), and for cardiac monitoring for 2 to 3 hours after its use (7). Ventricular dysrhythmias, asphyxia from aspiration, or respiratory depression from seizures have been postulated as the cause of sudden death with therapeutic doses of antipsychotics, particularly phenothiazines (6).

Gastrointestinal (GI) absorption of antipsychotics is relatively slow and unpredictable, with peak levels occurring 2 to 4 hours after ingestion. Bioavailability after parenteral administration is two to ten times greater than with oral dosing because presystemic (GI and

hepatic) metabolism occurs after ingestion. Antipsychotics are highly bound to plasma proteins, are highly lipophilic, and have large volumes of distribution (10 to 40 L/kg). Thus, therapeutic serum concentrations are low (one to several hundred ng/mL), and drug accumulates in the brain and fat and readily crosses the placenta.

Therapeutic doses vary widely (see Table 338.1) and are adjusted on the basis of clinical response and side effects, not by monitoring drug levels. Pharmacologic effects generally last 24 hours or more, allowing once or twice daily dosing. Elimination occurs slowly by hepatic metabolism, with serum concentration half-lives averaging 20 to 40 hours. Hepatic metabolism yields multiple metabolites, some of which are pharmacologically active (aripiprazole, risperidone, quetiapine, thioridazine and clozapine are known to have active metabolites). Metabolites are eliminated by urinary and, to some extent, biliary excretion and can be detected in the urine for more than a month after the cessation of chronic therapy. Concomitant use of agents that inhibit or stimulate hepatic cytochrome oxidases (CYP isoenzymes) can increase or decrease, respectively, the blood level and effect of these agents.

TABLE 338.1
Antipsychotic Agents

Structural Class	Generic Name	Trade Name	Oral Dose (Adult, mg)
Traditional (Typical) Antipsychotics			
Benzamide	Trimethobenzamide	Tigan	250–300
Butyrophenone	Droperidol	Inapsine	2.5–10.0[c]
	Haloperidol	Haldol	0.5–2.0
Dibenzoxazepine	Loxapine	Loxitane	10–50
Diphenylbutylpiperidine	Pimozide	Orap	0.5–1
Indole	Molindone	Moban	5–25
Phenothiazine	Chlorpromazine	Thorazine	25–50
	Fluphenazine	Prolixin	2.5–10
	Mesoridazine	Serentil	25–100
	Perphenazine	Trilafon	4–16
	Prochlorperazine	Compazine	5–10
	Promazine	Sparine	25–100
	Promethazine[a]	Phenergan	25–50
	Thiethylperazine[a]	Torecan	10–30
	Thioridazine	Mellaril	25–100
	Trifluoperazine	Stelazine	2–5
	Triflupromazine	Vesprin	5–15[c]
	Trimeprazine[b]	Temaril	2.5
Thioxanthene	Chlorprothixene	Taractan	25–50
	Thiothixene	Navane	2–15
Atypical Antipsychotics			
Benzisoxazole	Risperidone	Risperdal	1–3
Dibenzodiazepine	Clozapine	Clozaril	200–600
Dibenzothiazepine	Quetiapine	Seroquel	50–250
Piperazine	Ziprasidone	Geodon	20–80
Quinolone	Aripiprazole	Abilify	5–30
Thienobenzodiazepine	Olanzapine	Zyprexa	10–15

[a]Used only as antiemetic.
[b]Used only as antipruritic.
[c]Parenteral dose.

Side effects of therapeutically dosed antipsychotics include antimuscarinic sequelae (see Chapter 344, “Anticholinergic Agents”), extrapyramidal symptoms (EPS), neuroleptic malignant syndrome (NMS), hypotension, and sedation (3,4). Clozapine can cause agranulocytosis, myocarditis, and cardiomyopathy (3).

Antipsychotic agents have a high therapeutic index. Of the thousands of overdoses reported to poison centers each year, only 4% to 6% of patients develop serious toxicity, and <1% die. Thioridazine (because of its tricyclic antidepressant-like

cardiotoxicity) or mixed overdoses are involved in most successful suicides (3,5). Toxic doses for most of these agents are not well established and vary greatly.

CLINICAL PRESENTATION

Mild poisoning includes ataxia, confusion, lethargy, and slurred speech. Hypotension, both orthostatic and diastolic, may be caused by α-adrenergic blockade. Tachycardia may develop from antimuscarinic effects or as a reflex tachycardia. Miosis due to α blockade is common, but mydriasis due to antimuscarinic effects can also occur. Antimuscarinic signs and symptoms (Chapter 344, "Anticholinergic Agents") are often present, and patients may be hyperreflexic. Prolonged PR and QT intervals and nonspecific ST-segment, T-wave, and U-wave abnormalities may be seen.

Moderate poisoning is characterized by sedation, with or without respiratory depression, and systolic hypotension accompanied by reflex tachycardia. Hyperthermia and hypothermia (less common) may be present. Paradoxical agitation, delirium, and tachypnea are reported but are likely antimuscarinic effects. Sialorrhea may be seen after clozapine overdose and at therapeutic doses.

In severe poisoning, deep coma with loss of brainstem and deep tendon reflexes, apnea, hypotension, tachycardia, and cardiac dysrhythmias (especially with thioridazine and mesoridazine) are seen. Tachydysrhythmias, rare bradydysrhythmias, and cardiac conduction delays (especially with thioridazine and mesoridazine) may occur. QT interval prolongation and torsades de pointes are reported after haloperidol, loxapine, phenothiazine, pimozide quetiapine, risperidone, sertindole, and ziprasidone overdose and during high-dose IV droperidol and haloperidol therapy (6). Seizures are rare, except with chlorpromazine, loxapine, and clozapine (3).

The onset of symptoms of poisoning occurs within 1 to 2 hours of acute ingestion, with maximal severity usually apparent in 2 to 6 hours. Children appear more susceptible to toxicity than adults. Recovery can be expected within several hours to several days, depending on the severity and drug ingested. The mortality rate from acute poisoning is $<1\%$.

EPS may occur early (within days), or late (after 3 months or more) after beginning antipsychotic therapy, increasing the dose, or changing the agent. Dyskinesia or acute dystonic reactions (see Chapter 340), akathisia, NMS, and parkinsonism occur early whereas tardive dyskinesia or dystonias occur late. These idiosyncratic reactions are most common with older high-potency agents. Akathisia, a subjective sensation of motor restlessness, occurs in about 20% of patients treated with traditional antipsychotics and is sometimes associated with severe parkinsonism (see Chapter 162, "Parkinsonism and Other Movement Disorders"). Transient akathisia has been observed in up to 50% of those treated with IV droperidol or prochlorperazine for headache, nausea, and vomiting. Women are affected more often than men. Patients complain of feeling restless, jittery, and tense; they cannot sit or stand still and when standing may shift their weight from foot to foot as if walking in place. Vital signs remain normal. Semipurposeful or purposeless limb movements (especially of the lower extremities), frequent shifting of body position, and tremors and myoclonic jerking may be noted. Focal perioral tremor, also known as *rabbit syndrome,* is a rhythmic motion of the mouth and lips, resembling the chewing movements of a rabbit. In contrast to oral tardive dyskinesia, tongue movements do not occur in rabbit syndrome.

NMS can be precipitated by concurrent illness, surgery, dehydration, heat stress, acute agitation and, very rarely, by acute overdose of antipsychotic agents. It is estimated to occur in $<1\%$ of patients treated with antipsychotics for psychiatric conditions and appears to be more common with parental therapy. Of the cases linked to atypical antipsychotics, clozapine has been implicated in many of them, despite the relative rarity of extrapyramidal symptoms with this drug (3). NMS is characterized by elevated body temperature ($>38^{\circ}C$ or $100.4^{\circ}F$), altered mental status ranging from confusion and delirium to coma, autonomic dysfunction, increased motor activity, and laboratory abnormalities. Autonomic disturbances include hypertension ($>150/100$ mm Hg; diastolic or systolic blood pressure increased 20 or 30 mm Hg above baseline, respectively), tachycardia (heart rate >90 to 100 or increased by 30

beats/min), increased respiratory rate (alternatively dyspnea, hypoxemia, or respiratory failure), diaphoresis (often profuse), sialorrhea, and incontinence. Hypotension, rather than hypertension, sometimes occurs. Although "lead pipe" rigidity is the classic motor finding, lesser increases in muscle tone, akinesia, dystonia, dyskinesia, tremor, choreiform movements, opisthotonus, and parkinsonism (cogwheel rigidity) may be present. Hyperactivity of pharyngeal muscles may result in dysarthria, dysphagia, dysphonia, and trismus. Laboratory abnormalities include leukocytosis (white blood cells $>14{,}000/mm^3$ without a left shift), rhabdomyolysis (creatine phosphokinase >500 IU/mL or three times normal), and markedly elevated white blood cell count. Hyponatremia, hypernatremia, or hypokalemia may be present. Onset is typically insidious, and resolution occurs slowly, sometimes taking up to 2 weeks. Complications include aspiration pneumonia, coagulopathy, renal failure, rhabdomyolysis, myocardial infarction, heart failure, dysrhythmias, and venous thromboembolism. The mortality rate of NMS ranges from 12% to 20% and is primarily related to complications. Sequelae include dysarthria, dysphagia, myoclonus, and weakness.

DIFFERENTIAL DIAGNOSIS

Antidysrhythmic, tricyclic antidepressant, antimuscarinic, anticonvulsant, opioid, and sedative–hypnotic toxicity may all cause CNS or CV effects similar to those seen in antipsychotic poisoning. CNS infection, infarction, and trauma should also be considered in the differential diagnosis of antipsychotic poisoning.

EPS from antipsychotics may be misdiagnosed as anxiety or agitation related to an underlying psychiatric disorder. EPS can occur when beginning or increasing therapy with neuroleptic or nonneuroleptic dopamine antagonists (e.g., hydroxyzine, metoclopramide, reserpine), discontinuing or decreasing therapy with a dopamine agonist (e.g., amantadine, bromocriptine, carbidopa, levodopa, lithium, pergolide, pramipexole, ropinirole) or use of a catecholamine degradation inhibitor (e.g., catechol-o-methyltransferase inhibitors such as entacapone and tolcapone). The

differential diagnosis of NMS also includes dystonic reactions, lithium, monoamine oxidase inhibitor, salicylate, stimulant, and strychnine poisoning, heat stroke, malignant catatonia, malignant hyperthermia (MH), encephalitis, meningitis, pheochromocytoma, serotonin syndrome (SS), tetanus, thyrotoxicosis, and withdrawal states.

Distinguishing NMS from MH or SS (see Chapter 343, "Serotonin Reuptake Inhibitors") is difficult as clinical features overlap. The correct diagnosis relies primarily on the drug exposure history. Onset after general anesthesia or ketamine administration strongly suggests MH. Use of proserotonin drugs is suggestive of SS. SS also begins more abruptly and resolves more quickly than NMS (over hours rather than days). Myoclonus, hyperreflexia, and shivering are rare in NMS but common in SS.

Although specific criteria have been proposed for the diagnosis of NMS, the required elements are not universally agreed on, and patients can have NMS without manifesting a classic or characteristic feature (e.g., fever or rigidity). Diagnosing patients with attenuated forms of NMS relies primarily on the clinical settings and history of drug exposure (3).

ED EVALUATION

A complete history should always be obtained from the patient and, when possible, corroborated with the person who found or brought the patient to the emergency department (ED). The name, quantity, and time of ingestion should be determined. In patients taking antipsychotics for therapeutic purposes, a history of a recent medication or dosage change, illness, or surgery is important.

The physical examination should focus on the vital signs, CV system, and neurologic function. An initial rhythm strip and subsequent 12-lead ECG should be evaluated for prolonged QRS or QTc intervals or other dysrhythmias. Pulse oximetry can monitor oxygenation and end tidal carbon dioxide monitoring can monitor adequacy of ventilation. Because phenothiazines can be radiopaque, abdominal radiographs may be useful to quantify or verify ingestion, however, the lack of x-ray visualization does not rule out ingestion

or imply successful gastric decontamination. Laboratory evaluation should include a complete blood count, electrolytes, blood urea nitrogen, creatinine, and glucose to rule out concomitant abnormalities, urinalysis to check for myoglobin, and serum creatine kinase (CK) to evaluate for rhabdomyolysis. In patients with hyperthermia, liver function tests and coagulation profiles are useful to determine hepatic injury or disseminated intravascular coagulation. Computed tomography (CT) of the head and lumbar puncture should be considered as intracranial hemorrhage and meningitis may present in a similar manner as NMS. In seriously ill patients, toxicologic analysis of the urine and serum may confirm the identity of the agent, but results will often not be readily available. Quantitative drug levels are not helpful in predicting clinical toxicity or in guiding treatment. Urine drug immunoassays most often do not detect antipsychotics and are of little value in treating a patient who presents with an acute medication overdose. Although neither sensitive nor specific, the Forest, Mason, and Phenistix colorimetric urine tests may be positive with phenothiazine ingestions and can be used to rapidly screen for these agents.

KEY TESTING

- 12-lead ECG to evaluate for QRS or QTc interval abnormalities.
- Complete blood count, basic metabolic profile including magnesium, calcium, and phosphorus levels.
- Consider liver transaminase, creatine kinase, and coagulation panel.
- Head CT and lumbar puncture if altered mental status is of unclear etiology.
- Consider physostigmine challenge in the appropriate clinical setting.

ED MANAGEMENT

Advanced life-support measures should be instituted as necessary. All patients require cardiac and respiratory monitoring along with IV access. Core temperature should be monitored for evidence of hypo-

or hyperthermia with appropriate cooling or heating measures. Endotracheal intubation may be required for respiratory failure, CNS depression, or when paralysis is indicated for significant hyperthermia. If paralysis is required, nondepolarizing paralytic agents such as rocuronium (0.6 to 1 mg/kg IV) or vecuronium (0.08 to 0.1 mg/kg IV) are recommended, because succinylcholine (and other depolarizing neuromuscular blockers) can cause MH and potentiate rhabdomyolysis and hyperkalemia in antipsychotic-poisoned patients.

Hypotension should initially be treated with IV crystalloids. Norepinephrine and/or phenylephrine are the drugs of choice for refractory hypotension due to their α_1-adrenergic properties. Dopamine may be ineffective or even exacerbate the hypotension associated with antipsychotics agents. At modest doses, dopamine's activity may be impaired because it is unable to enter presynaptic terminals through the blocked catecholamine reuptake pump caused by the antipsychotic, whereas at higher doses, dopamine may encounter α-blocking effects of these drugs, leading potentially to unopposed β-receptor stimulation of blood vessels and vasodilation.

Unstable tachydysrhythmias should be treated with electrical cardioversion or defibrillation for ventricular fibrillation and nonperfusing monomorphic or polymorphic VT. If the QRS complex is wide prior to or after termination of unstable tachydysrhythmias, sodium bicarbonate (1 mEq/kg IV) may be effective (see Chapter 321, "Antidysrhythmic Drugs and Local Anesthetics," and Chapter 339, "Cyclic Antidepressants"). Amiodarone or lidocaine can also be used to treat refractory stable VT. Type Ia (disopyramide, quinidine, procainamide), Ic (encainide, flecainide, propafenone), II (β blockers), and IV (calcium channel blockers) antidysrhythmic drugs should be avoided in wide complex tachydysrhythmias. If the QTc interval is significantly prolonged (typically greater than 500 ms) or torsades de pointes is observed, magnesium (50 to 100 mg/kg IV over 1 hour), isoproterenol, or overdrive pacing are preferred. Increasing the heart rate shortens the QT interval and is recommended for preventing the recurrence of torsades de pointes. Bradydysrhythmias should be treated according to Advanced Cardiac

Life-Support protocols. Complete heart block may require temporary cardiac pacing after underlying metabolic abnormalities are corrected.

Seizures should be treated with benzodiazepines (e.g., lorazepam, 0.05 mg/kg IV, or diazepam, 0.1 mg/kg IV). Barbiturates (e.g., phenobarbital, 18 to 20 mg/kg IV, or pentobarbital, 5 mg/kg IV) and propofol may be added if necessary. Patients with refractory seizures may require propofol infusion or neuromuscular paralysis to prevent complications such as hyperthermia and rhabdomyolysis. Continuous or serial EEG monitoring should be instituted during paralysis. Aggressive IV fluid resuscitation with or without alkalinization of the urine may prevent myoglobinuric renal failure in patients with rhabdomyolysis. Physostigmine can reverse the delirium resulting from muscarinic receptor blockade if the QRS length on ECG is normal and if there is no seizure activity (see Chapter 344, "Anticholinergic Agents"). This is typically dosed in adults as 1 to 2 mg infused over 5 minutes. The patient should respond within 10 minutes, but the effect will be transient, lasting 45 minutes to an hour and the dose can be repeated. Antimuscarinic reversal is classified as a return to normal mental state which provides a window of opportunity to obtain confirmation of the patient's overdose and avoid the need for a more extensive diagnostic workup (8).

Early and aggressive treatment of muscular hyperactivity and hyperthermia in patients with NMS appears to improve outcome. Initial management includes benzodiazepines, but therapeutic paralysis may be required for patients with refractory seizures or severe hyperthermia. Active cooling measures (e.g., cooling blankets, ice packs, and evaporative cooling methods) are necessary for most severely hyperthermic patients. Antipyretics are not effective. The antipsychotic therapy must be discontinued. Although dantrolene (2.5 to 10 mg/kg/d IV) has been proposed to treat NMS, there are no convincing clinical data or theoretical reasons to suggest that it would be efficacious. The release of calcium from muscle sarcoplasmic reticulum is reduced by dantrolene through inhibition of ryanodine receptors. This mechanism is involved in the

pathogenesis of MH, but does not seem to cause or contribute to NMS. However, if MH cannot be definitely excluded, dantrolene sodium can be attempted as this may be a lifesaving intervention.

Activated charcoal may be considered in patients with a secure airway and ingestion within 1 hour who do not have suspected caustic injury or are at risk for aspiration. Repeated oral doses of activated charcoal are not beneficial for these poisonings. Diuresis, dialysis, and hemoperfusion are not effective. Patients in cardiovascular collapse from severe antipsychotic overdose have responded to use of lipid emulsion therapy (Intralipid) and extracorporeal life-support and these may be considered if resources are available (9,10)

Patients with EPS who require continued antipsychotic therapy can be managed by reducing the dose, switching to an agent of lower potency, or giving an antimuscarinic agent (e.g., benztropine or diphenhydramine). Benzodiazepines, clonidine, propranolol, and short-acting barbiturates have also been used with moderate success. Patients who develop akathisia after a single therapeutic dose of antipsychotic (e.g., for migraine or vomiting) should be reassured that symptoms will resolve within 24 hours.

CRITICAL INTERVENTIONS

- Establish IV access, cardiac monitoring, and ECG for QRS and QT intervals, and frequently reevaluate the vital signs and clinical status.
- Obtain a core temperature and CK in patients with suspected NMS (altered mental status, autonomic dysfunction, and muscle hyperactivity).
- Treat muscle hyperactivity, and seizures aggressively with benzodiazepines, barbiturates, therapeutic paralysis for refractory cases.
- Use physical cooling measures for hyperthermia, and alkaline diuresis for rhabdomyolysis.
- Administer sodium bicarbonate to patients with monomorphic VT. Lidocaine or amiodarone may be used in refractory VT.

- Administer magnesium, isoproterenol, or overdrive pacing to patients with torsades de pointes.

DISPOSITION

Asymptomatic patients with an acute overdose should be observed for 6 hours. Symptomatic patients with significant CNS depression, hypotension, seizures, or dysrhythmias should be admitted to an intensive care unit (ICU) or a monitored observation area. Alert patients with a history of overdose and abnormal ECG should be monitored as ECG abnormalities can be seen with therapeutic doses and have been implicated as a cause of sudden death.

Except for NMS, EPSs are not life-threatening and do not require admission, although the symptoms may be quite stressful to patients. Medication adjustment may be appropriate, but this should be done in consultation with the patient's psychiatrist. Patients with NMS will require ICU admission. Patients requiring transfer to a facility capable of providing intensive care should be accompanied by advanced life-support personnel and should have cardiac monitoring en route.

Common Pitfalls

- Failure to appreciate that antipsychotics can prolong QRS and QTc intervals, causing cardiac dysrhythmias.
- Failure to appreciate that atypical antipsychotics, although less likely to cause EPS than traditional agents, are more sedating and cause similar CV toxicity.
- Failure to appreciate that antipsychotics can lower seizure threshold.
- Failure to appreciate that attenuated forms of NMS can occur and to discontinue antipsychotic therapy in patients with any manifestation of NMS.
- Administration of Type Ia, Ic, II (β blockers), and IV (calcium channel blockers) antidysrhythmic agents in wide complex tachydysrhythmias.

- Failure to appreciate that dopamine is not as effective as norepinephrine or phenylephrine in treating antipsychotic-induced hypotension.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Christopher Linden, Michael Young, and Alexander Miller to the content of this chapter.

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CHAPTER 339 Cyclic Antidepressants

Jon B. Cole

Cyclic antidepressants (CAs) have been used to treat depression since the 1950s. Additional therapeutic use has included attention deficit disorder, anorexia nervosa, obsessive-compulsive disorder, phobias, chronic pain, migraine headaches, enuresis, and peptic ulcer disease. The term *CAs* refers to a family of drugs that have similar structure, pharmacology and toxicity (Table 339.1). In the 1980s, another group of antidepressants, the selective serotonin reuptake inhibitors (SSRIs; see Chapter 343), emerged and their use has superceded that of the CAs. SSRIs offer a wider margin of safety, with less central nervous system (CNS) and cardiovascular (CV) toxicity, compared with the CAs (1). During the 1990s and 2000s, the atypical antipsychotic agents (see Chapter 338) grew in popularity and are also being used to treat depression, especially in association with psychotic disorders. During this time the serotonin and norepinephrine reuptake inhibitors (SNRIs), venlafaxine and duloxetine, as well as the unique norepinephrine and dopamine reuptake inhibitor bupropion also came to prominence. The toxicity profiles of the atypical antipsychotics, SNRIs, and bupropion are dependent on the unique pharmacologic actions of each drug, but several of them share aspects that resemble CA poisoning, including coma, tachycardia, delirium, QTc prolongation, QRS prolongation, shock, and cardiac dysrhythmias. Even with these alternative drug classes, CAs are still commonly used. In 2011, 73 fatalities related to the ingestion of CAs were reported to American poison centers (2). Moreover, overdoses with CA continue to cause more toxicity than overdoses with other antidepressants (3). CAs also are still

commonly prescribed in children, and CA poisoning can be potentially lethal in younger children as well (4).

TABLE 339.1
Antidepressant Agents

Class	Drug	Trade Name(s)
Tricyclics		
Tertiary amines		
	Amitriptyline	Amitid, Amitril, Elavil, Endep, Etrafon, Triavil
	Clomipramine	Anafranil
	Doxepin	Adapin, Sinequan
	Imipramine	Janimine, Presamine, SK-Pramine, Tofranil
	Trimipramine	Surmontil
Secondary amines		
	Desipramine	Norpramin, Pertofrane
	Nortriptyline	Aventyl, Pamelor
	Protriptyline	Vivactil
Tetracyclics		
	Maprotiline	Ludiomil
	Mianserin	Bolvidon, Norval
Dibenzoxazepine		
	Amoxapine	Ascendin
Selective Serotonin Reuptake Inhibitors		
	Fluoxetine	Prozac
	Sertraline	Zoloft
	Paroxetine	Paxil
	Fluvoxamine	Luvox, Faverin
	Citalopram	Celexa, Cipramil, Seropram
	Escitalopram	Lexapro, Cipralex

The pharmacologic properties of the CAs contribute to their toxicity in overdose. In general CAs are highly lipophilic, with large volumes of distribution (Vd = 10 to 50 L/kg), and are highly protein-bound (>95%). The onset of CA toxicity is typically rapid; CAs are rapidly absorbed and quickly distributed to their target

organs. Most CAs are tertiary or secondary amines. Tertiary amines (e.g., amitriptyline and imipramine) are metabolized to their respective secondary amines (e.g., nortriptyline and desipramine), which are also active drugs. Tertiary amines block norepinephrine and serotonin reuptake, whereas secondary amines primarily block norepinephrine reuptake. Amoxapine and maprotiline are CAs that have unique structures that also primarily block norepinephrine reuptake. Tertiary amines have more anticholinergic and antihistaminic effects than the secondary amines. CAs have half-lives of >24 hours. Early reports described delayed recovery from toxicity but improved supportive care, particularly alkalinization therapy, is probably responsible for improving outcomes today. With good supportive care, most CA-poisoned patients make a full recovery within 1 to 3 days.

Therapeutic doses of CAs are typically <5 mg/kg but tolerance does develop with chronic use. Toxicity is often seen with ingestion >10 mg/kg, which is also considered to be a minimum fatal dose. Doses >15 mg/kg often result in severe and potentially fatal ingestions.

The CNS and CV toxicity of CAs result from their pharmacologic actions which include (1) delayed cardiac conduction from sodium-channel blockade, (2) initial sympathomimetic, and late sympatholytic actions resulting from the blockade of norepinephrine reuptake, and (3) anticholinergic, (4) antihistaminic, (5) $GABA_A$ receptor channel, (6) α_1-adrenergic blocking, and (7) block cardiac potassium delayed-rectifier channels. Some CAs present with either predominantly CNS or cardiac toxicity. For example, amoxapine produces seizures, including status epilepticus, but rarely causes cardiac conduction disturbances. In general, newer and safer antidepressants, such as the SSRIs, have a relative absence of sodium-channel blockade, catecholamine reuptake blockade, and anticholinergic effects.

CLINICAL PRESENTATION

CA poisoning may progress rapidly from asymptomatic to cardiopulmonary arrest within minutes as an alert patient may have seizures, become comatose, or develop hemodynamic and cardiac instability. CA-induced seizures typically occur early and are unlikely to recur beyond 12 hours after ingestion but may deteriorate into status epilepticus. Status myoclonic activity is seen with severe poisoning. Vital signs can be unpredictable in CA poisoning. Patients are often initially tachycardic and mildly hypertensive (as a result of the blockade of norepinephrine reuptake and anticholinergic effects), or they may be hypotensive (from α_1 blockade). Later, the metabolism of norepinephrine by enzymes such as catechol-O-methyltransferase (COMT) may lead to a catecholamine depletion state resulting in hypotension, bradycardia, and finally cardiogenic shock. Most patients recover in 24 to 72 hours with good supportive care but refractory hypotension is seen in most fatalities.

Cardiac dysrhythmias include both supraventricular tachydysrhythmias and ventricular dysrhythmias. A wide QRS seen with intraventricular conduction delay from sodium-channel blockade makes it difficult to distinguish ventricular tachycardia (VT) from a supraventricular tachycardia with aberrant conduction. Polymorphous VT (torsades de pointes) has also been reported though this is rare. Aspiration pneumonia is relatively common in comatose patients, and acute respiratory distress syndrome may occur. Rhabdomyolysis and compartment syndrome are additional complications particularly if patients experience status epilepticus or are comatose for a long period of time without medical care.

Patients with ingestions of <15 mg/kg often have a predominant anticholinergic syndrome with minimal cardiac conduction effects. Anticholinergic effects can also occur during recovery from severe poisoning and may last for days. Typical signs and symptoms include tachycardia, hypertension, absent bowel sounds, ileus, and urinary retention. Other anticholinergic effects, such as dilated pupils, flushed hot skin, and dry mucous membranes, however, are more variable. For example, the patient’s pupils may be large if

anticholinergic effects predominate, however if α_1 blockade is prominent, small pupils would be seen. Central anticholinergic findings may vary from agitation to psychosis to coma. Additional neurologic manifestations include choreoathetosis, ataxia, myoclonus, status epilepticus, and coma.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of coma, seizures, and cardiac dysrhythmias includes hypoxia, metabolic abnormalities, serotonin syndrome, and intrinsic neurologic and cardiac diseases. Other drugs with toxicities that can appear similar to CAs include the antidysrhythmics, antihistamines, antimalarials, atypical antipsychotics, dihydropyridine-type calcium-channel blockers, carbamazepine, phenothiazines, tramadol, and propoxyphene. Anticholinergic agents, camphor, cocaine, chloral hydrate, isoniazid, lithium, sympathomimetic poisoning, and drug withdrawal should also be considered.

ED EVALUATION

The history should be obtained from the patient, family, friends, roommates, and available prehospital personnel. The patient's pharmacy records may be useful as well. If possible, the time, amount, and identity of all agents ingested should be determined. When known, the amount of CA ingested can help predict the potential for deterioration. The therapeutic dose of 5 mg/kg should be tolerated by all, including children. Observation without intervention would be the best approach for these patients. Conversely, patients who ingest 15 mg/kg (roughly 1 g for a 70-kg adult) have the potential for serious poisoning.

The physical examination should focus on the vital signs, CV, and neurologic function. Vigilant observation of mental status is required. The potential for seizures and rapid deterioration requires that IV access and continuous cardiac and oxygenation monitoring be initiated immediately. Vital signs and neurologic status should be evaluated continuously, and a limb lead QRS duration (discussion

follows) should be checked every 30 minutes or if the monitor looks suspicious.

An electrocardiogram (ECG) should be performed early in the evaluation. A QRS duration >100 ms is associated with seizures, and a QRS duration >160 ms is associated with ventricular dysrhythmias. Patients with a QRS duration >120 ms who have a seizure are at great risk for sudden CV toxicity including CV collapse (5). More subtle, early ECG changes include a rightward axis of the terminal 40 ms of the QRS in the frontal plane. This manifestation can be quickly assessed by looking for the presence of a wide S wave in leads 1 and aVL, and an R wave in lead aVR (Fig. 339.1). These terminal 40-ms changes are good indicators for sodium-channel blockade, from CA poisoning, but they do not absolutely confirm or exclude the diagnosis.

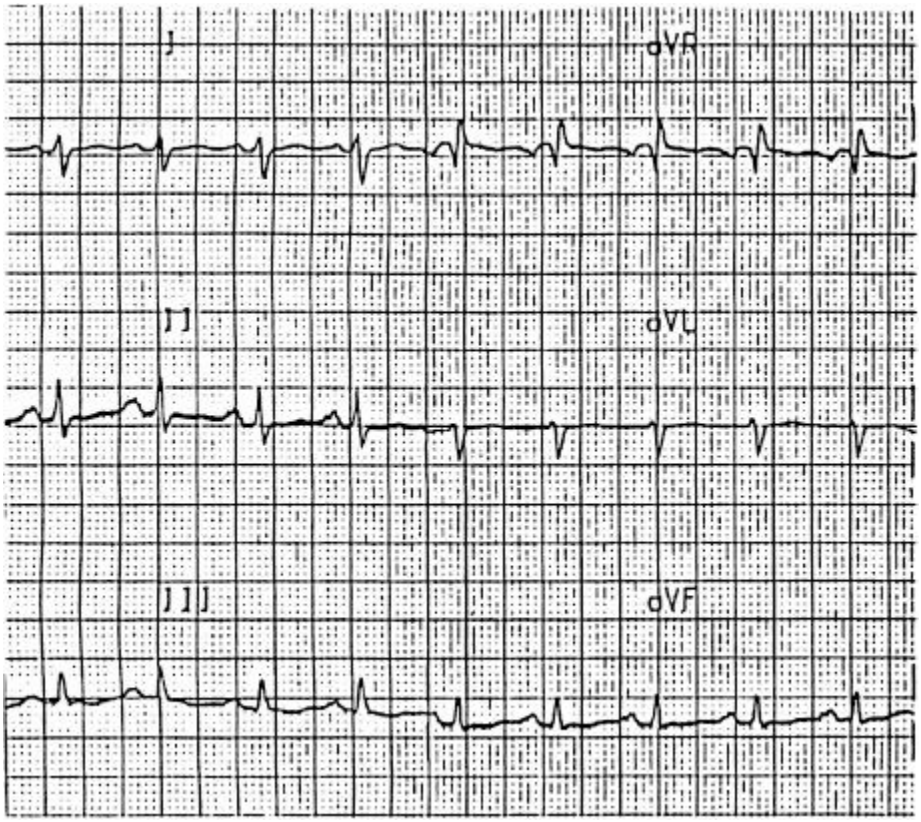

FIGURE 339.1 Terminal QRS changes in CA poisoning.

Other than a lactic acidosis secondary to seizures or shock, CAs are not known to produce biochemical disturbances. However, evaluation of patients with altered mental status or cardiotoxicity includes assessment of serum electrolytes, blood urea nitrogen, creatinine, and glucose. A blood gas, creatine phosphokinase, calcium, magnesium, phosphorus, liver chemistries, and a chest radiograph should be considered for ill patients with abnormal vital signs, significant CNS depression, seizures, or an abnormal ECG. Patients with an intentional ingestion should have a serum acetaminophen concentration to rule-out coingestion.

Drug screening for CAs has no place in the management of the acutely CA-poisoned patient. Urine qualitative immunoassays are the most common form of drug screening for CAs but many other drugs including diphenhydramine, cyclobenzaprine, quetiapine, cyproheptadine, carbamazepine, and most phenothiazines cause false positives. Although serum CA concentrations >1,000 ng/mL generally correlate with significant toxicity, levels do not assist in emergency management. Monitoring the changes on the ECG and the patient's mental status are more clinically useful indicators of ongoing CA toxicity.

KEY TESTING

- ECG and monitoring QRS width and dysrhythmias
- Acetaminophen level to detect coingestion
- Unstable patients need other laboratories for supportive care management
- Urine drug testing and serum levels are not clinically helpful

ED MANAGEMENT

Patients with coma, seizures, hypotension, and dysrhythmias include endotracheal intubation, administration of anticonvulsants, intravenous crystalloids, and serum alkalinization with parenteral sodium bicarbonate boluses.

Parenteral benzodiazepines such as diazepam (5 to 10 mg) or lorazepam (1 to 2 mg) are the agents of choice for the treatment of

seizures. They should be administered to any patient with seizures. Repeat doses may be required. When intubation is required, parenteral benzodiazepines such as lorazepam and diazepam may be useful as well for sedative and anticonvulsant effects, though propofol is a reasonable option if hypotension is not present. If repeat doses of benzodiazepines do not completely control seizures, phenobarbital or propofol should be added. Phenobarbital or propofol may be necessary for the treatment of myoclonus. In the intubated patient, a phenobarbital loading dose of 18 mg/kg is usually sufficient. The dose for propofol sedation of the intubated patient begins with a bolus infusion of 0.5 mg/kg; this can be repeated if blood pressure allows. The dose is titrated to the desired sedation level in increments of 20 to 80 μg/kg/hr as a constant infusion, titrated to the appropriate sedation level. Propofol's rapid onset and offset make it ideal for the management of these ventilated CA-poisoned patients. Seizures should be anticipated so benzodiazepines should be kept at the bedside to minimize the rapidly produced lactic acidosis that may further compromise the cardiac and hemodynamic status. In addition, an intravenous bolus of 1 to 2 ampules (44 to 100 mEq) of hypertonic sodium bicarbonate is recommended as adjunctive treatment for seizures.

Hypotension should be treated with intravenous crystalloid boluses. This treatment should overcome hypotension from α-adrenergic blockade and mild dehydration. For more seriously poisoned patients, vasopressors will be needed. Dopamine and norepinephrine have been used; however, many cases are refractory to dopamine. Because dopamine partially acts by causing catecholamine release from sympathetic nerve terminals, it may lose some of its effectiveness when norepinephrine stores are depleted as a result of CA poisoning. Norepinephrine has been demonstrated to have greater efficacy than dopamine in successfully treating refractory hypotension (6). Dosing of norepinephrine should start at 0.04 μg/kg/min and be titrated up as needed to a mean arterial pressure of 60 mm Hg. In patients unresponsive to these measures, bedside or formal echocardiography, pulse-contour analysis to determine cardiac output and systemic vascular resistance, or the

insertion of a pulmonary artery catheter may be useful to guide additional fluid and vasopressor management.

For patients in refractory shock, true extremis or cardiac arrest from CA poisoning, intravenous fat emulsion (IFE or Intralipid) has been successfully used (7). Though the mechanism of IFE is not fully elucidated, the infusion of lipid may create a “lipid sink” in the blood. Fat-soluble drugs diffuse into the lipid sink and away from the deleterious site of action. IFE was initially described and has now become standard care in the resuscitation of patients with local anesthetic overdose in the operating room. Its use subsequently expanded to other cardiotoxic drugs, including CAs (7). Results, however, have been mixed with regard to the use of IFE in CA poisoning. In animals IFE outperformed hypertonic sodium bicarbonate for treating hypotension for clomipramine (8) however was associated with worse survival and higher serum drug concentrations for amitriptyline (9). The differences in these studies may be evidence that IFE is effective for the treatment of poisoning from some CAs but not others. At this time the use of IFE in CA poisoning remains reasonable for the patient in true extremis refractory to sodium bicarbonate, norepinephrine, and usual supportive care. The dose is 1.5 mL/kg of 20% IFE over 2 to 3 minutes, followed by an infusion of 0.25 mL/kg/min over 30 minutes. The bolus dose may be repeated as needed up to two additional doses. As experience increases, the use of IFE may become better defined.

Cardiac dysrhythmias can be terminated with sodium bicarbonate. Sodium and bicarbonate have both proven to be beneficial treatments for toxins that have quinidine-like, sodium-channel blocking actions. In experimental models of amitriptyline toxicity, sodium loading and increasing pH each separately improve cardiac conduction, but both treatments together produced the greatest improvement. Although hypertonic saline, 7.5% in dextran, without bicarbonate dramatically increases blood pressure and narrows the QRS interval after nortriptyline poisoning in animals, hypertonic saline is not widely used in clinical practice. Sodium bicarbonate boluses and normal saline infusions are usually

sufficient but require careful monitoring as overuse can cause severe hypernatremia, fluid overload, and alkalemia.

Dysrhythmias should be treated with at least two or three ampules (100 to 150 mEq, or a dose of 1 to 2 mEq/kg) of sodium bicarbonate. This bolus dosing should occur every 3 to 5 minutes until the QRS narrows; this dosing scheme can result in large doses of bicarbonate administration. Sodium bicarbonate has acutely terminated VT and wide-complex tachycardia. The QRS duration shortens, and the terminal 40-ms changes become less evident. Respiratory alkalosis is advocated by many clinicians, but the pH increase is not as instantaneous as with bolus bicarbonate administration, and sustained respiratory alkalosis will lead to compensatory renal bicarbonate excretion, resulting in a relative deficiency state. The target pH for alkalinization is 7.45 to 7.55, but caution is needed to avoid overshooting the desired pH or causing hypernatremia or ionized hypocalcemia. In addition, the administration of large amounts of bicarbonate for a number of hours may lead to respiratory acidosis and hypoventilation in the nonintubated patient.

Dialysis is not helpful because of high protein-binding and the large volume of distribution.

Because in overdose, CAs are, epileptogenic and benzodiazepines can be therapeutic, the use of flumazenil is in general contraindicated for patients with coma and a history or ECG suggestive for moderate or severe CA poisoning. Anticholinergic delirium is common in moderate TCA poisoning, and physostigmine has been effective in reversing anticholinergic toxicity. The use of physostigmine in CA poisoning is controversial. Because of case reports of asystole after physostigmine use in unstable CA-poisoned patients, physostigmine was avoided for many years. It was contraindicated for patients with a prolonged QRS interval or dysrhythmias suggestive of CA cardiotoxicity. More recently, one center reported uncontrolled use of physostigmine for delirium and coma with improvement in 236 of 252 retrospective and 62 of 63 prospective CA-poisoned patients. No patients in either arm suffered significant ventricular dysrhythmias or asystole (10). While

physostigmine may improve delirium, coma, or agitation from the anticholinergic syndrome in those not critically ill, it is unclear if this surpasses routine intensive care. Care must be taken to administer physostigmine over 3 to 5 minutes since an IV push bolus is associated with seizures and bradycardia. Concomitant use of benzodiazepines is recommended. Benzodiazepines alone do not effectively control anticholinergic delirium unless heavily sedating doses are used, which may extend the length of stay and increase complications and intubations.

Gastrointestinal decontamination should be accomplished after the institution of any necessary life-support measures. AC in a dose of 1 g/kg is the method of choice for gastric decontamination, when safe to administer. Multiple doses of AC have not been of clinical benefit and are not recommended. Care should be taken to avoid aspiration of charcoal into the lung, which can dramatically prolong hospital stays. Though no longer routinely recommended for most poisonings, gastric lavage, may benefit some early presenting (within 1 to 2 hours) CA-poisoned patients because the toxicity of this overdose is so high.

CRITICAL INTERVENTIONS

- Establish IV access and initiate continuous cardiac and oxygen saturation monitoring.
- Administer benzodiazepines quickly and aggressively for seizures to avoid increasing acidosis.
- Use sodium bicarbonate at 1 to 2 mEq/kg IV every 3 to 5 minutes for dysrhythmias and cardiac conduction disturbances >100 ms.
- Administer intravenous fluids and norepinephrine for hypotension.
- Administer propofol or phenobarbital for refractory seizures or myoclonus.

DISPOSITION

The maximal severity of CA poisoning is usually apparent within 2 to 6 hours of an overdose. Patients who develop coma, hypotension, seizures, or dysrhythmias require intensive care unit admission. Those who remain or become asymptomatic including lack of sinus tachycardia after 6 hours of observation can be medically cleared for discharge or psychiatric evaluation. Patients with persistent but mild symptoms, such as lethargy or tachycardia, require additional monitoring and observation in emergency department (ED) observation units or intermediate care units are appropriate.

If critically ill and complicated poisoned patients are transferred, either an air ambulance or an advanced cardiac life-support–equipped crew, accompanied by a nurse or physician, is required to treat ongoing complications.

Common Pitfalls

- Failure to appreciate that awake and stable-appearing patients with recent CA overdose may rapidly deteriorate.
- Failure to recognize the subtle electrocardiographic changes consistent with CA poisoning.
- Failure to wait for conduction delay or wide QRS before starting bicarbonate therapy.
- Failure to aggressively prevent and treat seizures and correct the resultant metabolic acidosis.

ACKNOWLEDGMENTS

The author would like to thank William J. Cimikoski and Keith K. Burkhart who contributed to this chapter in previous editions.

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CHAPTER 340

Dystonic Reactions

Jennifer Cullen and Richard F. Clark

Dystonic reactions are seldom life-threatening, but the discomfort of the bodily contortions and panic that can develop prompt the victim to seek help in the emergency department (ED).In addition, iatrogenic dystonic reactions and *akathisia* are common with the administration of antiemetic and antipsychotic medications in the ED. These effects appear early and are reversible with reduction or discontinuation of the offending agent. *Tardive dyskinesia* refers to the sometimes irreversible involuntary movements that develop later and results from withdrawal of the antipsychotic agent. *Primary dystonia,* abnormal movements that occur spontaneously in the absence of drug treatment, is a separate neurologic diagnosis with similar manifestations. Dystonias may begin at any age, for both the primary and secondary or drug-induced types (1).

Dystonias of all types likely result from an abnormality in neurotransmitter function in the basal ganglia. Proposed mechanisms include (a) direct blockade of central dopaminergic receptors, (b) an imbalance of dopamine and acetylcholine, resulting in excessive cholinergic activity, and (c) a combination of dopamine blockade and dopamine activation in the nigrostriatal system (2). Dopamine synthesis and release increase in response to an initial blockade of dopamine receptors. A single dose of an antipsychotic drug increases the sensitivity of dopamine receptors for 24 to 48 hours after drug administration. This occurs at a time when plasma and red blood cell drug concentrations are usually falling. Therefore, enhanced dopamine release, occurring

simultaneously with the unblocking of supersensitive receptors, may result in acute dystonias.

The true prevalence of acute dystonic reaction is unknown, but is estimated to occur in 2.3% to 60% of patients treated with typical antipsychotic agents, and 2% to 3% of patients treated with atypical antipsychotics (3). Most acute dystonic reactions occur within 5 days of starting therapy with neuroleptics and are more common in men than in women. Although less common, dystonias have been reported with other neurologic agents such as lamotrigine (4).

Symptoms seem to develop earlier with haloperidol than other neuroleptics. The development of a dystonic reaction depends more on individual susceptibility than on the chemical structure, milligram potency, dosage, or duration of treatment. The drugs currently known or suspected to produce acute dystonic reactions are listed in Table 340.1.

TABLE 340.1
Drugs Reported or Suspected to have Caused Acute Dystonic Reactions

Generic Name	Trade Name	Generic Name	Trade Name
Albendazole		Loxapine	Loxitane
Amitriptyline	Elavil	Mesoridazine	Serentil
Amoxapine	Asendin	Methohexital	Brevital
Aripiprazole	Abilify	Methylphenidate	Ritalin
Azatadine	Optimine	Metoclopramide	Reglan
Bupropion	Zyban, Wellbutrin	Nefazadone	Serzone
Cetirizine	Zyrtec	Olanzapine	Zyprexa
Chlorpromazine	Thorazine	Ondansetron	Zofran
Chlorprothixene	Taractan	Paroxetine	Paxil
Chloroquine		Perphenazine	Trilafon
Cimetidine	Tagamet	Phenelzine	Nardil
Cisapride	Propulsid	Phenytoin	Dilantin
Cocaine		Pimozide	Orap
Clomipramine	Anafranil	Prochlorperazine	Compazine
Clozapine	Clozaril	Promazine	Sparine
Cyclizine	Marezine	Promethazine	Phenergan
Dextrometho-rphan		Propofol	Diprivan
		Quetiapine	Seroquel
Diazepam	Valium	Quinine	
Diphenhydramine	Benadryl	Ranitidine	Zantac
Diprivan	Propofol	Risperidone	Risperdal
Doxepin	Sinequan	Rivastigmine	Exelon
Etomidate	Amidate	Sertraline	Zoloft
Fentanyl		Thiethylperazine	Torecan
Fluoxetine	Prozac	Thiopental	Pentothal
Fluphenazine	Prolixin	Thioridazine	Mellaril
Fluvoxamine	Luvox	Thiothixene	Navane
Foscarnet	Foscavir	Tiagabine	Gabitril
Gabapentin	Neurontin	Tranylcypromine	Parnate
Haloperidol	Haldol	Trifluoperazine	Stelazine
Imipramine	Tofranil	Triflupromazine	Vesprin
Ketamine	Ketalar	Ziprasidone	Geodon
Lamotrigine	Lamictal		

Although also seen in the elderly, patients younger than age 15, those with a family history of dystonia, and a history of drug or alcohol use are at greatest risk of developing drug-induced dystonias (5).

Akathisia is an uncomfortable condition of motor restlessness and agitation that occurs in association with the same drugs that induce dystonic reactions and probably with the same pathophysiology. Prochlorperazine (Compazine), commonly used as an antiemetic and for the treatment of migraine, frequently induces akathisia. When patients are carefully monitored for signs and symptoms, prochlorperazine may induce akathisia in up to 44% of patients within 1 hour of administration and, in a few percent more, in a delayed fashion up to 48 hours later (6). The rate of IV administration (15-minute infusion vs. 2-minute bolus) does not appear to significantly affect the incidence of akathisia. The use of adjuvant diphenhydramine (50 mg IV) in association with prochlorperazine (10 mg IV) reduces the incidence of akathisia from 36% to 14% in one study but also causes more sedation (7). Akathisia and dystonia are rarely reported with ondansetron (8).

CLINICAL PRESENTATION

Any striated muscle group may be involved in a dystonic movement. Blepharospasm, progressing to *oculogyric crisis,* is the most common form of dystonia in the upper face. It usually begins with increased blinking of the eyelids. In the lower face, the muscles of the pharynx and tongue are most commonly involved. *Oromandibular dystonia* describes the involvement of any combination of the jaw muscles. Specifically, *mandibular dystonia* is manifested as a pulling down or up of the jaw, and *lingual dystonia* is either a sustained protrusion of the tongue or an upward deflection so that the tongue curves and touches the hard palate. In the neck, *torticollis* is most common, although retrocollis and anterocollis may also occur. In most cases, the shoulder is elevated on the side toward which the chin is pointing. Jerking, rhythmic movements of the head may also occur. When the trunk is involved, twisting movements and postures such as lordosis, scoliosis, kyphosis, tortipelvis, and opisthotonos develop. Dystonic movements may begin focally but become segmental as they spread in a contiguous manner. *Generalized dystonia* refers to involvement of the leg plus other body parts, with

or without the trunk. Dystonic movements are usually continual, repetitive, and twisting, varying in speed from rapid to slow and being sustained from seconds to minutes at the height of the involuntary contraction.

The prognosis is excellent for patients with drug-induced dystonias when promptly and correctly treated. While the symptoms can result is significant distress and anxiety, the vast majority of patients will improve with treatment. Though rare, cardiorespiratory arrest and death have been reported in acute drug-induced laryngeal dystonia (2).

DIFFERENTIAL DIAGNOSIS

Dystonic reactions have been misdiagnosed as generalized anxiety, hysterical conversion, tetanus, and even seizure disorders. Children with such abnormal movements have been thought to have encephalitis or meningitis (9). Strychnine poisoning and the choreiform movements sometimes seen with sympathomimetic abuse ("crack dancing") or with rheumatic fever may appear similar to dystonic reactions as well. Some rigid patients with serotonin syndrome may also appear dystonic.

Patients taking antipsychotic agents are also at risk for neuroleptic malignant syndrome (NMS), which presents with muscle rigidity that may be mistaken for a dystonic reaction. It is critical to distinguish this life-threatening condition from acute dystonia. For further discussion of NMS, please see Chapter 338.

ED EVALUATION

The patient, family, or friends should be asked about the recent use of medications. Physical examination is remarkable for typical abnormal posturing or movements. Response to antimuscarinic treatment supports the diagnosis.

KEY TESTING

- There is no relevant laboratory or imaging testing for dystonic reactions.

ED MANAGEMENT

As dystonic reactions are not usually associated with an acute drug overdose, gastrointestinal decontamination is not necessary. Administration of an antimuscarinic medication rapidly reverses the symptoms of dystonia in most cases, presumably because of restoration of the cholinergic–dopaminergic balance in nigrostriatal neurons. Diphenhydramine (Benadryl) and benztropine mesylate (Cogentin) are the two medications most frequently used. IV administration is preferable to IM or oral administration and symptoms typically abate within 2 minutes and completely resolve within 15 minutes when the IV route is used. Muscle relaxation begins within 30 minutes but may not be complete for 90 minutes when the treatment is given IM or orally. Benztropine has been advocated over diphenhydramine because of less sedation and more rapid improvement of both objective and subjective findings, regardless of route of administration. Diphenhydramine should be used in children younger than age 3, as the greater antimuscarinic effects of benztropine are considered contraindicated in children this age, who may be more sensitive. Drowsiness should be anticipated as a side effect of antimuscarinic drug administration, especially with diphenhydramine.

After reversal of the reaction, some clinicians advocate an oral agent be continued for 72 hours to prevent a relapse (10). However, extended therapy may not be needed in all cases.

The usual dose of benztropine is 1 to 2 mg for adults and 0.02 to 0.05 mg/kg for children age 3 years or older, given IV over 2 minutes, followed by the same dose orally twice a day for 3 days if needed. The dose of diphenhydramine is 50 to 100 mg for adults and 1 to 2 mg/kg for children, given IV over 2 minutes, followed by 12.5 to 50.0 mg orally three or four times a day for 3 days if needed. Some patients may require more than one dose of IV medication to control the reaction.

Rare cases of dystonia may not respond to antimuscarinic therapy, and benzodiazepines should be used as a second-line agent. Unlike diphenhydramine and benztropine, side effects from the

benzodiazepines are limited to drowsiness. Antimuscarinic sequelae such as dry mouth, blurred vision, and urinary retention are not expected. Although any benzodiazepine should be effective, diazepam and lorazepam are favored because of their longer duration of action. Diazepam can be administered IV in 5-mg increments every 5 minutes as needed for reversal, or lorazepam 2 mg IV may be given every 5 minutes as needed.

Prophylactic use of benztropine and diphenhydramine has reduced the incidence of dystonic reactions in patients receiving either antiemetic or antipsychotic medications (10). Sedation may be increased, however, and should be considered.

CRITICAL INTERVENTIONS

- Recognize acute dystonia as an adverse drug reaction rather than another medical or psychiatric disorder.
- Treating dystonic reactions with antimuscarinic medications, such as benztropine or diphenhydramine, can be diagnostic and therapeutic.
- Prescribe oral antimuscarinic medication for 3 days after acute treatment to prevent relapse.

DISPOSITION

The patient may be discharged after the acute dystonia resolves. Notifying the prescribing psychiatrist may be advisable if the patient is to remain on neuroleptic medication. When antimuscarinics are prescribed, patients should be advised not to drive or perform potentially dangerous activities for 72 hours. They should be instructed to return if symptoms recur.

Common Pitfalls

- Dystonic reactions may be delayed 12 to 24 hours from the time of drug ingestion.
- Dystonic reactions are not usually from an overdose; so gastrointestinal decontamination is seldom indicated and may be dangerous in patients with head or neck involvement.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Megan Demott, Michael C. Young, to previous editions of this chapter.

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CHAPTER 341

Lithium

Fiona M. Garlich

Lithium has been used in the management of depression and bipolar disorders for over 50 years (1). In the United States, lithium is available as both immediate- and sustained-release formulations. Because lithium has a narrow therapeutic index and numerous adverse effects, relatively small changes in dose or health status can result in toxicity in patients on chronic lithium therapy. The therapeutic serum concentration is generally cited as 0.6 to 1.2 mEq/L (mmol/L).

Understanding the kinetics of lithium is important for the proper management of patients with lithium overdose. Immediate-release preparations are rapidly and completely absorbed from the gastrointestinal (GI) tract, with peak serum concentrations seen at 1 to 2 hours (2). Delayed absorption may occur in large overdoses, in the presence of coingestants that slow gastric emptying, or with the ingestion of sustained-release preparations. Delayed peak serum concentrations have been reported from 18 to 72 hours following large overdoses of sustained-release lithium tablets (1,3,4).

Following absorption from the GI tract, lithium, as a charged ion, is distributed slowly into tissues, especially across the lipophilic blood–brain barrier. The final volume of distribution is 0.6 to 0.9 L/kg, equivalent to that of total body water (1). After an acute overdose, the patient may initially appear well with a high serum concentration, but then may deteriorate as lithium distributes from the blood to the brain. The serum concentration may actually decrease while levels in the brain rise.

Lithium is eliminated almost entirely by renal excretion. The renal handling of lithium is similar to that of sodium; it is filtered and reabsorbed by the proximal tubule. Toxicity is more likely in the setting of dehydration, hyponatremia, decreased sodium intake, renal compromise, and the use of thiazide diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), or angiotensin-converting enzyme (ACE) inhibitors (5). Lithium itself can be nephrotoxic and may result in renal insufficiency (1). Chronic lithium therapy can also induce nephrogenic diabetes insipidus which can lead to dehydration, resulting in toxicity even without a change in dosage.

CLINICAL PRESENTATION

Lithium is primarily a neurotoxin, and poisoning can result in tremor, fasciculations, hyperreflexia, rigidity, clonus, nystagmus, ataxia, and in more severe toxicity, altered mental status, coma, seizures, and death (1,5,6). See the clinical classification in Table 341.1 (6). It is useful to classify an overdose as (1) acute (single ingestion), (2) acute-on-chronic (overdose in the setting of chronic therapy), or (3) chronic. In acute toxicity, nausea, vomiting, and diarrhea may predominate early on, with the late development of neurologic symptoms. Neurotoxicity with gradual deterioration is the predominant finding in chronic poisoning, which can occur in patients who develop dehydration or renal insufficiency even without a change in dosage. Greatest toxicity is seen in patients with chronic and acute-on-chronic overdoses, who have prolonged exposure to high-tissue lithium concentrations. In this setting, permanent neurologic sequelae can result and aggressive interventions are warranted (7).

TABLE 341.1
Severity of Lithium Poisoning

Grade 1 (mild): Nausea, vomiting, tremor, hyperreflexia, agitation, muscle weakness, ataxia

Grade 2 (moderate): Confusion, dysarthria, rigidity, hypertonia, hypotension, stupor

Grade 3 (severe): Convulsions, myoclonic jerking, coma, cardiovascular collapse

Acute lithium toxicity can also result in electrocardiographic (ECG) changes, including nonspecific ST-segment changes, T-wave flattening or inversion (which may mimic cardiac ischemia), prolongation of the QT interval, and first-degree atrioventricular block (8). Clinically significant dysrhythmias or cardiac dysfunction are rare.

DIFFERENTIAL DIAGNOSIS

The neurologic symptoms of lithium toxicity may closely resemble serotonin syndrome, although hyperthermia and autonomic instability are typically absent. Neuroleptic malignant syndrome (NMS), parkinsonism, and tardive dyskinesia should be considered in patients with rigidity. Neurologic manifestations of lithium toxicity might mimic a cerebrovascular accident, a postictal state, meningitis, hypercalcemia, hyperthyroidism, or toxicity from coingestion of other psychiatric medications such as antipsychotics, antidepressants, carbamazepine, and valproic acid. The common nausea and vomiting seen after an acute overdose may be easily confused with gastroenteritis or food poisoning.

ED EVALUATION

Attention should focus on the patient's mental status and neurologic motor examination, searching particularly for tremor, myoclonus, hyperreflexia, and rigidity. In the patient with chronic motor findings, the presence of worsening and increased disability should be determined. Hydration status, serum electrolytes, and renal function must be assessed. A serum lithium concentration should be obtained, and should be repeated serially in the setting of an acute overdose, particularly with sustained-release preparations. Because of the delay in tissue distribution, neurologic symptoms may lag

behind the serum concentration. Symptoms often worsen after the peak concentration is reached, and clinical improvement may be delayed despite a decreasing concentration. Green-top tubes may contain lithium heparin and should not be used. Testing for coingestants, including acetaminophen, salicylates, and ethanol should be considered in patients with intentional self-poisoning. An ECG should be obtained primarily to check for prolonged QT interval.

KEY TESTING

- Obtain a serum lithium concentration and repeat to determine if rising
- Check serum electrolytes and creatinine
- Obtain an ECG

ED MANAGEMENT

Advanced life-support measures should be instituted as necessary. Aggressive intravenous hydration with normal saline should be performed until euvolemia is achieved, to enhance renal perfusion and increase lithium elimination in dehydrated patients (1,9). Caution should be used in patients who are susceptible to fluid overload. There is no benefit to overhydrating or "forced diuresis" (9).

Whole-bowel irrigation (WBI) with polyethylene glycol should be considered for acute ingestions of sustained-release lithium preparations (9). Activated charcoal does not bind small ions such as lithium and should only be given if significant coingestants are suspected and the airway is protected. Gastric lavage is not likely to be useful, as immediate-release preparations are rapidly absorbed and sustained-release tablets are too large to fit through lavage tubes.

There is experimental evidence that sodium polystyrene sulfonate (Kayexalate), an ion-exchange resin usually used to treat hyperkalemia, can prevent absorption of lithium and enhance its removal once absorbed (9). However, clinical efficacy is unproven

and the development of hypokalemia limits the broad applicability of this technique.

Hemodialysis is the most efficient method of removing lithium from the body. However, redistribution from the brain to the intravascular compartment is slow, and clinical improvement lags behind the fall in serum lithium concentrations (2,10). A significant rebound of the serum lithium concentration usually occurs, which may necessitate a second or third round of dialysis in the sickest patients. Hemodialysis is recommended for patients with severe or progressive lithium toxicity (especially those with significant alterations in mental status or seizure), those with renal failure, and those who cannot tolerate sodium repletion therapy. Serum lithium concentrations do not correlate well with toxicity, and the patient's clinical status is a much better indicator of the need for hemodialysis than a serum concentration. However, by the time a patient is severely toxic, much of the lithium has distributed out of the blood compartment and is not available for removal by dialysis, making late hemodialysis of limited utility. Historical guidelines recommend hemodialysis in any patient with a lithium concentration above 4 mEq/L, or greater than 2.5 mEq/L in chronic toxicity (6). It is important to note that significant toxicity necessitating hemodialysis can be manifested in patients with concentrations below these cutoffs, especially those on chronic therapy. Conversely, young, healthy patients who are asymptomatic after an isolated acute overdose may not need dialysis at all despite lithium concentrations that are quite elevated. Some neurologic symptoms such as tremor or ataxia may persist after the lithium concentration has normalized.

CRITICAL INTERVENTIONS

- Administer normal saline intravenously for rehydration and treatment of hyponatremia.
- Consider early WBI for large ingestions of sustained-release tablets.

- Consider hemodialysis in patients with significant clinical toxicity and high lithium concentrations, and those with renal insufficiency.

DISPOSITION

Patients should be admitted if they have a high or rising lithium concentration, renal failure, dehydration, or significant neurologic findings such as confusion, lethargy, increased tremor, hyperreflexia, or rigidity. The presence of seizure or coma should prompt admission to an intensive care unit. Consultation with a poison center or toxicologist is strongly recommended. Although hemodialysis may not be necessary, early nephrology consultation can result in the dialysis team's being mobilized more quickly when needed. In patients who are asymptomatic following acute ingestions, serial lithium concentrations should be obtained every 4 to 6 hours until they start to fall. Patients who have ingested sustained-release products should be monitored for a minimum of 12 hours to ensure serum concentrations start to fall. In all cases of overdose with suicidal intent, psychiatric consultation should be obtained before discharge.

Common Pitfalls

- Failure to consider the possibility of chronic lithium toxicity in patients taking lithium who develop dehydration, renal compromise, or hyponatremia.
- Failure to obtain serial lithium concentrations in patients with acute overdose, especially with a sustained-release lithium preparation.
- Failure to appreciate that severe lithium poisoning can lead to permanent neurologic impairment and that aggressive treatment is warranted.

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CHAPTER 342

Monoamine Oxidase Inhibitors

Diana Felton and Michael J. Burns

The monoamine oxidase (MAO) inhibitors have been used to treat major depression since the 1950s (1) but are infrequently used today because of their risk for producing dangerous food and drug interactions and serious toxicity after overdose. These agents are generally reserved for the management of atypical, drug-resistant, neurotic, or reactive depression and occasionally to treat anxiety states, bulimia, hypertension, migraine headaches, narcolepsy, obsessive–compulsive disorder, attention deficit hyperactivity disorder, tobacco addiction, Parkinson disease, and phobias (1) and most recently, as a possibility for Alzheimer dementia. Newer selective, reversible inhibitors of MAO have a lower propensity for adverse effects (1,2,3). All of these agents block MAO, the oxidative deamination of endogenous and exogenous monoamines, in the outer mitochondrial membranes of most tissues (1). The two subtypes of MAO (MAO-A and MAO-B) differ in their substrate and inhibitor specificities and tissue distribution (1,2,4). MAO-A is found in the brain (monoaminergic neurons), peripheral sympathetic postganglionic neurons, intestinal mucosa, and liver. MAO-B is located in the brain (glial cells and some serotonergic neurons), platelets, liver, and intestinal mucosa (1).

Noradrenergic neurons contain predominantly MAO-A; serotonergic neurons contain both MAO-A and MAO-B. Inhibition of MAO-A is necessary for the treatment of depression (1). MAO enzymes function to maintain low body concentrations of

monoamines (1,2,5). Hepatic and intestinal MAOs prevent the absorption of and systemic effects from dietary monoamines (e.g., tyramine) (1).

All MAO inhibitors are false substrates for the MAO enzyme and bind competitively to the active site of MAO and prevent further activity (1). MAO inhibitors may be classified by their differential selectivity for MAO subtypes, reversibility of MAO binding (inhibition), or by chemical structure (Table 342.1).

TABLE 342.1
Classification of Monoamine Oxidase Inhibitors

Agent (Trade Name)	Inhibition	Selectivity	Structure
Befloxatone	Reversible	MAO-A	Oxazolidinone
Brofaromine	Reversible	MAO-A	Piperidylbenzofuran
Clorgyline	Irreversible	MAO-A	Acetylenic agent
Furazolidone (Furoxone)	Reversible	Nonselective	Oxazolidinone
Iproniazid (Marsilid)	Irreversible	Nonselective	Hydrazine (Hydrazide)
Isocarboxazid (Marplan)	Irreversible	Nonselective	Hydrazine (Hydrazide)
Linezolid (Zyvox)	Reversible	Nonselective	Oxazolidinone
Moclobemide (Aurorix)	Reversible	MAO-A	Benzamide
Nialamide (Niamid)	Irreversible	Nonselective	Hydrazine
Pargyline (Eutonyl)	Irreversible	MAO-B	Acetylenic agent
Phenelzine (Nardil)	Irreversible	Nonselective	Hydrazine
Procarbazine (Matulane)	Irreversible	Nonselective	Hydrazine
Rasagiline (Azilect)	Irreversible	MAO-B	Acetylenic agent
Selegiline, l-deprenyl (Eldepryl, Emsam)	Irreversible	MAO-B	Acetylenic agent
Toloxatone (Humoryl)	Reversible	MAO-A	Oxazolidinone
Tranylcypromine (Parnate)	Irreversible	Nonselective	Cyclopropylamine

Currently, only irreversible inhibitors of MAO are available in the United States (1). Nonselective inhibitors include isocarboxazid, phenelzine sulfate, and tranylcypromine sulfate. Selegiline and rasagiline are selective inhibitors of MAO-B used to treat Parkinson disease (1,6). They are not associated with dangerous food and drug

interactions at doses used clinically (1,3). Their specificity for MAO-B, however, is dose dependent and lost at supratherapeutic doses (1,3). Selegiline (Emsam) is approved and available as a transdermally delivered patch, as well as a transmucosal dissolving lozenge (7). The dangerous food interactions (as occurs from ingested monoamines) are less likely with cutaneous MAO inhibitor delivery that does not readily inhibit intestinal and hepatic MAO (3,7). Certain pharmaceuticals (e.g., furazolidone, linezolid, procarbazine) and herbal preparations (e.g., St. John's Wort, yohimbe alkaloids, kava kava, and ayahuasca) also have MAO inhibitor activity (1,6). These agents are all weak, reversible, nonselective inhibitors of MAO but still have the potential for adverse drug and food interactions.

Reversible selective inhibitors of MAO-A (befloxatone, brofaromine, cimoxatone, moclobemide, and toloxatone) are used outside the United States (1,2). With these agents, MAO inhibition is short-lived (enzyme activity commonly restored within 24 hours) and may be overcome by increasing levels of amine substrate. Initial experience with these agents has demonstrated greater safety after overdose and a significant reduction of adverse effects when combined with other pharmaceutical agents or dietary amines (1,2,3).

Most MAO inhibitors are structurally similar to amphetamines and other sympathomimetic agents; in fact, both selegiline and tranylcypromine are partly metabolized to amphetamine and methamphetamine (1,8,9). MAO inhibitors exert their pharmacologic and toxic effects by decreasing the degradation of MAO substrates, MAO inhibitors result in expansion of cytosolic and vesicular storage of NE, DA, and 5-HT in presynaptic nerve terminals (Fig. 342.1). This subsequently increases their release from vesicles during normal neurotransmission, causes spontaneous spillover into the synaptic cleft independent of nerve activity, and decreases concentration-dependent reuptake by nerve-ending amine transporters (1,2). Spontaneous hypertensive episodes with therapeutic doses of MAO inhibitors are likely a result from spontaneous release of NE from nerve terminals (4,9). MAO inhibitors further enhance the release of

cytoplasmic amines from the nerve ending in the absence of vesicle exocytosis (1,9). They bind competitively to the amine uptake transporter and prevent reuptake of natural amine neurotransmitters. When the MAO inhibitor is transported into the neuron, reverse transport of cytosolic biogenic amines occurs that further increases their synaptic concentrations. MAO inhibitors similarly prevent uptake from glial cell transporters that scavenge extracellular (synaptic) monoamines (1,2).

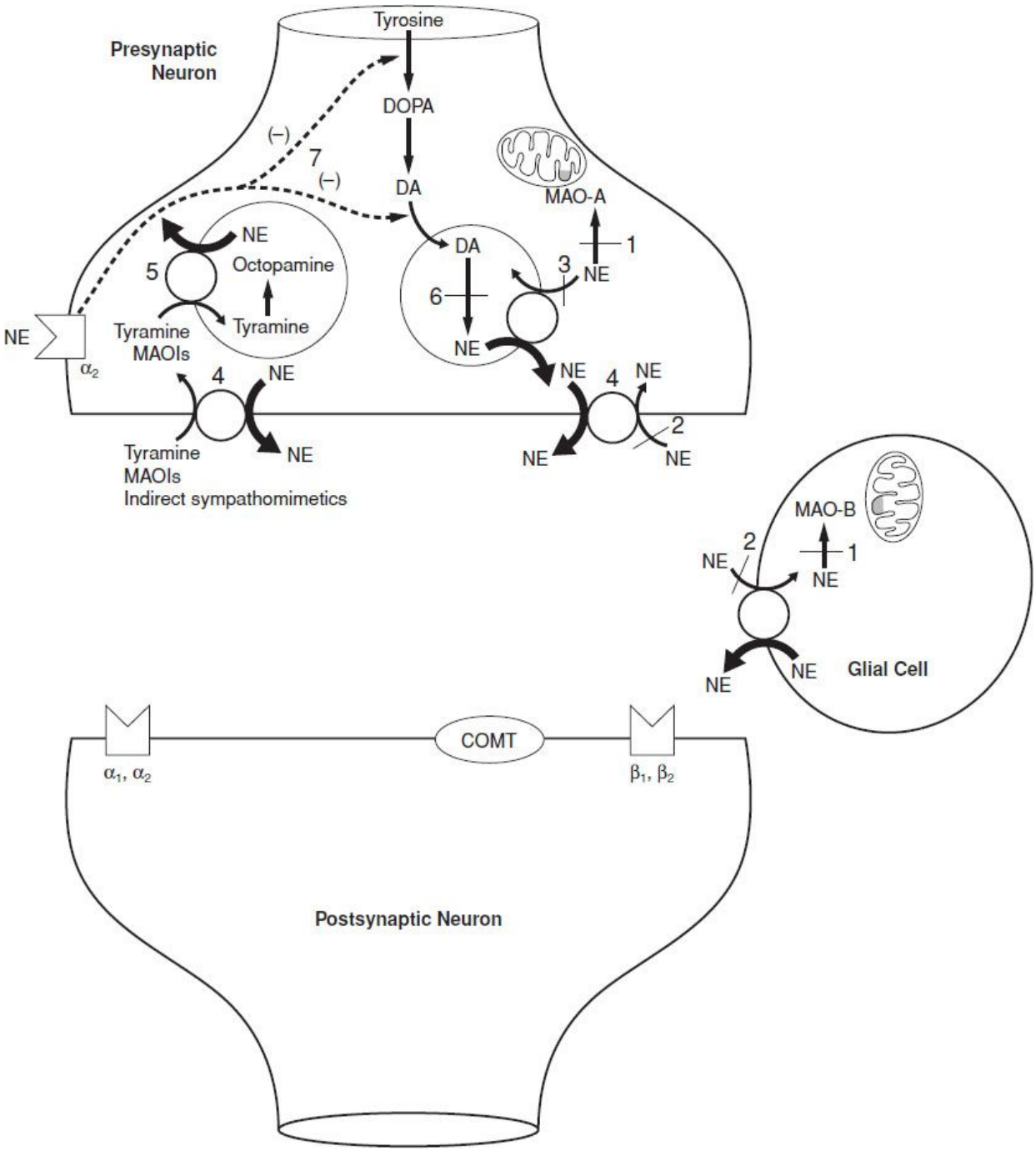

FIGURE 342.1 Diagram of a noradrenergic synapse illustrating the mechanisms underlying monoamine oxidase inhibitor (MAOI) toxicity: (1) Inhibit MAO to prevent norepinephrine (NE) degradation; (2) inhibit NE reuptake by monoamine transporter; (3) inhibit NE reuptake by vesicles; (4) promote reverse transport of NE from nerve ending; (5) promote reverse transport of NE from vesicles; (6) block dopamine (DA) β-hydroxylase; (7) indirectly

inhibit enzymes necessary for production of NE. Similar mechanisms operate at dopaminergic and serotonergic nerve endings (α- and β-adrenergic receptors; COMT, catechol-o-methyltransferase, another enzyme that degrades catecholamines.)

Overdose of MAO inhibitors produces an exaggeration of these neuronal effects resulting in profound hyperadrenergic, hyperdopaminergic, and hyperserotonergic states. The delay of signs and symptoms after overdose is due to initial reversible binding with MAO and the time required for significant enzyme inhibition and cumulative effects to occur (e.g., neuronal accumulation of NE, DA, 5-HT) (1,4,9). The neuromuscular abnormalities (e.g., rigidity, myoclonus), hyperthermia, and unusual ocular movements associated with MAO overdose appear to be mediated primarily by enhanced serotonergic neurotransmission in the brainstem and spinal cord. Stimulation of 5-HT1 A receptors from raphe bulbospinal neurons results in myoclonus and rigidity. These neuromuscular effects combined with stimulation of 5-HT2 receptors in the diencephalon result in hyperthermia. Enhanced raphe serotonergic neurotransmission, which controls saccadic eye movements, may produce an unusual “ping-pong” gaze in patients with severe MAO inhibitor toxicity (5). These effects are also seen in the serotonin syndrome (Chapter 343).

The most serious adverse reactions associated with drug and food interactions are also the result of exaggerated neuronal effects (3,6). The administration or ingestion of any agent that increases CNS dopamine, norephinephrine, or serotonin levels may result in potentially life-threatening toxicity (1,3,6). Enhanced serotonergic neurotransmission, known as the serotonin syndrome (see Chapter 343, Serotonin Re-uptake Inhibitors and the Serotonin Syndrome), occurs when MAO inhibitors are combined with agents that enhance serotonin synthesis (e.g., *L*-tryptophan), promote serotonin release (e.g., methylenedioxymethamphetamine, fenfluramine, tramadol), or block serotonin reuptake (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants, lithium, phenylpiperidine, meperidine, dextromethorphan, propoxyphene, methadone) (1,3,6).

Indirectly acting sympathomimetic agents (e.g., amphetamine, cocaine, synthetic cathinones ("bath salts"), ephedrine, phenylpropanolamine, methylphenidate) act primarily by causing the release of NE from the presynaptic nerve terminal, resulting in the release of the expanded pool of NE to cause signs and symptoms of catecholamine poisoning (hypertensive crisis) (4,6,9).

A similar sympathomimetic effect, called the "cheese reaction," may occur when food containing tyramine (e.g., aged cheeses; aged, pickled, or smoked meats; certain beers; red wines; and yeast extracts) and other indirectly acting monoamines (e.g., ephedrine, phenylethylamine, phenylethanolamine, pseudoephedrine, octopamine, reserpine, and tryptamine) are ingested (3,6). Inhibition of MAO in the liver and intestine allows for systemic absorption of these amines which may precipitate a rapid, massive release of NE when taken up into noradrenergic nerve endings.

MAO inhibitors are rapidly and completely absorbed, with peak plasma concentrations 1 to 4 hours after ingestion (1,8,9). For irreversible MAO inhibitors, plasma drug concentrations do not correlate with level of MAO inhibition (4,9) and maximal inhibition of MAO occurs after 5 to 10 days of therapy (1,8) and the potential for drug or dietary interactions may last for 2 to 3 weeks after discontinuation of treatment (4,6). The ingestion of 2 to 3 mg/kg or more of an irreversible MAO inhibitor is potentially life-threatening (4,9), with 4 to 6 mg/kg reported to be fatal (9). For reversible inhibitors, however, maximal MAO inhibition is achieved within a few hours after the first dose but MAO activity is restored within 24 hours after the last dose, and the potential for drug and dietary interactions is much less (1,2).

CLINICAL PRESENTATION

Drug or food interactions with MAO inhibitors are common, with hypertensive crisis in 1% to 8% of those taking MAO inhibitors therapeutically (1,4). The clinical presentation includes headache, hypertension, tachycardia (or reflex bradycardia), diaphoresis, agitation, hypertonicity, hyperreflexia, myoclonus, rigidity, seizures, coma, hyperthermia, intracranial hemorrhage, and death. Toxicity

begins within 30 to 90 minutes of the ingestion or administration of sympathomimetic amines (1). The duration of effect is variable but often resolves within a few hours.

MAO inhibitor overdose follows a completely different time course (5,9,10). The absence of early symptoms is typical with nonselective irreversible agents. Onset of toxicity is usually delayed 6 to 12 hours after overdose, peaks in 24 to 48 hours for severe cases, and may last for 72 to 96 hours (9). A latent period as long as 29 hours has been described after tranylcypromine overdose (1). During the latent phase, the patient usually appears well or mildly sedated (1,9,10). Classic symptoms include alterations in behavior, cognition, autonomic nervous system function, and neuromuscular activity and may be classified as mild, moderate, or severe (Table 342.2) (9). Signs and symptoms vary greatly in their onset, severity, and duration. Patients with early or mild toxicity may demonstrate mild lethargy or restlessness, dysarthria, nausea, headache, ataxia, palpitations, flushing, shivering, sweating, tremor, nystagmus, incoordination, or hyperreflexia. Moderate toxicity includes confusion, hallucinations, disorientation, agitated delirium, mutism, salivation, diarrhea, marked diaphoresis, myoclonus, fasciculations, trismus, writhing movements, and mild to moderate elevations of temperature, pulse, respiratory rate, and blood pressure. Severe toxicity is characterized by unresponsive coma; fixed, dilated pupils; “ping-pong” gaze; pathologic reflexes; generalized rigidity; seizures; hyperthermia (>104°F); marked tachypnea or respiratory depression; extreme sinus tachycardia or bradycardia; malignant cardiac dysrhythmias; hypotension; and death (1,5,9,10). Death from cardiovascular (CV) collapse is most likely in patients with severe hyperpyrexia (9,10).

TABLE 342.2
Clinical Course of Monoamine Oxidase Inhibitor Poisoning

Phase-Severity[a]	Time after Ingestion[a]	Cognitive–Behavioral Dysfunction	Autonomic Dysfunction	Neuromuscular Dysfunction
0-Latent	0–24 hrs	Mild lethargy	Absent	Absent
I-Mild	6–12 hrs	Mild lethargy	Nausea	Mild tremor
		Dysarthria	Flushing	Hyperreflexia
		Ataxia	Diaphoresis	Incoordination
		Headache	Shivering	Nystagmus
		Anxiety	Irritability	Mydriasis
		Insomnia		
II-Moderate	10–24 hrs	Confusion	Mild hyperthermia (temperature <104°F)	Myoclonus
		Disorientation	Marked diaphoresis	Fasciculations
		Agitated delirium	Salivation	Trismus
		Mumbling/rambling speech	Piloerection	Facial grimacing
		Mutism	Hypertension	Writhing extremities
		Hyperactivity	Sinus tachycardia (P <150 beats/min)	
			Hyperventilation	
III-Severe	16–72 hrs	Incomprehensible speech	Hyperventilation to respiratory arrest	Generalized rigidity
		Coma	Extreme sinus tachycardia to sinus bradycardia	Opisthotonus
		Seizures	Malignant dysrhythmias (VT, VF, bradyasystole)	Fixed, dilated pupils
			Hypotension	"Ping-pong" gaze
			Pale, clammy, mottled skin	Pathologic reflexes (decorticate, decerebrate, Babinski)
			Severe hyperthermia (temperature <104°F)	
IV-Complications	24–96 hrs	Aspiration pneumonitis	Anion gap metabolic acidosis	Rhabdomyolysis
		Adult respiratory distress syndrome	Hemolysis	Acute renal failure
				Disseminated intravascular coagulation
				Hepatic failure

[a]Signs and symptoms vary greatly in their onset, severity, and duration.

Although seizures may occur after MAO overdose, they are rare and can be confused with the neuromuscular hyperactivity produced by these agents (1,10). Secondary complications in patients with moderate to severe toxicity include aspiration pneumonitis, adult respiratory distress syndrome, rhabdomyolysis, acute renal failure, metabolic acidosis, and disseminated intravascular coagulation (DIC) (9). The likelihood of secondary complications (e.g., rhabdomyolysis, DIC) and death is related to the degree and duration of hyperthermia. Patients with severe toxicity can manifest fixed, dilated pupils, posturing, and extensor plantar response, yet make a complete neurologic recovery (1,5,10).

When taken alone, reversible MAO-A inhibitors have a benign course after acute overdose with doses as high as 20.5 g resulting in only mild to moderate toxicity. Large overdose is characterized by mild CNS depression, agitation, tachycardia, hypertension, and mydriasis. Although death is rare after overdose with moclobemide alone, many fatalities have been reported from the serotonin syndrome with moclobemide and other serotonin-potentiating drugs

(e.g., citalopram, clomipramine, methylenedioxymethamphetamine, paroxetine, and sertraline). Chronic use of irreversible nonselective inhibitors has been associated with hyperadrenergic adverse effects similar to the chronic use of amphetamines. These effects include agitation, confusion, hallucinations, hyperhidrosis, hypomania, insomnia, tremors, and seizures (1).

DIFFERENTIAL DIAGNOSIS

Overdose of stimulants such as amphetamine, cocaine, and sympathomimetic (including over-the-counter appetite suppressants) produces a clinical picture similar to the hypertensive reactions associated with MAO inhibitors and dietary and drug monoamines. The clinical presentation of anticholinergic, hallucinogen (e.g., lysergic acid diethylamide, phencyclidine), lithium, salicylate, sympathomimetic (e.g., amphetamines, synthetic cathinones known as “bath salts,” cocaine), and strychnine poisoning may be similar to that of MAO inhibitor overdose. MAO inhibitor toxicity may be confused with the neuroleptic malignant syndrome and withdrawal from alcohol or sedative hypnotic agents. Clinical features of the serotonin syndrome are nearly identical to those after overdose with MAO inhibitors. Medical emergencies such as hypoglycemia, malignant hyperthermia, intracranial hemorrhage, meningitis, encephalitis, pheochromocytoma, septicemia, tetanus, and thyrotoxicosis may present in a similar manner. The history is most useful to narrow the differential diagnosis.

ED EVALUATION

The history should include the time, dose, and duration of exposure; the time of onset, nature, and severity of symptoms; the type of first aid undertaken; and the medical and psychiatric history. Accurate and complete historical data are essential in differentiating the toxic syndromes related to MAO inhibitors. The physical examination should focus on the vital signs and CV and neurologic functions. Except for “ping-pong” gaze, there are no pathognomonic physical findings or laboratory abnormalities. Initial testing for patients with suspected intentional overdose should include electrocardiogram,

acetaminophen and salicylate, and routine serum chemistries. Patients with toxicity may need complete blood count; prothrombin and partial thromboplastin times; creatine phosphokinase, calcium, magnesium, lactate measurement, and a urinalysis for supportive care. Patients with altered mental status should have a bedside fingerstick glucose determination and intervention, as necessary. A lumbar puncture and computed tomography scanning may be appropriate to rule out intracranial hemorrhage, meningitis, and encephalitis.

Toxicology screening has many false positive and false negatives, especially with amphetamines (see Chapter 348, Amphetamines and Stimulants). Drug screening rarely detects MAO inhibitors because of their low concentrations in blood and urine samples (9). Overdose of selegiline or tranylcypromine may produce a false-positive qualitative screen for amphetamines (9). Quantitative MAO inhibitor levels and MAO enzyme activity are not generally available and do not correlate with the severity of poisoning (4,9).

KEY TESTING

- Routine blood or urine tests cannot confirm or rule out toxicity from MAO inhibitors
- Toxicology screens have many false positive and negatives
- For patients with moderate to severe toxicity, supportive care includes measurements of serum chemistries, lactate, magnesium, calcium, creatine phosphokinase, liver function tests, PT and PTT, and a urinalysis
- Electrocardiogram

ED MANAGEMENT

Supportive care is the primary treatment for MAO inhibitor overdose. Advanced life-support measures with glucose, oxygen, naloxone, and thiamine should be considered for patients with altered mental status. Activated charcoal is the preferred method of GI decontamination for recent MAO inhibitor overdose. Before any

drug or food is given, the potential for an adverse interaction with MAO inhibitors must be considered.

Agitation, neuromuscular hyperactivity, and seizures should be treated promptly with liberal doses of benzodiazepines (e.g., diazepam, lorazepam) or barbiturates (e.g., phenobarbital) (9). Phenytoin is unlikely to be effective for seizures. Pyridoxine is recommended for seizures that occur after overdose with a hydrazine MAO inhibitor.

Rapid cooling is essential to minimize morbidity and mortality. Because hyperthermia is almost invariably associated with CNS agitation and neuromuscular hyperactivity, initial treatment with benzodiazepines or barbiturates is recommended in conjunction with evaporative and convective cooling methods, such as wet sheets or cool mist sprays and fans (9). Antipyretics and cooling blankets are ineffective. If these initial maneuvers do not provide rapid patient cooling, neuromuscular paralysis is strongly recommended (5,9,10) with cooling times of <1 hour. Although dantrolene (2.5 mg/kg orally or intravenously every 6 hours) has been reported to be effective, it is itself toxic and does not terminate muscular rigidity and hyperthermia as rapidly as paralyzing agents. Because the pathophysiology of serotonin syndrome overlaps with MAO inhibitor overdose, nonspecific serotonin receptor antagonists (e.g., cyproheptadine, methysergide) could be of theoretical benefit but without clinical data in this regard, such therapy cannot currently be recommended.

Severe hypertension may be treated with rapid-onset, short-acting, intravenous agents such as sodium nitroprusside, clevidipine, or phentolamine (4,9). Clevidipine (Cleviprex) is a short-acting, intravenous, dihydropyridine calcium channel blocker that is easy to administer and effective for rapid control of severe hypertension. It is given without a bolus starting at 1 to 2 mg/hr and doubled every 90 seconds until the blood pressure improves. Phentolamine (2 to 10 mg IV) is attractive because it blocks α-adrenergic receptors and antagonize the effects of NE. It is effective for the treatment of hypertension associated with the cheese reaction. Dexmedetomidine is a parenteral, titratable, selective, α_2-adrenergic agonist, but the

lack of published data precludes a recommendation. Long-acting agents (tolazoline, clonidine) can worsen the severe hypotension that often follows the hypertension (9). Unopposed α-adrenergic vasoconstriction with β-adrenergic antagonists can exacerbate the hypertension.

Hypotension should be treated with fluid resuscitation. When pressors are required, direct-acting agents (e.g., epinephrine, NE) are recommended (4,9). Indirectly acting agents such as dopamine, require the release of intracellular amines for their pressor effect which may either precipitate a hypertensive crisis or be ineffective with depleted stores of endogenous catecholamines (1). Additionally, MAO inhibition is less likely to potentiate the effects of exogenously administered, direct-acting pressors, which circulate extracellularly and are primarily metabolized by catechol-o-methyltransferase. Regardless, low doses of direct-acting pressors should be used initially to minimize the risk of an exaggerated pressor response. Phenylephrine has been associated with an exaggerated pressor response and is not recommended for MAO inhibitor poisoning.

Ventricular dysrhythmias and severe bradycardias, usually premorbid signs, should be treated according to current advanced cardiac life-support protocols.

Diuresis, urinary acidification, hemodialysis, and hemoperfusion have no role in the management of MAO inhibitor poisoning (1,4,8).

CRITICAL INTERVENTIONS

- Admit all patients with known or suspected MAO inhibitor overdose for 24-hour monitoring even if they have no initial symptoms.
- Treat neuromuscular hyperactivity with benzodiazepines or barbiturates; with neuromuscular paralysis if severe or accompanied by hyperthermia or rhabdomyolysis
- Rapidly and aggressively cool patients with hyperthermia.
- Administer a direct-acting pressor (e.g., norepinephrine) for hypotension unresponsive to fluid administration.

DISPOSITION

All patients with suspected MAO inhibitor overdose should be admitted for extended observation (24 hours) in a monitored setting. Symptomatic patients and those with abnormal vital signs should be admitted to an intensive care unit or transferred to an institution with this capacity.

Patients who present with drug or dietary interactions may not require hospital admission if the clinical response has been mild. Patients with severe reactions, any disorientation, hyperthermia, persistent symptoms, or abnormal vital signs after a 4- to 6-hour observation period, and those with symptoms that necessitate active intervention should be admitted. The level of in-hospital care required (intensive care or floor) depends on the severity of symptoms. For patients well enough to eat, an MAO inhibitor diet (e.g., low tyramine) should be ordered.

Common Pitfalls

- Failure to check for or recognize MAO inhibitor use before prescribing sympathomimetics or giving pain medications, particularly meperidine.
- Failure to appreciate that the history is key to differentiating acute overdose from drug and food interactions, including the serotonin syndrome.
- Failure to appreciate that the onset of toxicity may be delayed and gradual in onset after MAO inhibitor overdose.
- Failure to anticipate that early sympathetic stimulation may be followed by catecholamine depletion and CV collapse in patients with acute MAO inhibitor overdose.

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CHAPTER 343

Serotonin Re-uptake Inhibitors and the Serotonin Syndrome

Claudia L. Barthold and Jennifer A. Oakes

Serotonin re-uptake inhibitors (SRIs) are a diverse class of antidepressant agents that act by inhibiting re-uptake of serotonin (5-HT) at presynaptic receptors. Some of these drugs also have effects at norepinephrine receptors to varying degrees. These agents can be divided into two main categories: (1) selective serotonin re-uptake inhibitors (SSRIs) including fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and escitalopram, and (2) the serotonin–norepinephrine re-uptake inhibitors (SNRIs) including venlafaxine, desvenlafaxine, duloxetine, nefazodone, and milnacipran which is approved by the FDA for the treatment of fibromyalgia (but not depression) in the United States.

SRIs are widely prescribed as first-line therapy for depression and generalized anxiety disorder, obsessive–compulsive disorder, and neuropathic pain. The therapeutic effects of these antidepressant medications are mediated by blockade of the re-uptake of serotonin and/or norepinephrine into the presynaptic nerve terminal, allowing for buildup of these neurotransmitters in the synaptic cleft where they are active. Though these biochemical changes, and some behavioral changes, occur fairly rapidly, the full clinical therapeutic effects are delayed for up to 6 weeks (1).

In general, the SRIs have a wide therapeutic margin and safe side-effect profile. Because significant cardiac or neurologic toxicity is

rarely seen with overdose, these agents have replaced the more toxic, cyclic antidepressants (CAs) and monoamine oxidase inhibitors (MAOIs) (2). The most significant toxicity typically seen with SRIs is sedation and QTc prolongation. Seizures, antimuscarinic (anticholinergic) effects, and QRS prolongation are also reported in overdose with some of these agents. Fatalities are uncommon. A significant form of toxicity seen with this group is serotonin syndrome, which is a syndrome of serotonergic excess resulting from either drug interactions between two or more serotonergic agents or after overdose of SRIs or other serotonergic drugs. The SRIs are well absorbed from the gastrointestinal tract but may be delayed after an overdose, especially if coingested with agents that slow gut motility and absorption, such as anticholinergic agents or opioids. The SRIs are highly protein-bound and have large volumes of distribution, therefore not generally amenable to hemodialysis.

Half-lives range from 3 (paroxetine) to 144 (fluoxetine) hours and many agents have active metabolites and complex metabolism involving multiple hepatic microsomal enzymes. Activity at a variety of P450 sites contributes to drug–drug interactions seen with SRIs, and may increase the risk of developing serotonin syndrome. This risk is increased further when SRIs are used in combination with other drugs with serotonergic effects (e.g., MAOIs, dextromethorphan, or other SRIs).

Side effects of therapeutic use of SRIs are typically mild. These can include disruptions of sleep–wake cycles, sexual side effects, and weight gain. Symptoms such as mild agitation can occur with therapeutic use but are also an early sign of serotonin syndrome. A full history and physical examination can help differentiate between serotonergic toxicity and normal therapeutic side effects. There is a concern that the initiation of antidepressants can cause an increase in suicidal ideation or attempts especially in children and adolescents. This may affect the appropriate disposition or follow-up for a depressed patient newly started on SRIs.

There is no clear data on risks to the fetus after a single acute accidental or overdose exposure to an SRI in a pregnant woman. The severity of the mother’s symptoms, the fetus’ gestational age,

and any evidence of fetal distress should be considered in determining the need for evaluation or follow-up with the patient's obstetrician. In some cases, SRIs are prescribed therapeutically in pregnant women. Initiation of an SRI for a pregnant patient should be done in concert with her obstetrician and a mental health professional for concerns regarding fetal and neonatal effects of SRI exposure in utero.

CLINICAL PRESENTATION

Typically, signs and symptoms of toxicity occur in the first 6 hours especially for nonextended release preparations. Most SRIs are well tolerated in moderate overdoses presenting with little more than nausea or tremor, but more significant symptoms such as sedation, QTc prolongation, and seizures do occur (3). Patients can present with serotonin syndrome after overdose of an SRI. Citalopram and venlafaxine appear to be the most toxic of the SRIs with seizures and cardiac conduction abnormalities being more common than with other agents (3,4). Venlafaxine also been reported to cause widening of the QRS, similar to toxicity seen with TCAs (3).

In overdose, antimuscarinic (anticholinergic) effects can be seen with some agents. These may manifest as sedation, delirium, coma, hyperthermia, tachycardia, hypertension, dry mucous membranes, decreased bowel sounds, or urinary retention (see Chapter 344).

DIFFERENTIAL DIAGNOSIS

Because polydrug ingestions are the norm rather than the exception, especially in intentional adult overdoses, other agents with sedating or antimuscarinic properties must be considered as coingestants. Sympathomimetic agents (such as cocaine or amphetamines); dextromethorphan; anticholinergic agents such as diphenhydramine; hallucinogens such as lysergic acid diethylamide (LSD) or phencyclidine (PCP); alcohol; or withdrawal from benzodiazepines or alcohol can present with altered mental status, hallucinations, agitation, seizures, or autonomic instability. When evaluating a patient with hyperthermia and altered mental status, one should

always consider a possible infectious etiology such as meningitis, encephalitis, or septicemia as well as the possibility of neuroleptic malignant syndrome (NMS) which may also mimic serotonin syndrome but has a different etiology entirely. Neurotrauma, hypoxia, hyponatremia, and hypoglycemia should also be considered with altered mental status. Though cardiac conduction delays can be common in SRI intoxications, they can also be a sign of ischemic injury, so the patient's underlying cardiac status should be taken into account.

EMERGENCY DEPARTMENT EVALUATION

Since profound sedation can be seen in SRI intoxications, evaluation of a patient's ability to protect the airway is vital. Breathing and circulation should be immediately assessed. The patient should have cardiac monitoring with telemetry and serial electrocardiograph (ECG) evaluations. Blood chemistries should be obtained to look for acid–base and electrolyte abnormalities. Serum acetaminophen levels should be obtained on intentional overdose patients.

KEY TESTING

- There is no specific testing for SRIs
- EKG for conduction delay

ED MANAGEMENT

Excellent symptomatic and supportive care is essential. The emergency physician should protect the airway and assist breathing, with endotracheal intubation in the rare case of respiratory depression. Though hypotension is rare, blood pressure should be supported with fluids and vasopressor agents to maintain perfusion if needed. Glucose (with thiamine) and naloxone can be considered for patients with altered mental status. Flumazenil is not advised in suspected SRI overdoses or any suspected polydrug overdose. It may not reverse the sedation from the SRIs and may induce withdrawal seizures in a benzodiazepine-dependent patient (see Chapter 308). Additionally, as benzodiazepines are the first-line therapy for

seizures, flumazenil may impair the ability to control seizures should they occur from the overdose. Physostigmine to reverse the antimuscarinic side effects is probably best avoided because SRIs have some of the sodium channel blocking seen with the tricyclic antidepressants.

Seizures should be treated with benzodiazepines as first-line agents. If seizures persist and are not controlled by benzodiazepines consider barbiturates, propofol, and finally general anesthesia with electroencephalographic monitoring. Status epilepticus is not a typical feature of SRI-induced seizure activity, and its presence should prompt consideration of other causes such as trauma, infection, a secondary toxic exposure, or an unknown coingestant such as isoniazid.

If there is QRS prolongation ($>$100 msec or increasing on serial ECGs), serum alkalinization with sodium bicarbonate ($NaHCO_3$) should be considered. Initial dosing of one to three ampules (50 mEq each) IV, usually followed by continuous infusion of three ampules $NaHCO_3$ in 1 L of D_5W at a high maintenance infusion rate. The goal is normalization of the QRS or a maximum serum pH of 7.5 to 7.55. $NaHCO_3$ is the main treatment for TCA-induced QRS prolongation. The efficacy of this modality in QRS prolongation from other psychotropic agents including SRIs is variable, but it should be attempted if the patient has no contraindication to the sodium and volume load.

Drug-induced QTc prolongation from SRIs should be followed closely with serial ECGs, as the patient is at increased risk of torsades de pointes. QTc $>$470 msec on serial ECGs should be considered abnormal. Potassium, magnesium, and calcium levels should be normalized if possible, to mitigate their potential contribution to QTc prolongation.

Hyperthermia is a rare but potentially life-threatening result of SRI overdose or serotonin syndrome. Hyperthermic patients should be treated with active cooling and IV benzodiazepines if muscle hyperactivity and rigidity are contributing components.

Oral activated charcoal (1 g/kg) should be considered in any patient within 1 to 2 hours of acute overdose who is alert enough to protect the airway. Orogastric lavage is not indicated, as these agents have relatively low toxicity. Whole bowel irrigation (WBI) with polyethylene glycol solution should be considered for large acute ingestions of extended release preparations. The WBI solution should be given at 1 to 2 L/hr per nasogastric tube until the rectal effluent is clear. There is no role for hemodialysis, given the high level of protein binding and large volumes of distribution.

Beta-blockers or calcium channel blockers should generally be avoided in attempts to control drug-induced tachycardia or hypertension, unless there are signs of end-organ injury from these vital sign abnormalities. If necessary, it is best to use agents with a short duration of actions (e.g., nitroglycerin, nitroprusside, or esmolol), as they can be titrated down rapidly as appropriate.

CRITICAL INTERVENTIONS

- Establish IV access and cardiac monitoring with serial ECGs for QRS and QT prolongation.
- Benzodiazepines for agitation, muscle hypertonicity, hyperthermia, and seizures.
- Bicarbonate for QRS prolongation.

DISPOSITION

Admission to the hospital is indicated for the rare patient with persistent sedation, significant antimuscarinic effects, QRS or QT prolongation, seizures, or any clinical manifestations of serotonin syndrome. Persistently asymptomatic patients with no evidence of drug-induced conduction delays on their ECGs who have had an ingestion of a nonsustained release preparation can be observed and discharged 6 hours after ingestion. Psychiatric services should be considered for all intentional overdoses. Patients who have ingested large amounts of sustained release preparations may benefit from prolonged observation for possibly delayed toxic effects or serotonin syndrome.

SEROTONIN SYNDROME

Serotonin syndrome is the result of excess serotonergic stimulation in the CNS and remains the most common significant complication of SSRI overdose. Serotonin syndrome can occur with overdose of single SRI, when a second agent with serotonergic properties is added during therapeutic dosage of an SRI, and rarely after therapeutic initiation of a single SRI medication. The 5HT-2 A receptor has been implicated in most of the manifestations of serotonin syndrome, but it is likely that there is a significant contribution from other serotonergic receptors and possibly interactions with other neurotransmitters (5). As some of the SSRIs have prolonged elimination half-lives and pharmacologically active metabolites, serotonin syndrome can occur when a patient is switched from one SRI to another SRI or if multiple serotonergically active agents are combined. The emergency physician should be aware of this possibility and record a careful medication history that includes discontinued medications when evaluating someone for serotonin syndrome (Table 343.1).

TABLE 343.1
Common Drugs with the Potential to Produce Serotonin Syndrome (3,6)

Increased serotonin production
L-tryptophan
Increased presynaptic serotonin release
Amphetamines
MDMA (Ecstasy)
Cocaine
Decrease serotonin breakdown by MAO
MAOIs such as phenelzine, tranylcypromine, isocarboxazid, moclobemide, selegiline
St. John's Wort
Inhibition of serotonin reuptake
SRIs such as fluoxetine, citalopram, escitalopram, paroxetine, sertraline, fluvoxamine
Cyclic antidepressants
Clomipramine
Meperidine
Dextromethorphan
Tramadol

The syndrome is evident in up to 16% of patients who overdose on SSRIs (5). Clinical effects occur on a spectrum of mild to severe, and the history is vital in making the diagnosis and differentiating it from other etiologies, in particular NMS (Table 343.2).

TABLE 343.2
Comparison of Serotonin Syndrome and NMS

	Serotonin Syndrome	NMS
Cause	Serotonin excess	Dopamine blockade/ depletion
Onset of symptoms	≤24 hrs	Days to weeks
Neuromuscular effects	Hyperreflexia, clonus, hypertonicity (greater in lower extremities)	"Lead pipe" muscle rigidity in all muscle groups Bradyreflexia (tremor, hyperreflexia and clonus not as common)
Length of symptoms	Days	Days to weeks

Note: Varying degrees of altered mental status and autonomic instability are seen with both syndromes.

The signs and symptoms of serotonin syndrome can be divided into three major categories: (1) neuromuscular hyperactivity, (2) altered mental status, and (3) autonomic nervous system instability (Table 343.3). There may be abnormalities in only one or two of these categories. The most common clinical findings are myoclonus, hyperreflexia, confusion, hyperthermia, diaphoresis, and sinus tachycardia (1), but there is no single abnormality that is required for the diagnosis (7). Patients often have a combination of signs and symptoms, and these may not match one another in severity (e.g., a patient may have significant muscle hypertonicity with only mildly altered mental status and autonomic abnormalities). The diagnosis should thus be considered in patients with a history of recent exposure to serotonergic agents and findings in any of the major categories with some of the typical findings.

TABLE 343.3
Summary of Potential Clinical Findings Associated with Serotonin Syndrome (3,6)

Autonomic Instability	Altered Mental Status	Hyperactivity Neuromuscular
Tachycardia	Anxiety	Myoclonus
Fluctuating blood pressure	Confusion	Hyperreflexia
Diaphoresis	Drowsiness	Muscle rigidity
Flushed skin	Hallucinations	Tremor
Hyperthermia	Coma	Agitation
Tachypnea	Insomnia	Restlessness
Mydriasis	Dizziness	Ataxia
Unreactive pupils		Nystagmus
Diarrhea		Trismus
Abdominal pain		Opisthotonus
Excessive salivation		

The time of onset of symptoms after exposure to serotonergic agents is variable. Symptoms are often reported to develop within 1 to 2 hours of exposure (2). The syndrome has also been reported to occur several days after gradual increases in dosing of

antidepressant medications (5). There appears to be no relationship between the amount of drug ingested and the risk of serotonin syndrome, as it can occur with both therapeutic dosing and in overdose. Serum drug levels measured in patients with the serotonin syndrome have been either at therapeutic or below therapeutic levels in up to 90% of cases (1).

Mild neuromuscular effects can include tremor and akathisia that progress to increased reflexes and clonus and then to frank hypertonicity of muscles, which contributes to hyperthermia. Hypertonicity is often greater in the lower extremities. Mild confusion, agitation, and sedation can worsen to profoundly altered mental status, coma, and seizures. Autonomic instability ranges from minimally elevated heart rate, blood pressure, and temperature to frankly unstable vital signs with significant hypertension, tachycardia, and life-threatening hyperthermia ($>41^{\circ}C$).

Laboratory abnormalities may include evidence of rhabdomyolysis, with elevation of creatine phosphokinase, serum creatinine, and lactic acidosis from muscle tissue breakdown, seizures, or hyperthermia. Coagulation abnormalities (including disseminated intravascular coagulopathy), hypotension, and death have also been reported (7).

The differential diagnosis of serotonin syndrome includes sympathomimetic toxicity from agents such as cocaine, amphetamines (muscle hyperactivity, autonomic instability, potentially altered mental status), tetanus (opisthotonus, muscle spasms), strychnine poisoning (muscle spasms and rigidity), lithium toxicity (altered mental status, tremor, and clonus), and severe dystonic reaction infectious etiologies and metabolic derangements. The most similar condition, however, is the NMS. In contrast to patients with the serotonin syndrome, those with NMS have a history of recent commencement of, or increase in, dosage of neuroleptic medications; or a decrease or cessation in dopaminergic medications such as antiparkinsonian agents. Symptoms of NMS tend to develop (and later resolve) over days rather than hours; muscular hyperactivity is characterized by sustained “lead pipe”

rigidity rather than by myoclonus; and hyperreflexia is rarely, if ever, seen (see Chapter 338, Antipsychotic Agents).

Both the history and physical examination should focus on excluding other causes of the clinical picture. In patients presenting with a clinical picture suggestive of serotonin syndrome the history should focus on drug and medication usage. The vital signs should be repeated frequently, as autonomic instability can result in fluctuating blood pressure and pulse. Laboratory investigation should focus on excluding other causes of the clinical picture and evaluating for potential complications of the serotonin syndrome.

The treatment of serotonin syndrome is discontinuing all serotonergic agents along with aggressive symptomatic and supportive care. This includes active external cooling, airway management, and control of muscle tone with benzodiazepines. Agitation, myoclonus, hypertonia, or hyperpyrexia should be treated with intravenous benzodiazepines, crystalloids, and rapid external cooling measures. If no response is observed, paralysis and sedation will reduce muscle tone and decrease hyperthermia. All medications with serotonergic activity should be discontinued, and care should be used in choosing medications for treatment avoiding those with serotonin activity (e.g., ondansetron, fentanyl, valproate, metoclopramide) (5).

Various serotonin receptor antagonists have been used to treat serotonin syndrome, with inconsistent efficacy and unclear impact on outcome. Cyproheptadine is an oral antihistamine with antagonist effects at 5HT-1 A and 2 receptors that has shown some efficacy in case reports in mitigating symptoms (8). Initial control of symptoms can be attempted using 4 to 12 mg of cyproheptadine orally (or per nasogastric tube), followed by dosing of 2 mg every 2 hours until symptoms improve, followed by maintenance dosing of 8 mg every 6 hours (5,8). The maximum dose in a 24-hour period is 32 mg. It is most effective with mild to moderate toxicity typically within 1 to 2 hours of initial administration (8). Patients with more severe or progressive serotonin syndrome do not respond as well, if at all (8).

The antipsychotic chlorpromazine is a serotonin receptor antagonist that can be used for parenteral administration. It has been used successfully in doses of 50 to 100 mg IV and IM but should be preceded by adequate intravenous fluid hydration to prevent hypotension. Other side effects include sedation and dystonic reactions. The use of chlorpromazine in patients with NMS misdiagnosed as serotonin syndrome has the potential to worsen the former condition. Preliminary observations suggest that olanzapine antagonizes 5-HT-2-receptors and may be effective in reversing serotonergic toxicity (9). Further study is required to delineate its role in the treatment of serotonin syndrome.

Serotonin syndrome is usually self-limited and resolves in days after cessation of any serotonergic agent and aggressive symptomatic and supportive care.

CRITICAL INTERVENTIONS

- Aggressive active cooling for hyperthermia
- Aggressive benzodiazepine therapy and paralysis for neuromuscular stimulation

Any patient manifesting even mild signs and symptoms of serotonin syndrome should be admitted to the hospital for further care until symptoms resolve. Patients with significant autonomic instability are best managed in an intensive care setting.

SELECTIVE SEROTONIN RE-UPTAKE INHIBITOR DISCONTINUATION SYNDROME

After abrupt discontinuation of an SSRI, a mild and transient syndrome can occur. Typically starting in the first few days after discontinuation of an SSRI and lasting 1 to 2 weeks, symptoms can include headache, dizziness, nausea, irritability, insomnia, and paresthesias (10). Symptoms resolve spontaneously, but resolution is more rapid when the medication is restarted (10). Though abrupt cessation of SSRIs is to be avoided in the outpatient setting because of these symptoms, this should not be a concern for the emergency

physician in patients with an overdose. Resumption of treatment with an SSRI should be delayed until after any acute toxicity has resolved.

Common Pitfalls

- Prescribing medication with serotonergic effects (e.g., meperidine, tramadol, or dextromethorphan) in patients who are already taking serotonergic medications, especially MAOIs.
- Failing to admit patients with cardiac conduction delays (e.g., prolonged QTc) for telemetry.
- Failure to measure the temperature and begin cooling measures as indicated.
- Failure to recognize that a diagnosis of serotonin syndrome does not require all three elements of altered mental status, autonomic instability, and neuromuscular hyperactivity.

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PART 9 • STIMULANTS AND HALLUCINOGENS

CHAPTER 344 Anticholinergic Agents

Fiona M. Garlich

Anticholinergic toxicity is a common side effect of many pharmaceutical agents, natural remedies, and plants in both the therapeutic and overdose settings. These agents are often abused recreationally for the desired effects of anticholinergic delirium and hallucinations. Anticholinergic symptoms result from inhibition of normal transmission of the neurotransmitter acetylcholine (ACh) in the peripheral and the central nervous system (CNS). ACh is released from cholinergic neurons and then acts upon two types of postsynaptic ACh receptors: nicotinic and muscarinic. Anticholinergic toxicity is more accurately referred to as antimuscarinic toxicity since it results from blockade of muscarinic ACh receptors, which are located in the brain and in organs innervated by parasympathetic nerve endings, such as the heart (via the vagus nerve), gastrointestinal (GI) tract, skin, lungs, bladder, salivary glands, lacrimal glands, and pupillary constrictor muscles.

Signs and symptoms of anticholinergic toxicity range from mild (e.g., dry mouth and blurred vision) to severe delirium with agitation, hallucinations, aggressive behavior, seizures, and vital sign abnormalities.

Numerous pharmaceuticals and toxins have anticholinergic activity (see Table 344.1). Muscarinic antagonists are commonly used therapeutically to treat parkinsonism, urinary incontinence, and motion sickness. Often overlooked exposures include ophthalmic mydriatic and cycloplegic drops such as scopolamine, and anticholinergic drops used to treat infantile colic (1). Anticholinergic toxicity may be seen with overdose and as an

iatrogenic complication of therapy with these medications, particularly in susceptible populations such as infants and the elderly (2). Agents such as tricyclic antidepressants (TCAs) and some antipsychotics have antimuscarinic activity in addition to their effects on norepinephrine, dopamine, and serotonin transmission. Anticholinergic symptoms can be a prominent part of the toxicity seen with overdose of these agents, contributing primarily to altered mental status and sinus tachycardia.

TABLE 344.1
Causes of Anticholinergic Toxicity

Anticholinergic Agents

Atropine

Scopolamine

Antiparkinsonian agents: benztropine, biperiden, procyclidine, trihexyphenidyl

Bladder antispasmodics: darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium

Tricyclic Antidepressants

Amitriptyline

Clomipramine

Desipramine

Doxepin

Imipramine

Nortriptyline

Antipsychotics

Phenothiazines: chlorpromazine, loxapine, mesoridazine, thioridazine

Atypical antipsychotics: clozapine, olanzapine, quetiapine

First-Generation H_1 Blockers

Chlorpheniramine

Cyproheptadine

Diphenhydramine

Dimenhyrdrinate

Doxylamine

Hydroxyzine

Meclizine

Pheniramine

Promethazine

Other Medications

Amantadine, cyclobenzaprine, carbamazepine

Disopyramide, orphenadrine, procainamide

Botanicals

Datura spp, especially *D. stramonium* (Jimson weed, thorn apple, "datura")

Brugmansia spp (angel's trumpet)

Atropa belladona (deadly nightshade)

Hyoscyamus niger (black henbane)

Mandragora officinarum (mandrake)

Chinese herbal medicines (including *Datura metel, Mandragora officinarum*)

The most commonly encountered pharmaceuticals with anticholinergic properties are the antihistamines, specifically the

"first-generation" H_1-receptor antagonists. These agents are competitive antagonists of histamine at H_1-receptor sites, but also have significant antimuscarinic activity. They are also more lipophilic and thus more sedating than the newer "second-generation" antihistamines. H_1-receptor blockers are widely available in both prescription and over-the-counter (OTC) formulations, and are used for the treatment of allergic conditions, as sleep aids, and as antiemetics. These agents are often combined with analgesics, sympathomimetics, caffeine, or anticholinergic compounds which can significantly alter the clinical presentation in overdose (3). Many OTC antihistamines are coformulated with acetaminophen, phenylephrine, or dextromethorphan. Abuse or overdose of these combination products can result in mixed symptomatology and concurrent poisoning by acetaminophen. Children and the elderly may develop anticholinergic toxicity or encephalopathy following exposure to topical antihistamines, especially if applied to broken skin (4).

First-generation antihistamines have other toxic effects in overdose, the most significant of which is sodium channel blockade. This can result in prolongation of the cardiac action potential, leading to widening of the QRS interval, as seen in TCA poisoning. Wide-complex tachycardia and cardiac arrest have been reported, especially with diphenhydramine and dimenhydrinate (4,5). The first-generation antihistamines astemizole and terfenadine were withdrawn from the US market due to prolongation of the QT interval and reports of torsade de pointes. Mild QTc prolongation has been reported with diphenhydramine (4).

Agents with anticholinergic side effects are often abused recreationally for their ability to produce sedation, hallucinations, or an altered mental state. Diphenhydramine is the most commonly abused medication in this group, but recreational use of benztropine, chlorpheniramine, dimenhydrinate, promethazine, and pheniramine is also reported. Abuse of OTC medications, especially sedating antihistamines and cough and cold preparations, has become increasingly popular among adolescents (6). Significant

toxicity can occur with recreational abuse and is complicated by the presence of coformulants.

Several plant species of the *Solanacea* family have potent anticholinergic properties and are used recreationally to induce hallucinations. The most common of these is *Datura stramonium,* or Jimson weed, which contains the tropane alkaloids atropine, scopolamine, and hyoscyamine. All parts of the plant are toxic, but the highest concentration of anticholinergic alkaloids are found in the seeds, which are harvested from locally grown plants or ordered online, and then eaten or brewed into teas. Recreational ingestion of *D. stramonium* can result in severe prolonged anticholinergic toxicity and death (7). Other plants with anticholinergic properties are listed in Table 344.1. See Chapter 355.

Another cause of anticholinergic toxicity is the adulteration of illicit drugs. Scopolamine is used as an adulterant in heroin and cocaine, leading to outbreaks of agitated anticholinergic delirium in drug users (8). Scopolamine can also be added surreptitiously to drinks, often in liquid form as so-called "knock-out drops," with the intent to facilitate sexual assault or robbery. See Chapter 309.

CLINICAL PRESENTATION

The patient presenting with anticholinergic toxicity may exhibit peripheral or central manifestations, or, more commonly, a combination of both (See Table 344.2). The classic anticholinergic toxidrome is characterized by mydriasis, dry skin and mucous membranes, flushing, fever, altered mentation, decreased bowel sounds, and tachycardia. These features provide the basis for the mnemonic "blind as a bat, dry as a bone, red as a beet, hot as a hare, mad as a hatter." Although this mnemonic describes the majority of anticholinergic symptoms, it ignores tachycardia, one of the most consistent and reliable clinical findings. However, in patients taking β-blockers or calcium channel blockers, infants, the elderly, and alcoholics with autonomic neuropathy, tachycardia may be absent. Hence, the absence of tachycardia does not rule out anticholinergic toxicity. Central anticholinergic effects range from

mild confusion and delirium to profound agitation, hallucinations, sedation, and coma. The severity and duration of central symptoms vary with lipid solubility, which affects the ability of an agent to penetrate the CNS. Pronounced, prolonged, and relatively isolated CNS effects have been described in patients exposed to lipophilic scopolamine and benztropine. At the extremes of age, and when anticholinergic agents are combined, delirium may persist for several days. Of note, the peripheral features of the toxidrome may be absent in patients who present to the hospital several hours following poisoning with an anticholinergic agent (2).

TABLE 344.2
Anticholinergic Symptoms and Signs

Peripheral Muscarinic Effects	Central Nervous Effects
Tachycardia	Fever
Mydriasis	Delirium
Loss of accommodation	Seizures
Dry skin and mucous membranes	Coma
Flushed skin	Agitation
Urinary retention	Psychotic behavior
Decreased bowel motility	Respiratory depression
Ileus	Cardiovascular collapse

While the majority of patients with pure anticholinergic toxicity demonstrate mild to moderate symptoms, severe complications and death have been reported (7). Significant morbidity can result from prolonged agitation, hyperthermia, acidosis, cardiovascular collapse, and the consequence of dangerous behavior due to impaired perception and judgment.

Patients with severe toxicity from overdose of H_1-receptor blockers can present with seizures, hypotension, rhabdomyolysis, hyperthermia, wide-complex tachycardia, and respiratory or cardiac arrest (4,5). It is likely that these complications result from the combination of anticholinergic effects with other pharmacologic properties of the agents involved. In adults with less severe

overdoses of first-generation antihistamines, CNS depression (drowsiness, ataxia, coma) is common due to central antihistamine effects. CNS excitation in children is more common as a result of their sensitivity to the anticholinergic effects (4). After antihistamine exposures, coma and seizures may occur within 30 minutes of ingestion. In children <2 years old, seizures have occurred with ingestion of 150-mg of diphenhydramine. Fatal diphenhydramine doses in adults may range from 20 to 40 mg/kg, but in infants as little as 12 mg/kg may result in death (4).

Overdose of TCAs often causes early anticholinergic signs such as sinus tachycardia and altered mental status, but toxicity following large ingestions is dominated by hypotension, seizures, and cardiac conduction delay resulting from other mechanisms (see Chapter 339).

DIFFERENTIAL DIAGNOSIS

Anticholinergic toxicity should be considered in any patient who presents with altered mental status, fever, urinary retention, tachycardia, or seizures. Anticholinergic symptoms may easily be misdiagnosed as a CNS infection, dehydration, heat illness, psychiatric disorder, or sepsis. Intoxications with salicylates, sympathetomimetics, hallucinogens, TCAs, antipsychotics, and drug withdrawal should also be considered in the differential diagnosis. The anticholinergic and sympathomimetic toxidromes can appear quite similar, but a patient with anticholinergic toxicity can be distinguished by the absence of diaphoresis and a diminished pupillary light reflex. Serotonin syndrome should also be considered, but should demonstrate neuromuscular findings that are typically absent in anticholinergic toxicity.

ED EVALUATION

A detailed history and complete physical examination are essential in the evaluation of anticholinergic toxicity or antihistamine poisoning. The physical examination should specifically search for anticholinergic features including pupil size, skin dryness, flushing,

bladder distention, and bowel sounds. Dry skin, which may not be overtly obvious on physical examination, can be assessed by placing a gloved hand in the patient's axilla. The absence of any moisture indicates pathologic dryness. Bladder distention can be assessed with a bedside ultrasound or placement of a foley catheter. Bowel sounds are typically absent or significantly diminished, though auscultation for bowel sounds is often impractical in the ED setting. Flushing of the skin may be present, but this occurs infrequently. A neurologic examination, including assessment of mental status, should be performed. Cardiac monitoring and an electrocardiogram (ECG) should be obtained to assess for prolongation of the QRS or QT intervals, particularly in the presence of tachycardia.

If seizures or altered mentation are present, further diagnostic testing such as computed tomography (CT) scan or lumbar puncture (LP), should be considered, especially if the history is unclear. Administration of physostigmine may obviate the need for further investigations if complete normalization of mental status occurs, confirming anticholinergic toxicity (9). In patients with significant symptoms, routine laboratory evaluation such as electrolytes, blood urea nitrogen, creatinine, glucose, and creatine kinase can direct supportive care. Checking serum concentrations of acetaminophen and salicylate can detect coingestion of these agents, especially from OTC products. Delayed absorption of acetaminophen may occur because of anticholinergic-induced slowed gastric emptying, making interpretation of the Rumack–Matthew nomogram difficult.

Toxicology screens are rarely useful. None of the medications or plants that cause anticholinergic toxicity are detected by standard immunoassay tests for drugs of abuse. Comprehensive testing with thin-layer and gas chromatography may assist in identifying an unknown or suspected xenobiotic, but delayed results rarely impact clinical management. As a result, the diagnosis must be made predominantly by the history and physical examination.

KEY TESTING

- Routine laboratory analysis including electrolytes, creatinine, and glucose
- Acetaminophen and salicylate concentrations with ingestion of OTC medication
- Consider head CT or LP for altered mentation or seizure

ED MANAGEMENT

The mainstay of therapy for poisoning with anticholinergic agents is supportive care, with the institution of advanced life support measures as necessary. Most patients with symptoms require a safe environment in which they cannot do themselves any harm. Comatose or hypoventilating patients should have appropriate airway intervention. Hypotension should be treated initially with intravenous (IV) crystalloid boluses followed by the use of pressor agents such as norepinephrine as needed. Agitation and seizures can be controlled with parenteral benzodiazepines. Occasionally large doses are required, resulting in impaired airway reflexes and necessitating endotracheal intubation.

GI decontamination with appropriate airway protection should be considered in patients presenting shortly after an ingestion of anticholinergic medications. A single dose of activated charcoal is adequate in most instances, but more aggressive interventions such as gastric lavage should be considered in patients with large ingestions of potentially toxic medications such as TCAs or diphenhydramine. An anticholinergic-induced delay in gastric emptying may result in the prolonged presence of pills in the stomach. There is no benefit for hemodialysis or multiple doses of activated charcoal to enhance elimination.

Physostigmine rapidly reverses central and peripheral signs of anticholinergic toxicity (9). It is a short-acting reversible inhibitor of the enzyme acetylcholinesterase, physostigmine allows ACh to accumulate in neuronal synapses and to overcome blockade of muscarinic ACh receptors. In pure, isolated anticholinergic poisoning, dramatic resolution of symptoms occurs within minutes of physostigmine administration, allowing the patient to verbally

confirm the history of poisoning with an anticholinergic agent, discuss coingestants, and deny symptoms consistent with alternative diagnoses (e.g., preceding fever, headache, and neck stiffness). This may prevent the need for escalating doses of benzodiazepines to control agitation, and obviate further diagnostic workup.

The use of physostigmine is not without risks and should be undertaken with caution. Case reports document asystole following physostigmine administration to critically ill patients with TCA overdose and wide QRS intervals (10; see Chapter 339). While controversial, physostigmine can be a safe and effective therapy when used in the appropriate clinical setting, that is, in a patient with a clear anticholinergic toxidrome, a supporting history of exposure, lack of coingestion of TCAs, and no ECG evidence of cardiac conduction delay (QRS prolongation or terminal r-wave in lead AVr). Other contraindications include bowel obstruction, significant cardiac or peripheral vascular disease, asthma, chronic obstructive pulmonary disease, and pre-existing urinary tract obstruction.

Physostigmine should be administered with continuous cardiac monitoring and atropine immediately available at the bedside. One to 2 mg is given slowly over at least 5 minutes (0.02 mg/kg in a child to a maximum of 0.5 mg). The onset of action is typically within minutes. If the response is incomplete, a repeat dose can be administered after 10 to 15 minutes. Clinical effects may last from 30 to 120 minutes, and dosing may be repeated as needed for recurrence of symptoms. If excessive cholinergic symptoms such as bradycardia, diaphoresis, bronchorrhea, or hypersalivation occur following physostigmine administration, atropine should be administered and titrated to effect (an atropine dose of half the administered dose of physostigmine is typically recommended).

When the diagnosis of anticholinergic toxicity is uncertain, or physostigmine administration is not safe or feasible, agitation may be controlled with parenteral benzodiazepines. Neuroleptic agents such as phenothiazines should be avoided because of their associated anticholinergic effects.

Wide-complex tachycardia associated with massive overdose of first-generation H_1-receptor antagonists (e.g., diphenhydramine) should be treated with a bolus of sodium bicarbonate to overcome sodium channel blockade, with consideration of serum alkalinization with sodium bicarbonate infusion (5). Class IA antiarrhythmics (e.g., procainamide) and class III agents (e.g., sotalol) should be avoided, as they can promote dysrhythmias as a result of prolongation of cardiac muscle cell repolarization.

CRITICAL INTERVENTIONS

- Rapidly control agitation with IV benzodiazepines to prevent rhabdomyolysis, hyperthermia, and injury to the patient or staff.
- Consider IV physostigmine to reverse agitation and coma after obtaining a normal ECG without cardiac conduction delay.
- Treat wide-complex tachycardia from first-generation H_1-receptor antagonist poisoning with IV sodium bicarbonate.

Patients with anticholinergic toxicity should be observed until they have normal vital signs, normal mental status, and all anticholinergic signs have resolved. This observation often requires admission to a monitored bed. Patients with agitation, coma, seizures, or cardiovascular instability should be admitted to an intensive care unit. The duration of anticholinergic delirium may be from 12 hours to several days depending on the agent and dose ingested. Patients with antihistamine poisoning who become or remain asymptomatic after a 4- to 6-hour observation period may be medically cleared. Suicide risk should be evaluated in patients with intentional overdoses.

Common Pitfalls

- Failure to consider the diagnosis of anticholinergic toxicity in patients with altered mental status (particularly agitated delirium), tachycardia, urinary retention, fever, or seizures.
- Failure to appreciate that anticholinergic symptoms may present as isolated central or peripheral manifestations.

- Use of physostigmine in patients with a history of TCA ingestion, with ECG evidence of cardiac conduction delay, or without adequate monitoring and resuscitation capability.
- Use of neuroleptics to treat anticholinergic agitation and hallucinations.
- Failure to obtain acetaminophen and salicylate serum concentrations in the patient who has ingested OTC medications.

ACKNOWLEDGMENT

The author gratefully acknowledges the contributions of Andis Graudins to this chapter in previous editions.

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CHAPTER 345

Cocaine

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Cocaine (benzoylmethylecgonine) has been used for social, religious, and medicinal purposes for many centuries. Over the past several decades, its illicit use as a drug of abuse has risen dramatically. An estimated 40 million Americans have used cocaine at least once and for ages 12 and older, 4.2 million have used cocaine in the past year, and 1.4 million have used cocaine in the past month (1), making cocaine the most commonly involved drug of abuse for visits to emergency departments (EDs).

Cocaine is well absorbed on contact with mucous membranes or by pulmonary inhalation. It is derived from the *Erythroxylum coca* plant, which is found in abundance in Central America, South America, the West Indies, and Indonesia. In the manufacturing process, leaves are initially dissolved in hydrochloric acid to form the cocaine hydrochloride salt which is the form most often abused via nasal insufflation or IV injection. Crack cocaine or cocaine freebase are the alkaloid forms of cocaine that are produced by an extraction process utilizing a basic solution, a solvent (usually ether), and heat. The freebase form is close to 100% purity, whereas crack is approximately 75% pure. Crack and freebase are heat stable and thus can be smoked and absorbed by the lungs.

By the IV or inhalational routes, cocaine is rapidly distributed throughout the body with peak central nervous system (CNS) effects in 3 to 5 minutes. With nasal insufflation, absorption is slower and the effects peak at approximately 20 minutes. Although not a typical route of abuse, oral ingestion has even slower absorption with peak effects occurring at 40 to 60 minutes.

Cocaine has a half-life of 0.5 to 1.5 hours. It is predominantly metabolized by hydrolysis to the active metabolites ecgonine methyl ester and benzoylecgonine (BE). These two metabolites account for approximately 80% of cocaine metabolism and these metabolites have half-lives of 4 to 8 hours and many effects similar to their parent compound, cocaine. Other metabolites include cocaethylene, ecgonine, and norcocaine. Urine drug tests typically test for BE, which is usually present for 48 to 72 hours after use. Cocaine's effects typically last for several hours and may wear off while the urine test is still positive for urine cocaine metabolites.

Cocaine has a number of pharmacologic effects peripherally and in the CNS. It acts to augment the peripheral sympathetic system, producing tachycardia, hypertension, diaphoresis, arterial vasoconstriction, and dilated pupils. In addition, cocaine has local anesthetic effects. Because it is the only topical anesthetic agent in the amide group that has vasoconstrictive effects to control secretions and bleeding, it is often used for otolaryngology procedures and wound repair. The central effects of cocaine are very complex and not completely understood. It affects a number of neurotransmitters in the CNS; however, the net effect is augmentation of the sympathetic nervous system.

"Body packers" are individuals who have ingested containers of an illicit drug (most commonly cocaine and heroin). A packer, or "mule," is an individual who ingests a large number of carefully wrapped packages of highly pure drug as a means of concealing and smuggling it into the United States from a foreign country or into jail. These containers can be plastic bags, plastic vials, elastic wraps, elastic condoms, or other packaging material. In contrast, a "body stuffer" is someone who hastily ingests containers just before being arrested by police so as to conceal the evidence. The body stuffer typically has the drug in a plastic baggie or loose wrapping and is more likely to experience effects of cocaine.

CLINICAL PRESENTATION

The most commonly seen manifestations in the ED involve the cardiovascular (CV) and neurologic systems. Signs and symptoms of mild cocaine intoxication include normal or minimally increased blood pressure, pulse, respiratory rate, and temperature; agitation; anxiety; euphoria; headache; hyperreflexia; nausea; vomiting; mydriasis; pallor; diaphoresis; tremors; and twitching. Moderate intoxication may result in more severe hypertension, tachycardia, dyspnea, tachypnea, hyperthermia, confusion, hallucinations, marked hyperactivity, increased muscle tone and deep tendon reflexes, abdominal cramps, formication, and generalized but brief tonic–clonic seizures. Severe intoxication can result in hypotension, tachycardia (or preterminal bradycardia), ventricular dysrhythmias, Cheyne–Stokes respirations, apnea, cyanosis, severe hyperthermia, coma, flaccid paralysis, and status epilepticus.

Chest pain is a common chief complaint associated with cocaine use in EDs. Myocardial infarction (MI) associated with cocaine use is well established (2,3) and occurs in approximately 6% of patients presenting with this complaint (4). Cocaine causes coronary ischemia through coronary artery vasoconstriction, in situ thrombus formation, platelet activation, inhibition of endogenous fibrinolysis, and triggering an increase in the myocardial oxygen demand through generation of tachycardia and hypertension (2). Chronic users develop left ventricular hypertrophy, which can further exacerbate the oxygen supply–demand mismatch (2). It was previously thought that chronic cocaine use was associated with premature atherosclerosis but that has now been disproven (5). Other less common but equally important CV complications of cocaine use include atrial and ventricular dysrhythmias, both systolic and diastolic congestive heart failure, coronary and aortic dissection, dilated cardiomyopathy, and ischemia in other vascular beds (e.g., intestinal, renal).

Euphoria, the impetus for the recreational use of cocaine, is typically short-lived and without serious sequelae. The stimulatory effects of cocaine can lead to seizures. Cocaine-induced seizures are typically single and generalized with rare status epilepticus (6). Focal neurologic events such as hemorrhagic cerebral infarction and

subarachnoid hemorrhage are uncommon. Severe, persistent lethargy with an altered mental status can occur after prolonged and intense cocaine usage and has been termed the *cocaine wash-out syndrome.* This diagnosis should be made only after exclusion of the aforementioned neurologic catastrophes (i.e., after a normal computed tomography (CT) of the head and lumbar puncture, if indicated). The syndrome is thought to be from depletion of essential neurotransmitters following excessive cocaine usage and require 12 to 24 hours to resolve.

Rhabdomyolysis is another common manifestation of cocaine toxicity. Cocaine's stimulatory effects lead to severe agitation and marked muscular agitation and rigidity. Ischemia of the skeletal muscle beds may also contribute. Profound elevations in creatine kinase (CK) may be seen. Acute kidney injury is a result of muscle breakdown and renal tubular precipitation of the released muscle myoglobin. Concurrent development of severe hyperthermia and acute kidney injury can be life-threatening. Hyperthermia most commonly results from a combination of environmental exposure and heat production from excessive muscle activity from agitation and is often noted to be agitated delirium.

Cocaine has a number of direct and indirect effects on the lungs. Many of these effects are a result of the inhalation rather than direct toxin effects. Asthma exacerbations are frequently reported with crack cocaine, most likely a result of particulate byproducts of combustion. Crack use is typically associated with deep Valsalva maneuvers to maximize drug delivery, which can cause pneumothorax, pneumomediastinum, and noncardiogenic pulmonary edema. Other less common effects on the lung include pulmonary infarction, bronchiolitis obliterans, pulmonary artery hypertrophy, and alveolar hemorrhage. Treatment of these conditions follows standard management protocols, whether or not they are related to cocaine.

The intestinal vascular system is very sensitive to the effects of cocaine. Acute intestinal vascular infarction has been associated with all routes of administration. Although oral ingestion is not a common route of abuse, local intestinal and systemic effects can

occur when containers of cocaine leak or rupture in body stuffers and packers. Body packers are most often discovered by customs officers and present asymptomatically.

Habitual cocaine usage during pregnancy is associated with low birth weight, small head circumference, developmental problems, and a number of birth defects. Acute toxicity can also induce premature labor, eclampsia, and abruptio placentae. After delivery, neonates exposed to cocaine in utero are at risk for the development of neonatal withdrawal. This is a diagnosis of exclusion presenting with irritability, jitteriness, and poor eye contact.

DIFFERENTIAL DIAGNOSIS

Cocaine toxicity is associated with sympathomimetic effects which can be similarly seen with hypoglycemia, environmental and malignant hyperthermia, pheochromocytoma, manic psychiatric conditions, status epilepticus, and thyroid storm. Drugs with anticholinergic or sympathomimetic (i.e., amphetamines and bath salts) properties can present with a similar picture. Patients with persistent altered mental status need to be evaluated for possible meningitis and CNS lesions. Table 345.1 lists the differential diagnosis of chest pain related to cocaine use, which also includes reasons to be short of breath. New-onset seizures, epistaxis, hypertension, MI, intracranial hemorrhage, or psychiatric illness, especially in young patients, should suggest the possibility of cocaine use as well as other causes.

TABLE 345.1
The Differential Diagnosis of Cocaine-Associated Chest Pain

Aortic dissection	Pericarditis
Bacterial endocarditis	Pleurisy
Bronchospasm	Pneumonia
Esophageal illnesses	Pneumomediastinum
Gastrointestinal illnesses	Pneumothorax
Musculoskeletal injury	Pulmonary emboli
Myocardial infarction	Pulmonary infarction
Myocardial ischemia	
Myocarditis	

ED EVALUATION

The diagnostic evaluation of patients with cocaine toxicity relies on a history of cocaine use, recognition of signs and symptoms consistent with a sympathomimetic toxidrome, and evaluation of specific organ system complaints. The history should include the total amount and time of cocaine use in relation to symptom onset. Friends or witnesses of confused patients should be questioned about a history of seizures or syncope and antecedent activities. Many patients will deny cocaine use unless approached with reassurance and compassion or confronted with a positive urine test.

The physical examination should include complete vital signs and a detailed examination of the cardiac, pulmonary, and neurologic systems. Patients should initially have continuous cardiac monitoring.

When the history is clear and symptoms are mild, laboratory evaluation is unnecessary. In contrast, if the history is absent or unreliable or the patient manifests moderate or severe toxicity, laboratory evaluation may provide evidence of the severity or identify other causes. These include a complete blood count; determination of electrolyte, glucose, blood urea nitrogen, and creatinine levels; blood gas analysis; urinalysis; CK; and cardiac troponin. Qualitative toxicologic screening of blood and urine can confirm the diagnosis and rule out other intoxicants, but toxicology testing is indicated only when confirmation of drug use would change management, counseling, or referral patterns.

An electrocardiogram (ECG) should be obtained and a chest radiograph considered in patients with chest pain or moderate to severe toxicity. Those with prolonged, unexplained pain should have serial ECG and cardiac biomarker measurements to rule out MI. Many of the clinical parameters to assess ischemia or infarction are less reliable when compared to patients with traditional coronary artery disease. The ECG is less sensitive and specific for identifying ischemia or infarction in this setting, the CK is often elevated as a result of associated rhabdomyolysis, and false elevations in the MB fraction can occur. Cardiac troponin I testing identifies myocardial injury and MI (7). Observation for a 9- to 12-hour period can be used to evaluate patients with cocaine-associated chest pain. Patients without new ischemic changes on ECG, a normal troponin test, and no cardiovascular complications during this observation (dysrhythmias, acute MI, or recurrent symptoms) can safely be sent home with follow-up and a planned outpatient workup (8).

Persistent headache despite normalization of blood pressure is an indication for head CT scan and possible lumbar puncture to rule out intracranial hemorrhage. Patients with severe abdominal or back pain should be evaluated for intestinal or renal infarction and possible aortic dissection. The urine should be inspected and the serum CK level determined, to detect myoglobinuric renal failure.

Occult infections should be excluded in patients with fever, even though fever can be due solely to cocaine toxicity. A brief seizure clearly related temporally to cocaine use in an otherwise healthy person should be evaluated with CT to exclude serious underlying pathology, but does not require further workup, provided the patient is alert and coherent, has no headache, and has a normal neurologic examination. Patients suspected of body packing or stuffing should be evaluated by abdominal imaging and cavity searches (digital or visual examination of the rectum or vagina). Toxicity lasting for more than 4 hours suggests continued drug absorption and should prompt a similar workup.

The route of administration may influence the patient’s chief complaint or which organ system is affected. Intravenous users may present with fever and malaise secondary to infectious

complications such as cellulitis, endocarditis, hepatitis, pneumonia, and the acquired immunodeficiency syndrome. Chronic nasal use may lead to rhinitis, septal perforation, and epistaxis. Inhalational use may produce dyspnea, cough, or hemoptysis from reactive airway disease, “crack lung” pneumonitis, or pulmonary edema or may result in pulmonary barotrauma (e.g., pneumothorax, pneumomediastinum, pneumopericardium) from a Valsalva maneuver or from blowing smoke into the mouth of a partner. Patients with barotrauma may also complain of neck and chest pain with tachypnea, subcutaneous emphysema, or Hamman sign.

Behavioral disorders (e.g., agitation, combative behavior), headache, back pain (renal infarction or aortic dissection), abdominal pain (mesenteric ischemia), altered level of consciousness, or cardiopulmonary arrest are other presentations that may follow the use of cocaine by any route. Patients with excited delirium, severe agitation, an elevated temperature, and metabolic acidosis deserve immediate attention. Patients may present as victims of trauma because of the violent, irrational, and risk-taking behavior associated with drug use. Delayed CV complications can sometimes occur and MI has been reported in the first few days after cocaine use but has also been reported 1 to 2 weeks after last use.

Manifestations of chronic cocaine abuse include anorexia, insomnia, formication, depression, impotence, weight loss, paranoia, and psychosis. Halo vision (lights around objects) and “snow lights” (flashes in the peripheral fields) have also been described.

KEY TESTING

- Mild Toxicity
  None necessary
- Moderate to Severe Toxicity
  CBC, electrolytes, glucose, BUN, UA
  CK for rhabdomyolysis
  CXR for persistent SOB and chest pain
  ECG and troponin for suspected ischemia

CT (head/chest/abdomen) for persistent complaint

ED MANAGEMENT

Management depends on the specific complaint and presentation. Patients presenting with a sympathomimetic toxidrome are at risk for hyperthermia and rhabdomyolysis. After initial attention to the airway and CV status, management should focus on lowering any elevated core body temperature, halting further muscle agitation and heat production, and giving IV fluids to ensure a good urinary output. The agents of choice for muscle relaxation in this setting are benzodiazepines and in severely agitated individuals, control should be obtained with rapid use and use of supranormal cumulative doses may be necessary.

Patients with severe hypertension or tachycardia needing pharmacologic measures can usually be safely treated with benzodiazepines. When large doses of benzodiazepines are not effective, intravenous nitroprusside or phentolamine should be considered (4). β-Antagonists or compounds with partial β-blocking effects are contraindicated as the use of β-antagonists in the setting of cocaine intoxication can lead to unopposed α-stimulation, with resultant marked increases in hypertension and worsening coronary vasoconstriction (2,4).

Patients with suspected cocaine-induced ischemia or MI should be treated similarly to those with traditional acute coronary syndromes (ACSs), with some notable exceptions (2,4). Aspirin, nitroglycerin, and heparin remain important initial therapies. Intravenous benzodiazepines should be provided as early management (2,4,9). They will decrease the central stimulatory effects of cocaine, thereby indirectly reducing the CV toxicity of cocaine (2,4). β-Antagonists are contraindicated, as they exacerbate cocaine-induced coronary artery vasoconstriction (2,4). Percutaneous interventions (angioplasty) are preferred over fibrinolysis, which has no proven efficacy in the setting of cocaine-associated MI and a possible reduced safety profile. There is an increased likelihood of interventions being performed in patients who are not sustaining an

acute infarction because young patients have a high prevalence of early repolarization and “false-positive” ST-segment elevations on the ECG. Such a therapy should, therefore, be used with caution. Finally, there are anecdotal reports of the safety and efficacy of phentolamine, an α-antagonist, for treatment of cocaine-associated ACS (2,4). Verapamil reverses cocaine-induced vasoconstriction, but several animal experiments suggest that it exacerbates CNS toxicity. Thus, it may have a role in patients with continued ischemia who do not have signs of central stimulation from cocaine.

Supraventricular dysrhythmias due to cocaine toxicity may be difficult to treat. Adenosine can be administered, but its effects may be only temporary. Use of calcium channel blockers in association with benzodiazepines appear to be most beneficial. β-Blockers should be avoided (2,4).

Ventricular dysrhythmias may be a result of excess adrenergic tone or cocaine’s sodium channel blocking effects. Management with benzodiazepines, lidocaine, and/or sodium bicarbonate appears to be most useful (2,4). Bicarbonate is preferred when patients have dysrhythmias directly after the use of cocaine. In this setting, the dysrhythmias are presumably related to the type I antiarrhythmic effects of cocaine. Bicarbonate reverses cocaine-associated QRS widening. Lidocaine can be used when dysrhythmias appear to be related to cocaine-induced ischemia (10). ECG evidence for the type I antiarrhythmic effects of cocaine has often disappeared by the time symptomatic ischemia develops. There is no data regarding the use of amiodarone.

Cocaine-induced seizures are typically brief and self-limited. For refractory cases, benzodiazepines and phenobarbital are the first- and second-line agents, respectively. Phenytoin is not recommended.

Patients with suspected cerebrovascular infarctions and hemorrhage should be treated the same as other patients with these conditions. Intracranial and systemic hypertension necessitating treatment is accomplished using standard therapies, except that β-blockers should not be utilized.

The main objective with asymptomatic body packers is to eliminate the packages out of the gastrointestinal system. Whole-bowel irrigation with subsequent radiologic verification of passage of all drug-filled containers may be warranted.

Body stuffers who show clinical signs of toxicity should be treated similar to other cocaine-exposed individuals. In addition, activated charcoal should be administered liberally.

Symptomatic body packers should be treated aggressively, because rapid deterioration and severe toxicity can result from leakage from a single package causing potentially massive exposures. Immediate surgical removal of the ruptured package(s) may be lifesaving. Aggressive supportive care with activated charcoal and benzodiazepines is warranted as preparations are made for surgery.

CRITICAL INTERVENTIONS

- Rapidly cool and sedate the hyperthermic and agitated patient.
- Assess patients with cocaine toxicity for myocardial ischemia/MI, dysrhythmias, hyperthermia, and rhabdomyolysis.
- Administer intravenous benzodiazepines for CNS and cardiovascular toxicity.

DISPOSITION

Patients with severe agitation, hyperthermia, and possible rhabdomyolysis need to be admitted. Patients with cocaine-associated chest pain need to be assessed for risk of CV events. Criteria for patients with a low risk of CV events that are safe for ED discharge after a brief observation period include lack of ischemic changes on ECG; normal serial cardiac troponin I values; and no dysrhythmias, or recurrent symptoms during a 9- to 12-hour observation period (8). Most patients with ED cocaine-associated chest pain (~70%) will meet these criteria (8). Coronary computerized tomographic imaging of the coronary arteries can be used to identify low-risk individuals and shorten the duration of observation (11).

The disposition of patients with neurologic complications is the same as for other patients with these conditions. The likelihood of compliance with outpatient follow-up should be considered when contemplating the discharge of patients who may need further evaluation. If definitive care cannot be provided at the site of presentation, transfer may be necessary. Personnel with advanced life-support training should accompany patients requiring transfer. Substance abuse counseling and treatment should be discussed with all patients with referral if possible.

Body stuffers who remain asymptomatic for 4 to 6 hours may be discharged after treatment with activated charcoal. Body packers need to be admitted until packets have been removed.

Common Pitfalls

- Failure to aggressively treat patients with agitated delirium from cocaine.
- Failure to consider cocaine toxicity in the differential diagnosis of patients with chest pain, seizures, agitation, altered mental status, and dysrhythmias.
- Failure to recognize the limitations of the ECG in the evaluation of cocaine-related chest pain.
- Failure to appreciate the differences between the management of cocaine-related chest pain and traditional therapy for ACS.
- Failure to recognize the dangers of using β-adrenergic antagonists to treat cocaine toxicity.
- Failure to ensure the rectal passage of cocaine-filled packages in body packers prior to discharge.

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CHAPTER 346

Hallucinogens

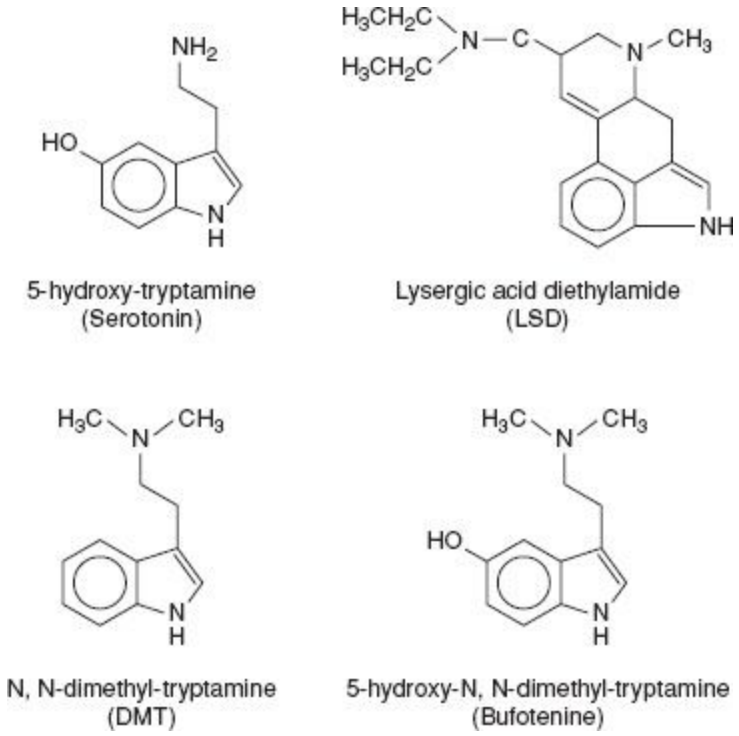
Howard A. Greller

Hallucinogens, from the Latin *alucinari* (to "wander in mind"), are a diverse class of xenobiotics that primarily alter sensory perception and interpretation, without altering orientation. The term *hallucinogen* is the medicolegal descriptor for this group of related compounds, whereas *psychedelic* is a common layperson descriptor. *Hallucination* is the perception of phenomena or objects that have no basis in reality (e.g., pink elephants). Visual hallucinations tend to have toxic metabolic causes, whereas auditory hallucinations tend to be primarily psychiatric or organic. The term hallucination contrasts with *illusion,* in which there is misinterpretation of a sensory perception (e.g., a coat hanging in a dark room is perceived as being a person). A *synesthesia* is a mixed perception (e.g., hearing color or seeing taste). *Psychotomimetic* describes a substance that causes psychological and behavioral changes resembling psychosis. An *entactogen* is a substance that enhances feelings of empathy, love, and emotional closeness and facilitates expression of emotions (e.g., methylene-dioxy-methamphetamine [MDMA]—ecstasy), whereas an *entheogen* ("generating the divine within") is a psychoactive xenobiotic used in a ritualistic religious or spiritual context (e.g., 3,4,5-trimethoxyphenylethylamine—mescaline) (1).

Plant and animal species have been used in religious, spiritual, and other practices for centuries. The Rig-Veda, an Indian text more than 3,000 years old, praises soma, believed today to be the mushroom *Amanita muscaria,* containing the psychoactive compound muscimol (2,3). The modern era of hallucinogens had its origins with Albert Hofmann, who synthesized lysergic acid

diethylamide-25 (LSD) in 1938. LSD was subsequently used as a therapeutic adjunct for psychotherapy but found its way into recreational use in the 1960s. As a result of concerns about birth defects and other toxicity, federal law in the mid-1960s banned LSD. Many hallucinogens are Food and Drug Administration (FDA) schedule I agents (4). In adolescents (age 12 to 17), overall hallucinogen use has declined in the 10-year period between 2002 and 2012 whereas the 18- to 25-year-old group had the highest prevalence of use within the last year. There has been a recent increase in the use of other hallucinogenic compounds, such as "foxy" (5-methoxy-*N, N*-diisopropyltryptamine), DMT (*N, N*-dimethyltryptamine), psilocybe mushrooms, phencyclidine (PCP), and ketamine (5).

The mechanism of hallucinogenesis has not been completely elucidated. Although derived from widely different sources and often chemically distinct, most hallucinogens share a structural similarity to serotonin (eFig. 346.1), and can be classified by structure. The tryptamine derivatives share the pyrrole structure of the indole ring. The amphetamine derivatives typically considered "hallucinogenic," such as MDMA, share the methoxylated or methylenedioxylated catechol ring. Each of these structural features appears to be essential to hallucinogenic activity (1,3,6). The similarity of LSD and other hallucinogenic compounds to serotonin provides them with agonist activity at the 5-HT_2 receptor. Specifically, the 5-HT_{2A}-receptor subtype found predominantly on a population of postsynaptic neurons in the cerebral cortex has been implicated by functional studies in the modulation of hallucinations (7). Additional mechanisms for the generation of hallucinations include activity at the κ-opioid receptor, as is the case with *Salvia divinorum* and ibogaine (8), which are structurally unrelated to serotonin.



eFIGURE 346.1 Hallucinogenic compounds and their structural similarity to serotonin.

LSD is a semisynthetic lysergamide compound derived from the ergot fungus *Claviceps purpurea.* There are other naturally occurring analogs of LSD found in the seeds from plants of the morning glory family (*Convolvulaceae*), including the South American morning glory, the Mexican morning glory, and Hawaiian woodrose (2,9). LSD is very potent, with hallucinogenic doses in the range of a few hundred micrograms. It is most commonly administered through the oral route, generally as a fancifully designed blotter paper. The perforated paper defines a dosing unit, and the designs provide "branding." Other forms include impregnated gelatin ("window panes") or microdots (small pills or tablets), and occasionally as a liquid (4).

Mescaline, or 3,4,5-trimethoxyphenylethylamine, is a phenylethylamine compound that is derived from the peyote cactus (*Lophophora williamsii*). Although mescaline can be isolated from the cactus, this is a difficult process, and most of the time the compound is ingested in its natural form. Typically, a few of the small cactus

crowns or “buttons” are removed, dried, and then ingested (4). The phenylethylamine analogs of mescaline are also used in an attempt to produce similar hallucinosis. Although the primary clinical effects of recreational doses of ecstasy (MDMA; see Chapter 348) do not involve hallucinations, hallucinations may occur at very high doses. The seeds of nutmeg (*Myristica fragrans*) are known to contain myristicin and elemicin, two mescaline-like substituted amphetamines with hallucinogenic properties (2,9). Up to 20 g of the ground spice need to be ingested to produce the hallucinatory effects, at the expense of significant gastrointestinal (GI) distress. Other phenylethylamine compounds include the “2 C” compounds including 2 C-B (4-bromo-2, 5-dimethoxyphenethylamine) and 2 C-T-7 (2, 5-dimethoxy-4-N-propylthiophenethylamine.)

The tryptamines are a group of structurally related compounds that produce hallucinosis. Psilocybin (4-phosphoryloxy-*N, N*-dimethyltryptamine) and psilocin (4-hydroxy-*N, N*-dimethyl-tryptamine) are two compounds of the indolalkylamine class isolated from mushrooms of the *Psilocybe* genus (1,2,9). The two most common species are the “liberty cap” (*Psilocybe semilanceata*) and *Psilocybe cubensis*. The spores of these mushrooms are not considered a controlled substance (although the mature mushrooms are), are readily available through a variety of sources, and are easy to grow into mature mushrooms. Being a natural product, the amount and type of hallucinogenic compound contained within any singular mushroom vary widely, and therefore there is no “typical” dose (see Chapter 354).

“Foxy” or “foxy methoxy” (5-methoxy-*N, N*-diisopropyltryptamine, 5-MeO-DIPT) and α-methyltryptamine (AMT) are tryptamine derivatives (1,4,5). Both drugs are available as capsules filled with powder and are orally bioavailable. DMT (*N, N*-dimethyl-tryptamine) is a tryptamine derivative of the Yakee plant (*Virola calophylla*). Ayahuasca is a psychotropic plant that is used as a tea throughout the Amazon basin in traditional medicine and shamanistic practices. Ayahuasca is made by steeping the pounded stems of the vine *Banisteriopsis caapi* alone or in combination with the leaves of *Psychotria viridis*. This combination is

ethnopharmacologically interesting because *P. viridis* contains DMT and *B. caapi* contains alkaloids such as harmine and tetrahydroharmine. DMT is normally metabolized by GI monoamine oxidase (MAO), and harmine and the other β-carboline alkaloids are MAO inhibitors (1,2,9). Thus the combination of the two plants allows for the increased bioavailability of the DMT.

Secretions of the modified parotid gland of the Colorado River toad, *Bufo alvarius,* contain a mixture of "defensive" chemicals designed to protect from predators. These chemicals include catecholamines, cardioactive steroids, and *bufotenine* (5-methoxy-*N,N*-dimethyltryptamine, 5-MeO-DMT), a potent hallucinogenic compound. People engage in the practice of "toad-licking" in attempts to experience the psychedelic properties of this chemical. This practice is often complicated with the consequences of the other compounds contained within the secretions, most notably cardioactive digoxin-like steroids (see Chapter 325) (1).

S. divinorum, a member of the mint family, has been used for centuries by the Mazatec Indians of Oaxaca, Mexico. The active compound is a neoclerodane diterpene, salvinorin A, structurally unrelated to any of the previously described hallucinogenic compounds and believed to exert its clinical effects through action at the κ-opioid receptor. *S. divinorum* is taken orally, with rapid oral–mucosal absorption, and by smoking (5,8).

Ibogaine is derived from the root of the *Tabernanthe iboga* plant, found primarily in West African nations. Ibogaine has gained recent attention as a potential treatment for addiction to compounds such as cocaine and heroin and is being investigated by the FDA for such purposes. Ibogaine is taken orally (2,4,5,9).

CLINICAL PRESENTATION

Unlike most other drugs of abuse, users of hallucinogens rarely present acutely to the healthcare provider (4,5). Hallucinogens in general have few significantly dangerous adverse side effects, and patients generally present to the emergency department (ED) for secondary reasons (e.g., trauma) or for "bad trips." The unique

nature of hallucinogens defines their clinical presentation. Unless combined with other drugs, patients should be alert and fully oriented and able to give a history of use. A clear sensorium is a key historical and examination point, suggesting the use of LSD. This contrasts with drug-induced delirium, such as that associated with PCP, in which, by definition, the patient's orientation is altered. In addition, in an attempt to obtain a hallucinogen, patients are commonly exposed to more sympathomimetic compounds (such as 25I-NBOMe) and have more physiologic derangements.

Hallucinations or illusions are alterations in the perception of time and body image and changes in the interpretation of sensory information. Hallucinogenic experiences are commonly referred to as a "trip," and the experience tends to be an extremely personal one. The perceptual changes that users perceive can affect any of the senses: hearing, taste, smell, touch, or sight. The person can experience exaggeration, diminution, or mixing (synesthesias) of their sensory perception. The users' sense of time may be altered, generally slowed, as may their sense of space. Body dysmorphisms are common, in which personal physical features take on abnormal proportions. Events can be perceived as hyperreligious or evil. Additional clues to the diagnosis include the sympathomimetic effects of some of the compounds involved, although these effects are usually mild and rarely dangerous. Common physical signs and symptoms of acute intoxication include mydriasis, diaphoresis, piloerection, tremors, and mildly elevated blood pressure, pulse, respiratory rate, and temperature. These findings may be masked by the coingestion of ethanol or other sedative–hypnotic agents.

Injury is the predominant adverse event related to hallucinogen use, as a result of the acute behavioral effect of the drug. There are few, if any, dangerous physiologic effects of the drugs themselves. The psychological effects can be overwhelming, and occasionally the hallucinations can be perceived as frightening or threatening ("bad trips") causing the patient to panic or respond in a manner causing injury. These experiences can include or engender paranoia, acute psychosis, panic, and significant depression. Suicide and unintentional death have been reported (2,5). There is no

withdrawal syndrome from hallucinogens, although tolerance and crosstolerance between compounds can occur.

Mescaline use is associated with significant, unpleasant side effects. Initial signs and symptoms include nausea, vomiting, abdominal pain, diaphoresis, nystagmus, and ataxia. These symptoms typically resolve within 1 to 2 hours of ingestion and precede the onset of the hallucinations, which begin within 4 to 6 hours and typically last for 6 to 12 hours (5).

Hallucinogenic doses of nutmeg cause severe side effects, such as dizziness, flushing, tachycardia, nausea, vomiting, constipation, and panic. Because of the relative severity of the side effects, it is not a popular means of producing hallucinations. When ingested, the hallucinations begin within 1 to 4 hours and last 12 to 24 hours. Many users report an extended period of sleep after use (upward of 16 hours).

Ingestion of psilocybe mushrooms is typically associated with nausea and sometimes vomiting. Onset of effect is approximately 30 minutes, and the duration is typically 4 to 6 hours. The effects are described as being typically “less intense” and more illusionary than those produced by LSD (1,2,9). AMT has a longer duration of effect (approximately 12 to 24 hours) than that of Foxy (between 3 and 6 hours). Toad licking has resulted in digoxin-like bradycardia and significant adverse effects from other components of toad secretions (1).

The hallucinogen persisting-perception disorder (HPPD), commonly known as “flashbacks,” associated with the use of LSD should not be confused with prolonged sensory perception (afterimages), also known as palinopsia. Patients with HPPD characteristically experience, in the absence of the drug, recurrent perceptual disturbances similar to those encountered during acute intoxication. HPPD is often triggered by stress, illness, or other challenges. HPPD can occur after a single use of the drug and may last for a prolonged period (up to years) (1,10). HPPD is associated with the use of phenothiazine antipsychotics to control the acute behavioral symptoms of acute intoxication, suggesting that sedatives such as benzodiazepines, rather than antipsychotics, should be used

for this purpose. Proposed therapies for HPPD include clonazepam, carbidopa, and psychotherapy. A rare reported adverse effect of LSD is permanent psychosis (10).

The time of onset and duration of effect can help determine the identity of the hallucinogen (see Table 346.1). Long-acting agents include LSD, mescaline, and nutmeg. Medium-acting agents include psilocybin, psilocin, Foxy, AMT, and *Bufo* sp–toad toxins. Short-acting hallucinogens include DMT, ibogaine, and salvinorin A.

TABLE 346.1
Common Hallucinogenic Compounds

Common Name	Name	Onset (hrs)	Duration (hrs)
DMT	*N,N*-dimethyl-trypt-amine	Rapid	0.5 to 1
Salvia divinorum	Salvinorin A	Rapid	1 to 2
Foxy	5-methoxy-*N,N*-diiso-propyltryptamine	Rapid	3 to 6
Psilocybin	4-phosphoryloxy-*N,N*-dimethyltrypt-amine	0.5	4 to 6
LSD	Lysergic acid diethyl-amide	1 to 4	4 to 12
Mescaline	3,4,5-trimethoxyphenyl-ethylamine	4 to 6	6 to 12
Nutmeg	5-allyl-1,2,3-trime-thoxybenzene	1 to 4	12 to 24
AMT	α-Methyltryptamine	Rapid	12 to 24
Ibogaine	Ibogaine	4 to 8; 10 to 20	12 to 24

Smoking DMT leads to effects that typically begin within minutes and last between 30 and 60 minutes. Rapid onset and short duration of action has earned DMT the moniker “the businessman’s lunch,” because the user can experience a “trip” in the time allotted for a meal (1,4,5). Following the ingestion of ayahuasca, DMT also has a rapid onset of action and short duration of effect (1,2,9).

The ingestion of *S. divinorum* produces effects that begin in 5 to 10 minutes and last approximately 1 to 2 hours. When the vapor is

inhaled or the plant is smoked, effects begin in seconds and last about 30 minutes (5,8). Ibogaine ingestion can cause both early (4 to 8 hours after ingestion) and late (10 to 20 hours after ingestion) hallucinations (2,4,5,8).

DIFFERENTIAL DIAGNOSIS

Other abused agents that can cause hallucinations include sympathomimetics, anticholinergics, and dissociative anesthetic agents and related compounds. Cocaine and amphetamines are associated with psychosis at high doses or following binges and those atients characteristically develop a delusional state that does not always involve clear hallucinations. Symptoms may last for several days but typically respond to antipsychotic medications. Anticholinergic agents (e.g., scopolamine and atropine) may produce dramatic epidemic hallucinations when teenagers discover Jimsonweed (*Datura stramonium*) and ingest the seeds. Patients generally have other manifestations of the anticholinergic syndrome and are almost always delirious. Dissociative anesthetic agents, such as PCP, ketamine, and the related compound dextromethorphan, produce hallucinations that are generally described as dysphoric which can cause wild and unreasoned behavior. Clinical features include delirium and prominent nystagmus. Autonomic manifestations are usually more prominent than hallucinations in each of these conditions. In contrast, with traditional hallucinogens such as LSD, hallucinations are prominent, and autonomic effects are usually mild.

Hallucinations have been reported as idiosyncratic reactions to almost all medications. Street-drug adulterants (e.g., cyanide, local anesthetics, quinine, quinidine, caffeine, theophylline, and strychnine) should be considered in the differential of hallucinosis. Because central nervous system (CNS) structural, infectious, and psychiatric conditions can cause hallucinations, exposure to a hallucinogenic agent should be a diagnosis of exclusion. With or without the history of hallucinogen exposure, these conditions should always be considered in the differential diagnosis.

ED EVALUATION

The history from family, friends, or the patient, who is usually cooperative and oriented, should include the name or description of the hallucinogen, the time of ingestion, amount(s) taken, the route of exposure, and the nature and time of onset of hallucinations and other symptoms. Slang names may provide a presumptive identity, if the chemical name is not known. A history of previous drug use, psychiatric problems, and medical conditions, particularly cardiovascular disease, should be documented. The clinician should specifically explore the possibility of concomitant traumatic injuries.

The physical examination should focus on the mental status, neurologic evaluation, and cardiovascular system. Vital signs documented and repeated frequently. The patient should be examined carefully for evidence of trauma, underlying disease, and heat-related illness.

Ancillary testing is neither necessary nor useful in patients with mild hallucinogen intoxication, except to rule out other diagnoses. Patients with moderate or severe symptoms (e.g., excessive agitation and significantly abnormal vital signs) should have a chest radiograph; cardiac monitoring and a 12-lead electrocardiogram (ECG); complete blood count; determination of electrolyte, glucose, blood urea nitrogen, creatinine, and creatine kinase levels; and urinalysis performed to exclude other conditions or exposures. Significant psychomotor agitation can occur with a variety of perceived stimuli, and rhabdomyolysis should be considered. Routine toxicology screens are rarely sensitive or specific enough to provide confirmation or exclusion of another agent as the causative etiology of a specific clinical presentation. Quantitative blood (or urine) hallucinogen levels are not clinically useful or routinely available.

KEY TESTING

- Rapid glucose measurement and core temperature are useful in all patients

- ECG and other tests as needed for supportive care or to exclude other causes
- Radiographs to evaluate suspected trauma

ED MANAGEMENT

Management is supportive. Standard life-support measures should be instituted as needed, but an intravenous line is often not needed. The focus of care should then be to provide a calm, quiet environment for the patient. Providers should attempt to reduce the patient's anxiety, help to provide a foundation for reality testing, and provide continued, empathetic reassurance. In cases in which the experience is causing the patient significant agitation or distress, pharmacologic sedation with a benzodiazepine should be provided. Phenothiazines should be avoided because they have been implicated in HPPD (10). Although activated charcoal can bind most, if not all, of these compounds, the efficacy of this intervention is undefined. Because consequential morbidity is exceedingly rare and because GI decontamination may be particularly unpleasant for a patient who is hallucinating, its use is unnecessary except for patients with significant coingestions.

CRITICAL INTERVENTIONS

- Provide a calm, quiet environment with continuous observation and repeated reassurance.
- Administer benzodiazepines for persistent or severe agitation or psychological distress.

DISPOSITION

For the majority of patients presenting after use of a hallucinogen, their disposition will be discharged. In the absence of any adverse sequelae (e.g., trauma, rhabdomyolysis, electrolyte abnormality, etc.), the patient should be watched until reality testing is assured, and appropriate referral to a psychiatrist or substance abuse program can be provided. Admission is warranted only for

persistence of psychosis or if the patient has a concomitant medical or surgical issue that makes this necessary.

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of Lewis S. Nelson and Christopher H. Linden to previous editions of this chapter.

Common Pitfalls

- Failure to obtain a complete set of vital signs, especially an accurate core temperature.
- Failure to differentiate between hallucinations and delirium; patients with drug-induced hallucinations have clear orientation with altered content.
- Failure to make safety of the patient and staff a priority.
- Failure to consider metabolic, structural, infectious, traumatic, and psychiatric etiologies of the hallucinatory state.
- Failure to screen for occult conditions caused by the behavioral abnormalities of these compounds, such as rhabdomyolysis.
- Failure to consider coingestants or nonclassical hallucinogen-producing compounds (i.e., anticholinergic agents) and their specific toxicities.

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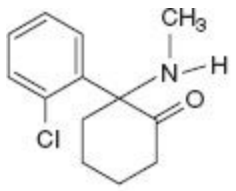
CHAPTER 347 Phencyclidine and Ketamine

Cyrus Rangan

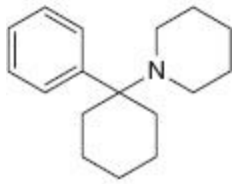
Phencyclidine [PCP, 1-(1-phenylcyclohexyl)-piperidine], first synthesized in 1926, is a powerful analgesic and amnestic with minimal respiratory depression. It was used as a general anesthetic (Sernyl) in the 1950s but use in humans ceased in 1965 because of emergence reactions; veterinary use ceased in 1979. PCP was a popular street drug in the late 1960s (e.g., "angel dust") and was also known as "crystal," "killerjoints," or "supergrass" when smoked with tobacco, parsley, mint, oregano, or marijuana. It is rapidly absorbed via ingestion, snorting, injection, or smoking. In recreational use, its dose ranged from 1 to 10 mg per dose; toxic psychosis occurred with more than 5 mg. It is cleared by both hepatic (major) and renal (minor) elimination (1).

Ketamine (2-[2-chlorophenyl]-2-methylaminocyclohexanone), synthesized from PCP in the 1960s, has been used as a pediatric and veterinary anesthetic since 1970. Recreational ketamine abuse began in 1980 in association with thefts from veterinary clinics but has declined since then. Ketamine is used today as a short-term anesthetic (Ketalar) and is still a popular hallucinogenic, sometimes utilized as a "date-rape" drug (2). Street names include "K," "K-blast," "kit-kat," "lady K," and "special K," "vitamin K." Its pharmacodynamic effects are similar to those of PCP, but with less potency, a smaller volume of distribution, and a shorter half-life and duration of action. Like PCP, it is rapidly absorbed and has a rapid onset of action via ingestion, snorting, injection, or smoking. The

dose varies from 10 to 500 mg. PCP is hepatically metabolized to bioactive norketamine, which is eliminated by the kidney (3). PCP and ketamine have similar chemical structures (eFig. 347.1). Both drugs bind to the PCP binding site on the N-methyl-D-aspartate (NMDA)-receptor complex (dissociative anesthetic effects via noncompetitive inhibition of calcium influx) (4). At sympathetic nerve terminals, both drugs act as catecholamine reuptake inhibitors. At higher doses, these drugs stimulate σ-opioid receptors (causing lethargy, obtundation, or coma) and variably stimulate muscarinic, dopaminergic, γ-aminobutyric acid (GABA)-ergic, and non–σ-opioid receptors, possibly by modulation of potassium conductance (1).



Ketamine



Phencyclidine (PCP)

eFIGURE 347.1

CLINICAL PRESENTATION

Effects begin within minutes after administration, lasting 8 to 24 hours for PCP and 30 minutes to 4 hours for ketamine. The effect is of longer duration in patients with impaired hepatic or renal function. Psychological dependence and tolerance may occur. Significant mental impairments are common but because there are minimal respiratory effects, deaths from direct effects are rare (2,5,6). Traumatic injuries and deaths from drug-related behavior are common, however (6).

PCP effects include euphoria, severe auditory hallucinations, short-term memory impairment, visual distortions, aggressiveness, and disconnection from reality. There may also be extreme behavioral swings between catatonia and excessive agitation, severe violence, combativeness, and "superhuman strength" (5). The superhuman strength is thought to come from its effect as a "dissociative anesthetic" where the patient does not feel pain associated with exertion or injury. Children exhibit primarily motor effects, with less aggressive behavior (7). Acute psychosis with PCP is clinically indistinguishable from schizophrenia. Other findings include ataxia, dystonia, hypertonia, seizures, and sympathomimetic effects. Hypertension may be associated with intracranial hemorrhage and focal neurologic signs, with or without associated trauma (8). Hyperthermia occurs from excessive muscular rigidity, hyperactivity, or sustained seizures. Rhabdomyolysis and crush injury can occur from agitation and struggling against restraints. Lacrimation and hypersalivation is secondary to cholinergic stimulation. The pupils are paradoxically small because of cholinergic and opioid receptor stimulation. Nystagmus occurs in over 50% of PCP overdoses and may be horizontal, vertical, or rotatory (5).

Ketamine's effects are less severe than those of PCP. There is dose-dependent perception disturbance, with mild agitation (8). A "floating" feeling is described, with prolonged, numbing, out-of-body experiences and perception of paralysis—the so-called "K-hole." (2). Impaired attention span, pain perception, and memory; miosis, nystagmus, ataxia, and mumbling speech; and delirium, hallucinations, tachycardia, and hypertension can also occur. Ketamine is a mild bronchodilator, but also induces bronchorrhea and sialorrhea (2).

DIFFERENTIAL DIAGNOSIS

PCP intoxication should be suspected with any acute onset of psychosis, especially when there is fluctuating mental status. Clues to PCP include violence, indifference to pain, and difficulty

restraining the patient, although these can be seen with other intoxications such as cocaine and methamphetamines.

Both drugs mimic adrenergic agents, anticholinergic agents, and opiates. There is tachycardia and hypertension, but accompanied by miosis, nystagmus, and hypersalivation. Withdrawal from these agents can mimic ethanol and sedative–hypnotic withdrawal (5,6).

Because PCP or ketamine may be taken with other drugs, additional signs or symptoms may be present (9). Cyanide poisoning should be considered after smoking PCP. Occult traumatic injury should always be considered (8). Acute psychiatric illness is always in the differential, especially in patients with a similar history.

ED EVALUATION

History should include the time, amount, and route of exposure, and circumstances and events prior to arrival. Additional details should be obtained from police and sources other than the patient. A physical and mental status examination should focus on vital signs (including temperature), neurologic findings, evidence of trauma, pulmonary aspiration, and complications of injection drug use. An early temperature assessment can identify patients who need immediate cooling. Serum electrolytes, complete blood count, blood gas, creatine phosphokinase (CPK), and serum ethanol level can assist in supportive care for lethargic, comatose, or extremely violent patients. A rapid urine drug screen may confirm the presence of PCP but many screens do not test for PCP. Ketamine is not reliably detected on rapid screens. False-positive testing for PCP can occur with ketamine and dextromethorphan (9). Send-out quantitative PCP or ketamine levels do not correlate with toxicity and are not useful. Urine testing for PCP or ketamine by gas chromatography/mass spectroscopy can confirm exposure but the patient will have recovered long before the results are available. Urinalysis may be positive for hemoglobin, suggesting rhabdomyolysis (6), but patients who are at risk should also have CPK measured. Brain computed tomography (CT) and other imaging

may be necessary when there are signs of head injury or other trauma (8).

KEY TESTING

- Urinalysis and CPK for patients at risk for rhabdomyolysis
- Imaging may be needed for patients with concurrent trauma
- Toxicology screening and quantitative testing are not helpful clinically
- Electrolytes, blood gases, CBC, and ethanol level may be helpful for general supportive care

ED MANAGEMENT

Because of unpredictable violent behavior, adequate security personnel should be present when these patients arrive. Advanced life support measures are followed by aggressive supportive care. Comatose patients require rapid bedside glucose, thiamine, and naloxone. Naloxone does not bind to σ-opioid receptors so opioid effects are not reversed and a poor response to naloxone may suggest PCP or ketamine toxicity.

Violent and aggressive behavior may worsen acidosis and hyperthermia, and places patient and staff at risk for injury. Agitation may be attenuated by a darkened room with minimal sensory stimulation, but immediate physical restraint may be necessary to avoid self-harm but chemical restraint should be started as soon as safely possible with intravenous (IV) diazepam (0.1 mg/kg/dose) or lorazepam (0.1 mg/kg/dose). The dose may need to be titrated to effect every 5 to 10 minutes. IV access may be delayed and so haloperidol 5 to 10 mg or droperidol 2 to 10 mg intramuscular (IM) (0.5 mg for children) may be given every 30 to 60 minutes. These are generally effective but butyrophenones may exacerbate hypertonia, as well as the risk of QT interval prolongation and possible torsade de pointes (10) Lorazepam can also be given IM. Phenothiazines are not recommended (may lower seizure threshold, exacerbate hyperthermia, contribute to systemic acidosis, and induce hypotension). Neuromuscular paralysis with

intubation may be necessary in refractory cases of violent psychosis (6).

Seizures should be treated with benzodiazepines: diazepam 0.1 to 0.2 mg/kg/dose IV, lorazepam 0.05 to 0.1 mg/kg IV, or midazolam 0.1 to 0.2 mg/kg IV. Refractory seizures may be treated with phenobarbital 10 to 15 mg/kg IV. Phenytoin is ineffective.

Severe hypertension is generally transient, but if it is symptomatic may be treated with esmolol 0.025 to 0.1 mg/kg/min IV or nitroprusside 2 to 10 μg/kg/min IV. Hyperthermia should be treated with evaporative cooling and sedation, and with chemical paralysis in refractory cases (see Chapter 360 Heat-related illness). Patients with rhabdomyolysis should be given IV saline to restore and maintain adequate urine flow, along with standard management interventions to prevent complicatons.

Activated charcoal can be administered, but is often unpractical because time of ingestion is unknown and the patient is uncooperative. Neither continuous gastric suctioning nor multiple-dose activated charcoal enhance drug clearance or shorten the duration of symptoms (1).

Urinary acidification with ammonium chloride theoretically enhances PCP and ketamine excretion, but does not shorten the duration of toxicity, can worsen acidemia, and may promote renal failure by inducing tubular myoglobin precipitation. Hemodialysis or hemoperfusion do not enhance elimination because of high protein binding and large volumes of distribution.

CRITICAL INTERVENTIONS

- Obtain a core temperature, ABG, and serum CPK to assess for hyperthermia, acidosis, and rhabdomyolysis, respectively, in patients with agitation, psychosis, and seizures.
- Administer IV benzodiazepines or haloperidol for agitation so as to avoid physical restraint.
- Administer IV benzodiazepines and barbiturates for seizures and neuromuscular hyperactivity.

- Treat hyperthermia with evaporative cooling, sedation, and neuromuscular paralysis as needed.
- Administer saline, with or without mannitol and sodium bicarbonate, to patients with rhabdomyolysis.
- Administer IV esmolol or nitroprusside for persistent, symptomatic, or severe hypertension.

DISPOSITION

Patients with a history and examination consistent with drug use and without injury can be sedated and observed, and may be discharged if their condition improves in the ED. Ketamines often resolve in the ED, but PCP patients may need to be admitted for more prolonged observation. Neurosurgical, orthopedic, and trauma consultation may be necessary for physical trauma associated with intoxication. Patients with continued altered mental status after 4 to 6 hours, major trauma, or hemodynamic instability should be transferred to a critical care setting. Patients with persistent psychiatric symptoms after resolution of drug toxicity should be referred to a psychiatrist. All patients should be referred for substance abuse counseling.

Common Pitfalls

- Exposure of healthcare personnel to harm because of inadequate preparation for security, restraint, and sedation.
- Delay in sedation and control of agitation.
- Exclusion of PCP or ketamine intoxication on the basis of a negative drug screen.
- Failure to appreciate that ketamine and dextromethorphan can result in a false-positive PCP on immunoassays.
- Failure to consider the possibility of intracranial hemorrhage and trauma in patients with altered mental status.

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CHAPTER 348

Amphetamines and Stimulants

Michael J. Lynch and Anthony F. Pizon

Sympathomimetic agents represent a wide range of legal and illegal drugs. As the name implies, the physiologic response to these medications is a result of stimulation of the sympathetic nervous system. In therapeutic doses, these medications are used as stimulants, appetite suppressants, attention-deficit hyperactivity disorder (ADHD) therapy, decongestants, and bronchodilators. However, in supratherapeutic ingestions, patients may suffer cardiovascular and central nervous system (CNS) toxicity.

Sympathomimetics are typically divided into direct- and indirect-acting drugs. Direct-acting sympathomimetics (e.g., albuterol) bind postsynaptic receptors, stimulating them directly. Indirect-acting sympathomimetics (e.g., methamphetamine and amphetamine) raise synaptic concentrations of biogenic amines (norepinephrine, epinephrine, dopamine, serotonin) by (a) enhancing transmitter release from presynaptic vesicles, (b) inhibiting neurotransmitter reuptake, and (c) decreasing transmitter degradation. Mixed-acting agents such as dopamine and pseudoephedrine stimulate receptors both directly and indirectly (1).

Several different neurotransmitters may be affected, leading to variation in clinical presentation, therapeutic use, and toxicity. Stimulation of α- and β-receptors by epinephrine and norepinephrine leads to tachycardia and vasoconstriction, and central norepinephrine release leads to anorexia and CNS excitation. Excess dopaminergic stimulation plays a role in the addictive nature

of many of these drugs. Dopamine-mediated glutamate activity coupled with γ-aminobutyric acid (GABA) inhibition leads to seizures as well as "crack dancing," choreoathetoid-movement disorders that occur with acute intoxication (1). Euphoria and altered perception have been attributed to increased serotonin.

"Stimulants and street drugs" were responsible for 65,856 human exposures reported to US poison centers in 2011 and was associated with nearly 6% of all fatalities reported (2). Abuse of both legal and illegal stimulants is a growing problem that will be encountered by emergency physicians.

DRUGS OF ABUSE

Amphetamines are phenylethylamine derivatives, structurally similar to catecholamines, with different enantiomers and chemical substitutions that account for the variety of clinical effects. Amphetamines are a class of drugs that should not be confused with the drug amphetamine, which has a very specific structure and function. Drugs in the class of amphetamines are all based on the phenylethylamine structure. Compared to amphetamine, *methamphetamine* causes more powerful cardiovascular and CNS stimulant effects and *methylenedioxymethamphetamine (MDMA)* also known as ecstasy, is a much more potent serotonergic drug. Amphetamine metabolites also weakly inhibit monoamine oxidase.

MDMA and several of its derivatives are available as oral formulations, and methamphetamine is typically ingested or injected ("crank" or "speed"). Methamphetamine may also be smoked when in its purest crystalline formulation ("ice" or "crystal meth"). Metabolism takes place primarily by the liver cytochrome p450 system with renal elimination. Amphetamines are bases, and the elimination half-life of the drug is dependent upon urine pH, with more rapid elimination in acidic urine. Half-lives range from roughly 5 to 10 hours for MDMA to 12 to 34 hours for methamphetamine (3). These drugs are manufactured illegally and may be significantly contaminated with impurities. Moreover, because of the volatile nature of the chemicals involved in

production of methamphetamine, explosions occurring during their synthesis pose a significant chemical hazard to the public, law enforcement officers, and emergency medical service (EMS) providers.

Cathinone is the active ingredient in khat (*Catha edulis*), a plant that is chewed or brewed into tea in eastern and central Africa and the Middle East for its stimulant effect. In 2009, the United States experienced an explosion of cathinone-derived drugs sold as legal highs and marketed as "*bath salts,*" "plant food," and "stain remover." Though largely made illegal on either the state and/or federal level, cathinones are still widely abused with similar chemical structure to methamphetamine and MDMA. Commonly abused cathinone derivatives include mephedrone, methcathinone, and methylenedioxypyrovalerone (MDPV).

PHARMACEUTICALS

Prescription amphetamines used to treat ADHD, including methylphenidate and amphetamine/dextroamphetamine, are widely abused. Much of this abuse is related to the fourfold increase in amphetamine prescriptions since the late 1980s, leading to greater availability (4), so that 15% of 12th graders admit to their illicit use. These medications have effects and pharmacokinetics similar to those of methamphetamine but are significantly less potent. Selegilene, a monoamine-oxidase inhibitor (MAOI) used in the treatment of Parkinson disease, is metabolized to L-methamphetamine, but there are no reports of overdose.

Phentermine, diethylpropion, and mazindol are centrally acting stimulants that have direct anorectic effects. These drugs are available as schedule IV prescription weight loss drugs. Fen-Phen, which contained phentermine in combination with the serotonergic drug fenfluramine, was voluntarily taken off the market because of its association with valvular heart disease and primary pulmonary hypertension.

Oral and topical decongestants, as well as some weight loss drugs, act via direct and indirect effects at α- and/or β-adrenergic

receptors to induce vasoconstriction and decreased localized edema. *Phenylephrine* is a potent direct $\alpha_{1,2}$-receptor agonist while phenylpropanolamine is a direct- and indirect-acting $\alpha_{1,2}$ agonist. Toxicity of these medications includes hypertension with reflex bradycardia caused by the lack of β-adrenergic stimulation. *Ephedrine* and its less potent *d*-isomer, *pseudoephedrine,* are both direct and indirect-acting $\alpha_{1,2}$- and $\beta_{1,2}$-adrenergic–receptor agonists. Consequently, toxicity consists of both tachycardia and hypertension, as seen with other sympathomimetic stimulants. CNS stimulation and seizures are also reported with these classes of decongestants. Because of its association with intracranial hemorrhages, *phenylpropanolamine* was removed from the market by the FDA (5). The sale of ephedrine, although not illegal, has also been restricted in many states because of its abuse potential and reported toxicity.

Another class of decongestants is the *imidazolines* (oxymetazoline, tetrahydrozoline, and naphazoline). Typically, the imidazolines are used as topical decongestants in nasal sprays and eye drops, but they can cause systemic toxicity. These drugs are central and peripheral α_2-agonists like clonidine and therefore lead to peripheral α-mediated adrenergic symptoms, including hypertension with reflex bradycardia, followed by centrally mediated sympatholysis, bradycardia, and hypotension. CNS and respiratory depression caused by central α-agonism can also occur. See Chapter 322.

Prescription sympathomimetics also include β_2-agonists such as *albuterol, salmeterol, and terbutaline.* These medications are used to treat asthma and bronchospasm but are rarely abused. Nevertheless, in therapeutic and supratherapeutic doses, these drugs may lead to supraventricular or sinus tachycardia, increased inotropy, and hypotension secondary to β-agonism without α-agonism. Other toxic effects include hypokalemia, rhabdomyolysis, nausea, and vomiting. *Clenbuterol,* a long-acting β_2-adrenergic agonist, is abused as a performance-enhancing drug as well as used as an adulterant in heroin (6). Heroin overdoses that present with tachycardia,

hypotension, and hypokalemia are suggestive of clenbuterol exposure.

HERBAL SUPPLEMENTS

Herbal supplements are extremely popular adjuncts for weight loss regimens in the United States. *Ma huang,* a Chinese herbal supplement, contains ephedra alkaloids that comprise six different sympathomimetic amines, including ephedrine and pseudoephedrine. Because of the incidence of significant cardiovascular toxicity, including stroke, cardiac arrest, and MI, the sale of ephedra was banned in 2005 (7). As a result, many herbal supplements have been reformulated to include bitter orange extract (*Citrus aurantium*), which contains synephrine, an isomer of the direct-acting α-agonist phenylephrine. Cases of variant angina, cerebral ischemia, and compartment syndrome with rhabdomyolysis and renal failure have been reported in association with synephrine use (8). A careful history, including over-the-counter medications and herbal supplements, must be taken in patients with suspected sympathomimetic toxicity.

CLINICAL PRESENTATION

Patients presenting to the ED with acute sympathomimetic toxicity typically display tachycardia, hypertension, diaphoresis, and hyperactivity. Pupils may be normal or dilated. Some patients exhibit psychotic behavior. Tremor and hyperreflexia can progress to seizures. In cases of severe toxicity, hypertension can lead to cerebral ischemia or intracerebral hemorrhage (7). Because the hypertension is usually acute, it can cause neurologic injury at pressures lower than those typically seen in patients with chronic hypertension; this is presumably caused by the lack of autoregulatory mechanisms. Sustained increases in muscle activity and seizure may result in rhabdomyolysis with significant elevation in creatine kinase (CK) and myoglobinuric renal failure. Patients with continued untreated muscle activity are at risk for severe metabolic acidosis and hyperthermia. Hyperthermia is a late and

ominous finding in patients suffering from sympathomimetic toxicity.

Common mental status changes include euphoria, agitation, psychosis, anxiety, and confusion. These changes are usually related to the expected drug effects, but other causes such as intracranial hemorrhage, ischemia, or cerebral edema must be considered. Hyponatremia related to markedly increased free water intake and elevated antidiuretic hormone (ADH) levels may be seen in patients who have been "clubbing" or "raving" (3). Bruxism, or jaw clenching and teeth grinding, occurs with MDMA (ecstasy) ingestion (3).

Amphetamine and other sympathomimetics have been associated with acute myocardial infarction (MI), supraventricular and ventricular tachydysrhythmias, and cardiomyopathy with heart failure in a variety of age groups (3,7). Myocardial ischemia is thought to be related to vasospasm rather than occlusive disease. Chronic use of sympathomimetic drugs, even in therapeutic doses, has led to elevations in blood pressure and heart rate. Long-standing amphetamine abuse has also been associated with vasculitis that is responsive to treatment with immunosuppressants.

Sympathomimetic drug use and abuse can cause significant toxicity, disability, and death. Recognition of the disease process and rapid and aggressive treatment are necessary to prevent progression of symptoms.

DIFFERENTIAL DIAGNOSIS

Sympathomimetic toxicity should be considered in any patient with some or all of the clinical findings described previously. In particular, young patients with intracerebral hemorrhage, myocardial ischemia/infarction, arrhythmia, severe hypertension, or altered mental status should be interviewed with particular emphasis on legal and illegal drug use. However, a variety of toxicologic and organic disease processes may produce similar signs and symptoms. Toxicity from anticholinergic agents, cocaine, phencyclidine, MAOI interactions, and serotonin syndrome may

produce a similar clinical picture. Classically, anticholinergic toxicity has dry skin while the skin with sympathomimetic symptoms should be clammy. Withdrawal syndromes, as seen with alcohol, clonidine, γ-hydroxybutyrate (GHB), or sedative–hypnotics, should also be considered.

The differential diagnosis of sympathomimetic toxicity also includes thyroid storm, pheochromocytoma, infection, nondrug-induced intracerebral hemorrhage, ischemic stroke or seizure, brain tumor, MI, aortic dissection, and psychiatric disease.

ED EVALUATION

The initial evaluation should focus on the vital signs. The sympathomimetic poisoned patient develops tachycardia, hypertension, and hyperthermia. Hyperthermia is the most important determinant of mortality, and accurate temperature measurement should be a priority. An axillary temperature is not adequate for these patients, and a rectal or esophageal measurement is best. Once the vital signs have been addressed, a neurologic assessment is paramount. Hallucinations, agitation, dystonias, and seizures are noted in some patients. Choreoathetosis from excessive dopamine stimulation in the basal ganglia is often referred to as "crack dancing" but is seen with other sympathomimetic drugs. "Bath salts" commonly present with agitation and aggression, and symptoms may be prolonged after the abuse of long-acting cathinone derivatives like MDPV. The exact constellation of findings depends upon the specific sympathomimetic drug involved.

Laboratory testing includes electrolytes, blood urea nitrogen (BUN), creatinine, total CK, and urinalysis. These tests are important for the assessment of hydration, hyponatremia from excessive hypotonic water intake during periods of excessive drug abuse, rhabdomyolysis, and signs of acute kidney injury from myoglobinuria. An electrocardiogram (ECG) and troponin may be helpful with chest pain, to measure QRS and QTc intervals for potential ventricular dysrhythmias and along with continuous monitoring, to monitor response to treatment. Additionally, QRS

and QTc interval evaluation is critical to identifying potential for ventricular dysrhythmias and response to treatment. A head computed tomography (CT) scan may be helpful, if there are signs of trauma or intracranial hemorrhage, but is likely to be of low yield in most patients. A urine drug screen (e.g., EMIT assay) is not considered a useful diagnostic test. A negative amphetamine screen on an EMIT assay does not eliminate a sympathomimetic as the cause of symptoms, because many sympathomimetic drugs do not produce positive tests. Similarly, a positive test does not mean the patient took an amphetamine or amphetamine-like drug immediately prior to arrival, because an amphetamine screen may remain positive for days after drug use. Clinical suspicion for sympathomimetic poisoning should be based on history and physical examination.

KEY TESTING

- Immediately obtain vital signs with an emphasis on an accurate temperature.
- Electrolytes, BUN, creatinine, and total CK are used to evaluate for hyponatremia, dehydration, acute kidney injury, and rhabdomyalysis.
- An EKG is useful for the evaluation of dysrhythmias or cardiac ischemia.

ED MANAGEMENT

The initial management of sympathomimetic poisoning should focus on treatment of the vital signs. Because hyperthermia is the most important determinant of mortality, aggressive cooling should be initiated early. Any elevation in temperature should be taken seriously, and a reasonable goal is to reduce temperature to below 38°C. Because hyperthermia is a result of excessive muscle contraction or shivering, sedation or even paralysis should precede cooling measures for cooling to be more effective (see Chapter 360).

Chemical sedation treats hyperthermia and is also an effective treatment of other vital-sign abnormalities (e.g., tachycardia and

hypertension) and agitation. Benzodiazepines are the best first-line agents in these cases. Benzodiazepines should be quickly titrated to the point of making the patient noticeably comfortable; when used by themselves, they rarely result in airway compromise. In addition, benzodiazepines treat possible seizures and other syndromes that may be included in the differential diagnosis (e.g., GABA-agonist withdrawal or other drug-induced delirium). Reasonable intravenous (IV) adult starting doses are diazepam 5 to 10 mg or lorazepam 2 to 4 mg every 5 to 10 minutes. Besides benzodiazepines, sympathomimetic-induced delirium may also benefit from haloperidol (9). Antipsychotics like haloperidol or droperidol antagonize central dopamine receptors and may offer additional benefit by a mechanism distinct from that of benzodiazepines. In particular, choreoathetosis associated with sympathomimetic poisoning will disappear after antipsychotic administration. Antipsychotics should be used with caution, because they can lower the seizure threshold, can lead to dysrhythmias from QT prolongation, and may alter temperature regulation. Haloperidol 5 mg IV, with increasing doses every 20 minutes, can be an effective addition to benzodiazepines.

At times, agitation and aggression may be prolonged and difficult to manage with benzodiazepines and antipsychotics. This is most commonly observed in patients who abuse “bath salts.” In these circumstances, pharmacotherapy should be rapidly titrated but under these extreme presentations, appropriate management includes intubation and use of general anesthetics like propofol (Diprivan).

Hypertension is usually controlled by sedatives alone. However, when additional treatment is needed, nitroglycerin (5 to 400 μg/min IV), phentolamine (5 to 15 mg IV every 20 minutes), and nitroprusside (0.25 to 10 μg/kg/min) are good adjuncts. It is difficult to specify a target blood pressure for treatment, but a pressure $<$180/110 mm Hg is generally recognized as a reasonable goal while avoiding overtreatment. If there is evidence of hypertensive encephalopathy or intracranial hemorrhage, more aggressive treatment may be necessary. β -Blockers should be

avoided. Paradoxical hypertension may result from blockade of β_2-mediated vasodilation and unopposed α_1-adrenergic vasoconstriction. Coronary artery vasospasm has been noted when propranolol is used after cocaine administration in human volunteers (10).

Rhabdomyolysis requires aggressive fluid resuscitation, with a target urine output of 1 to 2 mL/kg/hr. Sympathomimetic-poisoned patients are often volume depleted, and routine fluid administration is good practice in this population.

Gastrointestinal (GI) decontamination is rarely of benefit. In patients who present after the onset of symptoms, activated charcoal administration is not expected to be helpful. The exception is in "body stuffers." Patients who have ingested poorly packaged stimulants to hide contraband from the police may benefit from activated charcoal because they may be subject to absorption (often erratic) of the drug. Body stuffers who present before the onset of symptoms should routinely receive activated charcoal. Other forms of GI decontamination are not routinely recommended for this patient population. "Body packers" are smuggling well-packaged stimulants and are treated differently.

CRITICAL INTERVENTIONS

- Measure the temperature in a timely manner in patients with agitation, hyperactivity, seizures, and abnormalities of other vital signs.
- Rapidly sedate and cool patients with hyperthermia while instituting core body temperature monitoring.
- Use benzodiazepines to treat hyperthermia, hypertension, and tachycardia from sympathomimetic poisoning.

DISPOSITION

Because the duration of toxicity is often brief, patients with mild signs or symptoms may be monitored in the ED. Observation and monitoring of vital signs is advised for a minimum of 6 hours or until symptoms abate. Patients with persistent headache or

neurologic signs may require a head CT scan. Patients with persistent CNS stimulation or vital-sign abnormalities should be admitted to an intensive care unit. The most ill patients, who present with hyperthermia, often require prolonged hospitalization for treatment of rhabdomyolysis and the associated renal failure. However, most cases require only short hospital stays for benzodiazepines, IV fluids, and monitoring of vital signs.

Common Pitfalls

- Failure to consider sympathomimetic toxicity in the differential diagnosis of tachycardia, hypertension, intracranial hemorrhage, and cerebral or myocardial ischemia.
- Failure to appreciate that headache, even without focal neurologic signs, may be the result of intracerebral hemorrhage.
- Failure to identify hyponatremia as a cause of cerebral edema and altered mental status.
- Failure to obtain a CK to check for rhabdomyolysis in patients with agitation and hyperthermia.
- Failure to appreciate that bradycardia in patients with hypertension as a result of sympathomimetic abuse is a normal reflex response. Treating bradycardia with atropine in this situation could aggravate hypertension.

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PART 10 • MISCELLANEOUS AGENTS AND CONDITIONS

CHAPTER 349

Biologic Warfare Agents

Jeffrey R. Suchard

Biologic weapons are microorganisms or toxins derived from microorganisms that are intentionally used to cause death, disability, or damage to humans, animals, or plants. Although small-scale biologic warfare (BW) has been practiced since antiquity, it is only in the past several decades that such weapons could be mass-produced and have the potential to cause widespread casualties. Even limited releases of BW agents can have major public health impact, causing widespread fear and affecting far more than simply the medical disease, as with the 2001 outbreak from anthrax spore-contaminated mail (1). Biologic weapons may hold particular appeal to terrorists, because the investment is less than for other weapons of mass destruction, although the potential morbidity and mortality remain high.

BW agents fall into three general categories: (1) bacteria, (2) viruses, and (3) toxins. The first two categories are infectious agents, although these diseases are now rarely encountered in clinical medicine (e.g., anthrax, plague, Q fever, viral equine encephalitis) or no longer occur naturally (e.g., smallpox). Although most of the diseases caused by infectious BW agents cannot be contracted by interaction with the patient, some (e.g., pneumonic plague, smallpox, viral hemorrhagic fevers [VHFs]) are able to cause secondary casualties, necessitating careful precautions and patient isolation to prevent uncontrolled outbreaks. Toxins are not transmissible, because they cannot reproduce, effectively making them chemical weapons from a biologic source.

The most efficient method of producing mass casualties from BW agents is by aerosol inhalation. The ideal aerosol particle size to promote deposition in the respiratory tract is 1 to 5 μm, which corresponds to the size of individual bacteria or spores and would not be detectable by sight, smell, or taste. A likely scenario following BW-agent exposure would be an epidemic of persons with a nonspecific acute respiratory syndrome (i.e., fever and cough).

Although chemical weapons produce acute symptoms within minutes to hours, the effects from BW agents may take many hours, days, or sometimes weeks to manifest, depending on the incubation period of the agent. Thus, the epidemic curve of case incidence will be more difficult to detect than for chemical weapons, as patients will present less tightly clustered in time and location. An obvious ploy to avoid early detection would be to release an agent causing an endemic infection (or disease resembling an endemic infection) during its season of peak incidence. For example, in areas where bubonic plague is endemic, an intentional release of *Yersinia pestis* may elude detection until many more cases develop. Similarly, the early symptoms of inhalational anthrax could easily be missed during influenza season, and it might not be until an unusually high morbidity was evident that a biologic weapon's attack was suspected. On the other hand, even a single case of smallpox or a VHF in a nonendemic area would immediately raise suspicion of a BW attack.

High-risk potential BW agents include smallpox, anthrax, plague, botulism, tularemia, and several hemorrhagic fever viruses. These agents are easily disseminated or transmitted from person to person, cause high mortality with the potential for major public health impact, and may cause panic and social disruption requiring special action for public health preparedness. Moderate-risk agents include Q fever, brucellosis, the equine encephalitis viruses, ricin, and staphylococcal enterotoxin B. Although other biologic agents could potentially be used as weapons, this chapter will focus on agents of greatest concern for causing mass casualties.

ANTHRAX

Bacillus anthracis is a spore-forming gram-positive rod. Anthrax spores are found in the soil in many parts of the world and mostly cause disease among grazing animals. Human anthrax generally occurs in farmers, ranchers, and among workers handling animal carcasses, hides, hair, and bones. Different clinical forms of anthrax occur depending on the route of exposure. (1) Cutaneous anthrax occurs from direct inoculation of spores into the skin via abrasions and accounts for approximately 95% of human cases. (2) Gastrointestinal anthrax follows the ingestion of insufficiently cooked meat of infected animals. (3) Inhalational anthrax occurs after exposure to aerosolized spores. The inhaled spores are taken into the lymphatic system, where they germinate, reproduce, and cause swelling of the mediastinal lymph nodes. Although this form of anthrax is very rare, it is closely associated with occupational exposures called woolsorter's disease. Inhalational anthrax is the most likely form of a BW attack, because the spores would be most effectively disseminated by aerosol. In the 2001 anthrax attack in the United States, 11 cases were inhalational (all five fatalities were in this group), and 12 were cutaneous (2).

PLAGUE

Y. pestis is the gram-negative bacillus that causes plague. Like anthrax, plague occurs in different clinical forms. (1) Bubonic plague is the most common naturally occurring form of the disease, transmitted from the bites of infected fleas. (2) Pneumonic plague may be secondary to septicemia during cutaneous plague seeding the lungs, or it may occur primarily from the inhalation of infected respiratory droplets or an intentionally disseminated BW aerosol. Primary pneumonic plague would be the expected form of the disease from an aerosol BW agent release and should occur in the absence of bubonic plague (3).

TULAREMIA

Francisella tularensis is a small, aerobic, gram-negative coccobacillus. Tularemia may occur in (1) ulceroglandular or (2) typhoidal forms, depending on the route of exposure. Ulceroglandular tularemia is

more common, occurring after skin or mucous membrane exposure to infected animal blood or tissues. Exposure to aerosolized bacteria may result in typhoidal tularemia with prominent respiratory symptoms (4).

SMALLPOX

Variola, the virus that causes smallpox, is a large DNA-bearing orthopoxvirus with a host range limited to humans. Naturally occurring smallpox was eradicated by a global vaccination campaign in the 1960s and 1970s, yet stocks of the virus still remain in labs in the United States, Russia, and possibly elsewhere. Smallpox remains a significant potential BW threat, because a large portion of the current population has not been immunized and the degree of immunity conferred by remote vaccination is not clear. Transmission occurs through inhalation of droplets or aerosols but may also occur through contaminated fomites (5).

VIRAL HEMORRHAGIC FEVERS

Several diverse RNA viruses produce VHF, an acute febrile illness with increased vascular permeability that cause bleeding manifestations in the more severely affected. The VHF agents of greatest concern are those that may be intentionally disseminated by an aerosol route; these include the Marburg, Ebola, and Hanta viruses and those causing Lassa fever, yellow fever, Rift Valley fever, and Crimean-Congo hemorrhagic fever (6).

BOTULISM

Botulinum toxin would most likely be disseminated through food contamination or by aerosol. Either method would result in the clinical syndrome of botulism (see Chapter 352) (7). Rarely, inhalation botulism from laboratory accidents has occurred.

Several clinical syndromes may occur from exposure to BW agents. Because inhalation of an aerosol is a likely method of exposure, development of an acute respiratory syndrome is common to many agents. Other syndromes include influenza-like illnesses, cutaneous lesions or ulcerations, fever with lymphadenopathy or arthralgias,

acute neurologic syndromes (with or without fever), and hemorrhagic diathesis. An individual case of illness from BW agent exposure may be very difficult to detect, because many commonly occurring diseases also fit into such clinical syndromes. It is quite likely that a BW agent attack will be detected by the presence of an unusual epidemiologic curve, when a cluster of patients with unusual findings or with a fulminant clinical course present within a short period of time.

CLINICAL PRESENTATION

The clinical presentation of patients exposed to BW agents will obviously vary depending on the agent.

Cutaneous anthrax results in a black eschar with significant surrounding edema at the site of skin entry. Most lesions will heal spontaneously, although 10% to 20% of untreated cases progress to septicemia and death. Cutaneous anthrax fatalities are rare with antibiotic therapy. Gastrointestinal anthrax causes nausea, vomiting, fever, abdominal pain, and mucosal ulcers, which can cause hemorrhage, perforation, and sepsis; mortality is high (2).

Inhalational anthrax has an incubation period of one to six days. Patients then develop fever, malaise, fatigue, nonproductive cough, and mild chest discomfort. Symptoms may abruptly progress to severe respiratory distress with dyspnea, diaphoresis, stridor, and cyanosis. Bacteremia, shock, metastatic infection (meningitis occurs in approximately 50% of cases), and death follow within 24 to 36 hours. Inhalational anthrax is a mediastinitis, rather than a pneumonia. Chest radiography and computed tomography typically show mediastinal widening and pleural effusions, although pneumonic infiltrates are also reported (2).

Historically, the mortality rate from inhalational anthrax was nearly 100% once symptoms develop, even with antibiotics. Experience from the 2001 outbreak in the United States shows that over half of the patients with inhalational anthrax survived with aggressive supportive care and antibiotic therapy. Earlier hospitalization appeared to correlate with improved outcome (1).

Bubonic plague has an incubation period of 2 to 10 days preceding the onset of fever, malaise, and painful, enlarged regional lymph nodes (buboes). Septicemia may occur and can be accompanied by disseminated intravascular coagulation (DIC) and acral gangrene. Necrosis of the digits and nose seen with septicemic plague is a likely origin of the term “black death” (3).

Pneumonic plague has an incubation period of two to three days. The onset of disease is acute and often fulminant. Patients develop fever, malaise, and cough productive of bloody sputum, rapidly progressing to dyspnea, stridor, cyanosis, and cardiorespiratory collapse. Plague pneumonia is almost always fatal unless treatment is begun within 24 hours of symptom onset.

Ulceroglandular tularemia is characterized by local skin ulceration and associated lymphadenopathy, fever, chills, headache, and malaise. Typhoidal tularemia presents with fever, prostration, and weight loss without adenopathy. Exposure to aerosolized bacteria should result in typhoidal tularemia with prominent respiratory symptoms like a nonproductive cough and substernal chest discomfort. Chest radiographs may show infiltrates, mediastinal lymphadenopathy, or pleural effusions. A temporarily incapacitating infection is most likely (4), but fatalities may occur.

Smallpox has a 12- to 14-day incubation period. Initial symptoms include fever, malaise, and prostration with headache and backache. Oropharyngeal lesions appear first, shedding virus into the saliva. Two to three days after the onset of fever, a papular rash develops on the face and spreads to the extremities. The fever continues as the rash becomes vesicular and then pustular. The pustules scab over and eventually separate, leaving pitted and hypopigmented scars. The mortality rate of smallpox can be as high as 30%, with death most commonly occurring during the second week of the illness (5).

VHF is characterized by fever, malaise, prostration, and hemorrhagic rash. Clinical features, such as the extent of renal, hepatic, and hematologic involvement, vary according to the agent involved. Mortality rates also vary, from $<1\%$ for Rift Valley fever up to 50% to 90% for the ebola virus (6).

Botulism results in multiple bulbar nerve palsies and a symmetric descending paralysis, with death occurring from respiratory failure (see Chapter 352). Onset of symptoms can occur within 24 to 36 hours or take several days (7).

DIFFERENTIAL DIAGNOSIS

Familiarity with the expected clinical syndromes produced by BW agents will aid in the differential diagnosis. An acute respiratory syndrome with fever may occur with inhalational anthrax, pneumonic plague, Q fever, hantavirus, and exposure to several other bacterial, viral, and fungal agents, as well as several common, endemic respiratory tract infections (e.g., influenza, the common cold, bronchitis, and community-acquired pneumonia). Patients with inhalational anthrax are more likely to have nausea or vomiting, tachycardia, elevated transaminases, low sodium levels, high hematocrit, low albumin levels, and normal white blood cell counts than those with influenza-like illnesses and community-acquired pneumonia, and patients with an influenza-like illness are more likely to have myalgias, headache, and nasal symptoms (8). The presence of pulmonary infiltrates on chest radiographs does not rule out inhalational anthrax, although anthrax patients are likely to also have an enlarged mediastinum and pleural effusions.

Agents producing cutaneous lesions include anthrax, plague, smallpox, tularemia, and many of the VHFs. Experience from the 2001 outbreak shows that cases of cutaneous anthrax may occur amidst other cases of inhalational anthrax. Small pustules or skin lesions may be found at the site of flea bites in cases of plague, whereas petechial rashes are common with VHFs. The individual lesions of smallpox closely resemble those from herpesvirus infections like chickenpox. Smallpox lesions will all be at the same stage of development, and they are found mostly in a centrifugal distribution (i.e., hand, feet, and face), in distinction from the typical centripetal pattern (chest and abdomen predominance) of chickenpox with patches of lesions at various stages of development.

An acute neurologic syndrome with fever suggests disease from a viral equine encephalitis, although other viral and bacterial BW

agents (Q fever, smallpox, typhus) may also have prominent headache, photophobia, and myalgias. A neurologic syndrome without fever from BW agents is likely to be as a result of botulism or other preformed toxins such as domoic acid, saxitoxin, or tetrodotoxin.

Botulism may resemble several other neurologic diseases, including myasthenia gravis, Guillain–Barré syndrome, tick paralysis, poliomyelitis, and organophosphate poisoning. Individual cases of such diseases occur but are rare so the simultaneous presentation of multiple patients with progressive paralysis should immediately suggest an environmental exposure, either to botulinum toxin or an organophosphate chemical warfare agent.

ED EVALUATION

It is likely that the first few cases will be missed but the best defense for detecting an abnormal pattern is an alert and curious clinician. Historical data to collect that might help the investigation include documentation of the time and place of BW agent exposure and if any other persons were potentially exposed and whether they are symptomatic. The time of onset, nature, progression, and severity of symptoms should be noted. The presence of any visualized suspect material (e.g., an unidentified white powder) should be determined, so that samples may later be taken by the proper authorities. Public health authorities may have to help and determine the exposure pattern and epidemiology. Respiratory precautions should be used by all clinicians when BW is in the differential diagnosis.

Physical examination should focus first on the vital signs and assessment of the patient's cardiopulmonary function and neuromuscular status to determine if emergent resuscitative efforts are necessary. Ideally, all patients should have continuous cardiac and oxygen saturation monitoring, although this may not be possible in a mass-casualty setting. Physical examination should be performed with particular attention to detecting pulmonary rales, diminished breath sounds, the presence and characteristics of any rash, lymphadenopathy, meningismus, and any neurologic deficits.

Patients with pulmonary symptoms should have a chest radiograph, looking for pulmonary infiltrates, mediastinal widening, and pleural effusions. Chest computed tomography was also used in several patients with inhalational anthrax in 2001 (1). Arterial blood gas analysis should also be considered.

Ill patients should have a broad panel of other laboratory tests, which may include a complete blood count, comprehensive metabolic panel, DIC screening, serologies, blood cultures, and Gram staining, depending on the suspected agent and clinical status of the patient. Laboratory personnel should be informed of the suspected pathogen(s). Antibiotic-susceptibility testing should be performed on all bacterial isolates, as strains may be deliberately modified by terrorists to enhance antibiotic resistance. Patients with suspected smallpox should have vesicle fluid from lesions cultured, and scrapings should be sent for electron microscopic analysis. Spirometry and arterial blood gas analysis should be performed on patients with suspected botulism to establish their ventilatory capacity.

Plague can be diagnosed by various staining techniques, immunologic studies, or culturing the organism from blood, sputum, or lymph node aspirate. *Y. pestis* appears as a "safety-pin" bipolar coccobacillus. Chest radiographs in pneumonic plague show patchy or consolidated bronchopneumonia. Leukocytosis with bandemia is common, as are markers of low-grade DIC and elevations of bilirubin and the hepatic transaminases. Diagnosing tularemia is often difficult, as the organism is hard to isolate by culture and the symptoms are nonspecific.

KEY TESTING

- Will vary depending on presenting clinical syndrome, but typically includes:
  - Chest x-ray, if pulmonary symptoms
  - CBC
  - CMP
  - Cultures: blood, sputum, lesion

- Pulmonary function tests (FVC, NIF) if patient has neuromuscular weakness

ED MANAGEMENT

Advanced life-support measures are instituted as necessary for patients requiring resuscitation. Unlike with chemical weapons, patient decontamination is rarely an issue with biologic weapons. Most BW agents, with the notable exception of anthrax spores, are degraded by sunlight and desiccation and do not survive well in the environment for more than 1 to 2 days. In the scenario of a covert BW agent release, by the time patients present for medical care several days after exposure, decontamination is futile and will only delay care. Even with an acute, efficiently dispersed release of a biologic weapon via aerosol (including anthrax spores), little surface contamination is produced. Clothing removal and a soap-and-water shower will remove 99.99% of any remaining organisms on the skin (9), and this may occur in the patients' home to reduce the strain on medical resources. Any grossly visible contamination with a BW agent, if present, should be removed by water irrigation, washing the skin with a sporicidal/bactericidal solution (e.g., 0.5% sodium hypochlorite, a 1:10 dilution of household bleach), and a final water rinse (9). If patient decontamination is performed at a healthcare facility, patients should remove their clothing and place it into sealed and labeled plastic bags, wash their hands, and shower thoroughly with soap and water.

For patients who present with symptomatic illness after a covert attack, decontamination is unlikely to be helpful, but healthcare provider protection is critical. Standard infection-control measures (gloves, gown, mask with eye shield) provide adequate protection from most agents. However, unless the offending BW agent is already known, it must be assumed that the patients have a potentially transmissible disease such as smallpox, pneumonic plague, or a VHF, which require airborne, contact, and droplet precautions. Patients with respiratory symptoms or a rash should be placed in a private negative-pressure room, and medical personnel caring for the patient should wear well-fitting N95 high-efficiency particulate air-filter

masks until the results of a more complete evaluation can guide treatment (9). If multiple casualties present at the same time, space limitations may require that patient isolation occurs in groups rather than individually.

Current treatment recommendations for anthrax rely primarily on ciprofloxacin and doxycycline (2) and are shown in Table 349.1. The currently recommended duration of therapy after bioterrorist exposure to anthrax is 60 days, to protect against the delayed development of inhalational anthrax which might occur.

TABLE 349.1
Antibiotic Treatment of Anthrax, Plague, and Tularemia[a,b]

Condition	Treatment
Cutaneous anthrax or	Ciprofloxacin 500 mg (10–15 mg/kg in children) PO twice daily, or
Postexposure anthrax prophylaxis	Doxycycline 100 mg (2.2 mg/kg in children) PO twice daily
	Amoxicillin 500 mg PO three times daily (80 mg/kg/d PO divided every 8 hrs in children) may be substituted if unable to tolerate other drugs
	Duration of treatment = 60 d with bioterrorism attacks
Inhalational anthrax	Ciprofloxacin 400 mg (10–15 mg/kg in children) IV every 12 hrs, or
	Doxycycline 100 mg (2.2 mg/kg in children) IV every 12 hrs plus one or two additional antimicrobials with in vitro activity against *Bacillus anthracis;* IV treatment initially, then switch to oral when clinically appropriate
	Duration of treatment = 60 d with bioterrorism attacks.
Active plague disease in contained casualty setting	Doxycycline 100 mg (2.2 mg/kg in children) IV every 12 hrs, or
	Ciprofloxacin 400 mg (10–15 mg/kg in children) IV every 12 hrs, or
	Chloramphenicol 25 mg/kg IV four times daily, or
	Streptomycin 1 g (15 mg/kg in children) IM twice daily, or
	Gentamicin 5 mg/kg IV once daily, or 2 mg/kg load and 1.7 mg/kg three times daily (2.5 mg/kg in children)
	Duration of treatment = 10 d
Postexposure plague prophylaxis or mass-casualty setting	Doxycycline 100 mg (2.2 mg/kg in children) PO twice daily, or
	Ciprofloxacin 500 mg (20 mg/kg in children) PO twice daily
	Duration of treatment = 7 d for postexposure prophylaxis; 10 d if disease present
Tularemia	Identical to treatment for plague, except duration of therapy = 14 d

[a]This table includes treatment regimens that are not FDA approved.
[b]References 2, 3, and 4 are adapted with permission from *JAMA* 2001;285:2763–2773; *JAMA*. 2000;283:2281–2290; *JAMA*. 2002;287:2236–2252.
PO, by mouth; IV, intravenous; IM, intramuscular.

Effective vaccines against anthrax are available (10). Anthrax vaccine adsorbed (AVA) is used in the United States, which consists of a sterilized filtrate of an avirulent bacterial strain. As with any vaccine, local reactions to AVA occur in a minority of recipients (up to 20% with mild, local reactions), and self-limited systemic reactions occur even more rarely (<1.5%); serious adverse events are very rare. The dosage schedule for AVA is 0.5 mL subcutaneously at 0, 2, and 4 weeks and 6, 12, and 18 months, with yearly boosters. For emergency use after confirmed exposure, the vaccine is given as

soon as possible and again at 2 and 4 weeks, along with prophylactic antibiotics.

Respiratory droplet precautions are necessary in pneumonic plague until the patient has received antibiotics for at least 48 hours and shows clinical improvement. Antibiotic choices are similar to anthrax, with a high reliance on ciprofloxacin and doxycycline (Table 349.1). Antibiotics must be initiated early after exposure, because waiting for symptoms will result in extremely high mortality (3). Antibiotic treatment for tularemia is virtually the same as for plague (4).

The treatment of smallpox is largely supportive. Persons exposed to smallpox but without clinical disease should also be isolated and observed for the development of fever and rash for 17 days; this observation period may occur at home. The antiviral drug cidofovir may be beneficial in preventing smallpox, if administered early after exposure, but is probably no better than postexposure vaccination (5).

Vaccination before smallpox exposure or within 4 days after exposure significantly ameliorates subsequent illness. Vaccination against smallpox carries some risk for adverse reactions. The two most serious reactions are postvaccinal encephalitis and progressive vaccinia. Postvaccinal encephalitis occurs in about three cases per million primary vaccinees. Forty percent of cases are fatal, and some survivors are left with permanent neurologic sequelae. Progressive vaccinia can occur in immunosuppressed individuals and is treated with vaccinia immune globulin.

Most VHF agents carry the risk of secondary infection through droplet aerosols, and careful patient isolation is critical. Ribavirin has been used for some VHFs, but supportive care is the mainstay of therapy (6).

The mainstay of botulism therapy is supportive care, with ventilation if necessary. An equine antitoxin for passive immunization is available in the United States from the Centers for Disease Control and Prevention (CDC) through contact with local and state health departments. The antitoxin prevents worsening of disease caused by the toxin serotypes responsible for foodborne

illness (A, B, and E) but does not reverse established effects. An investigational heptavalent antitoxin against serotypes A through G has been developed (7).

CRITICAL INTERVENTIONS

- Wear gloves, gown, eye shield, and an N95 high-efficiency particulate air-filter mask when evaluating and treating patients with possible exposure to transmissible BW agents.
- If possible, place patients with respiratory symptoms or a rash in a private negative-pressure room.
- Contact appropriate local public health and law enforcement authorities in cases of suspected BW agent exposure.

DISPOSITION

All cases of suspected exposure to BW agents should be reported to local public health and law enforcement authorities. Unless the patient contracted their illness through unintentional exposure in a research laboratory, each case is potential evidence of a criminal bioterrorist act, requiring contact also with law enforcement agencies such as the local Federal Bureau of Investigation field office. Consultation with a local physician resource familiar with BW agents, such as an infectious disease specialist, military physician, toxicologist, poison control center, or the CDC (770-488-7100) is recommended.

Patients with known or suspected acute exposures to infectious BW agents are likely to be asymptomatic and require no emergent interventions. Such patients require initiation of appropriate postexposure prophylactic antibiotics and/or vaccinations, depending on the agent involved. Asymptomatic patients acutely exposed to anthrax or plague may be discharged home with antibiotic prescriptions, if adequate follow-up can be arranged through the local public health agency or their private physicians.

Patients exposed to smallpox may require quarantine, which should be coordinated with the assistance of public health and law enforcement agencies. Patients acutely exposed to toxin weapons

might be asymptomatic at presentation but still require admission for a period of observation depending on the agent involved. Botulinum toxin exposure, for example, mandates admission to monitor for development of respiratory failure.

Unless part of a mass-casualty incident, all patients known or suspected to have illness from BW agent exposure should be admitted, with the level of care dependent on clinical severity. Outpatient management of cutaneous anthrax may be considered for patients without systemic toxicity, who can tolerate oral antibiotics, and in whom outpatient follow-up can be assured. Isolation precaution will be necessary for patients with pneumonic plague, smallpox, and many of the VHFs. In mass-casualty situations, admission may need to be more selective and reserved for patients who cannot tolerate outpatient therapy but who are not moribund.

Common Pitfalls

- Lack of familiarity with likely BW agents and the clinical syndromes they produce.
- Failure to appreciate that some BW agents are transmissible and others are not and that isolation requirements will vary.
- Failure to institute appropriate postexposure prophylaxis among patients with plausible exposure scenarios.
- Failure to have a plan with established contacts to hospital, local public health, infectious disease and other experts.

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CHAPTER 350 Chemical Warfare Agents

D. Adam Algren and Michael R. Christian

Chemicals have been used to impede, incapacitate, or kill the opposition throughout history. Although international treaties (e.g., 1925 Geneva Protocol, 1997 Chemical Weapons Convention) ban the development, production, stockpiling, and use of chemical weapons, Iraq used both nerve and blistering agents in its war with Iran and against Kurdish civilians in the 1980s. The Russian military used a gas thought to contain a fentanyl derivative and halothane to subdue Chechen rebels in a Moscow theater in 2002 and there is reported use of nerve agents in 2013 against rebels by the Syrian National Army (1).

Of greater concern is that chemical warfare agents (CWAs) may be used by terrorists. CWAs are fairly inexpensive and easy to acquire, synthesize, deploy, and hide. On three occasions, the terrorist group Aum Shinrikyo released nerve agents (sarin and VX) in Japan (2). The Tokyo subway incident in 1995 resulted in 12 deaths and more than 5,000 civilian casualties (2). The 1996 Defense against Weapons of Mass Destruction Act, directed the US Department of Defense to establish preparedness programs of local, state, and federal agencies to respond to chemical and biologic incidents (3) and these became better supported following the September 11, 2001 terrorist attacks.

CWAs can be lethal or nonlethal and fall into one of seven major categories: (a) chemical choking agents, (b) vesicating or blister agents, (c) lacrimating agents, (d) nerve agents, (e) vomiting agents, (f) systemic asphyxiants, and (g) incapacitating agents (Table 350.1)

(4). Lacrimating agents are also used for personal protection and by police for crowd dispersal and incapacitating criminal suspects.

TABLE 350.1
Chemical Warfare Agents

Classification	Military Code	Chemical Name/Common Name
Lethal Agents		
Blood agents	AC	Hydrogen cyanide
	CK	Cyanogen chloride
	SA	Arsenic trihydride/arsine
Choking agents	CL	Chlorine
	CG	Carbonyl chloride/phosgene
	DP	Trichloroethyl chloroformate/diphosgene
Vesicating agents		
Mustards	HD	Bis(2-chloroethyl)sulfide/distilled mustard
Nitrogen mustards	HN-1	2,2-Dichlorotriethylamine
	HN-2	2,2-Dichloro-N-methylethylamine
	HN-3	2,2,2-Trichlorotriethylamine
Arsenicals	MD	Methyldichloroarsine
	PD	Phenyldichloroarsine
	ED	Ethyldichloroarsine
	L	Dichloro(2-chlorovinyl)arsine/lewisite
Oximes	CX	Dichloroform oxime/phosgene oxime
Mixes	HL	None/ML mix (mustard–lewisite mixture)
	HT	None/HT mix (mustard–T mixture)
(Not produced)	Q	4,Bis(methylchloroethyl sulfide)/Q
	T	Bis(2-chloroethyl sulfide)monoxide/T
Nerve agents	GA	Ethyl *N*,*N*-dimethyl phosphoamicocyanidate/tabun
	GB	Isopropyl methyl phosphonofluoridate/sarin
	GD	Pinacolyl methyl phosphonefluoridate/soman
	GF	Cyclohexyl-methyl phosphonofluoridate/cyclosarin
	VR	O-isobutyl S-(2-diethylamino)ethyl methylphosponothioate
	VX	Ethyl S-2-diisopropyl aminoethyl methylphosphonothiolate/VX
Nonlethal Agents		
Vomiting agents	DA	Diphenylchlorarsine
	DC	Diphenylcyanoarsine
	DM	Diphenylaminochloroarsine/adamsite
Lacrimating agents	CA	Bromobenzeneacetonitrile/camite
	CN	2-Chloro-1-phenylethanone/chloroacetophenone
	CNB	None/chloroacetophenone, carbon tetrachloride, benzene mix
	CNC	None/chloroacetophenone chloroform mix
	CNS	None/chloroacetophenone, chloroform, chloropicrin mix
	CR	Dibenz-1,4-oxazepine
	CS	*o*-Chlorobenzlidene malonitrile/CS (tear gas)
	OC	Capsaicin/pepper spray
Incapacitating	BZ	3-Quinuclidinyl benzilate

CWAs can be aerosolized or vaporized and delivered in multiple ways. They may be dispersed from handheld or vehicle-mounted devices, low-flying aircraft, crop dusters, cruise missiles, and artillery. Sarin was dispersed by evaporation from punctured plastic bags left on Tokyo subway cars (2). Although CWAs could be added to water or food supplies, aerosolization is favored by terrorists and military groups as it allows for the greatest exposure with the goal of inflicting the maximum number of casualties (4).

Systemic asphyxiants incorrectly labeled as "blood agents" by the military include the gases cyanogen chloride, hydrogen cyanide (see Chapter 329), and hydrogen sulfide (see Chapter 332), and the hemolytic gas arsine (see Chapter 336) (4). Hydrogen cyanide (prussic acid) and cyanogen chloride are clear liquids with a bitter almond odor that readily volatilize at temperatures $>26^{\circ}$F (1). As warfare agents, their efficacy is limited by physical properties that result in ineffective dispersal (4).

The *choking agents* are pulmonary irritants introduced in World War I and include chlorine, phosgene, and diphosgene (see Chapter 336). Chlorine, a dense, water-soluble, yellow-green gas that smells like concentrated bleach, reacts with tissue water to form hydrochloric acid and oxygen-free radicals, which produce corrosive and cytotoxic effects. Toxicity is proportional to the gas concentration, duration of contact, and water content of exposed mucous membranes.

Phosgene (carbonyl chloride) was probably responsible for more than 80% of all chemical-agent fatalities in World War I (4) and can be formed by decomposition of chlorinated hydrocarbons. It is a colorless gas that is heavier than air. Its propensity to settle into low-lying areas, such as trenches, led to its tactical success. Phosgene smells like freshly mown hay, but odor is not a reliable indicator of exposure. Because of its low water solubility it is only mildly irritating to the eyes and upper respiratory tract and the initial exposure may go unnoticed (4). Phosgene hydrolyzes with terminal bronchial and alveolar mucosal water to produce

hydrochloric acid. This and other toxic by-products of phosgene (e.g., oxygen-free radicals) result in pulmonary edema that can be delayed up to 24 hours. The latency period is shorter with higher concentrations and longer durations of exposure.

Vesicating agents, which cause blistering of exposed surfaces, include mustard gases and organic arsenicals. Sulfur mustard was used in World War I and in the Iran–Iraq war (4). Most injuries were disabling but nonfatal; mortality during World War I was $<2\%$, and rates of 3% to 4% were reported in the Iran–Iraq war (4,5). Street clothing offers no protection, but military protective garments (chemical-resistant suit) can provide up to 6 hours of protection following exposure (6). Low volatility of the liquid results in persistence for several days in temperate climates, thereby restricting enemy use of contaminated equipment and terrain (4).

Sulfur mustard is an oily amber liquid that smells like burning garlic or mustard. Upon tissue contact, it spontaneously forms highly reactive and unstable episulfonium compounds, which irreversibly alkylate nucleic acids and cellular proteins within minutes of exposure (6). This permanently damages DNA and alters or inhibits cell replication, protein synthesis, and enzyme function often leading to cell death. Blisters form after destruction of anchoring filaments in the epidermal–dermal junction (6).

Lewisite, the best known organic arsenical, was developed in 1918 to complement sulfur mustard as a semipersistent blistering agent. Its vapor is about seven times heavier than air and will flow into lower terrain (4). It has low water solubility and persists in the environment for up to 24 hours under temperate conditions. Many countries have large stockpiles of lewisite, but its actual use in combat is not well documented (4).

Lewisite is an amber, oily liquid that smells like geraniums. It is rapidly absorbed after vapor inhalation and, as a result of high lipid solubility, penetrates intact skin within 15 minutes, more rapidly than mustard agents (4). In the dermis, it hydrolyzes to hydrochloric acid and chlorovinylarsenious oxide, the vesicating agent. The organic arsenical moiety binds to the dithiol component of pyruvate dehydrogenase, prevents formation of acetyl coenzyme A from

pyruvate, and produces systemic toxicity similar to other arsenicals (see Chapter 326). Increased capillary permeability and extensive interstitial fluid losses may result in hypovolemia or "lewisite shock" (4).

Nerve agents are similar in structure and function to organophosphorus pesticides (see Chapter 318) but are more potent and typically have a more rapid onset and shorter duration of action. The "G" (German) agents tabun (GA), sarin (GB), and soman (GD) were developed in Germany between 1936 and 1944 (4,7). A fourth, VX, with the "V" standing for "viper," was synthesized in 1952 in England (4,5). Although commonly referred to as gases, these agents are colorless, odorless liquids that under temperate conditions form vapors are heavier than air and concentrate close to the ground (4,7). Lethality correlates directly to the product of vapor concentration and time of exposure (LCt) (4,7). The G agents are moderately volatile, evaporate within several hours, and are environmentally nonpersistent (7,4). VX, an oily liquid, is much less volatile and persists for several weeks after dispersion (4). It is the most potent nerve agent, with an LCt_{50} (vapor concentration–time product necessary to kill 50% of an unprotected population) that is 5, 10, 40, and 500 times more potent than soman, sarin, tabun, and hydrogen cyanide, respectively (4,7). VX also has a slower rate of elimination than G agents and is expected to have a longer duration of action. In addition to inhalational exposures nerve agents can also be absorbed through the skin due to their high lipid solubility. Time of onset and severity are determined by the dose, agent, and skin integrity/location (4,7).

Toxicity of *nerve agents* results primarily from phosphorylation and inactivation of acetylcholinesterase (AChE) at its hydroxy group in its serine active site (see Chapter 318). AChE accumulates at nerve terminals, initially stimulating and then paralyzing cholinergic neurotransmission at both central and peripheral nicotinic and muscarinic receptors. Once inactivated, the phosphorylated AChE enzyme may be permanently inhibited or it may be reactivated by nucleophilic oximes to end the nerve gas

effect. Reactivation is impossible once dealkylation (“aging”) of the phosphorylated cholinesterase occurs. The rate of aging varies among the nerve agents. It occurs within 2 minutes after soman exposure making it difficult to treat, 5 to 8 hours after sarin exposure, and more than 40 hours after tabun or VX exposure (4,7).

Other mechanisms likely contribute to effects on central nervous system (CNS) neurotransmission that result in seizures and CNS neuropathology. This likely explains why some compounds that are neuroprotective do not reactivate AChE and why CNS-active oximes (e.g., pralidoxime) are not more effective than oximes that do not reach the brain.

Vomiting agents are arsenic-based compounds used for riot control (4). They are normally solids that are vaporized by heating and then condense to form aerosols that produce rapid irritation of exposed tissues.

Lacrimating, or riot-control, agents, include *o*-chlorobenzylidenemalonitrile (CS or tear gas), ω-chloroacetophenone (CN or mace), dibenz-1,4-oxazepine (CR), and oleoresin capsaicin (OC or pepper spray). Except for capsaicin, toxicity results from alkylation and inhibition of sulfhydryl-containing enzymes. Generation of bradykinin also contributes to their toxicity. Capsaicin is a lipid-soluble alkaloid that first stimulates release of substance P from nociceptive neurons and then blocks its synthesis and transport. Substance P depolarizes neurons to produce dilatation of blood vessels, stimulation of smooth muscle, and activation of sensory nerve endings that mediate pain. With repeated application, nociceptive fiber response and number are decreased (desensitization).

CN and CS are usually delivered as a vapor or cloud of suspended solid particles (smoke) produced by a thermal grenade. CS is the riot-control agent of choice in the United States. It is about 10 times more potent as a lacrimator than CN but is much less corrosive to tissues (6,7). Newer CS formulations consist of an unheated micropulverized powder that can remain active in the environment for several weeks. OC is used frequently by civilians for personal protection and by law-enforcement personnel for immobilization of

combative subjects. “Pepper mace” can contain CS, oleoresin of capsicum, or both.

Incapacitating agents include stimulants (e.g., amphetamines), depressants (e.g., opioids), psychedelics (e.g., d-lysergic acid diethylamide, LSD), and deliriants (e.g., anticholinergics) (4). Historically, the anticholinergic agent 3-quinuclidinyl benzilate (BZ) was the only incapacitating agent considered feasible for use by the US military (4). BZ is a potent, glycolate, anticholinergic agent that is a crystalline solid under normal atmospheric conditions but most likely dispersed as a vapor or liquid aerosol by military personnel or terrorists (4). Although ultrapotent fentanyl derivatives (alfentanil, carfentanil, remifentanil, and sufentanil) show some promise, these agents have unpredictable effects as a result of high lipid solubilities and large volumes of distribution (1). The unpredictable nature of these agents is evidenced by the tragic end to the October 2002 Moscow hostage crisis in which 127 of 800 hostages died from a fentanyl-halothane gas intended to incapacitate its victims (1).

CLINICAL PRESENTATION

Choking Agents

Clinical symptoms begin within minutes after significant chlorine exposure and include lacrimation, conjunctival irritation, rhinorrhea, cough, sore throat, chest burning, dyspnea, sputum production, nausea, headache, and respiratory failure. Corneal abrasions and cutaneous burns may result from eye and skin exposure, respectively. Following significant chlorine exposures, pulmonary edema develops within 2 to 4 hours and peaks at 12 to 24 hours (4). The chest x-ray may be normal or may show noncardiogenic pulmonary edema. Patients with significant phosgene exposure have a typical latency period of 4 to 6 hours (range, 1 to 24 hours) and then present with dyspnea, chest tightness, cyanosis, hemoptysis, hypotension, and pulmonary edema. Chest x-ray findings of pulmonary edema are rather late and nonspecific, occurring 6 to 8 hours after exposure. Following significant pulmonary agent exposure (e.g., chlorine gas), patients

may subsequently develop reactive airways dysfunction syndrome, a chronic asthma-like condition.

Vesicating Agents

After mustard exposure, there is typically a latency period of 4 to 12 hours before the onset of symptoms. The latency period is shorter with high concentrations and long exposures, with increased ambient temperature and humidity, and in victims previously exposed to or innately susceptible to mustard (4,6). Sites of injury principally involve the skin, eye, and respiratory tract and may follow vapor or liquid exposure. Heavy exposure may lead to systemic effects such as bone marrow depression and sloughing of intestinal mucosa.

Cutaneous injury resulting from mustard exposure ranges from erythema to blisters and skin necrosis. The moist, thinner skin of the neck, axilla, and groin is more severely affected. After of 4 to 12 hours, erythema and edema develop. Vesication typically starts within 24 hours and evolves over several days. Vesicles coalesce into blisters, and skin necrosis occurs over 24 to 72 hours (4). Blister fluid does not contain active mustard and is not toxic (4). Skin denudation occurs over 6 to 9 days, and healing may take 4 to 10 weeks.

The eye is the organ most sensitive to sulfur mustard. Tissue injury occurs rapidly, but symptoms develop gradually over 4 to 8 hours and include eye pain, lacrimation, photophobia, and blurred vision (4,6). Physical findings include blepharospasm, eyelid edema, conjunctival injection and edema, chemosis, anterior chamber cellular infiltrates, and decreased vision. Corneal edema begins within 1 hour after exposure, and the corneal epithelium vesicates and sloughs within 4 to 36 hours (4). Resolution of injury depends on the severity of exposure and typically takes 1 to 2 weeks. About 90% of victims are visually disabled for 10 days with conjunctivitis, photophobia, and corneal swelling. The remaining 10% are severely affected and are at risk for permanent blindness from corneal opacification, scarring, and ulceration (4).

Respiratory epithelial damage occurs several hours after exposure. Victims may develop rhinitis, nasal bleeding, sinus discomfort, hoarseness, sore throat, cough, sputum production, and dyspnea of increasing severity. Hemorrhagic inflammation and erosions of the upper airway mucosa are followed by fibrinous pseudomembrane formation and sloughing of necrotic, ulcerated mucosa. Bronchospasm and partial airway obstruction result. After high-dose exposures, severe bronchitis, secondary bronchopneumonia, and respiratory failure may develop within 24 to 48 hours (4,6). Pulmonary edema is uncommon, as mustard does not typically affect the pulmonary parenchyma. The need for mechanical ventilation is a poor prognostic sign, and the majority of these patients subsequently die from progressive respiratory failure.

Bone marrow and gastrointestinal (GI) mucosal toxicity may occur with high concentration or prolonged exposure. Leukopenia develops within 5 to 7 days, with the white cell nadir occurring 10 days after exposure. Thrombocytopenia and anemia typically follow. The development of hematologic effects from mustard poisoning is a grave prognostic sign (4). Respiratory failure, bone marrow suppression, or superimposed bacterial infection are the most common causes of death from sulfur mustard poisoning (5,6).

The clinical manifestations of lewisite poisoning are similar to those of sulfur mustard, although lewisite causes immediate severe pain on contact with the skin, eyes, and nasal mucosa. Vapor condensing on the skin causes erythema within 30 minutes and blister formation within 2 to 3 hours (4). The eyes are very sensitive to lewisite, and permanent blindness from corneal destruction may result if decontamination is not initiated within 1 minute. Inhalation of lewisite vapor can result in death within 10 minutes from rapid respiratory mucosal sloughing and bleeding, leading to asphyxiation. Pulmonary edema may also develop.

Nerve Agents

Toxicity may occur after inhalation of vapor, skin contact with vapor or liquid, or ingestion. The rate of onset and severity of effects

are determined by the route of exposure and dose (4). At high ambient temperature, skin absorption is rapid and increasing amounts of the agent are volatilized, leading to increased inhalation (4). Small amounts of vapor cause miosis, rhinorrhea, mild dyspnea, cough, and wheezing (4). This can occur within seconds to minutes. Symptoms include eye pain, blurred and dim vision, headache, and dizziness (2). As the dose of vapor increases, nausea and vomiting, increased respiratory difficulty, progressive muscular weakness, and agitation develop. A high vapor concentration causes rapid loss of consciousness, seizures, flaccid paralysis, and respiratory arrest within seconds to minutes. Following sarin vapor exposure in the Tokyo incident, the most common manifestations were miosis (99%), headache (75%), dyspnea (63%), nausea (60%), eye pain (45%), blurred vision (40%), and vomiting (37%) (2). After a mass-casualty incident due to a nerve agent, miosis may serve as a useful marker of exposure. Tachycardia and hypertension were common, but bradycardia and bronchorrhea were not. Electrocardiographic manifestations include supraventricular and ventricular dysrhythmias, ischemic ST–T changes, atrioventricular conduction disturbances, and QTc interval prolongation (7). Seizures may be single and brief or multiple and persistent; status epilepticus will often occur in severely poisoned patients (2,7). Death is primarily a result of depression of the central respiratory drive (4,7). Respirations cease before significant neuromuscular blockade or bronchoconstriction occurs.

Victims of vapor exposure are unlikely to deteriorate once removed from exposure (2). In contrast, those with dermal exposure may subsequently worsen. Skin absorption of a lethal dose may occur within 1 to 2 minutes, yet symptoms are commonly delayed and develop after a latency period of 30 minutes to 18 hours (4,6,7). Skin exposure may produce local sweating and twitching or fasciculations before systemic toxicity (4,7). Conversely, serious effects may also occur abruptly, without antecedent local or mild symptoms after dermal exposure (7). In contrast to vapor exposure, miosis is absent early following skin exposure. Miosis may be

present for weeks after exposure and does not readily respond to systemic treatment (7).

Lacrimating Agents

Within seconds to minutes of exposure, lacrimating agents cause intense eye discomfort, blepharospasm, lacrimation, stinging and burning of the mouth and nose, salivation, rhinorrhea, irritation of the respiratory tract and stomach with coughing and vomiting, and skin irritation leading to burning pain and erythema (4). Because they are miscible in sweat, skin irritation is amplified in areas of increased sweat, such as the axilla, buttocks, and popliteal, antecubital, and inguinal regions. Skin effects increase with concentrated liquid spray or aerosol exposures, in warm, moist environments, and in those with pre-existing skin conditions. Toxic effects following exposure to tear agents typically resolve within 20 to 30 minutes (4). High-concentration, enclosed-space exposures, however, may result in significant respiratory effects that include acute laryngotracheobronchitis, pulmonary edema, and death. Pulmonary edema can be delayed 4 to 8 hours; peak effects should be evident by 12 hours.

Prolonged or repeated exposures to lacrimating agents may produce malaise, skin blistering, chest tightness, coughing, wheezing, hemoptysis, shortness of breath, and a feeling of suffocation. Reactive airways dysfunction (RADS) and allergic contact dermatitis have been described in sensitized individuals. A severe dermatitis, labeled “Hunan hand syndrome,” has been described after prolonged skin exposure to capsaicin containing chili peppers.

Incapacitating Agents

Manifestations of BZ and fentanyl derivative poisoning are described in detail in Chapter 344 and Chapter 305, respectively. BZ poisoning may occur after inhalation of vapor or liquid aerosol, intravenous or intramuscular injection, or, to a small degree, skin contact with liquid. Following exposure by all routes (except skin), the onset of

effects takes 1 hour, peaks at 8 hours, and gradually subsides over 24 to 72 hours (4). Effects may be delayed up to 24 hours after dermal exposure. Doubling the dose produces incapacitation within 1 hour and prolongs recovery an additional 48 hours. Wide variability in the onset, severity, and duration of effects should occur after BZ deployment by aerosol or vapor (4). The rate of onset and duration of clinical effects after inhalation of aerosolized fentanyl derivatives has not been fully described (1). The gas mixture utilized in the Moscow hostage crisis produced effects within 15 minutes of exposure; toxicity lasted days in some survivors (1).

DIFFERENTIAL DIAGNOSIS

Deliberate release of chemicals by terrorists is likely to involve substances that cannot be immediately identified. Thus, the most likely diagnosis is likely to be made by history, physical examination, and initial diagnostic testing (8,9). Diagnosis is also strongly suggested by the complete reversal of toxic effects following empiric antidotal therapy (1,2,10).

CWA poisoning should be suspected when a group of patients present with the abrupt onset of a similar constellation of signs or symptoms, particularly if they involve the exposed mucosal or skin surfaces, the respiratory tract, or sudden systemic effects (8,10). Following a chemical attack, clinical effects will occur within minutes to hours, and large numbers of symptomatic patients from the same location will present to medical facilities within a short period of time (3,8,10). There may be an associated explosion and/or reported vapor cloud with or without a characteristic odor. In contrast, clinical effects after a biologic agent attack are delayed as a result of the incubation period of the illness and patients will present insidiously, often with nonspecific signs and symptoms. It will be difficult to identify the release site of the weapon, and the geographic distribution of patients may be wide by the time symptomatic disease develops (see Chapter 349) (8,10).

Irritant or corrosive gas inhalation, hydrocarbon aspiration, and vesicating agent and high-dose lacrimating agent exposures may produce pulmonary signs and symptoms similar to those caused by choking agents. Exacerbations of asthma, chronic obstructive pulmonary disease, and allergic or infectious pneumonitis may present similarly. The vesiculobullous skin lesions that result from vesicating agents are most pronounced on exposed skin but may mimic those resulting from Stevens–Johnson syndrome, toxic epidermal necrolysis, pemphigus vulgaris, bullous pemphigoid, scalded skin syndrome, thermal and chemical burns, and hypersensitivity reactions. Nerve-agent poisoning is nearly identical to organophosphate and carbamate pesticide poisoning. Other agents and conditions that can produce similar clinical effects are botulism; nicotine; cholinergic drugs such as bethanechol, carbachol, edrophonium, methacholine, neostigmine, pilocarpine, physostigmine, pyridostigmine, and succinylcholine; and pyrethroids.

Nerve-agent, cyanide, or fentanyl-derivative exposure should be suspected if victims become comatose within minutes of exposure (4,8,10). Although the presence of coma, miosis, and respiratory depression is likely following exposure to both opioid and nerve agents, the additional presence of a seizure, fasciculations, and/or cholinergic findings strongly suggest intoxication with a nerve agent (10). Although seizures may be present following exposure to both cyanide and nerve agents, the presence of intractable hypotension and acidemia despite adequate oxygenation suggests severe cyanide toxicity (4,8,10). BZ will produce effects identical to other anticholinergic agents (4). In the absence of history, unintentional atropine poisoning following use of a nerve-agent autoinjector cannot be differentiated from BZ toxicity. Lacrimating agents cause effects similar to those of irritant gas and lewisite exposure. Anxiety and hysterical reactions must also be considered in the differential diagnosis of patients exposed to warfare agents.

ED EVALUATION

Despite the probable confusion and panic and conflicting reports, an attempt should be made to document the amount, time, nature, and duration of exposure. The color and odor of the toxic agent may provide clues to its identity. The time of onset, nature, progression, severity of symptoms, and prehospital treatment should be noted.

Physical examination should first focus on vital signs and an assessment of neuromuscular and cardiopulmonary function and then on the eyes, skin, and GI tract. Following stabilization, patients with eye symptoms should have fluorescein and eventual slit-lamp examinations. If signs and symptoms of cyanide, choking, vesicating, or lacrimating agent toxicity are present, ancillary studies should include a chest radiograph, electrocardiogram (ECG), and arterial blood gas analysis, depending on the severity of symptoms. Additional laboratory evaluation after exposure to cyanide or a vesicating agent should include baseline complete blood count and serum electrolyte, blood urea nitrogen, creatinine, and glucose levels. Measurements of whole blood or plasma cyanide confirm cyanide poisoning but are rarely readily available. High blood lactate concentrations, a large anion gap metabolic acidosis, and high venous blood oxygen content suggest cyanide poisoning.

Patients with signs and symptoms of nerve agent toxicity should have a chest radiograph, ECG, arterial blood gas analysis, routine admission laboratory studies, and measurement of peak expiratory flow rate and plasma or red blood cell cholinesterase activity (see Chapter 318). Cholinesterase activity, however, will not be available in time to be useful in making treatment decisions, and it does not always correlate with the severity of disease (4,10). In the Tokyo sarin attack, 27% of patients with clinical manifestations of moderate poisoning had plasma cholinesterase levels in the normal range (2).

Routine toxicology testing will not identify CWAs. The diagnosis of CWA poisoning is confirmed by detecting chemical agents and their degradation products or cellular macromolecule adducts in environmental or body fluid samples. Formal identification of CWAs is likely to be performed at state and federal law enforcement laboratories with the assistance of federal public health authorities

(Centers for Disease Control laboratory). Rapid-detection kits are used by law enforcement in the prehospital setting to quickly identify the agent involved.

One of the objectives during the evaluation is to separate the truly exposed from the worried-well or anxious patients to focus the resources on patients who are in the greatest need.

KEY TESTING

- Obtain a chest x-ray in those with respiratory symptoms following exposure to choking, vesicating, nerve, or lacrimating agents.
- Obtain an arterial blood gas, serum chemistries, lactate level, and whole blood or serum cyanide level in those with findings suggestive of cyanide poisoning.
- Consider obtaining RBC and plasma cholinesterase levels in those with symptoms suggestive of nerve agent exposure.

ED MANAGEMENT

In the event of a chemical weapon attack, emergency field personnel will be responsible for performing on-scene triage, decontamination, and initial treatment prior to patient transport. Appropriate scene and decontamination control zones should be established. Emergency field personnel should wear appropriate personal protective equipment (PPE). If the hazardous substance is unknown, this consists of an encapsulated, vapor-impermeable, and chemical-resistant suit; chemical-resistant gloves and boots; and a positive-pressure, self-contained breathing apparatus (level A PPE) (3,5,8,10). The importance of first-responder personal protection was illustrated in the Matsumoto and Tokyo sarin gas attacks in which 10% to 35% of rescuers developed mild toxicity (2). In each incident, patients were not decontaminated, and rescuers wore standard work clothing without respiratory protection. Mouth-to-mouth rescue breathing should be avoided as 10% of inhaled nerve agents are expired and could result in rescuer toxicity. Hospitals should be prepared to activate their disaster plans and be able to

decontaminate those are inadequately decontaminated or those that arrive by self-transport (3,10). Details of disaster planning and management are discussed in Chapter 378. ED personnel treating a patient exposed to an unknown chemical agent should wear a chemical-resistant suit, gloves, and boots and an external self-contained breathing apparatus (SCBA) or positive-pressure supplied air respirator (level B PPE) until the threat of secondary exposure is cleared (3,5,10). Removal of dry substances along with removal of clothing eliminates up to 90% of the hazard and is the most effective step in decontamination (7–10). Clothing should be discarded in impervious plastic bags, particularly leather items (e.g., shoes, watchbands), which can absorb chemicals and result in reexposure. Dermal decontamination involves irrigation with tepid water, followed by 0.5% hypochlorite solution (household bleach diluted 1:10 with water) or alkaline soap, and then repeated, thorough water rinsing (3,4,10). The wastewater should be collected and isolated, if possible. If exposed, the eyes should be irrigated with copious amounts of water or saline. Rapid dermal decontamination is critical following exposure to the liquid or aerosolized formulations but less important following isolated vapor exposure (3).

After decontamination, management of victims includes establishing an airway and supporting breathing and circulation. Ideally, all patients should have oxygen provided and receive continuous cardiac and oxygen saturation monitoring, but in mass-casualty situations priority must be given to the most severely affected patients.

Other workup is dictated by clinical severity including management of traumatic injuries. For inhalation exposure initial treatment includes administration of 100% humidified oxygen, bronchodilators, and assisted ventilation, as necessary.

Choking Agents

Treatment of choking agent poisoning consists of providing humidified oxygen, β-adrenergic agonist bronchodilators,

ventilatory support, intravenous crystalloids for hypotension (4). Nebulized 2% sodium bicarbonate may provide symptomatic relief following acute chlorine gas exposure (8,10). Although frequently recommended for chlorine and phosgene exposure, corticosteroids have no proven benefit.

Vesicating Agents

Because of rapid and irreversible binding to tissues, immediate decontamination is the best form of treatment for mustard agent exposure (4,6,10). Water alone is ineffective, as mustard is relatively water-insoluble. Dilute bleach is recommended as it produces "free" chlorine, which inactivates the mustard compound. Copious water or saline irrigation is the favored method for ocular decontamination. Exposure to tissue or vesicle fluid will not produce secondary injury to healthcare personnel (5).

Treatment is otherwise supportive. Blisters and necrotic skin should be debrided. Skin burns should be treated with topical antibiotics. Ocular injury requires urgent ophthalmologic consultation. Treatment may include topical anesthetics, antibiotic ointment to prevent infection, and mydriatic or cycloplegic medication to prevent adhesions between iris and cornea (4,6,10). Respiratory care is the same as for choking agents.

Potential antidotes for sulfur mustard poisoning include mustard scavengers (glutathione, N-acetylcysteine, thiosulfate), antioxidants (vitamin E), NAD^+-level stabilizers (niacin and nicotinamide), anti-inflammatory drugs (corticosteroids, indomethacin), and nitric oxide synthase inhibitors (L-nitroarginine methyl ester) (4). Bone-marrow suppression may respond to granulocyte-colony–stimulating factor.

Treatment of lewisite exposure involves washing the skin with water, soap, solutions of dilute chlorine bleach (0.5%), or baking soda (sodium bicarbonate) (4). Neither scrubbing nor hot water is appropriate, because both enhance lewisite absorption and toxicity. Blisters, shown to contain arsenic, should be opened and drained of fluid. Other treatment is identical to that of thermal burns.

Historically, systemic lewisite poisoning has been treated by intramuscular British antilewisite (BAL, 2,3-dimercapto-propanol, or dimercaprol), an arsenic chelator antidote, along with supportive care (see Chapter 326). BAL has also been used topically as a 5% ointment for skin lesions and as a 5% to 10% oil solution for ocular symptoms. Newer, less toxic dithiol analogs of BAL, meso-dimercaptosuccinic acid (DMSA) or 2,3-dimercapto-1-propan-sulfonic acid (DMPS) can be administered and have equal efficacy (see Chapters 326 and 334).

Nerve Agents

Intubation, mechanical ventilation, and the use of muscarinic antagonists (e.g., atropine), oximes (e.g., pralidoxime), and benzodiazepines (e.g., diazepam) may be necessary. If endotracheal intubation is necessary, a nondepolarizing neuromuscular blocker such as rocuronium (1.0 mg/kg IV) is recommended to avoid prolonged paralysis from succinylcholine. Antidotal therapy is discussed in Chapter 318. Initially, atropine should be administered intravenously at a dose of 2 mg every 3 to 5 minutes (0.02 to 0.05 mg/kg in children) until respiratory secretions clear, bronchospasm resolves, and ventilation is normal (5,7,9). Heart rate and pupil size are poor endpoints for adequate atropinization (2,4,7,9). Cumulative atropine doses of 10 to 20 mg are usually adequate over the first 2 to 3 hours, with little or no therapy required thereafter (2,4). This differs from organophosphate pesticide poisoning, which may require significantly greater amounts of atropine and a longer duration of therapy. In the Tokyo sarin attacks, only 19% of poisoned patients required more than 2 mg of atropine; severely poisoned patients required 1.5 to 15 mg of atropine (mean, 6 mg) (2). Topical mydriatic cycloplegic eye drops such as tropicamide (Mydriacyl) may be used for intractable eye pain as a result of ciliary spasm. No treatment is needed for miosis as an isolated ocular finding.

Oxime therapy is recommended for all cases of nerve-agent poisoning. Because unlike with insecticides, nerve agents age

extremely rapidly, pralidoxime must be given as soon as possible after exposure to be effective. Initially, 1 to 2 g of pralidoxime should be administered as an intravenous bolus over 10 minutes (20 to 50 mg/kg in children), followed by a continuous infusion of 500 mg/hr (10 to 20 mg/kg/hr in children) (5,7,10). Side effects of pralidoxime include hypertension and tachycardia. Pralidoxime is given until signs and symptoms of intoxication have resolved (7). In the Tokyo sarin attacks, severely poisoned patients required 1 to 36 g pralidoxime (mean, 11 g) (2). Conventional oximes (pralidoxime preparations, obidoxime, trimedoxime) are not clinically useful against soman. Newer H-series (Hagedorn) oximes are superior in their ability to reactivate unaged soman-inhibited AChE. They also have direct antimuscarinic and antinicotinic (ganglia-blocking and nondepolarizing neuromuscular-blocking) actions but do not protect from nerve agent–induced seizures (4). HI-6, a bisquaternary pyridinum oxide, is currently the most promising AChE reactivator for the treatment of nerve-agent poisoning; it is effective against all nerve agents and does not result in significant side effects in human studies (4,10). Currently, other oximes are not commonly available in the United States.

Pretreating those at risk with a reversible AChE inhibitor, such as the carbamate pyridostigmine (Mestinon), is also effective against soman, in which enzyme aging is rapid and pralidoxime alone is unlikely to be effective (4). The intent is to carbamylate or bind 20% to 40% of AChE and limit subsequent nerve-agent binding. Carbamylated cholinesterase then spontaneously reactivates or is regenerated with oxime therapy, leaving the victim with enough AChE to function normally. Pyridostigmine pretreatment does not protect against sarin and VX, in which aging is slower and pralidoxime is effective. During the Persian Gulf War, US soldiers were given pyridostigmine bromide in blister packs containing 21 30-mg tablets (4,7). Pyridostigmine was taken orally every 8 hours without causing impaired performance. Side effects were minimal, but they can mimic mild nerve gas poisoning.

Seizure control can protect against sudden death and brain injury (1,4,10). Seizures should be aggressively treated with high-dose

benzodiazepines, such as intravenous diazepam 10 mg (0.2 to 0.4 mg/kg) or midazolam (Versed) (0.1 to 0.3 mg/kg), in addition to standard therapy with an antimuscarinic and oxime agents (7,9,10). Both antimuscarinic agents and benzodiazepines are effective in treating nerve-agent seizures in experimental animals. Trihexyphenidyl (Artane) and midazolam are the most potent and rapidly acting agents. Diazepam should be administered to all severely exposed victims (4).

Lacrimating Agents

Treatment of lacrimating agent exposure is frequently unnecessary because effects resolve quickly, even without irrigation. Symptomatic patients may require supportive care and decontamination with soap and water. Contact dermatitis may respond to topical corticosteroids and antipruritics. Tearing usually irrigates the eyes adequately, but topical anesthetics and saline irrigation may be helpful. Chemical conjunctivitis may benefit from symptomatic treatment with topical vasoconstrictors (see Chapter 56). Corneal injuries are treated with cycloplegics, topical antibiotics, and ophthalmologic follow-up (see Chapter 57). Patients exposed to high concentrations of aerosols, as in enclosed spaces or near exploding tear-gas canisters, should be observed for 12 to 24 hours because of delayed pulmonary effects (4). Treatment of pulmonary toxicity consists of humidified oxygen, bronchodilators, and assisted ventilation, as needed.

Incapacitating Agents

Treatment of incapacitating-agent toxicity includes supportive care and the administration of antidotes. Standard doses of physostigmine (1 to 2 mg or 0.02 mg/kg IV) are usually effective in reversing the anticholinergic effects of BZ (see Chapter 344) (4,10). For unclear reasons, however, physostigmine is ineffective if administered during the first 4 to 6 hours after the onset of clinical effects (4). The treatment of fentanyl-derivative poisoning is similar to that for other opioids (see Chapter 305). Because these agents

bind with high affinity to opiate receptors, large doses of naloxone may be required for complete reversal of toxic effects. As a result of high lipophilicity, fentanyl derivatives redistribute from tissue stores to the CNS and are more likely to produce recurrent CNS depression (1). Based on animal studies, naloxone antagonist redosing is likely to be necessary for a period of 2 to 24 hours (1).

CRITICAL INTERVENTIONS

- Decontaminate victims of CWA exposure by removing, bagging, and discarding all clothing, and washing the skin with copious amounts of soap and water.
- Wear level B PPE (e.g., chemical-resistant suit, gloves, boots, SCBA) when the CWA is unknown and protect caregivers from exposure.
- Notify local and federal law-enforcement authorities along with local or state health departments when CWA poisoning is suspected.
- Activate the hospital disaster plan and establish a decontamination area outside the ED for mass-casualty incidents.
- Administer oxygen, bronchodilators, and artificial ventilation to patients with respiratory symptoms following choking, vesicating, and lacrimating agent exposure.
- Administer antidotal therapy to victims with cyanide, nerve agent, anticholinergic, and opioid poisoning and titrate to clinical improvement.

DISPOSITION

Asymptomatic patients with choking agent exposure should be observed and monitored for at least 6 hours. Mild to moderately symptomatic patients may be discharged safely after several hours of observation if symptoms have improved or resolved with treatment. Victims of lacrimating agents may be treated and released if there is no significant pulmonary toxicity. Patients with phosgene exposures should be admitted and closely observed because of phosgene's varying latency period and high potential

morbidity. Asymptomatic patients with vesicating agent exposure should be admitted and monitored for 12 to 24 hours. Following exposure to nerve agent vapor, patients with signs and symptoms confined to the eyes may be discharged safely after a short period of observation (2). Those with skin exposure to nerve agents (liquid or aerosolized droplets) should be observed for 24 hours. All patients with systemic symptoms, pulmonary toxicity, and severe or extensive dermal injury should be hospitalized. Patients with corneal or skin burns should have follow-up with an ophthalmologist or plastic surgeon. As a result of the long duration and recrudescent nature of clinical effects from incapacitating agents, all symptomatic victims should be observed for a minimum of 24 hours. The appropriate level of care will depend on clinical severity.

ACKNOWLEDGMENTS

The authors acknowledge the contributions of Michael Joseph Burns and Christopher H. Linden to previous editions of this chapter.

Common Pitfalls

- Failure to protect rescuers and medical personnel from secondary contamination.
- Failure to decontaminate victims of chemical agent exposure in a timely fashion.
- Failure to appreciate that effects can be delayed and progressive and to observe asymptomatic victims for appropriate periods of time.
- Failure to administer antidotes in a timely manner.

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CHAPTER 351 Drug Withdrawal

Lewis Nelson

Withdrawal syndromes, which include discrete physiologic and psychological effects, occur following the discontinuation or dose reduction of certain drugs and medications. Anticipating and recognizing the early signs of withdrawal allow for timely treatment and may help prevent the development of serious withdrawal manifestations.

Ethanol withdrawal is a common, potentially life-threatening syndrome (see Chapter 282), and is similar to that occurring after the cessation or dose reduction of sedative-hypnotics such as benzodiazepines, barbiturates, and chloral hydrate, as well as γ-hydroxybutyrate (GHB) and its congeners (e.g., 1,4-butanediol), and baclofen. All of these drugs enhance the activity of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) at the $GABA_A$/benzodiazepine receptor/chloride–channel complex and induce long-standing adaptations in receptor function.

Withdrawal symptoms associated with opioids are common, although generally not life-threatening, and have grown increasingly important during the decade-long epidemic of prescription opioid misuse. Antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs), and cocaine are associated with discontinuation syndromes that are likened to withdrawal, but are less severe. Somatic and psychological symptoms predominate.

Physical dependence is a prerequisite for the development of a withdrawal syndrome, and is generally accompanied by tolerance. The dose of the drug, its duration of action, frequency of administration, and duration of abuse all contribute to the

development of dependence and are related to the severity of withdrawal. More severe withdrawal phenomena may be associated with a longer period of abuse or a history of previous withdrawal episodes. Sporadic use of a drug does not generally induce the receptor adaptations required for the development of dependence, and therefore withdrawal. For example, use of GHB recreationally (e.g., on weekends) does not result in dependence and withdrawal does not occur, whereas it does follow cessation in frequent, several-times-daily users, such as body-builders. Similarly, the withdrawal associated with heroin use is typically less intense than that associated with methadone since the later is long acting and blood concentrations remain elevated around-the-clock. Complete abstinence and a serum drug level of zero are not required, nor is abuse (i.e., use simply for pleasurable central nervous system [CNS] effects). Physiologic dependence does not require excessive doses, and it may occur after prolonged treatment with therapeutic doses for appropriate indications.

Withdrawal from sedative-hypnotics is characterized by intense sympathetic stimulation. The underlying mechanism is not fully elucidated, but it occurs when compensatory CNS mechanisms that counteract the depressant effects of sedative-hypnotics are activated. Such mechanisms involve changes in GABA and glutamate receptor activity, including down-regulation of the GABA receptor complex and upregulation of the *N*-methyl-D-aspartate (NMDA) glutamate receptors. Benzodiazepine withdrawal results in excitatory effects because there is less baseline GABA inhibition and enhanced neuronal activity through overactive NMDA receptors.

Withdrawal from opioids may also involve an increase in sympathetic discharge, but by a different mechanism. Decreased opioid receptor stimulation increases catecholamine release in the locus ceruleus of the CNS. The severe catecholamine surges seen with sedative–hypnotic withdrawal are not observed during typical opioid withdrawal.

CLINICAL PRESENTATION

The clinical presentation of drug withdrawal varies significantly among patients. Although this may relate to variations in the degree of drug use and reporting, there are also individual factors that underlie the severity of withdrawal. Some patients develop significant withdrawal following cessation of exposure, while others with similar use patterns develop minimal effects. Some patients may present with complications of drug abuse, such as pneumonia, endocarditis, and skin abscess, or an unrelated problem, such as a myocardial infarction or motor vehicle accident, and develop withdrawal symptoms while in the emergency department (ED) or after admission. Others present to the ED due to unintended abstinence or because they desire detoxification.

Sedative-hypnotic withdrawal may be indistinguishable from ethanol withdrawal except for differences in the time course (Table 351.1). Because many benzodiazepines have a long elimination half-life and active metabolites, withdrawal manifestations may be delayed after cessation of drug use. Lorazepam withdrawal may begin within 2 days of the last dose, whereas diazepam withdrawal may require a week or more before the onset of symptoms.

TABLE 351.1
Withdrawal Syndromes Commonly Seen in the ED

Type of Withdrawal	Onset after Use Ends
Ethanol	6–8 hrs
Sedative–hypnotic (e.g., benzodiazepines, barbiturates)	3–7 d (for long-acting drugs)
GHB	Hours
Baclofen	12–72 hrs
Opioids	4–8 hrs (heroin); 36–72 hrs (methadone)
Cocaine	Within hours after binge
Antidepressants	2–5 d

The clinical presentation of sedative-hypnotic withdrawal varies in intensity and duration. Mild withdrawal symptoms include anxiety, apprehension, irritability, dysphoria, and insomnia (1). Other symptoms may include anorexia, nausea, and vomiting. Mild

autonomic and CNS hyperactivity is characterized by tachycardia, hypertension, irritability, and hyperreflexia. Unlike patients with severe withdrawal, patients with mild withdrawal have a clear mental status. Most patients with mild withdrawal recover uneventfully after a few days, but some may develop more serious withdrawal manifestations.

Hallucinations, delusions, myoclonus, seizures, and agitation may appear in patients with more severe withdrawal. Tachycardia, hypertension, tachypnea, hyperthermia, diaphoresis, and mydriasis may develop, as may tachyarrhythmias. At times, a new-onset seizure heralds the onset of sedative-hypnotic withdrawal. These patients may or may not have tremulousness and other sympathetic hyperactivity before seizure activity begins. Seizures tend to be generalized and tonic-clonic. Severe withdrawal, including seizures, may occur after the administration of flumazenil to patients chronically taking benzodiazepines. Withdrawal from long-acting benzodiazepines may persist for 3 weeks.

Withdrawal from GHB, or its congeners γ-butyrolactone (GBL) or 1,4-butanediol, may also produce severe withdrawal (2). Withdrawal from these agents is frequently seen in body-builders, who ingest GHB multiple times per day as opposed to sporadic recreational users. Autonomic and CNS abnormalities are the most common effects and may include anxiety and tremor. More severe GHB withdrawal is characterized by severe agitation, tachycardia, hypertension, insomnia, auditory and visual hallucinations, and delirium. The onset of symptoms may appear as early as 1 to 6 hours after the last dose, and the symptoms may persist for as long as 5 to 15 days. Few deaths from GHB withdrawal have been reported (also see Chapter 309).

The withdrawal syndrome from oral or intrathecal baclofen generally starts 12 to 72 hours after discontinuation. Typical findings include sleeplessness, confusion, agitation, hallucinations, delusions, hyperthermia, and hypertonia. Interestingly, seizures may occur in the setting of either baclofen toxicity or withdrawal (3). In some cases, there is profound muscle rigidity resembling neuroleptic malignant syndrome or malignant hyperthermia.

Mild opioid withdrawal includes lacrimation, rhinorrhea, yawning, diaphoresis, anxiety, restlessness, and dysphoria. Piloerection is particularly characteristic. The patient may exhibit mild elevations in pulse, blood pressure, and respiratory rate, but these changes are usually not significant. More severe opioid withdrawal is characterized by vomiting, diarrhea, abdominal pain, and dehydration. Severe agitation, seizures (except in neonatal withdrawal), mental status changes, and dramatic vital sign abnormalities do not typically occur with opioid withdrawal due to abstinence but do occur with opioid withdrawal precipitated by naloxone.

The severity and time course of the opioid withdrawal syndrome depends on the pharmacokinetics of the opioid. Withdrawal from shorter-acting agents (e.g., heroin) usually begins within 4 to 8 hours after the last dose, peaking by 36 to 72 hours while that from longer-acting agents (e.g., methadone) typically occurs 36 to 72 hours after the last dose and may persist for up to 2 weeks. Withdrawal from long-acting opioids tends to be more severe than that from shorter-acting agents.

The sudden onset of opioid withdrawal may occur after an opioid antagonist such as naloxone is given to an opioid-dependent patient (4) and may be severe. As a result of naloxone's short half-life, withdrawal symptoms do not usually persist beyond 40 to 60 minutes. Treatment with additional opioid to reverse these short-lived effects is not indicated. Opioid withdrawal from the long-acting opioid antagonist naltrexone may result in a markedly prolonged withdrawal period lasting up to 24 hours and treatment is difficult. A cautious attempt to overcome the receptor blockade with an opioid is possible, though many simply provide supportive care including antiemetics and benzodiazepines. Giving opioids without full agonist properties, such as buprenorphine (Suboxone; a partial agonist), to a stable opioid-dependent patient may also precipitate withdrawal symptoms. Interestingly, buprenorphine can be used to quell existing or extant opioid withdrawal due to the same pharmacologic properties.

Antidepressant withdrawal/discontinuation may result in anxiety, insomnia, lethargy, nausea, vomiting, headache, imbalance, sensory abnormalities, and possibly aggressive and impulsive behavior. In most cases, these symptoms are mild and transient. Withdrawal from cocaine may result in lethargy, dysphoria, and depression (5).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for a patient with a withdrawal syndrome is broad and includes many other serious conditions that may require different therapy (Table 351.2). Because drug-dependent patients are particularly prone to develop many of these conditions, careful exclusion of other etiologies is critically important. Examination may help to distinguish an anticholinergic toxidrome (dry skin, decreased bowel sounds, urinary retention, mydriasis, tachycardia) from a sympathomimetic toxidrome (moist skin, normal bowel sounds, no urinary retention, mydriasis, tachycardia).

TABLE 351.2
Differential Diagnosis of Major Withdrawal Symptoms

Tremor	Seizures	Hallucinations	Delirium
Withdrawal	**Withdrawal**	**Withdrawal**	**Withdrawal**
Ethanol	Ethanol	Ethanol	Ethanol
Sedative–hypnotics	Sedative–hypnotics	Sedative–hypnotics	Sedative–hypnotics
			Methadone
Intoxications	**Intoxications**	**Intoxications**	**Intoxications**
Theophylline	Cocaine	LSD	Cocaine
Caffeine	Anticholinergics	Mescaline	Amphetamine
β-Agonists	Phenothiazines	Mushrooms	Phencyclidine
Mercury	TCAs	Peyote	Anticholinergics
Lithium	Theophylline	Phencyclidine	Sedative hypnotics
TCAs	Camphor	Anticholinergics	**Infectious**
Phenytoin	Isoniazid	Ergot	Meningitis
Metabolic	Phencyclidine	Nutmeg	Encephalitis
Hypoglycemia	Lidocaine	**Infectious**	Sepsis
Thyrotoxicosis	Organophosphates	Meningitis	**Metabolic**
Structural	**Infectious**	Encephalitis	Thyrotoxicosis
Cerebellar disease	Meningitis	Sepsis	Hypoglycemia
Other	Encephalitis	**Metabolic**	Hyperglycemia
Parkinsonism	**Metabolic**	Hypoglycemia	Hypocalcemia
	Hypoglycemia	Hypoxia	Hypoxia
	Hypoxia	**Structural**	Thiamine deficiency
	Hypothyroidism	CNS hemorrhage	**Structural**
	Thyrotoxicosis	Tumor	Head trauma
	Hypocalcemia	**Psychiatric**	CNS hemorrhage
	Hyperosmolar state	Schizophrenia	Tumor
	Hepatic failure	Other psychoses	Psychiatric
	Uremia	**Other**	**Other**
	Structural	Seizures	Seizures
	Head trauma	Heat-related illness	Heat-related illness
	CNS hemorrhage		
	Tumor		
	CVA		
	Other		
	Idiopathic epilepsy		
	Degenerative disease		

LSD, lysergic acid diethylamide; CNS, central nervous system.

Sedative-hypnotic withdrawal may be particularly difficult to distinguish from an underlying anxiety disorder. Differentiating withdrawal seizures from other types of seizures may also be difficult particularly without an accurate history. Other common causes include pre-existing idiopathic epilepsy, posttraumatic epilepsy, and

other complications of drug abuse (e.g., hypoglycemia, hypomagnesemia, hyponatremia, head trauma). Poor anticonvulsant compliance with underlying seizure disorders may add to the diagnostic confusion. In the setting of baclofen use, a seizure could result from either overdose or withdrawal.

Opioid withdrawal must be distinguished from ethanol and other sedative-hypnotic withdrawal because of the significant differences in therapy. Clinical findings of significant sedative-hypnotic withdrawal, such as confusion, agitation, and seizures, are not generally seen with opioid withdrawal; opioid withdrawal symptoms such as piloerection, yawning, lacrimation, and rhinorrhea are not seen with ethanol and sedative-hypnotic withdrawal. Some patients, however, may be withdrawing from both substances. Gastrointestinal (GI) manifestations of opioid withdrawal must be differentiated from abdominal pathology and gastroenteritis.

ED EVALUATION

Patients presenting with drug withdrawal require a comprehensive assessment. Patients initially should have cardiac monitoring and a fingerstick glucose and oxygen saturation analysis. The physician should obtain a complete history of substance abuse, previous withdrawal episodes, and all current and former medications. If possible, family, friends, and prehospital personnel can be interviewed to gain additional information.

Physical examination should focus on vital signs, including rectal temperature; cardiovascular, neurologic, and pulmonary systems; the skin; the abdomen; and the eyes. Close attention should be directed to any stigmata of chronic liver disease or evidence of intravenous (IV) drug use. There should be assessment for obvious and occult traumatic injury and complications of drug abuse, such as pneumonia, skin abscesses, bacterial endocarditis, acquired immunodeficiency syndrome, pancreatitis, liver disease, and GI bleeding (see Chapter 308).

Laboratory studies that may prove helpful include a complete blood count; electrolytes, glucose, blood urea nitrogen, and creatinine levels; liver function tests; lipase; coagulation profile; and

ethanol level. A urine drug screen may be positive or negative for the offending agent, but can also be misleading. For example, rapid urine drug screens may not detect synthetic or semisynthetic opioids such as methadone or oxycodone, respectively. In patients with significant agitation, a creatine phosphokinase determination may detect rhabdomyolysis.

An elevated temperature may require a sepsis workup, including urine and blood cultures, chest radiograph, and, often, a lumbar puncture. Obtaining a head computed tomography (CT) scan before lumbar puncture is suggested in patients presenting with either focal neurologic deficits or high risk for intracranial hemorrhage. Patients with a first-time seizure in the setting of withdrawal should be evaluated in the same manner as any other patient with a new seizure. Subsequent withdrawal seizures do not necessarily require extensive reevaluation.

KEY TESTING

- Screening laboratory testing is of limited value in diagnosis but important for identifying precipitating causes or comorbid conditions. This includes a complete blood count; electrolytes, glucose, blood urea nitrogen, and creatinine levels; liver function tests; lipase; coagulation profile; and ethanol level.
- Head CT may be useful in differentiating the etiology of other causes of altered mental status or seizure.
- Urine drug testing for abused substances is difficult to interpret given the high prevalence of concomitant use of substances unrelated to the clinical presentation and the limitations of the assay for detecting certain abused drugs.

ED MANAGEMENT

Drug withdrawal syndromes, particularly sedative-hypnotic withdrawal, must be recognized and treated in a timely fashion. A successful treatment strategy must address several basic goals: (1) alleviating symptoms, (2) preventing progression, (3) avoiding complications, and (4) recognizing and treating coexisting medical

problems. Planning for long-term rehabilitation and drug independence is usually better done as part of inpatient management.

Initial treatment should be directed at readily correctable causes of altered mental status. Oxygen should be given if the oxygen saturation is low, and an IV line should be established. Glucose and thiamine should be administered if there is evidence of hypoglycemia and malnutrition respectively. Volume resuscitation is often necessary, particularly in patients with severe withdrawal manifestations and dehydration.

Significantly agitated patients may initially need to be physically restrained to prevent injury, establish IV access, and facilitate sedation. Soft restraints should be used but prolonged use of restraints is discouraged, because continued struggling against them may lead to rhabdomyolysis, hyperthermia, and metabolic acidosis. Once IV access is obtained and chemical sedation has achieved behavioral control, physical restraints should be discontinued.

Achieving adequate sedation is the cornerstone of successful treatment of sedative-hypnotic withdrawal. It may prevent progression to agitated delirium with its attendant complications. Reinstitution of therapy with the withdrawn drug or a cross-tolerant one is required for proper sedation. Many agents have been used over the years, but benzodiazepines have proven to be the most effective. Compared with other sedative-hypnotic agents such as barbiturates, benzodiazepines are more easily titrated and produce less respiratory depression and cardiovascular effects (6).

Diazepam (Valium, oral and IV), chlordiazepoxide (Librium, oral only), midazolam (Versed, IV only), and lorazepam (Ativan, oral and IV) are the most commonly used agents for ethanol withdrawal and can also be used for sedative-hypnotic withdrawal. These agents are eliminated over several days and are preferred over benzodiazepines with shorter half-lives. Compared with short-acting agents, long-acting agents may be more effective in preventing withdrawal seizures and contribute to smoother withdrawal with fewer rebound effects. Active metabolites of diazepam and chlordiazepoxide prolong their therapeutic effect. In elderly patients and those with hepatic

dysfunction, lorazepam, which has no active metabolites, may be preferred. In other cases, lorazepam does not appear to offer any distinct advantage over diazepam or chlordiazepoxide.

IV dosing is preferred in most cases of sedative-hypnotic withdrawal. Agitation may preclude oral administration, and GI dysfunction may impair drug absorption. IV therapy can be readily titrated. Intramuscular (IM) lorazepam or midazolam may be useful in the agitated patient before IV access is established but IM diazepam absorption is erratic and should be avoided.

The dose of benzodiazepines required to achieve proper sedation must be individualized and varies considerably, depending on the patient's tolerance to the drug. Symptom-triggered therapy is preferred to fixed-schedule therapy. Frequent IV boluses should be given until the patient has achieved a calm state. Diazepam, 5 to 20 mg IV, can be given every 5 to 15 minutes until the patient is sedate but arousable. For ethanol withdrawal, chloridazepoxide, 50 mg PO titrated hourly, is a typical oral dose. Usually, sedation is obtained before respiratory depression develops, but close airway observation is always required.

Failure to obtain immediate sedation need not prompt switching to an alternative agent. Mixing different drugs or different routes of administration may increase the risk of adverse effects, particularly respiratory depression. However, if a patient does not respond completely to the chosen benzodiazepine, the use of another cross-tolerant agent at low dose may be valuable. Phenobarbital has a relatively slow onset of action, about 10 minutes, and a long duration of effect that allows gradual self-tapering. Phenobarbital is more likely to cause excessive sedation and respiratory depression and monitoring is important. For patients with sedative–hypnotic withdrawal resistant to benzodiazepines and barbiturates, propofol by bolus (20 mg/dose) or titrated infusions will almost always be successful. However, its use requires high-level monitoring and typically mechanical ventilation.

Withdrawal seizures should also be treated with benzodiazepines or barbiturates. Phenytoin is ineffective in treating or preventing withdrawal seizures and should be reserved for patients with an

underlying seizure disorder who require maintenance phenytoin therapy.

Neuroleptics such as the phenothiazines and butyrophenones (e.g., haloperidol) should not be used alone for sedative-hypnotic withdrawal. Although useful for severe agitation, these neuroleptics are not cross-tolerant with ethanol or sedative-hypnotics, do not prevent or suppress withdrawal, and may result in hypotension, impaired thermoregulation, a lowered seizure threshold, and dystonic reactions. Uncontrolled clinical experience suggests that neuroleptics may be adjunctive therapy for patients with refractory agitation and hallucinations and in treating concomitant nausea, vomiting, and GI cramps.

Sympatholytic therapy with β-blockers (e.g., propranolol) and central adrenergic agonists (e.g., clonidine, dexmedetomidine) has been used for sedative-hypnotic withdrawal, but have certain disadvantages. Sympatholytics are not cross-tolerant with sedative-hypnotics and do not prevent agitation, confusion, or seizures. Moreover, their ability to normalize vital signs may mask a deteriorating clinical situation.

Once withdrawal is controlled, the dose of sedative-hypnotic should be gradually reduced over a period of 3 weeks to 3 months, depending on the dosage and duration of prior use. To avoid precipitating another episode of withdrawal, the dose should generally be tapered by no more than 10% a day although in outpatient practice it is done considerably more slowly.

The approach to GHB withdrawal is similar to that for other sedative-hypnotic withdrawal. Severe cases are often resistant to benzodiazepine treatment and require barbiturates or propofol. Neuroleptics should be avoided if possible.

Reinstitution of baclofen is the initial step in the management of baclofen withdrawal. For patients exhibiting symptoms and signs of more significant withdrawal, high-dose IV benzodiazepine treatment in addition to resumption of baclofen may be required. For patients with acute opioid withdrawal, administration of an opioid treats both the physiologic effects of withdrawal and the psychological effects, particularly craving. Methadone, 10 mg IM or PO can be

administered in the ED, but it should not be prescribed for use after discharge. Parenteral administration guarantees absorption in the vomiting patient. Symptomatic improvement usually occurs within 30 to 60 minutes. Buprenorphine suppresses opioid withdrawal and the associated cravings and some EDs initiate buprenorphine therapy in the ED with prearranged follow-up in a buprenorphine clinic (7). Special credentialing is required to use buprenorphine in the treatment of opioid detoxification.

The decision to administer an opioid is based on clinical and social circumstances, and it is not uniformly done, especially since opioid withdrawal is not medically life-threatening. Clonidine may offer symptomatic relief because it decreases sympathetic activity in the locus ceruleus, although it does not eliminate craving. An initial oral dose of 0.1 to 0.2 mg is recommended. Because hypotension may be particularly problematic after the first dose, the blood pressure should be monitored for 2 hours while the patient remains in the ED. A dose of 0.1 to 0.2 mg every 4 to 6 hours may help prevent recurrence of opioid-withdrawal symptoms.

Detoxification is generally not initiated in the ED and requires referral to an appropriate facility. Federal regulations restrict the use of methadone for detoxification or maintenance to Substance Abuse and Mental Health Services Administration's (SAMHSA) designated programs. Rapid and ultrarapid opioid detoxifications for inpatients followed by naltrexone maintenance therapy have also been used in recent years. These controversial techniques utilize antagonist-precipitated opioid withdrawal as a quick "cure" for opioid dependence. Complications include persistent withdrawal symptoms, pulmonary edema, and death (8).

Reinstitution of drug therapy and gradual tapering of the dose is recommended for antidepressant discontinuation syndrome. Benzodiazepines can be used for signs and symptoms of adrenergic hyperactivity. The treatment of cocaine withdrawal is supportive.

CRITICAL INTERVENTIONS

- Administer diazepam or other long-acting benzodiazepine to patients with sedative-hypnotic withdrawal, adding barbiturates

or propofol for refractory cases.
- Administer opioids, such as methadone or buprenorphine, for the acute manifestations of opioid withdrawal. Clonidine and benzodiazepines are alternatives.

DISPOSITION

Patients with moderate to severe sedative–hypnotic withdrawal should be admitted. Because withdrawal usually persists for several days, admitted patients should be closely monitored for signs of progression and treated as necessary. The level of care depends on clinical severity. Because of potential complications, patients requiring IV sedation are best managed in an intensive or intermediate care unit. Patients with less severe withdrawal may be managed and observed on a medical floor, psychiatric floor, hospital-based detoxification unit, or detoxification unit outside of the hospital. Patients with mild withdrawal may also need to be admitted for the evaluation and treatment of concomitant medical problems that have not been adequately addressed. An inpatient setting, including detoxification, provides a protected environment away from the temptations of illicit drug use.

Outpatient management should be attempted only if the patient can be discharged home with a supportive family member or friend and appropriate outpatient follow-up can be arranged. Supervised withdrawal in the home setting, under the direction of a visiting nurse, may be appropriate in some of these circumstances.

Patients who present to the ED with opioid withdrawal may be discharged home if they do not have other concomitant medical problems that require hospital admission and they can tolerate oral fluids. Offering the patient a limited supply of clonidine (if tolerated in the ED) may help prevent further withdrawal symptoms. Prescriptions for opioids should not be given. A brief intervention and referral to a treatment program is strongly recommended.

Social service, detoxification, or substance-abuse counseling and psychiatric referrals should be offered to all patients with a history of substance abuse.

Common Pitfalls

- Failure to consider the possibility of drug withdrawal in patients with signs and symptoms of adrenergic hyperactivity.
- Failure to appreciate that sedative-hypnotic withdrawal is potentially life-threatening, whereas abstinence-induced opioid withdrawal, although uncomfortable, does not cause significant morbidity.
- Failure to appreciate that neuroleptics do not cross-react with sedative-hypnotics and are not the primary treatment of sedative-hypnotic withdrawal.
- Failure to appreciate that GHB withdrawal may begin within hours of the last dose and be relatively resistant to treatment.
- Failure to appreciate that baclofen withdrawal may occur in the setting of intrathecal baclofen pump dysfunction.

ACKNOWLEDGMENTS

We would like to thank Paul M. Wax and Richard Barrera who were authors of this chapter in previous editions.

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CHAPTER 352 Botulism

Louis Ling

Since 1870, botulism has been the term used to describe the illness associated with food contaminated with *Clostridium botulinum* and its toxin. *C. botulinum* is an anaerobic, spore-forming, gram-positive bacillus. The spores are ubiquitous and can be found in soil, water, and air. Spores are usually dormant and can tolerate 2 hours of boiling at 100°C. Germination of the spores, with resultant toxin formation, requires certain environmental conditions: pH >4.5 and sodium chloride content <3.5%. Unlike the spores, the toxin is heat-labile and can be destroyed by boiling for a few minutes or if heated for 5 minutes at 85°C. Low pH does not inactivate or destroy any preformed toxin.

Botulinum toxin is considered the most lethal substance known, with an estimated oral LD_{50} of 1 μg/kg in humans. Botulinum toxin enters presynaptic nerve terminals via endocytosis, where it irreversibly prevents the release of acetylcholine by inhibiting calcium-dependent exocytosis (1). The net result is a decrease in the acetylcholine concentration within the synaptic cleft both in the autonomic nervous system, resulting in anticholinergic symptoms (muscarinic and nicotinic) and yielding a flaccid paralysis at neuromuscular junctions.

Eight different serotypes of botulinum toxin have been identified (types A–H). Of these, subtypes A, B, and E are of clinical concern and have distinctive geographic distributions. Type A is found predominantly west of the Mississippi, type B predominantly east of the Mississippi, and type E in the Pacific Northwest, especially in

Alaska (2). During summer 2007, an outbreak of type A botulism affected eight patients from Indiana, Ohio, and Texas, who all ate contaminated commercial hotdog chili sauce that was improperly canned in Georgia. However, the vast majority of foodborne botulism is from ingesting home-processed foods (2).

Types A and B are typically found in improperly processed meats and vegetables (3). The food usually appears foul and may have an odor. By contrast, type E does not alter the smell or appearance of food. Human intoxications have been well documented with serotypes A, B, E, and rarely F. Type A accounts for more than one-third of the foodborne cases. Types C cause disease in birds, Type D in cattle, and disease with type G has yet to be documented in either humans or animals in the United States. Type H was identified along with type B in 2013 from an infant and its impact is yet unknown (4).

There are about 145 reported cases of botulism in the United States each year. Classically, there are four distinct diseases as a result of *C. botulinum:* (a) foodborne (adult) botulism occurs after consumption of preformed toxin and accounts for 15% of botulism cases. Smoked or salted meats and fish as well as canned vegetables are typical sources. Mortality ranges from 5% to 10%. (b) Infant botulism, under 1 year of age, occurs after ingestion and propagation of *C. botulinum* in the intestinal tract and accounts for 65% of cases. The vast majority of cases are a result of serotypes A (47%) or B (52%). It follows the ingestion of *C. botulinum* with toxin formation and absorption in the gut lumen (5). The gastrointestinal tracts of infants lack some of the bile acids and gastric acids that normally inhibit clostridial growth. Honey and corn syrup have been identified as sources of *C. botulinum* spores. Vacuum cleaner dust and soil have also been implicated. In the food samples tested, no preformed toxin has been identified, only clostridium spores. About 70% of cases are in breast-fed infants; presumably these infants have different gut flora when compared with their formula-fed counterparts. Almost half the cases reported over the past 30 years have been from California (2). (c) Wound botulism accounts for about 10% of cases and occurs after a wound that is

contaminated with spores that germinate and produce toxin over time. Most cases are associated with black tar heroin made in Mexico, affecting the western United States with the preponderance from California. In one report, only 1 out of 102 cases of wound botulism did not occur in a drug user (6). (d) Botulism of undetermined origin is the adult version of infant botulism, in which no food vehicle can be identified and there is no evidence of wound botulism in a patient older than 1 year of age. This type is rare and usually results from intestinal colonization in an adult.

The World Health Organization describes three more types of botulism in addition to the four classic forms (1): (e) Inhalational botulism is a potential threat if the toxin is aerosolized as a biologic weapon. (f) Waterborne botulism is only a theoretical concern, as water-treatment processes inactivate the toxin. (g) Iatrogenic botulism stems from the use of botulinum toxin for therapeutic or cosmetic purposes (11).

CLINICAL PRESENTATION

The initial symptoms of *foodborne botulism* are predominantly gastrointestinal, including nausea, vomiting, abdominal pain, and distention, likely a result of pathogenic agents or toxins in the contaminated food other than *C. botulinum.* Symptoms usually develop within 12 to 36 hours but may develop as early as 4 hours or as late as 10 days. Other initial symptoms are often mild and include fatigue, weakness, and vertigo. Additional symptoms include sore throat, dry mouth, and poor visual accommodation. If the toxin exposure is minimal, patients gradually recover. Otherwise, symmetric, descending flaccid paralysis with prominent bulbar palsies such as diplopia, dysarthria, dysphonia, and dysphagia develops. Physical examination may reveal weakness or paralysis of the upper extremities; dilated, nonreactive pupils; and ophthalmoplegia. The patient may be drooling and have difficulty speaking. Deep tendon reflexes are preserved, and ataxia is absent. Weakness of the extremities and paralysis of respiratory muscles are the most concerning symptoms. Patients maintain a normal mental

status and are afebrile. Autonomic instability, such as orthostatic hypotension, also occurs and may be the predominant or only symptom on presentation, confounding the diagnosis.

Infant botulism is characterized by constipation followed by neuromuscular paralysis. Cranial nerves are affected first, and paralysis progresses to peripheral and respiratory musculature. The term "floppy infant syndrome" best describes the presentation. Symptoms can vary from mild lethargy with poor feeding to hypotonia with respiratory compromise.

The neurologic symptoms of *wound botulism* are identical to that of foodborne botulism; however, gastrointestinal symptoms are absent. Wounds are typically in avascular areas, with crush injuries, and most often, in patients injecting black tar heroin subcutaneously (skin popping). *Iatrogenic cases* may vary from mild symptoms to profound respiratory compromise requiring intubation. Botulinum toxin is used therapeutically for spasticity, cervical dystonia, blepharospasm, and hyperhidrosis, as well as for cosmetic purposes. The history of recent botulinum toxin injection will make the diagnosis (7).

DIFFERENTIAL DIAGNOSIS

Regardless of the type of botulism, the neurologic manifestations are similar. The diagnosis is easier with large outbreaks; however, the majority of cases involve single patients. As a result, the diagnosis is often missed. Botulism should be considered in a patient presenting with gastrointestinal, autonomic, and cranial nerve dysfunction or in an infant with diminished sucking, feeding, and crying ability. The differential diagnosis for foodborne and infant botulism is listed in Table 352.1. Psychiatric illness should be a diagnosis of exclusion. Misdiagnosis as such has been fatal.

TABLE 352.1
Differential Diagnosis for Botulism

Foodborne Botulism	Infant Botulism
Cerebrovascular ischemia (CVA)	Electrolyte abnormalities
Chemical intoxication	Leigh disease[a]
Carbon monoxide	Meningitis
Barium carbonate	Metabolic encephalopathy
Methyl chloride	Myopathy (congenital)
Methyl alcohol	Reye syndrome
Cholinergic (organophosphate) agents	Sepsis
Diphtheria	Werdnig–Hoffman disease[b]
Elapidae envenomation (coral snake)	
Food poisoning	
Landry–Guillain–Barré syndrome	
Miller–Fisher variant	
Medication reactions (especially aminoglycosides)	
Multiple sclerosis	
Myasthenia gravis	
Eaton–Lambert syndrome	
Paralytic shellfish poisoning	
Poliomyelitis	
Polymyositis	
Psychiatric disorders	

[a]Subacute necrotizing encephalomyelopathy.
[b]Spinal muscular atrophy.

The gastrointestinal symptoms of botulism are nonspecific and do not demonstrate a distinctive pattern. Patients at this stage of the disease are often discharged with a diagnosis of food poisoning. Fever is absent in patients with botulism but can be present in certain types of food poisoning. A history of the consumption of canned foods, especially home-canned foods, may be helpful in arriving at the diagnosis.

Landry–Guillain–Barré syndrome usually results in ascending weakness or paralysis. In the Miller–Fisher variant of this syndrome, patients have bulbar palsies (diplopia, dysarthria, dysphonia, and dysphagia) and descending weakness or paralysis, making it extremely difficult to distinguish clinically from botulism. Gastrointestinal symptoms are lacking in Landry–Guillain–Barré

syndrome, unless they are part of the associated antecedent viral syndrome.

Myasthenia gravis may present as weakness, ptosis, and ophthalmoplegia; however, gastrointestinal symptoms are absent. A Tensilon (edrophonium) test may be necessary to differentiate myasthenia gravis from botulism (see Chapter 160). Edrophonium blocks the metabolism of acetylcholine in the synapse and has less effect in botulism, in which there is decreased neurotransmitter release, although some degree of clinical improvement may occasionally be seen.

The Centers for Disease Control and Prevention (CDC) criteria for the diagnosis of botulism requires a patient who presents with descending paralysis to have one of the following: *C. botulinum* isolated from stool or wound specimens; botulinum toxin in serum, stool, or implicated food samples; or a compatible illness in a person who is epidemiologically linked to a case confirmed by the previous methods (7). Although not included in the CDC diagnostic criteria, electromyography demonstrating findings typical of botulism may be required in order for antitoxin to be released. Botulism demonstrates a typical pattern on repetitive stimulation test (20 to 50 Hz) (8). Although this pattern is not pathognomonic for botulism, when it is combined with other clinical data it can be used to make the diagnosis.

ED EVALUATION

The history should include the time of onset; nature, progression, and severity of symptoms; and questions concerning diet, crush injuries, skin wounds, and injected drugs. The physical examination should focus on neurologic evaluation, particularly cranial nerve function, muscle strength, deep tendon reflexes, pupil size and reactivity, extraocular motor function, swallowing, and phonation. As death from botulism is from respiratory insufficiency, patients should have frequent assessments of vital capacity and negative inspiratory force.

Cell counts, serum electrolytes, and plain radiographs are usually normal in patients with botulism but may be helpful to exclude other diagnoses. Normal cerebrospinal fluid or slightly elevated spinal fluid protein may be seen in botulism and distinguishes it from other disease states such as meningitis. Landry–Guillain–Barré syndrome may reveal elevated protein without pleocytosis, but early in that syndrome the spinal fluid may be normal. Brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) is normal in patients with botulism but may yield the diagnosis of cerebral or cerebellar infarct.

The Tensilon test can help differentiate myasthenia gravis from botulism.

When botulism is suspected, electromyography should be performed as soon as possible.

Stool, serum, or wound cultures should be sent for *C. botulinum* to the state health department laboratory or the CDC. Serum and stool samples and wound tissue should also be sent for detection of botulinum toxin. In one study, at least one of these laboratory tests was positive in 65% of patients diagnosed with botulism. Stool and sera should be refrigerated but not frozen. Wound specimens should be placed in an anaerobic device. Suspected food should be left in their original containers and placed in sterile unbreakable containers if possible. Currently, the mouse bioassay used to detect botulinum toxin is complicated, and results are often delayed. Rapid assays under development may allow for more rapid confirmation (5).

KEY TESTING

- Supportive care testing for electrolytes, complete blood count (CBC), calcium, magnesium
- Lumber puncture (LP), Tensilon test, and brain imaging to investigate other potential causes
- Electromyography (EMG) is the fastest test to suggest botulism
- Send serum, stool, wound, and food samples to state laboratory or CDC for confirmation

ED MANAGEMENT

Supportive care is the mainstay of treatment. Endotracheal intubation with mechanical ventilation is recommended for patients with a vital capacity $<30\%$ of predicted (or <12 mL/kg). Fluids should be given to replete any gastrointestinal losses, and parenteral analgesics can be given for the pain associated with abdominal distention.

Despite the delay from ingestion of contaminated food to presentation, gastric decontamination should be considered in cases of foodborne botulism. Gastric lavage may remove any remaining toxin or contaminated food from the stomach. Activated charcoal has been shown to reduce morbidity and mortality in animals (9). Only sorbitol-based cathartics should be used, as magnesium may exacerbate weakness. Although whole-bowel irrigation can aid in removal of toxin from the gut, this has not been evaluated in a formal study.

A heptavalent (types A–G) botulism antitoxin (HBAT) has been developed by the US Army and was approved by the FDA in 2013 to replace previous monovalent and bivalent antitoxin preparations for patients older than 1 year (10). The equine-derived antitoxin is distributed by the CDC to nine local repositories in the United States and is available by contacting the state health department. Antitoxin is most effective when given within 24 hours of symptom onset and should be administered as soon as the diagnosis of botulism is suspected, without waiting for laboratory confirmation. The antitoxin does not reverse symptoms already present on administration. It can only prevent symptom progression, further stressing the necessity of early administration.

The initial dose of HBAT is one vial diluted 1:10 given intravenously, slowly to observe for allergy and adverse effects. The benefits of antitoxin therapy must be weighed against the potential adverse effects. Because antitoxin is an animal-derived biologic product, its use can result in anaphylaxis, hypersensitivity reactions, and serum sickness. It is not recommended to administer a test dose to assess hypersensitivity, because botulism can be fatal and

antitoxin is the only available therapy. Clinicians should be prepared to handle any adverse reactions and should have appropriate medications (e.g., epinephrine) readily available.

A human botulism immune globulin (Baby-BIG) was approved by the FDA in 2013 but it is in use for many years for infant botulism. It is only available from the California Department of Health Services Infant Botulism Treatment and Prevention Program.

Antibiotics should be administered for wound botulism. Penicillin G is usually the first-line agent, although many antibiotics have been shown to be effective against *C. botulinum*. Early surgical consultation should also be obtained for cases of wound botulism because debridement is considered a primary therapeutic intervention (8).

In contrast, antibiotics are not generally recommended for infant botulism. Aminoglycosides have been demonstrated both clinically and experimentally to potentiate neuromuscular blockade. Use of antibiotics in infant botulism can exacerbate the condition, as lysis of intraluminal *C. botulinum* may increase the amount of toxin absorbed (2). The benefit of antibiotic therapy for foodborne botulism has not been demonstrated and it is thus not recommended.

CRITICAL INTERVENTIONS

- Consider adult botulism when there is a history of ingestion of smoked, salted, or canned food.
- Consider infant botulism in a floppy baby with respiratory insufficiency.
- In cases of suspected wound botulism, consult a surgeon regarding debridement.
- Assess the vital capacity in patients with suspected botulism and perform endotracheal intubation on those with a vital capacity $<30\%$ of predicted (<12 mL/kg).
- Contact the state department of health or the CDC (770-488-7100) and administer botulism antitoxin as soon as possible.

DISPOSITION

Any patient suspected of having botulism should be admitted to a critical care setting. This allows for observation, frequent neurologic examinations, assessments of respiratory status, and monitoring for anaphylaxis, which is a risk with the administration of the antitoxin.

Consultants from infectious disease, toxicology, critical care, and neurology may aid in diagnosis and assumed care. Patients need frequent respiratory evaluations and should be admitted to an intensive care unit. Early surgical consultation should be obtained for cases of wound botulism because debridement is considered a primary therapeutic intervention (8). Contact with the state health department or CDC Emergency Operations Center (770-488-7100, available 24 hours a day) is also required as soon as possible to allow for early administration of antitoxin.

Prolonged admission is the usual course, as the recovery period can last from weeks to months and occasionally up to a year, but mortality has fallen from 50% to less than 5% currently for untreated cases. Patients who receive early and aggressive supportive care usually do well. Although patients can make a complete recovery, long-term sequelae are common and range from fatigue to persistent muscle weakness and dyspnea.

Common Pitfalls

- Failure to consider the diagnosis of botulism in patients with diplopia, dysphagia, dysphonia, and weakness, or in infants with constipation, feeding problems, and hypotonia.
- Failure to adequately monitor for respiratory insufficiency.
- Failure to appreciate that electromyography is the most rapidly available diagnostic test.
- Failure to appreciate that early antitoxin administration is the best therapy.
- Failure to administer antitoxin pending results of a test dose to assess for hypersensitivity.

ACKNOWLEDGMENTS

The author would like to thank Dr. Adhi Sharma for his contributions to previous editions of this chapter.

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CHAPTER 353

Oral Hypoglycemic Agents

Jeffrey R. Suchard

Diabetes mellitus is a common disease, with most patients having the noninsulin-dependent (Type II) form of the disease. Oral drug therapy is the main treatment modality in these patients. Several oral medications may be used, including the sulfonylureas, meglitinides, biguanides, α-glucosidase inhibitors, dipeptidyl peptidase inhibitors, and thiazolidinediones, which are collectively known as the "oral hypoglycemic agents." Of these drug classes, only the sulfonylureas and meglitinides are truly hypoglycemic agents, for they will lower the serum glucose concentration; the other classes have various mechanisms to improve glucose levels and tolerance but do not generally cause hypoglycemia by themselves. Sulfonylurea agent exposures result in the most medical evaluations, but biguanide toxicity causes the most reported deaths; this chapter will therefore focus mostly on these classes of drugs. Hypoglycemia in general is covered in Chapter 206.

The pharmacokinetics of oral antidiabetic medications are summarized in Table 353.1. Sulfonylurea agents inhibit potassium efflux from pancreatic β-islet cells, depolarizing the cell and triggering endogenous insulin release (1). Long-acting agents, such as glyburide, chlorpropamide, and extended-release glipizide, are more likely to result in hypoglycemia requiring hospital admission (2). Additional risk factors for hypoglycemia with sulfonylurea use include greater patient age, concurrent polypharmacy, and impaired renal clearance.

TABLE 353.1
Pharmacokinetics of the Hypoglycemic Agents

Generic Name	Trade Name	Peak (hrs)	Duration (hrs)
First-Generation Sulfonylureas			
Chlorpropamide	Diabinese	3–6	24–72
Acetohexamide	Dymelor	3	12–24
Tolazamide	Tolinase	4–6	12–24
Tolbutamide	Orinase	5–8	6–12
Second-Generation Sulfonylureas			
Glipizide	Glucotrol	1–3	12–24
Glipizide ER	Glucotrol XL	6–12	24
Glyburide	Micronase, DiaBeta Glynase	2–6	24
Glimepiride	Amaryl	2–3	24
Meglitinides			
Repaglinide	Prandin	0.5–1	1
Nateglinide	Starlix	0.3	1.5
Biguanides			
Metformin	Glucophage	2–3	5–6

In overdose situations, whether intentional or accidental, hypoglycemia may be expected with any of the sulfonylureas. If hypoglycemia occurs, it is typically within the first several hours after overdose. In adult volunteers ingesting glipizide, all subjects became hypoglycemic within 3 hours (3), and the mean time to hypoglycemia was 2 hours in a retrospective study of children <6 years old (4). Allowing these children access to food or prophylactic treatment with IV glucose increased the delay to hypoglycemia, when it occurred, to over 5 hours. A significant proportion (18%) of these patients with access to food had a delay to hypoglycemia >8 hours after sulfonylurea ingestion (4). Occasional cases of delayed hypoglycemia more than 24 hours after drug ingestion have been reported (5).

Meglitinides are a newer family of agents used to treat postprandial hyperglycemia. These drugs are derivatives of the nonsulfonylurea moiety of glyburide and include repaglinide

(Prandin or NovoNorm) and nateglinide (Starlix). These drugs have a similar mechanism of action to the sulfonylureas, although the time to onset and the duration of hypoglycemia are much shorter (Table 353.1) (1).

The biguanide class includes the drugs metformin and phenformin. Metformin is currently the only biguanide in common use, and it is the most commonly prescribed medication worldwide. Metformin increases insulin sensitivity and decreases hepatic gluconeogenesis and intestinal glucose absorption, without affecting insulin secretion. Metformin is often referred to as an antihyperglycemic medication because it corrects hyperglycemia in diabetics but does not cause hypoglycemia in nondiabetics. Hypoglycemia associated with metformin is rare and usually only occurs in the presence of other medications interfering with glucose homeostasis (6).

Lactic acidosis is the most serious side effect associated with metformin use. Metformin-associated lactic acidosis (MALA) occurs with an incidence of 0.03 cases per 1,000 patient-years and carries a mortality rate of 50% (7). Because lactic acidosis occurs mainly in patients with baseline renal insufficiency, metformin is contraindicated in patients with serum creatinine >1.5 mg/dL (7). Use of iodine-containing contrast media has been linked to MALA, leading the manufacturer to recommend that the drug should be discontinued 48 hours prior to IV contrast and withheld for the next 48 hours. MALA after contrast radiography appears to occur mostly in patients with underlying renal insufficiency. Lactic acidosis also occurs with acute metformin overdose.

The other classes of oral drugs used for diabetes are rarely associated with side effects that do not cause hypoglycemia and rarely need emergency department (ED) care.

CLINICAL PRESENTATION

Symptoms from hypoglycemia fall into two main categories: autonomic and neuroglycopenic. Autonomic symptoms are a result of excessive adrenergic tone, resulting from the release of counter-

regulatory hormones as the body reacts to increased serum glucose. Anxiety, palpitations, diaphoresis, irritability, and tremor are seen at serum glucose levels near 60 mg/dL in nondiabetic volunteers. Neuroglycopenic symptoms such as dizziness, tingling, blurred vision, difficulty thinking, and faintness begin at glucose levels near 50 mg/dL. However, there is a wide variation in the glucose level at which symptoms develop. Some individuals, particularly women and children, can be asymptomatic with glucose levels <50 mg/dL, and diabetics can develop symptoms of hypoglycemia at a "normal" or elevated glucose level when the level rapidly falls from a higher one. Additionally, concurrent therapy with β-adrenergic blockers or underlying diabetic neuropathy may mask the autonomic symptoms of hypoglycemia.

Hypoglycemia can cause focal neurologic deficits and, in severe cases, coma or seizures. Mild hypothermia may develop with prolonged hypoglycemia. Hypokalemia may result from intracellular potassium shifting.

MALA presents with nonspecific signs and symptoms. Patients may have nausea, vomiting, anorexia, epigastric pain, diarrhea, somnolence, or lethargy. Kussmaul respirations (hyperpnea and tachypnea) represent increased ventilation in response to the metabolic acidosis. Hypotension, hypothermia, and respiratory failure have also been reported. Various cardiac dysrhythmias, including premature ventricular contractions, bradycardia, asystole, and ventricular fibrillation, have been reported, probably secondary to severe acidemia.

DIFFERENTIAL DIAGNOSIS

Hypoglycemia is a potential etiology for any patient with altered mental status, neurologic findings, or signs of sympathetic stimulation such as diaphoresis or tremor. The differential diagnosis of patients with such findings is large and includes trauma, stroke, brain tumors, central nervous system infections, severe metabolic disorders, vasovagal episodes, and a wide variety of drug intoxications. Hypoglycemia should be considered as the underlying

cause for patients presenting with trauma or seizures. Patients particularly at risk are those with a personal or family history of noninsulin-dependent diabetes, with access to oral hypoglycemic drugs.

Diabetics presenting with an elevated anion-gap metabolic acidosis may have either MALA or diabetic ketoacidosis. These conditions may be differentiated based on the history (e.g., intercurrent illness, recent oral intake, intentional ingestion) and the presence or absence of hyperglycemia, ketosis, and hyperlactatemia.

ED EVALUATION

Assessment of the patient's airway, breathing, and circulation is the first priority. The history should differentiate between an overdose or only therapeutic doses, the type of medication(s), the amount ingested, and the time and course of symptoms. Physical examination should pay particular attention to the neurologic status, as hypoglycemia may present with subtle cognitive changes, such as irritability, distractibility, or even focal motor deficits. A rapid bedside glucose test should be performed early in patients with altered mental status.

Laboratory evaluation should include a confirmatory quantitative glucose determination. A serum chemistry panel is also indicated to check for electrolyte abnormalities and renal insufficiency. Repeat bedside glucose determinations should be performed at least every 1 to 2 hours during the initial evaluation and immediately whenever the patient shows signs of any autonomic increase or altered mental status.

Patients with suspected metformin toxicity need a chemistry panel to evaluate for an anion-gap metabolic acidosis and renal insufficiency as well as a serum lactate level. If an elevated anion gap is present, blood gas analysis will help define the degree of acidosis.

KEY TESTING

- Rapid and serial serum glucose determinations, preferably with stat bedside testing
- Chemistry panel, to check for renal insufficiency and/or an elevated serum anion gap
- With metformin toxicity: serum lactate, blood gas analysis

ED MANAGEMENT

Gastrointestinal decontamination with activated charcoal should be considered for patients presenting early after oral hypoglycemic agent ingestion. The first-line treatment for symptomatic hypoglycemia is intravenous (IV) dextrose. Adults should be given 1 to 2 mL/kg of 50% dextrose (typically 1 to 2 ampules D50W); children should receive 2 to 4 mL/kg of 25% dextrose. Repeat dextrose boluses may be necessary, as determined by serial serum glucose determinations, and an infusion of 5% to 10% dextrose can be initiated to maintain euglycemia (60 to 110 mg/dL). If higher dextrose concentrations are required, the infusion should be given via a central venous catheter. The transient hyperglycemia that occurs with bolus dextrose therapy can cause reflex secretion of additional insulin (1), exacerbating the underlying problem and increasing the overall dextrose requirements. Hence, excessive dosing of dextrose should be avoided.

Octreotide, a synthetic somatostatin analog that inhibits pancreatic insulin secretion (1,3,8), is increasingly used as an option for treating refractory or recurrent hypoglycemia as a result of sulfonylurea poisoning. Octreotide is superior to glucose alone in volunteer sulfonylurea overdose by decreasing hypoglycemia, glucose requirements, and circulating-insulin levels (3). In clinical experience, octreotide use significantly decreases recurrent hypoglycemic episodes in patients with sulfonylurea toxicity (8). Dosing of octreotide is not standardized, and it has been given both subcutaneously (SC) and IV. Suggested dosing is 50 to 100 μg SC or IV every 6 to 12 hours for adults and 4 to 5 μg/kg/d divided every 6 hours in children.

No specific therapy exists for MALA. Endotracheal intubation and correction of hypotension with IV fluids and vasopressors are likely to be needed in severe cases. Severe cases can be treated with hemodialysis, which will correct the acidosis as well as remove lactate and metformin.

CRITICAL INTERVENTIONS

- Obtain serial serum glucose levels on patients with potential sulfonylurea and meglitinide overdose.
- Obtain a serum lactate level on patients with metabolic acidosis who are taking metformin.
- Administer IV dextrose for hypoglycemia, but avoid inducing hyperglycemia.
- Administer octreotide to patients with recurrent hypoglycemia.

DISPOSITION

Patients developing hypoglycemia from sulfonylurea drugs should be treated with dextrose and admitted to the hospital. The half-lives of the sulfonylureas are long enough that recurrent episodes of hypoglycemia should be expected. Admission to a critical care unit is often necessary, as the frequency of glucose determinations (at least every 1 to 2 hours) may preclude observation on a general medical ward. Also, patients may require frequent adjustments in dextrose infusions or treatment with octreotide. Extended observation in an ED holding unit may be considered if the patient does not suffer from recurrent hypoglycemia requiring repeat dextrose boluses or infusions. Hypoglycemia from meglitinide toxicity theoretically should be of shorter duration than from sulfonylureas; however, as a result of a lack of published evidence that short-term observation is safe, such patients should be managed like sulfonylurea-toxic patients and be admitted for serial glucose determinations.

There is considerable controversy regarding the optimal management of asymptomatic patients exposed to oral hypoglycemic medications. Many of the patients evaluated for

sulfonylurea toxicity are children in whom the history of actual ingestion (vs. mere exposure to the pills) is unclear, who present with normal mental status and glucose levels, and who generally have a benign outcome. Nevertheless, because rapid drug detection to confirm actual exposure is not commonly available, these patients need a period of observation to monitor for hypoglycemia; the duration of this observation period is the crux of the controversy. Published evidence generally supports an observation period of 8 hours (9). Patients who develop hypoglycemia are treated and admitted, although those who do not manifest hypoglycemia may be discharged home or referred for psychiatric evaluation as appropriate. Prophylactic treatment of asymptomatic euglycemic patients with glucose should be avoided, as this may mask the development of hypoglycemia and lead to an inappropriate disposition. Cases of delayed hypoglycemia from sulfonylurea agents have occurred when the patients have been given parenteral glucose (9). Oral food intake is acceptable and seems less likely to mask hypoglycemic toxicity, although it may just delay its onset by a few hours (4). Because of the required length of observation and the potentially dire CNS consequences of discharging a patient who later becomes hypoglycemic, some authors recommend medical admission and at least 24 hours of observation for all patients with a known or suspected overdose of sulfonylurea drugs.

Patients with MALA also require admission, usually to an intensive care unit, because the associated mortality is high and these patients often have significant comorbidities. Serum lactate and pH levels do not correlate well with clinical outcome (10). Patients with an acute biguanide overdose, but without lactic acidosis, should be admitted for serial serum chemistry determinations.

Patients overdosing with the other oral agents for diabetes are unlikely to require admission, unless concerning co-ingestants or comorbidities are present. Consultation with a poison control center or medical toxicologist can assist in determining the optimal patient disposition.

Common Pitfalls

- Failure to appreciate that hypoglycemia can result in focal neurological deficits and focal seizures.
- Failure to observe patients with sulfonylurea and meglitinide overdose for at least 8 hours.
- Administering prophylactic dextrose to patients with sulfonylurea and meglitinide overdose who are asymptomatic or euglycemic.
- Failure to appreciate that excessive glucose administration promotes insulin secretion and can lead to recurrent hypoglycemia in sulfonylurea and meglitinide poisoning.

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CHAPTER 354

Mushrooms

Brandon K. Wills and Steven E. Aks

Serious poisoning from mushroom ingestion is relatively infrequent. Exposures most often involve (1) unintentional ingestion of toxic species obtained by inexperienced foragers, (2) individuals seeking mind-altering effects of some species, or (3) unintentional ingestion by children. Differentiating poisonous from nonpoisonous species can be difficult even for experts and often requires microscopic examination of the spores. For the clinician, evaluating a patient for suspected poisoning, identifying the fungus in question is even more challenging.

In 2011, there were 6,818 exposures to mushrooms reported to US poison centers, which included 5,560 cases of unknown species (1). There were two deaths, both from cyclopeptide species. There are several hundred toxic mushroom species, and these can be categorized into a syndromic presentation based on their mycotoxin (see Table 354.1).

TABLE 354.1
Presenting Symptoms/Signs, and Treatment by Mushroom Species

Predominant Effect	Associated Features	Mushroom Class/Toxin	Species	Treatment[a]
Hallucinations	Mydriasis, tachycardia, coma, seizures	Psilocin	*Psilocybe* and *Concocybe* sp	Benzodiazepines
	Mild hallucinations, coma, myoclonus, seizures	Ibotenic acid/muscimol	*Amanita muscaria, pantheria, gemmata*	Low-stimulus environment
Cholinergic signs	DUMBELS[b]	Muscarine	*Clitocybe* and *Inocybe* sp	Atropine for pulmonary symptoms
Disulfiram reaction	N/V/D, flushing, ↑HR association with ethanol use	Coprine	*Coprinus* sp	Antihistamines
Renal failure	Delayed GI symptoms	Orellanine[c]	*Cortinarius* sp	Supportive/hemodialysis
Renal failure	Early GI symptoms	Allenic norleucine[c]	*Amanita smithiana*	Supportive/hemodialysis
Rhabdomyolysis	Myalgias, fatigue	Unknown myotoxin[c]	*Tricholoma equestre*	Maintenance of urine output, ± urinary alkalinization
Early GI symptoms (2–3 hrs)	N/V/D	GI irritants	*Chlorophyllum* sp, many others	Supportive care only Antiemetics
Delayed GI symptoms (>6 hrs)	Delayed hepatotoxicity	α-Amanitin[c]	*A. phalloides, virosa, Lepiota* sp	Activated charcoal Penicillin G *N*-Acetylcysteine Silibinin Consider liver transplant
	Delayed nephrotoxicity	Orellanine[c]	*Cortinarius*	Supportive/hemodialysis
	N/V/D, CNS, hepatic	Gyromitrin[c] (monomethyl hydrazine)	*Gyromitra* sp	Pyridoxine

[a]In addition to supportive care, including IV fluids and antiemetics, and decontamination if appropriate.
[b]Diarrhea, urination, miosis, bradycardia, bronchorrhea, bronchospasm, emesis, lacrimation, salivation.
[c]Mushrooms that lead to potentially lethal poisoning.

The most deadly class is the cyclopeptide-containing, or amatoxin-containing, Amanita species. Cyclopeptide poisoning is a rare event in the United States, but exposures are much more common in Europe. Amatoxins are classically found in *Amanita phalloides* and *A. virosa* species but are also found in *Galerina autumnalis, G. venenata, Lepiota* sp, and *Conocybe filaris.* Amatoxins are bicyclic octapeptides that noncompetitively inhibit RNA polymerase II in the liver and, to a lesser extent, the kidney. Protein synthesis is interrupted, causing hepatocellular necrosis and acute tubular necrosis. Severe poisoning can result in fulminant hepatic and renal failure. Phallotoxins are another cyclopeptide toxin found in *Amanita* sp, which are thought to produce the gastrointestinal (GI) symptoms seen 6 to 10 hours after ingestion.

Mushrooms containing coprine include members of the *Coprinus* sp, including *C. atramentarius.* Metabolites of coprine can inhibit aldehyde dehydrogenase and result in a disulfiram-like reaction if ethanol is consumed concurrently or within 3 days of the meal (see Chapter 297).

There is a diverse group of mushrooms whose toxins are irritants that cause primarily GI symptoms. Nausea, vomiting, diarrhea, and abdominal pain usually occur within 2 to 3 hours of the meal, and

because the course is generally self-limited, identification of the specific species is unimportant.

Amanita muscaria, A. pantherine, and *A. gemmata* contain the toxins ibotenic acid and muscimol. Ibotenic acid is similar to the excitatory neurotransmitter glutamate and is an agonist at the *N*-methyl-D-aspartate (NMDA) receptor, whereas muscimol is a γ-aminobutyric acid (GABA) agonist. Symptoms can be diverse and may include somnolence, hallucinations, myoclonus, and seizures. Patients may seek to consume *A. muscaria* and *A. pantherine* species intentionally for their hallucinogenic effects.

Gyromitra esculenta or "false morel" and other species represent one-third of fatal mushroom poisonings in Eastern Europe; however, they are quite rare in the United States. These mushrooms contain gyromitrins, a family of hydrazones that are metabolized to monomethylhydrazine, which is structurally related to isoniazid and some types of rocket fuel. Hydrazines inhibit pyridoxine phosphokinase, which prevents the activation of pyridoxine (vitamin B_6). Activated B_6 is required for GABA synthesis, resulting in decreased GABA production. Poisoning results in delayed GI symptoms and hepatic and renal toxicity, and like isoniazid, often include seizures (see Chapter 317).

Muscarine is an alkaloid found in both *Clitocybe* and *Inocybe* genera that is structurally similar to acetylcholine. Symptoms are typically less severe than, yet similar to, the peripheral muscarinic effects seen in organophosphate/carbamate insecticide exposures (see Chapter 318).

Species of *Cortinarius* contain the toxin orellanine, whose metabolites cause damage to renal tubules and result in interstitial nephritis and renal failure several days to weeks after ingestion. The majority of these cases have been in Europe.

A. smithiana mushrooms contain alienic norleucine and pentanoic acid, which can cause renal failure several days after ingestion. Unlike *Cortinarius,* these mushrooms may cause GI effects as early as 2 hours of ingestion.

Psilocybe species, as well as *Concocybe smithii, Gymnopilus spectabilis,* and *Panaeolus subbalteathus,* are all known to contain

psilocybin. Ingestion of this class of mushroom is often intentional for its hallucinogenic effects. Psilocin is a serotonin agonist that often causes an initial sympathomimetic-like effect including tachycardia, hypertension, mydriasis, and tremor, followed by hallucinations.

Rhabdomyolysis has been attributed to a myotoxin found in *Tricholoma equestre* mushrooms.

CLINICAL PRESENTATION

Patients often present within several hours of a mushroom meal with nonspecific GI symptoms including nausea, vomiting, and diarrhea. Fortunately, the majority of these patients are suffering from GI irritants and require only supportive care. Patients who have consumed the more toxic mushrooms containing cyclopeptides, orellanine, or monomethylhydrazine generally have a delay of more than 6 hours before the onset of symptoms. A short time to symptom onset gives the clinician some reassurance that patients presenting early are likely to have a benign clinical course. A notable exception is with *A. smithiana* ingestion; patients ingesting this mushroom are likely to have GI symptoms within hours of ingestion but subsequently develop renal failure over the next 48 hours to several weeks. Fortunately, *A. smithiana* ingestions are rare, and the only cases reported in the United States have been in the Pacific Northwest. Another caveat applies to those who have consumed a "mushroom salad" that contained several species including both cytotoxic and GI irritant species and thus present with symptoms earlier than 6 hours.

Each class of toxic mushroom has a distinctive constellation of presenting symptoms, signs, laboratory abnormalities, and end-organ involvement (Table 354.1). Patients who have ingested cyclopeptide- or amatoxin-containing mushrooms will typically present after more than 6 hours of ingestion with nausea, vomiting, abdominal pain, and severe watery diarrhea. Symptoms may improve 24 to 48 hours into the illness, followed by hepatic injury marked by elevated transaminases, bilirubin, and often renal dysfunction (2). Within 2 to 6 days, fulminant hepatic and renal failure may develop, with subsequent hepatic encephalopathy, coagulopathy, seizures, and

death. With intensive supportive therapy, survival may be as high as 90% (3); however, with fulminant hepatic failure, orthotopic liver transplant may be required (4).

Mushrooms containing coprine are typically edible and cause no symptoms. If ethanol is consumed between several hours to 3 days after the ingestion, however, a disulfiram-like reaction may be seen. Symptoms include nausea, vomiting, facial flushing, hypotension, tachycardia, headache, vertigo, and metallic taste. Symptoms typically last up to several hours.

Mushrooms containing GI irritants cause symptoms similar to gastroenteritis, usually beginning 30 minutes to 6 hours after ingestion. Vomiting and diarrhea, sometimes bloody, may last for 48 hours and are typically self-limited.

Patients consuming mushrooms containing ibotenic acid and muscimol can have a varied presentation as a result of both GABAergic and glutamate effects. Symptoms usually begin within 30 to 180 minutes of ingestion and may include a combination of euphoria, mild hallucinations, obtundation, agitation, myoclonus, and seizures.

The “false morel” *G. esculenta* is often confused with the edible true morel or *Morchella* species and results in significant toxicity. The severity of symptoms depends on the amount ingested and method of preparation. Parboiling or drying may eliminate the gyromitrin toxins. Patients often become symptomatic 5 to 8 hours after ingestion and present with nausea, vomiting, and diarrhea. These symptoms may last up to several days before resolving. Central nervous system (CNS) effects, including fatigue, headache, ataxia, tremor, and (rarely) seizures, may be seen. After 24 to 72 hours, there may be evidence of hepatic and/or renal damage, as well as hemolysis and methemoglobinemia.

The onset of symptoms following ingestion of muscarine-containing mushrooms is rapid, usually within 30 minutes. Cholinergic signs and symptoms include those identified by the commonly used mnemonic DUMBELS: diaphoresis, urination, miosis, bronchorrhea/bradycardia, emesis, lacrimation, and salivation. With

supportive treatment, patients typically recover with no long-term effects.

Rhabdomyolysis with myalgias, weakness, and fatigue begins 24 to 74 hours after ingesting *T. equestre* mushrooms. Symptoms usually improve over the following 2 weeks, but death can occur. Fatal cases have had persistent creatine kinase (CK) elevations and evidence of myocardial damage on autopsy.

Toxicity from orellanine-containing *Cortinarius* sp is most often seen in Europe and is relatively uncommon in the United States. GI symptoms, including nausea, vomiting, diarrhea, and abdominal or flank pain, begin 2 to 14 days after ingestion, at which time renal damage has already occurred. Progression to end-stage renal failure may ensue.

Similar to poisoning by *Cortinarius* sp, the ingestion of alienic norleucine–containing *A. smithiana* produces renal damage 2 to 4 days after ingestion. One distinguishing feature is that *A. smithiana* may cause early GI symptoms.

Abuse of psilocin-containing mushrooms is common among young adults, frequently in combination with alcohol and other drugs. Patients often present to the emergency department with severe anxiety from the unpleasant hallucinations. Other signs and symptoms may include mydriasis, tachycardia, GI symptoms, coma, and seizures. As with other hallucinogens, an increased association with high-risk behavior and poor decision-making often leads to other traumatic injuries (see Chapter 346, “Hauucinogens”).

DIFFERENTIAL DIAGNOSIS

Toxic mushroom ingestion should be considered in the differential diagnosis of patients presenting with GI symptoms, hepatic or renal damage, delirium or hallucinations, disulfiram-like reactions, seizures, or rhabdomyolysis. The GI symptoms from both GI irritant and the more toxic mushrooms will often be indistinguishable from gastroenteritis. The history of recent wild mushroom ingestion may be the only clue to the diagnosis.

Hepatotoxicity similar to that caused by *Amanita* ingestion can occur with overdose of acetaminophen and iron, chronic isoniazid

(INH) therapy, and many nontoxicologic etiologies, including viral hepatitis. In addition to coprine-containing mushrooms, a large number of chemicals and pharmaceuticals can cause a disulfiram-like reaction when ethanol is consumed (see Chapter 297). Other hallucinogens, CNS depressants, γ-hydroxybutyrate (GHB), or withdrawal syndromes may cause symptoms similar to those seen after the ingestion of mushrooms containing ibotenic acid and muscimol. Agents causing toxicity similar to hydrazine-containing mushrooms include isoniazid and some types of rocket fuel. Direct muscarinic agonists or acetylcholinesterase inhibitors produce cholinergic toxicity similar to that seen with muscarine-containing mushrooms. The differential diagnosis of renal failure includes prerenal causes, intrinsic nephrotoxins, and postrenal causes. Conditions that may be confused with psilocin intoxication include use of LSD, mescaline, morning glory, hallucinogenic amphetamines (e.g., methylenedioxymethamphetamine [MDMA]), synthetic cathinones, tryptamines (e.g., dimethyltryptamine [DMT]); alcohol withdrawal; or medical causes of delirium.

ED EVALUATION

The goal of evaluation is to identify patients who may have ingested a cyclopeptide, amatoxin, or other potentially dangerous mushroom. Of greatest importance is the time interval between ingestion of the mushroom and the onset of GI symptoms. Other information that may be helpful include the quantity consumed, cooked versus raw, fresh versus dried, and if ethanol was consumed within 3 days of the meal. Positive identification of the mushroom involved will be very difficult but may be possible if the patient brings a sample of the offending mushroom. The Illinois Poison Center can consult a mycologist to review digital images of the mushroom in three planes that the physician has sent electronically to the poison center (5). The mushroom does not have to be positively identified if the most toxic species can be ruled out. Contacting a regional poison center (800-222-1222) can be helpful in this regard.

Patients with prolonged GI symptoms or clinical evidence of dehydration should have measurement of serum electrolyte, blood

urea nitrogen (BUN), creatinine, and glucose as well as a urinalysis. Evaluation of patients presenting with weakness or myalgias should include a serum creatine phosphokinase (CK). Those with possible amatoxin poisoning should have liver function tests, chemistries, and coagulation studies. A serum creatinine >1.2 mg/dL with an international normalized ratio (INR) >2.5 may predict mortality (6). Except for muscarine, which can be identified by thin-layer chromatography, other mushroom toxins are not easily detected by routine toxicology screening. Thus, the best strategy is to have the mushroom in question identified by a mycologist.

KEY TESTING

- Mushroom identification if possible
- For dehydrated patients: serum electrolytes, BUN, creatinine, urinalysis
- For patients with weakness or myalgias: CK
- For suspected cyclopeptide exposure: transaminases, INR

ED MANAGEMENT

Supportive care is the mainstay of management for any toxic mushroom ingestion. Most patients will need no treatment other than intravenous (IV) fluids if dehydrated and antiemetics. Benzodiazepines should be administered for seizures, severe agitation, or hallucinations. Activated charcoal should be considered for patients presenting within 1 to 2 hours of ingestion.

There is no clear antidote for amatoxin-containing mushrooms though many therapies are empirically used (7). Multiple-dose activated charcoal has been recommended because amatoxins are enterohepatically recirculated. Charcoal hemoperfusion may also enhance toxin elimination if performed in the first 24 hours. High-dose IV penicillin (1 million units per kilogram per day for the first day, followed by 0.5 million units per kilogram per day for 2 more days) appears to have variable efficacy. The mechanism is postulated to prevent or reduce hepatic uptake of amatoxins. Silibinin is thought to reduce hepatic uptake and interrupt enterohepatic

circulation of amatoxins (8). Intravenous silibinin can be obtained in North America by calling the Madaus-sponsored hotline at (866) 520-4412. *N*-Acetylcysteine (NAC), traditionally used for the treatment of acetaminophen poisoning, may also be effective for nonspecific causes of hepatic injury. One comparative animal model demonstrated no benefit from NAC, penicillin, cimetidine, thioctic acid, or silymarin (9). When fulminant hepatic failure occurs, orthotopic liver transplantation is the only successful therapy (4,6).

Patients with coprine-containing mushroom ingestion should be counseled to avoid alcohol. Antihistamines may provide symptomatic relief.

Monomethylhydrazine-containing mushrooms (*Gyromitra* spp) may cause seizures. If benzodiazepine therapy is not immediately successful, the patient should be given IV vitamin B_6 (10). Gyromitrin causes an inhibition of glutamic acid decarboyxylase, similar to isoniazid, and B_6 is effective in this setting. Suggested doses are 1 g for children and 5 g for adults.

Muscarine-containing mushrooms (e.g., *Clitocybe* sp) will generally respond well to supportive care alone. Atropine may be used for severe cholinergic symptoms. Atropine dosing should be continued until reversal of pulmonary symptoms of bronchorrhea and bronchospasm.

Patients with hallucinations should be placed in a quiet, low-stimulus environment, if possible. Haloperidol or droperidol and lorazepam or another benzodiazepine can be used for severe agitation and hallucinations.

The treatment of rhabdomyolysis includes maintenance of urine output by infusion of IV fluids, consideration of urinary alkalinization, and possibly dialysis.

CRITICAL INTERVENTIONS

- Determine the time of onset of symptoms with respect to the time of ingestion.
- Consult a regional poison center, toxicologist, or mycologist to assist with mushroom identification and management.

- Administer IV fluids and antiemetics to patients with GI symptoms and dehydration.
- Admit patients with symptoms that begin 6 to 8 hours after ingestion and monitor for liver and renal dysfunction.

DISPOSITION

Patients who present with GI symptoms that begin within 2 hours after ingestion, have not had a mixed mushroom ingestion, and have low likelihood of *A. smithiana* ingestion may be considered for discharge after favorable response to IV fluids and oral challenge. Patients who have ingested hallucinogenic mushrooms may be safely discharged when their mental status returns to normal. Those who develop GI symptoms 6 to 8 hours after ingestion or whose ingestion is identified as a possible cyclopeptide-containing species should be admitted to the hospital, and liver and renal function should be followed. In the case of delayed presentation with hepatotoxicity from *A. phalloides* or other cyclopeptide-containing mushroom, consultation with a gastroenterologist and transfer to a transplant center is prudent.

Common Pitfalls

- Failure to include wild mushroom ingestion in the differential diagnosis of gastroenteritis, altered mental status, and liver or renal dysfunction of unknown cause.
- Assuming that a potentially lethal mushroom has not been ingested along with less toxic species because symptoms began soon after ingestion.
- Failure to appreciate that therapy is based primarily on clinical symptoms and should not be delayed or withheld until the mushroom is identified.

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CHAPTER 355

Common Toxic Plants

Alicia B. Minns

There are nearly 50,000 calls to American poison centers every year regarding plant exposures (1). This represents about 2% of all calls. The majority of these exposures are accidental ingestions in children younger than 5 years of age. In the majority of calls, the type of plant is unknown. There are very few fatalities reported each year (1). The most serious poisonings typically involve adults who intentionally ingest the raw plant or tea made from the plant for perceived medicinal or hallucinogenic properties, or those who have mistaken the plant as edible. Plant identification can be very challenging. Plant chemistry is complex and most plants contain multiple chemicals and chemical classes that work independently or additively. Additionally, members of the same family of plants can have different toxic effects. A single plant may contain several different toxins. With exception of plants containing cardiac glycosides and anticholinergic plants, the treatment of plant toxicity is mainly supportive.

When evaluating a patient who presents to the emergency department (ED) with a possible plant exposure, identification of the plant should be attempted if possible. Communication with a poison center, medical toxicologist, or botanist is recommended, especially in a symptomatic patient. The most clinically important categories of plant toxicity are discussed below. For a more comprehensive list of plant toxicity, see Table 355.1.

TABLE 355.1
Toxic Principles

Toxin	Type of Toxin	Representative Plant	Toxic Part	Symptoms	Onset of Symptoms
Aconitum	Diterpene and norditerpene alkaloids	Delphinium, wolfbane, monkshood (*Aconitum* species)	Raw roots especially	Early, tingling or burning sensation in the fingers and toes, diaphoresis and chills, generalized paresthesias, numbness, a feeling of intense cold; later, severe vomiting, colicky diarrhea, skeletal muscle paralysis, cardiac rhythm disturbances, and intense pain	10–20 min
Anthroquinones	Anthraquinone glycosides	Aloe, cascara, senna, buckthorn	Probably all parts	Nausea, vomiting, diarrhea, abdominal cramps, palpitations; severe poisonings: nephrotoxicity, GI hemorrhage, seizures, dyspnea, fluid depletion; red color seen in alkaline urine, yellow-brown color in acidic urine can be seen	<6 hrs but no specific information
Anticholinergic	Belladona alkaloids varying with the individual plant: hyoscyamine, hyoscine, atropine, and scopolamine	Jimson weed, deadly nightshade, *Atropa belladonna*, henbane	All parts	Hyperthermia; dry, red, hot skin; dry mucus membranes; mydriasis; tachycardia; decreased GI motility; urinary retention; delirium; hallucinations; and coma in severe cases	Minutes to 2 hrs, varies with route of exposure
Aristolochic acid	Aristolochine	Asarum, snake root, colic root, Indian ginger	Herbal products especially	Acute: tachycardia, weak pulse, decreased heart tonus, constipation, polyuria, urogenital tract irritation, hepatitis; chronic: rapidly progressive fibrosing interstitial nephritis called "Chinese herb nephropathy" or "aristolochia herb nephropathy"	No information
Arnica	Helenalin, a sesquiterpene lactone	Arnica, leopard's bane, mountain daisy, mountain snuff, sneezewort	All parts (also found in herbal products and teas)	Vomiting, diarrhea, bleeding, CNS depression, muscle weakness, hypertension cardiotoxicity; uterine contractions may occur; allergic contact dermatitis	No information
Berberine	Berberine, a benzo-dioxoloquinolizine alkaloid	Barberry, jaundice berry, mahonia	Root and root bark (berries sour but edible)	Weak depressant action on heart and CNS causing hypotension, bradycardia, and vasodilation; acts as a weak local anesthetic; diarrhea, jaundice, dermatitis, stimulates bile production	No information
Calcium oxalates	Insoluble calcium oxalate crystals	Dieffenbachia, dumb cane, pothos, devil's ivy, philodendron, caladium	All parts	Drooling, irritation, stinging and pain of the mouth, tongue, throat; plants containing calcium oxalate crystals are not generally ingested in large enough quantities to produce a systemic intoxication	Immediate
Capsaicin	Oleoresin of capsicum (trans-8-methyl-*N*-vanillyl-6-nonen-amide)	Jalapeno peppers	Juice, pulp, seeds	Dermal irritation, erythema, burning pain, blisters, rash; GI effects; nasal and pulmonary irritant effects; coughing, bronchospasm	Rapid
Cardiac glycosides	Digoxin, digitoxin, other cardiac glycosides	Foxglove, oleander, yellow oleander, lily of the valley	All parts	GI effects seen early; bradycardia with AV block, hypotension, lethargy, dizziness seen later; seizures, electrolyte imbalances, hypertension, and coma are seen rarely; poisoning from acute accidental small-taste ingestions by children is rare	No information
Chinaberry	Meliatoxins A1, A2, B1, and B2 that are tetranorterpinoids of the liminoid class	Chinaberry (*Melia azedarach*)	Ripe fruit more toxic than unripe fruit, which is more toxic than other plant parts	Severe vomiting, diarrhea leading to dehydration and fluid-electrolyte depletion, nephrotoxicity, diaphoresis, pallor, lethargy, ataxia, respiratory failure, seizures, paralysis, coma	1 hr up to several hours
Cimicifuga	Triterpene alkaloids: actein, cimicifugoside, deoxyacetylacteol, and 27-deoxyactein	Black cohosh, black snakeroot, black root, bugbane, bugwort	Seeds, resin, extracts	Nausea and vomiting, dizziness, tremors, headaches, bradycardia or tachycardia; herbal preparations have been used as an abortifacient	No information
Colchicine	Colchicine alkaloids	Autumn crocus, naked lady, meadow saffron	All parts	Nausea, vomiting, diarrhea, abdominal pain, tachycardia, chest pain, later hypotension, bradycardia, seizures, bone marrow suppression, coagulopathy, ECG changes, and death	2–12 hrs

Toxin	Type of Toxin	Representative Plant	Toxic Part	Symptoms	Onset of Symptoms
Coniine	Piperidine alkaloids: coniine and gamma-coniceine with nicotine-like effects	Poison hemlock (*Conium maculatum*); fool's parsley (*Aethusa cynapium*)	Probably all parts	Vomiting, drooling, burning sensation in the throat, confusion, seizures, respiratory depression, tachycardia followed by bradycardia, intense muscle pain, muscle paralysis, rhabdomyolysis; CNS stimulation followed by CNS depression, respiratory paralysis, and death	No information but death may occur within 2 hrs
Cyanogenic glycoside	Amygdalin, the cyanogenic diglucoside D-mandelonitrile-β-D-gentiobioside	Hydrangeas, cotoneaster, braken fern, chewed pits of plum, apricot, bitter almonds, cherry, apple, pear, peach	Chewed pits and seeds from plums, apricots, bitter almonds, cherries, apples, pears, peaches	Nausea, vomiting, diarrhea, dyspnea, cyanosis, weakness, lightheadedness, excitation followed by seizures, stupor, disorientation, paralysis, weakness, coma, and cardiovascular collapse; poisoning from acute accidental ingestions is rare	1.5–2 hrs
Cytisine	Cytisine, a quinolizidine alkaloid which has action similar to nicotine	Wild indigo, Spanish broom, Kentucky coffee tree, golden chain tree	All parts	Profuse persistent vomiting, abdominal pain, hypotension, tachycardia, confusion, dyspnea, agitation, tremor, headache, fatigue, ataxia, drowsiness, headache, delirium, hallucinations, depressed spinal reflexes	15–60 min
Daphne	Mezerein and daphnetoxins are irritant diesters	Daphne, garland flower, flax olive	All parts; juice can be absorbed through broken skin to produce systemic symptoms	Burning, ulceration of throat, mouth, stomach, nausea, vomiting, bloody diarrhea, fluid and electrolyte imbalance, dermatitis, hematuria, albuminuria, weakness, coma, death; clinical picture similar to appendicitis	No information
Depressants	Various	Kava, valerian root, nicotine, hellebore, anticholinergics, monkshood, corn lily, death camus, mescal, rhododendron, golden chain	Depends on the plant	CNS depression: sedation, delirium, coma may be mild to severe, depending on the plant and the amount involved; depression may be one of other symptoms; hepatotoxicity may lead to CNS depression; usually large amounts are needed to produce severe CNS depressant effects	Rapid or delayed
Gelsemium	Indole alkaloids gelsemine, gelsemicine, sempervirine, and others.	Carolina jasmine, Caroline jessamine	All parts, contaminated honey	Headache, dry mouth, diaphoresis, mydriasis, difficulty speaking, muscle weakness, rigidity, seizures, dyspnea, bradycardia	No information
Grayanotoxin	Resinoid diterpenes	Azalea, rhododendron, mountain laurel	Nectar, flowers, leaves, and stems	Burning of the mouth, perioral numbness and tingling, nausea, vomiting, diaphoresis, hypotension, bradycardia, coma, altered level of consciousness, and seizures	30 min–2 hrs
Hellebore	Hellborin, a steroidal saponin (digitalis-like glycosides in some plants)	Hellebore, lenten rose, Easter rose, Christmas rose	Potentially all parts	Acrid taste, vomiting, colic, diarrhea, abdominal pain; dermatitis; kidney irritation; cardiac glycoside-containing plants can produce sinus bradycardia and escape beats; ingestion by pregnant women has resulted in abortion	No information
Hydroquinone	Hydroquinone	Bearberry, whortleberry, sandberry, uva-ursi	Leaves; no information on other plant parts	Vomiting and GI irritation, dermatitis, dizziness, headache, delirium, hepatotoxicity, hematuria with green or brown urine, respiratory failure, cardiovascular collapse, carcinogen	No information
Lobeline	Lobeline	Lobelia, cardinal flower, Indian tobacco, red lobelia, mordilla	Roots and seed pods are most toxic parts	Irritation of the mouth, nausea, vomiting, abdominal pain, bradycardia, transient tachypnea, hypertension, tremors, seizures, paralysis; with large doses, a curare-like paralysis can be seen; usually exposures occur from using lobelia as a smoking deterrent and not from plant ingestion	No information

Toxin	Type of Toxin	Representative Plant	Toxic Part	Symptoms	Onset of Symptoms
Nicotine	Nicotine alkaloids	Commercial tobacco, ornamental tobacco, wild tobacco	All parts	Violent vomiting, hypertension, and tachycardia followed by hypotension and bradycardia, seizures, hallucinations, muscle weakness, paralysis, respiratory failure	15–60 min
Oxalic acid (soluble oxalates)	Soluble oxalic acid and sodium, potassium, and ammonium oxalates	Rhubarb, sorrel, Virginia creeper, star fruit	All parts	Gastroenteritis, confusion, weakness, renal and liver damage, hypocalcemia, weak, irregular pulse, bradycardia, hypotension, and cardiac dysrhythmias, coma, seizures	2–12 hrs up to 48 hrs
Protoanemonine	Protoanemonin	Anemone, ranunculus, clematis	All parts, but highest concentrations seen in flowering stage	Acrid taste, burning sensation in mouth and throat; systemic symptoms are rare due to the bad taste and oral pain; abdominal pain, diarrhea, oral pain and ulceration, hematemesis, severe gastroenteritis may result from large ingestions; blisters and dermatitis	Usually rapid
Pyrethrum	Pyrethrum and the natural pyrethrins	Chrysanthemums, daisy, marguerites	Flower heads but possibly all parts	Allergic symptoms including sneezing, rhinitis, wheezing, dyspnea, scratchy throat, bronchospasm, dermatitis; numbness of lips, nausea, vomiting, tremors, headache, dizziness, paresthesia	10–60 min
Pyrrolizidine alkaloids	Various pyrrolizidine alkaloids depending on the plant species	Ragwort, groundsel, locoweed, crotalaria, trumpetweed, comfrey, senecio species; about 3% of ALL flowering plant species contain pyrrolizidine alkaloids	Mature leaves contain least concentration; contaminated honey and herbal teas are other sources	Veno-occlusive liver disease with vomiting, severe abdominal pain, hepatomegaly, right-upper-quadrant abdominal sensitivity, ascites; jaundice may or may not be seen; symptoms may be confused with Reye syndrome in children; onset may be delayed days to weeks after exposure; transplacental pyrrolizidine poisoning can occur	Delayed days to weeks
Solanine	A glycoalkaloid combination of an alkamine aglycone (solanidine) and a glycoside linkage to galactose, glucose, and rhamnose	Potato, tomato, eggplant (green parts), black nightshade	Green berries most toxic; leaves, shoots, ripe berries least toxic	Nausea, vomiting, headache, diarrhea, fever, mydriasis; mild hypotension, bradycardia, muscular cramping, increased salivation, paresthesias, and dyspnea are not common; anticholinergic symptoms can also be seen, leading to a confusing picture	2–24 hrs
Stimulants	Cicutoxin, thujone calycanthidine oenanthotoxin	Water hemlock, nux vomica, coriaria, Carolina moonseed	All parts should be considered toxic	Quick-onset seizures, drooling, vomiting, diarrhea, abdominal pain, tachycardia, hypothermia, mydriasis, muscle rigidity, acidosis, rhabdomyolysis, renal failure	5 min–1 to 2 hrs
Strychnine	Strychnine alkaloid and less-active brucine alkaloid	Strychnine tree, poison nut, quaker buttons, dog buttons, nux vomica	Seeds mainly, but all parts contain some toxin	A prodrome of muscle cramps (especially in the neck and back), stiffness, tightness, agitation; increased responsiveness to sensory stimulation may precede generalized muscle spasms; spasms and seizures are extremely painful and can be precipitated by any stimulation; patients can be awake and lucid during seizures; early deaths from respiratory failure and cardiac arrest; late deaths result from anoxic brain damage or multiple-organ failure due to hyperthermia	15 min
Tannins	An astringent that acts locally to precipitate proteins	Nutgall, oak, sumac	Raw acorns, young sprouts, and buds	Nausea, vomiting, abdominal pain, hepatotoxicity, and nephrotoxicity after large doses	No information
Toxalbumins	Toxalbumins consists of two approximately equal-size subunits (A and B) bound by disulfide linkage; structure similar to insulin, botulism, tetanus, cholera, and diphtheria	Castor bean, black locust, jequirity bean, Barbados nut	If seeds swallowed whole, minimal toxicity, but if seeds chewed or mashed thoroughly, severe symptoms may occur with only one seed	Severe GI irritation and possible lesions of the oropharynx, esophagus, or stomach with hemorrhage and sloughing of tissue; symptoms similar to an alkaline corrosive exposure; dehydration leading to fluid and electrolyte loss that can lead to shock; hepatotoxicity, nephrotoxicity, and CNS involvement can develop 2–5 d later allergic dermatitis	Usually within 2– 6 hrs but can be delayed 1–5 d

Toxin	Type of Toxin	Representative Plant	Toxic Part	Symptoms	Onset of Symptoms
Veratrum alkaloids	Zigadenus alkaloids, veratrum alkaloids, sabadilla—a veratrum-type alkaloid	Skunk cabbage, death camus, corn lily, false hellebore	All parts	Severe nausea, bitter taste, drooling, vomiting, diarrhea, diaphoresis, followed by bradycardia, syncope, dyspnea, paresthesias, weakness, hypotension, and ECG changes (sinus bradycardia, shortened PR interval, shortened QTc interval, bundle-branch block, nodal rhythm, depressed ST segment); animal teratogen	30 min–4 hrs
Vincristine Vinblastine	Vinca alkaloids: vincristine, vinblastine, and vindesine	Vinca, periwinkle, myrtle	All plant parts, plant usually smoked	Fever, nausea, and vomiting reported to occur within 24 hrs of an overdose; neuropathy, loss of deep tendon reflexes, delirium, hallucinations, coma, seizures, and death may occur the first week following exposure; severe bone marrow suppression, SIADH, paralytic ileus, alopecia	Within 24 hrs

AV, arteriovenous; CNS, central nervous system; ECG, electrocardiogram; GI, gastrointestinal.

CARDIAC GLYCOSIDES

Plants containing cardiac glycosides have been used medicinally for centuries as an emetic, abortifacient, antimalarial, in the treatment of heart disease, and in suicide (2). More than 200 naturally occurring cardiac glycosides have been identified to date, with *Nerium oleander* (common oleander) being responsible for the greatest number of toxic exposures each year. Other cardiac glycoside–containing plants include *Digitalis purpurea, Digitalis lanata* (foxglove), *Strophanthus gratus* (oubain), *Thevetia puruviana* (yellow oleander), *Convallaria majalis* (lily of the valley), and *Urginea indica* (squill). The seeds and the roots contain the highest percentage of cardiac glycosides, although all parts of the plant contain the toxin. Deliberate self-harm via ingestion of *T. peruviana* is a major problem in South Asia, where thousands of cases are reported each year with a case fatality rate between 4% and 10% (3).

Cardiac glycosides bind to and inactivate the Na^+/K^+ ATPase pump on the cytoplasmic membrane of the cardiac cell resulting in increased concentration of intracellular Na^+, and increased concentration of extracellular K^+ (3). The increased intracellular Na^+ concentration affects the Na^+/Ca^{2+} exchange, resulting in an increase in intracellular Ca^{2+}, ultimately leading to increased cardiac contractility and automaticity.

CLINICAL PRESENTATION

The toxic dose of a particular plant is difficult to determine and depends on factors such as the plant part ingested, the toxin concentration in the plant, age and heath of the patient, and the amount of toxin absorbed from the gut. Patients will usually develop symptoms within a few hours of ingestion, however time to clinical symptoms depends on how the plant was prepared. For example, a more rapid onset of poisoning occurs if the seeds are crushed compared to if the seeds are ingested whole.

After an acute ingestion, nearly all patients will have nausea and vomiting. The vomiting may be self-protective and limit the amount of toxin absorbed. Abdominal pain and diarrhea are also common. The main life-threatening clinical manifestation is cardiac toxicity. A wide range of cardiac conduction abnormalities and ECG abnormalities have been described such as sinus bradycardia, atrioventricular (AV) block, depressed ST segment, inverted T waves, and ventricular dysrhythmias such as bidirectional ventricular tachycardia. Refractory ventricular fibrillation and cardiogenic shock can occur in severely poisoned patients. Hyperkalemia is a marker of severe toxicity. Patients may have neurologic symptoms as well, such as tremor, drowsiness, ataxia, visual disturbances (yellow vision), and weakness (2–4).

Poisoning by natural occurring cardiac glycosides such as oleander is clinically indistinguishable from digoxin poisoning, however the toxicity from plant ingestion may last longer than the clinical effects seen with digoxin poisoning.

ED EVALUATION

An initial ECG to detect any rhythm disturbance, followed by continuous cardiac monitoring should be performed. Cross-reactivity of cardiac glycoside plants on digoxin immunoassay has been described but the digoxin level does not correlate with toxicity, so the test best serves as confirmation of the presence of cardiac glycosides. Serum chemistries should be checked and in an acute ingestion, hyperkalemia is a marker of more severe toxicity and associated with a worse outcome (4).

ED MANAGEMENT

Intravenous fluids should be given to treat the volume depletion that can occur from the gastrointestinal (GI) effects, as well as antiemetics to treat vomiting. The use of activated charcoal (AC) as a form of GI decontamination is controversial. The presence of nausea and vomiting in cardiac glycoside toxicity usually precludes the use of AC, however it can be considered in a patient with normal mental status who presents within 1 hour of ingestion without vomiting (adults: 50 to 100 g; pediatrics: 1 mg/kg). Use of digoxin-specific Fab antibody fragments, atropine, insulin/dextrose, sodium bicarbonate calcium, and pacing have been used successfully and are discussed in Chapter 325 How long a patient should be monitored depends on the patient's clinical status and some recommend cardiac monitoring for a minimum of 24 hours to monitor for delayed cardiac effects (4).

ANTICHOLINERGICS

Most plants with anticholinergic properties are from the family Solanaceae, and can be identified from their characteristic flowers. The Solanaceae family is extensively utilized by humans for food and medicine but is often rich in alkaloids that can cause life-threatening toxicity in humans. Plants that have anticholinergic properties include *Atropa belladonna* (deadly nightshade), *Mandragora officinarum* (mandrake), *Hyoscyamus niger* (henbane), *Datura,* and *Brugmansia* (2). *A. belladonna* contains berries that are particularly dangerous for children because they can be sweet. The alkaloids are generally distributed throughout the plant, so all ingested parts are toxic. Because the alkaloid concentrations vary with each plant and among parts of the plant, users are unaware of the amount of chemicals they are ingesting. Alkaloids in anticholinergic plants are also called tropane alkaloids and include atropine, hyoscyamine, and hyoscine (scopolamine). Tropane alkaloids are found in about 25 genera and 2,000 species of plants.

The tropane alkaloids competitively inhibit postsynaptic muscarinic receptors producing the classic anticholinergic syndrome (2). Since nicotinic cholinergic receptors are not affected, a more accurate characterization would be *antimuscarinic toxicity,* but

conventional literature most often uses the term “anticholinergic.” Some of the more commonly ingested plants are *Datura* species, known as Jimsonweed (*Datura stramonium*) and moonflowers (*Datura inoxia*), and *Brugmansia* species, generally known as Angel’s Trumpet. Jimsonweed seeds contain the highest concentration of tropane alkaloids, the equivalent of 0.1 mg of atropine per seed. The lethal dose of atropine is thought to be in the range of 10 mg. *D. inoxia* has the largest amount of scopolamine of any plant, with its leaves containing 3.85 mg/g. Scopolamine’s effects are similar to atropine and because it is also a tertiary amine, it can easily penetrate the central nervous system. In therapeutic doses, scopolamine antagonizes acetylcholine at muscarinic receptors; however, at high doses, it can also antagonize nicotinic receptors leading to flaccid paralysis. The lethal dose of scopolamine has been reported to be 2 to 4 mg (5). In previous case reports of patients who ingested either *D. inoxia* or *D. stramonium,* there were not significant differences in the clinical manifestations because both plants contain atropine, scopolamine, or both (5).

CLINICAL PRESENTATION

Various species contain different concentrations of tropane alkaloids; however, the clinical manifestations are usually similar. The onset of symptoms usually occurs within 1 to 4 hours of ingestion. If the plant is smoked or consumed as a tea, symptoms may occur more rapidly. The duration of effect may last from hours to weeks. Anticholinergic findings suggesting poisoning include hyperthermia, tachycardia, blurred vision, flushed dry skin, absent bowel sounds, urinary retention, agitation, hallucinations, lethargy, mumbling speech, undressing behavior (generally due to hyperthermia), and repetitive picking behavior. Blurred vision and photophobia may be due to mydriasis. Seizures and coma are reported in severe cases, but seizures may be a manifestation of hyperthermia. Anticholinergic effects delay gastric emptying, resulting in a prolonged duration of action. Patients may be amnestic to the events (2,5).

ED EVALUATION

Diagnosis is usually based on a history of exposure and the presence of typical features such as dilated pupils, flushed skin, and a rapid heartbeat. Positive identification of the plant should be attempted whenever possible, but identification of the plant is often difficult and common names often refer to more than one plant. Serum toxin levels are not available for most plant toxins but an ECG can detect plant-induced dysrhythmias.

ED MANAGEMENT

Treatment of anticholinergic plant exposure consists primarily of decontamination and supportive care. Mild cases of anticholinergic intoxication may be treated by discontinuing the offending agent alone. However, more serious cases may need to be hospitalized for more prolonged monitoring and observation. Activated charcoal is commonly administered despite the limited evidence of its efficacy. Supportive care is necessary to primarily maintain hydration and treat hyperthermia if present. Foley catheterization may be needed if bladder distension develops. Benzodiazepines can be used for agitation. Physostigmine is a carbamate that inhibits the enzyme cholinesterase and can be used for diagnosis and to treat symptoms (5). Management is discussed further in Chapter 344.

OXALATES

There are many plants that contain oxalates including common household plants such as *Dieffenbachia* spp (dumbcane), *Philodendron* spp (philodendron), *Spathiphyllium* spp (peace lily), and *Rheum rhabarbarum* (rhubarb). Plants containing oxalates are the most frequent class of toxic plants reported to poison centers (1). These plants contain calcium oxalate crystals (raphides) within specialized cells called idioblasts, which are released in response to mechanical pressure, such as chewing, leading to the clinical effects (6).

CLINICAL PRESENTATION

Upon ingestion of oxalate-containing plants, the needle-like oxalate crystals cause immediate pain, burning, and irritation to the lips, mouth, and throat. Swelling in the mouth and salivation may be

observed (7). Irritation in the GI tract manifests by nausea, vomiting, diarrhea, abdominal pain, and occasionally hematemesis (6). Most pediatric accidental exposures produce vomiting and diarrhea that resolve within a few hours. Although most exposures result in only minor symptoms, severe toxicity including airway compromise and renal failure from deposition of oxalate crystals has been reported (7). There are multiple other causes of oxalosis including primary oxalosis caused by genetic disorders, and secondary oxalosis from endogenous production, increased dietary intake, or increased absorption. Hyperoxaluria can also result from ethylene glycol ingestion, ingestion of high doses of vitamin C, or vitamin B6 deficiency (8).

ED EVALUATION

Symptomatic patients should receive a complete blood count, serum electrolytes including serum calcium and creatinine. A urinalysis to look for oxalate crystals may be obtained, although the presence of crystals is not specific to this ingestion. In a severe ingestion, oxalate-induced hypocalcaemia may occur and an ECG should be obtained. Patients should be monitored for facial and oral swelling that could lead to airway compromise.

ED MANAGEMENT

Decontamination is generally not needed following ingestion of oxalate-containing plants as most patients present with GI symptoms. Symptomatic treatment for oral irritation includes antihistamines, such as diphenhydramine. Intravenous fluids and antiemetics should be considered for patients with vomiting and diarrhea. Mild ingestions in patients who demonstrate clinical improvement in the ED may be discharged home. Any concern for airway compromise and/or renal dysfunction should prompt a longer observation period or admission to the hospital.

CICUTOXIN

The species of plants traditionally called water hemlock include *Cicuta* spp and *Oenanthe* spp. Water hemlock is also known as beaver

poison, children's bane, death-of-man, poison parsnip, and false parsley. Water hemlock plants are commonly mistaken for edible plants. They grow in swampy wet habitats and have roots that have been mistaken for wild carrots. Water hemlock plants are considered to be among the most toxic plants in North America and the United Kingdom (9). Similar to other poisonous plants, all components of the plant are toxic, however the tubers or roots are the most toxic portions of the plant. It smells like fresh turnips and tastes sweet. Case reports suggest that any amount ingested can lead to significant toxicity (9).

The main toxin in water hemlock, cicutoxin, is thought to be a noncompetitive gamma-aminobutyric acid (GABA) antagonist in the central nervous system. Blockade of the chloride channel on the GABA receptor allows for unopposed cellular depolarization that clinically causes seizures (9).

Water hemlock needs to be differentiated from poison hemlock, *Conium maculatum,* which was the poison Socrates was condemned to drink. *C. maculatum* resembles water hemlock and can also be found on banks of streams and rivers, however it has a purple-spotted stem and single tap root, and water hemlock has branched roots without purple spots (9). *C. maculatum* contains multiple different piperidine alkaloids including coniine and γ-coniceine, which act in a similar manner to nicotine. Their primary action is activation, then blockade, of nicotinic acetylcholine receptors, which are located throughout the body including brain, autonomic nervous system (sympathetic and parasympathetic), and neuromuscular junction. A variety of clinical effects can be observed including salivation, lacrimation, emesis, abdominal cramping, miosis, bradycardia or tachycardia, bronchospasm, and fasciculations. Severe poisoning results in weakness, seizures, coma, and paralysis. Coniine can cause rhabdomyolysis either by a direct effect on skeletal muscle or from producing convulsions. Although many symptoms of water hemlock and poison hemlock overlap, water hemlock causes seizures and potentially status epilepticus, and poison hemlock primarily causes respiratory paralysis (9).

CLINICAL PRESENTATION

The hallmark of water hemlock poisoning is recurrent, and occasionally refractory seizures. Mild toxicity results in nausea, vomiting, and abdominal pain within 15 to 90 minutes. In severe toxicity, salivation, diaphoresis, increased bronchial secretions, and respiratory distress develop soon after ingestion. Seizures and death resulting from status epilepticus soon follow (10). Seizures are typically grand-mal seizures which can lead to multisystem organ dysfunction including hyperthermia, rhabdomyolysis, lactic acidosis, acute kidney injury, and cerebral edema (10). Symptoms can persist for 24 to 96 hours after ingestion and many patients are amnestic to the events after ingestion. Death, if it were to ensue, usually occurs from respiratory failure secondary to seizures within 8 hours postingestion.

ED EVALUATION

The diagnosis of water hemlock poisoning is based on history and the presence of seizures. There is no routine test to confirm the presence of cicutoxin. Identification of the plant by a botanist or poison specialist is very helpful.

ED MANAGEMENT

There is limited utility for activated charcoal in this poisoning as vomiting and seizures are common clinical manifestations and put the patient at risk for aspiration. Treatment is mainly supportive with emphasis on stabilizing the airway and seizure control. Seizures should be treated aggressively with a benzodiazepine initially (e.g., in an adult lorazepam 4 to 8 mg, or diazepam 10 to 20 mg IV), and phenobarbital, 15 to 20 mg/kg IV loading dose, if seizures continue. Dosing should be titrated to effect. Phenytoin is most often ineffective in seizure control. Continuous EEG monitoring should be considered especially in patients who are intubated.

OTHER PLANTS

There are other plants which have a variety of other toxins and can cause symptoms, most often nausea and vomiting. These usually resolve spontaneously, or occasionally with minimal supportive care. Despite the number of ingestions, primarily by children, the case fatality rate is extremely low. Table 355.1 describes many of those toxins and plants.

CRITICAL INTERVENTIONS

- Obtain complete vital signs, including temperature, on all patients with suspected plant ingestions.
- Obtain an accurate name of the plant, including the common and scientific name.
- Evaluate patients with plant ingestions for possible upper airway obstruction.
- Provide supportive care as clinically necessary.

Common Pitfalls

- Failure to appreciate that plant poisoning can affect virtually any organ system.
- Failure to inquire about plant exposure and herbal use in patients with unexplained complaints, particularly GI and CNS symptoms and rashes.
- Failure to appreciate that different plants may have the same common name, which may include both toxic and nontoxic plant species.
- Failure to appreciate that some edible plants also have toxic components.
- Failure to appreciate that specific antidotes are available for the treatment of anticholinergic, cardiac glycoside, and cyanogenic glycoside plant poisoning.

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CHAPTER 356

Dietary Supplements and Herbal Medications

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In 1994, the Dietary Supplement and Health Education Act (DSHEA) (accessible online at http://www.fda.gov/Food/DietarySupplements) was enacted to amend the Federal Food, Drug, and Cosmetic Act with respect to dietary supplements. DSHEA defines dietary supplements as products other than tobacco that are intended to supplement the diet and that contain a vitamin, mineral, amino acid, herb, or other botanical, enzyme, or animal derivative such as glandular or organ tissues. Americans spend more than $28 billion on dietary supplements and they are consumed by more than 100 million Americans (1).

Dietary supplements may not be represented as conventional food items, but they are regulated as a special subcategory of food and not as medication. This distinction has important consequences for the types of evidence documenting safety and efficacy that are required of the manufacturers of dietary supplements. Unlike medications, dietary supplements need not be proven safe or effective prior to marketing, and most have never been studied in controlled trials.

Nevertheless, there is a common public misperception that dietary supplements are safe, in large part because they are “natural.” Yet the implication that they contain one or more active ingredients should logically raise concerns for the possibility of adverse effects. As with any pharmacologically active substance, the dose defines the poison and while low doses may be safe, high doses may lead to exaggerated or unexpected clinical effects.

Unlike the case of pharmaceuticals, if the US Food and Drug Administration (FDA) wants to restrict sale or use of a dietary supplement, it must prove that the product is dangerous (2). Unfortunately, no formal postmarketing safety-review mechanism exists, but if the FDA does find a product unsafe, it can warn the public, suggest changes in the formulation, urge the manufacturer to recall the product, recall the product, or ban it entirely. This last option has only been exercised once, when sales of ephedra-containing products were banned in light of hundreds of reported adverse events, including 10 deaths. The FDA has also issued warnings about hepatotoxicity from comfrey and kava, renal failure from products containing aristolochic acid, and the risk of stroke or myocardial infarction from tiratricol (thyroxine), the stimulant DMAA, or 1,3-dimethylamylamine, in geranium extract, and the presence of potentially dangerous anabolic steroids in vitamin supplements. Despite these dangers, none of these products have been removed from the market.

Assurance of quality control in the manufacture of dietary supplements falls under the Current Good Manufacturing Practices (CGMPs) standard. This requires that production be done under sanitary conditions and manufacturers have the responsibility to substantiate the safety of their products and to ensure the identity, purity, quality, strength, and composition of their ingredients. Unfortunately, the FDA has few resources available to enforce these standards.

Contamination of products is an important cause of toxicity from dietary supplements. In 1990, L-tryptophan was pulled from the US market when a Japanese brand was associated with more than 1,500 cases of eosinophilia myalgia syndrome (EMS), including 30 fatalities. It is believed that this epidemic was caused by inadvertent contamination with an impurity, 1,1′-ethylidenebis[tryptophan], also called EBT or “Peak E,” during the manufacturing process.

Herbal supplements may be particularly prone to contamination during the harvest and storage of wild plants. Investigation of two cases of cardiac glycoside exposure reported to the FDA in 1997 revealed that a bulk shipment of plantain imported from Germany

had been contaminated with *Digitalis lanata*. The contaminated plantain had been shipped to more than 150 manufacturers in the United States over a period of about 2 years before this was discovered and the products could be tested and recalled.

Misuse of herbal supplements may also be due to confusion between species with similar common names but very different pharmacologic properties. An epidemic of renal fibrosis occurred in Belgium in the 1990s when the manufacturers of a Chinese weight-loss supplement confused two products with similar common names and substituted the nephrotoxic *Aristolochia westlandi* (*guang fang ji*) for *Stephania tetandra* (*han fang ji*). Similarly, there have been multiple reported deaths from hepatic veno-occlusive disease after chronic use of teas from *Senecio longilobus,* a shrub containing hepatotoxic pyrrolizidine alkaloids. In Mexico, where "gordolobo" (big wolf) tea is used as an expectorant and anti-inflammatory, *Gnaphallium* species are generally implied. However, numerous plants are called by this name throughout Latin America, including the highly toxic *S. longilobus*.

A significant portion of both Chinese and Indian traditional remedies—more than 90% in one study—contain metals such as arsenic, lead, cadmium, copper, thallium, or mercury. This may not be inadvertent because therapy with metals has been an accepted part of these medical traditions and the inclusion of metals in patent medicines may be deliberate. Yet cases of heavy-metal toxicity have been clearly linked to such preparations.

Herbal preparations may also be adulterated with pharmaceutical medications. Chinese patent medicines have also been particularly implicated in this regard. Patent medicines are standard herbal preparations manufactured and sold in pill form. Analyses of Chinese patent medicines being sold internationally have estimated that between 7% and 24% of these products contain undeclared pharmaceutical medicines such as corticosteroids, ephedrine, benzodiazepines, and nonsteroidal anti-inflammatory drugs (NSAIDs). Numerous analyses of this type have been published (3). Drug–herb interactions are another source of adverse actions (Table 356.1) (4). For example, St. John wort is a potent inducer of

CYP3A4. Patients taking medications that are metabolized by this enzyme have decreased therapeutic effectiveness. Common medication classes include antiretrovirals, antidepressants, and antineoplastics (5).

TABLE 356.1
Dietary Supplement/Herb–Drug Interactions

Dietary Supplement/Herb	Drug	Interaction
Coenzyme Q	Warfarin	May reduce anticoagulant effect
Dong quai (*Angelica sinensis*)	Warfarin	May increase anticoagulant effect
Evening primrose oil	Warfarin	May increase anticoagulant effect
Garlic (*Allium sativum*)	Warfarin	May increase anticoagulant effect; should not be used with other anticoagulant drugs such as aspirin and other NSAIDs
Gingko (*Ginkgo biloba*)	Antiplatelet drugs	May increase effects
	MAOIs	May potentiate effect of MAOIs
Ginseng, American (*Panax quinquefolius*)	MAOIs	May cause headaches and manic episode
Ginseng, Chinese (*Panax ginseng*)	MAOIs	May cause headaches and manic episode
	Insulin	Hypoglycemic effects may be additive
	Stimulant drugs	May potentiate effect
	Warfarin	May decrease effectiveness
Glucosamine	Diabetes medicines	May increase insulin resistance
Kava Kava (*Piper methysticum*)	Sedative hypnotics	May potentiate effect
St. John wort (*Hypericum perforatum*)	HIV drugs, digoxin, blood thinners, chemotherapy agents, theophylline, SSRIs	May decrease effectiveness through CYP 450 induction Increased serotonergic effect
Valerian (*Valeriana officinalis*)	Alcohol and sedative hypnotics	Potentiates effects
Yohimbine	α_2-Blockers	Increased α_2-adrenergic blockade
	Tricyclics	Hypertension
	MAOIs	Additive effects

MAOI, monoamine oxidase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.
Reproduced with permission from the Report to the Chairman: Special Committee on Aging: U.S. Senate. *Health Products for Seniors: "Anti-Aging" Products Pose Potential for Physical and Economic Harm* (GAO-1–1129). Washington, DC: U.S. General Accounting Office, 2001.

A 1-year observational study in 14 US poison centers found that of 1,466 calls reporting ingestion of dietary supplements, 489 had symptoms that were likely to have been caused by the exposure. Of these, 31% (149 cases) were considered moderate to severe reactions, including 5 deaths (6). Although these numbers suggest that the adverse effects are uncommon, harm is well demonstrated. Given the undefined, but likely relatively small benefit of dietary supplements on improving human health, the risk–benefit relationship is highly unclear (7).

Much remains to be learned about the specific pharmacology, toxicology, and clinical utility of most dietary supplements (8). Very few supplements have been tested in randomized controlled trials. In 1991, the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health (NIH) was

created with the explicit mission to explore complementary and alternative medicine in the context of rigorous science. Billions of dollars in grant monies have been disbursed through this program to fund all complementary health practices (including body manipulation and energetic healing techniques), and clinical trials of dietary supplements comprise only a small portion of this work. Recently, the result of the NCCAM-funded, highly controversial, and negative study of chelation therapy for heart disease called "Trial to Assess Chelation Therapy," or TACT, was published (9).

CLINICAL PRESENTATION

Dietary supplements form a category that is broadly unified in terms of intended use but not by any equivalence of biochemical composition or physiologic effect. Manifestations of toxicity are therefore varied. Acute effects may include allergy, any of the toxidromes, cardiac dysrhythmias, gastrointestinal distress, hepatitis, hepatic veno-occlusive disease, renal impairment, metabolic or electrolyte disturbance, hemorrhage, nervous system (CNS) stimulation or depression (see Table 356.2). Detailed information about specific agents and central potential interactions can be found at the NCCAM website (http://nccam.nih.gov). The Natural Medicines Comprehensive Database (http://www.naturaldatabase.com) is also a credible source of information.

TABLE 356.2
Toxic Manifestations of Selected Dietary Supplements by Presenting Complaint

Anticholinergic toxidrome: bittersweet (*Celastrus scandens*); burdock (*Arctium lappa*); deadly nightshade (*Atropa belladonna*); henbane (*Hyocyamus niger*); Jimsonweed (*Datura stramonium*); lobelia (*Lobelia inflata*); mandrake (*Mandragon officinarum*)

Bradycardia: cardioactive steroids: e.g., *Bufo* sp venom; dogbane (*Apocynum cannabimum*); foxglove (*Digitalis purpurea, D. lanata*); lily of the valley (*Convallaria majalis*); oleander (*Nerium oleander*); red squill (*Urginea maritima*)

Cardiac dysrhythmias (other): metals; monkshood (*Aconitum* species; "Caowu"), larkspur (*Delphinium* sp) [Na^+ channel activation]; quinine (*Chinchona* species) [Na^+ channel blockade]; see also "Stimulants"

Coagulopathy: danshen (*Salvia miltiorrhiza*); dong quai (*Angelica polymorpha*); garlic (*Allium sativum*); ginko (*Ginko biloboa*); tonka beans (*Dipteryx* sp)

Gastroenteritis: common: e.g., pokeweed (*Phytolacca americana*); senna (*Cassia angustifolia*); salmonella infection from rattlesnake meat; particularly concerning if due to metals

Hepatitis: borage (*Borago officinalis*); boron; chaparral (*Covillea tridentata, Larrea tridentata*); coltsfoot (*Tussilago farfara*); germander (*Teucrium chamaedrys*); kava kava (*Piper methysticum*)

Hepatic veno-occlusive disease: comfrey (*Symphytum officinale*); gordolobo (*Senecio* sp); heliotrope (*Crotalaria specatabilli; Heliotropium europaeum*); T'u-san-chi (*Gynura segetum*)

Hypotension: black cohosh (*Cimicifuga racemosa*); false hellebore (*Veratrum* sp); Hawthorn (*Craetaegus laevigata*); white cohosh (*Actea* sp)

Renal failure: aristolochic acid (*Aristolochia fangchi*); autumn crocus (*Colchicum autumnale*); colloidal silver; germanium (dioxide); juniper (*Juniper communis*), licorice (*Glycyrrhiza glabra*)

Peripheral neuropathy: clove oil (*Eugenia aromatic*); metals (arsenic, germanium, lead, mercury, thallium); podophyllum (*Podophyllum peltatum*); pyridoxine (B6); selenium

Sedative hypnotic: hawthorn (*Crataegus oxyacantha*); hops (*Humulus lupulus*); kava kava (*Piper methysticum*); valerian (*Valeriana* sp)

Seizures: camphor (*Cinnamomum camphora*); Chinese cucumber (*Compound Q*); fennel oil (*Foeniculum vulgare*); wormwood (*Artemesia absinthium*); see "Anticholinergics" and "Stimulants"

Stimulants: betel (*Areca catechu*); methylxanthines (cocoa [*Theobromo cacao*], coffee [*Coffee arabica*], tea [*Camellia sinensis*], kola [*Cola nitida/acuminata*], maté [*Ilex paraguariensis*], guarana [*Paullinia cupana*]); ephedra-like alkaloids (*Ephedra sinica;* ma huang; "herbal ecstasy"), ephedrone (khat [*Catha edulis*]), synephrine (bitter orange [*Citrus aurantium*]); nicotine (*Nicotiana tobacum*); nutmeg (*Myristica fragrans*)

DIFFERENTIAL DIAGNOSIS

The toxic effects of various herbal preparations are varied, and an appropriate differential diagnosis should be constructed with respect to these specific signs and symptoms. Conversely, because herbal preparations can affect every organ system, toxicity from dietary supplements should be considered in the differential diagnosis of any unexplained metabolic aberration or organ dysfunction. Inquiring about herbal and dietary supplements is the only way to increase the likelihood of considering these products as contributors to the patient's symptoms.

ED EVALUATION

The initial evaluation of a patient with potential toxicity from dietary supplements should proceed as for any other emergency department patient, with immediate attention given to the stabilization of the ABCs (airway, breathing, and circulation) and vital signs. A history of exposure to dietary supplements is clearly helpful in evaluating the potential for adverse effects but patients may not connect their symptoms with supplement use. Clinicians should be aware that many patients believe that dietary supplements are benign and may not include them on a list of "medications" unless explicitly prompted. Others may be hesitant to admit their use of herbals and

supplements to a physician for fear of censure or judgment. Clinicians should also be aware that products may be contaminated or that labeling may be unclear or misleading. Ultimately, the best gauge of toxicity is a focused history and physical examination in conjunction with selected ancillary tests of metabolic and organ-system dysfunction.

KEY TESTING

- Obtain sample of the product for potential testing by FDA or other analytical laboratory.
- Clinical testing is based on the patient's symptoms and findings on history and examination.
- In the uncommon patient with a suicide attempt using a dietary supplement, a serum acetaminophen concentration and pregnancy test, as appropriate, should be performed.

ED MANAGEMENT

The acute care of a patient with actual or potential toxicity from a dietary supplement is based on the nature and severity of illness. Gastrointestinal decontamination may be appropriate for patients who present early after a significant ingestion of a potentially toxic substance. Good supportive care is sufficient to treat most overdoses, but there are some notable exceptions. For example, poisoning with cardiac glycosides warrants therapy with multidose activated charcoal or digoxin-specific Fab fragments. Cyanide toxicity warrants specific therapy with sodium thiosulfate or hydroxocobalamin. Metal poisoning may require chelation therapy. Patients with anticholinergic toxicity may benefit from judicious use of physostigmine. All patients with possible adverse effects from a dietary supplement should be advised to discontinue its use. News about contaminated herbal and dietary products are in constant flux and all toxicity from herbals and dietary supplements should be discussed with the regional poison center who may help identify products that are contaminated, misrepresented, or pose significant

public health risks in addition to serving as an up-to-date informational resource for the clinician.

CRITICAL INTERVENTIONS

- Routinely ask about the use of dietary supplements while taking the medication history.
- Report all suspected drug interactions and adverse effects of dietary supplements by calling your regional poison center, or the FDA MedWatch program at 1–800-FDA-1088. (You may also report these online at http://www.fda.gov/Safety/MedWatch.)

DISPOSITION

Patient disposition depends on the presentation. Significant organ dysfunction demands admission to a higher level of care and a rigorous examination of all potential causes. Patients who take intentional overdoses should have psychiatric evaluation prior to discharge.

Common Pitfalls

- Failure to recognize that most people regard herbals and dietary supplements as benign and may not alert the clinician to their use unless specifically prompted.
- Failure to consider toxicity from herbals and dietary supplements in the differential diagnosis of unexplained organ dysfunction.
- Failure to contact knowledgeable resources for up-to-date trends on contaminated products.
- Failure to warn patients of potential interactions between medications and herbals and dietary supplements.

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CHAPTER 357 Seafood Toxins

Brenna M. Farmer

Seafood has been a dietary staple, safely eaten for thousands of years. However, occasional poisoning from seafood can result in many clinical syndromes, which mainly involve the gastrointestinal (GI) or neurologic systems, and with the popularity of world travel and importation of seafood, seafood toxin–related syndromes may be encountered anywhere. For emergency physicians, understanding the diagnosis and treatment of these syndromes is essential.

Ciguatera poisoning follows ingestion of large carnivorous fish containing high concentrations of ciguatoxin, which is produced primarily by the dinoflagellate, *Gambierdiscus toxicus*. *G. toxicus* is found in tropical and subtropical waters along coral reefs. Ciguatoxin is a colorless, tasteless, heat- and acid-stable, lipid-soluble polyether that bioaccumulates in the organs (particularly, the liver and gonads) of predator fish (1). Outbreaks typically occur in the Caribbean, Australia, and the South Pacific but have been reported worldwide, with more than 400 species of fish, mostly reef fish, implicated. Barracuda, grouper, red snapper, amberjack, eel, sea bass, and Spanish mackerel are most commonly involved. Fish larger than 2 kg are more likely to be contaminated with significant quantities of toxin. Ciguatoxin acts to open sodium channels, which increases sodium permeability through voltage-gated sodium channels (1).

Scombroid poisoning occurs with ingestion of fish containing histamine, also known as scombrotoxin (1). Bacteria under the scales of the fish convert histidine, a normal component of fish muscle, into histamine when the fish is poorly stored or improperly

refrigerated. The bacteria are commonly found on the surface of dark or red-fleshed fish of the Scombroidae family (tunas, skipjack, bonito, and mackerels) and other fish with dark flesh, such as dolphin fish (mahi mahi), bluefish, amberjack (yellowtail), herring, sardines, and anchovies. Scombrotoxin is heat-stable and can sometimes impart a metallic or peppery taste (1). Patients taking isoniazid or MAOI, inhibitors of diamine oxidase, are more sensitive to scombrotoxin. The histamine content of spoiled flesh can vary considerably throughout a fish, being highest near the gut cavity. Individual sensitivity to scombroid poisoning also varies considerably; females are thought to be more susceptible.

Tetrodotoxin is a heat-stable, water-soluble neurotoxin found in the skin and viscera of puffer fish (saltwater and freshwater varieties), porcupine fish, sunfish, toadfish, the blue-ringed octopus, some species of salamanders, and *Atelopid* frogs. Puffer fish, the most common source of tetrodotoxin, is eaten as the delicacy *fugu* in some Asian countries. Although tetrodotoxin is concentrated in the fish's skin and internal organs, it can be found in all parts of the fish. Most poisonings still occur in Japan, where sushi chefs must be licensed in the proper technique of preparing puffer fish to minimize risk of death with improper preparation. Tetrodotoxin is a sodium-channel inhibitor and reduces neuronal conduction (1,2). Tetrodotoxin bioaccumulates in the liver and gonads of the puffer fish like ciguatera (1).

Paralytic shellfish poisoning results from the ingestion of bivalve and gastropod mollusks (mussels, clams, oysters, scallops, and cockles) and occasionally some univalve mollusks, starfish, crustaceans, and fish (including puffer fish, which are more commonly associated with tetrodotoxin). These creatures become toxic when dinoflagellates, especially *Gonyaulax* spp., multiply explosively, causing red tides. Red tides are visible marine overgrowths of phytoplankton and dinoflagellates. Ingestion of filter-feeding shellfish from regions with red tides can lead to epidemic poisonings, such as paralytic shellfish poisoning. Toxic shellfish are commonly found in the cold, temperate waters of the Americas, the western coast of Europe, and the coastal waters of

Japan but are increasingly reported in warmer climates. Outbreaks have occurred in Nova Scotia, New Brunswick, Maine, and Alaska (3). The toxins do not harm shellfish but are concentrated in viscera and can take several weeks to be eliminated. Seabirds, several fish species, and mammals are susceptible to poisoning. Saxitoxin, a potent, heat-stable, water-soluble neurotoxin of paralytic shellfish poisoning, acts by blockading fast sodium channels in nerve and muscle during depolarization, and results in a conduction block that principally affects motor neurons and muscle (1). There is no reliable taste, smell, or color to identify contaminated shellfish.

Another seafood toxin–associated illness seen with red tides is neurotoxic shellfish poisoning, which also results in a ciguatera-like syndrome but is generally less severe. It is caused by brevetoxins from *Ptychodiscus brevis,* a dinoflagellate found off the coast of southeastern North America and Western Europe during algae blooms. The toxins are accumulated by clams and oysters. Brevetoxin opens sodium channels similarly to ciguatoxin (1).

A third shellfish poisoning, amnestic shellfish poisoning, a toxic encephalopathy, is caused by ingestion of shellfish, mainly mussels, containing domoic acid (1). The largest outbreak was in Prince Edward Island, Canada. The heat-stable toxin is derived from *Nitzschia pungens,* another dinoflagellate that causes red tides. Domoic acid acts as an excitatory neurotransmitter at the glutamate receptor (4).

Diarrheic shellfish poisoning can occur after ingestion of mussels, *Dinophysis* spp., containing okadaic acid and dinophysistoxins. Outbreaks have been reported in the Netherlands, Japan, Europe, and most recently in Greece (1,5). Okadaic acid and dinophysistoxins are lipophilic, fat-soluble, and inhibit essential protein phosphatases (1).

A syndrome similar to diarrheic shellfish poisoning occurs with ingestion of azaspiracid-contaminated mussels, *Mytilus edulis.* Outbreaks have occurred in the Netherlands and Ireland. Azaspiracid is a lipophilic, highly oxygenated polyether found in *Protoperidinium* spp., another dinoflagellate (6).

Another poorly understood seafood toxic syndrome is hallucinatory fish poisoning, ichthyoallyeinotoxism. It is reported around the world, particularly in areas near the Indian and Pacific Oceans and the Mediterranean Sea. The sea bream, *Sarpa salpa,* related to the porgie is implicated in carrying an unknown toxin responsible for this type of seafood poisoning (7).

CLINICAL PRESENTATION

Seafood toxin poisoning typically affects the GI and neurologic systems.

Ciguatera poisoning typically occurs 2 to 30 hours after ingestion of ciguatoxic fish. Patients characteristically present with circumoral and/or extremity paresthesias, arthralgias, myalgias, diarrhea, vomiting, bradycardia, and pruritus. A classic, though uncommon, finding is hot–cold temperature sensation reversal in which a burning or painful sensation is associated with touching cold objects (8). Patients may present initially with only neurologic symptoms; which may be delayed up to 72 hours after ingestion or may occur without GI symptoms. Hypotension is common and may be due to fluid loss, bradycardia, peripheral vasodilatation, or myocardial depression. Symptoms vary among different patients and depend on where the fish were caught and what parts were eaten. More severe toxicity, especially hypotension and bradycardia, occurs in patients who have been previously poisoned by ciguatera. Other common neurologic symptoms include asthenia, paresis, tremors, and pain affecting the joints, head, and abdomen. The paresthesias do not conform to dermatomal or peripheral nerve distribution. A sensation of looseness of the teeth is another unusual symptom. Insomnia, neurosis, depression, and hallucinations may occur. Other features include dyspnea, diaphoresis, salivation, tearing, chills, neck stiffness, pruritus, rashes, and tachycardia. In pregnant patients, violent fetal movements have been described. Less commonly, transient blindness, convulsions, rhabdomyolysis, polymyositis, or paralysis may occur. Death, although uncommon, may result from severe dehydration or cardiac or respiratory failure (8).

The onset of scombroid poisoning is normally within 1 hour of ingestion. The presentation is similar to, but generally less severe than, IgE-mediated allergic (anaphylactic) or anaphylactoid reactions. Patients experience intense flushing of the upper trunk and face, nausea, vomiting, hives, pruritus, tachycardia, bronchospasm, and occasionally hypotension. Severe reactions, such as bronchospasm, hypotension, and supraventricular tachyarrhythmias, are more likely to occur in patients with pre-existing cardiac or respiratory disease. Findings usually resolve within 6 to 12 hours from the time of ingestion.

Patients with *tetrodotoxin poisoning* usually present within 10 to 45 minutes after ingesting the toxic seafood. However, case presentations delayed up to 20 hours are reported. Early symptoms include a feeling of exhilaration. Four stages of poisoning have been described. Initially, circumoral paresthesias, salivation, nausea, and vomiting occur, followed by peripheral paresthesias and numbness. Sensory symptoms then become more generalized, with ascending paralysis of the extremities, although deep-tendon reflexes remain intact. In the third stage, ataxia and paralysis of peripheral and bulbar muscles occur. Finally, respiratory muscles are affected, although patients may still be conscious. Patients may become unconscious and completely paralyzed, with dilated nonreactive pupils and loss of all brainstem reflexes. Because of its effect on the sodium channel, cardiac arrhythmias, including A-V blocks, are also reported (2). Recovery occurs over a period of days and, unless complicated by anoxia, is complete. Death is usually due to paralysis of the respiratory muscles.

Paralytic shellfish poisoning occurs within minutes of ingestion and usually begins with neurologic symptoms including perioral, hand, and finger paresthesias, with associated nausea and abdominal pain. These are followed by paresthesias of the face and extremities and progressive muscle paralysis. Bulbar muscles are often affected, causing dysarthria, dysphagia, diplopia, and loss of the gag reflex. Other features include vertigo, ataxia, transient blindness, altered temperature perception, hypotension, headache, and low back pain. The paresthesias then become generalized, and a

progressive paralysis including loss of deep-tendon reflexes and fixed-dilated pupils develops. Respiratory paralysis may be fatal without rapid intervention. Complete recovery typically occurs within 24 to 48 hours (3).

Neurotoxic shellfish poisoning causes a syndrome similar to ciguatera. Circumoral paresthesias that generalize, headache, tachycardia, and muscle cramps are common. Nausea, abdominal pain, vomiting, and diarrhea also occur. Seizures and coma have occurred with severe poisonings.

Amnestic shellfish poisoning also produces neurologic and GI findings, with onset of effects from minutes to 38 hours. Abdominal pain, nausea, and diarrhea, with loss of memory, severe headache, confusion, and disorientation commonly occur. Severe intoxication can result in seizures and coma. Improvement occurs 24 hours to 12 weeks after ingestion of mussels containing domoic acid (4).

The main symptoms from *diarrheic shellfish poisoning* and *azaspiracid poisoning* are GI. Onset occurs from 30 minutes to 10 hours after ingestion of seafood (5), and the predominant effects are diarrhea, nausea, vomiting, abdominal cramps, and chills. Patients usually do not have a fever (5,6). Full recovery from this self-limited illness occurs within 3 to 4 days (1).

Ichthyoallyeinotoxism, *hallucinatory fish poisoning,* begins within minutes to 2 hours of ingestion of toxic fish. Initial symptoms resemble ethanol intoxication and include ataxia, incoordination, and general malaise/weakness. Within hours, patients report hallucinations (visual and/or auditory) and become delirious. Nightmares can occur. Some patients experience less common symptoms of vomiting and diarrhea. Symptoms usually resolve within 24 to 36 hours, although weakness can persist for days (7).

DIFFERENTIAL DIAGNOSIS

Patients who present with illness related to seafood toxins generally have a predominance of GI and neurologic signs and symptoms. The clinical presentations of ciguatera, neurotoxic shellfish, tetrodotoxin, and paralytic shellfish poisoning may be difficult to distinguish, as

all may involve symptoms of paresthesias, weakness, and ataxia. Geographic location, predominant symptoms, and the type of fish eaten are used to determine the specific etiology. A common shellfish origin has been found for toxins associated with tetrodotoxin and paralytic shellfish poisoning.

Infectious viral and bacterial gastroenteritis must also be considered in any patient presenting with GI complaints. Common seafood pathogens include hepatitis A, Norwalk virus, and *Vibrio* spp. (including *V. cholerae, V. parahaemolyticus,* and *V. vulnificus*).

Encephalitis, meningitis, Guillain–Barre, botulism, and transient ischemic attack, or stroke, should be considered in patients presenting with paralysis or other neurologic findings. In patients presenting with seizures, electrolyte and metabolic abnormalities, other toxins or an underlying seizure disorder should also be considered.

Anaphylaxis to seafood should be considered, especially in patients with signs and symptoms of scombroid poisoning. A metallic or strong peppery taste to the fish and the type of fish may distinguish scombroid from a true allergic reaction. Skin flushing can occur with scombroid poisoning but also with red man syndrome, niacin ingestion, monosodium glutamate ingestion, and ethanol–disulfiram interactions.

ED EVALUATION

One should obtain a history of foods ingested in patients with the combination of GI and neurologic symptoms. Special attention should be paid to the type of seafood ingested, locale, time of ingestion, and onset of symptoms. The origin of the seafood should be identified if possible, as this may help to differentiate poisonings specific to certain regions. Public health officials may be able to assist in this process and provide information about similar cases or known quarantined fishing areas.

Physical examination should focus on vital signs, respiratory function, and the neurologic examination, including deep-tendon

reflexes and sensation. Patients with tachycardia or hypotension should be evaluated for hypovolemia.

KEY TESTING

- Fingerstick glucose: To assess for cause of altered mental status
- Electrolytes: To exclude nontoxin-related neurologic problems, or disturbances due to vomiting and diarrhea
- Forced vital capacity/negative inspiratory force: To assess for severity of neuromuscular involvement or impending respiratory failure in patients with severe neurologic involvement
- Seafood toxin assay: To assess for toxin in the seafood (if any food is available)

ED MANAGEMENT

Supportive care is the mainstay of therapy in all seafood toxin–related syndromes. Airway, breathing, and circulation (ABCs) should be addressed initially. Patients should have intravenous access and cardiac monitoring as appropriate. In patients with abnormal ventilation as demonstrated by decreased vital capacity, negative inspiratory force, or hypopnea or apnea, intubation and mechanical ventilation should be considered. Abnormal heart rhythms such as bradycardia should be addressed (see Chapter 84, Bradydysrhythmias). Patients with tachycardia or hypotension should initially receive intravenous saline, but vasopressors such as dopamine, norepinephrine, or phenylephrine may be required if hypotension is unresponsive to saline.

In patients who may still have seafood in their stomach, activated charcoal (1 g/kg) should be considered. Antiemetics should be used for nausea and vomiting.

Specific therapy has been used in *ciguatera poisoning.* Although there are conflicting data on its efficacy, *mannitol,* 1 g/kg, is often recommended for patients with severe neurologic toxicity such as coma (9,10). Amitriptyline, which may act by blocking sodium channels, usually provides some relief from the chronic neurologic symptoms of ciguatera poisoning. Other agents used with varying

degrees of success include fluoxetine, nifedipine, vitamins B_{12} and C, calcium gluconate (1 to 3 g intravenously over 24 hours), lidocaine, and tocainide. Two patients who were treated with gabapentin (400 mg orally three times daily) experienced a rapid improvement and recurrence of symptoms after therapy was discontinued. Other medications commonly used for neuropathic pain have been used for persistent paresthesias. Indomethacin and cyproheptadine are commonly used to relieve arthralgia and pruritus, respectively.

For *scombroid poisoning,* treatment includes H_1- and H_2-receptor antagonists. H_2-blockers such as cimetidine appear more effective than type 1 blockers such as diphenhydramine (3). Epinephrine may benefit the rare severely ill patient with hypotension who is not responsive to intravenous saline or with bronchospasm not responsive to albuterol. Corticosteroids are of little benefit, as this poisoning is due to histamine only (i.e., no secondary mediators such as leukotrienes are released). Once stabilized, patients with scombroid poisoning can be discharged on oral antihistamines for 48 hours.

Benzodiazepines are useful to manage the disturbing hallucinations and nightmares experienced by patients with *hallucinatory fish poisoning.* Edrophonium and neostigmine have been used to reverse motor paralysis due to tetrodotoxin poisoning but have not been studied in controlled trials.

Besides supportive care, prevention is the best treatment of all. Fish weighing >2 kg or of those types known to be frequently affected should be avoided to prevent ciguatera. Patients should also avoid eating specific organs in which the toxins accumulate, such as the liver and gonads for ciguatera and tetrodotoxin. The government bans the sale of certain fish known to carry the toxin. In Miami, barracuda is banned from sale due to the risk of ciguatera poisoning. The local health department also periodically tests shellfish for certain toxins and when red tides occur, and quarantines are instituted as appropriate.

CRITICAL INTERVENTIONS

- Assess ABCs and evaluate pulmonary function early with measurements of forced vital capacity and negative inspiratory force.
- Provide supportive care, including antiemetics for nausea and vomiting and intravenous saline for dehydration and hypotension.
- Treat scombroid poisoning with H_1- and H_2-receptor antagonists.
- Consult a regional poison center and/or public health officials for current treatment advice and to report outbreaks.

DISPOSITION

Most patients may be discharged home after evaluation and supportive treatment in the emergency department. Outpatient follow-up should be arranged. Patients with abnormal vital signs, neurologic symptoms, persistent vomiting, or inability to tolerate oral fluids should be admitted to the hospital. Patients with neurologic symptoms or those at risk for development of respiratory weakness or paralysis should be admitted to an intensive care unit for close monitoring. Local or state departments of health should be notified of all cases of suspected seafood poisoning, as timely intervention may prevent additional exposures.

Common Pitfalls

- Failure to consider seafood poisonings in patients with gastroenteritis and/or neurologic symptoms.
- Failure to admit patients with neurologic findings for monitoring.
- Failure to treat scombroid poisoning with antihistamines.

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SECTION XXIV
Environmental Emergencies

Section Editor: LOUIS J. LING

PART 1 • PHYSICAL EXPOSURE INJURIES

CHAPTER 358
Hypothermia

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Hypothermia is defined as a core body temperature $<35^{\circ}C$. It is further classified into mild (32° to 35°C), moderate (28° to 32°C), and severe ($<28^{\circ}C$) hypothermia.

CLINICAL PRESENTATION

Many organ systems are significantly impacted by low body temperature. The clinical presentation varies with the degree of hypothermia (Table 358.1) but may be as subtle as confusion or disorientation.

TABLE 358.1
Effect of Temperature

	Mild (32°–35°C, 89.6°–95°F)	Moderate (28°–32°C, 82.4°–89.6°F)	Severe (<28°C, <82.4°F)
Cardiovascular		Bradycardia, conduction delay, AV block	Bradycardia, hypotension, AV block
	Tachycardia, elevated BP	Atrial arrhythmias, Osborn waves	Ventricular and atrial arrhythmias, asystole
	Increased CO, Increased SVR	Decreased CO, increased SVR	Paradoxical vasodilatation, decreased CO
Respiratory	Tachypnea, decreased minute volume	Hypoventilation, loss of airway reflexes, risk of aspiration	Progressive hypoventilation, apnea
	Bronchospasm and bronchorrhea	Decreased O_2 consumption and CO_2 production, respiratory acidosis	ARDS, pulmonary edema
			Respiratory acidosis
Neurological	Apathy, disorientation, confusion, amnesia	Paradoxical undressing, hallucinations	Loss of cerebral autoregulation, decreased CBF and cerebral metabolism
	Shivering, increased muscular tone	Decreased shivering, joint rigidity	Shivering lost, muscle rigidity, areflexia
	Ataxia, dysarthria, lack of coordination	Sluggish pupils, hyporeflexia, decreased LOC	Fixed and dilated pupils, unresponsiveness, no neurologic signs of life
Hematologic	Early inhibition of clotting factors	Hemoconcentration, hypovolemia, increased vascular permeability	Coagulopathy, DIC
		Hypocoagulable or hypercoagulable state	Bleeding diathesis, thrombocytopenia
Renal/Metabolic	Cold-induced diuresis, increased metabolism	Decreased renal blood flow and GFR, decreased metabolism	Oliguria, possible renal failure, rhabdomyolysis
	Hypokalemia	Hyperglycemia, hyperkalemia	Hyperglycemia, hyperkalemia
	Metabolic and respiratory alkalosis	Metabolic acidosis	Metabolic and respiratory acidosis
Gastrointestinal	Ileus, decreased GI absorption, Bowel wall edema	Hepatic insufficiency, pancreatitis, gastric erosions	Hepatic insufficiency, lactic acidosis

A general guiding principle is that no patient is dead unless he or she is warm and dead. Aggressive resuscitation should, therefore, be provided to almost all hypothermic patients, as traditional markers of death, including loss of brainstem reflexes with fixed and dilated pupils, rigor mortis, and dependent lividity, do not preclude a survivable condition. There are few exceptions to this, such as when there are clearly nonsurvivable traumatic injuries or the chest wall is frozen and incompressible. If there is any doubt, rewarming should be initiated (1). Severe acidosis, hyperkalemia, hyperammonemia, and hypofibrinogenemia may be poor prognostic indicators (2,3), but they should not be used in isolation to determine potential survivability. Survival has been reported with an initial pH of 6.51 or an initial potassium of 11.8 mEq/L. Likewise, temperature on arrival or seemingly nonsurvivable circumstances are not indications to withhold aggressive rewarming. Complete neurologic recovery has been observed with presenting temperatures of 14.2°C (57.5°F) in a child and 13.7°C (56.7°F) in an adult. A patient survived after therapeutic hypothermia at 9°C (48.2°F), and the longest reported period of cold water submersion with good neurologic recovery is 66 minutes. Patients in whom hypothermia and its neuroprotective effects occur rapidly and prior to cardiovascular collapse have the most favorable prognoses. Death can be declared when the patient's core temperature has been higher than 32°C (89.6°F) for 30 minutes (1).

DIFFERENTIAL DIAGNOSIS

The diagnosis of hypothermia is unequivocally established by core temperature measurement. However, the events leading to thermoregulatory failure and hypothermia vary widely causing overlap of the traditional definitions of primary hypothermia solely due to overwhelming environmental cold stress and secondary hypothermia due to cold stress complicated by impaired thermoregulation. In both primary and secondary hypothermia, patients tend to have circumstances that preclude an appropriate adaptive behavioral response to cold such as insufficient shelter or clothing, wilderness activities, substance intoxication, and medical or

traumatic co-morbidities. Evaluating and addressing these precipitating factors is an essential component of ED management to prevent recurrence and treat underlying illness. Secondary hypothermia frequently has a worse prognosis due to an increased resistance to rewarming and organ dysfunction from underlying illness. Causes of secondary hypothermia and thermoregulatory impairment are listed in Table 358.2 (4).

TABLE 358.2
Causes of Secondary Hypothermia

- Extremes of age
- Sepsis
- Multiple trauma
- Malnutrition
- Central nervous system
  - Cerebrovascular accident
  - Traumatic brain injury
  - Intracranial infection
  - Intracranial mass lesion
  - Hypothalamic dysfunction
    - Wernicke
    - Anorexia
  - Spinal cord injury
- Peripheral nervous system
  - Autonomic dysfunction
  - Peripheral neuropathy
- Endocrine system
  - Hypothyroidism
  - Hypoadrenalism
  - Hypopituitarism
  - Ketoacidosis
  - Hypoglycemia
- Dermatologic system
  - Burns
  - Desquamative skin conditions
- Pharmacologic influences
  - Opiates
  - Benzodiazepines
  - Barbiturates
  - Phenothiazines
  - Tricyclic antidepressants
  - Alpha blockers
  - Ethanol use
- Iatrogenic causes
  - Exposure during resuscitation
  - General anesthesia
  - Therapeutic cooling
- Psychiatric disease

ED EVALUATION

The initial evaluation focuses on the degree of hypothermia, cardiovascular stability, and searching for any precipitating factors.

As standard thermometers do not read below 34°C (93.2°F), special equipment is required for the accurate measurement of low body temperatures. The pulmonary artery temperature is considered "gold standard" (5); however, this is impractical in an ED setting and undesirable in a hypothermic patient with an irritable myocardium. Esophageal probes approximate myocardial temperatures (1) but should be placed in the lower esophagus (45 cm from nares in adults) to avoid inaccurate measurements from inspired gases in the trachea. Bladder temperatures reasonably estimate core temperature (5) and are well tolerated but may be inaccurate during warm water peritoneal lavage. Rectal temperatures can be accurate, though readings may lag during rewarming due to cold feces in the rectal vault (1,5,6). Tympanic membrane temperatures obtained by a thermistor or a thermocouple placed in direct contact with the tympanic membrane are accurate, but the placement and maintenance of such devices is difficult in an emergent resuscitative setting (5). Infrared devices which measure the temperature in the external auditory canal do not have sufficient accuracy or precision (7). Skin, oral, or axillary temperatures do not accurately reflect core temperatures and should not be used when hypothermia is suspected. Of the monitoring devices commonly available, esophageal probes appear to best approximate core temperature in static or dynamic situations and do not have the lag time seen with rectal, and to a lesser extent, bladder probes (5). If body cavity lavage is employed for rewarming, the temperature probe should be placed at a distant site.

It can be difficult to palpate a pulse in the hypothermic, bradycardic, and hypotensive patient. Some authors feel that a narrow-complex organized rhythm, even without palpable pulses, is a contraindication to cardiopulmonary resuscitation (CPR) due to concern over precipitating ventricular fibrillation. However, it seems most reasonable, and in keeping with American and European guidelines, to apply the same criteria to hypothermic patients as

normothermic patients: if there is no pulse after careful assessment for 1 minute, CPR should be performed concurrently with the initiation of rewarming procedures (7–10). Cardiac ultrasound or auscultating pulses with Doppler ultrasound can assist in this evaluation and inform decisions about the necessity of CPR (11).

Many physiologic functions are altered at low temperatures (see Table 358.1). A bedside glucose test should be obtained early. Hypoglycemia may represent underlying pathology or exhaustion of glycogen stores by shivering and should be corrected. Hyperglycemia and hypokalemia are common and frequently resolve spontaneously during rewarming. Laboratory studies include a blood gas, lactate, electrolytes, magnesium, calcium, and phosphorus levels, complete blood count, PT, aPTT, INR, fibrinogen, renal function tests, liver function tests, lipase, urinalysis, creatine kinase, and cardiac enzymes. Blood and urine cultures, toxicology screen, blood alcohol level, cortisol level, thyroid function tests, and pituitary function tests may also be considered depending on the clinical scenario. Blood gas values should not be corrected for temperature when determining resuscitation treatment (1,12,13). Although this is an inaccurate representation of in vivo pH and pCO_2, it best represents the appropriate intracellular–extracellular pH gradient from the influences of temperature fluctuations on the pH and should guide treatment toward the goal of an uncorrected pH of 7.40 and an uncorrected pCO_2 of 40, as acid–base disturbances predispose to ventricular arrhythmias (7,12,14).

An electrocardiogram (ECG) and a chest x-ray should be obtained (14). ECG Osborn waves (also known as J waves) can be seen and bradycardia is expected below 32°C (89.6°F) (Fig. 358.1), whereas atrial and ventricular arrhythmias are frequent with core temperatures below 30°C (86°F). Although hyperkalemia may be present, typical ECG findings are often masked by hypothermia. Appropriate imaging for traumatic injuries should follow rewarming. Patients with persistent altered mental status after rewarming should have a head CT to evaluate for contributing intracranial pathology.

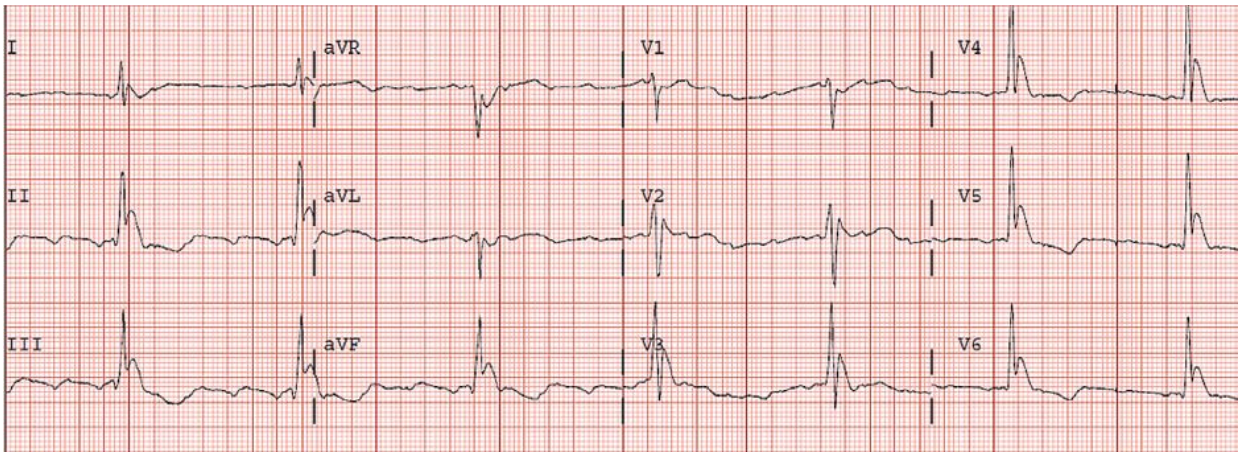

FIGURE 358.1 ECG in hypothermia: prominent Osborn wave in the QRS complex. Arrhythmias are common. This case demonstrates slow atrial flutter in 3:1 block.

Dysfunction of the coagulation system begins as the temperature drops below 35°C (95°F) and alters coagulation enzyme kinetics. Thrombocytopenia, platelet dysfunction, platelet sequestration, and prolongation of the PT and aPTT are frequently noted (4,14). Since standard laboratory equipment automatically heats samples to 37°C (98.6°F), in vitro measurements often underestimate in vivo coagulopathy (4). Rewarming generally reverses the coagulopathy and, with the exception of major trauma, replacement of platelets and coagulation factors is often unnecessary (4,14).

KEY TESTING

- Core temperature with an appropriate low-reading temperature probe
- ECG
- Blood glucose
- Initial laboratory studies: Blood gas, lactate, electrolytes, complete blood count, creatine kinase, urinalysis, coagulation studies, cardiac enzymes
- With failure to rewarm or with no clear environmental etiology: thyroid function tests, cortisol level, blood and urine cultures, head CT or brain MRI, toxicology screen, pituitary function tests

ED MANAGEMENT

As with other critically ill patients, management begins with the airway, breathing, and circulation (ABCs). If protective airway reflexes are absent or respiratory failure is present, endotracheal intubation is necessary and confers a low risk of precipitating ventricular arrhythmias (1,15). When neuromuscular blockade is required, duration will be extended due to globally slowed metabolism, and cold-induced masseter spasm may persist despite paralytics (7). Therefore, some authors recommend avoiding paralytics below 30˚C (86˚F) (11). If spasm interferes with orotracheal intubation, a jaw spreader may be useful and alternative techniques including nasotracheal intubation or cricothyrotomy should be considered (11).

Asystole, the natural culmination of severe hypothermia, and ventricular fibrillation from concomitant metabolic derangements or physical manipulation, becomes increasingly likely below 28˚C (82.4˚F) (14). CPR should be initiated if a central pulse cannot be palpated within 1 minute or if there is no organized cardiac activity on ultrasound. Given the possibility of prolonged CPR (hours) and a stiff chest wall, mechanical compression devices (Lucas, LifeStat, AutoPulse, etc.) may provide superior CPR. Placement of internal jugular or subclavian central venous catheters, transvenous pacing catheters, and rough handling of the patient can disturb an irritable myocardium and should be avoided when possible in favor of transcutaneous pacing and femoral central venous catheters. Although ventricular arrhythmias are most concerning, atrial fibrillation and sinus bradycardia are more common.

The treatment of arrhythmias in hypothermia is controversial. Perfusing stable arrhythmias typically resolve with rewarming and do not require specific treatment. However, unstable or nonperfusing arrhythmias may benefit from treatment. Optimizing the cardiac environment is essential for all unstable arrhythmias, best obtained by working toward an uncorrected pH of 7.40 with sodium bicarbonate and ventilator parameters. The few studies using amiodarone have yielded conflicting results (16,17), whereas lidocaine appears to be safe but of limited efficacy (1,7). Atropine is

frequently ineffective in hypothermic bradycardia and, traditionally, vasopressors were also thought to be ineffective below 30°C while conferring a risk of toxic accumulation due to delayed metabolism. However, recent animal data have found that vasopressors (epinephrine and vasopressin) increase the rate of return of spontaneous circulation when compared with controls while anti-arrhythmics (amiodarone and bretylium) appear to have no effect (16). The American Heart Association's guidelines allow vasopressor administration and defibrillation per usual ACLS protocols while recognizing the paucity of data (8). In contrast, the European Resuscitation Council continues to recommend withholding vasopressors until temperature rises above 30°C and doubling the time between administrations until the temperature exceeds 35°C (9). With these guidelines and limited data, it would seem reasonable to administer epinephrine and/or vasopressin during resuscitation less frequently and in fewer total doses while below 30°C. Alternatively, a single dose of vasopressor prior to warming above 30°C may reduce the risk of vasopressor-related toxicity during rewarming while preserving some of the benefits. Intramuscular or subcutaneous medications are not recommended due to prolonged and erratic absorption with severe peripheral vasoconstriction.

Although data are limited, conventional teaching limits cardioversion attempts to one shock in patients with cardiopulmonary arrest below 30°C (86°F). In contrast, some authors recommend subsequent attempts for every increase in temperature of 1° to 2°C (11). Defibrillation should be initiated per ACLS protocols once the temperature is >30°C. Given the lack of established efficacy, neither defibrillation nor vasopressor administration should delay rapid rewarming efforts in an arrested patient below 30°C. In a few case reports, transcutaneous pacing has successfully treated bradycardia with hypotension, but as bradycardia and hypotension may be physiologic and reflect decreased tissue oxygen utilization, the clinical utility of transcutaneous pacing remains uncertain (18).

Once a patient is stabilized, causes of secondary hypothermia should be considered and, if identified, treated (7). Empiric antibiotics in hypothermic neonates, elderly, and

immunocompromised patients are widely accepted, as an underlying infection is common (14). If there is an inadequate response to rewarming, empiric steroids and/or levothyroxine should be considered for potential adrenal failure or myxedema coma (7).

Core afterdrop and *rewarming shock* are important concepts in rewarming. *Core afterdrop* is the continued decline in core body temperature during the initial phases of rewarming as cooled blood from the extremities returns to the core circulation (7,10). Although of greatest theoretical concern with active external rewarming, its clinical significance is unclear. *Rewarming shock,* conversely, is a complex phenomenon with greater clinical significance (10). Vasodilation, returning metabolic products, and acidemia from rewarming peripheral tissues may manifest as an unforeseen decline in blood pressure, decrease in cardiac output, or cardiopulmonary arrest.

Rewarming methods (Table 358.3) are classified as passive external rewarming, active external rewarming, simple active core rewarming, and invasive active core rewarming. The optimal rewarming method depends on the degree of hypothermia, cardiovascular stability, and available resources. Multiple rewarming modalities are frequently utilized simultaneously.

TABLE 358.3
Warming Method

Method of Rewarming			Rate of Temperature Increase
Passive Rewarming			
Indications: Previously healthy patient with mild primary hypothermia			
	Blankets, dry environment, cover head		0.5°–2°C per hour, reliant upon shivering
Active External Rewarming			
Indications: Mild to moderate hypothermia without cardiovascular instability			
	Radiant heating		Not well reported, likely clinically insignificant
	Electric heating blankets		0.3°–0.8°C per hour
	Forced air (BairHugger, etc.)		0.8°–2.4°C per hour
	Plumbed blankets (Arctic Sun, etc.)		2.5° –3.0°C per hour
	Warm water immersion		2°–4°C per hour
Active Simple Core Rewarming			
Indications: Any degree of hypothermia			
	Warmed IV fluids with heated and humidified oxygen		0°–2°C per hour, frequently clinically insignificant
Active Invasive Core Rewarming			
Indications: Moderate to severe hypothermia, cardiovascular instability, or cardiopulmonary arrest			
	Body cavity lavage		
		Stomach	Minimal, clinically insignificant
		Bladder	Minimal, clinically insignificant
		Colon	Minimal, clinically insignificant
		Peritoneum	1°–4°C per hour
		Hemithorax, closed	1°–6°C per hour
		Open mediastinal irrigation[a]	8°C per hour
	Endovascular warming (Alsius, etc.)	Femoral catheter	1°–3°C per hour
	Extracorporeal circulation	Hemodialysis/hemofiltration (HD/HF)	1°–3°C per hour
		Continuous arteriovenous rewarming (CAVR)	3°–4.5°C per hour
		Continuous venovenous rewarming (CVVR)	1.5°–4.7°C per hour
		Cardiopulmonary bypass (CPB)	6.9°–9.8°C per hour

[a]For cardiopulmonary arrest only.

Passive external rewarming is effective in mild primary hypothermia (7), essentially minimizing further heat loss and enabling the patient to generate heat shivering by placing the patient in a warm, dry environment, removing all wet garments, insulating the head and body, and providing sufficient calories to sustain shivering.

Active rewarming measures are recommended for core body temperatures $<32^{\circ}C$, cardiovascular instability, suspicion of a secondary cause of hypothermia, impaired thermogenesis, multiple trauma, chemically induced or central nervous system–induced vasodilatation, or failure of passive rewarming methods (7).

Active external rewarming is used for mild to moderate hypothermia without cardiovascular instability and includes any technique that places the patient in direct contact with a heat source (7). Despite theoretical concerns regarding core afterdrop due to rapid peripheral warming, studies investigating forced air rewarming (BairHugger, Mistral-Air, WarmAir, etc.) have not observed clinically significant

core afterdrop (19). Recent literature suggests that circulating water-filled garment systems (Arctic Sun, ThermoWrap, CoolBlue, etc.) may be more effective than forced air rewarming and can approach cavity lavage rewarming rates (20,21). Many devices used for therapeutic hypothermia can be repurposed for rewarming accidental hypothermic patients. Immersion in warm water is effective but creates difficulty with monitoring and resuscitation while diathermy, the transfer of heat by ultrasonic or low-frequency microwave radiation, has been studied but is not clinically available (7). Caution must be applied with any rewarming mechanism involving direct conduction, since vasoconstricted skin is easily burned (7).

Simple active core rewarming, in combination with other techniques, is appropriate for any degree of hypothermia. Intravenous rehydration is frequently required as cold-induced diuresis and vascular permeability deplete and hemoconcentrate the intravascular space. Heated intravenous fluids (40° to 42°C) and warmed, humidified inspired oxygen (40° to 45°C) help prevent further heat loss but are inadequate for rewarming (2,7,22). Use of a high-flow countercurrent (Level 1) fluid infuser allows the heating and infusion of both crystalloid and blood products. Commercial fluid warmers or a microwave oven are alternative options for heating fluids; however, neither dextrose-containing solutions nor blood should be warmed in a microwave (4,7).

Invasive active core rewarming should be employed swiftly in cardiopulmonary arrest, cardiovascular instability, and severe hypothermia <28°C. Body cavity lavage is performed with sterile fluid heated to 39° to 45°C. Lavage of the stomach, colon, and bladder can be used as adjunctive measures, but small surface areas limit rewarming when these techniques are used in isolation (2,4,7). Peritoneal lavage with a technique similar to diagnostic peritoneal lavage (DPL) is more effective (2,3,22), whereas closed thoracic lavage is the most effective. In thoracic lavage, large-bore chest tubes are inserted both anteriorly and posteriorly, preferentially in the right chest due to theoretical concerns with irritating the heart in the left chest. Thoracic lavage rewarming rates begin around 2° to 3°C per hour (2,22), with rates up to 6°C per hour with a high-flow

countercurrent infuser (7). Adequate drainage through the posterior thoracostomy must be ensured to avoid an iatrogenic tension hydrothorax (7). Open mediastinal irrigation through a thoracotomy incision is effective in hypothermic patients with cardiopulmonary arrest, with rewarming rates up to 8°C per hour (2,3,7).

Endovascular devices are frequently used to induce therapeutic hypothermia (Alsius, InnerCool, etc.). Off label, these devices can also rapidly rewarm patients at an hourly rate of 1° to 3°C using femoral access (23). Case reports suggest that endovascular or plumbed blanket devices designed for therapeutic hypothermia may achieve rates equal to body cavity lavage and are less traumatic.

Extracorporeal methods have been successful in the resuscitation of both moderate and severe hypothermia. Hemodialysis and hemofiltration provide the benefits of eliminating toxic substances but have slower rewarming rates than other extracorporeal methods. Continuous arteriovenous rewarming offers faster rewarming rates but, since there is no external pump mechanism, requires a systolic blood pressure of at least 60 mm Hg to drive the flow. For the placement of 8.5 French arterial and venous catheters, either percutaneous or cutdown techniques can be utilized, with lines generally placed at contralateral femoral sites. The catheters' size mandates that the patient weigh at least 40 kg (7). Continuous venovenous rewarming may offer another option, but require a dedicated pump and are not generally available in the ED (22).

Cardiopulmonary bypass (CPB) provides complete circulatory support with extracorporeal oxygenation, and is the optimal method of rewarming patients in cardiac arrest (2,3,7). Some authors recommend CPB for all core body temperatures <25°C regardless of perfusing cardiac activity, and in patients with frozen extremities CPB may result in less tissue loss. Medical centers without CPB capability face a difficult choice in whether to attempt rewarming or to transfer severely hypothermic patients to a CPB facility for optimal therapy. This decision should be informed by the availability of CPB at the receiving facility, estimated time of transit, and cardiovascular stability.

There is conflicting evidence regarding the optimal rate of rewarming and the goal temperature of rewarming. Some studies have shown that hemodynamically stable patients with moderate to severe hypothermia experience good outcomes after rewarming with minimally invasive techniques (24), and there is currently no evidence that rapid rewarming of a patient with a perfusing rhythm improves outcome (7). However, rewarming times longer than 12 hours are associated with poor outcomes (7), and prolonged hypothermia can be associated with depressed cardiac function after rewarming (25). Regarding goal temperature, some authors recommend that hypothermic patients with cardiac arrest be warmed only to a therapeutic hypothermic state and thereafter follow therapeutic hypothermia protocols. There is insufficient evidence to make firm recommendations regarding therapeutic hypothermia after arrest or the rate of rewarming in hemodynamically stable patient with severe hypothermia (24).

CRITICAL INTERVENTIONS

- Use an appropriate low-reading temperature probe to make the diagnosis of mild, moderate, or severe hypothermia
- Use active core rewarming for severe hypothermia, cardiovascular instability, or cardiopulmonary arrest
  - external rewarming can be used in uncomplicated mild to moderate hypothermia
- Identify and treat causes of secondary hypothermia
- Monitor and correct acid–base status to prevent arrhythmias
- Rewarming must be continued to a core temperature of at least 32°C for 30 minutes before survivability can be determined

DISPOSITION

Disposition depends on the degree of hypothermia and the available resources at the presenting hospital. Healthy individuals with mild primary hypothermia may be discharged after rewarming. Patients with moderate or severe hypothermia, cardiovascular instability, secondary hypothermia, appreciable frostbite, or significant

comorbidities should be admitted for further evaluation and management. If the patient requires transfer to another facility, available rewarming strategies should be employed as swiftly as possible without significantly delaying transport. If there is consideration of cardiopulmonary bypass, early notification of the receiving facility is critical.

Common Pitfalls

- Failure to recognize hypothermia in elderly patients with altered mental status.
- Failure to adequately assess circulatory status prior to the initiation of CPR.
- Failure to appreciate that survivable hypothermic patients can nonetheless appear clinically dead.
- Failure to appreciate the limited efficacy of many medications at low core temperatures ($<30^{\circ}C$) and the potential for significant delayed toxicity upon rewarming.
- Failure to recognize that dysrhythmias and cardiopulmonary arrest are frequently resistant to conventional ACLS treatments until core temperature rises above 30°C.
- Failure to appreciate that mechanical irritation of the myocardium with central line placement, chest tube placement, or rough handling of the patient can result in ventricular fibrillation.

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CHAPTER 359

Cold-Induced Tissue Injuries

Joseph M. Weber and Scott C. Sherman

While retreating from Moscow in the winter of 1812 to 1813, Napoleon's surgeon general, Baron Dominique-Jean Larrey, recognized the ill effects of the freeze–thaw–freeze cycle when he witnessed soldiers thawing their feet by campfires at night, only to march again in the cold the next day. He proposed that the limbs should be rewarmed slowly by rubbing them with wet snow, which then became the accepted practice for more than a century. In the 1930s and 1940s, research described the benefits of rapid rewarming. In the 1960s, Mills popularized what has become the cornerstone of treatment today—warm the frozen limb in a 40° to 42°C water bath, avoid additional trauma, and use whirlpool baths to debride necrotic tissue (1).

Today, as a result of better availability of shelters among the homeless, improved patient awareness, and better protective clothing, the number of cases of frostbite has decreased. Immersion foot, however, is still common, especially among the homeless (2). These injuries can occur in any climate. Recreational inhalation of nitrous oxide and fluorinated hydrocarbons have caused frostbite to the face and cold-induced swelling that can compromise the airway (3,4). Another example is frostbite resulting from the inappropriate application of ice packs (5). As tissue temperatures drop to 10°C, cutaneous sensation is lost, and capillary blood flow decreases. With temperatures from 3° to 11°C, cutaneous capillary blood flow is reduced by 60%, and 5- to 10-minute cycles of vasodilatation and

vasoconstriction begin to occur to both preserve core temperatures and provide blood flow to the extremity. When core temperatures are threatened, however, blood flow to the extremity becomes negligible, and skin temperatures may drop as much as 0.5°C per minute.

In frostbite, ice crystals form in the extracellular space at tissue temperatures below 0°C. Frostbite requires ambient temperatures of −6° to −15°C, as radiation of heat from deeper tissues maintains surface temperatures somewhat above the environment. Irreversible tissue damage begins when extracellular ice crystal formation draws water from intracellular spaces by osmosis, causing intracellular dehydration and enzymatic disruption. With further cooling or rapid freezing (10°C per minute), intracellular ice crystals cause further cellular damage. The vascular endothelium and nerve tissues are more sensitive to cold than muscle, bone, and cartilage and are the first to be injured.

On rewarming, reperfusion creates an environment of progressive microvascular ischemia. This secondary insult is the result of multiple factors. Fluid extravasates through previously damaged endothelium. The interstitial fluid is rich in inflammatory mediators (prostaglandin and thromboxane) that promote vasoconstriction and platelet and leukocyte aggregation. Edema formation and endothelial injury may arrest capillary and arteriolar blood flow. Blister formation occurs secondary to vascular injury. Clear blisters form from extracellular exudation of fluid. Hemorrhagic blisters occur when deeper subdermal vessels are disrupted, indicating more severe tissue injury. The end result is arterial thrombosis, ischemia, and ultimately necrosis.

Nonfreezing cold-induced tissue injury has many similarities to frostbite. *Frostnip* is a reversible superficial ice crystal formation and intense vasoconstriction without tissue destruction. The tissue changes of *chilblains* result from vascular inflammation and tissue hypoxia secondary to cold-induced vasoconstriction. With *immersion foot,* the tissues are saturated with water so that the thick stratum corneum of the soles and feet becomes swollen, thickened, and fragmented. There is variable edema of the upper dermis. An

inflammatory response ensues, influenced by the water itself in most cases, not a concomitant fungal or bacterial process. The thinner stratum corneum of the dorsum of the foot does not absorb as much water and, therefore, is less likely to be involved. With exposure to much colder water, there is an added insult of vasospasm, intravascular thrombosis, and damage to nerve, fat, and muscle. Thus, the threshold for developing immersion foot is decreased in cold environments. Cold water causes injury in <48 hours versus up to 72 hours in warmer conditions.

The development of frostbite depends on more than ambient temperature. Duration of exposure, wind chill, humidity, and wet skin (and clothing) all increase the likelihood of frostbite. Other predisposing factors include alcohol consumption, psychiatric illness, vehicular failure, and drug abuse (6). Longer duration of exposure worsens outcome and is more predictive of injury than the ambient temperature alone (7).

CLINICAL PRESENTATION

Cold-induced tissue injuries present in various forms—*frostnip, chilblains, immersion foot, and frostbite*. Frostnip is the mildest form and presents with numbness, pain, pallor, and paresthesias to the affected extremity. The distal extremities—fingers, toes, ears, and nose—are most commonly involved. Frostnip usually resolves within 30 minutes, so persistent symptoms suggest a more serious diagnosis.

Chilblains usually occurs in patients with an underlying vasculitis after repeated exposure to dry, above-freezing cold temperatures. Patients present with erythema, edema, pruritus, and a burning sensation. Rarely, ulcerations, vesicles, and bullae may form. The lesions may have a purple or blue appearance. Commonly affected areas include the hands, feet, and pretibial areas. Manifestations occur 12 to 24 hours after cold exposure. The condition is recurrent in some individuals with repeated exposures, and this form is often bilateral and symmetric.

Immersion foot (also known as *trench foot*) can occur at any temperature but is more severe when wet exposure is combined with a cold environment. Although a wet environment is a prerequisite, perspiration and absorbent socks may be all that is required. Immersion foot usually develops slowly over hours to days. Immersion foot is the most commonly encountered cold-induced injury and occurs frequently in the homeless. Numbness and pain are common and may be so severe that the patient is unable to walk. The affected foot is cool, erythematous, and edematous (2). The distinction between immersion foot and the post-thaw phase of frostbite may be difficult and, therefore, a detailed history is essential.

Frostbite, like frostnip, commonly occurs on the digits, nose, and ear. Initially, the frozen tissue is mottled and violaceous. As rewarming occurs, the tissue becomes hyperemic, and the initially insensate extremity regains some sensation. After rewarming, frostbite can be classified into superficial (first- and second-degree) and deep (third- and fourth-degree) injury (Table 359.1).

TABLE 359.1
Classification of Frostbite Severity

Severity	Symptoms
First-degree: partial thickness	
Erythema, edema, hyperemia	Stinging, burning
No blisters or necrosis	Possible throbbing and aching
Occasional skin desquamation (5–10 d later)	Possible hyperhidrosis
Second-degree: full thickness	
Erythema, significant edema	Numbness
Clear vesicles	
Blisters may desquamate and form blackened eschar	
Third-degree: involves subcutaneous tissue	
Violaceous/hemorrhagic blisters due to injury to the reticular dermis and subdermal plexus	Initially insensate; later, shooting pains, burning, throbbing, aching
Skin necrosis	
Blue-gray skin	
Fourth-degree: involves muscle, tendon, and bone	
Little edema	Possible joint discomfort
Initially mottled, deep red, or cyanotic	
Later dry, black, mummified	

Adapted from Britt L, Dascombe W, Rodriguez A. New horizons in management of hypothermia and frostbite injury. *Surg Clin North Am.* 1991;71:345–370.

The appearance of first-degree frostbite is of a pale, white epidermis with surrounding erythema. Second-degree frostbite is heralded by clear blister formation with surrounding erythema and edema (Fig. 359.1), whereas third-degree frostbite consists of hemorrhagic blister formation, indicating deeper tissue injury. Fourth-degree frostbite consists of deeper necrosis and tissue loss (Fig. 359.2). Caution must be exercised, however, as this classification system does not always provide an accurate prognosis, nor does it alter initial management. Poor prognostic indicators include hemorrhagic blisters, nonblanching cyanosis, and hard, nondeforming skin (indicating loss of dermal viability). Positive prognostic signs include maintenance of pinprick sensation, normal skin color, and large clear blisters (7). In general, patients with

superficial frostbite will recover with little or no tissue loss, and patients with deep injury will ultimately have tissue necrosis.

FIGURE 359.1 Second-degree frostbite (partial thickness). Notice the clear blisters. (Photo credit: Scott Sherman, MD.)

FIGURE 359.2 Chronic demarcated fourth-degree frostbite with necrosis of the toes. (Photo credit: Scott Sherman, MD.)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of frostbite includes the other causes of cold-induced injury—frostnip, immersion foot, and chilblains. Other diseases that can appear similar include peripheral vascular disease, cellulitis, and dermatologic conditions such as stasis dermatitis, erysipelas, and bullous diseases but can be differentiated by history. Trauma to an extremity or compartment syndrome may mimic or coexist with a cold-induced injury. Chemical or thermal burns should also be considered if an accurate history cannot be obtained.

ED EVALUATION

Initial evaluation begins with a survey of the patient for systemic hypothermia (see Chapter 358) and major trauma. Treatment of either of these conditions supersedes care of a frostbitten limb. A

detailed history includes exposure temperature and duration, wind conditions, and moisture. A history of thawing in the field and refreezing should be documented as it portends a poorer prognosis. A previous history of frostbite doubles the patient's risk for recurrent cold-induced tissue injury in the same location (8). A history of psychiatric illness or alcohol and drug use is common in patients with frostbite. Finally, other risk factors such as peripheral vascular disease, diabetes, and smoking should be ascertained.

Physical examination begins with a core temperature and trauma primary and secondary surveys followed by a thorough examination and description of any frostbitten areas. A neurologic and vascular examination should include pulses (by Doppler if necessary), capillary refill, motor exam, and two-point discrimination. Wound description should include skin color and temperature, blister formation and color (clear or hemorrhagic), and soft-tissue consistency.

Laboratory studies are not helpful in the initial evaluation of the frostbitten patient. They may be helpful in patients with concomitant illness or associated conditions, such as rhabdomyolysis. Radiographic evaluation is limited to evaluation for trauma.

KEY TESTING

- Most patients do not need testing
- Testing and imaging for associated conditions such as hypothermia, rhabdomyolysis, and trauma

ED MANAGEMENT

Prehospital care should focus on avoiding mechanical trauma and refreezing injury. A frostbitten extremity should not be rewarmed in the field if there is a risk of refreezing before reaching definitive care. A victim who must walk through snow should do so before thawing frostbitten feet. Rubbing the frozen extremity with a warm hand or snow, once thought to be beneficial, does not augment blood flow and causes increased tissue damage (7). In the

emergency department (ED), general management of any cold-injured patient includes removal of wet clothing and complete exposure. Treatment begins by addressing hypothermia and dehydration.

Thereafter, therapy should be directed to the patient's specific type of tissue injury. Frostnip usually resolves spontaneously with dry rewarming in ambient temperatures, and no further therapy is necessary. Management of chilblains is also supportive. The affected skin should be rewarmed, washed, dried, and dressed in dry, soft, sterile bandages. Elevation is important to minimize edema that can predispose to infection (7). Nifedipine improves symptoms and helps prevent recurrences in patients with repeated exacerbations. A dose of 20 mg three times a day is recommended as tolerated by its effect on blood pressure (9). Prazosin has been effective for both acute exacerbations and prophylaxis. Patients should avoid further exposure to cold temperatures.

Treatment of immersion foot is supportive, consisting of bed rest, elevation of the legs, and air-drying at room temperatures (2). In the homeless patient, who is most often affected, admission may be necessary. Nonsteroidal anti-inflammatory agents are useful for pain relief, but parenteral opioid analgesics may be required. Although recovery is usually complete, severe complications, such as nerve and muscle injury and gangrene, occur infrequently. If the distinction between immersion foot and frostbite is unclear, the patient should be treated for frostbite.

Frostbite therapy is aimed at abating the specific pathophysiologic mechanisms causing tissue destruction. Rapid rewarming of tissues in a warm water bath decreases direct tissue damage caused by ice-crystal formation and greatly improves frostbitten tissue survival (10). Rapid rewarming is achieved by immersing the frozen extremity in a warm water bath at 40° to 42°C (104° to 107.6°F) for 15 to 30 minutes. Gentle motion of the extremity may aid in thawing; however, rubbing or massaging should be avoided, as this may increase tissue damage.

Temperatures <40°C delay the speed of tissue thawing, whereas temperatures >42°C can cause a superimposed thermal injury and

worsen outcome (11). Maintaining the proper temperature is best achieved with hydrotherapy whirlpools. Because most EDs do not have these devices, a warm water bath can be quickly obtained using a mixture of hot and cold tap water from a standard hospital sink. A thermometer should be used to verify the proper temperature. The water will cool quickly, and the intermittent addition of warm water or complete replacement of the bath will be necessary to maintain the desired temperature. Facial frostbite should be treated with warm water–soaked gauze or washcloths.

The extremity should be rewarmed until tissue becomes pliable and erythematous, usually occurring in 15 to 30 minutes. Rapid rewarming can be extremely painful as sensation returns, and parenteral opioid analgesia is usually required. Rapid return of skin warmth, sensation, and early formation of large clear blebs are good prognostic signs, whereas persistence of cold, anesthetic, cyanotic skin, and formation of small dark blebs portend a worse outcome. Compartment syndrome is a rare cause of persistent cyanosis, so compartment pressures should be checked in suspect cases, and fasciotomy or escharotomy may be indicated. Post-rewarming edema, which occurs within 3 hours of rewarming and persists for up to 5 days, should be treated with limb elevation. Vesicles and bullae appear 6 to 24 hours after rewarming and coincide with a renewed loss of sensation in the extremity. This secondary loss of sensation may persist until complete healing of the tissue (up to 4 years), but may be permanent (7).

Other adjunctive treatments for frostbite aim at preventing secondary tissue loss caused by inflammation and thrombosis. McCauley et al. (12) designed a protocol that has been shown to decrease the progressive microvascular ischemia that occurs in the post-thaw period (Table 359.2).

TABLE 359.2
Treatment Protocol for Frostbite

- Address systemic hypothermia and/or concomitant trauma
- Rapidly rewarm the frostbitten tissue in warm water at 40°–42°C (104°–107.6°F) for 15–30 min or until thawing is complete
- After rewarming, treat the affected tissue
  - Provide appropriate analgesia in the form of an opioid
  - Debride clear blisters
  - Leave hemorrhagic blisters intact
  - Apply aloe vera (Dermaide aloe) every 6 hrs to affected parts
  - Elevate the affected tissue/extremity and splint as needed
  - Administer tetanus prophylaxis (toxoid or Ig) as any other wound
  - Administer a nonsteroidal anti-inflammatory agent (ibuprofen 400 mg orally every 12 hrs)
  - Administer benzyl penicillin 600 mg every 6 hrs for 48–72 hrs
- For documentation, obtain photographic records of wounds, if possible
- Admit frostbite patient to a specialist unit, if possible
  - Perform daily hydrotherapy for 30–45 min at 40°C
  - Prohibit smoking

Adapted from McCauley RL, Hing DN, Robson MC, et al. Frostbite injuries: A rational approach based on the pathophysiology. *J Trauma*. 1983:23;143–147.

After rapid rewarming, most authors support the debridement of clear blisters to prevent further contact of prostaglandin- and thromboxane-containing fluid with the underlying tissues. Hemorrhagic blisters, which indicate deeper damage to subdermal plexus, should be left intact (12,13). Some authors advocate debridement of hemorrhagic blisters, but this practice can lead to tissue desiccation and, therefore, is not generally endorsed (8).

Adjunctive measures prevent progressive microvascular ischemia. Topical inhibition of thromboxane and prostaglandin is achieved with aloe vera cream (12,13). Aloe vera (Dermaide) should be applied to debrided clear blisters and intact hemorrhagic blisters every 6 hours. Oral ibuprofen at a dose of 400 mg every 12 hours (12 mg/kg/d) is used to inhibit the arachidonic acid cascade (8,13). Sterile dressings should be applied, and the extremity should be elevated to minimize subsequent edema. Edema formation increases progressive dermal ischemia and inhibits the skin's bactericidal properties, ultimately predisposing to infection (7). Although there has been no randomized clinical trial showing definite benefit, most

protocols advocate the use of prophylactic penicillin, 500,000 units IV, every 6 hours for 48 to 72 hours or until edema resolves (12). Others advocate IM or PO antibiotics for the same duration (8,13). One study demonstrated increased efficacy of topical bacitracin and silver sulfadiazine over systemic antibiotics for infection prophylaxis, although no prospective trials have addressed this topic (6). Finally, frostbite is a tetanus-prone wound, and tetanus prophylaxis should be instituted (14).

Many other adjuvant therapies have been studied to prevent progressive microvascular ischemia that occurs in the post-thaw phase of frostbite. These agents include low–molecular-weight dextran, heparin, thrombolytics, vasodilators, sympathectomy, hyperbaric oxygen, limaprost (a prostaglandin E1 analog), prostacyclin, and pentoxifylline. No studies, however, present conclusive evidence supporting their routine use (15–22). Two studies evaluating tissue plasminogen activator (tPA) in the treatment of severe frostbite have shown significantly decreased amputation rates (23,24). In general, thrombolytic therapy should only be considered within 24 hours of thawing, for deep frostbite injury with potentially significant morbidity (25) but the small number of patients precludes against a specific recommendation (23,24).

The natural history of the frostbitten extremity is described by the phrase “frostbite in January, amputate in July.” This adage describes the delay in demarcation between viable and nonviable tissues. Usually about 9 to 15 days after initial injury, severely frostbitten skin develops a black, hard, dry eschar. A line of demarcation between viable and nonviable tissue usually occurs at 22 to 45 days after injury. There have been multiple attempts to define the zone of demarcation earlier so that tissue in the transition zone may possibly be salvaged through early surgical intervention. Technetium bone scanning has been used with some success (26). However, a case report suggests that magnetic resonance angiography is superior to bone scan for the early determination of viable tissues (27). Residual pain and cold intolerance are the most common late sequelae of frostbite. Vasomotor instability resulting in

hyperhidrosis, pigment changes, skin atrophy, and post-healing ulcers also occur. Some patients request late amputation of cold-injured parts as a result of the severity of these symptoms. Osteoporosis and subchondral bone loss may occur and result in joint contracture. In children, epiphyseal damage may occur, even without skin loss.

CRITICAL INTERVENTIONS

- Completely undress the patient and address systemic hypothermia and trauma.
- Rapidly rewarm frozen tissue in a warm water bath of 40° to 42°C.
- Avoid re-exposure to cold.
- Administer adjuvant therapies as directed in Table 359.2.
- Admit almost all frostbite victims to the hospital.

DISPOSITION

With all cold-induced tissue injuries, care should be taken to ensure that patients will not re-enter the same environment that exposed them to injury. Patients with frostnip and chilblains may be discharged to follow up with a primary care provider. Patients with immersion foot can be discharged if an environment that allows for proper treatment can be provided. Patients with frostbite, conversely, should be admitted to the hospital in all but the most superficial cases.

Common Pitfalls

- Failure to differentiate frostbite from the more superficial but related injuries of frostnip, chilblains, and immersion foot.
- Discharging a patient into the same environment that caused the cold-induced injury without arranging proper protection from the elements.
- Failing to recognize superimposed vascular injury or compartment syndrome after rewarming of a frostbitten extremity.

- Failing to use a thermometer to accurately measure temperature of the warm water bath. Temperatures of 40° to 42°C are effective in reducing tissue injury, whereas those >42°C can be harmful.

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CHAPTER 360 Heat-Related Illness

Eric W. Schmidt and Constance G. Nichols

Heat illness can be defined as the inability of normal regulatory mechanisms to cope with heat stress. Minor heat-related problems, such as muscle cramps, edema, rash, syncope, and tetany, account for significant morbidity. *Heat exhaustion* and *heatstroke* are major heat syndromes that may cause organ damage or death if left untreated. Among high school athletes, heatstroke is the third leading cause of death (1). In elderly patients, mortality is directly correlated with increased ambient temperature (2). Sunburn and other photodermal ultraviolet (UV) injuries may exacerbate all other heat syndromes or present separately.

Heat cramps are a result of muscle fatigue combined with water and salt depletion (3). *Heat syncope* is the result of vasodilatation, usually compounded by volume depletion or the use of drugs that interfere with cardiovascular reflexes. *Heat tetany* appears to be due to hyperventilation-induced respiratory alkalosis, resulting in decreased ionized serum calcium. It may be an attempt to compensate for exercise-induced lactic acidosis. *Heat rash* is caused by the plugging, dilation, and rupture of sweat glands following skin maceration resulting from sweating. The mechanism of heat edema is unknown.

When exposed to a variety of temperatures, humans maintain a relatively constant body temperature by balancing heat loss with heat gain. Any condition that increases heat gain or decreases heat loss may result in a major heat illness (Table 360.1). Heat gain may be from (1) increased endogenous heat production from basal metabolism and muscle activity or from an (2) environmental heat

load. For example, basal metabolism generates 65 to 85 kcal/hr, which may increase five- to sixfold with exertion. Underlying illness or stimulant drugs may also increase endogenous heat production. Hot environments decrease heat loss and increase the heat load. The average sunbather may absorb 150 kcal/hr. At rest and without heat dissipation, the average human temperature would increase 1.1°C/hr.

TABLE 360.1
Factors Predisposing to Heat Illness

Endogenous Factors	Exogenous Factors
Increased Heat Gain	
Infection	High ambient temperature
Drugs	Malignant hyperthermia
Stimulants	Direct sunlight
Hallucinogens	Dark clothing
Increased activity	
Exercise	
Seizures	
Drug withdrawal	
Psychosis	
Neuroleptic malignant syndrome	
Thyrotoxicosis	
Decreased Heat Loss	
Lack of acclimatization	High ambient temperature
Dehydration	High humidity
Hypokalemia	Restrictive clothing
Drugs that decrease sweating	Protective garments
Anticholinergics	
Neuroleptics	
Barbiturates	
Anti-Parkinson agents	
Diuretics	
β-Blockers	
Alcohol	
Extremes of age	
Skin disorders	
Cystic fibrosis	
Obesity	
Debilitated/chronic disease/elderly	
Impaired voluntary responses	

Heat exhaustion is the result of dehydration with inadequate fluid and electrolyte replacement. Water or salt depletion or both may be present. Without treatment, heat exhaustion progresses to heatstroke. *Heatstroke* is a result of severe dehydration with thermoregulatory failure, resulting in body temperatures $>40^{\circ}C$ (105° to $106^{\circ}F$) and a mortality rate of up to 70%.

Acclimatization is the process of physiologic adaptation to repeated heat stress that occurs over 10 to 60 days. It results in decreased heat production and increased heat loss for a given amount of work. Metabolic function improves through an increase in skeletal muscle mitochondria and glycogen stores, which enhances aerobic work capacity producing less heat. Cardiac efficiency is improved, with an increase in maximum cardiac output, a decreased peak heart rate, and increased stroke volume. Fluid and electrolyte balance is altered by aldosterone secretion, which helps to conserve sodium stores by both sweat and renal mechanisms and by increasing extracellular volume. In addition, the threshold core temperature for sweating is decreased, and the volume of sweat is increased. With further acclimatization, sweat volumes may decrease as well. However, potassium loss during acclimatization peaks at 8 to 10 days and often increases susceptibility to heat illness (4). Although acclimatization protects against heat illness, as the wet-bulb temperature approaches 30°C (86°F) even young well-acclimated persons are susceptible during vigorous or prolonged physical activity (1,5).

UV exposure varies 40- to 80-fold over the course of the year at any given location. UV intensity peaks between 10 AM and 2 PM daily. The degree and extent of UV injury is a direct function of the total energy absorbed. UV tissue injury occurs at multiple cellular levels. Initially there is an inflammatory reaction similar to other tissue insults. Individual response ranges from mild transient erythema to urticaria with exacerbation of underlying medical conditions, depending on exposure, skin type, *photoallergy,* or *photodrug reaction* (Table 360.2). The maximal response may be delayed up to 30 hours and last for several days.

TABLE 360.2
Drugs Causing Phototoxicity and Photoallergy

Drugs That Increase Direct Phototoxicity

Amiodarone
Doxycycline
Furosemide
Naproxen sodium
Phenothiazines
Sulfonamides

Drugs That Promote Photoallergy

Phenothiazines
Sulfonamides
Sunscreens

UVB frequencies (290 to 320 nm) are up to 1,600 times more injurious than UVA (320 to 400 nm), but there is a preponderance of UVA in the environment (6).

CLINICAL PRESENTATION

Heat cramps are painful spasms of heavily used muscle groups. They often occur in acclimatized persons, during or up to several hours after exertion. The victim often has been sweating heavily with insufficient or hypotonic fluid replacement for several days. Serum sodium levels are normal.

Heat edema is manifested by ankle and wrist swelling. It occurs in the first few days of heat exposure and sometimes results in pitting (7).

Heat rash (prickly heat) is most common early in acclimatization, in tropical areas, and with wearing of tight clothes. It is an intensely pruritic, red, papular, occasionally vesicular dermatitis. Complications include infection and the formation of large nonpruritic plugs, which take several weeks to desquamate. Advanced and extensive heat rash increases the risk for heat exhaustion or heatstroke as a result of loss of sweat gland function (1).

Heat syncope is a transient loss of postural tone, with or without brief loss of consciousness occurring early in exposure to a new heat stress. It is often preceded by dehydration or is associated with the

use of drugs that affect the body's normal compensatory mechanisms (4). By the time patients are examined, vital signs have usually normalized.

Heat tetany presents as carpopedal spasm and is frequently seen in conjunction with other heat syndromes or other causes of hyperventilation. In contrast to heat cramps, it does not involve the heavily used proximal muscles. Arterial blood gas (ABG) analysis may reveal a respiratory alkalosis.

Heat exhaustion usually occurs in nonacclimatized persons who have been working in the heat for several days. It can also occur at or below room temperature in those wearing protective garments (e.g., in nuclear, biologic, and chemical operations). Symptoms caused by water depletion include thirst, weakness, dizziness, anxiety, muscular incoordination, agitation, confusion, palpitations, oliguria, and elevated temperature. Those caused by salt depletion include fatigue, weakness, headache, anorexia, vomiting, diarrhea, and skeletal muscle cramps; thirst is absent. Body temperature is usually normal or subnormal in both types of heat exhaustion. The skin is cool and clammy, and tachycardia and hypotension are common. Most victims present with a combined picture of water and salt depletion. Laboratory findings may include hyponatremia, high urinary specific gravity, and mildly elevated serum creatine phosphokinase and liver enzyme levels. Without elimination of the heat stressor and immediate treatment, heat exhaustion may progress to frank heatstroke (7,8).

Classic *heatstroke* usually affects the very young or the debilitated elderly and develops over several days, mostly during heat waves (9). The gradual onset may result in severe dehydration. Exertional heatstroke usually occurs in a nonacclimatized younger person after a few hours of severe heat stress. Victims usually can still sweat. Vital sign abnormalities include hyperthermia (usually $>40^{\circ}C$), tachycardia, tachypnea, and hypotension. The presenting temperature may not predict severity or outcome because a high core temperature for a short period of time and a lower temperature for a longer period can produce the same injury. Widespread damage to almost every organ system, especially the cerebellum,

has been described. The central nervous system is one of the first systems involved and the last to recover. Family or witnesses may describe a malaise or flu-like prodrome. Mental confusion begins at a core temperature of 38°C, and brain function is severely compromised at temperatures >42°C. Coma, seizure activity, and abnormal posturing have been described. The liver is also particularly susceptible to heat injury. Serum transaminase levels may initially be in the thousands and peak up to 2 weeks later at more than 10,000. Coagulopathies and hypoglycemia are common. The kidneys are at high risk for acute tubular necrosis. Rhabdomyolysis may contribute to renal injury in victims of exertional heatstroke (7,8). ABG measurements usually reveal a respiratory alkalosis. Lactic acidosis may also be seen following heavy exertion (10). Death is usually secondary to disseminated intravascular coagulation, acute renal failure, liver failure, or adult respiratory distress syndrome (4,8,11).

DIFFERENTIAL DIAGNOSIS

The key to diagnosing any heat illness is a history of heat stress. During a heat wave, the diagnosis is easily considered. Vigorous exercise in moderate temperatures or working in a closed, hot environment may also result in significant heat stress. The clinician should remember the predisposing factors in Table 360.1. Rhabdomyolysis should be excluded in patients with heat cramps. Electrolyte abnormalities should be ruled out in victims of heat cramps and tetany. An extensive evaluation may be necessary to exclude other causes of edema and syncope. The differential diagnosis of heatstroke also includes infection, particularly meningitis, thyroid storm, salicylate, anticholinergic, sympathomimetic or stimulant drug intoxication, and the neuroleptic malignant syndrome.

ED EVALUATION

The history should include the duration, magnitude, and conditions of heat exposure, recent activity, the nature, progression, and

duration of symptoms, medications, drug use, and underlying medical problems. In young, healthy victims, a typical history and physical examination that reveals no other pathology is all that is necessary for a diagnosis of minor heat-related problems. Normal laboratory findings are helpful in supporting the diagnosis in questionable cases and in those with advanced age or coexisting medical problems.

The temperature should be checked with a rectal thermoresistor temperature probe capable of measuring high temperatures (up to 44°C), particularly if the temperature measured by electronic thermometer approaches its upper limit. Continuous cardiac and oxygen saturation monitoring should be performed for patients with abnormal vital signs. For most symptomatic patients, laboratory evaluation should include measurements of electrolytes, blood urea nitrogen, creatinine, glucose, creatine kinase (CK), and liver enzymes; and urinalysis. Patients with elevated levels of creatine kinase, abnormal electrolyte or liver enzyme levels, or higher temperatures (>40°C) should also have coagulation studies; calcium, magnesium, phosphorus, and uric acid measurements; blood gas analysis; a complete blood count (CBC); an electrocardiogram (ECG); and a chest radiograph (8).

KEY TESTING

- Use temperature thermistor capable of measuring high temperatures
- LABS: blood gas, CBC, electrolytes, BUN, creatinine, glucose, total CK, liver enzymes
- If >40°C coagulation studies, calcium, magnesium phosphorus, uric acid, chest x-ray, and ECG

ED MANAGEMENT

Heat cramps are treated with oral or intravenous (IV) fluid and salt replacement. Heat edema is self-limited and resolves if the limb is elevated and support hose are worn. Patients with heat rash should keep their skin cool and dry and avoid tight clothing.

Antihistamines may be given for pruritus, but powders should be avoided to prevent further plugging. Desquamating agents (e.g., salicylic acid) and antibiotics effective against staphylococci may be prescribed for secondary infection. Heat syncope is treated with rest, fluids, salt, and gradual return to activity. Heat tetany should resolve with the reversal of hyperventilation.

The treatment for heat exhaustion is replacement of fluid and electrolyte losses with isotonic saline. Orthostatic patients may require 4 L or more of IV fluids. In mild cases, oral fluids can substitute for or supplement IV fluid. Rare cases present with severe hyponatremia, requiring hypertonic saline infusion (4,7,8).

The cornerstone of the treatment of heatstroke is rapid cooling. Immersing or covering the patient in ice was not recommended in the past because it was thought that skin cooling would cause vasoconstriction and shivering and could increase the core temperature. However, recent studies have shown that ice water immersion is the most effective method of cooling heatstroke especially the exertional type. The main drawback is the need for sedation in the conscious patient and the difficulties in immersion in a hospital setting (12). Cooling rates similar to ice immersion can be achieved by immersion in 15°C water. Application of ice packs in the areas of large vessels, such as the groin and axillae, and infusion of large volumes of cool IV fluids are useful for field management if immersion is unavailable but insufficient for definitive cooling.

Other methods of cooling include peritoneal and thoracic lavage using iced dialysate with cooling rates of 0.5°C/min, but the combination of evaporative cooling (0.3°C/min) and iced gastric lavage (0.2°C/min) with water or saline is more practical and just as effective. Evaporation is maximized without inducing shivering by keeping the patient wet with lukewarm water or wet towels and blowing air over the towels with a fan. Helicopter-blade fanning has also been used (13). Cooling blankets may be adequate for patients with mild heatstroke. The rectal temperature should be monitored with a probe capable of measuring high temperatures (up to 44°C).

Cooling is continued only until the temperature drops to 38.5° to 39°C, to avoid overshooting to hypothermia. Rectal temperature

monitoring should be continued, as the patient may rebound hours later and have thermal instability for days. Along with cooling, these patients frequently need sedation, intubation, and large volumes of IV normal saline. A central venous pressure line and Foley catheter may be necessary to monitor fluid therapy. Acid–base, electrolyte, and coagulation abnormalities should be corrected. Alkaline diuresis may be needed if rhabdomyolysis is present.

Shivering may be treated with chlorpromazine (25 mg IV), benzodiazepines, or thiopental. Seizure activity is best treated with benzodiazepines or phenobarbital. Phenytoin is ineffective. Dantrolene sodium has not proven efficacious in canine studies, although there are anecdotal reports of success. Poor prognostic indicators are a serum glutamic–oxaloacetic transaminase (SGOT) level $>1{,}000$ after 24 hours, coma that lasts more than 8 hours, or a presenting temperature of $\leq 42.2^{\circ}C$ (7,8). Sunburn can be prevented by avoiding unnecessary sun exposure (especially between 10 AM and 3 PM); wearing protective clothing, hats, and sunglasses; using broad-spectrum sunscreens with a sun protection factor (SPF) of 15 or higher on exposed areas; and avoiding artificial tanning lights. Treatment is otherwise supportive. Anti-inflammatory drugs and topical aloe vera and steroid spray may be useful for mild cases. More severe cases may require therapy similar to that for thermal burns (see Chapter 46, Burns).

CRITICAL INTERVENTIONS

- Institute continuous rectal temperature monitoring.
- For heatstroke, administer large volumes of IV fluid and perform ice water immersion, evaporative (fan and water) cooling and/or gastric lavage with iced saline or water.
- Avoid provoking shivering, and if necessary treat with chlorpromazine, benzodiazepines, or thiopental.

DISPOSITION

Patients with minor heat-related problems may be discharged. Patients with heat exhaustion should be admitted to a floor bed if

they have abnormal vital signs or laboratory findings or remain symptomatic after fluid therapy. Patients with heatstroke should be admitted to an intensive care unit. Discharged patients should be advised to avoid the conditions that precipitated their illness. Acclimatization with frequent water breaks and rest periods during hot-weather activity should avoid future problems. Consultation with a dermatologist may be helpful in patients with photosensitivity reactions.

Common Pitfalls

- Failure to recognize heat-related illness as a result of nonenvironmental causes.
- Failure to assess carefully for mental status changes in potential heatstroke victims.
- Failure to obtain a timely and accurate rectal temperature in patients with suspected heat illness.
- Failure to warn patients to avoid reexposure until acclimatization has occurred.
- Prescription of medications that predispose to or exacerbate heat- or sun-related illness to patients at risk.

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CHAPTER 361 High Altitude Illness

Nicholas C. Kanaan and Grant S. Lipman

BACKGROUND

Increasing numbers of people are visiting high altitude (elevations above 2,500 m [8,250 ft]) for work and recreation. In the western United States alone, more than 20 million visitors per year travel to these altitudes, with 25% to 40% of them suffering from some form of high altitude illness (5). These visitors often have pre-existing medical problems and medication regimens that may complicate the diagnosis of high altitude illnesses. Thus, practitioners require an understanding of the pathophysiology of symptoms to provide appropriate prevention, diagnosis, and treatment of high altitude illness.

High altitude illness is a spectrum of disease ranging from high altitude headache (HAH), to acute mountain sickness (AMS), to potentially lethal high altitude cerebral edema (HACE). High altitude pulmonary edema (HAPE) is specifically a pulmonary manifestation of altitude illness. AMS has been defined as presence of a headache in addition to one or more symptoms of gastrointestinal disturbance (anorexia, nausea, or vomiting), insomnia, dizziness, or fatigue in a person who has recently ascended to altitudes above 2,500 m (8,250 ft) (18). The spectrum of high altitude illness is directly attributed to hypobaric hypoxia, despite the fraction of inspired oxygen in air remaining constant at 21%. Barometric pressure decreases with increasing altitude, resulting in a decreased partial pressure of arterial oxygen (Pa_{O_2}). This self-limited disease can be debilitating when severe, and occurs

in up to 50% to 75% of hikers and mountaineers in the high mountains of the Unites States (11,21).

The incidence, severity, and duration of AMS are associated with the rate and altitude of ascent and modified by individual susceptibility, physical exertion, and high sleeping altitudes (9,19). Symptoms vary widely but remain consistent on repeated episodes in the same person, with 20% developing recurrent symptoms of AMS (6). AMS demonstrates no gender preference, but HAPE is more common in males (6). On ascent to high altitude, spontaneous diuresis occurs in response to complicated fluid shifts, increased cardiac output, and increased sympathetic tone (6,7). Increased cerebral blood flow and volume lead to ensuing hyperperfusion of the brain parenchyma (3,5). In most cases, symptoms abate in 2 to 3 days, but full acclimatization may take up to 7 days. Chronic mountain sickness, or Monge disease, may develop in some patients who do not acclimatize despite prolonged altitude exposure. Chronic mountain sickness is characterized by persistent hypoxia, polycythemia (hematocrit >60), and the development of congestive heart failure (9).

HAPE is a form of noncardiac pulmonary edema associated with elevated pulmonary arterial pressures resulting in pulmonary artery hypertension. Those suffering from HAPE have pulmonary arterial hypertension with alveolar endothelium and capillary leak. Uneven constriction of the vasculature (hypoxic pulmonary vasoconstriction) leads to scattered diffuse pattern of disease with symptoms usually occurring 2 to 4 days after ascent to altitude. HAPE develops in 0.5% to 6% of persons who ascend rapidly to high altitudes, has an overall mortality of 11%, and accounts for most of the fatalities that result from high altitude illness (12).

HACE affects an estimated 1% of travelers to high altitude and can be considered an end-stage presentation of severe AMS. Symptoms are a result of blood–brain barrier leak leading to increased vasogenic (extracellular) and cytotoxic (intracellular) edema, culminating in increased intracranial pressures causing the symptoms of encephalopathy and ataxia.

Hypobaric hypoxia can exacerbate pre-existing cardiac and pulmonary disease (9). Relative contraindications to high altitude travel include: advanced age, chronic kidney or cardiac diseases, unstable coronary artery disease, chronic obstructive pulmonary disease, pulmonary hypertension, sickle cell disease, and other diseases that compromise cardiopulmonary function (7,9).

PREVENTION

A staged, gradual ascent is the most effective way to achieve acclimatization. Remaining at 2,000 to 3,000 m (6,600 to 9,800 ft) several days before going higher, and increasing the sleeping altitude less than 500 m (1,640 ft) a day with a rest day every 2 to 3 days at altitudes above 3,000 m [9,840 ft] (12). Climbing high but sleeping low is also effective in reducing the results of hypobaric hypoxia exacerbated by nighttime hypoventilation (7). Drinking plenty of fluids, eliminating salt intake, and limiting overexertion may also decrease symptoms (6,9,12).

By causing a bicarbonate diuresis, resulting in a metabolic acidosis and a compensatory respiratory alkalosis (17), the carbonic anhydrase-inhibitor acetazolamide mimics the acclimated state of acid–base balance. Acetazolamide at a dose of 125 mg twice a day or 500 mg of the sustained-release formula each day, beginning 24 hours before ascent and continuing during the ascent to high altitude (4,17) can decrease symptoms in 30% to 50% of patients. Side effects include paresthesias, dysgeusias, and mild dehydration if fluid intake is insufficient (17).

Dexamethasone is a powerful glucocorticoid that limits transmigration of fluid across the blood–brain barrier, reducing cerebral edema, and AMS symptoms to a greater extent than acetazolamide (4,6). However, dexamethasone does not assist with acclimatization, and symptoms can return (the “rebound” effect) if glucocorticoids are abruptly discontinued before acclimatization is complete. It is advisable to avoid further ascent for at least 24 hours after discontinuation. For these reasons, dexamethasone is not considered a first line choice for prophylaxis of AMS, and caution is

is warranted if using on ascent. The recommended dose for AMS prevention is 2 mg every 6 hours or 4 mg every 12 hours. Higher doses (4 mg every 6 hours) should only be considered for military or search and rescue operations requiring rapid ascent to high altitudes (4).

Ibuprofen, 600 mg three times a day starting 6 hours before ascent can decrease the odds of getting AMS by about three, with a number needed to treat of four. The mechanism of action is thought to be the prevention of the inflammatory cyclooxygenase cascade of factors that are known to increase vascular permeability and vasodilation (11). The maximum altitude this was studied was at 3,810 m (12,500 ft), and caution should be used ascending to higher elevations with this drug than those studied.

CLINICAL PRESENTATION

Early symptoms of AMS are nonspecific and generally develop within 6 to 12 hours of arriving at altitude (range of 6 to 48 hours) (6). Headache, anorexia, nausea, vomiting, malaise, insomnia, lassitude, dizziness, and dyspnea on exertion comprise the most common constellation of symptoms (7–9,12,19). The headache is usually throbbing, worse in the morning and when supine, increases with exercise or Valsalva maneuver, and may be responsive to aspirin or ibuprofen (7). Sleep is generally poor and often exacerbates symptoms as a result of hypoventilatory hypoxia, so the patient often feels worse on waking (6,7). Findings on physical examination include tachypnea, tachycardia, and peripheral or periorbital edema, and patients may complain of decreased urine output. Tachypnea and tachycardia serve to maximize oxygenation and oxygen delivery to tissues. Despite having peripheral edema, the patient is often dehydrated and hypovolemic (6).

High altitude retinal hemorrhage, seen as flame hemorrhage, is usually asymptomatic and resolves without residual (6,9). Macular involvement is manifested by central scotoma (6). Laboratory studies may reveal mild leukocytosis, hemoconcentration, and elevated creatine phosphokinase (6,7).

Manifestations of HAPE include worsening dyspnea on both exertion and rest, cough, rales, hemoptysis, cyanosis, and orthopnea (12). The chest radiograph (CXR) reveals a normal-sized heart and diffuse bilateral patchy infiltrates, in contrast to the typical butterfly distribution of alveolar edema (7,12). Arterial blood gases may show hypoxia, hypocapnia, and respiratory alkalosis. Pulmonary function tests show decreased vital capacity and peak expiratory flow rates (7,12). The electrocardiogram (ECG) most often shows only sinus tachycardia, but sometimes shows evidence of right-sided heart strain (6,7). Patients with HAPE who undergo pulmonary artery catheterization have pulmonary hypertension with normal left atrial pressure and normal pulmonary artery wedge pressure (12).

Signs and symptoms of HACE include those of AMS plus ataxia, altered mental status, somnolence, and encephalopathy (6,7,9). Other findings may include cranial nerve palsy and papilledema. HACE can progress to coma and death within 24 hours of onset if untreated, and may leave neuropsychological sequelae, even if promptly recognized and treated. White matter edema, traditionally seen in the splenium of the corpus callosum may be seen on magnetic resonance imaging (MRI). HAPE and HACE can frequently present concurrently in the same patient.

DIFFERENTIAL DIAGNOSIS

It is important to understand that not all patients who have high altitude exposure are suffering from altitude illness. Patient presentations can mimic altitude illness or present as exacerbations of underlying medical problems. A patient presenting with altitude exposure can pose a diagnostic dilemma and thorough medical history should be taken and underlying illnesses must also be addressed. The differential diagnoses of AMS, HACE, and HAPE are shown in Table 361.1. Nonspecific symptoms of early AMS may mimic viral upper respiratory infection, gastroenteritis, or an alcohol hangover. Poor central nervous system (CNS) function in those patients exposed to adverse or extreme environments can also

be a result of hypothermia, hypoglycemia, hypovolemia, exhaustion, or even carbon monoxide toxicity (6,7,10). Pulmonary symptoms may be confused with acute exacerbations of chronic respiratory diseases such as asthma or chronic obstructive pulmonary disease (6,7). Other etiologies of noncardiogenic pulmonary edema should be considered (e.g., medications, neurologic disorders). Low-grade fever and leukocytes expand the differential to more serious infections, including pneumonia and meningitis. The differential diagnosis of CNS dysfunction also includes metabolic, psychiatric, toxic, and traumatic disorders (9). A thorough consideration of the differential diagnosis is key to appropriate and effective treatment.

TABLE 361.1
Differential Diagnosis of High Altitude Illness

AMS	HACE	HAPE
Carbon monoxide	Delirium	Asthma
Dehydration	Drug or Alcohol	Bronchitis
Diabetic ketoacidosis	Ingestion	Heart failure
Fatigue/overexertion	Hypothermia	MI with CHF
Hangover	Hyponatremia	Pneumonia
Hypoglycemia	Seizure	Pulmonary embolism,
Hypothermia	Stroke	COPD exacerbation
Migraine	Sepsis	
Viral syndrome	CNS infection	

AMS, acute mountain sickness; HACE, high altitude cerebral edema; HAPE, high altitude pulmonary edema; MI, myocardial infarction; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CNS, central nervous system.

ED EVALUATION

A history of recent, rapid ascent to high altitude or history of similar episodes at altitude should alert the physician to the potential diagnosis of AMS. The rapidity of ascent, altitude, activities, length of stay at altitude, the time of onset, nature and duration of symptoms, previous altitude exposure and pre-existing medical conditions should be noted.

The physical examination should focus on vital signs and evaluation of CNS, cardiac, and respiratory function. All patients should have an oxygen saturation measured, but pulse oximetry alone has proven unreliable in diagnosing AMS (15). A funduscopic examination for papilledema should be performed. Laboratory evaluation of patients with constitutional symptoms of AMS should include a complete blood count, electrolytes, blood urea nitrogen, creatinine, and glucose. Those with tachypnea, hypoxia, altered mental status, or abnormal findings on cardiopulmonary examination should have analysis, cardiac monitoring, an ECG, and a CXR. A CT scan of the head should be considered in those with an abnormal mental status or severe headache.

KEY TESTING

- Patients with symptoms of moderate/severe AMS, HACE, or HAPE: complete blood count, electrolytes, blood urea nitrogen, creatinine, and glucose.
- Patients with signs of HAPE, shortness of breath, tachycardia, or chest pain: ECG, CXR.
- Patients with symptoms of HACE or altered mental status: noncontrast head CT.

ED MANAGEMENT

The symptoms and management of high altitude illness are summarized in Table 361.2. In the field, descent is the most effective treatment for AMS. Second-line measures include oxygen, limiting further ascent until symptoms have resolved, and pharmacologic therapy. Patients with dehydration should be given oral fluids. Patients with vomiting should be given antiemetics and intravenous saline. Acetaminophen or a nonsteroidal anti-inflammatory agent can be given for headache.

TABLE 361.2
Symptoms and Management of High Altitude Illness

Prevention and Prophylaxis	
Travelers with history of mild-to-moderate AMS who are planning an ascent to high altitude	A staged, gradual ascent above 2,800 m, ascending in sleeping altitude <500 m/d; acetazolamide 125 mg bid for 24 hrs prior to rapid ascent; ibuprofen 600 mg q8h 6 hrs prior to ascent
Mild AMS	
Mild headache with nausea, dizziness, fatigue, sleep disturbance during first 12 hrs after rapid ascent to high altitude	Stop ascent and acclimatize; descend 500 m or more; or treat with acetazolamide 250 mg PO bid; treat headache and nausea symptoms with ibuprofen and antiemetics
Moderate/Severe AMS	
Moderate to severe nausea, headache, insomnia, dizziness, dyspnea on exertion after 12 hrs at high altitude	Descent of >500 m is primary treatment. If descent impossible, use a portable hyperbaric chamber and/or oxygen 1–2 L/min. Acetazolamide 250 mg PO bid, dexamethasone 4 mg PO or IM q6h until symptoms resolve
HAPE	
Dyspnea at rest, cough, copious sputum, severe weakness, rales, tachypnea, cyanosis, hemoptysis, tachycardia	Immediate descent. Oxygen 4–6 L/min. Minimize exertion, use a portable hyperbaric chamber; Sildenafil 50 mg PO q8h or Tadalafil 10 mg bid; Nifedipine SR 30 mg q12h; Salmeterol inhaled 125 µg bid
HACE	
AMS for 24 hrs, confusion, ataxia, poor judgment, vomiting, seizure, coma	Immediate descent or evacuation. Oxygen 2–4 L/min; use a portable hyperbaric chamber; dexamethasone 8 mg IV, IM, or PO initially, then 4 mg q6h; consider acetazolamide 250 mg PO bid

Acetazolamide is effective for treating AMS (4). Acetazolamide is also effective in treating Monge disease by reducing erythropoietin and hematocrit levels by improving arterial oxygenation and preventing further impairment of pulmonary gas exchange (17). Administration of 250 mg orally twice per day (pediatrics: 2.5 mg/kg every 12 hours) until symptoms of AMS resolve is recommended (17). Acetazolamide 125 mg before bed also helps

decrease symptoms of periodic breathing often experienced while sleeping at altitude.

Dexamethasone, 4 mg every 6 hours orally, intramuscularly (IM), or intravenously (IV) can be given for severe AMS. HACE is treated with an initial dose of 8 mg of dexamethasone followed by 4 mg every 6 hours orally, IM, or IV (7,13). In children, the dose should be 0.15 mg/kg.

Patients with moderate symptoms not improving with appropriate medications or severe symptoms require immediate descent to a lower altitude, but when descent is impossible, lightweight, portable hyperbaric chambers can be used to treat AMS. Portable hyperbaric chambers are inflatable zippered cylndrical bags with a window that simulates descent to a lower altitude when pressurized to 100 mm Hg by a foot-pump, and protected from over-inflation by a pop-off valve vent (usually 2 psi). The patient is placed in the bag, and ambient air is pumped in with or without supplemental oxygen (19).

HAPE should be treated initially with oxygen, and evacuation to a lower altitude while minimizing exertion (1,12). The calcium channel blocker nifedipine is effective in preventing and treating HAPE (2). Nifedipine SR 30 mg twice daily is the recommended dose both for HACE prophylaxis and treatment. Sildenafil 50 mg every 8 hours or Tadalafil 10 mg twice daily has also been shown to decrease pulmonary artery pressure, improve oxygenation, and decrease subjective symptoms in patients with HAPE (16). Sildenafil at 25 mg orally three times daily can be used chronically (up to 3 months) for the treatment of high altitude pulmonary hypertension (1). Hypotension may occur, especially in the setting of additional medications, such as nitroglycerin or α-blockers. The inhaled beta-agonist Salmeterol 125 μg bid can also be helpful as supplemental therapy in the treatment of HAPE (20).

Continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) by mask or endotracheal intubation and mechanical ventilation with positive end-expiratory pressure may be necessary for patients with respiratory failure (8). Diuretics are not helpful and may be harmful in patients with underlying

hypovolemia. On the contrary, fluid therapy may be required for the treatment of dehydration. If recognized early and treated aggressively, nearly all young, physically fit, otherwise-healthy patients with all forms of AMS will improve quickly, often with full resolution of symptoms within 24 hours.

CRITICAL INTERVENTIONS

- Administer acetazolamide and dexamethasone to patients with AMS and HACE.
- Administer oxygen and positive airway pressure ventilation by mask or endotracheal tube to patients with severe HAPE.
- Descend to lower altitude for severe AMS, HAPE, and HACE.

DISPOSITION

Young, healthy patients with mild to moderate AMS may be discharged with instructions not to resume ascent until after symptoms have subsided and only if preventative measures are taken. Medications should never be used to allow further ascent with persistent symptoms. Patients who are asymptomatic when seen in the ED after descent may be discharged with the proviso that return to altitude may result in recurrence of symptoms and appropriate acclimatization techniques should be followed. Patients with HAPE, HACE, severe AMS, moderate AMS with persistent symptoms, complications such as chest pain, ECG evidence of ischemia, or other significant ongoing medical problems should be admitted for supportive care.

Common Pitfalls

- Failure to consider the diagnosis of AMS in patients who become ill after rapid ascent to high altitude.
- Failure to consider pre-existing conditions, underlying disease, or a thorough differential diagnosis when treating patients for altitude illness.
- Treatment of AMS with medications to allow for further ascent or continued exposure.

- Failure to use adjunctive medications and hyperbaric therapy (if available) when descent is not immediately possible.
- Failure to evacuate seriously ill patients to lower elevations in a timely manner.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of David Richardson, Shaun C. Spalding, and Vincent J. Markovchick to the content of this chapter.

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CHAPTER 362

Diving Injuries

Brian K. Snyder

Underwater diving, with or without the breathing of compressed gas, usually takes place without incident. However, injuries during diving can occur. These injuries are generally secondary to pressure changes (barotrauma) or the effect of gas bubbles in the vascular system and tissues (arterial gas embolism [AGE] and decompression sickness [DCS]). Other injuries associated with compressed air diving include gas toxicity and immersion pulmonary edema. Aviators and others exposed to hypobaric environments can be similarly injured, also as a result of atmospheric pressure changes.

Any discussion of diving injuries requires an understanding of gas physics (Table 362.1). In diving medicine, pressure is commonly referred to in units of atmospheres absolute (ATA) or feet of seawater (fsw) (Table 362.2). As the most basic concept, pressure and volume are inversely related (Boyle law). Changes of volume and pressure in gas-containing organs of the body during descent and ascent lead to barotrauma. According to Dalton law and Henry law, compressed gas breathing at depth will lead to an increase of partial pressures of gas within the lung, vascular system, and tissues of the diver. A subsequent decrease in ambient pressure allows the gas to expand in volume and this is what can lead to DCS.

TABLE 362.1
Gas Laws

Boyle law: Given a constant temperature, the pressure and volume of an ideal gas are inversely related.

Dalton law: The total pressure exerted by a mixture of gases is the sum of the partial pressures of each gas.

Henry law: At equilibrium, the quantity of a gas in solution in a liquid is proportional to the partial pressure of the gas.

TABLE 362.2
Pressure Units and Equivalents

1 ATM = 760 mm Hg = 14.7 psi = 101.325 kPa = 33 fsw

At a depth of 66 fsw, total pressure would be 3 ATA (atmospheres absolute): 2 ATM for the pressure exerted by the water column and 1 ATM for the pressure of the atmosphere at sea level.

ATM, atmosphere; fsw, feet of seawater; kPa, kilopascal (SI units); mm Hg, millimeters mercury; psi, pounds per square inch.

Barotrauma occurs either during descent (more common) or ascent (more dangerous). Structures potentially injured during descent are the middle and inner ear and the sinuses. The lung is the structure most likely to be injured during ascent, but fortunately, this is uncommon.

DCS or “the bends” occurs during ascent and is the result of the occlusive and inflammatory effects of inert gas bubbles in the tissues and vascular system (1). At depth, inert gas will diffuse into and eventually saturate the tissues. During a controlled ascent, the gas leaches out of the tissue slowly in equilibrium with the saturation and does not form physical bubbles. If the ascent is too rapid, the ambient pressure decreases too quickly for the gas to stay dissolved and gas bubbles will form in the tissue and vascular system. The exact mechanism of bubble formation is unclear, although pre-existing micronuclei of gas may serve as the nidus for further bubble growth (1). In addition, inflammatory vascular microparticles resulting from decompression stress may be the mechanism of DCS (2). Given that bubbling often occurs without symptoms, the presence of bubbles are necessary but not sufficient to cause DCS, suggesting that there is a threshold beyond which symptoms occur.

Divers use decompression tables or special diving computers to determine safe dive exposures. Although unusual, DCS can occur even when dives conform to accepted decompression tables or computer algorithms. Factors that increase the risk of DCS include multiple dives, rapid ascent, and flying following a dive. Symptoms from DCS may improve during a subsequent dive (essentially recompression therapy) but can get worse on resurfacing (as the inert gas load increases). Because flying after diving further decreases pressure and may elicit or worsen DCS symptoms, divers are advised to refrain from flying for at least 12 to 24 hours after the last dive (3).

Bubbles may form in the circulation (usually the low-pressure venous system) or directly in tissues. Venous bubbles may cross right-to-left shunts in the heart (e.g., a patent foramen ovale) or the lungs and arterialize, leading to AGE. The pathophysiology of spinal cord DCS appears to be initial bubbling in the venous plexus system, causing first a decrease and then complete cessation of venous blood flow from the cord. Decreasing venous blood flow prevents dissolved nitrogen in spinal cord tissues from off-gassing, thereby forming in situ bubbles within the spinal cord (4).

Other mechanisms beside direct ischemic effects are prominent in DCS and AGE. The air–blood and air–endothelial interfaces are highly reactive, and initiate thrombotic and inflammatory processes. This causes leaky endothelium, leading to third spacing of fluids. Furthermore, adhesion and activation of neutrophils on the endothelium leads to the release of reactive oxygen species and other tissue-toxic neutrophil-derived moieties, causing a histopathology similar to an ischemia/reperfusion injury (5). Again, microparticles may be a mediator of this inflammation (2).

Inert gas, especially nitrogen, can cause narcosis at depth. Typically, symptoms start at depths of 100 ft or greater if breathing air. Further depth increases symptoms, including loss of fine motor skills and high-order mental processes and causes behavior similar to alcohol intoxication and may make activities at depth difficult or dangerous. Unconsciousness occurs below 300 ft. Symptoms

improve on ascent. In addition, nitrogen narcosis may impair the diver's memory of events during the dive (6).

Oxygen toxicity mainly affects the pulmonary system and the central nervous system (CNS). Pulmonary oxygen toxicity is unusual but can occur at partial pressures of oxygen at or below 1 ATA, as seen in patients requiring prolonged mechanical ventilation with high fractions of inspired oxygen. Symptoms include dyspnea, chest pain, cough, and decreased pulmonary function.

The CNS effects of oxygen usually begin to occur at depths when the partial pressure of oxygen in the breathing mixture is >1.6 ATA (220 fsw if breathing compressed air). Some divers may breathe oxygen-enriched air ("Nitrox") with fractions of oxygen of 32% to 36%. Cerebral oxygen toxicity can occur at lesser depths and actually is the factor that limits diving depth with Nitrox. In addition, there are "oxygen rebreather" systems where the diver breathes in a continuous circuit of gas with more than 95% oxygen. With these systems, cerebral oxygen toxicity can occur at depths as little as 25 ft.

Clinical hyperbaric oxygen (HBO) treatments use oxygen partial pressures up to 3 ATA, although oxygen toxicity in hyperbaric chambers is unusual. Divers are more prone to cerebral oxygen toxicity as they are exerting themselves in a cold, wet environment. Cerebral oxygen toxicity is affected by cerebral blood flow and $PaCO_2$. The mechanism is under investigation but may be caused by an increase in nitric oxide production (7).

CLINICAL PRESENTATION

The most common form of barotrauma seen in diving is a middle ear "squeeze." During descent, air within the middle ear contracts as the pressure increases, causing inward movement of the tympanic membrane (TM). If the pressure in the middle ear is not equalized (by opening the eustachian tube with a Valsalva or other maneuver) the TM can be injured (8). Bleeding can occur within the TM or within the middle ear space, leading to a hemotympanum, or the TM may rupture. Similarly, a closed space in the external ear canal

from occlusive material (e.g., wax or ear plugs) can bend the TM outward during descent and cause injury. The diver with otic barotrauma will present with a history of difficulty clearing the affected ear, pain, a conductive hearing loss, and sometimes vertigo.

Without adequate sinus ventilation during descent, pressure will increase in the sinuses, leading to pain and possibly a bloody nasal discharge as the mucosa is stripped from the periosteum. This may cause dramatic bleeding into the diver's face mask.

The inner ear can also be injured secondary to pressure changes. During descent, a forceful Valsalva maneuver can damage the round or oval window of the cochlea, potentially forming a fistula. The diver with inner ear barotrauma will present with a history of difficulty clearing the ears, the use of a forceful Valsalva maneuver, and sudden onset of severe vertigo, tinnitus, and hearing loss. On examination, the patient will have severe vertigo, a sensorineural hearing loss, and possibly a positive "fistula test." The fistula test involves insufflation of air onto the TM. The test is positive if eyes deviate to the contralateral side. The patient with inner ear barotrauma may also have signs of middle ear barotrauma (8).

During ascent, gas volumes increase as the pressure decreases. Generally, divers have no problems with their ears or sinuses during ascent (with some exceptions, see alternobaric vertigo below), because gas leaves the middle ear as the eustachian tube opens spontaneously or leaves the sinuses through the ostia. Barotrauma of ascent generally involves the lung. The most common scenario leading to pulmonary barotrauma is a panicked, rapid, or out-of-air ascent. With breath-holding during ascent, the glottis is closed, and the expanding gas cannot escape, causing rupture of alveoli. Congenital or acquired gas-trapping pulmonary processes (e.g., a cyst or bleb or asthma) may also result in lung barotrauma. Once the lung ruptures, gas can collect in the mediastinum (pneumomediastinum), interstitium of the lungs (pulmonary emphysema), in the pleural space (pneumothorax), or in the vascular system as an AGE. Divers with pneumomediastinum or pneumothorax will present with chest pain, dyspnea, and possibly

subcutaneous emphysema. A chest radiograph will generally show the abnormal collection of gas but is not completely sensitive (4).

Although gas from an AGE will systemically embolize, the most prominent organ involved is the brain (cerebral arterial gas embolism or CAGE). A diver with CAGE will develop symptoms during ascent or immediately on surfacing. Symptoms include altered level of consciousness, hemiplegia or hemiparesis, seizure, or other cerebral dysfunction. Sudden death may occur. If the patient survives the initial event, he may spontaneously improve as gas is forced through the cerebral vascular system by a spike in blood pressure. Any neurologic symptoms in the setting of pulmonary barotrauma should be thought to be secondary to CAGE and appropriate therapy quickly initiated (4). CAGE can also be caused by the iatrogenic introduction of gas into the vascular system, such as the inadvertent injection of air, the insertion or removal of central vascular catheters, neurosurgical procedures or procedures requiring cardiopulmonary bypass, cesarean section, or peritoneal insufflation for laparoscopy. Symptoms and classification of DCS depend on the organs affected. Type I DCS (“pain only”) involves the joints, extremities, and skin. Lymphatic obstruction can cause lymphedema, which usually takes days to resolve despite recompression therapy. Type II DCS (or “serious” DCS) includes “neurologic DCS” involving the CNS (mainly the spinal cord in compressed-air sport divers), vestibular DCS (“staggers”), and cardiopulmonary DCS (“chokes”).

The symptoms of DCS usually occur minutes to several hours after surfacing, but cases of DCS symptoms occurring days after diving have been reported. The pain of type I DCS is typically described as deep and unrelieved, but not worsened, with movement. Since divers can injure themselves in other ways (strains, direct trauma), pain from DCS can be confused with or attributed to pain from these injuries. Distention from bubbles in ligaments, fascia, and long bones or the activation of stretch receptors caused by bubbles in tendons are thought to be the mechanism of pain. This mechanism is supported by the rapid improvement of type I DCS symptoms with recompression. The most common locations for type I DCS are knees

and shoulders, and frequently only a single joint is involved. Diffuse and difficult to describe back pain may herald the more serious signs of spinal cord DCS.

The classic description of neurologic DCS (type II) begins with this sensation of truncal constriction or girdle-like pain. A "wooly feeling" may begin in the feet and develop into an ascending paralysis. This produces a presentation similar to a transverse myelitis. This form of neurologic DCS is usually rapid in onset and has a tendency to affect the lower cervical and thoracic regions.

In type II DCS, neurologic deficits do not necessarily follow distinct spinal cord syndromes seen with trauma or ischemia. Furthermore, because lesions are scattered throughout the spinal cord, a definitive "level" is frequently not found. Incontinence and sexual dysfunction from autonomic involvement is common.

Pulmonary DCS, or "the chokes," is generally seen only after prolonged, deep diving. This syndrome is caused by large numbers of pulmonary artery bubbles and presents with cough, hemoptysis, dyspnea, substernal chest pain, or cardiovascular collapse. Vestibular DCS, or "the staggers," also usually occurs after deep, long dives, although it is increasingly being reported in sport divers. It presents with vertigo, hearing loss, tinnitus, and disequilibrium. These symptoms are similar to inner ear barotrauma; however, they occur more gradually and after ascent whereas other historical clues are also helpful in distinguishing the two distinct processes (4).

Cerebral oxygen toxicity manifests itself with twitching, nausea, paresthesias, dizziness, and seizures. A seizure may be the initial manifestation of cerebral oxygen toxicity and may cause drowning when it occurs in the water. Immersion pulmonary edema can occur while diving and swimming. Typical symptoms include dyspnea, chest discomfort, and coughing of pink frothy secretions. The mechanism of this condition is unknown. It is not caused by decompression. Hydrostatic forces, thermal stress, and possibly increased capillary permeability may be involved (9,10).

DIFFERENTIAL DIAGNOSIS

The diver with vertigo may present a diagnostic challenge. Vertigo caused by transient unequal clearing of the ears is called alternobaric vertigo and can be confused with more dangerous processes such as inner ear barotrauma or vestibular DCS (Table 362.3). The diagnosis can be complicated by a combination of injuries: for example, a diver sustains inner ear barotrauma, causing panic, leading to a rapid ascent and CAGE. The major confusion in the diagnosis of vertigo is differentiating inner ear barotrauma from CAGE. Because HBO treatment for CAGE can worsen inner ear barotrauma, this distinction is important. However, if one cannot distinguish between the two conditions or both may have occurred, myringotomies to decompress the middle year can be performed before commencing HBO.

TABLE 362.3
Differential Diagnosis of Vertigo in the Diver

Cause of Vertigo	Risk Factors	Onset of Symptoms	Symptoms and Physical Examination Findings
Alternobaric	Unequal clearing of ears	During descent or ascent	Self-limited
Middle ear barotrauma	Difficulty clearing ears	Occurs during descent	Signs of barotrauma on otoscopic examination, conductive hearing loss
Inner ear barotrauma	Difficulty clearing ears, forceful Valsalva	Occurs during descent, occurs immediately after attempt to clear ears	Severe vertigo, tinnitus, sensorineural hearing loss, possible fistula test (see text), may have signs of middle-ear barotraumas
Vestibular decompression sickness	Deep, prolonged dives, switching of breathing gas	Occurs after dive completion, usually 15 min to hours	May have other signs of DCS
Cerebral arterial gas embolism	Rapid or panic ascent	Occurs on surfacing or within minutes of surfacing	Will have other signs of CAGE (altered or loss of consciousness, hemiplegia) (see text)

Another difficult distinction is between CAGE and DCS. In fact, the two conditions can occur concurrently (type III DCS) (4). Some authorities do not distinguish between the two entities and call all bubble-related diving injuries decompression illness (DCI). The argument for this approach is that sometimes DCS and AGE cannot be reliably distinguished and the primary treatment is the same. Some oppose the term DCI because although sometimes indistinguishable, the two processes can often be separated. In addition, although primary therapy may be the same, adjunctive therapies may be specific (e.g., lidocaine in CAGE), and research may be hindered by such a lack of distinction.

CAGE usually occurs immediately or soon on surfacing after a rapid or uncontrolled ascent with mainly cerebral symptoms, such

as altered level of consciousness, seizure, or hemiplegia. On the other hand, symptoms of DCS begin minutes to hours after the dive and although cerebral symptoms can occur, neurologic symptoms and signs usually refer to the spinal cord. CNS trauma, near-drowning, and hypothermia should be considered in the differential diagnosis of these conditions.

ED EVALUATION

The history should include details regarding the dive profile, symptom latency, severity, progression, and pre-existing health. Vital signs should include measurement of oxygen saturation. The physical examination should focus on the cardiopulmonary and neurologic systems and the ears, nose, and throat. Patients with chest signs and symptoms or altered mental status should have an ECG and undergo continuous cardiac monitoring. Evaluation for cardiac ischemia or dysfunction should be considered in patients with an abnormal ECG, pulmonary edema, or unexplained chest complaints, particularly those with risk factors for cardiovascular disease. Although routine laboratory studies are not helpful in the diagnosis or treatment of diving injury, they may evaluate for other conditions, if clinically indicated.

KEY TESTING

A chest radiograph is likely the only “routine” test in evaluating injured divers with potential cardiopulmonary complaints, CAGE or DCS. CNS imaging should not delay definitive treatment (HBO).

ED MANAGEMENT

Patients with uncomplicated barotrauma to the middle ear or sinuses should be treated symptomatically with decongestants such as oxymetazoline (Afrin) or pseudoephedrine and analgesics. Antibiotics can be prescribed in the cases of a perforated TM or sinus barotrauma occurring in contaminated water.

Patients with inner ear barotrauma should constantly sit up and avoid maneuvers that increase intracranial pressure (nose blowing,

etc.). Some otolaryngologists advocate conservative treatment with antivertigo and antiemetic drugs such as meclizine (Antivert), reserving surgical intervention to those who do not improve spontaneously, although others advocate for immediate surgical exploration (8).

Patients with pneumomediastinum but no sign of CAGE can be managed conservatively. Those with more than a very small pneumothorax should have it evacuated, and a chest tube must be inserted if HBO therapy is to be employed.

Patients with suspected DCS or CAGE should receive 100% oxygen by nonrebreather face mask or endotracheal tube if necessary to ensure an intact airway. Recompression with HBO should occur as soon as possible, with transfer to a recompression center if necessary. Outcomes seem to correspond to the timeliness of HBO therapy. Although there are several recompression treatment tables employed in the treatment of DCS or CAGE, the most common is the US Navy Treatment Table 6 (with a maximum treatment pressure of 60 ft or 2.8 ATA). Lower treatment pressures have also been used with good results (11). If symptoms do not fully resolve, some centers will continue HBO treatments daily or twice daily until symptoms plateau. Divers with DCS have responded to HBO days after injury, and therefore this should be instituted even if presentation is delayed.

There are several beneficial physiologic effects of HBO. Increased pressure reduces bubble size. Increased partial pressure of oxygen dissolved in serum creates a gradient, causing nitrogen to move from bubbles into serum, increasing off-gassing of inert gas. Oxygen, in turn, moves into bubbles, but because it is metabolically active, it subsequently moves into cells, leading to further dissolution of bubbles. HBO increases the oxygen dissolved in the plasma which increases oxygen delivery to ischemic tissues, as well as decreasing edema and intracranial pressure, and reducing the adherence and activation of leukocytes on vascular endothelium (12).

Divers with CAGE should be kept supine with the head in a neutral position. The Trendelenburg position should not be employed.

Nondextrose-containing isotonic intravenous (IV) fluids should be infused to preserve tissue perfusion in divers with DCS and CAGE. Various pharmaceutical adjuncts have been used in the treatment of DCS and CAGE, including aspirin, corticosteroids, and heparin but animal studies and human experience have generally shown no definite benefit (13). IV lidocaine in the treatment of CAGE has been shown to be effective in animal models and in a human study examining neuropsychiatric outcomes after cardiopulmonary bypass (where neuropsychiatric deficits are thought to be secondary to intravascular air) (14). Typical cardiac doses are generally used.

Oxygen and nitrogen toxicity and immersion pulmonary edema resolve spontaneously. Treatment is primarily supportive. If immersion pulmonary edema is severe or persistent, standard treatments for this condition can be administered (9).

Clinicians unfamiliar with the treatment of underwater diving injuries should consult a diving or hyperbaric medicine specialist or the Divers Alert Network (DAN; phone: 1-919-684-9111; website: http://www.diversalertnetwork.org). DAN has staff available 24 hours a day to provide assistance to divers and clinicians and can provide the location of the nearest hyperbaric facility.

CRITICAL INTERVENTIONS

- Obtain a chest radiograph on patients with cardiopulmonary complaints. If the chest radiograph is normal, consider evaluation for acute coronary syndrome or other cardiac or pulmonary process, especially if the dive profile and symptoms do not suggest a high probability of DCS or AGE
- Administer oxygen and IV fluids and arrange for HBO therapy for patients with DCS and CAGE.
- Remember that medical conditions not related to barotrauma or decompression can occur in or around the water and the physician must be careful to evaluate for such processes.

DISPOSITION

Patients with pulmonary barotrauma but without evidence of CAGE do not require recompression therapy. Those with suspected DCS or CAGE should be transferred to a facility capable of providing HBO therapy. A diver may require hospitalization or repetitive treatments after initial therapy.

Given that treatment of inner ear barotrauma is controversial, emergent otolaryngology consultation may be obtained for patients with this condition.

Patients with barotitis or sinus barotrauma should not return to diving until symptoms resolve. Those with a perforated TM must not dive until it heals. Otolaryngology referral in 4 to 6 weeks is warranted.

Ideally, divers with DCS or CAGE should be examined by a physician experienced or trained in diving medicine before returning to diving. Counseling of divers experiencing immersion pulmonary edema is difficult as it cannot be predicted who will experience another episode.

Common Pitfalls

- Failure to appreciate that significant barotrauma can occur at shallow depths.
- Failure to consider the possibility of DCS or CAGE in any patient with neurologic symptoms after underwater diving.
- Failure to consult a diving or hyperbaric medicine specialist or the Divers Alert Network for advice and to consider HBO even when the diagnosis is not clear.
- Failure to consider inner ear DCS or barotrauma in the vertiginous diver and failure to differentiate between the two processes.
- Failure to have divers' follow-up with a physician experienced in diving medicine beforereturning to diving.

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CHAPTER 363

Drowning (Submersion Injuries)

Eric W. Ling

The World Health Organization defines drowning as “the process of experiencing respiratory impairment from submersion/immersion in a liquid medium.” This is further subdivided into drowning with subsequent fatality, morbidity, or no morbidity; a clinical submersion event without respiratory impairment is simply a water rescue. Drownings occur most frequently in a bimodal distribution with one peak in the toddler years, generally associated with lapses in supervision, and another peak in the late adolescent and early adult years associated with swimming, water sports, and substance intoxication (1). Respiratory dysfunction and ensuing anoxic brain injury are the primary drivers of morbidity, though hypoxic injury to the heart, liver, and kidneys also plays a role. Concurrent trauma or comorbid medical conditions must always be considered, including events that may precipitate drowning such as intoxication, seizure, or primary cardiac arrest. Hypothermia and environmental exposure often complicate resuscitation (see Chapter 358).

The pathophysiology of drowning begins with submersion in a liquid and an inability to reach safety or maintain the mouth and nose consistently above the surface. Voluntary breath holding follows, lasting up to a minute, then involuntary aspiration as the respiratory drive overwhelms resistance. This initial aspiration often generates laryngospasm that prevents further aspiration, and the patient can swallow copious amounts of liquid working to inhale against a closed glottis. Laryngospasm relaxes as the brain becomes

hypoxic. Significant aspiration then occurs until the respiratory drive is blunted by brain anoxia and apnea results. The initial sympathetic surge generates tachycardia, but progressive hypoxia leads to bradycardia, pulseless electrical activity, and finally asphyxial asystolic arrest (2).

Aspiration washes out surfactant and disrupts the alveolar membranes, decreasing lung compliance with a corresponding five- to ninefold increase in the work of breathing. Greater membrane permeability permits the development of massive pulmonary edema —a given aspiration may generate three times that quantity in pulmonary edema (3). Bronchospasm also arises from direct irritation of airway epithelium. Theoretical differences between fresh and salt water aspirations are born out in microscopic analyses of injured lung tissue when greater than 11 mL/kg is aspirated, but appear to have minimal clinical effect in nonfatal human drownings where aspirations typically involve less than 3 to 4 mL/kg (2,3).

The brain is exquisitely sensitive to the partial pressure of oxygen. In healthy volunteers, PaO_2 drops to 43 mm Hg within 85 seconds of breath holding and strenuous activity (3). This progressive hypoxia prior to arrest differentiates asphyxial arrest from primary cardiac arrest and results in far greater anoxic brain injury for circulatory arrests of comparable duration. Reperfusion injury is believed to be considerable, and cerebral edema develops in proportion to the degree of brain injury (4). Subtle cognitive deficits may persist despite a normal neurologic examination, and for toddler drownings, the full extent of injury may not be evident until the child begins schooling (5).

Hypoxia causes cardiac, liver, and renal dysfunctions. Cardiac injury is more likely with pre-existing coronary artery disease or heart disease. Liver injury is generally mild while renal injury may rarely require dialysis but remains reversible. Renal injury from hemoglobinuria or myoglobinuria has been reported but is likely related to concomitant circumstances and not to the pathophysiology of drowning.

Up to 10% of drowning victims have minimal fluid aspiration on autopsy. While this was traditionally thought to be from laryngospasm preventing aspiration ("dry drowning"), there is no supporting literature and it is more likely that, in these cases, apnea secondary to another etiology preceded the submersion event (3). The "immersion syndrome" describes sudden cardiac arrest upon immersion to cold water, mediated by a sympathetic surge from cold water immersion and subsequent dysrhythmias (6). Prolonged QT syndromes are vulnerable to immersion syndrome, though autopsy studies have not found evidence of associated genetic mutations in unexplained fatal drownings (2).

Hypothermia is common due to submersion in cold water and ongoing cooling during rescue and resuscitation. Hypothermia dramatically reduces brain metabolism and offers neuroprotective effects with reasonable neurologic recovery after 66 minutes of submersion in ice water (5). In general, hypothermia portends a poorer prognosis than normothermia, presumably due to increased duration of submersion, prolonged transport, or insufficient circulation. Hypothermia is responsible for many of the arrhythmias noted in drowning victims, most typically atrial fibrillation. In severe hypothermia, ventricular arrhythmias may be present but are rare with a core temperature $>32^{\circ}C$ and, if present, should raise the prospect of additional occult pathology.

CLINICAL PRESENTATION

Drowning victims may be awake, lethargic, combative, comatose, or in cardiac arrest on presentation. A history of coughing, choking, or vomiting is common. Though the history may clearly identify a submersion event, drowning injury should also be considered in any patient with altered mental status found near a body of water. In mild cases, the pulse, blood pressure, and respiratory rate are often elevated, but with severe hypoxia vital signs may be decreased or absent. Varying degrees of hypothermia are often present. Aspirated or regurgitated food, water, or other foreign material may be present in the mouth and airway. Rhonchi, rales, or wheezing can

be audible on pulmonary examination. Gastric distention is common. Associated traumatic injuries may also be present. Victims of scuba diving accidents may have signs and symptoms of concomitant barotrauma and decompression sickness (see Chapter 362). In severe cases, decorticate or decerebrate posturing, flaccid paralysis, unreactive pupils, or absent corneal, brainstem, and deep tendon reflexes may be present. With the exception of clear signs of death, such as decapitation, hemisection, or putrefaction, moribund presentations do not exclude aggressive resuscitation. Between 10% and 20% of patients presenting with coma and initially fixed and dilated pupils will recover completely.

DIFFERENTIAL DIAGNOSIS

In patients found unresponsive in or near a body of water or other fluid, the possibility of preceding trauma (especially to the head and neck), alcohol or substance intoxication, myocardial infarction, seizure, cerebrovascular accident, attempted suicide or murder, child abuse or neglect, cerebral air embolus (in scuba divers), and other causes of altered mental status should be considered.

ED EVALUATION

The history should include details such as estimated submersion time, medium, and temperature; events surrounding the submersion; level of consciousness and vital signs at the scene; and signs, symptoms, and treatment before arrival. For children who fall into pails of liquid (e.g., detergent, insecticide) or industrial workers who may be submerged in a medium other than water, the type of liquid and its potential toxicity should be established. A submersion near rocks, near high ledges, in heavy surf, while engaging in motor sports, or while diving, raises suspicion for concomitant traumatic injury.

If the patient arrives in critical condition, evaluation begins with evaluation of airway patency, spontaneous respirations, and palpation of a pulse. Of note, in hypothermic patients, pulses may be extremely difficult to palpate and assessment of circulatory

function requires a full minute palpating central pulses (8). If available, bedside cardiac ultrasound enables more rapid appraisal of cardiac function.

After an initial assessment, physical examination focuses on vital signs, cardiopulmonary status, and neurologic findings. Continuous monitoring of arterial oxygen saturation and cardiac telemetry is essential. Temperature should be taken using a low-reading thermometer: rectal if awake or esophageal if intubated. Serial coma grading (for instance, the Glasgow Coma Scale) is helpful in monitoring progress. In all symptomatic and comatose patients, a chest radiograph should be obtained. The development of pulmonary edema is often delayed, and repeat chest radiographs are recommended whenever symptoms worsen or shortly before ED discharge, even if a patient is asymptomatic (2,9). Electrocardiogram (ECG) is warranted in most symptomatic patients.

Baseline laboratory studies should include a point-of-care blood glucose, an arterial or venous blood gas analysis, lactate, complete blood count, electrolytes, glucose, blood urea nitrogen, creatinine, and urinalysis. Critically ill patients should have cardiac enzyme; liver function tests; calcium, magnesium, and creatine kinase measurements. Urine drug testing may suggest a cause for the drowning.

In persistently altered patients or patients with a history of trauma, a computed tomography (CT) scan of the head should be performed. Routine cervical spine imaging is not indicated, as demonstrated by a series of 2,244 drowning victims which found a 0.49% prevalence of cervical spine injuries, with injuries only in those with a history of trauma or traumatic examination signs (7). Magnetic resonance imaging (MRI) is more sensitive for cerebral edema and anoxic brain injury than CT but neither study is sufficient to inform prognosis in the ED. Since cerebral edema develops over time, MRI becomes significantly more helpful in guiding therapy and prognosis discussions when obtained 3 to 4 days after the drowning event (4).

KEY TESTING

- Core temperature with a low-reading temperature probe
- Chest radiograph initially and, if discharging from the ED, prior to discharge
- Initial laboratory studies: blood gas, lactate, glucose, complete blood count, electrolytes, blood urea nitrogen, creatinine, urinalysis
- Secondary laboratory studies if pertinent: cardiac enzymes, liver function tests, calcium, magnesium, creatine kinase, urine drug screening
- Advanced imaging: CT head for persistently altered or traumatic patients; cervical spine imaging only with a history of trauma or traumatic examination signs

ED MANAGEMENT

Rapid prehospital response and early initiation of resuscitation are the principal factors influencing morbidity and mortality. Rescuers must be cognizant of personal danger during rescue attempts, as dangerous conditions may result in injury to rescue teams. In contrast to basic life-support recommendations to initiate resuscitation with chest compressions, the resuscitation of drowning victims should start with rescue breathing, while still in the water if possible (8,10). Chest compressions are ineffective in the water and must await extrication to a dry firm surface. The Heimlich maneuver is indicated only when there is clear foreign body obstruction of the airway. In other cases, the Heimlich maneuver and postural draining techniques have no proven benefit and increase the risk of aspiration from vomiting (2,3,8,10).

Cervical spine immobilization during rescue and resuscitation is not indicated in routine drownings without history or signs of trauma (7). As noted above, cervical spine injury is rare, and immobilization attempts may significantly delay extrication while interfering with essential airway management-–optimal early airway management with rescue breathing is life saving and takes precedence over all other prehospital interventions.

After extrication, cardiopulmonary resuscitation and advanced cardiac and trauma life-support measures are instituted as necessary and by established guidelines. Immediate ED therapy is directed toward securing the airway, ensuring adequate oxygenation, performing chest compressions if necessary, reversing hypothermia, and correcting hypoglycemia and hypotension. There are no clinical, laboratory, or imaging criteria that can determine survivability on ED arrival (2–4,8,10). Thus, every arrested drowning patient should receive 20 to 30 minutes of high-quality advanced cardiac life support before discontinuing resuscitation. Hypothermic arrested patients should be rewarmed as rapidly as possible and cardiopulmonary resuscitation should continue until the patient is $>32^{\circ}C$ for 20 to 30 minutes. Traumatic injuries should be managed as usual but with emphasis on respiratory management and neuroprotective strategies.

Awake patients should be placed in a lateral decubitus position as tolerated to prevent aspiration from vomiting. After drowning with subsequent rescue breathing, the chance of vomiting is about 65%. After chest compressions, the chance of vomiting rises to 86% (8). Patients who are protecting the airway but are unable to maintain oxygen saturations above 90% on high-flow oxygen or who are becoming increasingly fatigued may benefit from a trial of noninvasive positive pressure ventilation (CPAP or BiPAP). With any type of respiratory support, hyperoxia should be avoided to reduce the brain injury associated with oxidative reperfusion stress, and the goal for oxygen saturations should be 94% to 98% (4). Bronchospasm may be present and should be treated with inhaled bronchodilators.

Patients who are inadequately protecting the airway require a secure endotracheal intubation; due to the high airway pressures required to inflate drowned lungs with greatly reduced compliance, supraglottic airways may be ineffective (3). Ventilator settings should be set in accordance with acute respiratory distress syndrome guidelines, with high positive end-expiratory pressures (PEEPs) to recruit respiratory units and reduce ventilation–perfusion mismatch, low tidal volumes, and increased respiratory rates. Gastric

decompression by nasogastric or orogastric tube is recommended for all intubated patients. For patients with severe lung injury who cannot be oxygenated despite optimal endotracheal ventilation, consider emergent bronchoscopy to remove possible foreign bodies such as sand, mud, algae, or vomitus. With continued treatment failure, extracorporeal membrane oxygenation (ECMO) has been employed in case reports with good success (2). Corticosteroids for drowning-related lung injury have not been shown to be effective and are not recommended.

Initially clear chest radiographs may be falsely reassuring as the development of pulmonary edema can be delayed. Pediatric literature suggests that patients who are asymptomatic after 6 to 8 hours of observation are unlikely to require treatment, and this has become the standard for ED observation (2,11). Infiltrates present on chest radiograph are difficult to differentiate between pulmonary edema, chemical pneumonitis, and aspiration pneumonia. While patients with exposure to contaminated fluids (sewage, etc.) should receive prophylactic antibiotics, it is unclear which other patients benefit from antibiotic therapy. Several retrospective chart reviews show no benefit to prophylactic antibiotics and one review noted a trend toward increased resistance in pneumonia that developed on prophylactic antibiotics, but there are no prospective or randomized trials (9,12,13). The typical diagnostic clues to pneumonia are obscured in drowning: Pulmonary edema or chemical pneumonitis may mimic infectious infiltrate on chest radiograph, fever may not be clinically apparent with therapeutic hypothermia treatment, and leukocytosis is common in drowning regardless of infection. Waiting for the presence of purulent sputum or positive sputum cultures may secure the diagnosis, but pneumonia in acute respiratory distress syndrome may present as a fulminant process and delays may be lethal. Broad spectrum antibiotics, covering typical gastric aspiration as well as the *Aeromonas spp.* and *Pseudomonas aeruginosa* common in bodies of water (13), should therefore be started with a very low threshold on all critically ill patients with infiltrate on chest radiograph and one of the following: persistent tachycardia,

hypotension, or leukocytosis; fever; or failure to respond to maximal therapy.

Acidosis results from both metabolic lactic acidosis and hypercarbia secondary to inadequate ventilation. Serum bicarbonate is frequently low but does not require specific therapy as it typically resolves with appropriate oxygenation, ventilation, and circulatory support.

Hypotension may develop from primary or hypoxic cardiac dysfunction, cold diuresis, acidosis, or as a systemic inflammatory response to aspirated material. Normal saline is isotonic and is the preferred resuscitation fluid for nontraumatic drownings. Volume overload may worsen pulmonary or cerebral edema and should be avoided. Vasopressors may be employed for refractory hypotension (14).

To manage hypothermia wet clothing should be removed immediately and warm blankets applied with additional external forced air blankets or plumbed blankets for hypothermic patients above 32˚C. Patients below 32˚C or with unstable vital signs benefit from concurrent external and internal warming techniques including endovascular catheterization, thoracic lavage, and ECMO (see Chapter 358).

Data from primary cardiac arrest and newborn asphyxia suggest that therapeutic hypothermia may also be neuroprotective in arrested drowning victims (4). Hypothermic patients in arrest should not be actively rewarmed above 32˚C and any arrested drowning patient may benefit from therapeutic hypothermia with goal temperatures of 32 to 34˚C for 12 to 72 hours and slow 0.5˚C per hour rewarming. Hyperthermia should absolutely be avoided in all drowning patients (15).

In addition to appropriate oxygenation and therapeutic hypothermia, neuroprotective critical care for anoxic brain injury and cerebral edema also includes meticulous attention to seizure activity, hypocarbia or hypercarbia, hypotension, hypoosmotic state, hypoglycemia or hyperglycemia, and head positioning (4). Seizures should be treated swiftly with benzodiazepines and with antiepileptics. Electroencephalogram (EEG) should be considered for

any suspicion of nonconvulsive seizure. Because hypercarbia and prolonged hypocarbia both result in reduced cerebral perfusion, the goal is normocarbia and a $PaCO_2$ of 40 mm Hg. Arterial hypotension underperfuses cerebral tissues and a goal of normal blood pressure is essential. Hypoosmolar states, due to hypoosmolar fluids or renal wasting, increase intracranial pressure by means of an osmotic gradient, and these should be avoided. Both hyperglycemia and hypoglycemia have demonstrated deleterious effects on injured brain and normoglycemia should be maintained. Finally, appropriate position with the head midline and the head of the bed elevated to 30 degrees helps mitigate intracranial pressure. Prolonged hyperventilation, barbiturate coma, aggressive diuresis, and routine pharmacologic paralysis have no benefit in drowning. Elevated intracranial pressure likely represents the degree of cerebral edema due to anoxic injury and in and of itself may not be a driver of cerebral dysfunction. Attempts to manage intracranial pressure independently appear to have no significant impact on patient outcome and should be avoided (4).

CRITICAL INTERVENTIONS

- Resuscitate aggressively with emphasis on optimal airway management.
- Administer oxygen or noninvasive positive pressure ventilation and perform endotracheal intubation with elevated PEEP as necessary to maintain oxygen saturations from 94% to 98%: avoid hypoxia or hyperoxia.
- Assess for concomitant traumatic injury.
- Use a low threshold for initiating broad spectrum antibiotics for aspiration pneumonia in critically ill drowning patients.
- Maintain normoglycemia, normotension, normovolemia, normocarbia, normoosmolar state, and elevate head of bed to 30 degrees.
- For critical patients, induce therapeutic hypothermia to, and do not rewarm above, 32° to 34°C.

DISPOSITION

Patients who have been apneic or unconscious; those with extremes of age; those with hypoxia, dysrhythmias, ECG evidence of ischemia, or an abnormal chest radiograph; and those whose symptoms persist after ED treatment should be admitted to an appropriate level of care. Due to the delayed onset of pulmonary edema, patients are candidates for ED discharge only if they are asymptomatic after 6 to 8 hours of observation with a normal physical examination, normal oxygen saturation, and a normal chest radiograph obtained 6 to 8 hours after the drowning event. Discharged patients are instructed to return immediately if any respiratory symptoms develop (cough, sneezing, dyspnea, fever). Patients who did not have respiratory distress at any time are, by definition, considered water rescues rather than drownings. Water rescue patients who are asymptomatic on arrival with normal vital signs and physical examination may be discharged from the ED without prolonged observation. Indications for transfer include lack of necessary intensive care facilities, pulmonary specialist capable of performing bronchoscopy, or perfusionist capable of initiating ECMO.

Common Pitfalls

- Failure to appreciate that an initially moribund presentation does not preclude good neurologic recovery and, conversely, that those who present with mild symptoms may later deteriorate rapidly.
- Failure to consider the possibility of accidental or nonaccidental trauma, myocardial infarction, cerebrovascular accident, seizure, cerebral air embolism, alcohol or substance intoxication, hypothermia, and medical or psychiatric illness as precipitating or complicating aspects of drownings.
- Continuing cervical spine immobilization when it is interfering with rescue and airway management in patients with no history or signs of trauma.

- Failure to observe ED patients with a history of drowning for at least 6 to 8 hours and failure to obtain a chest radiograph shortly before discharge.
- Failure to employ neuroprotective strategies to minimize anoxic and reperfusion brain injury, including avoiding hyperoxia.

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CHAPTER 364 Electrical Injuries

Scott E. Rudkin and Jennifer A. Oman

Electrocution is an infrequent cause of injury but can damage multiple organ systems. Unlike a thermal burn, electrical injuries can cause extensive internal injury without any significant sign of external injury. In the United States, electrical injuries annually kill nearly 1,000 patients, with high-voltage injuries accounting for two-thirds of the total (1). Most adult injuries occur in the workplace; electrical injuries are the fourth leading cause of traumatic, work-related deaths (2). Most fatalities from electrical injuries occur from ventricular fibrillation (VF), asystole, or interruption of the central respiratory control (1).

Luckily, the majority of household injuries have been mitigated by changes in building codes that require a ground plug. However, misuse or malfunction of home appliances still account for 200 deaths annually (3). Children constitute 30% of all electrical injuries. The large majority (60% to 70%) results from inquisitive toddlers who are exposed to electrical cords (3). The extent of an electrical injury is related to voltage, tissue resistance, type of current, duration of exposure, and electrical current pathway. For instance, although a direct lightning strike is an extremely high voltage, the short duration explains why survival is possible (see Chapter 365).

Electricity is the flow of electrons through a conductor. The flow of these electrons, the current (I), is measured in amperes and is responsible for tissue damage. The relative force of this electron flow is the voltage (V); impedance to the flow of electrons is called resistance (R) and is measured in ohms (1). All of these variables are

interrelated by Ohm's law, which defines a given current as the voltage divided by the resistance: $I = V/R$, or $V = IR$. By definition, a high-voltage injury is more than 1,000 V.

The relative resistance of various body tissues explains the relative sensitivities of certain organ systems to electrical injury. Dry, calloused skin has a resistance (40,000 to 100,000 ohms) and is relatively impervious to electrical injury, although wet, thin skin can have a resistance of $<1{,}000$ ohms and is highly susceptible (1). The least resistance is found in nerves, blood, and mucous membranes, while bones, fat, and tendons have higher resistance (2). The low resistance of nervous tissue explains why the nervous system is frequently injured in electrical injuries. Higher current densities, which are inversely related to the cross-sectional area of the current path, create more heat and more subsequent damage. Appendages, which have a smaller cross-sectional area, sustain much higher damage with a similar current than the trunk or torso. Heat generation is proportional to the current involved, the resistance of the tissue, and the duration of contact (1).

The type of current also determines injury severity. In alternating current (AC), the current flows through the conductor in a back-and-forth fashion. In the United States, the majority of residential electricity is transmitted with AC at 60 Hz (cycles/sec). AC is three times as dangerous as direct current (DC) (3). AC causes tetanic muscle contraction with a prolonged duration of contact. Flexor muscles typically are stronger than the extensors, so that muscle contraction can create a "locked-on" phenomenon where victims cannot release themselves from an electrical source. In addition, AC is more likely to induce VF (1). DC moves "directly" along a given circuit in a single direction and is safer than AC.

Lightning is a special form of DC; the voltage of a lightning bolt is extremely high ($>1{,}000{,}000$ V) but the duration of contact is very small (1 to 2 ms) (1). Lightning causes injury in four ways: direct strike (pathway through the victim), side-flash (lightning first strikes an object, then secondary discharge strikes patient), stride potential (current passes from ground, up one leg and down the other), and flash-over phenomenon (where the current travels outside the body

and causes vaporization of surface water) (3). See Chapter 365 for more details about lightning injuries.

Current pathway also determines the severity of injury. A current that traverses the body in the vertical axis is much more deadly than a similar horizontal current because virtually every organ is affected. However, a horizontal pathway from hand to hand can affect the heart or lungs and induce a dysrhythmia or paralysis of the respiratory muscles (3).

Of particular interest for emergency physicians is the utilization of electrical energy by police officers and more recently, by civilians for self-defense. These conductive electrical devices, sometimes called "stun guns" and commonly referred to as Taser devices, deliver a less-than-lethal force to subdue violent suspects. These devices deploy two to four metal barbs attached to a wire with an effective range of up to 35 ft. Upon contact, it delivers a 1,200- to 5,000-V, low-amperage (2.1-mA) pulse train, causing involuntary muscle clonus, which effectively paralyzes the assailant. The energy delivered is small and ranges between 0.07 to 0.50 J. The morbidity and mortality of these devices is low compared to those with conventional weapons (4). The danger is generally limited to secondary injuries such as sprains and contusions from falls. The overwhelming majority of deaths following the use of conductive energy devices have been from drug intoxication, underlying health defects, and acidotic delirium states. As of 2011, the manufacturer of Taser devices reports more than 3.1 million human exposures, which includes a combination of training and field use (5).

CLINICAL PRESENTATION

Electrical injuries range from a simple tingling sensation to multisystem organ failure. Frequently, the cutaneous signs of injury are limited, leading the clinician to underestimate the extent of the electrical injury. Electrical burns are best viewed as crush injuries and not thermal burns because of the potential for multisystem injury. Given their lower inherent intrinsic resistance, the cardiac and neurologic systems are most commonly injured. Electrical injury

deaths are usually due to VF (low voltage), asystole (high voltage), or respiratory arrest from central respiratory center interruption.

The heart is sensitive to electrical injury with one-third of electrical injuries having a cardiac complication (6). Injury to the myocardium occurs either from direct disruption of normal electrical signal or direct myocardial damage; the latter is more common with high-voltage injuries. Rhythm disturbances can occur with relatively low currents; 50 to 100 mA (one-half of normal household current) can induce VF in transthoracic injuries (1). In addition to VF and asystole, common electrically induced dysrhythmias include sinus tachycardia, nonspecific ST–T wave changes, ventricular tachycardia, ectopic beats, and bundle branch blocks (6). Electrical injuries can cause direct myocardial necrosis through thermal damage. Although ST–T wave changes and increased elevation of the CK–MB fraction are common, these usually are not from myocardial infarction but the elevation of the CK–MB is usually related to skeletal muscle damage (6). Patients with upper and lower body locations for entry and exit wounds are more likely to have myocardial damage (6). Electrically injured, autopsied heart specimens show scattered areas of myocardial damage with subpericardial microhemorrhage (6). Transmural necrosis is rare and usually related to injury of coronary vessels (7).

The nervous system is also highly sensitive to electrical injury; 70% of electrical injuries have some neurologic component (7). Peripheral nervous system involvement is usually peripheral neuropathy and motor dysfunction related to direct electrothermal injury, ischemia from microvascular injury, or compartment syndrome. Central nervous system (CNS) involvement can present with amnesia, loss of consciousness, confusion, impaired recall, mood lability, anxiety, depression, motor deficits, coma, or injury to the respiratory control center with resulting respiratory arrest (2,8). In addition, visual disturbances, seizures, deafness, and hemi- or quadriplegia may occur (2). In high-voltage injuries, acute insults to the spinal cord can occur from direct electrical injury or associated fractures or ligamentous injuries. C4 to C8 level injury is most common with hand-to-hand, transthoracic flow (2). Neurologic

symptoms may be delayed for up to 2 years and may include ascending paralysis, amyotrophic lateral sclerosis, transverse myelitis, and incomplete cord transection (6).

Blood is an excellent conductor of current, resulting in extensive vascular damage. Electrical injuries damage the intima and media of the vessel walls and form thrombi in the blood. Both lead to vessel narrowing, ischemia, and necrosis. Smaller vessels are more sensitive, with their smaller diameter and inherent higher resistance and heat generation. Coagulation necrosis, disseminated intravascular coagulation, and delayed vessel rupture can occur (9). Arterial insufficiency and compartment syndrome may occur.

Muscle injury occurs through direct heat damage, ischemia from injured blood vessels, and direct electrical injury (8). Direct heat damage causes rhabdomyolysis, which can also lead to acute renal failure. Edema and vascular insufficiency can cause a compartment syndrome. Electrically induced tetanic contractions or secondary blunt trauma can cause dislocations and fractures, including long bone, vertebral compression, and scapular fractures and shoulder dislocations (8).

Injuries to skin can range from asymptomatic lesions to extensive thermal damage. The upper extremities are common locations for entrance wounds, and although the exit site is variable, it is usually the point nearest to the ground or where the electrical circuit can easiest complete. Injuries at these entrance/exit sites usually have erythema, charring, and edema. The skin can also suffer “flash burns” from electrical arc production, electrothermal burns from electrical conduction, and flame burns from ignition of clothing (2).

Of particular concern are oral burns in young children who may chew on an electrical cord. The mucosa of the mouth has a very low resistance and the current arcs through the lip. This can cause a full thickness burn of the lip with involvement of the mucosa, submucosa, muscle, nerves, and blood vessels (2). The resultant eschar usually falls off in 2 to 3 weeks and can be associated with significant labial artery bleeding.

Gastrointestinal (GI) tract involvement includes nausea and vomiting found in 25% and gastric stress ulcers in 13% of electrical

injuries (8). Solid organ injuries may result from associated blunt trauma. Paralytic ileus, hepatic and pancreatic necrosis, and bowel perforation can occur from direct electrical injury.

Direct pulmonary injury is rare given the poor conductivity of air. Direct injury to the respiratory drive center can cause respiratory arrest, although diaphragmatic tetany can also lead to respiratory paralysis. Associated blunt trauma can cause rib fractures, hemothoraces, and pneumothoraces.

Although infrequent, cataracts, vitreous and anterior chamber hemorrhage, retinal detachment, macular laceration, and central retinal artery occlusion can occur (8). Glaucoma is more common in those who survive electrical injuries. Irritation of the anterior chamber can cause miosis, Horner syndrome, or mydriasis. This mydriasis can be mistaken as a fixed pupil, leading to early termination of resuscitation efforts. Rupture of the eardrum is frequently associated with lightning injuries.

Pregnant patients may be completely asymptomatic yet the fetus may suffer significant morbidity and mortality, as the amniotic fluid is an ideal current conductor. Conduction of this current can cause fetal cardiac arrest and abortion.

DIFFERENTIAL DIAGNOSIS

The diagnosis of electrical injury is frequently apparent from the initial history. The real challenge is differentiating between damage caused by direct electrical damage and that caused by associated thermal injuries. Electrical sources of thermal injury include electrical arc, flash burns, and ignition of surface clothing. The diagnosis of these thermal burns is relatively straightforward as the extent of the injury can be judged from the signs of external injury (Chapter 46). The extent of electrical injuries, however, can be very difficult, as the degree of external injury can underestimate the true extent of damage.

ED EVALUATION

Low-voltage exposure will not destabilize patients and local evaluation will be adequate. Prehospital rescuers of high-voltage victims making certain that they do not become victims, must secure the electrical source before intervening. Blunt trauma is common and cervical spine precautions implemented. Patients who are struck by lightning do not retain a static charge and can receive immediate care. Standard advanced cardiac life-support (ACLS) protocols should be followed, and all patients should be transported since many apparently deceased patients have had recovery after high-voltage injury.

All patients with high-voltage injuries should be approached as if they may have multisystem failure and concomitant trauma. Airway, breathing, and circulation (ABCs) should be immediately assessed on arrival and treated appropriately. The patient must be completely exposed to discover evidence of any secondary blunt trauma or burns. Cervical spine precautions should be maintained and imaged as needed to exclude cervical fracture. Cardiac monitoring, pulse oximetry, and supplemental oxygen as needed, should be started. The patient should be questioned about the voltage, type (AC vs. DC), duration, and presumed pathway of the current.

Laboratory studies can help determine the extent of injury. An electrocardiogram (ECG) is indicated for all high-voltage injuries, especially for cases of transthoracic injury (10). A complete blood count, arterial blood gas, coagulation studies, serum electrolytes, calcium, creatine, blood urea nitrogen (BUN), liver function tests, and urinalysis, including urine myoglobin, should be obtained in patients with high-voltage injuries. Cardiac enzymes, including isozymes, and a type and cross should be considered. Vascular and nerve function should be tested to exclude a compartment syndrome. Ophthalmologic and otologic evaluation should look for cataracts and tympanic injuries. Serial laboratory testing of electrolytes, liver function tests, creatinine, BUN, and calcium may be needed to assess ongoing tissue necrosis and injury.

After a Taser incident, patients should be evaluated for their initial agitation, such as a psychiatric condition or drug intoxication,

which may have instigated the use of the device. Most patients will be calm and cooperative by the time of their arrival in the ED. Barbs do not penetrate deep enough to cause significant local injury to most tissues and can be carefully removed.

KEY TESTING

- ECG, cardiac enzymes, and myoglobin for high-voltage injuries
- Complete blood count, blood gas, coagulation studies, metabolic panel, liver function tests for supportive care
- Radiographic imaging for suspected secondary trauma

ED MANAGEMENT

Low-voltage and household electrical injury only requires local evaluation and local care. For high-voltage injury, general supportive care includes management of the ABCs, and advanced cardiac and trauma life support. Cervical spine immobilization should be maintained until fracture is excluded. Cardiopulmonary resuscitation should be initiated in the prehospital setting for nonperfusing dysrhythmias, and resuscitative efforts should be maintained for extended periods of time since many electrically injured, apparently dead patients have been successfully resuscitated (8).

Cutaneous injury from high-voltage exposure does not correlate with tissue injury and extensive internal damage with shock can require aggressive hydration through large-bore intravenous (IV) catheters or central access catheters. Brisk urine output should be maintained to reduce the likelihood of acute renal failure from rhabdomyolysis. Mannitol (1 g/kg IV) should be utilized if urine output is $<$50 to 100 mL/hr in adults or if dark/pigmented urine is noted. Bicarbonate therapy (1 to 2 mEq/kg IV) should also be initiated for any cases where rhabdomyolysis is suspected; the arterial pH should be kept at more than 7 (3,8).

Nasogastric decompression will aid in cases of ileus and help to decompress the GI tract. Prophylactic H_2-blocker therapy is

warranted to prevent stress ulceration. Tetanus status should be updated as needed.

CRITICAL INTERVENTIONS

- Consider the potential for rhabdomyolysis in all but the smallest burns.
- Admit patients for cardiac monitoring when the patient has experienced a loss of consciousness, has a transthoracic injury pattern, or shows signs of dysrhythmia or external injury.
- Provide adequate hydration to reduce the risk of renal failure from rhabdomyolysis.
- Ensure adequate follow-up for children at risk for labial artery bleeding.

DISPOSITION

Loss of consciousness, possible compartment syndrome, and high-voltage injuries should be admitted for observation with possible transfer to a regional burn center. Cases of dysrhythmia, abnormal ECG, signs of myocardial injury, or transthoracic injuries should have 24-hour cardiac monitoring and serial cardiac enzymes (6,10). All cases of rhabdomyolysis warrant admission for treatment to reduce the chance of acute renal failure.

Most low-voltage injuries may be discharged, assuming the patient has not had a loss of consciousness, cardiac dysrhythmia, or tissue damage and a thorough ED evaluation has not found evidence of internal injury. Children with oral injury from chewing on electrical cords require special instruction and follow-up for delayed hemorrhage from labial artery bleeding when the eschar sloughs off. Discharge only those patients with reliable follow-up; admit all questionable cases.

Common Pitfalls

- Failing to recognize that surface injury does not correlate with the extent of internal injury.

- Putting the rescuer at risk by trying to remove a patient from an electrical source before stopping the current.
- Failing to examine all patients for compartment syndrome in cases where neurovascular compromise is suspect.

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CHAPTER 365

Lightning Injuries

N. Stuart Harris and David F.M. Brown

Lightning injuries are second only to flooding as the leading cause of weather-related death in the United States (1,4). Lightning is responsible for 75 to 100 deaths per year and as many as 1,000 injuries (1,4). The incidence of lightning injuries parallels the frequency of thunderstorms, with clear seasonal (summer) and daily (afternoon) variations. Victims are most often those who work or play outdoors and are predominantly male (4,8). Although frequent thunderstorms make the Gulf Coast States a leading site of lightning injury, states with major mountain ranges and tidal river basins are also at increased risk (1,8).

Electrical charges in clouds are produced by the movement of ice particles in convective currents, which create a layering of ionic charges: the uppermost cloud gains a net positive charge, and the bottom of the cloud gains a net negative charge (3). The cloud's negative charge gathers positively charged particles along the ground, creating a large potential difference. Eventually this potential difference becomes so great that the atmosphere's electrical resistance is overcome and an ionized plasma channel forms. This ionized channel advances from the cloud towards the earth in a downward-branching "stepped leader" pattern at 1/1,000th to 1/2,000th the speed of light. As the stepped leader pattern nears the ground, a "return stroke" ascends from the ground at about one-tenth the speed of light, completing the plasma channel between the cloud and the ground. The channel is now complete, and a massive transfer of electrical charge occurs,

producing an instantaneous brightening of the ionized pathway (the visible lightning flash) (3).

Thunder results from the rapid expansion of warmed air and the air's subsequent contraction and implosion. Although not technically accurate, lightning behaves physiologically as direct current, with an energy level of 2,000 to 2 billion V and 2,000 to 300,000 A (4,8). Although lightning's voltage and amperage are much higher than conventional electricity, the extremely short duration of lightning contact (0.1 to 1 milliseconds) usually limits cutaneous penetration and commensurate deep tissue injury (4,8). Except for direct strikes, most of the lightning current is thought to "flash over" the outside of the victim, with a relatively limited amount of current leaking internally to interfere with cardiac automaticity, respiratory center function, and autonomic stability (4,8).

There are several major mechanisms of lightning injury. A direct strike occurs when the major pathway of current runs directly through the victim; this results in the highest morbidity and mortality (4,8). When the lightning current strikes an object in contact with the victim, the injury mechanism approximates a direct strike. With "side splash," current arcs from an object through the air to the victim. "Ground current," also known as "ground potential," occurs when lightning strikes the ground and spreads to involve the victim. If ground resistance is greater than the victim's resistance, current may enter one leg and exit through the other (3). Ground current and side-flash mechanisms are capable of producing multiple casualties.

Associated trauma should be expected and may result from a variety of mechanisms: myotonic extremity or neck contractions, blunt or penetrating injuries from debris or fall, and thermal burns potentially exacerbated by metal jewelry or caused by ignition of clothing.

CLINICAL PRESENTATION

Because of the short duration of lightning exposure, current usually passes over the outside of the body ("flashover" phenomenon),

commonly producing superficial or partial-thickness burns (4,8). Pathognomonic fern-like, erythematous patterns known as Lichtenberg figures may be observed (4). Entry and exit wounds and deep internal burns with resultant rhabdomyolysis and myoglobinuria are rare.

The most common cause of death in the lightning victim is cardiopulmonary arrest (CPA) (3,4,8). Internal propagation of the lightning's electrical potential acts as a massive direct current counter shock, which depolarizes the entire myocardium and causes cardiac asystole (3,4). As a result of cardiac automaticity, an organized electrical rhythm may re-emerge, restoring spontaneous circulation (4). However, primary respiratory arrest as a result of lightning-induced paralysis of the medullary center may occur concomitantly and can outlast cardiac arrest (CA) (3,4,8). Without prompt and prolonged ventilatory support, any return of cardiac rhythm and circulation is likely to deteriorate to hypoxia-induced ventricular fibrillation (3,4). Survivors of lightning exposure can exhibit a variety of cardiac abnormalities, with dysrhythmias and ST–T-wave changes frequently reported (4,7). Acute life-threatening (and often reversible) left-ventricular dysfunction or pericardial tamponade, as demonstrated by echocardiography, has been reported (6,7).

A variety of neurologic effects of lightning injury are frequently encountered. Complete loss of consciousness is common (2,9). In the absence of CPA, consciousness eventually returns, occasionally after a prolonged period. Other common findings include paraplegia, hemiparesis, hemiplegia, localizing sensory deficits, and autonomic dysfunction (2,8,9). The extremities may initially appear cold, mottled, pulseless, and insensitive secondary to vascular spasm and autonomic instability: a phenomenon known as keraunoparalysis (2,4,8). This vasospasm should not be treated with interventions beyond supportive measures.

Virtually all lightning-struck patients have altered mental status and anterograde amnesia; retrograde amnesia is common as well (2,3,4,9). Persistent neuropsychologic, cognitive, and behavioral abnormalities are commonly found (2,8). Intracranial hemorrhage

(particularly in the basal ganglia and brainstem), epidural and subdural hematomas, coagulation of brain parenchyma, and thrombosis of vessels have been described (2,3,8,9). Associated trauma may cause cervical spine fracture with spinal cord injury.

Half of patients with lightning injuries have ocular sequelae (4,8). Cataracts are common and may develop in a few days or up to several years after the injury (4,8). Corneal lesions are also common; hyphema, iritis, vitreous hemorrhage, retinal detachment, and optic nerve injury have been described (4,8). Unreactive, dilated pupil(s) as a result of transient autonomic instability may occur and should not be mistaken for a sign of brain death (2,3,8,9).

Tympanic membrane rupture, the most common otologic injury, occurs in 50% of victims of lightning injury and is probably a result of the shock wave of expanding hot air (thunder) during the strike (3,9). Less common findings are hemotympanum, basilar skull fracture, and various acoustic and vestibular sensorineural deficits (4,8,9).

DIFFERENTIAL DIAGNOSIS

Lightning injuries may mimic a range of potentially life-threatening diseases. Neurologic disease processes that can mimic lightning injury include cerebrovascular accidents, seizure disorders, and craniocerebral, spinal cord, or other neurologic trauma (4). Cardiovascular disorders in the differential diagnosis of lightning injury include myocardial infarction, Stokes–Adams attacks, and cardiac dysrhythmias (4,8). The differential should also include toxic ingestions, envenomations, and physical assault. Cutaneous injuries may be misdiagnosed as electrical burns.

As in most clinical situations, the history is crucial to making the correct diagnosis. Obtaining information from bystanders is essential when the victim is incapacitated. Important points include a history of thunderstorm and outdoor occurrence of the accident. Physical examination findings of the arborescent erythematous pattern of Lichtenberg figures are pathognomonic. Tympanic membrane rupture is also highly suggestive.

ED EVALUATION

The history should include a description of events at the scene of injury. Any prehospital interventions and their times should be documented. Present complaints and medical history prior to presentation should also be noted.

The physical examination should focus initially on vital signs; assessment of the airway, breathing, and circulation; and evaluation for trauma and neurologic dysfunction. Serial neurovascular examinations should be performed in patients with signs of peripheral vascular insufficiency. All patients should initially have cardiac monitoring, an electrocardiogram (ECG), and oxygen saturation measurement. Laboratory evaluation can include a complete blood count, serum electrolytes, blood urea nitrogen, creatinine, glucose, and creatine phosphokinase. Urine should be tested for myoglobin. Patients with cardiac dysrhythmias or ischemia, respiratory arrest, or loss of consciousness should have a chest radiograph and cardiac biomarker analysis. Cervical spine radiographs and a cranial computed tomography (CT) scan might be helpful with altered mental status or neurologic deficits. Other radiographs and tests should be obtained as indicated by the history or physical findings.

KEY TESTING

- For all patients: cardiac monitoring, an ECG, and oxygen saturation measurement. Laboratory evaluation should include a complete blood count, serum electrolytes, blood urea nitrogen, creatinine, glucose, and creatine phosphokinase. Urine should be tested for myoglobin.
- For patients with cardiac dysrhythmias or ischemia, respiratory arrest, chest pain, or loss of consciousness: Obtain chest radiograph and cardiac biomarker analysis.
- For patients with altered mental status or neurologic deficits: Consider cervical spine radiographs and a cranial CT scan.

ED MANAGEMENT

Prehospital care of victims with lightning injuries may place initial responders at risk of lightning strike (10). Although acute medical intervention is paramount to reduce mortality, care should be taken to prevent harm to rescuers. Once scene safety has been assured, management should begin with assessment and stabilization of the airway, ventilation, and circulation (10,11). Victims should be treated as trauma patients, with special attention given to cervical spine immobilization. In a mass-casualty event, "reverse triage" should be employed. In a reversal of the usual dictum, rescuers should focus initially on victims in CPA (3,4,8,10,11) because virtually all victims of lightning strike who do not suffer CPA or respiratory arrest survive (4). Standard advanced life-support (ACLS and ATLS) protocols are appropriate however, and aggressive, persistent resuscitative efforts are indicated for all victims, especially those with spontaneous cardiac rhythms and prolonged apnea or coma (4,8,10,11). Ventilatory support may be required for several hours, but, even in these cases, there is potential for full recovery (4,8). Full support should be continued until cerebral function can be assessed.

All patients should initially be given supplemental oxygen, should have intravenous access established, and should be placed on a cardiac monitor. Intravenous fluids should be minimized to reduce any risk of cerebral edema unless hemorrhage, hypotension, or dehydration is evident or rhabdomyolysis is a concern (e.g., with deep or extensive burns or associated crush injury). Although not common, rhabdomyolysis, as indicated by myoglobinuria and elevated serum muscle enzyme levels, may necessitate fluid loading, osmotic diuresis, and urine alkalinization. Standard burn and wound care and tetanus prophylaxis should be given, if appropriate. Patients with cardiac or neurologic abnormalities should have serial ECGs, cardiac biomarker analyses, and routine supportive care. All patients require comprehensive and repeated physical and neurologic examinations.

CRITICAL INTERVENTIONS

- Reverse triage. In a mass-casualty incident involving lightning injury, give the highest priority to patients in cardiac or respiratory arrest when making triage decisions.
- Institute advanced cardiac support measures, and make a prolonged effort to resuscitate patients found pulseless or apneic after a lightning strike.
- Evaluate patients struck by lightning for traumatic injuries.
- Treat keraunoparalysis (cool, potentially pulseless, or numb extremities) conservatively with supportive care.

DISPOSITION

Patients with suspected direct strike or those with cardiac or neurologic abnormalities require admission for at least 24 to 36 hours of observation and continuous cardiac monitoring. Those patients with associated trauma, burns, or rhabdomyolysis also may require admission for their injuries (4,8,11). Patients who have sustained cardiac or respiratory arrest should be admitted to an intensive care unit. Long-term follow-up with neuropsychiatric support is recommended for all patients.

The decision to transfer a patient to another facility depends on the severity of injury and the ability of local resources to provide adequate care. If the necessary services are unavailable, the decision and the timing of transfer should be coordinated with the receiving physician at the nearest appropriate hospital. Emergency personnel with advanced life-support (ALS) capability should accompany the patient.

Common Pitfalls

- Failure to appreciate the difference between lightning injuries and high-voltage injuries.
- Misdiagnosing lightning injury as an isolated cutaneous burn or a primary neurologic or cardiovascular event.
- Misinterpreting unreactive, dilated pupils as a sign of death in patients struck by lightning.

- Failure to admit patients with neurologic complaints or deficits for observation.

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CHAPTER 366

Radiation Injuries

Joe Suyama

Radiation injuries can arise from a range of potential scenarios ranging from accidental exposure to nuclear power or medical devices, a radiologic dispersion device (RDD), or “dirty bomb,” to the intentional poisoning of an individual.

Radiation is defined as the transfer of energy in the form of waves, rays, or particles. Ionizing radiation originates from the decay of inherently unstable radionuclides and is emitted in the form of α- and β-particles, γ- and x-rays, and neutrons. Positively charged α-particles consist of two neutrons and two protons and do not penetrate further than 0.05 to 0.1 mm into tissue. However, they cause high linear energy transfer (LET) to tissues. Simplistically, the amount of subsequent cellular damage increases with increasing LET. Internalization of α-particles is associated with the potential for significant radiologic damage. Polonium-210 is an example of an α-particle emitter, which must either be inhaled or ingested to be radiotoxic (1). After entering the blood stream, it is deposited in the liver, spleen, bone marrow, and other soft tissues of the reticuloendothelial system, causing death at high enough doses. Negatively charged β-particles are low LET particles with a penetration depth of 5 to 30 mm. γ- and x-rays lack both charge and mass and are low LET rays, but they are highly penetrating. Neutrons lack a charge, are deeply penetrating, and are classified as high LET particles. Neutrons do not ionize tissues directly but rather transfer energy to atoms in the tissues, which then create α- and β-particles, γ- and x-rays, and subsequent tissue effects. Tissue effects are either deterministic, immediate and clinically apparent tissue

damage, or stochastic, which largely refers to the teratogenic effects of radiation (2).

The amount of energy transferred to tissues per unit mass of the target is quantified by the radiation absorbed dose (rad). One hundred rads equals one Gray (Gy). Potential for tissue injury is dependent on both the dose and radiation quality, which refers to varying biologic effects based on LETs. The radiation equivalent in man (rem) reflects the biologic impact of the absorbed radiation dose. The rem is expressed as sieverts (Sv) in SI nomenclature, with 100 rem = 1 Sv, which is now the more widely accepted unit for expressing the health effects of radiation.

Ionizing radiation can produce adverse health effects from both internal and external exposure. Ingestion or inhalation of contaminated materials can cause significant local effects. Incorporation occurs when the body replaces regular components with its radioactive counterpart or similar molecule. Bone and thyroid are particularly prone to the replacement of elements with radionuclides. Radium (Ra-226) and uranium (U-235) accumulate in bone, radioactive iodine (I-131) can replace its nonradioactive isotope in thyroid, and from a more therapeutic and diagnostic perspective, radioactive phosphorus (P-32) can replace phosphorus in a multitude of biochemical processes and structures. Radionuclides that are incorporated are difficult to eliminate and have the potential to produce long-term health effects in addition to acute symptoms. External radiation sources produce local effects from direct skin or clothing contamination or by dosing the entire body with irradiation.

Ionizing radiation initiates a cascade of detrimental chemical reactions by generating free radicals as tissue is energized. Tissue is energized directly by α- and β-particles but γ- and x-rays excite atoms in the tissue by transferring energy to an electron, which subsequently ionizes other molecules in proximity. Although subcellular damage can occur by structural protein or enzyme degradation, the majority of cellular damage and death occurs through disruption of DNA and the mitotic apparatus. The most radiosensitive cells and tissues are those with high turnover rates,

such as hematopoietic, reproductive, gastrointestinal (GI), and epithelial cells. Relatively radiation-resistant tissues include bone, solid organs, muscle, and neuronal tissues.

Radioactive substances can be found in many settings and forms. Radioactive materials are found in medical settings, research facilities, industrial sites, and nuclear power plants (3). Naturally occurring background radiation exposure accounts for 3 to 3.6 mSv per year; this and other radiation doses from medical procedures are listed in Table 366.1. According to the Department of Energy–Radiation Emergency Assistance Center/Training Site (REAC/TS) Radiation Accidents Registry, the majority of radiation accidents occur in the medical, energy production, or industrial settings (4). Current occupational exposure limits for individuals working with radiation sources are 0.05 Sv per year and 5 mSv per year for pregnant women. For the general public, current limits are 1 mSv per year (5).

TABLE 366.1
Dose Ranges from Background Radiation Exposures and Selected Medical Procedures

Radiation Exposure	Dose Range	Body Part Affected
Background radiation	3–3.6 mSv/yr	Total body
Smoking 1 PPD/yr	160 mSv	Respiratory system, body
Transcontinental flight	0.05 mSv	Total body
Diagnostic chest x-ray single view	0.10–0.15 mSv	Collimated field
Diagnostic chest x-ray two view	0.60 mSv	Collimated field
CT head	10 mSv	Head
CT abdomen	20–50 mSv	Abdomen
Fluoroscopy	10 mSv	Collimated field
Bone scan	50 mSv	Total body
Annual exposure limit—public	1 mSv/yr	Total body
Annual exposure limit—occupational	50 mSv/yr	Total body
Annual exposure limit—occupational, pregnant	5 mSv/yr	Total body
LD_{50}	4.5 Sv	Total body

Rem converted to Sv.

Reproduced with permission Frame P. *Radiation fact sheet*. Oak Ridge, TN: Oak Ridge Institute for Science and Education/Oak Ridge Associated Universities; 1995.

Radiation accidents are typically secondary to the improper use of radiation devices and improper use of radioisotopes. Between 1944 and 2002, a total of 428 radiation accidents have been documented worldwide, resulting in 133,815 persons affected and 134 fatalities. Nearly 90% of these victims were the result of the 1986 Chernobyl nuclear reactor accident. More recently, the near-critical event and leakage of radioactive materials from the Fukushima Daiichi plant after the 2011 Great East earthquake and tsunami in Japan reinforced the need to be locally prepared to respond to the immediate and long-term medical needs of the people living in proximity to nuclear facilities and of the emergency responders to radiologic incidents. Other historically important mass-casualty radiation accidents include the rupture of an iridium source in Venezuela; a cobalt-therapy unit accident in Ciudad Juarez, Mexico; and the theft and subsequent large exposure of a cesium source in Goiania, Brazil (4). A comprehensive planning guide to these and other types of radiation events has been produced by the

International Commission on Radiological Protection to assist local medical planning and response and recovery efforts (6).

Individuals and groups may intentionally use radiologic materials for terrorist purposes. Such use may introduce new combinations of radiologic injury, or radiation injury may be misdiagnosed as other routine medical conditions. For example, an RDD may combine blast and radiation injuries and may disperse radioactive substances, creating a contamination hazard for the environment and both real and psychological casualties (7). Initial fatalities from an RDD are anticipated to be minimal and related to blast injuries (8), but the greater threat from the unrecognized radioactivity of RDD detonation is the contamination of receiving facilities. The mysterious death of Alexander Litvinenko in November 2006 from multisystem organ failure was initially difficult to recognize as Polonium-210 ingestion without further specialized diagnostic testing. Finally, direct attacks on nuclear power plants would not yield a nuclear explosion, but intentional meltdown of the core may cause similar environmental and health effects as seen at Chernobyl (9). Such events may not create a large number of immediate casualties, but the public health risk related to carcinogenesis may be significant over time. The greatest impact may be the fear and uncertainty that follows these events.

CLINICAL PRESENTATION

Acute radiation injury to the skin and underlying structures causes changes that clinically resemble thermal burns, with desquamation and blistering. Unlike thermal burns, these signs develop after a period of at least 48 to 72 hours after the contact. The clinical effects of dermal radiation exposure are listed in Table 366.2. Delayed skin effects include carcinogenesis, vascular insufficiency, and chronic nonhealing ulcers.

TABLE 366.2
Cutaneous Manifestations of Radiation Exposure

Cutaneous Effect	Radiation Dose Threshold (Sv)
Early transient erythema	2
Temporary epilation	3
Prolonged erythema	6
Dry desquamation	10
Moist desquamation	20
Tissue necrosis	20–30

Whole-body radiation exposure clinically manifests as acute radiation sickness (ARS), a progression of systemic effects from derangements of the hematopoietic, GI, and neurologic systems. ARS has four general phases: (1) prodromal, (2) latent, (3) illness, and (4) recovery or death. Depending on the dose rate and total absorbed dose, ARS may progress rapidly to death or be completely asymptomatic (Table 366.3). Larger total-body doses correlate with increasing severity of symptoms and decreasing time interval to onset (10). The prodromal phase usually lasts 48 to 72 hours and manifests as nausea, vomiting, diarrhea, and nonspecific constitutional symptoms. The latent phase, which may last 3 weeks, is characterized by the lack of clinical symptoms and apparent recovery from the prodromal phase (7). The latent phase is followed by the illness or hematopoietic syndrome, in which initial damage to the bone marrow becomes clinically apparent. Pancytopenia and the subsequent sequelae of immunosuppression, bleeding diathesis, and anemia often lead to death from sepsis unless adequately supported. If the patient survives the illness phase, which lasts up to 30 days postexposure, recovery occurs 3 to 6 weeks after initial exposure.

TABLE 366.3
Acute Radiation Syndrome and Dose-Related Effects

Whole-Body Dose (Gy)	Effect
0.05–0.5	No clinical symptoms, minor lymphocyte reductions, potential chromosomal damage
1	Nausea and vomiting within 48 hrs of exposure (10% of patients)
2	Nausea and vomiting within 24 hrs of exposure (50% of patients), prominent decreases in lymphocytes and granulocytes
4	Nausea and vomiting within 12 hrs of exposure (90% of patients), mortality of 50% without medical support
6	Mortality of 100% within 30 d without medical support
10	Maximum survivable dose with aggressive medical support
50–100	CNS and cardiovascular collapse within 24–48 hrs, mortality of 100%

Patients receiving total body doses in excess of 7 Sv manifest a distinct entity referred to as the GI syndrome, in addition to the prodromal symptoms (Table 366.4). The GI syndrome results in significant fluid and electrolyte losses, loss of bowel integrity to enteric bacteria, and subsequent death in more than 80% of patients. A pulmonary syndrome is noted at doses of 5 to 10 Sv, manifesting as pneumonitis, respiratory failure, and subsequent pulmonary fibrosis and cor pulmonale. Patients with total-body doses of 9 to 17 Sv develop a cerebrovascular syndrome, and patients receiving more than 50 Sv develop acute encephalopathy, with rapid (hours to days) progression of cerebral edema, cardiovascular collapse, and 100% mortality.

TABLE 366.4
Acute Radiation Syndrome: Symptoms and Radiation Dose

Symptoms	Radiation Dose (Gy)
Prodromal symptoms	
Anorexia	1
Nausea	1.4
Vomiting	1.8
Diarrhea	2.3
Hematopoietic syndrome	2–4.5
Pulmonary syndrome	5–10
Gastrointestinal (GI) syndrome	7–15
Cerebrovascular syndrome	9–17
Acute encephalopathy	50–100

DIFFERENTIAL DIAGNOSIS

Early symptoms of nausea and vomiting are nonspecific, resembling gastroenteritis or food poisoning. Lymphopenia, immunosuppression, and anemia are not only characteristics of radiation sickness but also can be manifestations of HIV and other viral infections, leukemia, use of chemotherapeutic agents, toxic ingestions, and blood dyscrasias.

The differential diagnosis of radiation-induced dermal injury includes chemical, ultraviolet and thermal burns. In contrast to these entities, radiation-associated dermal injury is typically delayed up to 2 weeks. Other dermal lesions to consider include bullous pemphigoid, necrotic arachnidism, and stasis ulcers.

Concomitant radiation contamination should be suspected in any potential terrorist event. Although extraordinarily large doses of radiation can cause rapidly progressive shock, radiation typically does not cause sudden death. It is also unlikely to cause the immediate incapacitation of large numbers of people resulting from weapons of mass destruction incident. Other agents should be suspected should such scenarios arise.

ED EVALUATION

Because of the extreme rarity and potential calamity of an unexpected radiation exposure, the Joint Commission requires that every hospital develop a formal plan to deal with such an event.

Prudence also dictates that every regional emergency management system includes radiation accidents in its disaster management protocol. Specific prehospital management guidelines have been developed by REAC/TS, and are available online at http://www.orau.gov/reacts/manage.htm.

When notified that a radiation accident may have occurred in which many people were exposed to high levels of radiation, the physician should invoke the hospital and regional plans, following them as closely as the circumstances of the particular incident allow. The hospital's radiation safety officer, and the radiation safety officer employed at the site of the accident (or at the company whose truck has crashed, for instance), must be contacted immediately. Police and fire authorities and a public relations official should be called. The physician should communicate with the scene while the area designated in the hospital to receive patients is prepared. Specialized radiation detectors can be used in emergency departments (EDs) to identify patients who are emitting radiation from nonmedical radionuclides that should not be present in a healthcare environment. Such devices help to filter out the noise of the background medicinal and diagnostic radionuclides typically present in hospitals, and can provide an early warning of the presence of inappropriate radiation contamination (11).

It must be determined exactly what sort of accident has happened: an exposure to external radiation, contamination by radioactive matter, or possible incorporation of ionizing substances via open wounds or the GI or respiratory tracts. A history of trauma or other toxic exposures and the nature, severity, and time of onset of any symptoms should be noted. The duration of exposure (partial or whole body), the nature of and distance from the source, and shielding and dosimeters used, if any, all constitute important data.

Patients require careful evaluation by a designated radiologic emergency response team to minimize contamination of the ED (12). When possible, arriving patients should be undressed in the ambulance, and clothes should be collected, bagged, and stored at a point distant from the patient care areas. A designated receiving area large enough to manage the anticipated number of casualties

should be established. The decontamination area should be prepared and ready for use for both ambulatory and nonambulatory patients. Areas that are likely to be traversed by contaminated patients and workers should be cordoned off. Paper or plastic sheets should be placed on the floor. Entry points to the radiation treatment areas need to be staffed by radiation officers trained to scan for contamination as workers exit the radiation treatment area, and large numbers of gloves, boots, gowns, and masks need to be available for workers entering the area. Strict isolation and double-bagging procedures should be maintained, and a buffer zone should be established for additional contamination control. No special ventilation controls are currently recommended.

All care providers must wear barrier protection, masks, and eye protection to prevent internal and external contamination. Furthermore, four ALARA (As Low As Reasonably Achievable) principles provide the foundation for radiation protection: timing, distance, shielding, and quantity. For timing, all personnel must wear a radiation detector to determine the whole body dose accumulated during patient contact. Personal dosimeters with real-time displays are preferred over radiation badges to limit any unnecessary exposure and to determine when to rotate teams of care providers. For routine procedures and care, teams should be rotated once 5 rem have been accumulated. The upper limit to provide lifesaving interventions must be predetermined by the radiation safety officer. For those performing lifesaving interventions, the recommended limits for total effective dose range from 0.25 to 1.5 Sv, or a rate of exposure $\leq$0.1 mGy/hr, depending on the radiation organization cited (13). For simplicity, a total-body exposure of 0.5 Sv is the National Council of Radiation Protection and Measurements/International Council of Radiation Protection and Measurements (NCRP/ICRP) recommended dose acceptable for preserving life (5). Workers in this setting should be volunteers chosen on the basis of age (older) and lowest accumulated lifetime effective doses.

Distance from a radiation source should be maximized when feasible, because the exposure dose decreases in proportion to the

square of the distance from the source. Shielding high-density materials such as lead or concrete provides greater relative levels of protection from ionizing radiation than do less dense materials. Most structural elements (e.g., walls, floors, etc.) and personal protective equipment (PPE) will not block high-energy γ-rays. PPE will, however, provide a physical barrier to contamination from radioactive fallout and debris from RDDs. PPE is also effective in blocking the effects of α-particles and a proportion of β-particles as well. The quantity of ionizing radiation can also be limited by removing the radioactive source material from the area.

If no life-threatening illness is present, a rapid survey of patients using a "pancake" detector or a GM counter should be performed. Ideally, survey meters capable of detecting both high-range (up to 5 Sv/hr) and low-range (up to 0.2 Sv/hr) exposures and also common (γ and β) or uncommon (α and neutron) sources should be available. The initial scan should progress rapidly from head to toe, focusing on any open wounds or obvious debris. For the ambulatory patient, the survey should focus on areas, such as the hair and shoulders, where fallout generally accumulates. If the patient is unstable, critical interventions should be performed in conjunction with the radiation survey (14).

Anatomic charts should be used to document the location of all radiation emission and the radiation counts. Example charts and forms can be downloaded from http://www.afrri.usuhs.mil/www/outreach/pdf/afrriform331.pdf. Samples with cotton swabs should be taken of all orifices if external contamination is suspected. The physical examination should include evaluation for concomitant trauma. In all cases of radiation injury, a complete blood count and differential, a type and screen, and serum electrolytes and urinalysis should be obtained to determine kidney function. Subsequent investigations are driven by the patient's clinical presentation.

KEY TESTING

- A CBC with differential count should be obtained for the purposes of identifying the absolute lymphocyte count and should be interpreted in the context of the temporal relationship to the radiation injury.
- Trauma laboratory work and imaging should be performed as warranted, and should be performed in conjunction with decontamination.
- Radiation dosimetry should be attempted, and initial and persistent contamination severity and the affected anatomical areas should be documented with a portable GM counter.
- Radiation spectrometry can be performed to determine if radiation sources are typical hospital radioisotopes or are nonmedicinal in nature.
- Biologic samples and fluids should be obtained and stored for analysis by radiation safety and health physics consultants.

ED MANAGEMENT

The organized delivery of care to radiation-injured patients can increase the survival of those with whole-body radiation injury (4). A tremendous amount of information and relevant protocols for the ED management of radiation injuries can be found on the REMM website: http://www.remm.nlm.gov. ED management of radiation injuries is summarized here, starting with initial contact and decontamination procedures (6,12,15).

Decontamination procedures begin with the removal of all clothing. This eliminates 80% to 90% of external contamination. Because radioactive debris may remain in the hair after removal of grossly contaminated clothing, surgical caps should be placed on the unstable contaminated patient to provide some limited shielding and contamination containment to protect staff while performing advanced life-support procedures. All clothes, debris, and bandages must be properly stored. The hospital radiation safety officer must properly dispose of the waste once surveyed. When contaminated debris or shrapnel are removed from patients, they should be placed

in appropriate lead-shielded containers and removed from patient-care areas.

Wounds should be decontaminated aggressively, then treated as usual and covered with plastic and tape prior to decontamination of intact skin. External decontamination should proceed from the area with the most debris to the area with least. Uncontaminated areas should also be covered and taped. Using tepid water and mild soap or nonionic detergent, very gentle scrubbing should be done for 3 minutes with the patient lying either on a special decontamination table (similar to an autopsy table) or on a makeshift plastic trough placed on a stretcher in slight reverse Trendelenburg. Hot water should be avoided because it causes capillary vasodilation and raises the potential for increased radionuclide absorption. Aggressive scrubbing should likewise be avoided because of the potential for abrasions that can increase dermal absorption. This procedure should be repeated with serial radioactive screening and continued as long as counts are decreasing. Gentle brushing under nails, in hard to clean areas such as between fingers, axilla, groin, of skin folds, hair and clipping of hair, including body hair (not shaving, which might leave small open wounds) may be required. All fluids should be collected if possible. If the patient is stable, decontamination attempts can stop when the radioactivity level cannot be further reduced with serial GM counter testing.

Most isolated radiation injuries are not medical emergencies and only require supportive care, baseline laboratory testing, and follow-up for specialty care such as burns, infectious disease, and hematology/oncology. Specific antidotes and chelation agents are available that may assist in mitigating the effects of the radionuclide burden from internally contaminated patients. These agents do so by decreasing the overall radionuclide burden by dilution, displacement, blockage, or chelation. However, it is difficult to differentiate between radionuclides without scintillators or other advanced laboratory equipment that is found only in select laboratory settings. If identification is possible or a likely radionuclide is suspected from the type of radiation accident, antidotes must be administered promptly or the effectiveness will be

limited. There are several tools, such as the Biological Assessment Tool (available at the Armed Forces Radiobiology Research Institute website: http://www.afrri.usuhs.mil) and the Radiation Injury Severity Classification (RISC) system, that can help the clinician determine the total whole-body radiation delivered based upon clinical symptoms (biologic dosimetry) alone (16).

Treatment of ingestions should begin with attempts to decrease the chance of internal irradiation or incorporation. Whole-bowel irrigation, using a polyethylene glycol bowel prep solution (e.g., GoLYTELY, Colyte) at 0.5 to 2 L/hr until the rectal effluent is clear, may be beneficial. Activated charcoal is also recommended. Washings should be saved, surveyed, and disposed of by the radiation safety officer. Bronchoalveolar lavage may be helpful if stained or radioactive sputum confirm that radioactive dust has been inhaled.

Specific therapy for radiation injury includes medical countermeasures, prophylaxis, and supportive care. There are specific medical countermeasures for certain radionuclides, such as Prussian blue for thallium, cesium, or rubidium; and barium sulfate or aluminum-based antacids for radium or strontium. Prussian blue (Radiogardase) works by increasing fecal elimination of the radionuclide. Prussian blue is taken orally and will not compete with other treatment agents such as oral potassium iodide (KI). Clinical side effects include constipation and GI upset. Prussian blue is most effective when administered soon after exposure but should be administered as soon as cesium or thallium has been identified as the radionuclide in question. In the Goiania incident involving cesium, Prussian blue at doses ranging from 3 to 10 g/day resulted in a 71% reduction in mean dose (3).

Potassium iodide (KI) should be administered to those in whom exposure to iodine-131 (I-131) is likely (18). Such events include an RDD contaminated with medical I-131, release of radioisotopes from a nuclear reactor, and nuclear detonation. Children may benefit most from the protective effects of KI AsKI works by competition to prevent the incorporation of radioactive iodine by the thyroid gland, the maximum benefit is conferred when KI is administered before

exposure to I-131. It will protect the thyroid from increased risk for cancer but will not mitigate any other forms of acute or long-term radiation effects. The dose of KI is approximately 2 mg/kg. The protective effects of KI last approximately 24 hours, and daily dosing for up to 2 weeks, is usually at the discretion of the local health department. Short-term treatment of KI at thyroid-blocking doses is safe, although side effects of sialadenitis, GI upset, rashes, and allergic reactions are most common. As internal contamination of radioiodine will partition into breast milk, lactating mothers should not breastfeed their infants until public health authorities have deemed it safe to consume the milk.

Other countermeasures include pentetate calcium trisodium injection (Ca-DTPA) and pentetate zinc trisodium injection (Zn-DTPA). Both agents are now approved by the US Food and Drug Administration (FDA) to treat internal contamination with plutonium, americium, or curium (17). For specific conditions relating to ARS, such as the hematopoietic syndrome, use of hematopoietic colony–stimulating factors may enhance neutrophilic recovery by increasing the absolute numbers of white blood cells and decreasing the period of neutropenia (20).

Supportive care is needed for ARS, for medical and surgical comorbidities, and for psychological trauma. The initial management of concomitant trauma is the same as for other patients. Wound healing is adversely affected by radiation, and the likelihood of infection is increased due to fibroblast damage, bleeding diathesis, and loss of bone marrow that occurs over time. In light of this, definitive surgery should be performed within the first 48 hours of exposure. Otherwise, nonemergent procedures such as internal fixation of fractures is best delayed at least 3 to 60 days until bone marrow production returns to normal (19). Prophylaxis against bacterial infection in neutropenic patients may require empiric antibiotic therapy, specifically with antipseudomonal agents.

Children may have greater health effects with regard to radiation injury. Children are more metabolically active, and have potential greater risks for both deterministic and stochastic effects. They are

also more likely to incorporate radioisotopes by ingestion or inhalation. Although psychological support is necessary for all patients, the pediatric population may be particularly susceptible to long-term psychological sequelae from real or suspected radiation injury (21).

During the UK Health Protection Agency investigation of the death of Alexander Litvinenko, approximately 596 individuals tested positive for polonium-210 (22), although only 13 were found to have had significant exposures. However, fears of polonium-210 contamination led thousands to seek medical attention. Physical manifestations of acute stress reaction, including nausea, vomiting, and vague constitutional complaints, can mimic those of acute radiation syndrome and can complicate the appropriate disposition of these patients (20,23).

CRITICAL INTERVENTIONS

- Notify the hospital radiation safety officer and activate the hospital radiation exposure plan for patients with possible radionuclide contamination.
- Use time, distance, shielding, and quantity-reduction techniques to minimize exposure.
- Wear barrier protection, masks, eye protection, and dosimeter, if available.
- Perform resuscitation and stabilization as necessary.
- Perform external and internal decontamination and isolate and remove contaminated clothes, debris, and fluids.

DISPOSITION

After initial ED management, patients may be discharged for outpatient management depending on extent of prodromal symptoms and absolute lymphocyte count at presentation. Onset of prodromal ARS symptoms <30 minutes after exposure indicates a total-body dose >6 Sv, although onset >2 hours after exposure indicates a dose <2 Sv. Onset of prodromal symptoms more than 24 hours after exposure indicates a dose <0.7 Sv (Table 366.4) (15).

Severe nausea and vomiting indicate a substantial whole-body dose, (i.e., 2 to 10 Gy) that will require inpatient monitoring for supportive care.

The lymphocyte count is routinely used to aid in disposition and management of radiation injuries. If the patient is asymptomatic and has a normal lymphocyte count, early follow-up and frequent complete blood counts may be appropriate. Prognosis is directly tied to the 48-hour lymphocyte count, which is dose-dependent (Table 366.5). Lymphocyte counts >1,200/μL indicate a good prognosis, and counts <300/μL indicate a poor prognosis (24). Individuals with total-body doses >10 Sv will likely need admission, and those with doses >30 Sv may require reverse isolation precautions.

TABLE 366.5
Relationship Between Absolute Lymphocyte Count and Outcome After Total-Body Radiation Exposure

Outcome	Lymphocyte Count/ mm^3 at 24 hrs	Lymphocyte Count/ mm^3 at 48 hrs
Normal	1,750	>1,500
Moderate injury	1,500	1,000–1,500
Severe injury	1,000	500–1,000
Very severe injury	500	100–500
Lethal	<100	<100

Hematology consultation will be required to administer growth-factor therapy and colony-stimulating factors, treat anemia and thrombocytopenia, and provide advanced cytokine therapy or cord/placental-blood progenitor cells. Burn, infectious disease, and bone marrow transplant consultation may also be necessary (25).

Questions regarding radiation accidents and exposures can be referred to the US Department of Energy through the REAC/TS, Oak Ridge, TN, by the web, http://www.orau.gov/reacts, or by phone, 865-576-1005. Other online references include the Radiation Event Medical Management website (http://www.remm.nlm.gov) hosted by the Department of Health and Human Services, which provides

guidance in the diagnosis and treatment of radiation injuries, and the Centers for Disease Control website (http://www.bt.cdc.gov/radiation/clinicians.asp), related to radiation emergencies.

Common Pitfalls

- Failure to consider and identify radioactive contamination or irradiation injury.
- Failure to conduct disaster training, or performing such drills without addressing decontamination, use of PPE, and radiation surveys.
- Failure to manage concomitant injuries appropriately and to accomplish this prior to decontamination in critically ill patients.
- Failure to obtain an initial lymphocyte count for comparison to a follow-up 48-hour count.
- Failure to request appropriate consultation or to provide indicated chelation or antidote therapy.
- Failure to address psychological components of radiation exposure with patients and staff.

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PART 2 • BITES AND ENVENOMATIONS

CHAPTER 367

Crotaline Snake Envenomation

Richard C. Dart and John B. Sullivan, Jr.

There are several thousand poisonous snakebites in the United States each year, resulting in several deaths (1). Most of these bites involve members of the *Crotalinae* genera: (1) *Crotalus* (rattlesnakes), (2) *Agkistrodon* (copperheads and water moccasins or cottonmouths), and (3) *Sistrurus* (pygmy rattler and massasauga). Although all states except Alaska, Hawaii, and Maine have poisonous snakes, most bites occur in the southeast, southwest, and western regions. The incidence is greatest between March and October, when snakes and victims are the most active.

The crotaline snakes have a temperature (prey)—sensing pit below and in front of the eye (the pupil of which is elliptical)—hence the common name “pit viper.” Venom is injected through a pair of maxillary fangs. Venom is mainly a mixture of digestive enzymes that cause local tissue necrosis and systemic vascular damage, hemolysis, fibrinolysis, and neuromuscular dysfunction resulting in pain and swelling that can migrate up an extremity over minutes to hours. Venom shock and pulmonary injury result from increased vascular permeability and coagulopathy, leading to edema and hemorrhage. Direct cardiac depressant effects may also contribute to shock (2). Venom composition varies with the species and also with the age of the rattlesnake. For example, young snakes tend to have more coagulopathic venom.

Up to 25% of bites do not result in envenomation (“dry bites”) (2). Most envenomations result in a combination of local and

systemic effects. However, some populations of Mojave rattlesnakes have venom (type A) that may cause presynaptic neuromuscular blockade with delayed respiratory failure and mild or absent local effects (3–5). Envenomations by *Agkistrodon* and *Sistrurus* sp tend to be less severe than those of *Crotalus* sp.

The size and species of snake, the location and depth of the bite, the victim's size and health, first-aid measures performed, the time to definitive therapy, and the type of therapy all influence the severity and outcome. The worst scenario is a small, victim deeply bitten by a large snake in the central body, neck, or face. Improper first-aid measures, delay in arriving at medical care, delayed diagnosis, and inadequate or unnecessary treatment adversely affect the outcome.

Bites by exotic snakes may occur in zoo and pet snake handlers and require specific antivenoms. A regional poison center (1-800-222-1222) or zoo can provide information on snake identification, expected toxicity, and antivenom location.

CLINICAL PRESENTATION

Dry bites produce no signs or symptoms other than those of a puncture wound. If envenomation has occurred, the victim (often an intoxicated male) typically notes sudden, severe pain at the bite site, soon followed by progressive swelling and, sometimes, paresthesias. Swelling is generally progressive.

Examination may show one, two, or more puncture wounds exuding bloody fluid. However, there are many reports of serious envenomation associated with scratches and single or multiple puncture wounds. Other local findings include erythema, ecchymosis, bullae, and, eventually, necrosis and ulceration. (Fig. 367.1) Bites about the face may lead to airway obstruction; those of the extremities may lead to compartment syndrome. Wound infection is a potential complication (6), although this is rarely seen clinically (7).

FIGURE 367.1 Blebs and ecchymosis from snakebite on the hand.

The most common clinical effects are pain and edema followed by coagulation defects. Systemic effects include nausea, vomiting, diarrhea, perioral paresthesias, salivation, lethargy, and weakness. Severe envenomations may lead to cardiovascular collapse, coma, seizures, dyspnea, respiratory depression, and gastrointestinal and pulmonary hemorrhage. Initial vital signs often show tachycardia and mild hypertension. Laboratory evaluation may reveal hemolysis, anemia, thrombocytopenia, coagulopathy (including severe fibrinolysis), and blood, protein, and glucose in the urine in severe cases. In severe cases, the chest radiograph may reveal pulmonary edema, and the electrocardiogram (ECG) may show dysrhythmias or ischemic changes.

DIFFERENTIAL DIAGNOSIS

Victims at the extremes of age, those with altered mental states, and those who are bitten while reaching into concealed areas may not realize they have been bitten. Snakebite may be misdiagnosed as a nonvenomous bite or sting or as puncture wounds and scratches from thorns and brush. A possible diagnosis of snake venom

poisoning can be excluded only by observation, documenting a lack of progressive local and systemic manifestations.

ED EVALUATION

On the patient's arrival in the emergency department (ED), vital signs and a rapid patient survey should be performed to determine the patient's clinical stability. The time and circumstances of the bite, the nature and severity of symptoms, any first-aid measures taken before arrival, and any history of allergies, medical problems, previous bites, and antivenom therapy should be noted. The bite site should be examined, noting the nature and extent of local findings. Progression of edema should be noted and can be marked (with the time recorded) on the extremity to help determine rapidity of spread (Fig. 367.2). Distal neurovascular status should be noted in extremity bites. Initially, the local evaluation should be repeated every 15 minutes. The general examination should focus on the cardiovascular, pulmonary, and neurologic systems.

FIGURE 367.2 Serial Measurement of swelling noted on a leg after a snakebite from a Western Diamondback.

The clinically relevant characteristics to describe when assessing severity are (a) local manifestations, (b) coagulation abnormalities, and (c) systemic effects. The change in these parameters over time is particularly important. An initially mild envenomation may progress to become moderate, severe, or even life-threatening over a period of minutes to hours. Coagulation abnormalities may peak as late as 3 days after envenomation.

KEY TESTING

- Mild bites: complete blood count; serum electrolytes, blood urea nitrogen, and creatinine levels; prothrombin time (PT or INR); platelet count; and urinalysis.
- Severe or progressive envenomation: above tests, plus creatine kinase, fibrinogen, and arterial blood gas analysis.
- A chest radiograph and an ECG are needed in patients with systemic signs or symptoms.
- Frequent reassessment of coagulation is critical.

ED MANAGEMENT

Advanced life-support measures should be instituted, as necessary. Prehospital personnel should establish intravenous (IV) access, give oxygen, and transport victims of venomous snakebites to a medical facility that possesses antivenom. Loose (lymphatic) tourniquets may be effective if used within 30 minutes of envenomation, but they are not substitutes for definitive care. If a tourniquet has been placed, it should not be removed until IV access has been established since hypotension may occur. The limb should be immobilized in a neutral position. Local wound care and tetanus prophylaxis should be provided.

Antivenom is the mainstay of crotaline snakebite treatment. Immunoglobulins in the antivenom neutralize venom proteins by forming antigen–antibody complexes. The primary indication for *Crotalidae* polyvalent immune Fab (ovine) (FabAV, CroFab) therapy is progressive worsening of local injury (e.g., pain, ecchymosis, or swelling), laboratory abnormalities (e.g., worsening platelet count,

prolonged coagulation times, decreased fibrinogen), or systemic manifestations (e.g., unstable vital signs or abnormal mental status) (8). If, after several hours, pain and edema remain localized to the bite site and coagulopathy does not develop, antivenom is unnecessary. Frequent reassessment for worsening of local, systemic, and laboratory manifestations cannot be overemphasized. The extent of swelling at presentation should be outlined with a marking pen, and the limb circumference should be measured at several sites above and below the bite. If any of these parameters worsen, antivenom therapy is usually warranted (see Fig. 367.3).

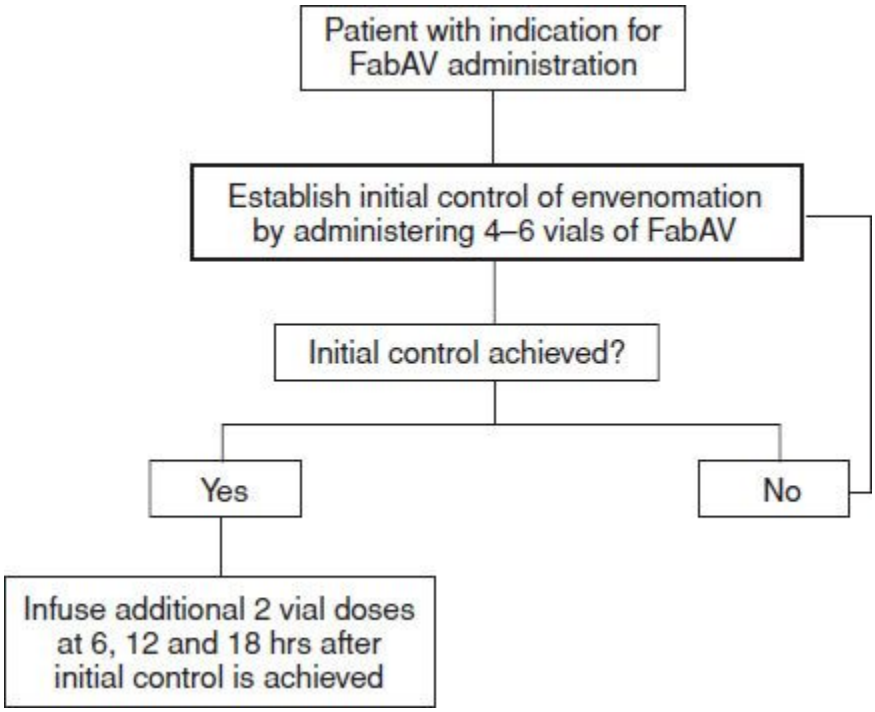

FIGURE 367.3 Algorithm for the use of crotaline snake antivenom.

The initial dose of FabAV for adults or children is four to six vials (Fig. 367.1). Six vials are used in patients with systemic effects or rapidly progressive local effects. Each vial of FabAV is reconstituted with 10 mL of sterile water. The contents of all vials are injected into a 250-mL bag of sterile water or saline. A smaller volume (but the same number of vials) is used in children or patients in whom large volumes could be detrimental. The initial infusion rate should be slow (e.g., 10 to 25 mL/hr) and then increased every few

minutes, until a rate is reached that will allow for infusion of the entire dose over 1 hour (e.g., 250 mL/hr). Continuous respiratory and cardiovascular monitoring should be performed. Antivenom should be given only in a critical care setting with epinephrine and antihistamines readily available to treat anaphylaxis, should it occur. The incidence of immediate hypersensitivity is 8%, and serum sickness occurs in 13% (9). Skin testing is not indicated prior to use of FabAV, as with some other antivenom products.

At the end of the initial infusion, the patient's condition should be reassessed. If local progression has not ceased and improvement in systemic and coagulopathic effects has not occurred, or if the patient continues to worsen, the initial dose of antivenom should be repeated. This process is repeated until initial control has been achieved. With severe envenomation, a large number of vials may be required for control. After initial control has been established, three maintenance doses of FabAV should be given: two vials administered every 6 hours for a total of six vials in an effort to maintain a clinically effective F(ab) plasma level. In clinical trials, patients receiving scheduled maintenance doses of CroFab have a lower incidence of local recurrence than those with repeat doses "as needed" (8).

Recurrence is defined as the return of any venom effect after the abnormality had initially resolved. Recurrences occur to some degree with most antivenoms (10). Local recurrence involves return of progressive local swelling after initial control is achieved. Coagulopathy recurrence involves the return of thrombocytopenia, prolonged PT or international normalized ratio (INR), or elevated fibrin split products. Local recurrences are uncommon. They usually occur within 12 to 24 hours of treatment. They should be distinguished from redistribution of blood/edema, secondary infection, venous thrombosis, and other causes of extremity swelling. Typically, local recurrence is managed with another two to four vials of FabAV, followed by regular maintenance infusions.

The recurrence of coagulopathy is more common, developing within 2 to 3 days and usually presenting after hospital discharge. Recurrent coagulopathy is often only partially responsive to further

antivenom administration. If given early, further FabAV may be effective in correcting the abnormality, but the beneficial effect may be weak and is often transient. Whether additional antivenom should be administered in such circumstances is controversial. Although coagulation tests are often abnormal, the risk of clinically significant hemorrhage is very low. Consequently, current recommendations suggest that recurrent coagulopathy be treated only if it is extreme and involves more than one coagulation abnormality or if there is evidence of significant bleeding (11,12). Most coagulopathy recurrences can be safely managed expectantly with close serial laboratory monitoring and bleeding precautions.

Concomitant supportive care (e.g., fluids and pressors for hypotension, blood component replacement for severe hematologic abnormalities, and respiratory support) is extremely important but often neglected (13). Blood products should be used only if the patient is actively bleeding or cannot receive antivenom (14). Serum sickness may range from a mild viral-like illness to severe urticarial rash, arthralgias, and other complications. In contrast to the immunoglobulin antivenom used in the past, FabAV usually does not cause serum sickness (10,15). Most cases can be treated as outpatients, with anti-inflammatory analgesics, antihistamines, and corticosteroids.

The effectiveness of antivenom in the treatment of snake venom poisoning has been extensively documented. Surgical interventions such as excision of the bite site or fasciotomy are not recommended. Experimental evidence in animals shows no beneficial effect (16–18). Fasciotomy should only be considered for documented increased intracompartmental pressure that is unresponsive to limb elevation, mannitol (1 to 2 g/kg IV), and antivenom (four to six vials of FabAV), (18). Cultures and antibiotic therapy should be initiated only if clinical signs of infection develop (7).

CRITICAL INTERVENTIONS

- Monitor patients closely for progressive local, systemic, and hematologic effects, which are indications for antivenom

therapy.
- Perform intensive care unit–level monitoring and have epinephrine and antihistamines (e.g., diphenhydramine) available at the bedside when giving antivenom, as anaphylactic reactions may occur.

DISPOSITION

Patients with dry bites who do not develop systemic or local progressive venom effects during an 8- to 12-hour observation period may be discharged. Those with severe or life-threatening bites and those receiving antivenom should be admitted to an intensive care unit. Admission to a floor bed is appropriate for the observation of patients with mild or moderate envenomations. Mobilization of the affected extremity can begin when the progression of swelling has ceased. Discharge is appropriate when swelling is decreasing, any coagulopathy has reversed, and the patient is ambulatory. Outpatient follow-up may be necessary for several days to monitor for infection and manage serum sickness.

Common Pitfalls

- Failure to diagnose envenomation because of a lack of history or inadequate observation of patients with suspicious wounds of unclear cause.
- Failure to provide supportive care and adequate doses of antivenom to patients with severe envenomation.
- Unnecessary administration of antivenom.

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CHAPTER 368 Elapid Snake Envenomation

Richard C. Dart and John B. Sullivan, Jr.

Coral snakes are the only native North American snakes belonging to the elapid family. These brightly colored snakes are known for the potency of their venom. Fortunately, these snakes are usually small, nocturnal, and retiring, so few bites actually occur.

Coral snakes in the United States include (1) the Eastern coral snake (*Micrurus fulvius fulvius*), (2) the Texas coral snake (*Micrurus fulvius tener*), and (3) the Arizona (*Sonoran*) coral snake (*Micruroides euryxanthus*). The Eastern coral snake is found in the deep southeast United States; the Texas and Arizona subspecies are found primarily in the states whose names they bear (1). All these snakes are brightly colored, with black, red, and yellow rings that encircle their bodies. The red and yellow rings touch in coral snakes but are separated by black rings in nonpoisonous snakes, hence the rhyme, "Red on yellow, kill a fellow; red on black, venom lack." Unfortunately, victims may confuse the rhyme, especially when intoxicated (e.g., "Red on yellow, good fellow"). Elapids lack the facial pits seen in pit vipers and have nearly round pupils.

Coral snakes are docile and usually bite only during handling. When biting, they hold on or chew, allowing them to envenomate. Their venom is discharged through grooves on two small, fixed anterior fangs. Their small size makes it difficult, but not impossible, to envenomate humans seriously. The Eastern and Texas subspecies are larger and have seriously envenomated many patients (1). The Eastern coral snake appears to cause more severe envenomation

than the Texas coral snake; the Sonoran coral snake has not caused severe envenomation (1,2).

CLINICAL PRESENTATION

Coral snake envenomation can be difficult to diagnose and easy to underestimate. The typical bite shows little local damage and few initial symptoms. Minor pain without swelling may be present. This may be followed by numbness and weakness of the affected part. Systemic symptoms, which may take hours to develop, include drowsiness, apprehension, weakness, fasciculation, tremors, difficulty swallowing, dyspnea, salivation, nausea, and vomiting (3). Death may occur from respiratory muscular paralysis (2).

Physical examination may show fang marks and associated scratches. It is often possible to express a drop of blood. However, the history is particularly important, because significant envenomation has occurred even without bite marks being apparent, despite close examination. In such cases, injecting lidocaine under the suspected area may show minute beads of serosanguineous fluid exuding from fang punctures. Signs of systemic toxicity may be delayed in onset and include weakness of extraocular muscles, miotic pupils, bulbar paralysis, ptosis, respiratory depression, and convulsions. A creatine kinase level may be elevated.

DIFFERENTIAL DIAGNOSIS

The diagnosis of coral snake envenomation is usually clear from the history, because the snake frequently hangs on to the victim and has bright, identifiable coloring. When the patient cannot clearly communicate, the rapid development of cranial nerve palsy and progressive paralysis distinguishes it from other motor neuron diseases. If other causes are suspected, myasthenia gravis, Guillain–Barré syndrome, botulism, heavy metal toxicity, and central nervous system depressant medications may be considered.

Envenomation by other members of the elapid family such as the Australian red-bellied black snake, Ingram's brown snake, death

adder, and cobra, krait, mamba, Taipan, and tiger species may cause similar neurotoxicity. Amateur herpetologists are the typical victims, but zookeepers and other professionals are occasionally bitten. Specific exotic antivenoms may be available. A poison center (1-800-222-1222) can be consulted for assistance in evaluation, locating antivenom and management.

ED EVALUATION

The time and circumstances of the bite, a description of the snake, first-aid treatment before arrival, allergies, previous bites and antivenom therapy, medical history prior to presentation, and the nature, onset, and progression of symptoms should be noted. Although positive identification of the offending snake is helpful, it should not delay treatment. The physical examination should focus on the neurologic status, particularly cranial motor nerve and respiratory muscle function. Routine testing and imaging are not needed but the patient should be assessed for hypoventilation using tidal volume and blood gas analysis, and for muscle injury by creatine kinase if necessary. Other studies (laboratory, chest radiograph, electrocardiogram) should be obtained if clinically indicated.

KEY TESTING

- Blood gas for ventilation assessment if necessary.
- Creatine kinase for muscle injury in symptomatic patients.

ED MANAGEMENT

All patients with a history of coral snake bite should be examined. In symptomatic patients, prehospital care should consist of intravenous line insertion, maintenance of airway, and timely transport to a health care facility capable of antivenom therapy. Immobilizing the bitten extremity with a splint and applying elastic pressure bandages to retard venom spread may be useful.

Wound cleansing and tetanus prophylaxis should be provided. Patients who have clearly been bitten or who have developed

symptoms or signs of envenomation should be given at least five vials of *M. fulvius* antivenom (equine) by IV infusion. It is best not to wait for signs of toxicity to develop because the antivenom may not reverse them or prevent further deterioration once they appear. If symptoms progress, the dose of antivenom should be repeated. Allergic reactions can occur, and the same precautions as described for crotaline antivenom administration should be taken when giving coral snake antivenom (see Chapter 367). Although *M. fulvius* antivenom is neither effective nor necessary in Sonoran coral snake envenomation, it should be administered, unless a positive identification of this species has been made. The elective intubation of patients with bulbar signs or symptoms may prevent aspiration pneumonia (3).

The prognosis is excellent. There is normally no tissue loss or permanent neurologic dysfunction. Even without antivenom treatment, recovery can be expected over days to weeks if appropriate supportive care is provided (3,4). Hence, patients with allergic reactions to horse serum or antivenom can be managed successfully without antivenom therapy.

CRITICAL INTERVENTIONS

- Admit and monitor all patients with possible coral snake envenomation and monitor for neurologic dysfunction and hypoventilation.
- Administer *M. fulvius* antivenom to patients with known coral snake bites, even before the onset of symptoms.

DISPOSITION

All patients in whom the diagnosis of coral snake envenomation is entertained should be admitted to an intensive care area for at least 12 hours of close monitoring of vital signs and neurologic function. This disposition applies to patients with a definite bite, either by history or examination, regardless of whether they are symptomatic. After 12 hours of observation, patients with no evidence of

envenomation may be discharged. Those with severe envenomation may require several days of hospitalization.

Common Pitfalls

- Failure to appreciate that the onset of symptoms after coral snake envenomation may be delayed in onset and slowly progressive.
- Using antivenom inappropriately in patients with documented Arizona (*Sonoran*) coral snake envenomation and in those with allergic reactions to horse serum or antivenom.
- Failure to take the precautions for allergic reactions when giving coral snake antivenom.
- Failure to monitor for worsening toxicity after antivenom administration and to provide concurrent supportive care, especially airway protection and ventilatory assistance.

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CHAPTER 369

Hymenoptera Envenomation

Paul F. Kolecki

The order *Hymenoptera* ("membrane-winged") includes bees, wasps, hornets, yellow jackets, and ants. Honeybees and bumblebees belong to the family *Apidae,* although wasps, hornets, and yellow jackets belong to the family *Vespidae.* Ants belong to the family *Formicidae;* fire ants are the most medically important species in this family. Anaphylaxis to *Hymenoptera* species affects up to 0.5% of the US population and causes about 50 deaths annually (1).

Winged Hymenoptera species are found throughout the United States, although fire ants are localized mainly in the southern states. Yellow jackets live in nests in the ground and in walls, while hornets live in nests built in trees or under branches. Wasps often build nests under roofs, behind shutters, and in dryer vents. Domestic honeybees in the United States are generally passive and do not sting unless provoked. Africanized honeybees (also called "killer bees"), indigenous to Central and South America and the southwestern United States, attack animals and humans in large; aggressive swarms cause mass envenomation.

The venom of winged Hymenoptera insects consists mainly of proteins, enzymes, and vasoactive amines; there is strong cross-reactivity between the venom within families. The venom of Africanized honeybees is very similar to that of domestic honeybees. Winged Hymenoptera species inject their venom quickly, typically causing immediate reactions. The main constituents of fire ant venom are piperidine alkaloids, which differs from the other

Hymenoptera. Fire ants are named because of the burning pain inflicted by their unique venom, which they inject more slowly, taking seconds to minutes. Significant morbidity and even mortality may occur in allergic individuals after a single envenomation by any of the Hymenoptera species.

Reactions to Hymenoptera stings are classified by the time of onset and the severity of the clinical reaction. Classification by time is subdivided into immediate and delayed reactions. Immediate reactions occur within minutes to a few hours after an envenomation and are mediated by IgE and vasoactive compounds within the venom. Delayed reactions are much less common than immediate reactions and typically develop several days to a week after the sting. These reactions are not IgE mediated.

Classification of a Hymenoptera reaction by severity is subdivided into three groups: local, systemic (e.g., anaphylactic), and toxic. Local reactions are common, with swelling, erythema, and a burning sensation at the sting site. These reactions are benign, resolve within hours to a couple of days, and are not predictive of systemic reactions to subsequent stings (2). Large local reactions can occur, perhaps involving an entire extremity. Patients suffering a large local reaction are at minimal risk (approximately 5%) of systemic anaphylaxis from subsequent stings.

Systemic reactions to Hymenoptera stings are either generalized or develop at a site remote from the sting site. Systemic reactions that produce life-threatening signs and symptoms are IgE mediated and commonly known as anaphylaxis. Potential physiologic effects associated with an immediate and severe systemic reaction include bronchiolar constriction, vasodilation, myocardial depression, increased capillary permeability, and the production of mucous. Most anaphylactic fatalities are a result of laryngeal edema and bronchospasm. An envenomation in someone with no history of a previous systemic reaction results in an anaphylactic reaction $<1\%$ of the time. However, a negative history of prior systemic reaction does not rule out the possibility of a severe reaction in the future. The risk of anaphylaxis to a subsequent Hymenoptera sting for a patient who has previously suffered venom-induced anaphylaxis is

30% to 60%. Because of the very strong cross-reactivity between the venoms within each Hymenoptera family, individuals sensitized to one species may also react to a sting by another species. Envenomation victims with Hymenoptera venom allergy and high levels of total IgE predominantly develop mild and moderate systemic reactions and may be protected from developing severe systemic reactions (3).

Toxic reactions, also known as direct systemic reactions, typically follow a massive envenomation, as seen with Africanized honeybees and result in the absorption of larger amounts of venom. Depending on the size of the victim, 10 to 50 simultaneous stings may be serious or fatal. The dose that will be lethal to 50% of humans (LD50) for honeybee stings has been estimated to be between 500 and 1,200 stings. Toxic reactions may occur immediately or may be delayed, and fatalities are a result of multisystem organ failure (4).

CLINICAL PRESENTATION

Local reactions caused by Hymenoptera envenomations are characterized by pain, wheal and flare formation, warmth, and pruritus at the sting site. These types of reactions occur in nonallergic individuals. Reactions to stings by winged species typically begin immediately and last for several hours. Fire ant stings often occur in clusters and develop into painful vesicles and sterile pustules during the first 24 hours and require up to 10 to 14 days for resolution. Large local reactions from fire ants typically are pruritic, erythematous, edematous, and indurated.

Local allergic reactions result in persistent swelling, pain, and erythema at the site of the sting. These reactions may progress to involve a large area (e.g., an entire extremity) during the first 2 to 3 days and may last for more than a week. Stings after accidental insect inhalation or ingestion by sensitive individuals may cause life-threatening swelling and obstruction of the pharynx, larynx, or esophagus.

Most anaphylactic reactions develop within minutes of envenomation and peak within an hour. Rarely, reactions may be

delayed as long as 6 hours after the envenomation. Recurrent reactions may occur for up to 2 days. Mild anaphylactic reactions are characterized by generalized flushing and urticaria, although moderate reactions are characterized by generalized weakness, chest or throat tightness, nausea, vomiting, diarrhea, and generalized angioedema. Cyanosis, dyspnea, stridor, hoarseness, confusion, coma, and collapse are seen in severe cases of anaphylaxis. Physical findings include hypotension, tachycardia, urticaria, wheezing, and laryngeal and pulmonary edema. Secondary complications associated with severe Hymenoptera-induced anaphylaxis include cerebral and myocardial infarction and coagulopathies (5,6). Systemic reactions also occur from fire ant stings and anaphylaxis occurs in 0.6% to 6% of envenomated fire ant victims.

Signs and symptoms of direct venom-induced systemic toxicity usually begin within minutes and include vomiting, diarrhea, generalized edema, collapse, loss of consciousness, confusion, headache, muscle spasms, and seizures. Vital signs typically reveal hypotension and tachycardia. Severe cases of direct systemic toxicity may be complicated by hemolysis, thrombocytopenia, disseminated intravascular coagulation (DIC), rhabdomyolysis, acute renal failure, hepatotoxicity, and encephalopathy. Systemic toxicity from mass envenomation may be delayed by many hours (4). A study of pediatric patients suffering mass Hymenoptera envenomations reported that vomiting does not portend involvement of other organ systems (7).

Serum sickness is an unusual delayed reaction that typically occurs within 1 week of envenomation Serum sickness is characterized by fever, arthralgia, myalgias, rash, and adenopathy and may include headache, glomerulonephritis, nephrotic syndrome, and necrotizing vasculitis. Delayed atypical hematologic and/or neurologic reactions may also occur following envenomations. These types of reactions include hemolytic anemia, thrombocytopenic purpura, Guillain–Barré syndrome, optic neuritis, other neuropathies, parkinsonism, and transverse myelitis (8).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for local reactions and anaphylaxis resembling Hymenoptera envenomations is extensive. Fortunately, the history of an encounter with a bee, yellow jacket, wasp, or fire ant is typically present.

Virtually any stinging or biting insect may produce limited local reactions of similar appearance. Extensive local reactions must be differentiated from an infectious cellulitis. Progressive extension of the initial reaction beginning shortly after the envenomation usually indicates an allergic component to the reaction. Inflammation, fever, leukocytosis, and lymphangitis beginning more than 24 hours after envenomation suggest a superimposed infection.

Anaphylactic reactions may be caused by a wide variety of drugs, foods, and environmental allergens. Anaphylaxis from Hymenoptera envenomation should be considered in any patient discovered outdoors during the spring and summer months with unexplained hypotension, urticaria, wheezing, and/or airway obstruction.

Patients who present with delayed reactions should be asked about recent insect stings, illnesses, and medication use within the previous several weeks.

Toxic reactions (e.g., direct systemic reactions or massive envenomation) can be differentiated from anaphylaxis in that systemic toxicity typically progresses more slowly, requires many stings, and causes multiorgan failure. Urticaria, pruritus, and wheezing are not part of a direct systemic reaction and suggest anaphylaxis.

Fire ant envenomations produce pustules within 24 hours. The differential diagnosis for pustule formation is also extensive, although the history of fire ant exposure is often evident. Risk factors for exposure include outdoor activities in endemic areas, especially when the affected areas are not covered by protective clothing.

ED EVALUATION

The history should include information pertaining to the time of stinging, estimated number of stings, previous Hymenoptera reactions, and past medical history. The time of onset, progression, and nature of symptoms should be noted. The physical examination should focus on the vital signs, airway patency, the cardiovascular system, and the skin. Lateral soft tissue neck radiographs and/or nasopharyngoscopy should be considered for patients experiencing stridor or voice changes without complete obstruction.

Patients with hypotension, loss of consciousness, or who suffer multiple envenomations (10 or more for children, 50 or more for adults) should have measurements of the complete blood count (CBC), serum creatine phosphokinase (CPK), liver function tests (LFTs), prothrombin time (PT), partial thromboplastin time (PTT), urinalysis (UA), and a metabolic panel to check for various manifestations of systemic toxicity (4). Measurements of the fibrinogen level and fibrinogen split products (FSP) should be considered with massive envenomation. Patients who experience hypotension, chest pain, or loss of consciousness should have an electrocardiogram (ECG) to rule out myocardial injury, ischemia, or infarction.

KEY TESTING

- Local reactions do not need any testing.
- Neck film or laryngoscopy is helpful for stridor or voice change.
- Systemic laboratories are important with hypotension and mass envenomation.

ED MANAGEMENT

The treatment of local reactions includes general wound care and symptomatic therapy for pain, swelling, and pruritus with analgesics, cool compresses or ice packs, elevation, and antihistamines. Envenomation sites should be cleaned, and tetanus prophylaxis should be updated, if necessary. Large local reactions can be treated with a short course of antihistamines, analgesics, and

steroids. Secondary infections are unusual; if present, they should be treated with appropriate antibiotics to cover skin flora.

With honeybee envenomation, the stingers often remain embedded in the victim's skin, and these should be removed. Previous recommendations were to remove stingers by scraping with the edge of a needle, scalpel, or credit card, rather than by pinching or use of tweezers, to avoid injecting any remaining contents from the attached venom sacs. However, in vivo experiments show that nearly all venom is injected within several seconds, and by the time a patient presents for emergency department (ED) care, stinger removal by pinching does not increase envenomation effects. Bee stinger removal by any method is acceptable.

The treatment for anaphylaxis as a result of Hymenoptera stings is very similar to that for anaphylaxis of other etiologies. Advanced life-support measures should be instituted as necessary. Prehospital personnel should give epinephrine at the first sign of an anaphylactic reaction. The dose and route of epinephrine depend on the severity of the symptoms and the victim's underlying medical problems; patients suffering from anaphylaxis should receive intramuscular or intravenous (IV) epinephrine (see Chapter 175).

Hypotensive patients should receive aggressive volume replacement with IV crystalloid. In addition, envenomated patients suffering anaphylaxis should receive an oral or IV antihistamine (e.g., diphenhydramine 0.5 to 1 mg/kg) and steroids (e.g., oral prednisone 0.5 to 1 mg/kg or methylprednisolone 1 to 4 mg/kg IV). A H_2-blocker (e.g., ranitidine) may also be helpful.

Severe anaphylactic reactions or marked local reactions that involve the nose, mouth, and/or throat require immediate airway control. Because most deaths are as a result of airway obstruction, early airway control by endotracheal intubation may be lifesaving in patients with respiratory distress from upper obstruction. A delay in airway control may result in further swelling, an unstable and difficult airway, and the potential need for a surgical airway. Patients who are wheezing or who have decreased lower-airway

movement should have inhaled α-1 adrenergic agonists (e.g., nebulized albuterol 2.5 mg). Continuous infusions of vasopressors (e.g., epinephrine, norepinephrine) may be necessary for recurrent or refractory hypotension. Higher-than-usual doses of α-adrenergic agents may be required when treating patients taking β-adrenergic blocking agents and those patients on chronic β-agonist medications.

The treatment of direct toxic reactions associated with multiple or massive envenomation is entirely supportive. These patients need to be monitored closely. These patients are potentially at risk for delayed organ dysfunction. Serial laboratory determinations of CBC, metabolic profile, LFTs, CPK, UA, fibrinogen, and FSP every 6 to 8 hours for 24 hours should be considered (4).

Delayed hypersensitivity reactions typically are treated with analgesics, antihistamines, and a tapering dose of corticosteroids.

Local fire ant reactions can be treated with cool compresses and cleansing with soap and water. Large local reactions may be treated with oral corticosteroids, antihistamines, and analgesics. Secondary infections should be treated with antibiotics. Anaphylactic reactions should be treated in the manner previously described.

CRITICAL INTERVENTIONS

- Administer epinephrine, corticosteroids, antihistamines, and IV fluids to patients with anaphylaxis who have abnormal vital signs, oxygen saturation, or dyspnea.
- Assess patients with dyspnea for upper airway obstruction, and perform endotracheal intubation in patients with severe or progressive signs and symptoms.

DISPOSITION

Patients who present immediately after envenomation should be observed for 1 to 2 hours for signs and symptoms of anaphylaxis. Asymptomatic patients may then be discharged. Milder anaphylactic reactions may be delayed, and patients should be instructed to return immediately if systemic symptoms ensue. In asymptomatic

patients with a history of previous anaphylactic reactions or severe local reactions, a prophylactic 3-day course of antihistamines and corticosteroids, beginning with a dose before discharge, should be considered.

Patients with mild to moderate anaphylaxis should be treated and observed for 4 to 6 hours or until asymptomatic. Patients suffering persistent or recurrent symptoms (excluding isolated urticaria), life-threatening reactions, persistent hypotension, or cardiac complications should be hospitalized with level of care determined by the severity of symptoms. All patients with anaphylactic reactions should be treated with a 3-day course of antihistamines and corticosteroids to prevent a relapse.

Patients with anaphylactic or severe local reactions should be given an epinephrine prescription (e.g., EpiPen or Ana-kit) and instructions for use. They should be cautioned about outdoor work and recreation, advised to wear shoes, long-sleeved shirts, and long pants, and to avoid wearing bright colors and perfumes. The use of insect repellents may be helpful. Referral to an allergist (directly or through the primary care physician) for possible desensitization immunotherapy should also be provided prior to discharge. Finally, the patient should be advised to obtain and wear a Hymenoptera allergy identification bracelet.

Patients suffering direct toxic reactions and multiple envenomations need careful observation for delayed end-organ damage and may need to be hospitalized depending on the number of stings and symptoms. Patients with local or delayed hypersensitivity reactions can be treated as outpatients with ED or primary care follow-up. Atypical reactions may require admission and referral to an allergist.

Common Pitfalls

- Failure to consider Hymenoptera-induced anaphylactic reaction in an unconscious or hypotensive patient found outdoors during the warm seasons.

- Failure to prescribe antihistamines and corticosteroids for 3 days after anaphylaxis.
- Failure to prescribe an emergency epinephrine kit for victims of severe local and anaphylactic reactions.
- Failure to refer patients with severe local and anaphylactic reactions to an allergist.

ACKNOWLEDGMENTS

The author gratefully acknowledges the contributions of Paul A. Janson and Richard J. Iseke to the content of this chapter.

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CHAPTER 370 Marine Envenomations

Alexandra E. DiTullio and Paul S. Auerbach

Encounters with venomous marine animals occur predominantly in warm tropical oceans. Because people may travel far from home for marine recreation, emergency physicians everywhere need to be familiar with the injuries and illnesses caused by aquatic life. This chapter reviews the most common invertebrate and vertebrate marine envenomations. We begin with descriptions of these unique animals and the mechanisms by which they cause injury and envenomation.

Members of the phylum Cnidaria exist either as sedentary polyps or as free-swimming, dome-shaped medusae and are divided into four main groups: (a) hydrozoans, which include fire coral, hydroids, and Portuguese man-of-war; (b) scyphozoans, considered to be "true" jellyfish (Fig. 370.1A); (c) anthozoans, including corals and anemones; and (d) cubozoans, such as "box" jellyfish (Fig. 370.1B). Considered to be the most dangerous are scyphozoans and cubozoans, in particular the box jellyfish *Chironex fleckeri* and the jellyfish *Carukia barnesi,* the latter known to cause the catecholaminergic Irukandji syndrome. Cnidarians possess venom-bearing stinging cells called *cnidocytes.* Each cnidocyte contains a stinging organelle known as a *nematocyst,* which carries a venom-laden coiled tubule released after stimulation of a "trigger." Nematocysts, predominantly located on the outer tentacles or near the mouth of the creature, are activated by physical contact and discharge with sufficient force to penetrate the dermis. The stinging process may trigger millions of nematocysts, as in the case of the Portuguese man-of-war. Cnidarian venom is a viscous mixture of

toxic and antigenic substances capable of stimulating hemolytic, proteolytic, cholinergic, histaminergic, serotonergic, and adrenergic activities. The venom can be neurotoxic, cardiotoxic, and/or dermatonecrotic (1).

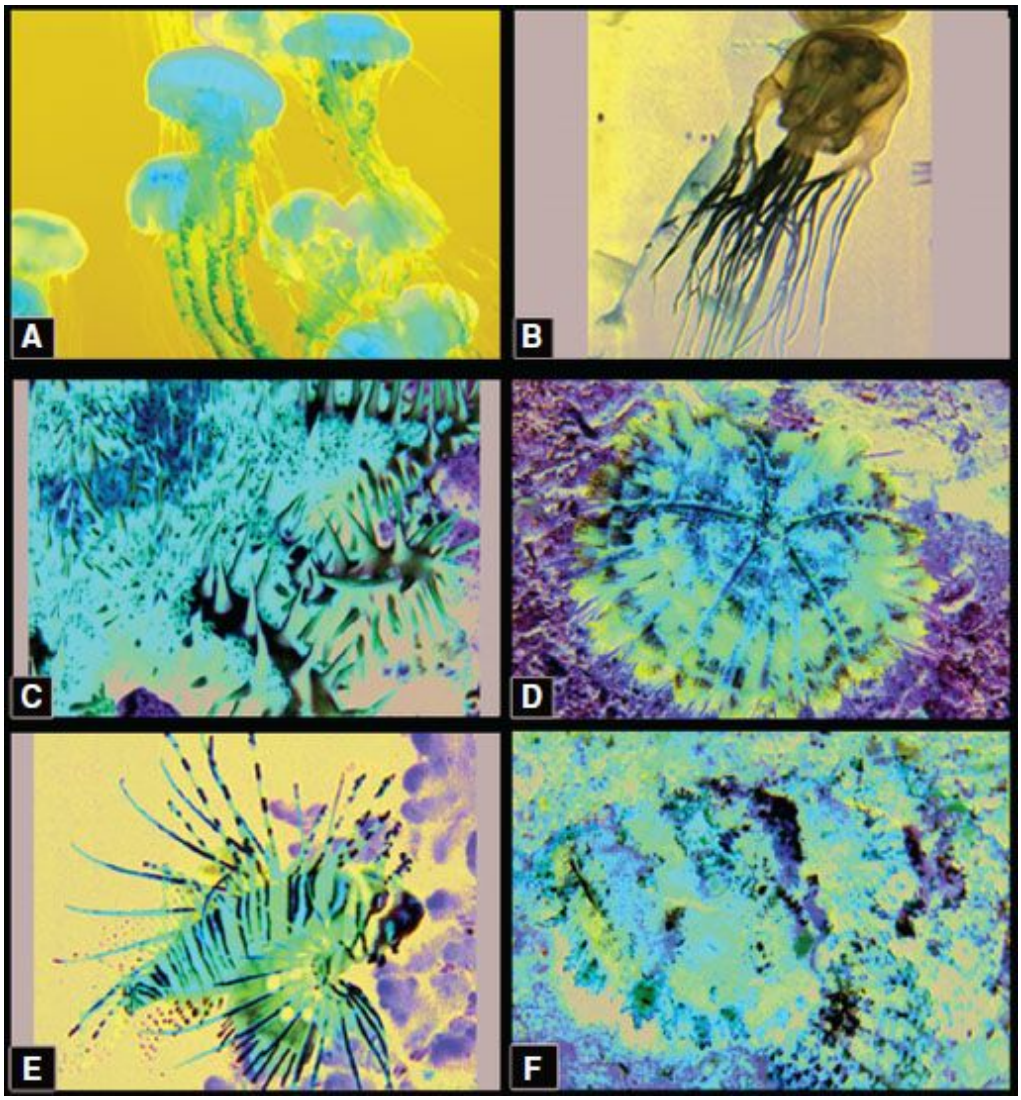

FIGURE 370.1 **A:** Jellyfish, "Pacific sea nettle." (Photo by Alexandra DiTullio) **B:** Box jellyfish. (Photo by Alexandra DiTullio) **C:** Crown-of-thorns starfish. (Photo by Paul Auerbach) **D:** "Fire" sea urchin. (Photo by Paul Auerbach) **E:** Lionfish. (Photo by Paul Auerbach) **F:** Scorpionfish. (Photo by Paul Auerbach)

Echinoderms include starfish, sea urchins, and sea cucumbers (1). Some starfish are covered with thorny spines of calcium carbonate

and produce a venom-containing slime. The potent crown-of-thorns species has ice pick–like spines that can puncture a diver's wetsuit. Crown-of-thorns starfish (Fig. 370.1C) venom has hemolytic, myotoxic, myonecrotic, and anticoagulant effects. Sea urchins (Fig. 370.1D) are protected by a hard shell and regularly arranged spines. Some venomous spines are sharp and brittle and break off easily; others may be blunt and nonvenomous. Sea urchin venom contains various toxic fractions, including steroid glycosides, hemolysins, proteases, serotonin, and cholinergic substances. If "seizing organs" (pedicellariae) become attached to a victim, they may be torn from the urchin's shell and continue to sting the victim for several hours (1). Sea cucumbers are wormlike bottom feeders that produce a liquid toxin called *holothurin,* which is concentrated in the tentacular organs that can be extended in defense. Some cucumbers ingest cnidocysts and secrete their venom as well (1).

Although most mollusk toxicity results from ingestion (1), cone snail stings and blue-ringed octopus bites are most hazardous to humans (2). Cone snails, found in Indo-Pacific seas, attack by injecting potent neurotoxins via a harpoon-like detachable tooth. Octopus bites are rare, but a bite from the tiny (<20 cm) Australian blue-ringed octopus releases venom similar to tetrodotoxin, which blocks peripheral nerve conduction (1). Most cases of envenomation are related to octopus handling.

Stingrays cause an estimated 2,000 injuries annually in US coastal waters (2). Injuries usually result when a human steps on the animal's dorsal surface, causing the barbed caudal appendage ("tail") to whip upward in a reflexive defensive response. The venom mechanism consists of a serrated spine or spines, venom glands, and enveloping integumentary sheaths. As the spine penetrates the victim the sheath ruptures, releasing venom and organic debris. Most injuries occur on the lower extremities. However, there have been cases of cardiac penetration. Stingray venom consists partially of heat-labile toxic components. Some stingrays generate electrical energy that can stun their victims (3).

Venomous fish from the family Scorpaenidae, found in the Indian and Pacific Oceans, are prized by aquarium enthusiasts. There are

three groups based on venom organ structure: The mildly venomous lionfish (Fig. 370.1E); the moderately toxic scorpionfish (Fig. 370.1F); and the deadly stonefish (3). Spines located on the dorsal, pelvic, and anal surfaces of these fish are covered with an integumentary sheath, under which venom travels along grooves from paired glands at the base. Envenomation occurs when a spine punctures the skin, causing the sheath to tear and expose the venom. Stonefish venom is commonly compared to that of the cobra snake and may retain full potency for 24 to 48 hours after death of the fish. The principal component (stonustoxin) is a nondialyzable, antigenic, and heat-labile protein. The toxin causes paralysis of cardiac, skeletal, and smooth muscles (3).

Catfish, both seawater and freshwater species, are endowed with venomous spines. Few are known to be aggressive toward humans, but some, including the oriental catfish, can inflict extremely painful stings. The tiny freshwater South American catfish *Vandellia,* also known as the "urethra fish," is more feared by native Amazonians than the piranha. At 2.5 to 7.5 cm in length, this fish sports short spines on its gill covers and has fins that can be locked in place when the fish becomes excited. *Vandellia* has been observed to implant itself in urogenital apertures, causing extreme pain and inflammation. It is unknown what attracts this fish to the human urethra, but swimmers should take precautions to avoid genital exposure (3).

CLINICAL PRESENTATION

Cnidarian envenomation may cause any or all three types of reactions- an immediate allergic reaction, immediate toxic (painful) reaction, and delayed allergic/immune response (1). Severity of envenomation is contingent on the species, the number of nematocysts discharged, and the sensitivity, size, and underlying health of the victim (1). In most envenomations, burning or stinging pain occurs immediately and can be very severe. Blister formation and pruritus lead to linear, urticarial, and painful eruptions that can take up to 10 days to resolve. The most common result of envenomation is localized dermatitis at the point of contact, which,

if left untreated, will often resolve in 1 to 2 weeks with occasional residual skin irritation and/or hyperpigmentation lasting up to 2 months. Further progression can lead to vesicular, ulcerative, hemolytic, or necrotizing lesions and possibly erythema nodosum or even gangrene (4).

Stings from the jellyfish *Physalia physalis* and *Stomolophus meleagris* have been reported to induce repeat eruptions for up to 2 to 3 weeks after the primary insult without repeated exposure to the animal (4). Sea bather's eruption, commonly misnomered "sea lice," is a dermatitis caused by larvae of the thimble jellyfish *Linuche unguiculata* (1). The eruption can occur within minutes or up to 12 hours after contact with ocean water and predominately affects covered areas of the body where the larvae are trapped, particularly underneath bathing suits. The reaction is intensely pruritic, with erythematous wheals, papules, or vesicles that persist for up to 2 weeks and may recur if the same bathing suit is worn again (4). Some victims develop gastroenteric symptoms after being stung.

In more severe envenomations, there are the local symptoms described above plus systemic involvement. Systemic signs and symptoms may appear immediately or be delayed by several hours. These include malaise, weakness, ataxia, dizziness, local cramping, muscle spasms, paresthesias, low-grade fever, nausea, vomiting, conjunctivitis, corneal ulcerations, anxiety, tachycardia, and hypotension. Fatal envenomations are due to arrhythmias, heart failure, respiratory arrest, and anaphylaxis (5). The Pacific box jellyfish *C. fleckeri* contains one of the most potent marine venoms, and fatalities from its sting have occurred within a few minutes of envenomation (6). Severity of envenomation appears to correlate with increasing size of the bell and length of tentacles. Some victims are able to struggle only for a minute before collapse (1).

The Irukandji *C. barnesi* causes symptoms similar to those seen with pheochromocytoma. Within 40 minutes of envenomation, the victim develops back, chest, and abdominal pain, nausea, vomiting, diaphoresis, agitation, hypertension, and tachycardia. The symptoms are due to massive catecholamine release. Victims may develop

pulmonary edema and myocardial injury 6 to 18 hours after the sting (5).

Sea anemones contain biologically active substances, such as neurotoxins, cardiotoxins, and hemolysins. The sting is compared in severity to that of a bee, characterized by a halo of erythema and petechial hemorrhage. The dermatitis may cause skin vesiculation and necrosis. The toxins of the sea anemone *Actinia equina* may cause coronary vasospasm leading to cardiorespiratory arrest, and those of *Condylactis* may cause hepatic failure (1).

Envenomations by the spines of starfish, sea urchins, and sea cucumbers cause immediate intense pain, which evolves into local muscle spasm, dermal erythema, and localized edema. The puncture sites often bleed profusely. Sea urchin spines frequently break off and may lodge deeply. Some contain purple or black dye that causes subcutaneous staining, giving a false impression of retained spines (4). Embedded spines in or adjacent to a joint or peripheral nerve may cause synovitis or neuropathy. Infrequent systemic symptoms, usually seen only if multiple spines enter simultaneously, include nausea, vomiting, paresthesias, abdominal pain, syncope, hypotension, and respiratory distress (1). Delayed reaction can occur weeks after the injury, consisting of a granuloma surrounding a retained spine fragment or diffuse inflammation at the puncture site. Puncture-induced infections are common. Of note, holothurin from sea cucumbers has caused conjunctivitis and blindness (1).

Most cone snail stings occur on the fingers or hands when handling the animal. Mild stings produce burning pain, followed by localized ischemia, cyanosis, and numbness. Severe envenomations produce paresthesias at the wound site, which may become perioral and then generalized (4). Partial paralysis may progress to respiratory failure. Systemic effects include pruritus, dysphagia, aphonia, and diplopia, with cerebral edema, coma, cardiopulmonary arrest, and death within a few hours. Victims usually recover within 6 to 8 hours, although some symptoms may take 2 to 3 weeks to resolve completely (1).

Octopus bites usually occur as a result of handling the creature and consist of one or two small puncture wounds. The initial bite often

goes unnoticed. Within 10 minutes, a burning sensation spreads to involve the entire limb, with erythema, swelling, tenderness, warmth, and pruritus. Most often there is no local reaction or only a tiny blanched area (1). If the bite is from a blue-ringed octopus, within 15 minutes the victim may experience neurologic symptoms that include perioral and facial paresthesias, diplopia, aphonia, dysphasia, ataxia, weakness, nausea, vomiting, muscle paralysis, and respiratory failure leading to death. Rapid neuromuscular blockade of the phrenic nerve, leading to paralysis of the diaphragm, causes respiratory failure (2). Because the toxin does not directly affect the heart, cardiac arrest is attributed to anoxia (1).

A stingray tail barb may cause a puncture wound or jagged laceration that is contaminated with stingray soft tissue and often spine fragments. Although lower extremity wounds are most common, infrequent truncal injuries cause most fatalities (2). Envenomation causes immediate and intense pain, which peaks at 30 to 60 minutes and may last up to 48 hours. A severe wound initially appears cyanotic and rapidly becomes erythematous and hemorrhagic, with possible early necrosis of muscle and fat. Systemic symptoms include weakness, nausea, vomiting, diaphoresis, vertigo, syncope, seizures, fasciculations, paralysis, hypotension, and, rarely, dysrhythmias and death (3,7). The stingray's mouth generates considerable suction and utilizes grinding plates for feeding, which have caused large hematomas or severed fingers (3).

Scorpionfish and stonefish are well camouflaged, so a sting usually occurs on the hands or feet of the unwary diver or fisherman who grasps or steps on the animal. Fish handlers and aquarists are also at risk. The puncture wound is immediately painful, with radiation proximally up the extremity. Untreated, the pain typically peaks at 60 to 90 minutes and resolves in 8 to 12 hours (3,8). Pain from a stonefish envenomation may be excruciating and persist for days. Rare deaths occur within the first 6 to 8 hours. The wound is first ischemic and then becomes cyanotic, with surrounding erythema and edema. Vesicles often form, and tissue sloughing with cellulitis may occur within 48 hours (4). Systemic symptoms are similar to cnidarian envenomation and include pulmonary edema, pericarditis,

syncope, hallucinations, and atrioventricular block (3). Wound complications include infection, neuropathies, and cutaneous granulomas that may require months to heal (4).

Catfish stings cause instantaneous stinging, throbbing, or scalding pain centrally, with pain radiating into and up the affected limb. Pain normally subsides within 30 to 60 minutes but may last up to 48 hours. Common sequelae include muscle spasm, diaphoresis, and fasciculations. Bleeding is often more severe than expected. Death is extremely rare (3).

Sea snakes found in the warm Pacific and Indian Oceans possess venom with neurotoxic, hemolytic, and cardiotoxic fractions, but cause mostly neurotoxic syndromes. The bite itself is usually not painful and may even go unnoticed. It is estimated that less than 10% of sea snake bites actually inject venom, yet worldwide 3% result in fatalities. Symptoms include muscle pain, peripheral weakness, paralysis, and respiratory failure (3).

DIFFERENTIAL DIAGNOSIS

The main considerations in the differential diagnosis are allergic reactions, trauma, infections, retained foreign bodies, and envenomations by other marine animals. Remember that there can be associated delayed reactions or systemic symptoms. For instance, sponges may cause erythema multiforme or an anaphylactoid reaction that may develop days to weeks after a severe exposure (1). There are also case reports of mononeuritis multiplex and Guillain–Barré syndrome occurring after jellyfish stings, sea urchin punctures, and envenomation from other marine creatures (1).

ED EVALUATION

The history should include the identity or description of the suspected envenoming animal and the time of onset, quality, and progression of symptoms. The specific geographic location visited should be noted. The physical examination begins with the skin, looking for wounds, rashes, and signs of infection. Many wounds need to be explored and/or x-rayed for radiopaque foreign bodies. Magnetic resonance imaging (MRI) is a fairly reliable method to

identify a foreign body; ultrasound techniques or computed tomography (CT) may also be useful. If there is no clinical sign of infection, "prophylactic" wound cultures have not been shown to be useful (1). Patients with abnormal vital signs, systemic symptoms, or altered sensorium should have an electrocardiogram and routine laboratory evaluation, including urine hemoglobin.

KEY TESTING

- Wound exploration and imaging to evaluate for foreign bodies.
- Wound culture if there are signs of infection.
- Troponin if suspected cardiotoxic envenomation with abnormal vital signs.
- Urine hemoglobin and creatine kinase for evaluation of rhabdomyolysis.

ED MANAGEMENT

An algorithmic approach to managing marine envenomations is depicted in Figure 370.2. Supportive care should be initiated in all marine envenomations. These injuries can be extremely painful, so do not hesitate to liberally treat pain locally and systemically, using opiates if needed (2). Because both fresh water and salt water contain an abundance of microbes, wound care is paramount, including irrigation, debridement of devitalized tissues, and removal of foreign bodies. Infected wounds should be cultured for both aerobes and anaerobes. Bacteria of concern include *Aeromonas hydrophila, Bacteroides fragilis, Chromobacterium violaceum, Clostridium perfringens, Erysipelothrix rhusiopathiae, Escherichia coli, Mycobacterium marinum, Pseudomonas aeruginosa, Salmonella enteritidis, Staphylococcus aureus, Streptococcus* spp., and *Vibrio* spp (4). Immunocompromised patients, especially those with hepatic disease, should be empirically started on broad-spectrum prophylactic antibiotics covering *Vibrio* spp. Minor wounds can be adequately treated with oral ciprofloxacin, trimethoprim–sulfamethoxazole, doxycycline, or cefuroxime. Extensive lacerations, deep punctures, joint involvement, or grossly contaminated exposures require a

parenteral third-generation cephalosporin, aminoglycoside, or other agent that covers *Vibrio* spp. A second antibiotic may be necessary to cover more common organisms, such as *Staphylococcus* (1,4). Tetanus prophylaxis should be administered according to the patient's immunization status.

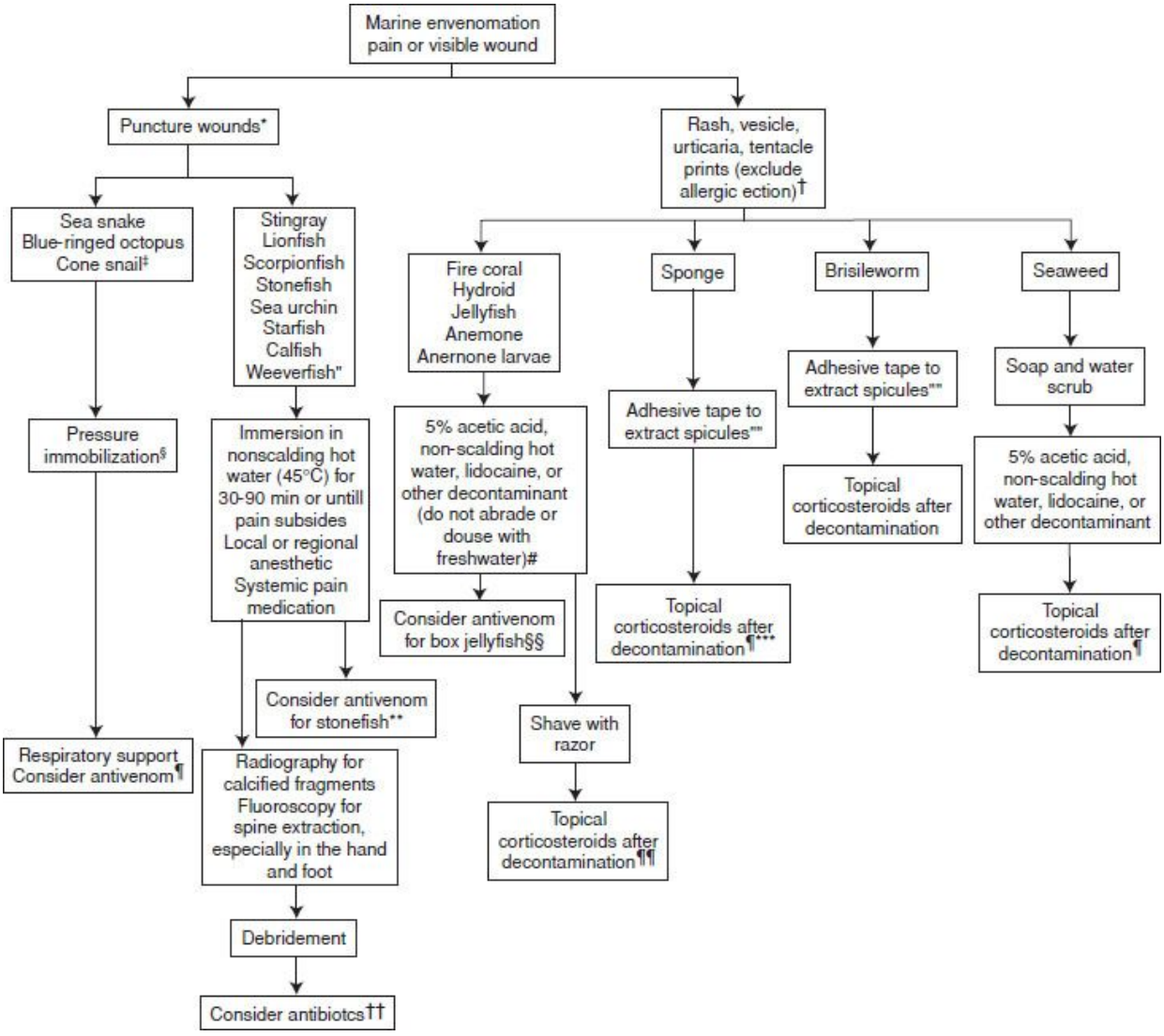

FIGURE 370.2 Algorithmic approach to marine envenomation. *A gaping laceration, particularly of the lower extremity, with cyanotic edges suggests a stingray wound. Multiple punctures in an erratic pattern with or without purple discoloration or retained fragments are typical of a sea urchin sting. One to eight (usually two) fang marks are usually present after a sea snake bite. A single ischemic puncture wound with an erythematous halo and rapid swelling

suggests scorpionfish envenomation. Blisters often accompany a lionfish sting. Painless punctures with paralysis suggest the bite of a blue-ringed octopus; the site of a cone shell sting is punctate, painful, and ischemic in appearance. †Wheal and flare reactions are nonspecific. Rapid onset (within 24 hours) of skin necrosis suggests an anemone sting. Broad “tentacle prints” with cross-hatching or a frosted appearance after application of aluminum-based salts suggests a box jellyfish (*C. fleckeri*) envenomation. Ocular or intraoral lesions may be caused by fragmented hydroids or cnidarian tentacles. An allergic reaction must be treated promptly. ‡Sea snake venom causes weakness, respiratory paralysis, myoglobinuria, myalgias, blurred vision, vomiting, and dysphagia. The blue-ringed octopus injects tetrodotoxin, which causes rapid neuromuscular paralysis. §As soon as possible, venom should be sequestered locally with a proximal venous-lymphatic occlusive band of constriction or (preferably) the pressure immobilization technique, in which a cloth pad is compressed directly over the wound by an elastic wrap that should encompass the entire extremity at a pressure of 70 mm Hg or less. Incision and suction are not recommended. ¶Early ventilatory support has the greatest influence on outcome. The minimal initial dose of sea snake antivenom is one to three vials; up to 10 vials may be required. ||The wounds range from large lacerations (stingrays) to minute punctures (stonefish). Persistent pain after immersion in hot water suggests a stonefish sting or a retained fragment of spine. The puncture site can be identified by forcefully injecting 1% to 2% lidocaine or another local anesthetic agent without epinephrine near the wound and observing the egress of fluid. Do not attempt to crush the spines of sea urchins if they are present in the wound. Spine dye from already extracted sea urchin spines will disappear (be absorbed) in 24 to 36 hours. **The initial dose of stonefish antivenom is one vial per two puncture wounds. ††The antibiotics chosen should cover *Staphylococcus, Streptococcus,* and microbes of marine origin, such as *Vibrio.* ‡‡Acetic acid 5% (vinegar) is a good all-purpose decontaminant and is mandated for the sting from a box jellyfish. Alternatives, depending on the geographic region and indigenous jellyfish species, include isopropyl alcohol, bicarbonate (baking

soda), lidocaine, papain, and preparations containing these agents. Application of water heated to 45°C may be effective for relieving pain. §§The initial dose of box jellyfish antivenom is one ampule IV or three ampules IM. ¶¶If inflammation is severe, steroids should be given systematically (beginning with at least 60 to 100 mg of prednisone or its equivalent), and the dose should be tapered over a period of 10 to 14 days. || ||An alternative is to apply and remove commercial facial peel materials. ***An alternative is to apply and remove commercial facial peel materials followed by topical soaks of 30 mL of 5% acetic acid (vinegar) diluted in 1 L of water for 15 to 30 minutes, several times a day, until the lesions begin to resolve. Anticipate surface desquamation in 3 to 6 weeks. (Adapted from Auerbach PS. Envenomation by aquatic invertebrates. In: Auerbach PS, ed. Wilderness Medicine. 6th ed. Amsterdam: Elsevier; 2012:1596–1628.)

Therapy for cnidarian envenomation includes field and/or emergency department application of a detoxicant, appropriate analgesia, and general supportive care. If a detoxicant is available (see later discussion), apply it immediately. Otherwise, rinse the wound with normal saline or hypertonic saline. Avoid applying fresh water (unless it is heated) or rubbing the affected area, because both actions are thought to cause discharge of nematocysts. Ice packs (preferably without external moisture) may alleviate pain, but application of nonscalding hot water (up to 45°C [113°F]) may be more useful (9). Remove any large tentacles with forceps or while wearing dishwashing-thickness gloves (1). If nitrile surgical gloves are worn, “double gloves” should be used if possible.

Topical therapy for jellyfish stings is guided by recommendations largely derived from empiric observations and the opinions of experts, and not from evidence-based randomized blinded clinical trials. Pouring vinegar (5% acetic acid) on the victim for 30 seconds inactivates the toxin of the box jellyfish *C. fleckeri.* A slurry of isopropyl alcohol and papain (meat tenderizer) has been effective against many other jellyfish species, presumably causing hydrolysis of proteinaceous toxins. It should remain on the skin for 15 minutes

or until the pain is relieved. Acetic acid may also cause relief of pain from Portuguese man-of-war stings, although this is still controversial in the literature (1). Other topical decontaminants that carry some favor for certain species include lidocaine, household ammonia (which may itself cause skin irritation), concentrated lemon or lime juice, or baking soda. Pain not resolved by nematocyst inhibition can be treated with lidocaine ointment or benzocaine spray to provide relief (9).

After the detoxicant has been applied, the adherent nematocysts need to be removed by applying shaving cream, baking soda, or talc to the affected area and shaving with a razor. Alternatively, a paste of sand and seawater can be prepared and the victim's skin scraped with a sharp-edged tool. It is possible that this shaving activity alone may be beneficial in relieving pain, even if this is not preceded by application of a topical decontaminant. If a sting is severe, the envenomed area should be immobilized, which might decrease venom distribution (1). However, the pressure-immobilization bandaging technique is no longer recommended (9).

Generally, only severe Portuguese man-of-war or box jellyfish stings result in rapid physiologic decompensation. Cardiopulmonary supportive care should be given as needed, and anaphylaxis should always be anticipated. Box jellyfish attacks have resulted in at least 67 deaths in Australia. Antivenom should be administered as soon as possible for any severe box jellyfish envenomation presenting with cardiopulmonary instability or extensive skin involvement (5). The initial dose is 20,000 units (one vial) over 5 minutes IV, or three vials IM, with standard hypersensitivity precautions. Additional treatment with magnesium sulfate may be of benefit, but remains controversial (2). Treat also for the renal sequelae of rhabdomyolysis. Although antibiotics are not always indicated, wounds should be closely followed for signs of infection. In addition, a topical antihistamine or mild corticosteroid may be soothing (4). A delayed reaction may recur after 1 to 2 months at the area of skin contact and should be treated with a 10- to 14-day taper of a glucocorticoid (1).

Along with the previously mentioned measures employed to treat cnidarian envenomations, patients presenting with the Irukandji syndrome, which is due to excessive catecholamine stimulation, may also need administration of IV phentolamine (5 mg initially, followed by 5 to 10 mg doses as needed) for control of hypertension (2). The use of IV $MgSO_4$ has recently been challenged (10). Beta-adrenergic blocking agents should not be used to control tremor, because these may precipitate hypotension or myocardial ischemia from unopposed alpha-adrenergic stimulation (1).

For starfish, sea urchin, and sea cucumber envenomation, the affected area should immediately be immersed in nonscalding hot water (up to 45°C [113°F]) as tolerated until the pain is relieved. Foreign bodies should be removed. Although some venomous spines may be absorbed within 24 hours to 3 weeks, it is best to remove those that are easily reached (1). External percussion to achieve spine fragmentation is contraindicated, and surgical exploration for embedded particles should be delayed until diagnosis can be made by soft tissue radiography, ultrasound, CT, or MRI. Spines within a joint or adjacent to a neurovascular structure should be referred to a surgeon for extraction of all fragments as soon as possible (1). For a possibly retained urchin spine, note whether the color change that was initially present has resolved over 48 hours. If this is the case, it is unlikely that a spine will be easily extracted from the surface, because it is unlikely that one is still present. Systemic analgesia is helpful, and prophylactic antibiotics should be given for deep puncture wounds (4). Systemic corticosteroids are for patients with diffuse delayed reaction with cyanotic induration, fusiform swelling in the digits, or focal phalangeal bony erosion. Sea cucumber envenomation management should include cnidarian detoxification and dermatitis treatment. If an eye is involved, it should be anesthetized and irrigated to remove residual foreign matter. The cornea should be examined with a slit lamp for defects. If there is no sign of infection, the inflammation should be treated with regular instillation of cycloplegic, mydriatic, and corticosteroid ophthalmic solutions. The patient should be referred to an ophthalmologist promptly for continuation of treatment (1).

No antivenom exists for treatment of cone snail or blue-ringed octopus envenomations, so management is limited to supportive measures. It is recommended, in addition to soaking the wound in nonscalding hot water, that the pressure-immobilization bandaging technique to contain the venom be used (2). Rapid respiratory failure can occur, so it is important to anticipate the need for oxygenation and mechanical ventilatory support. The clinical duration of blue-ringed octopus envenomation is 4 to 10 hours, after which a victim who has not suffered significant hypoxia usually begins to show improvement (1). Although some authors recommend wide excision to remove sequestered toxin and others favor irrigation, debridement, and wound observation, there is no compelling evidence that surgical therapy is routinely efficacious (1).

Treatment of stingray envenomation focuses on inactivating the toxin, alleviating pain, and preventing infection. The success of therapy is likely related to the rapidity with which it is initiated (3). The injury should be soaked in nonscalding hot water (up to 45°C [113°F]) for 30 to 90 minutes. If hot water is unavailable, the wound should be immediately irrigated with water or saline (7). Soaking the injury may not cause sufficient pain relief, so local or systemic analgesics may be necessary. Visible pieces of the spine or integumentary sheath will continue to envenom the victim and must be removed early. The wound tract needs to be explored, thoroughly debrided, and packed open for delayed primary closure. Prophylactic antibiotics are generally recommended owing to the high-risk nature of these injuries with respect to infections (3,7). Wounds to the abdomen or thorax must be fully evaluated by appropriate imaging studies. The patient should be observed for 3 to 4 hours for delayed onset of systemic symptoms before discharge (3). If the spine is lodged in the chest, abdomen, or neck, it should be managed as an impalement, with the spine immobilized in place until the victim is brought to a controlled operating room setting.

Management of scorpionfish or catfish envenomation is similar to that for stingray injuries. The wound should immediately be immersed in nonscalding hot water (up to 45°C [113°F]) for 30 to 90 minutes until symptoms subside. Recurrent pain that occurs after

several hours may respond to repeat hot water soaks. Appropriate treatment includes irrigation and thorough wound cleansing to ensure debris removal. Deep puncture wounds may need to be evaluated in the operating room (3). Stonefish antivenom is available for severe pain or systemic symptoms. One ampule should neutralize approximately two puncture wounds. As with any horse serum–based product, the possibility of a hypersensitivity reaction must be anticipated. Antivenom is rarely used for scorpionfish envenomation (3).

Treatment of sea snake envenomation includes the pressure-immobilization bandaging technique, early anticipation of respiratory failure, and administration of sea snake antivenom as soon as there is any evidence of envenomation. Victims who remain asymptomatic after 8 hours of observation can be safely discharged (3).

CRITICAL INTERVENTIONS

- Inactivate heat-labile toxins from stingrays, stonefish, scorpionfish, lionfish, catfish, and sea urchins by immersing the affected area in nonscalding hot water to tolerance.
- Administer specific antivenom for severe local tissue reaction and/or systemic toxicity as a result of box jellyfish or stonefish envenomation.
- Irrigate wounds, remove foreign bodies, and use appropriate antibiotic coverage to prevent infection.
- Provide appropriate supportive care, including pain and nausea control.

DISPOSITION

Some marine envenomations cause a delayed onset of symptoms, so a few hours of patient observation may be necessary. Victims with significant systemic signs and symptoms should be admitted to the hospital. A poison center can be consulted for treatment advice and to assist in locating antivenom. When discharged, patients need to be educated about wound infection, and follow-up care is essential.

Patients should be instructed to clean ulcerated wounds three times a day and have wounds first checked in 2 days.

Education on prevention of envenomations is important prior to discharge. Prevention of jellyfish stings is best accomplished by keeping exposed skin covered by a protective dive skin or wetsuit. Safe Sea is a topical sunscreen-jellyfish sting inhibitor that can be applied prior to entry into the water to prevent or diminish the severity of stings. To prevent stingray injuries, shuffling along the bottom when walking in the ocean is recommended. Ocean goers should be instructed to avoid handling marine life and always wear protective equipment.

Common Pitfalls

- Failure to appreciate that cnidarian envenomation pain can be reduced by topical lidocaine, vinegar, baking soda, isopropyl alcohol, or nonscalding hot water soaks and exacerbated by gentle freshwater irrigation.
- Failure to treat spine-induced envenomation pain with nonscalding hot water immersion.
- Failure to consider concomitant traumatic injuries and retained foreign bodies.
- Failure to consider appropriate antibiotic administration in certain circumstances for prophylaxis, and then for established marine bacterial infections.
- Failure to appreciate the severity of pain associated with marine envenomation.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contribution of Jamie Goodis to the content of this chapter.

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CHAPTER 371 Scorpion Envenomation

Jeffrey R. Suchard

Several dozen scorpion species are found in the United States. Envenomation from almost all of these species causes only local pain and inflammation, which respond well to minimal supportive therapy. The Arizona bark scorpion, *Centruroides sculpturatus* (alternately *C. exilicauda* by an older taxonomy), is the only native species known to produce a potentially life-threatening envenomation. This scorpion is found throughout Arizona and in parts of some neighboring states and northern Mexico (1). Stings may occasionally occur elsewhere, as scorpions have been reported to stow away in a person's belongings (e.g., shoes, duffel bags) and be transported long distances before encountering their victims. Mild-to-moderate systemic effects have been reported in a minority of stings by the common striped scorpion, *Centruroides vittatus,* found in the Southwest and Texas and into southern Indiana and Illinois (2).

C. sculpturatus specimens generally measure about 5 cm (range, 1.3 to 7.6 cm) in length, have a thin tail and claws, and are a uniform tan, yellow, or light brown (Fig. 371.1). The last tail segment contains a venom apparatus and stinger. The bark scorpion prefers to reside in or near trees but may also hide in ground debris, camping equipment, clothing left unattended in natural desert areas, or even in areas long inhabited by humans. Scorpions are most active at night in warm weather, lying quietly while waiting to ambush prey. In defending themselves, they grasp the victim's flesh with pincers and repeatedly sting by thrusting their tails over their bodies.

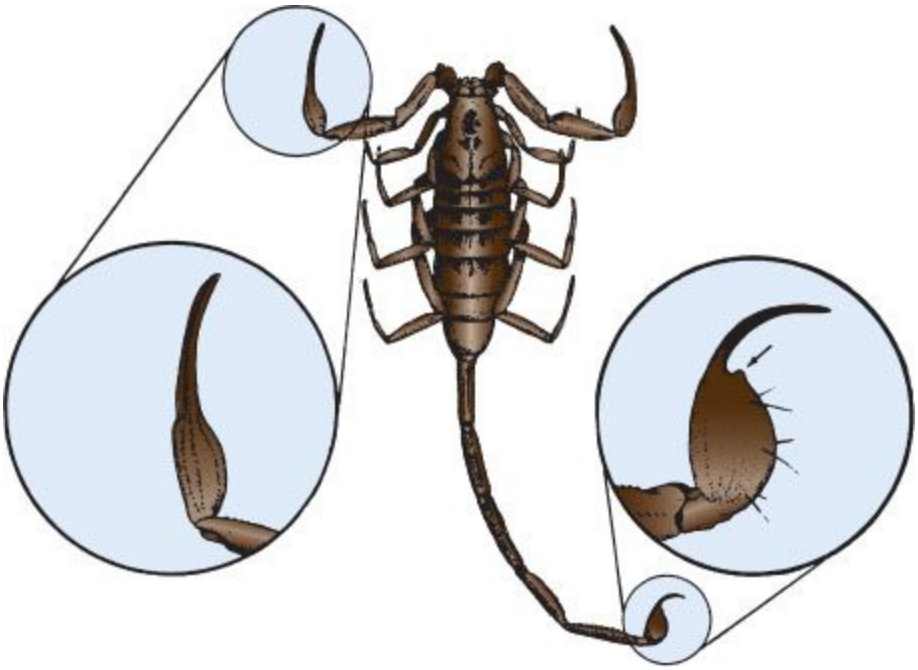

FIGURE 371.1 The sixth tail segment of *C. Sculpturatus* (bark scorpion) contains venom apparatus and stinger.

Although a sting from any scorpion can produce local pain, *C. sculpturatus* venom contains protein neurotoxins that cause repetitive firing of neurons by binding to sodium channels and preventing channel inactivation (1). Prolonged and excessive firing of parasympathetic, sympathetic, and somatic motor neurons produces various autonomic effects and uncoordinated, spontaneous activity in skeletal muscle. No destructive enzymes are present in the venom, so there is no inflammation or necrosis.

Scorpion stings are fairly common in endemic areas. Several thousand *C. sculpturatus* stings are reported annually to poison control centers in Arizona (3), although the majority of envenomations are not serious enough to require medical attention. Death from direct venom effects has not been reported in Arizona for several years; the lack of recent fatalities probably reflects advances in supportive medical care.

Severe envenomations by *C. sculpturatus* occur in 15% to 20% of children younger than age 10 who are stung and almost all severe envenomations occur in this age group. In contrast, 95% of

envenomations in those older than age 10 result in only mild-to-moderate effects. The life-threatening effects (myocarditis, pulmonary edema, shock) associated with dangerous scorpion species in other parts of the world have not been reported with species found in the United States.

CLINICAL PRESENTATION

C. sculpturatus envenomation results in the immediate onset of a painful tingling or burning sensation at the sting site. Tapping the sting site may produce severe pain, although no lesion is usually visible. Over minutes to several hours, pain and paresthesias may become generalized. Victims may complain of "thick tongue" and "trouble swallowing" yet lack objective abnormalities on examination. Young children frequently rub their noses, eyes, and ears and may present with unexplained crying.

Autonomic dysfunction is characterized by tachycardia, excessive secretions and, occasionally, vomiting and wheezing. Somatic motor abnormalities include roving eye movements, blurred vision, fasciculations (especially of the tongue), and poor control of pharyngeal muscles. Continuous jerking of extremities may be noted and misinterpreted as restlessness, seizures, or hysteria. The combination of uncoordinated pharyngeal musculature and muscles of respiration, increased secretions, and occasional wheezing may produce stridor, hypoxia, aspiration, and respiratory arrest in severe cases. Mild hyperthermia may also be noted, probably related to motor hyperactivity.

Envenomations can be graded on the basis of signs and symptoms (Table 371.1). In serious envenomations, abnormal motor activity may last 10 to 20 hours (1,4). Paresthesias may last up to 2 weeks.

TABLE 371.1
Scorpion Envenomations: Signs and Symptoms

Grade	Description
I	Local pain and/or paresthesias at site of envenomation
II	Pain and/or paresthesias remote from the site of sting
III	Either cranial nerve or somatic skeletal neuromuscular dysfunction:
	Cranial nerve dysfunction: Blurred vision, wandering eye movements, hypersalivation, trouble swallowing, tongue fasciculations, stridor, slurred speech
	Somatic skeletal neuromuscular dysfunction: Jerking of extremity(ies), restlessness, severe involuntary shaking and jerking, which may be mistaken for seizures
IV	Both cranial nerve and somatic skeletal neuromuscular dysfunction

DIFFERENTIAL DIAGNOSIS

Bites and stings from other arthropods should be considered. The pain at the site of envenomation may appear similar to that seen after a black widow spider bite. However, patients severely ill from scorpion stings appear unable to lie still, whereas those bitten by black widow spiders can maintain a position for short periods before moving in an attempt to become comfortable. Black widow envenomations do not produce abnormal eye movements, fasciculations, and paresthesias. Tapping over the site of envenomation produces severe pain in the patient stung by a scorpion but not in someone bitten by a spider. Black widow spider bites frequently produce a characteristic halo lesion at the site of the bite; no lesion is usually visible after *C. sculpturatus* stings.

Tachycardia, excessive secretions, wheezing, and respiratory distress accompanying serious scorpion stings may be mistaken for asthma, airway obstruction from a foreign body, or poisoning with cholinergic agents such as organophosphate insecticides. Without a witnessed scorpion sting, other entities to be considered include central nervous system infections, seizures, and intoxication with sympathomimetics, phencyclidine, and nicotine. Methamphetamine toxicity is sometimes mistaken for *C. sculpturatus* envenomation in scorpion-endemic areas when young children present with unusual neurologic findings such as agitation or choreiform movements, occasionally leading to the inappropriate use of antivenom.

ED EVALUATION

If a sting was not witnessed, it should be determined whether there are scorpions near where the patient became ill. Physical examination should focus on vital signs, the airway, and neuromuscular function. No specific diagnostic tests are available. In patients with suspected aspiration, chest radiography is indicated, and arterial blood gas analysis should be considered. Rarely, severe envenomations can cause pancreatitis, rhabdomyolysis, and myocarditis, which would warrant obtaining baseline laboratory tests including serum amylase and/or lipase, creatine kinase, and an electrocardiogram.

KEY TESTING

- If signs of systemic illness: Pulse oximetry
- There is no confirmatory test available and patients without systemic illness require no specific testing

ED MANAGEMENT

Advanced life-support measures, with particular attention to airway management, should be instituted as necessary. Patients with grade I or II envenomations are treated symptomatically. Application of ice or oral analgesics is effective in most cases, but parenteral analgesia may sometimes be needed. As with any puncture wound, the patient's tetanus immunization status should be addressed.

Several therapeutic interventions have been used historically, although few have been rigorously tested and are not generally recommended. Except for very rare cases of anaphylaxis in patients previously sensitized to scorpion venom, there is no demonstrable benefit from steroids, epinephrine, or antihistamines. Respiratory distress associated with hypersalivation has been treated with atropine, sometimes obviating the need for aggressive airway interventions (5). The ideal dosing of atropine has not been determined nor is this practice considered a standard of care.

The marked motor hyperactivity seen in young children with high-grade envenomations has been treated with IV sedatives.

Barbiturate infusion was a former mainstay of therapy, although continuous midazolam infusions in the pediatric intensive care unit (ICU) have had good results. The median length of stay was just over 15 hours, and only 4 patients of 104 had transient hypoxemia (6). Sedation in a closely monitored setting has become the default therapy for high-grade scorpion envenomations since local production of a goat-derived *Centruroides* antivenom ceased in 2001 and the last vials expired in 2004 (3).

An equine-derived *Centruroides* (Scorpion) Immune $F(ab')_2$ antivenom product was approved by the US FDA in 2011 and is indicated for high-grade envenomations (7). It is available at a limited number of hospitals in the desert Southwest, primarily in Arizona, but also some in Nevada and Utah. Initial dosing is 3 vials IV diluted in normal saline to 50 mL and given over 10 minutes; additional 1 vial doses may be given as needed every 30 to 60 minutes (8). Patients need close monitoring with attention to airway control and the possibility of needing to treat severe allergic reactions. The great majority of patients (95%+) treated with this antivenom have resolution of systemic findings within 4 hours. Antivenom-treated patients should be advised that serum sickness may occur within a few weeks, which usually responds well to typical doses of steroids and antihistamines. The cost of scorpion antivenom therapy in the United States can be tremendous, with some reports of patients being charged tens of thousands of dollars.

CRITICAL INTERVENTIONS

- Airway control is of primary importance. Severely envenomated patients may require airway interventions as a result of hypersalivation and poor control of the oropharyngeal musculature.
- ICU admission for close observation is often necessary when complication such as aspiration pneumonia have occurred.
- Antivenom therapy can be effective in rapidly reversing toxicity in patients with severe systemic findings.

DISPOSITION

Patients with local pain and inflammation from a non-*Centruroides* scorpion sting should only require symptomatic treatment and can be discharged home.

Patients with grade I or II *Centruroides* envenomations should be observed for 3 to 4 hours after a sting for evidence of progression of symptoms. Those who do not manifest increased envenomation severity can be discharged to home with oral analgesics and follow-up with their personal physician as needed.

Antivenom therapy should be considered for patients with more severe *Centruroides* envenomations. If successful, these patients may be discharged home after ED observation with information about serum sickness and a treatment plan should it occur. In the absence of antivenom, children with grade III or IV envenomations should be admitted to an ICU. Adults without respiratory difficulties who require admission for pain control may be admitted to an unmonitored bed. Adults with more severe envenomations generally require intensive care.

Common Pitfalls

- Mistaking symptoms of severe envenomation for hysterical or uncooperative behavior or for seizures, especially in children.
- Relying on the absence of a visible lesion at the site of the sting to rule out scorpion envenomation.

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CHAPTER 372

Black Widow Spider Envenomation

Dany K.M. Quan and Daniel E. Brooks

Originally used to describe *Latrodectus mactans,* black widow spider (BWS) is now used as the generic reference for up to 30 species of the genus *Latrodectus,* including *L. bishopi* (red-legged widow), *L. geometricus* (brown widow), *L. hesperus* (black widow), *L. indistinctus* (in Africa), *L. mactans hasselti* (redback spider), *L. Pallidus* (Asia), *L. paykulliana* (Europe), and *L. tredecimguttatus* (Mediterranean) (1). BWSs are found in the temperate regions of six continents and are widespread throughout North America, including the entire continental United States. There is evidence that their range is increasing. *L. mactans* and *L. hesperus,* most common in the western United States, are the classic black spider with a red, sometimes yellow, hourglass marking on the ventral abdomen. Several other species (including *L. variolus, L. bishop,* and *L. geometricus*) are found within the United States, varying in appearance depending on species, maturity, and region.

BWSs are commonly encountered in rural and suburban areas, typically in barns, garages, and woodpiles. Their irregularly shaped webs are usually spun in solitary environments, typically from the underside of low-level structures (e.g., a bench). The spiders can be found anywhere, however, and some species are arboreal. The female's larger size, up to 15 mm in body length with a 40-mm leg span, allows for a larger envenomation apparatus compared to the male, whose fangs and venom glands are often too small to penetrate human skin (2).

The active protein in *Latrodectus* venom (alpha-latrotoxin) is a potent neurotoxin, leading to the release of neurotransmitters (including acetylcholine and norepinephrine) at neuromuscular, central, and pancreatic synapses (3).

The *Latrodectus* spiders share a variety of venom components that are specific to different prey (i.e., vertebrates vs. crustaceans) (4,5). Furthermore, different envenomated species have significant differences in alpha-latrotoxin susceptibility and LD50, resulting in different clinical effects (1). Although research into the exact mechanism continues, it appears that alpha-latrotoxin utilizes several presynaptic membrane receptors and regulatory pathways to initiate exocytosis of secretory vesicles, with or without calcium involvement. In addition, the toxin forms membrane pores that disrupt neuronal membrane potential through ion exchange and compromised cell integrity (3,5).

Differences in venom structure and lethality depend on *Latrodectus* species, geographic location, and season, which may be important in human envenomations (5). A brown widow spider envenomation, for example, appears to be less toxic. BWSs may be able to control the amount of venom injected, another factor explaining the variance in clinical effects.

Latrodectism, defined as systemic effects from a BWS envenomation, affects thousands of patients each year and is the most important spider-related medical issue worldwide (1). Deaths worldwide from BWS bites are reported sporadically but previous estimated mortality rates of 10% are most likely overestimated due to selection bias or cases occurring prior to the development of antivenom. Each year, US poison control centers receive approximately 2,400 reports of suspected human BWS envenomations, but there has not been a reported fatality in the United States for over 25 years.

CLINICAL PRESENTATION

Envenomations typically occur from defensive bites and are more common in warmer, summer months. Males appear to be bitten

more often, and approximately 75% of bites occur on extremities (1,6). Reports of bites to the genitalia are historically related to the use of outdoor toilets but are now very rare.

The initial bite of a BWS is usually described as a sharp, transient pinprick or burning sensation but may go unrecognized. The bite site may reveal two small puncture wounds with minimal erythema or inflammation. A pathognomonic "target lesion" is commonly found, described as an erythematous ring, 2 to 6 cm in diameter, with a pale center at the bite site (7). This lesion usually develops within 2 hours of the envenomation and can last up to 24 hours, with varying degrees of tenderness. Other signs and symptoms typically begin within 30 to 120 minutes of the envenomation. A severe envenomation will progress from local to systemic symptoms that can include diffuse pain, muscle cramps (typically of the abdomen or back), tachycardia, and hypertension. Diaphoresis and piloerection can occur, sometimes isolated to the bite site (Table 372.1).

TABLE 372.1
Latrodectism

Pain
Muscle cramps
Abdominal rigidity
Headache
Restlessness
Diaphoresis
Nausea

Additional signs and symptoms include nausea, headache, fever, tremor, and weakness. Rarely reported signs are periorbital edema or ecchymosis, priapism, cardiac dysrhythmias (including reflex bradycardia), paralysis, myocardial ischemia, regional lymph node tenderness, and compartment syndrome. Herpes zoster and Horner syndrome have been reported after BWS envenomation, though causality has not been established. Young children may simply

present with inconsolable crying or restlessness. The onset of symptoms occurs about 1 hour after the bite (immediate to 12 hours) and, if untreated, wanes over several days. Symptoms peak within several hours but can be delayed for up to 24 hours. There are reports of symptoms lasting months.

In several case series of BWS envenomations the top three complaints most patients report are pain at the bite site (38% to 79%), abdominal pain (56% to 71%), and chest pain (17% to 30%). In a small case series of brown widow spider bites, pain at the bite site predominated at 93% of patients with systemic symptoms less likely (8).

The associated catecholamine surge can compromise patients at the extremes of age or those with significant underlying cardiopulmonary disease. Myocarditis with EKG changes, pulmonary edema, elevated troponins, and hypotension, has been reported (9). Pregnant patients may be at risk for uterine contraction, preeclampsia-like manifestations, and fetal complications (10). A series of 97 pregnant patients bitten by BWSs did not reveal any fetal loss (11).

DIFFERENTIAL DIAGNOSIS AND ED EVALUATION

BWS envenomation may be confused with any acute pain syndrome, such as acute coronary syndrome or an acute abdomen, where it can be confused with appendicitis and other surgical emergencies. Other, unwitnessed arthropod (hymenoptera, scorpion) or rattlesnake envenomations can mimic the associated signs or symptoms. Inconsolable crying in a child, particularly while playing or getting dressed (i.e., putting on shoes) outside, should raise the suspicion of an envenomation.

There is no diagnostic test to confirm a BWS envenomation, so a careful history, including activity just prior to the onset of symptoms, may aid in making the diagnosis. Leukocytosis and an elevated serum creatine kinase (CK), though nonspecific, are the most commonly reported laboratory abnormalities (1). Elevated CK, cramps, and diffuse myalgia may suggest rhabdomyolysis. Other

signs, such as fever (infection), roving eye movements with a tender bite site (scorpion sting), or gross hematuria (urolithiasis) suggest other acute clinical entities. Finally, a significant BWS envenomation may present with little, if any, objective clinical evidence, allowing patients with drug-seeking behavior to use this chief complaint when requesting narcotics or benzodiazepines.

KEY TESTING

There is no diagnostic test for the diagnosis or confirmation of BWS bites.

ED MANAGEMENT

After addressing the patient's airway and cardiovascular status, attention should focus on pain relief. Patients with mild-to-moderate discomfort should be offered oral opioid analgesics to manage the resolving pain over 24 to 48 hours. Those patients with significant pain should be treated with IV opioids, such as morphine or fentanyl, in titrated doses, and if necessary, a benzodiazepine, such as lorazepam, may be useful for agitation and anxiety. Effective amounts can vary tremendously; specific dosing should take into account the patient's weight, mental status, and comorbidities.

There are several equine-derived *Latrodectus* antivenoms, each targeted against the venom of one species. In the United States, the antivenom (Merck & Co., Inc.) is targeted against *L. mactans,* yet it is effective in treating envenomation from all North American species (12). This antivenom is available on a limited basis from the manufacturer but there is no indication whether it will continue to be manufactured. The presence of the common active venom component (alpha-latrotoxin) in all species allows for clinically useful cross-neutralization of venoms between different antivenoms, even those from different continents (13).

There are significant differences in experiences and recommendations for the use of antivenoms throughout the world (1,6,12,14,15). These differences are based on the *Latrodectus* species, patient presentation, antivenom, and physician training and

experience (especially for the use of *L. mactans* antivenom in the United States). The use of antivenom should be reserved for patients with severe pain or profound hypertension uncontrolled with opioids and benzodiazepines. A lower threshold for use is indicated for pregnant patients, particularly those with evidence of fetal distress, and patients with known cardiac disease and uncontrolled hypertension. The decision to treat with antivenom should be made as soon as possible, yet there are reports of (varying) effective antivenom use weeks to months after the reported envenomation.

A known allergy to the antivenom or horse serum (other equine-derived antivenoms) is a contraindication to its use. Relative contraindications include a history of severe allergic reactions, severe reactive airway disease (increased risk of anaphylaxis), and the use of a beta-blocker (may hinder the management of anaphylaxis). Decision making should take these risks into account. Anaphylaxis and death from the use of *L. mactans* antivenom are rare but reported (16,17).

An antivenom, commercially available in Mexico, called Antivenin Latrodectus (Black Widow) Equine Immune F(ab)2 (*Analatro*) is available as a clinical trial drug in the United States. This purified F(ab)2 is less immunogenic so the side effect profile is more favorable than the current FDA-approved antivenom and effectiveness of the antivenom is promising (18).

As with all antivenom administration, the patient should be in a closely monitored setting, have established IV access, and have a physician available at all times. Epinephrine, steroids, and antihistamines should be at the bedside in the rare case of an antivenom reaction. The manufacturer recommends routine skin testing; however, this procedure is neither sensitive for identifying patients at risk for allergic reaction nor safe from potential allergic reactions. A single vial of antivenom should be reconstituted in 50 to 100 mL of solution and administered IV over 30 minutes. Symptoms typically begin to resolve within 30 minutes, with complete relief within 2 hours. Rarely is the administration of a second vial required.

Patients with adequate analgesia but uncontrolled hypertension should be treated with an antihypertensive medication, preferably an infused short-acting agent that can be tapered as vital signs normalize. Beta-blockers, though used successfully, should not be used if antivenom administration is being considered, to minimize the theoretical risk of complicating an allergic reaction. Though once considered to be first-line agents, the use of IV calcium or "muscle-relaxants" is not supported by objective evidence and is no longer recommended.

Patients with severe, prolonged pain and myalgia may be at risk for rhabdomyolysis. Serum CK and urine output should be monitored.

Frequent reassessment is the key to rapid, effective pain control. Ultimately, the use of antivenom or the dosing of opioids and benzodiazepines are best determined by the patient's presentation, response to initial therapy, mental status, and vital signs. For those unfamiliar with spider bites, consulting a poison center (800-222-1222) may be helpful.

CRITICAL INTERVENTIONS

- Opioid analgesia for pain
- Benzodiazepines for anxiolysis
- Short-acting antihypertensive agents as necessary
- Antivenom with anaphylaxis precautions

DISPOSITION

Asymptomatic patients with a history or suspicion of BWS envenomation can be discharged to home after an observation period of at least 3 hours. Tetanus immunization should be offered, but prophylactic antibiotics are not indicated. Follow-up instructions should include monitoring for signs of infection.

Patients with mild symptoms typically respond well to oral analgesics, but one should consider the early use of parenteral medications for those with more significant pain. If the presenting pain and discomfort are rapidly relieved with initial IV medications,

a trial of oral medications is justified. However, the patient should be monitored for continued relief by oral analgesics prior to discharge.

Patients with severe symptoms requiring repeated administrations of parenteral analgesics or sedatives, or those with complicating medical conditions (i.e., cardiac disease, malignant hypertension, pregnancy) should be observed longer or admitted. Some patients may benefit from a patient-controlled analgesia pump.

Patients receiving antivenom can be discharged home after several hours of observation if they are asymptomatic and without evidence of anaphylaxis. They should be instructed about the signs and symptoms of serum sickness (malaise, myalgia, rash, and pruritus) and the need for follow-up if they occur. Serum sickness is treated with a tapering dose of oral steroids in most cases. The incidence of BWS antivenom-induced anaphylaxis and serum sickness is not known but appears to be low (2,6,14,18). Patients who receive antivenom should be counseled that they are at risk for anaphylaxis if reexposed to horse serum–containing medications.

Common Pitfalls

- Failing to consider the diagnosis, particularly in a patient with unexplained pain, muscle cramps, tachycardia, and hypertension.
- Using muscle relaxant or IV calcium for muscle spasms.
- Providing inadequate doses of analgesics and benzodiazepines for severe pain.
- Risking severe anaphylaxis with the inappropriate use of antivenom
- Failing to address other medical issues (such as fetal compromise, rhabdomyolysis, or hypertensive emergency) related to black widow envenomation.

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CHAPTER 373

Brown Recluse Spider Envenomation

Dan Quan and Timothy Davie

Spiders of the genus *Loxosceles* are distributed throughout the world. *L. reclusa,* the brown recluse spider (BRS) and most important of these species in the United States, is most common in the southern Midwest states. Depending on the temperature, it prefers living outdoors (under rocks, woodpiles, and debris) or in structures (basements, attics, and storage areas). The name *reclusa* describes its behavior: It is nocturnal, avoids areas of activity, hides its web, and is seldom seen. The spiders are most often encountered from May to August (1). Bites may occur anywhere on the body, but are rare unless the spider is disturbed or threatened. Most victims are bitten while asleep, dressing, or working in the yard or house, and they may not initially be aware that envenomation has occurred.

L. reclusa is fawn to dark brown and has, on its dorsal cephalothorax, a violin- or fiddle-shaped, dark brown marking with the larger end toward the head. The body of a large spider will measure 1 cm in length by 0.5 cm in width. The short-haired abdomen is oval, and the legs are long and slender, measuring 1 to 5 cm. Three pairs of eyes, rather than four, is a distinctive but not unique feature of this genus. Although all Loxosceles species are often called *brown, violin,* or *fiddleback* spiders, the recognized common name *brown recluse* should be reserved only for *L. reclusa.*

Loxosceles venom contains at least 11 components, mostly enzymes with cytotoxic activity (e.g., protease, *S*-ribonucleotide phosphohydrolase, hyaluronidase, collagenase, esterase,

sphingomyelinase-D), which cause both local and systemic toxicity (2–4). Dermonecrosis is caused by endothelial cell damage by venom and ischemia secondary to thrombosis, inflammation caused by leukocyte infiltration, hemolysis, complement activation, and intravascular coagulation (5).

CLINICAL PRESENTATION

Most bites from the BRS have a benign clinical course. Cutaneous (necrotic arachnidism) and systemic toxicity (visceral loxoscelism) may occur, and the systemic reaction is not necessarily proportional to the local reaction. Systemic symptoms may develop before a necrotic lesion appears. Severity relates to the amount of venom injected, the bite location, and the victim's immune status. Children and debilitated victims are at greater risk for severe reaction, but the elderly are often asymptomatic, possibly because of immunity that developed from earlier bites in their lives. Children are more susceptible to severe systemic loxoscelism because of venom dose relative to body size. There is no clinical evidence that risk is greater during pregnancy.

Typically, the bite itself feels like a pinprick that, in a few hours, may itch, tingle, swell, become tender, red, or blanch and has a gravitational spreading. Frequently, a blister or purpuric lesion, or both, form. Necrosis with induration and eschar formation may occur within hours or as late as 2 weeks after the bite. The eschar then falls off, leaving an ulceration that may take months to heal. The most severe necrotic lesions occur in fatty areas such as the abdomen, thighs, and buttocks (6). Occasionally, an erythematous or violaceous reaction at the bite site, surrounded by a ring of pallor ("halo," "target," or "bull's eye" lesion), may be seen soon after envenomation. Vast edema may occur at the general bite site, especially on the neck and face. Angioedema of the airway may be life-threatening (7). The inflammatory reaction (pain, redness, induration, swelling, fever, lymphangitis, and leukocytosis) can be severe. A rarely seen immunodermatologic sequela of loxoscelism in adults is pyoderma gangrenosum with recurrent deep ulcerations.

Systemic effects develop within hours after the bite and include fever, chills, headache, malaise, weakness, nausea, vomiting, arthralgia, myalgia, and rash. These signs and symptoms progress for 48 to 72 hours and then resolve over another 24 to 48 hours. Laboratory findings may include anemia, thrombocytopenia, leukocytosis, hemolysis, and consumptive coagulopathy. Hemolysis may directly result in hemoglobinuria, renal failure, jaundice, and shock or indirectly cause congestive heart failure, coma, convulsions, and death (6). There are a variety of rash presentations. The more common scarlatiniform rash may appear within days and persist a few days. This pruritic scarlatiniform-like eruption represents a toxigenic erythroderma reaction to the venom rather than a *Streptococcus* or *Staphylococcus* infection. Because the spider does not transport bacteria, early infection is very unlikely. Cellulitis, bacteremia, or sepsis, is secondary to the victim's own flora (usually staph or strep). Envenomation may cause toxic hepatitis, pancreatitis, hematuria, and cardiac manifestations. Death, although rare, has occurred from multisystem organ failure, especially in young children (7).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes bites and stings from several other arthropods and many medical conditions (Table 373.1). "Spider bite" is overdiagnosed. It is controversial whether the other species of spiders in the United States cause necrosis, although there may be specific regional differences (6). Although there are other species of *Loxosceles* spiders in the United States, especially in the Southwest, their venom is less potent, so the dermal reaction and systemic effects are less severe. Erythema that evolves into a violaceous macule distinguishes a necrotic from a nonnecrotic bite. In addition, as the macule widens, the edge becomes irregular and the center sinks below skin level. In contrast, nonnecrotic lesions remain edematous, raised, and red (5). The diagnosis often becomes clear only in retrospect. There are only a few other natural toxins that cause hemolysis and possibly dermonecrosis (see Table 373.1)

(7). Unless an offending spider is positively identified, a more generic diagnosis such as "cutaneous necrosis," "necrotic arachnidism," or "necrotic arthropod bite or sting" should be used.

TABLE 373.1
Differential Diagnoses of Loxoscelism

Bites/stings from many marine, flying, and crawling creatures causing dermonecrosis
Suspected spiders in the United States: Argiope (orb weaver), Chiracanthium (running or sac spider), Loxosceles genera (fiddle or violin), Lycosa (wolf spider), Phidippus (jumping spider), Tegenaria agrestis (northwestern brown spider or hobo spider)
Dermatoses of many types
Stevens–Johnson syndrome, polyarteritis nodosa, sporotrichosis, lymphomatoid papulosis, purpura fulminans, erythema multiforme, toxic epidermal necrolysis, fixed drug and anticoagulant reactions, ecthyma gangrenosum, orf, herpetic whitlow, pyoderma gangrenosum
Medical conditions causing dermonecrosis
Emboli/thrombi, vasculitis/angiitis/periarteritis, frostbite, thermal injury, ischemic vascular ulcers, fat infarction, factitious ulcers (self-inflicted), foreign bodies, infectious hemorrhagic lesions (gonococcal, anthrax, zoster, pox), traumatic lesions, neoplasms, cryoglobulinemia
Other natural toxins causing hemolysis (and possibly dermonecrosis)
Coelenterata (Portuguese man-of-war jellyfish), hymenoptera (bees, wasps, fire ants, etc.), snakes (rattlesnakes, cobra, viper venoms), infections (Clostridium, Streptococcal/Staphylococcal)
Medical conditions causing hemolysis
Hereditary hemolytic anemias
Acquired hemolytic anemia
Autoimmune conditions caused by medications (methyldopa, penicillin, quinidine), underlying diseases, idiopathic
Nonimmune conditions caused by microangiopathic disorders, medications (nitrofurantoin, sulfonamides), chemicals (heavy metals), cardiac valve prostheses, physical agents (lightning, fresh-water drowning)

Source: Modified from Wasserman GS. Brown recluse and other necrotizing spiders. In: Ford MD, Delaney KA, Ling LJ, et al., eds. *Clinical Toxicology*. Philadelphia, PA: W.B. Saunders; 2001: 878–881.

ED EVALUATION

The history should include timing and circumstances of a lesion, description of the spider (seldom known), and progression of signs

and symptoms. The skin should be examined closely for typical lesions and a delayed rash in patients with acute hemolysis and/or coagulopathy of unknown etiology. The general examination should focus on vital signs, skin, musculoskeletal, and neurologic function.

All patients with suspicion of BRS envenomation should have a baseline complete blood count and urinalysis. Those with suspected hemolysis or significant systemic reactions should have plasma-free hemoglobin levels, coagulation studies including fibrinogen, and *d*-dimer measurement. Other helpful tests include liver function studies, renal function studies (electrolytes), lactase dehydrogenase (LDH), and serum amylase/lipase and rarely serum haptoglobin level/haptoglobin–binding capacity, biopsy, culture, or Gram stain. Inflammatory markers are almost always elevated. Hemolysis may be intravascular and/or extravascular. Extravascular hemolysis is not detected by finding hemoglobin in blood or urine and should be considered in any patient with a falling hemoglobin/hematocrit and elevated LDH or reticulocyte count. Several immunoassay tests have been developed to identify *Loxosceles* venom but are currently only research tools (6,8,9).

KEY TESTING

- Tests for hemolysis and coagulopathy include CBC, UA, plasma-free hemoglobin levels, fibrinogen, LDH, and blood type and cross
- Tests for supportive care as needed include liver and renal function, and amylase

ED MANAGEMENT

Treatment of necrotic arachnidism should be the same, regardless of the specific species of spider. A "benign neglect" approach nearly always results in an excellent dermal outcome. It is impossible to make an early prediction about which bite will result in a disfiguring lesion. General wound care usually suffices and includes tetanus prophylaxis, cleansing, and topical antibiotics. Corticosteroids injected locally or systemically and vasodilators

have not proven helpful in preventing or decreasing dermonecrosis (5). Routine antibiotics are not needed initially but may be indicated for secondary bacterial infection. Antipruritic or antianxiety drugs and cool compresses are often comforting (avoid heat, because it may stimulate a toxin-produced cascade of inflammatory reactants) (7). The bite site should be protected from further trauma, but immobilization is not necessary.

Analgesics can be given for pain, but drugs that affect platelet functioning are contraindicated because of possible bleeding problems. Early wide excision is ineffective, unnecessary, and expensive; produces complications, potentially allows venom to penetrate deeper into tissues and may cause disability or worsen scarring. Trimming rapidly enlarging bullae seems to stop their progression but does not necessarily reduce the risk of necrosis within the blister borders (7). Corrective surgery should be delayed for 4 to 8 weeks or longer, until necrosis is clearly demarcated (6). Necrotizing fasciitis or abscess warrants surgical intervention.

The treatment of systemic arachnidism consists mainly of aggressive symptomatic and supportive care. Corticosteroids (methylprednisolone, or equivalent, 1 to 2 mg/kg IV loading dose followed by 0.5 to 1 mg/kg IV every 6 hours) for 3 to 7 days ameliorate hemolysis, and a tapering dosage schedule can be used as necessary. Aggressive hydration can prevent acute renal tubular necrosis due to hemoglobinuria. Anemia and thrombocytopenia should be treated with component therapy (e.g., packed red cells, platelets), as needed. Complement in cryoprecipitate and fresh-frozen plasma reacts with venom components and contributes to further red blood cell destruction, so these products are not recommended (4,10). Blood type and screen/cross-match may be difficult because of interfering antibodies. In severe cases, newer coagulopathy therapies such as antithrombin III or recombinant factor VIIa may be useful.

Though early literature suggested that a polymorphonuclear leukocyte inhibitor such as dapsone may prevent ulceration if started early, there is no evidence supporting dapsone’s effectiveness in preventing dermonecrosis. Dapsone has potentially adverse

effects in patients with glucose-6-phosphate dehydrogenase deficiency hemolysis, methemoglobinemia, super infection, leukopenia, rash, toxic epidermal necrolysis and is especially dangerous for children.

Other treatments such as hyperbaric oxygen, colchicine, and triamcinolone have not been shown to be beneficial or effective. In animal studies, there is some evidence that tetracycline may be effective in the treatment of cutaneous loxoscelism by inhibiting matrix metalloproteinases (11). Although experimental antivenoms have been produced, they are not commercially available in the United States (12).

CRITICAL INTERVENTIONS

- Perform standard wound care for necrotic skin lesions.
- Perform serial clinical and laboratory assessments to rule out systemic toxicity.
- Treat hemolysis with high-dose parenteral corticosteroids, hydration, urine alkalinization, and packed red blood cell transfusion as needed.
- Avoid dapsone.

DISPOSITION

Patients who present immediately after a suspected spider bite should be followed as outpatients every 24 to 48 hours with at least a complete blood count and urine dipstick for 4 to 5 days after the bite. Patients who present with or develop large dermonecrosis or ulceration should be referred to a wound care surgeon for follow-up. Patients with significant systemic symptoms or hematologic abnormalities should be admitted for treatment and monitoring progression. Physicians unfamiliar with arachnidism should consult a regional poison control center or toxicologist for advice. Those hospitalized and having a benign course with stable physical and laboratory evaluations for 4 to 5 days can be discharged with follow-up in 2 to 3 days. Liberal admission for observation may be

prudent in very young or debilitated patients and in those judged to be unreliable regarding follow-up.

Common Pitfalls

- Diagnosing "BRS bite" rather than "necrotic arthropod bite/sting" or "necrotic skin lesion" when positive identification of the offending creature has not been made and alternative diagnoses have not been fully considered.
- Failure to appreciate that hemolysis secondary to *L. reclusa* envenomation may be rapid or insidious in onset and be intravascular and/or extravascular.
- Failure to perform laboratory evaluations on patients with signs and symptoms, especially skin lesions, highly suspicious for loxoscelism.
- Failure to discuss to warn patients about potential but unpredictable complications such as hemolysis, coagulopathies, secondary infections, and delayed wound healing and to arrange for follow-up.
- Overly aggressive early debridement of skin lesions.

ACKNOWLEDGMENT

The author thanks Gary S. Wasserman, MD for his contribution to previous editions of this chapter.

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CHAPTER 374 Insect, Tick, and Mite Bites and Infestations

Michael James Burns

This chapter reviews the recognition and clinical management of bites and infestations associated with arthropods that are members of Class *Insecta* (*Hexapoda*) (insects) and Class *Arachnida,* subclass *Acari* (ticks and mites). Exposure to these arthropods may result in minor annoying local reactions, systemic allergic reactions, secondary bacterial infections, and the transmission of a host of serious systemic infectious diseases.

BIOLOGY, GENERAL DESCRIPTION, AND CLINICAL PRESENTATION

Arthropods are invertebrates having an exoskeleton, segmented bodies, jointed appendages, and bilateral symmetry (1). Insects have six legs and three distinct body regions—head, thorax, and abdomen —and include cockroaches, termites, lice, the true bugs (bedbugs, wheel bugs, assassin or kissing bugs), fleas, flies (which include mosquitoes), beetles, ants, wasps, bees, and others. Ticks and mites have eight legs as adults and nymphs, with one disk-shaped body region and no true head. Tick and mite larvae have six or fewer legs. Adult ticks are pea-size, whereas nymphal ticks and adult mites are about the size of a grain of sand or smaller. The arthropods most important to humans are hematophagous, meaning they must feed on warm-blooded vertebrates for blood or tissue fluid, with mouthparts that are designed for probing and sucking blood and

tissue fluids and saliva that contains substances that counteract host hemostasis.

Skin lesions from arthropod bites include wheals, papules, vesicles, and blisters which are produced by hypersensitivity reactions to salivary components or venom (1,2). Secondary bacterial infections can occur, and late cutaneous allergic responses may occur in atopic individuals and be confused with many infectious and noninfectious conditions.

BEDBUGS

Bedbugs (*Cimex lectularius*) are blood-sucking reddish-brown wingless insects about 5 mm long (adults), oval and flattened, smell like rotten raspberries, and can survive for long periods without feeding (1,3,4). The nymphal stages are smaller and also take blood meals. Except when venturing out to bite, they remain hidden on and in mattresses and in cracks and crevices of walls and floors near beds. Feeding is painless, occurs at night, and takes only 5 to 10 minutes, during which anticoagulants and vasodilators are injected. They often leave black specks on sheets and mattresses, a mix of feces, and heme. Common in tropical and underdeveloped countries, bedbug infestations have increased greatly in North America and Europe, not only in homeless shelters and places of overcrowding but in apartments, single-family homes, and upscale hotels. They are not known to transmit any disease. Bites may produce allergic reactions or no reaction at all. The typical presentation consists of extremely pruritic red papules or vesicles, sometimes painful, often in a linear or clustered pattern, most concentrated on skin that is exposed while sleeping. Anaphylaxis and urticarial and bullous lesions may occur. The rash is usually responsive to topical corticosteroids and oral antihistamines. Bedbugs are extremely difficult to eradicate. Resistance to insecticides is common. Excessive use of insecticides for treating bed bug infestations, usually pyrethroids and pyrethrins, their use contrary to label directions, failure to wash or change pesticide-treated bedding, and inadequate notification of pesticide application can cause human toxicity in the United States. The most

frequent manifestations of toxicity are headache, dizziness, respiratory tract irritation, dyspnea, nausea, and vomiting (5).

CONENOSE OR KISSING BUGS

Triatomine insects (Hemiptera, Reduviidae), commonly known as conenose, kissing, assassin, or reduviid bugs, are 1 to 3 cm long, brown or black, and good fliers (1,6). They are widely distributed in the western and southwestern United States, Mexico, and Central and South America. Usually found in the wild, they can adapt to live in cracks and holes of substandard dwellings and come out at night to feed on human blood. Their bites are usually painless, but allergic reactions to their bites can result in papular or nodular lesions and even anaphylaxis. They have been reported to be a common cause of anaphylaxis of unknown etiology in children living in endemic areas of the United States (7). Some species can produce intensely painful bites with marked swelling at the bite site. Several members of this group (*Triatoma, Rhodnius*) transmit the protozoan parasite *Trypanosoma cruzi* (causative agent of American trypanosomiasis or Chagas disease) to humans. These insects are plentiful in southern Arizona and southern California and a high proportion in these regions have been found to be infected with *T. cruzi* (8). Wheel bugs (*Arilus cristatus*) are true bugs that bite humans only in self-defense (1). They are 3 cm long and gray, have a small narrow head and a cogwheel-like crest on their thorax, and are found in the southern United States. The bite causes immediate intense pain with swelling and inflammation, but they do not transmit any diseases. Blister beetles are large plant-feeding insects, commonly found in the southeastern, central, and southwestern United States, whose body fluids produce large painless blisters within a few hours after contact with live or dead beetles (1). Mild tingling or burning can occur prior to onset of blistering. The blisters are usually not serious and resolve within several days. Ingestion of beetles or their products may cause vomiting, abdominal cramps, and diarrhea.

CATERPILLARS AND CENTIPEDES

Some caterpillars have urticating hairs or spines that secrete a toxin when exposed to human skin, causing a burning sensation, swelling, numbness, or intense stabbing pain (1). Other caterpillars may cause a self-limited, pruritic, papular dermatitis after the skin comes in contact with hairs of the caterpillars. Outbreaks of caterpillar dermatitis have been reported among children at childcare facilities, and are frequently misdiagnosed by physicians as varicella, scabies, flea bites, mosquito bites, contact dermatitis, viral exanthems, and methicillin-resistant *Staphylococcus aureus* MRSA infections (9). Because the hairs or spines can remain embedded in the skin, repeated application of adhesive tape at the site to remove the spines may be needed, in addition to cold compresses, topical corticosteroids, and oral antihistamines.

Centipedes (Class *Chilopoda*), which are not insects or arachnids, can cause a painful "bite," which can become red and swollen (1). The bite is produced and injected by sharp claws on their first pair of legs, which have attached venom glands. Treatment includes washing with soap and water, applying cool compresses, and oral analgesics, with anecdotal benefit after immersing the area in hot water.

FLEAS

Fleas feed exclusively on blood (1). The cat flea (*Ctenocephalides felis*), which also infests dogs and other mammals, is the predominant flea species in North America. Fleas, which are wingless and cannot fly, are easily recognized by their jumping behavior. Fleabites in humans cause allergic reactions and result in clusters or irregular groups of several to a dozen or more where the flea has explored and probed. In the allergic person, a pruritic wheal forms around each probe site within 5 to 30 minutes. Indurated papules and occasionally vesicular or bullous lesions develop within 12 to 24 hours, accompanied by intense itching, and may last a week or more. Fleas can transmit plague (*Yersinia pestis*), murine/endemic typhus (*Rickettsia typhi* and *Rickettsia felis*), and cat-scratch disease (*Bartonella henselae*). Children who ingest fleas containing the larval stage of the dog and cat tapeworm, *Dipylidium caninum,* may become

infected with the adult tapeworm. The small female chigoe flea, *Tunga penetrans,* burrows into the skin of persons living or traveling in tropical and subtropical areas of North and South America, the West Indies, and Africa, producing a disorder known as *tungiasis.* It grows to about 1 cm within 2 weeks and lays eggs beneath the dermis. It commonly infests the legs and feet, including the areas between the toes or under the toenails, and produces intense inflammation and itching. One sees a black dot in the center of a pustule. These are surgically removed by widening the cavity and removing the flea intact.

FLIES, GNATS, MOSQUITOES

Black flies are smaller than mosquitoes, travel in large swarms, and are vicious biters (1). Allergic reactions to the bites result in red itchy papules and nodules with surrounding swelling and occasionally systemic allergic reactions with fever, wheezing, and diffuse urticaria. Deer and horse flies are large flies whose bites produce deep, painful wounds that often become secondarily infected (1). Bite lesions are solitary or scattered, not grouped or linear. Local and systemic allergic reactions can occur. Stable fly bites produce small papular lesions. Biting midges, sometimes called "no-see-ums" or "biting gnats," are fierce biters and are so small that they can pass through ordinary screens. Their bites produce small papular lesions with red halos and wheals. Deer flies can transmit tularemia, but black, horse, and stable flies and biting midges do not transmit any diseases in North America.

Mosquito bites can result in allergic reactions, producing multiple, scattered lesions that are not linear or grouped (1). A wheal and flare may be seen 30 minutes after the bite, and delayed onset of pruritic papules is common. Mosquitoes are the most important arthropod vectors of disease in the world because of their transmission of malaria, filariasis, yellow fever, dengue, West Nile, and other encephalitis viruses (10,11).

MAGGOTS

Myiasis is an invasion or infestation by maggots, the larvae of two-winged flies (*Diptera*), and is most commonly found in debilitated or comatose persons, the homeless, alcoholics, those with peripheral vascular disease, or young children (1). It occurs when the female fly lays eggs near a wound or when the fly deposits freshly hatched larvae directly in a wound. The larvae of some fly species are able to penetrate skin and invade normal tissues, whereas others are capable of living only on the surface of the wound. Although usually occurring in wounds, myiasis can also occur in the nose, mouth, sinuses, eyes, anal region, vagina, and bladder. Myiasis is not contagious from person to person, as fly larvae are not capable of reproduction. Transmission occurs only via an adult female fly. Physical removal of each individual maggot, often surgically or by use of a large suction catheter, is the most effective treatment (1,12). If large numbers of maggots are found in a wound, soaking the area with vegetable oil followed by irrigation and then individual removal of remaining larvae may be effective. There are no medications or chemicals that will dislodge maggots. When exposed to a chemical insult, maggots retract into the wound, making it more difficult to remove them. Furuncular myiasis is produced by the larva of the human botfly (found in Mexico and Central and South America) and by the Tumbu fly (found in tropical Africa). The larvae burrow into host tissue, producing painful pruritic cutaneous nodules called *warbles,* each with a central opening or punctum. The person sometimes feels something moving. Visitors may acquire this disorder while traveling and return home before the maggot completes its development. These lesions are easily mistaken for staphylococcal boils. Furuncular myiasis is treated by surgical removal of the intact larvae or by applying petroleum jelly, suffocating the maggot, which may come wriggling out backward. “Bacon therapy” is also effective; the punctum is covered with raw meat, and in a few hours, the larvae migrate into the meat and are then easily extracted.

LICE AND MITES

Lice are tiny, elongate, soft-bodied, light-colored, wingless insects that feed on blood (1,13,14). Three species infest humans: (1) the human body louse (*Pediculus humanus corporis*), (2) the human head louse (*Pediculus humanus capitis*), and (3) the pubic or crab louse (*Phthirus pubis*). The body louse lives on clothing, lays its eggs (nits) on clothing, and leaves the clothing only to take a blood meal. It can transmit epidemic typhus (*Rickettsia prowazekii*), trench fever (*Bartonella quintana*), and louse-borne relapsing fever (*Borrelia recurrentis*). The head louse and pubic louse are not known to transmit any diseases. All lice are transmitted from person to person by close body contact, possibly by sharing of hats, combs, and brushes (head louse) or by sharing clothing (body louse). Humans infested with lice often develop itchy red papules with excoriated areas that can become secondarily infected. The adult lice are often difficult to see, but the nits of the head louse and pubic louse can be found attached on shafts of hair near the base. Head louse infestation is most common in white schoolgirls and affects all social and economic backgrounds. Pubic lice can sometimes be found in the eyebrows and eyelashes, in axillary hair, on the coarse trunk hairs of males and, rarely, in the scalp. Bluish-gray macules, known as *blue spots,* may sometimes be seen on the skin in pubic lice infestation. People infested with pubic lice often have other sexually transmitted diseases.

Mites look like tiny small hairy ticks, with one disk-shaped body segment and no true head. Many species bite humans that cause skin lesions from allergic reactions but the mites do not live on humans or their clothing (1). Chiggers is a condition caused by bites by the larvae of the chigger (or harvest) mite (Family *Trombiculidae*) (1). These mites are found in grasses and scrubs, especially at forest edges. Chigger mite larvae, which are tiny (0.2 mm long); round; and red, yellow, or orange in color, bite humans and inject saliva that dissolves host tissue, then feed on the dissolved tissue. Pruritic macules and wheals develop within 3 to 6 hours, followed by intensely pruritic papules and pustules at 10 to 16 hours. Lesions are often linear or grouped. Numerous other species of mites will bite humans, causing painful pruritic red papules. Persons bitten by

chicken mites and straw itch mites may have thousands of lesions. The tiny itch mite *Pyemotes herfsi* has recently caused outbreaks affecting thousands of people in Kansas, Nebraska, and Missouri; a person may have hundreds of bites resulting in a severe pruritic papular dermatitis. The house mouse mite transmits rickettsialpox (*Rickettsia akari*) to humans in the United States. Unlike the scabies mite, none of these mites live on humans.

SCABIES

Scabies, an infestation of the epidermis by *Sarcoptes scabiei* var. *hominis,* which spends its entire life on human skin, is transmitted by close body contact (15). The fertilized female mite, too small to see with the naked eye, burrows into the epidermis, and lays two to three eggs daily for 30 days (1). Larvae hatch in 3 to 4 days and migrate to the skin surface. Maturation from egg to adult takes about 10 to 14 days. The mites feed on cells of the stratum corneum. Their secretions and excretions sensitize the host and produce irritation and itching with pruritic crusted red papules, papulovesicles, pustules, and weeping eczematous lesions. Transmission is by direct skin-to-skin contact. Transmission by infested bedding, towels, or clothing is uncommon except in the case of crusted (hyperinfestation) scabies. The incubation period after infestation until symptoms appear is about 3 to 6 weeks for a first infestation but may be much shorter (as little as 48 hours) in recurrent infestations. A person may be very contagious before any symptoms or lesions even occur. There are 5 to 20 mites on the body in a typical infestation, usually found in burrows on the hands, wrists, elbows, knees, beltline, penis, the breasts of females, and the feet of children, but they are especially common in the webs of the fingers and the folds of the wrists. In infants, lesions are frequently found on the scalp, face, palms, and soles. Burrows are often difficult to find. Itching commonly occurs in locations where there are no mites present. Extensive excoriations and secondary bacterial infections can cause puzzling skin lesions. Diagnosis is made by gentle scraping of the burrows with a scalpel blade covered with mineral oil. The mineral oil and scraped material are transferred to a glass slide, a

coverslip is applied, and the slide is examined under a microscope for mites, eggs, or feces. Persons who are immunocompromised (e.g., AIDS) or debilitated (especially elderly or institutionalized persons) may develop crusted hyperinfestation also called "Norwegian" scabies, in which hyperkeratotic crusted nodules and plaques become widespread on the body. Millions of mites may be present in this condition, making it extremely contagious. It is easily misdiagnosed as eczema or another condition. Other closely related scabies mites infest domestic animals, especially dogs (sarcoptic mange). These mites can bite humans and produce pruritic papular lesions without burrows. They cannot complete their life cycle on humans, so no specific anti-scabies treatment is needed (1).

TICKS

Among the biting arthropods, ticks are second only to mosquitoes in the number of pathogens transmitted to humans. There are four stages in the life cycle: egg, larva, nymph, and adult. Even in highly endemic areas, ticks are not evenly distributed. *Ixodes scapularis* is most likely to be found in brushy areas at the interface between fields and forests (forest boundaries), whereas *Dermacentor variabilis* prefers meadows and roadsides. They "quest" for host animals by climbing vegetation (few inches to 3 ft) and passively wait for a host to pass by. Ticks cannot fly, jump, or swim. Larvae, nymphs, and adult females (but not adult males) increase in size enormously during feeding. They are capable of withstanding environmental stresses, and adults may live for several years. The soft-bodied ticks feed and engorge within a few minutes. The hard-bodied ticks attach for many days; once attached, feeding (and transmission of disease) may not begin for several days. When feeding, they excrete large amounts of saliva and feces containing pathogens. Tick bites are usually painless, and there is often no reaction at the bite site after the tick is removed or drops off. Sometimes, a hypersensitivity reaction to the bite occurs, or a red nodule may persist at the bite site for weeks to months (2).

I. scapularis (deer tick or black-legged tick), transmits Lyme disease (*Borrelia burgdorferi*), anaplasmosis (*Anaplasma phagocytophilum,* a

rickettsia-like organism), babesiosis (*Babesia microti,* a malaria-like protozoan), and Powassan disease (a type of viral encephalitis) to humans (1,16). Lyme disease is most common in the northeastern and upper Midwest United States because the primary host for the tick's nymphal stage in these regions, the white-footed mouse, is capable of high rates of spirochetemia and is an excellent transmitter to ticks. The nymph, not the adult tick, most often transmits Lyme disease to humans; the nymphs are more likely to remain attached undetected for long periods of time because of their small size (about the size of a poppy seed or the head of a pin). Adult ticks, which primarily feed on deer and are the size of an apple seed, are also capable of transmitting infection but are more easily seen and removed before disease transmission occurs. Lyme transmission requires >24 hours of attachment for nymphs and 36 hours for adults. *Ixodes pacificus* (western black-legged tick), found in the western United States, transmits Lyme disease (but infection rates in the tick are very low owing to their feeding behavior) and anaplasmosis. Both nymphal *I. scapularis* and *I. pacificus* ticks in the southern and western United States have very low rates of infection with the Lyme disease organism (1). They feed primarily on lizards, which are incapable of infecting ticks, and they rarely bite humans. Lyme transmission from *I. pacificus* requires >96 hours of attachment for nymphs. *D. variabilis* (American dog tick) transmits Rocky Mountain spotted fever (*Rickettsia rickettsii*) in the eastern United States, with disease transmission requiring >24 hours of attachment (1,16). Only adults feed on humans. Only 1% to 5% of ticks in an endemic area are infected with the rickettsial organism. This tick also transmits tularemia (*Francisella tularensis*) and can cause tick paralysis (owing to a neurotoxin secreted by the tick). For tick paralysis to develop, the tick must remain attached for at least 5 to 6 days. *Dermacentor andersoni* (Rocky Mountain wood tick) transmits Rocky Mountain spotted fever in the western United States, tularemia, and Colorado tick fever (*Coltivirus*) and can cause tick paralysis. *Amblyomma americanum* (Lone Star tick), whose primary host is the deer, transmits tularemia, ehrlichiosis (*Ehrlichia chaffeensis,* a rickettsia-like organism), and STARI ("Southern tick-

associated rash illness"), a newly described Lyme-like disease in the southeastern United States, whose cause is undetermined (1,16). People disrobing or lying on the ground in heavily infested wooded areas may be attacked in great numbers by larval *A. americanum* ticks, causing hundreds of pruritic papules (17). *Amblyomma maculatum* (Gulf coast tick), common in the southeastern United States, has been reported to transmit *Rickettsia parkeri,* a newly described spotted-fever-group rickettsia producing a mild febrile illness accompanied by multiple eschars and a maculopapular eruption (1,16). The brown dog tick, *Rhipicephalus sanguineus,* transmits Rocky Mountain spotted fever in eastern Arizona (16) Q fever (*Coxiella burnetii*) can be acquired from inhalation of dead tick parts or feces in dust.

Ixodes, Dermacentor, and *Amblyomma* spp. are all hard-bodied ticks, and prolonged attachment is required for feeding and disease transmission. Hard ticks will remain attached for 7 to 14 days before dropping off (1).

In contrast, soft-bodied *Argasidae* ticks of the genus *Ornithodoros* bite, feed, and drop off within a few minutes and prefer animal burrows or manmade animal or human shelters (1,16). Nymphs and adults transmit tick-borne relapsing fever (*Borrelia hermsii* and other spp.) in rodent-infested cabins in the high mountains of the western United States, Canada, and Mexico. Humans are bitten when they sleep in infested cabins.

Other tick species in the United States bite humans but do not transmit disease (1). Ticks in other parts of the world transmit a host of diseases that are important to travelers, including rickettsial diseases such as Boutonneuse fever and African tick bite fever, and arboviruses causing encephalitis and hemorrhagic fever (11).

Table 374.1 lists the biting arthropods of medical importance in North America, their geographic distribution, and the diseases they transmit.

TABLE 374.1
Diseases Transmitted by Biting Arthropods in North America

Arthropod	Geographic Distribution of Arthropod	Disease Transmitted
Conenose bugs ("kissing bugs")	Southwestern US, Mexico	American trypanosomiasis
Mosquitoes	Widespread	Malaria, Dengue, Chikungunya, Arbovirus encephalitides
Deer fly	Widespread	Tularemia
Fleas	Widespread	Plague, Murine (endemic) typhus, Cat-scratch disease
Human body louse (*Pediculus humanus corporis*)	Sporadic	Epidemic typhus, Trench fever
House mouse mite (*Liponyssoides sanguineus*)	Northeastern US	Rickettsialpox
Ixodes scapularis (Deer tick, black-legged tick)	Southeast, mid-Atlantic, northeast, upper Midwest US	Lyme disease, Anaplasmosis, Babesiosis, Powassan disease
Ixodes pacificus (Western black-legged tick)	Far western US and Canada	Lyme disease, Anaplasmosis
Dermacentor variabilis (American dog tick)	Eastern, Midwest US, Mexico	Rocky Mountain spotted fever, Tularemia, Tick paralysis (neurotoxin)
Dermacentor andersoni (Rocky Mountain wood tick)	Rocky Mountains of US and Canada, Great Basin of US	Rocky Mountain spotted fever, Tularemia, Colorado tick fever, Tick paralysis
Amblyomma americanum (Lone Star tick)	Southeastern, mid-Atlantic US	Ehrlichiosis, Tularemia, STARI "Southern tick-associated rash illness"
Amblyomma maculatum (Gulf coast tick)	Southeastern US	Spotted fever-like illness with eschars (*R. parkeri*)
Rhipicephalus sanguineus (Brown dog tick)	Widespread	Rocky Mountain spotted fever (eastern Arizona only)
Ornithodoros species (soft ticks)	Mountains of western US, Canada, and Mexico	Tick-borne relapsing fever (Borrelia spp.)

DIFFERENTIAL DIAGNOSIS

Reactions to arthropod bites are difficult to diagnose, as many patients may be unaware or cannot remember any exposure. The pruritic papules, vesicles, pustules, nodules, and bullae resulting from allergic reactions to arthropod bites may easily be misdiagnosed as allergic or irritant reactions to drugs or chemicals, atopic or contact dermatitis, *Herpes simplex,* staphylococcal and other bacterial infections, or cutaneous fungal infections (1,2). Multiple linear papules or vesicles should suggest bites by bedbugs or chigger mites, whereas irregular groups of papules and vesicles are typical for fleas and chiggers. Lesions caused by mosquitoes are multiple and scattered, not linear or grouped. A deer or horse fly bite that becomes secondarily infected and forms an ulcer could be misdiagnosed as a brown recluse spider bite. Arthropod bites and

infestations should also be considered in the differential diagnosis of any patient complaining of itching. “Insect bites” should generally not be diagnosed upon the basis of lesions alone. Scabies should be considered in the differential diagnosis of patients presenting with scattered pruritic papules, especially when found on the hands, wrists, elbows, and genital areas. Crusted “Norwegian” scabies should be considered in the differential diagnosis for immunosuppressed or debilitated patients presenting with subacute or chronic widespread hyperkeratotic plaques or eczematous lesions, even in the absence of pruritus. Scabies can easily be misdiagnosed as eczema, contact dermatitis, psoriasis, fungal infection, adverse drug reaction, senile pruritus of the elderly, “pruritus of AIDS,” and many other conditions.

An arthropod-borne infection should always be considered in the differential diagnosis of persons presenting with an acute febrile illness (10). The patient should be questioned about travel to endemic areas or outdoor exposures. Lyme disease or rickettsial infections may but not always, have a characteristic rash (11,16). Tick paralysis, which may be confused with Guillain–Barré syndrome, botulism, or spinal cord compression, presents initially with restlessness, irritability, paresthesias, and ataxia followed by rapidly progressive ascending flaccid paralysis, with a normal sensory examination, a clear sensorium, and lack of fever. Tick paralysis is especially likely in children and in girls, in whom the ticks are often concealed in long hair at the nape of the neck. Patients with pubic lice should be screened for sexually transmitted diseases.

Patients suffering from delusions of “parasitosis” have an unwarranted belief that live organisms, such as mites or insects, are present on the body (18,19). The typical patient is a well-educated, responsible, hard-working woman who may have an excessive preoccupation with cleanliness and has a single delusion and no other mental disorder. This belief often persists for many years despite numerous physician visits and repeated treatments of the house with pesticides and the patient by medication, usually physician-prescribed. Typical characteristics of the “bugs” include

that they change color; they jump; they appear and disappear while being watched; they enter the skin and reappear; they invade the hair; nose and ears; they infest the patient's hair, and can be combed or shaken onto a sheet or towel; and they sometimes come out of common household items (toothpaste, cosmetics) or teeth after brushing. Family members often support the patient but are never afflicted. Patients typically bring in samples of the supposed pest for examination, which consist of small bits of lint, cloth, dandruff, or scabs. These patients should be referred to a dermatologist to definitively rule out an infestation and to a psychiatrist, although the patients will generally not accept any suggestion that this is "all in their head." An entomologist may also need to be consulted (1). Delusions of parasitosis known as "cocaine bugs" may also be seen in persons abusing cocaine and amphetamines and in patients with schizophrenia, depression, anxiety disorders, and neurologic disorders.

ED EVALUATION

The emergency physician should be familiar with the biting insect, mite, and tick fauna in the local area. A complete history should include travel, outdoor activities, any known exposures to biting arthropods, and medications already used as these could affect or change the appearance of lesions (1). Patients complaining of itching or papules in the scalp or genital area should be asked about household or sexual contacts that may have head lice or pubic lice and should be examined carefully for adult lice and nits attached to the hair shafts. The skin should be examined carefully for evidence of bites, allergic reactions, secondary bacterial infections, burrows of scabies, or rashes typical for infections transmitted by arthropods.

KEY TESTING

- Skin scrapings for scabies
- Low power microscopic examination of suspected lice
- Serologic testing and stains for various virus, rickettsia, bacteria, and protozoa causing systemic illness
- Skin examination for embedded ticks

ED MANAGEMENT

Pruritic skin lesions should be treated with cold compresses, soothing lotions, topical corticosteroids, and systemic antihistamines. Systemic allergic reactions may require treatment with epinephrine, intravenous fluids, systemic corticosteroids, and antihistamines. Secondary bacterial infections, often seen with deer or horse fly bites or with excoriated mosquito or flea bites, are usually caused by *S. aureus* or *Streptococcus pyogenes* and should be treated with appropriate antimicrobial agents. A wound culture should be obtained for serious local infections, and empiric therapy for MRSA should be considered, and tetanus immunization should be given if needed. Patients who present with undifferentiated fever with or without generalized rash, rash without fever, or signs of encephalitis after an arthropod bite may require investigation for one of the many viral, rickettsial, or bacterial infections transmitted by these creatures (10,11).

Resistance of lice to topical pediculicides has increased dramatically (13,14). The Centers for Disease Control and Prevention recommends treatment of head lice only if live lice are detected or if nits are found attached to hair shafts less than one-quarter inch from the scalp (14). Of the topical agents available for treatment, malathion lotion 0.5% (not recommended in children younger than 2 years of age), and ivermectin lotion 0.5% (not recommended for children younger than 6 months of age), are the most effective; lindane is the least effective; and permethrin and pyrethrins are intermediate in effectiveness (20,21). If pyrethrins (combined with piperonyl butoxide) or permethrin lotion 1%, both available without prescription in the United States, are used, a second application should be done 7 to 10 days later. A second application of malathion may be needed 7 days later. Use of a fine-toothed comb on wet hair is recommended to remove nits. Lindane, which is banned in California, should be avoided because of neurotoxicity, high resistance rates, and the potential for contaminating the environment. Two other topical agents, benzyl alcohol lotion 5%, and spinosad suspension 0.9%, available by prescription only in the

United States, are also effective, but repeat treatments may be necessary. Oral ivermectin (not FDA-approved for this indication) is an alternative when topical treatments fail (22). Mechanical removal of lice with repeated wet combing every 3 to 4 days by parents is an alternative to malathion but is not nearly as effective. “Natural” herbal and chemical products marketed for treatment of lice are not effective and may be unsafe. Bedding, clothing, and towels used by the infested person in the 2 days prior to treatment should be washed and dried at high temperatures, dry cleaned, or kept in sealed plastic bags for 2 weeks. Household contacts of patients with head lice and sexual partners of those with pubic lice should be examined for lice and nits every 2 to 3 days and treated only if crawling lice or nits within one-quarter inch of the skin are found. Many schools routinely exclude children for head lice, but this practice is not recommended by the American Public Health Association.

Scabies should be treated with permethrin 5% cream applied to all areas of the body from the neck down and washed off after 8 to 14 hours, usually with a second treatment 1 week later recommended (15). Topical crotamiton 10% cream is safe for newborn babies and infants but is less effective than permethrin. Lindane-resistant scabies is now widespread in the United States. Ivermectin 200 μg/kg orally in a single dose for adults is effective in resistant cases, with a second dose 2 weeks later usually recommended (15,21,23). It is not FDA-approved for this indication, but its use is recommended by the Centers for Disease Control and Prevention, and by The Medical Letter, as an alternative agent. Crusted (“Norwegian”) scabies in debilitated or immunocompromised patients should be treated with topical keratolytic agents followed by repeated doses of total-body permethrin cream and oral ivermectin. An alternative treatment for pregnant and lactating women and children younger than 2 months is precipitated sulfur 6% in petrolatum, but there is little evidence for efficacy or safety. Itching may continue for up to 4 weeks after curative therapy and is not an indication for repeat treatment. Bedding, clothing, and towels used in the previous 48 to 72 hours should be washed and dried at high temperatures or dry cleaned or stored in sealed plastic bags for the same period of time.

The best method for preventing infection with tick-borne pathogens is to avoid exposure to ticks. If exposure is unavoidable, measures to reduce the risk of infection include the use of protective clothing and tick repellents, checking the entire body daily for ticks, and prompt removal of attached ticks. To remove an attached adult tick, the tick should be grasped with blunt curved forceps, narrow tweezers, or gloved fingers as close to the point of attachment as possible, then pulled firmly and steadily in the direction of attachment. Some back-and-forth motion may be needed, but the tick should not be twisted. If the tick's head breaks off in the skin, use tweezers to remove it. Disinfect the bite site and wash hands thoroughly. This method is most effective for the large adults of *Dermacentor* and *Amblyomma* tick species but may not be effective for adult *Ixodes* ticks or larval ticks of any species, which are much smaller. Application of viscous lidocaine 2% may be effective for these smaller adults or larval ticks. Application of isopropyl alcohol, petroleum jelly, a hot match, fingernail polish, or use of sharp forceps should be avoided, as this may cause the tick to salivate or regurgitate and increase the potential for disease transmission. Two other anecdotal methods of tick removal have been suggested: using a disposable razor to shave off the tick's body without squeezing the tick, and using cryospray with liquid nitrogen to instantly freeze the tick, then wiping it off or removing it in toto, but these methods and application of viscous lidocaine have not been subjected to clinical trials (24). An entomologist should be contacted if it is important to identify a tick or other biting arthropod that has bitten a person. The Centers for Disease Control and Prevention website on ticks at www.cdc.gov/ticks is an excellent resource on ticks found in the United States, including color pictures, geographic distributions, diseases transmitted by ticks, tick avoidance, tick removal methods, and tick life cycles.

Although some practicing physicians routinely prescribe antimicrobial agents to persons who have been bitten by ticks in areas highly endemic for Lyme disease, most experts believe that routine antimicrobial prophylaxis or serologic testing after a tick bite is not necessary (1,25). The risk of acquiring Lyme disease or any

other tick-borne infection after a tick bite is quite low, even in highly endemic areas. Doxycycline 200 mg orally in a single dose for adults may be effective in preventing Lyme disease in a highly endemic area if the tick is at least partially engorged or attached for greater than 72 hours. The Infectious Diseases Society of America recommends prophylaxis with single-dose doxycycline 200 mg for nonpregnant adults and children at least 8 years of age (4 mg/kg for children; maximum, 200 mg) only when all of the following are met: (a) The tick can be identified as an adult or nymphal *I. scapularis* tick that is likely to have been attached for >36 hours based on the degree of tick engorgement with blood or confidence about the time of exposure to the tick; (b) prophylaxis can be started within 72 hours of the time that the tick was removed; (c) the local rate of infection of ticks with *B. burgdorferi* is >20%; and (d) doxycycline is not contraindicated (25). Infection of >20% of ticks with *B. burgdorferi* is found in parts of New England, the mid-Atlantic states, Minnesota, and Wisconsin but is rare in other locations in the United States. Although amoxicillin is an effective treatment for early Lyme disease and is the preferred agent for pregnant women and children younger than age 8, there is no evidence that it is an effective preventive agent after a tick bite. There is no evidence that antimicrobial treatment is effective in preventing other tick-borne infections in the United States, and it is not recommended.

Tick paralysis is treated supportively. A rapid and complete recovery occurs after removal of the tick.

CRITICAL INTERVENTIONS

- Recognize that serious allergic reactions including anaphylaxis may be the result of arthropod bites, even when no arthropod was seen.
- Check the skin and scalp for ticks in patients with rapidly progressive ascending flaccid paralysis, particularly children and those with a normal sensory examination, clear sensorium, and no fever.
- Treat secondary bacterial infections with appropriate antimicrobials, with consideration for community-associated

MRSA.
- Institute infection control measures and offer treatment to those who have had close unprotected contact with patients with scabies.
- Consider an arthropod vector-borne disease in the differential diagnosis of an acute febrile illness in the appropriate circumstances, regardless of whether the patient has a rash or remembers a bite.

DISPOSITION

Almost all patients suffering from arthropod bites can be discharged unless they have life-threatening anaphylaxis or serious secondary bacterial infections of skin lesions or are suspected to have a serious arthropod-borne systemic infectious disease or tick paralysis. Patients should be advised to avoid tick-infested areas. If exposure is unavoidable, the use of protective clothing, wearing light-colored clothing (making it easier to spot ticks), daily inspections of the entire body with prompt removal of ticks, and application of tick and insect repellants to skin and clothing are recommended (1). Permethrin aerosol spray is very effective when used on clothing and tents but should not be applied to the skin. DEET is the most effective insect repellent that can be applied to the skin, and it repels a variety of mosquitoes, chiggers, ticks, fleas, and biting flies (1). Picaridin is an alternative effective insect repellent. Persons who have been bitten by ticks should be advised to promptly seek medical attention if they develop a fever or a skin lesion at the site of the bite up to 30 days later.

Common Pitfalls

- Failure to obtain a history of travel or exposure to environments where biting arthropods are present.
- Failure to recognize that an acute febrile illness, with or without generalized rash, may be caused by an arthropod vector-borne infection.

- Failure to screen for sexually transmitted diseases in persons with pubic lice.
- Misdiagnosis of scabies as eczema, contact dermatitis, fungal infection, psoriasis, nonspecific pruritus or other conditions, and failure to treat household contacts of patients with scabies.
- Routinely prescribing antibiotics to patients with reported tick bites.

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CHAPTER 375

Mammalian Bites and Associated Infections

Johanna C. Moore

Mammalian bite wounds, including dog, cat, and human bites, account for up to 1% of all visits to emergency departments (EDs). A majority of bite wounds are superficial and over 70% of patients are bitten by an animal known to them.

The majority of animal bites are from dogs. Dogs bite approximately 4.7 million persons in the United States every year. Nearly 20% of those sustaining dog bites seek medical attention, 1% to 2% require hospitalization and about 20 people die per year from their dog bites (1,2). Of those dog bites requiring medical attention, children are disproportionately affected; with 60% to 75% less than 20 years old and a majority are 5 to 9 years old. Males are more likely to be bitten, and in children, the face is frequently affected (1,3). Cat bites account for 3% to 15% of all animal bites and primarily affect the arms and face. Females are more likely to be affected (4).

Human bites account for up to 3% of bite wounds (3). Although less common than dog and cat bites, they have a higher complication and infection rate than animal bites. In children, most bite wounds occur while playing or fighting. Many human bites occur during an altercation, with the majority of bites located on the hands, fingers, or extremities in adults. Young males are at higher risk to sustain human bite injuries (5,6). Occupational exposure can occur in dental professionals, caretakers of the mentally impaired, daycare workers, and medical personnel involved in airway

management of the care of seizing or combative patients. “Love bites” often involve the neck, breasts, or genitalia, during passionate sexual encounters. Clenched-fist injuries (“fight bites”), which occur when a fist strikes teeth during an altercation, are among the most serious of human bites. The microbes contained in plaque and deposits around teeth may be carried to deep structures and relatively avascular tissue planes. The patient can present with an innocuous-appearing laceration, often with an initial alternative explanation of the mechanism of injury. These bites, however, are at risk for development of tenosynovitis, septic arthritis, or osteomyelitis. Tendon laceration, fracture, joint injury, or retained foreign body may occur as a result of the immediate injury.

Approximately 2% to 6% of dog bite wounds seen in the ED become infected, however, wounds extending through the dermis have a higher rate of infection at 6% to 13% (7). Cat bites have a higher rate of infection than dog bites, with cited rates at 30% to 50% (5), presumably due to sharper teeth and the deeper puncture wound usually sustained. Overall rates of human bite infection have been cited at 10% to 20% (6). Hand wounds from human bites have the highest rate of infection, up to 30% to 50% in some studies (3,8,9). However, a 2004 study of low-risk human bites, found an infection rate of 1.6% (10).

Important pathogens causing dog, cat, and human bite infections are often a mix of both aerobic and anaerobic pathogens. Pathogens include oral flora from the biter and skin flora from the patient. Pasteurella (*Pasteurella canis, Pasteurella multocida, Pasteurella septica*) is a frequent isolate in both dog bites (50%) and cat bites (75%) and commonly seen in abscesses and puncture wounds. Other common aerobes isolated are streptococci (46%), staphylococci (20% in dogs and 4% in cats), moraxella, and neisseria. Anaerobic bacteria include fusobacterium, bacteroides, porphyromonas, and prevotella (11,12). A significant pathogen found in dog bites is *Capnocytophaga canimorsus,* which can cause severe systemic infection, disseminated intravascular coagulation, or meningitis in the immunocompromised. This infection is traditionally thought of

in the asplenic or alcoholic patient, although infections are also reported in healthy hosts.

Human bite wound pathogens also include both aerobic and anaerobic bacteria. Streptococci and staphylococcus species are the most common isolates. Common anaerobic isolates include Eikenella, Fusobacterium, and Prevotella (13). Community-acquired methicillin-resistant *Staphylococcus aureus* (ca-MRSA) is now recognized as an increasingly common pathogen with a prevalence of up to 55% in a study of hand infections (14).

The organism responsible for cat-scratch disease, *Bartonella henselae,* can be transmitted from a cat bite or scratch, and also by a flea bite. Cats are the main reservoir for *B. henselae,* with bacteremia that can persist up to a year or even longer. The gram-negative organisms *Streptobacillus moniliformis* and *Spirillum minus* can cause rat-bite fever, commonly transmitted by a bite or via feces or secretions such as urine or mucous from an infected rodent.

Transmission of the human immunodeficiency virus (HIV) by human bite is rare but has been reported, usually in association with bloody saliva (15). The risk of transmission should be addressed on an individual basis. Exposure to saliva alone is not considered a significant risk factor and the skin must be broken for bloody saliva to be considered a significant exposure (5). Transmission of hepatitis B (HB) via human bite has been reported, with evidence that up to 75% of HB patients have detectable antigen in their saliva. Herpesvirus simiae (B virus), carried by rhesus and other macaque monkeys can spread to humans by bites or scratches and can lead to fatal encephalitis (8).

Rabies, caused by a variety of viral species within the genus Lyssavirus, is transmitted by the saliva of an infected animal. All mammals are thought to be susceptible to rabies, however the major reservoirs of rabies in the United States include bats, raccoons, skunks, and foxes (16). The majority (99%) cases of human rabies occur in countries where rabies is endemic, with much higher rates in Africa, Southeast Asia, and India. There are one to three annual cases of human rabies in the United States, which occur primarily

from bat exposure. Rabies transmission from domestic animals in the United States, Europe, and Canada is rare (3).

CLINICAL PRESENTATION

Animal bites can lead to trauma of the skin, tendons, joints, bones, major vessels, viscera, brain, and other organs. Immediate death from a bite is rare but usually a result of hemorrhagic shock. The visible wounds from a bite can vary greatly and include lacerations, punctures, abrasions, and avulsions. The clinician should have a high suspicion for clenched-fist injury when taking care of wounds over dorsum of the proximal phalanges or metacarpophalangeal joints, even if patients do not give this history. Patients who present more than 24 hours after injury are more likely to have signs of established local or systemic infection.

Cat-scratch disease, most common in children, usually begins with a papule or vesicle that develops at the bite or scratch site around 1 week after exposure. However, patients may not notice or give thought to the primary bite or rash. The characteristic regional tender lymphadenopathy of the disease develops proximal to the bite site approximately 2 weeks after inoculation. Less commonly, cat-scratch disease can have neurologic, ocular, and visceral involvement in immunocompetent patients, and should also be considered in fevers of unknown origin (17).

Patients with rat-bite fever from *S. moniliformis* typically develop sudden fever, headache, arthralgias, and myalgias several days (range of 1 to 22 days) after a bite or scratch from an infected rat, handling an infected rat, or ingestion of rat excreta. A rash (macular, petechial, purpuric, or pustular; centripetal or generalized) and asymmetric polyarthralgia or arthritis may also be present. Complications include bacteremia, soft tissue abscesses, meningitis, pneumonia, septic arthritis, and endocarditis (18).

The presentation of human rabies varies with the time elapsed after exposure. An asymptomatic incubation period is generally 3 to 12 weeks with a range of several days to months, followed by a nonspecific prodrome of 2 to 10 days of nonspecific symptoms such

as fever, headache, nausea, vomiting, and malaise. Pain and paresthesias of the initial bite wound or affected limb may be present. There may be evidence of wound infection. The ensuing acute neurologic phase lasts 2 to 10 days. In about 80% of cases, the "furious" or encephalitic rabies, signs of hyperactivity predominate; these include agitation, autonomic instability, hallucinations, thrashing, biting, and the classic hydrophobia or aerophobia caused by an exaggerated respiratory-tract protective reflex. In the remaining 20% of cases, called paralytic or "dumb" rabies, ascending paralytic signs predominate with intact sensorium. The prognosis of rabies is invariably fatal, with few case reports of survivors noted, and a majority of deaths occur after 2 weeks after coma onset (16).

DIFFERENTIAL DIAGNOSIS

With the exception of clenched-fist injuries, the history of patients presenting with animal bites is rarely obscure, and the differential diagnosis revolves primarily around determining the presence or absence of concomitant infection and underlying tissue injury.

The differential diagnosis of cat-scratch disease and rat-bite fever is extensive. The differential in cat-scratch disease mostly includes other causes of infectious causes of lymphadenopathy such as cytomegalovirus, Epstein–Barr virus, HIV, mycobacterium, streptococcal or staphylococcal adenitis, and toxoplasmosis. Malignancy such as lymphoma or leukemia should also be considered (17). The differential for rat-bite fever includes sepsis from bacteria such as *S. aureus, S. pyogenes, N. meningitides,* or *N. gonorrhoeae,* Lyme disease, Ehrlichiosis, Brucellosis, Rocky Mountain spotted fever, leptospirosis, and secondary syphilis. Viral illnesses include Epstein–Barr, parvovirus, and coxsackie. Alternate causes of relapsing febrile illness include malaria, typhoid, and *Borrelia recurrentis.* Noninfectious processes are drug reactions or collagen vascular disease.

Rabies must be differentiated from other infectious causes of encephalitis, including herpes, arboviruses (including West Nile

virus), tetanus, malaria, rickettsia, typhoid, poliomyelitis, and botulism. Noninfectious diseases that must be considered include Guillain–Barré syndrome, poisoning, alcohol withdrawal, acute porphyria, and behavioral disorders.

ED EVALUATION

Initial evaluation of acute injuries should include a primary survey, with attention to the basics of trauma care. The history should include details of the biting event: the time, the offending animal, and its identity (wild or domestic, immunization and health status, captured or not), and the nature of the attack (provoked or unprovoked). The patient's underlying health status, and compromised immunity should also be determined. The patient should be assessed not only for skin wounds but also for deep-structure injury, particularly of the brain, vessels, viscera, nerves, tendons, joints, bones, and spinal cord. Puncture wounds are particularly prone to cause deep and often undiagnosed injuries. Location of the wound on the hand, wrist, foot, or joint of a patient or on the face and scalp of an infant increases the likelihood of deep-structure injury.

Radiographs of the injured area should be considered for suspected foreign body or fracture. Skull radiographs and computed tomography (CT) scanning of the head and cervical spine are indicated for infants with significant face and scalp bites.

Cultures from clinically infected wounds should be obtained. Although Gram stain and culture of fresh bites do not predict infection, a Gram stain and culture (aerobic and anaerobic) may be helpful in clinically infected wounds. If sepsis is suspected, the Gram stain of the peripheral blood should be examined for evidence of *C. canimorsus,* and blood cultures (anaerobic and aerobic) should be obtained. With serious infection, complete blood count; blood urea nitrogen, glucose, electrolyte, and creatinine levels; prothrombin time; partial thromboplastin time; fibrin split products; and lumbar puncture with cerebrospinal fluid (CSF) analysis and culture may be helpful. Antibody titers (acute and convalescent) may be necessary.

KEY TESTING

- Bite wounds do not benefit from laboratory testing unless to help define the severity of an established infection.
- Strongly consider radiographs and/or CT scan in infants with significant face or scalp bites.
- Consider radiographs for fracture and/or retained foreign body.

ED MANAGEMENT

Beyond the initial primary and secondary surveys that should be performed, imperative to mammalian bite management is good wound care. A sensory and motor examination should be performed prior to any anesthesia. The wound should be cleansed with soap and water initially, and then the wound copiously irrigated (250 mL–1000 mL or more as indicated) with saline or tap water under high pressure. Solutions such as povidone-iodine, ethyl alcohol, and hydrogen peroxide can cause additional injury and should be avoided for irrigation. A full exploration of the wound should be performed, paying particular attention to possible foreign body (teeth), vessel, bone, tendon, or joint injury. If the bite occurred over a joint, the wound should be visualized over the full range of motion. Debridement may be performed for removal of devitalized tissue. If the clinician chooses to close the wound, deep sutures should be avoided as they may lead to higher rates of infection. Wounded extremities should be immobilized and elevated.

Facial wounds should be primarily closed with concurrent antibiotic administration to minimize scarring. This approach has been shown to be safe in children (19). Primary closure of other wounds, particularly the extremities, are controversial with some authors advocating no primary closure (4,12). There is limited evidence on this topic. In a single randomized controlled trial of primary wound closure versus no closure for dog bites, there were no overall significant difference in rates of infection. There was a significantly higher rate of infection in the hand overall with no difference between primary closure and wounds left open. Excluded were puncture wounds, clinically infected wounds, wounds

requiring plastic surgery or involving nerve, tendon, bone, or joints, and no prophylactic antibiotics were given (20). Delayed primary closure is also a good option if the clinician is unsure whether to primarily close.

Prophylactic antibiotic therapy for dog, cat, and human bites is controversial. Prospective controlled trials examining outcomes of mammalian bite wounds with and without prophylactic antibiotics are scarce. Rates of infection without prophylactic antibiotics vary widely between studies when taking the species, wound type, and location into account. The development of a bacterial infection following a bite wound depends on multiple factors including the species (human bites are at higher risk), possibly the type of wound, location of wound (hands are at higher risk), the type of wound care provided, and comorbidities of the individual (age, presence of immunocompromised conditions) (21).

Based on the limited evidence available and expert opinion, antibiotic prophylaxis for human or cat bites is most appropriate for bites to the face, hands, feet, skin overlying joints, or cartilaginous structures, crush wounds, puncture wounds, sutured wounds, wounds with a large amount of devitalized tissue, dirty wounds, and for bites that extends beyond the epidermis (Table 375.1) (3,8,21–23). The utility of prophylactic antibiotics for dog bites is unclear. Minor bites that occurred within 24 hours, or involve only epidermal stripping, scratches, and abrasions are less likely to benefit from antibiotic prophylaxis (3). Some authors advocate for antibiotic treatment for all bite wounds, except in patients who present 72 hours or more after injury and have no signs of infection (8).

TABLE 375.1
Indications for "Prophylactic" Antibiotics[a]

Wound	Patient	Source
Puncture	Age (<2 yrs, >50 yrs)	Human
Crush	Asplenic	Cat
Old (>8 hrs)	Alcoholic	Primate
Extremity (especially hand)	Diabetic	Pig
Sutured	Otherwise immunocompromised	

[a]Adapted from Cummings PC. Antibiotics to prevent infection in patients with dog bite wounds: A meta-analysis of randomized trials. *Ann Emerg Med*. 1994;23:535; Medeiros I, Saconato H. Antibiotic prophylaxis for mammalian bites. *Cochrane Database Syst Rev*. 2001;(2):CD001738; and Morgan M, Palmer J. Dog bites (clinical review). *BMJ*. 2007;334(7590):413.

Antibiotic therapy for infected dog, cat, and human bites should cover Pasteurella, Eikenella, streptococci, staphylococci, and anaerobes. First-generation cephalosporins, dicloxacillin, and erythromycin should be avoided due to poor coverage of Pasteurella and Eikenella (11). Based on expert opinion and the evidence available, amoxicillin and clavulanic acid are the recommended first-line agents for mammalian bite prophylaxis and treatment of ambulatory infections (4,8,11,13). Alternative regimens include a **combination** of an extended-spectrum cephalosporin, trimethoprim/sulfamethoxazole, doxycycline, penicillin VK, moxifloxacin for Pasteurella coverage, **and** metronidazole or clindamycin to cover anaerobes (Table 375.2).

TABLE 375.2
Oral Antibiotics for Treating or Preventing Mammalian-Bite Infections[a]

Antibiotic	Comments
Current Drug of Choice	
Amoxicillin-clavulanic acid (875 mg twice a day)	No activity against CA-MRSA. Safe in pediatrics.
Alternate Regimens	
Clindamycin PLUS second- or third-generation cephalosporin (cefuroxime, cefpodoxime)	Reasonable activity against CA-MRSA. Safe in pediatrics.
Cefoxitin	No activity against CA-MRSA. Safe in pediatrics.
Clindamycin PLUS fluoroquinolone (ciprofloxacin, moxifloxacin)	Safe in penicillin allergic adults. Reasonable activity against CA-MRSA.
Doxycycline PLUS Metronidazole	Safe in penicillin allergic adults. Reasonable coverage of CA-MRSA.
Clindamycin PLUS trimethoprim-sulfamethoxazole	Safe in penicillin allergic patients and pediatrics. Reasonable coverage of CA-MRSA.
Clindamycin PLUS penicillin VK	Reasonable coverage of CA-MRSA.

CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*.
[a]Adapted from Talan DA, Abrahamian FM, Moran GJ, et al. Clinical presentation and bacteriologic analysis of infected human bites in patients presenting to emergency departments. *Clin Infect Dis*. 2003;37; and Talan DA, Citron DM, Abrahamian EM, et al. Bacteriologic analysis of infected dog and cat bites. *N Engl J Med*. 1999;340:85; Brook, I. Management of human and animal bite wound infection: An overview. *Curr Infect Dis Rep*. 2009;11:389–395; and Esposito S, Picciolli I, Semino M, et al. Dog and cat bite-associated infections in children. *Eur J Clin Microbiol Infect Dis*. 2013;32:971–976.

For patients who require parenteral therapy, monotherapy of intravenous ampicillin/sulbactam, piperacillin-tazobactam, or a carbapenem should be used as first-line antimicrobials (4). Dual therapy with a third-generation cephalosporin or a fluoroquinolone plus an anaerobic agent such as metronidazole can also be given. Coverage for MRSA should be considered, especially if the patient is at risk for ca-MRSA. Colonization and transmission of MRSA by pets have been reported (24).

The duration of antibiotic therapy should be tailored to the individual, based on the location of the wound, any culture results, and response to treatment. A 7- to 14-day course of antibiotics is generally adequate. A longer duration will be needed for infection of bone or joints (8). A shorter course of 4 to 5 days is appropriate for prophylaxis.

Cat-scratch disease resolves spontaneously in 1 to 2 months or may resolve sooner if treated with azithromycin (10 mg/kg, up to 500 mg on day 1; then 5 mg/kg, up to 250 mg daily for 4 more days). Uncomplicated rat-bite fever should be treated with penicillin (1.2 million units per day IV for 5 to 7 days) followed by oral penicillin or ampicillin (500 mg four times daily for 7 days). Alternatively, tetracycline (500 mg four times daily) or streptomycin (7.5 mg per kg twice daily) can be used.

The HB vaccination status of the patient should be determined. If the patient has sustained an exposure to HB-infected saliva or blood, he is potentially at risk for seroconversion, although this is rare. If a patient has a possible exposure to HB-infected blood or saliva, HB vaccination or rarely HB immunoglobulin can be offered, depending on the vaccination status of the patient and the exposure source (5). The tetanus status of the patient should be reviewed and updated if needed. The rabies vaccination status of the animal should also be determined. Rabies is almost always fatal, and prevention depends on control of exposure, aggressive local wound care, and knowledge of transmission, which is usually by means of saliva contacting a laceration, scratch, abrasion, or mucous membrane. Postexposure prophylaxis is indicated if the offending animal is known or clinically suspected to be rabid or if it is a bat or wild carnivore. The silver-haired bat variant of rabies virus is able to replicate in the superficial dermis and has been associated with several recent cases of human rabies without known history of conventional exposure. For this reason, postexposure prophylaxis is recommended for persons who may have come in contact with a bat (e.g., an infant or a sleeping adult in a room with a bat, even if a bite or scratch wound is not apparent). Livestock and unprovoked dog and cat bites should be considered individually in consultation with public health officials (16).

Patients bitten by healthy dogs and cats do not require rabies prophylaxis, provided that the animal can be located and observed for 10 days for signs of illness. Rabbit and rodent (e.g., hamster, mouse, rat, and squirrel) have not been known to transmit the disease and bites do not require treatment. Patients who have not

been previously immunized should receive both human rabies immune globulin (20 IU/kg) at or near the bite site and the remainder given IM at a distant site and human diploid cell rabies vaccine (1 mL IM in the deltoid or anterolateral thigh but not gluteal area, on days 0, 3, 7, 14). Patients previously immunized need not receive rabies immune globulin but should be given a booster series of human diploid cell vaccine (1 mL IM, not gluteal, on days 0 and 3).

DISPOSITION

The vast majority of patients can be treated as outpatients and return for worsening of infection. Clenched-fist injuries with involvement of tendon, joint, or bone should be considered for admission. All patients who do not require admission should be rechecked in 24 to 72 hours for signs of infection. If signs of infection develop, sutures must be removed and the wound must be left open for drainage.

Those who require IV antibiotics (e.g., systemic, central nervous system, hand, joint, or other deep-structure infection or any infection in a high-risk patient) or who cannot receive proper care as outpatients should also be admitted. In the rare cases of septicemia or in cases of possible HIV or HB or C transmission, consultation with an infectious disease specialist and a microbiologist (for a careful search for organisms unique to animal bites). A surgeon (general, hand, plastic, or orthopedic, depending on local practices) should be consulted when there is violation of a deep structure (such as a joint, bone, tendon, or internal organ), extensive facial damage, tissue loss, or a clenched-fist bite.

Infants, some children and the very rare adult who sustain major trauma, significant blood loss, or injuries that require operative intervention need to be admitted. Transfer to another institution should be arranged whenever appropriate inpatient facilities or consultants are unavailable.

Bites by potentially rabid animals should be reported to state public health officials or local animal control officers.

Common Pitfalls

- Failure to diagnose joint penetration, tendon injury, retained foreign body.
- Failure to close facial wounds that are at low risk for infection.
- Failure to consider clenched fist injury in a patient that does not offer this history.
- Failure to provide rabies immunization after possible bat exposure.
- Failure to identify and admit infected immunocompromised patients.

ACKNOWLEDGMENT

The author gratefully acknowledges the previous contributions of Stephen J. Playe to the content of this chapter.

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SECTION XXV
EMS and Special Clinical Considerations

Section Editor: CARLO L. ROSEN

PART 1 • PREHOSPITAL CARE

CHAPTER 376

Emergency Medical Services

Alexander P. Isakov, Marc Restuccia, and Lawrence Mottley

HISTORICAL PERSPECTIVE

Prior to the rapid evolution of emergency medical services (EMS) in the 1960s and 1970s, only rudimentary systems of prehospital care and patient transport existed. Although hospital-based ambulance services had been functioning in Cincinnati, Ohio since 1865 and city services were initiated in New York in 1869, private ventures that combined transport services with another trade, such as funeral services, had the greatest market share. Such enterprises delivered prehospital care with little training, regulation, or benchmark for quality. The military advanced EMS in its care of wounded soldiers in Vietnam. Corpsmen and medics were trained in prehospital intervention and evacuation of the critically wounded to appropriate facilities for prompt surgical attention. The mortality of trauma patients surviving to a medical treatment facility sharply decreased.

In 1966, the National Academy of Sciences–National Research Council, which acts as a consulting body to the government, published what has been referred to as the "white paper" of prehospital systems, "Accidental Death and Disability: The Neglected Disease of Modern Society." This document summarized the inadequate delivery of emergency care, the lack of an emergency services infrastructure, and the lack of leadership in this area. It also made specific recommendations for a funded, organized, proactive, prehospital medical delivery system, launching the modern era of civilian EMS in the United States.

That white paper, along with others showing a rise in accidental deaths, especially on America's highways, prompted Congress to enact the National Highway Safety Act of 1966. This act authorized spending by the newly created Department of Transportation (DOT)/National Highway Traffic Safety Administration (NHTSA) for the improvement of essential prehospital infrastructure, training of personnel, and establishment of practice guidelines. Through this legislation, states developed regional EMS systems with funding for ambulances, personnel, and communication equipment. A nationally recognized curriculum for the training of ambulance attendants (emergency medical technician [EMT-A]) was established in 1971.

The success of prehospital cardiac care units in Dublin and of new methods of cardiopulmonary resuscitation (CPR) led EMS programs to expand their focus beyond trauma. The Department of Health, Education, and Welfare funded regional EMS demonstration projects in five states, and the Robert Wood Johnson Foundation offered grants for regional EMS development. The resulting improved communications, training, and transport capacity in these demonstration projects was viewed favorably in Congress and was followed by the EMS Systems Act of 1973, which legislated further federal funding of comprehensive regional EMS systems; this included money for operations, training, and research. Full-time medical directors and professional prehospital medical providers emerged.

National standards for EMT-A, EMT-I (intermediate level), and EMP-P (paramedic level) training evolved. Because some nonmedical public safety personnel were often the first to arrive at a scene with medical casualties, a first-responder curriculum was developed as well. NHTSA established such curricula, which came to be recognized as national standards.

Communications infrastructure, including 911 access, two-way radio communications, and centralized dispatch were developed, and criteria for optimal ambulance design and equipment were established. Regional EMS systems were intended to become financially independent as federal funding was phased out in favor of state discretionary funding of EMS through Preventive Health Block

Grants, a product of the Omnibus Budget Reconciliation Act of 1981. The result, however, was deterioration of the movement toward national standards as regional systems yielded to state and local concerns. A multitude of systems developed independently, providing a varied range of skill levels, training, and quality of care from one community to another.

Nationally, organizations like the National Association of EMS Physicians and the National Association of EMTs emerged to serve as professional bodies for consensus in the continuing development of EMS systems. At the federal level, the DOT maintained a leadership role through its Office of EMS at the NHTSA; however, EMS-related programs subsequently developed in a scattered fashion across many departments (i.e., the Department of Health and Human Services and the Department of Homeland Security). The absence of a single federal agency with the ability to comprehensively represent EMS issues with authority compromises strategic planning, advocacy, and adequate funding for out-of-hospital emergency care. Forty years after the first white paper was published, a reassessment of the future of emergency care in the US health system was undertaken by the Institute of Medicine, which offered as one of its many recommendations that a lead agency should be housed in the Department of Health and Human Services, and should have primary programmatic responsibility for the full continuum of EMS and emergency and trauma care for adults and children, including medical 9-1-1 and emergency medical dispatch (EMD), prehospital EMS (both ground and air), hospital-based emergency and trauma care, and medical-related disaster preparedness (1).

At present, the Federal Interagency Committee on EMS, supported by the National Highway Traffic Safety Administration (NHTSA), works to ensure coordination among the federal agencies involved.

EDUCATION

The Office of EMS at the NHTSA has served as the source of national standard educational curricula since the EMT-A curriculum was established in 1971. Curricula were developed for prehospital providers at the first responder, emergency medical technician-basic

(EMT-B), emergency medical technician-intermediate (EMT-I), and emergency medical technician-paramedic (EMT-P) levels of education. While these curricula were accepted as national standards, states variably adopted them, often with heavy modification for the training of EMS providers in their jurisdictions. As a result, a great variety of provider levels with differing scopes of practice emerged nationally. Although this diversity allows for the greatest flexibility to respond to local needs with local resources, it does not foster uniform scopes of practice or standards of care and creates confusion regarding interstate reciprocity of privileges. To address this issue, the NHTSA sponsored an EMS Education Task Force composed of EMS providers, administrators, educators, and physicians, which authored the "EMS Education Agenda for the Future: A Systems Approach." This document calls for more explicitly defined core educational content, scope of practice, and national standards for the education and certification of providers. The Agenda calls for an education system with five primary integrated components: (a) the National EMS Core Content, (b) the National EMS Scope of Practice Model, (c) National EMS Education Standards, (d) National EMS Education Program Accreditation, and (e) National EMS Certification. The National EMS Core Content, published in July 2005, specifies the knowledge and skills necessary for the provision of care in the out-of-hospital environment and was developed using the "Model of Clinical Practice of Emergency Medicine" as a template to facilitate common definitions and terminology with colleagues practicing emergency medicine in the hospital environment. The National EMS Scope of Practice Model, published in February 2007, defines and describes four levels of EMS licensure—Emergency Medical Responder, EMT, Advanced EMT, and Paramedic—each representing a unique body of knowledge and skill set. National EMS Education Standards are also published, that define the competencies that must be met by graduating EMS personnel to meet practice guidelines. These standards now replace the NHTSA national standard curricula at all levels of practice. This new educational model and the newly defined levels of licensure are gradually being adopted and implemented by the states.

Independent of the core curricula, there have also emerged specialized training programs, established for EMTs and paramedics who function in settings wherein additional education is desirable. Programs can be found to enhance education and training for critical care transport, wilderness medicine, law enforcement special operations and medical support among others.

The training of physicians for leadership roles in EMS continues to develop. Historically, any physician who had an interest and the fortitude would serve as an EMS medical director. No formal training existed. Today, emergency medicine residents are provided some education in EMS systems and prehospital care as part of their core curriculum in postgraduate training. Postgraduate EMS fellowship training has also been available through 1- and 2-year training programs. The 2-year programs concurrently offer a master's degree in public health, hospital administration, business, or other disciplines. In 2010, the American Board of Emergency Medicine formally accepted EMS as a certifiable subspecialty. The American College of Graduate Medical Education now provides accreditation for EMS fellowship programs in the United States that is based upon established standards and guidelines.

STRUCTURE

The structure of EMS systems varies widely across the United States, but common elements do exist: (a) activation of the system, most predominantly by use of 911, (b) medical interrogation of the call to facilitate the dispatch of appropriate responders and provision of prearrival instructions, (c) dispatch of EMS ambulance personnel and sometimes first responders to the scene, (d) treatment and transport of patients in the out-of-hospital environment, and (e) arrival of patients at a medical treatment facility and transition of care. The system design should ensure efficient and effective service and medical care, measured by desirable patient outcomes. Regionalization of EMS may yield operational efficiencies and facilitate agreement on the threshold of clinical encounters required by EMTs to maintain proficiency and skill, when compared with highly fractionated systems.

There are multiple delivery models currently in use.

Fire-Based Systems

Many fire departments (FDs), especially in the western United States, adopted EMS as part of their mission immediately after the federal legislation was enacted. Fire-based systems allowed dispatch and deployment of EMS units within a currently existing system. In most combined EMS/fire systems, EMS accounts for about three-fourths of the call load. In small cities and towns, existing personnel and facilities may be able to perform EMS duties without adding staff or infrastructure. However, because firefighters are usually among the highest-paid employees, larger systems that need additional staff will incur much higher costs as compared with the other EMS models.

In addition, because the FD's first priority is fire suppression, conflicts of interest may arise and lead to under resourced patient care. As the annual number of fire-suppression calls decreases and cities look more closely at the most efficient use of available resources, more FDs are becoming interested in EMS. Integration of established EMS systems with and under the direction of FDs is a politically charged topic that currently is the subject of heated debate in many cities.

Many FDs provide first-responder services regardless of the source of ambulance transport, using firefighter personnel trained to provide initial interventions for immediately life-threatening conditions such as cardiac arrest (CA), respiratory distress, chest pain, and loss of consciousness. In some systems, the FD may also provide the full scope of paramedic services and patient transport for every patient or alternatively for a sub-set of patients in partnership with a private ambulance provider.

Private Ambulance Services

Private ambulance services often bid for an exclusive contract with a governmental entity to provide EMS services, usually to a city, town, or county. The contract often stipulates that certain indirect measures of quality and performance be met, such as that all units be

equipped with defibrillators, that paramedics perform a minimum number of intubations, or that certain response-time parameters be met. The community establishes regulatory control over the private service, with oversight being provided by an EMS agency or a medical director.

Private ambulance services usually provide both advanced life-support (ALS) and basic life-support (BLS) services. To a greater extent than any of the other EMS models, private ambulances depend on efficient management of resources, such as peak-load staffing and system status management, to meet their dual demands: providing adequate EMS response and being a successful business. Personnel costs for the private sector are usually significantly below those for both the FD and third-service industries. The risk, however, is that the vendor could withdraw from nonlucrative markets, leaving the region or municipality searching for a means to provide uninterrupted service.

Third-Service Systems

Third service, simply defined, is an EMS system housed in a municipal department using municipality-owned and -operated ambulances and kept separate from police and fire services. Many medium and large cities continue to use municipal hospital–based ambulances as all or part of their EMS systems. Some third services are part of the city's health department, and a few are separate city agencies. This model allows for concentration on one mission—patient care—without the added complexity of managing, funding, and providing other services. EMT skill maintenance is rarely a problem in these mostly urban systems. A drawback is that the third-service agency must compete with other traditionally well-supported public service agencies for budgetary funding.

Volunteer Systems

Three-fourths of the United States is considered rural, and in these areas the EMS workforce depends largely on volunteers. The tax base cannot support a full-time professional EMS system, and the revenue

to attract a private contractor does not exist. The dedication of volunteers is remarkable, as are the challenges they face in finding medical oversight, time for training, the means to maintain their skills, and the financial resources to develop and maintain their systems' infrastructure. Depending on state regulation, some volunteer services may operate without medical direction. Turnover among these providers is high. Rural systems face the same challenge of delivery of quality care as urban ones but often with drastically different resources.

AMBULANCES

Ambulance vehicles are a very diverse fleet, including vans and light and heavy trucks, which have evolved without keeping stride with advances in the automotive and occupational safety industries. Vehicle crashes have been shown to be the number one cause of occupational mortality in EMS. Risky driving practices and noncompliance with use of seat belts contribute to high injury and fatality rates in ambulance crashes. Driver feedback technology has shown favorable results in modifying driver behavior. It has also become increasingly clear that the vehicles used for EMS operations are not optimally designed for occupant safety (2). There is increasing pressure to design ambulances that afford EMS personnel and patients maximum protection in the event of a motor vehicle collision. Cleared head strike zones, secured equipment, and appropriate restraint of patients and EMS personnel are issues that need to be addressed. Changes in driver and occupant practice and ambulance design deserve attention and will afford better protection for the occupants and greatly improve the chance of patients' and EMS personnel's surviving a traffic accident.

Federal and state laws, which can be extremely detailed, govern the configuration of each vehicle and its markings. In addition, each state mandates the minimum and allowable equipment and medications carried on any ambulance. Despite these regulations, there is wide variation of equipment and medications carried on individual ambulances. These variations reflect not only the medical director's equipment preferences, judgment, and vision for the

service but those of other personnel and the type and geographic location of the system.

Variation in equipment and supplies also reflects the level of service provided. The amount and variability of medical equipment on a BLS ambulance is typically much less than on an ALS vehicle.

MEDICAL OVERSIGHT

Medical oversight of out-of-hospital providers is essential to providing the best medical care. It may take the form of direct or indirect medical control. *Direct* or *online* medical control refers to the immediate direction and feedback, usually by radio or telephone that a physician provides to an EMS provider while caring for a patient. Although there is some controversy over whether such communication significantly improves the care provided, it gives EMS providers direct access to a physician's level of training and knowledge.

In some systems, *a specified physician or institution at a single base hospital provides online medical control.* In other systems, it is decentralized, with each receiving institution acting as a base station. Medical control physicians must have an in-depth knowledge of the skills and capabilities of the EMS provider on scene and the capabilities and availability of receiving institutions in the area. They must also know applicable state and regional or local protocols and the medico legal implications of situations such as refusal of treatment or transport and the care of minors, do-not-resuscitate patients, and deceased patients.

Indirect or *off-line* medical control consists of clinical guidance document (or protocol) development and implementation, equipment selection, ensuring adherence to clinical standards, education of EMS providers, and ongoing quality improvement within the system. Such functions are generally the responsibility of the EMS medical director. The highest-functioning EMS agencies are characterized by the triad of commitment to excellence in patient care, dedicated EMS personnel, and actively engaged medical directors. Care must be "patient-centric and physician-directed." Compliance with written clinical guidance and standards of care is usually accomplished by

reviewing EMS patient care records. This is accomplished by the EMS medical director or designee reviewing individual cases that were difficult or problematic or by reviewing the charts of selected conditions (e.g., CAs, pediatric cases, intubations, deaths, refusals of care) or individuals (e.g., new hires, those with whom there may be quality-of-care concerns, those who have just returned from a leave of absence). In addition, in a highly functional EMS agency, the medical director and other supervisory personnel must spend time "in the field" with their EMTs and paramedics. Chart review can never replace the invaluable experience of seeing how personnel function in their element. EMS agencies must be committed to continuously evaluating the quality of the service delivered and striving to seek ways to improve it.

The initial training and continuing education of EMS providers is a key element in medical direction. The implementation of new medications, interventions, and protocols is an ongoing process. Quality improvement includes not only identifying and correcting deficiencies in current practice but identifying areas that, although not necessarily deficient, can be improved (response time, scene time, timely completion of charts, documentation of procedures).

COMMUNICATION

EMS communication is a chain of events that can be best described using queuing theory. The call-taker queue consists of those who dial 911. In the past, most cities and towns had their own emergency call-receiving center, but with the advent of *Enhanced 911* (911E), many have now been consolidated into Public Safety Answering Points (PSAPs) serving one large local jurisdiction or multiple smaller ones. 911E provides the PSAP call taker with the physical address of the phone (street address and, in apartment buildings, the apartment number) and the telephone number of the caller. In most jurisdictions, once the last digit of 911 is dialed, the caller cannot disconnect by hanging up. Only the public safety dispatcher can release the 911 call. This prevents the panicked caller from disconnecting the call before all information is obtained and prearrival instructions are offered. The demographic information

allows patients who are unable to speak as a result of illness, injury, or danger to receive assistance. Protocols may also allow the call taker to ask a series of yes or no questions that mute callers can answer by pushing the appropriate button (1 or 2). In this way, the correct agency or agencies can respond. Technology is also available to approximate the location of cell phones within a few dozen meters, a feature useful for the location of automobile accidents and one that enables the direct routing of a 911 call to the appropriate PSAP. In 2006, approximately 59% of PSAPs had this capability, compared with 18% just 3 years prior (3).

EMS callers are then placed in the triage queue. Modern EMS systems use written telephone medical triage guidelines, known generically as EMD, to ensure consistent and appropriate triage and response. More important, by asking only for information that will assist in correctly prioritizing the call, they reduce the amount of time spent questioning the patient prior to dispatch. For example, if the caller is male, older than 50 years of age, and has nontraumatic chest pain, no further information is necessary for triaging the call as high priority (potential cardiac etiology). Gathering additional information and attempting to make a presumptive diagnosis is not appropriate and possibly detrimental, because it wastes time and is not relevant to the dispatch decision.

Triage protocols can reduce both type 1 and type 2 errors (over- and undertriage). They also protect the call taker from the abusive retrospective review that can occur after a high-profile adverse event. Because the medical director bears responsibility for the appropriateness of these medical triage guidelines, it is strongly suggested that a nationally recognized EMD product be used. Some of these products are customizable (within limits) to meet local preferences, whereas others require use “as is.”

EMS calls are usually triaged into one of three priorities: *Priority One:* life-threatening; *Priority Two:* emergent or unknown; and *Priority Three:* nonemergent. These categories are designed to reflect the instability of an illness or injury and its likelihood of deteriorating in a short period of time. They are not intended to characterize whether the condition justifies the use of an ambulance

or how serious it is. For instance, although a fractured hip is serious and appropriate for the use of an ambulance, it is not likely to deteriorate and, therefore, does not have top priority.

Once the call is prioritized, it enters the dispatch queue. The dispatcher then assigns an ambulance to respond. Assigning the closest ambulance to the call is preferred, but this process is not always straightforward. As the number of ambulances in a system increases, so does the complexity of dispatch. In larger cities, the dispatcher would have to know each street and the location of each ambulance at any given time. Most ambulances are available to be dispatched, or "in-service" 60% to 85% of the time, and they may be located outside their assigned districts, making it difficult to ascertain their position without polling multiple units over the radio.

Automatic vehicle locator (AVL) systems can help and are increasingly being used, particularly within the private sector. Using the federal government global positioning satellite system, AVLs can locate an ambulance within a few feet, calculate the travel time to a given call, and recommend the nearest units of each appropriate type —first-responder, BLS, and ALS.

EMS demand by time of day is remarkably predictable, especially in systems with a large call volume. System status management is the process of managing resources based on known patterns of calls in time and place and current demand. Additional ambulances are placed in service during known periods of higher demand. Available units do not remain static but are dynamically and proactively redeployed by EMS supervisors when call volume is high in certain areas. The practice of flat staffing, in which the same number of ambulances are on duty 24 hours a day, is less efficient; patients will have to wait longer than necessary during the busier times, and resources will be wasted during slack time.

DISASTER PLANNING

Mass casualty incidents (MCIs) require the response of multiple different public safety and EMS agencies. They threaten to overwhelm the capacity of the out-of-hospital care system and the medical facilities supporting them. Each EMS agency and hospital

must have a plan for dealing with MCIs in their service area. The importance of having a well-understood, rehearsed, and commonly recognized plan for responding to an MCI cannot be overemphasized. Practicing implementation of the plan provides training for all participants, prevents needless delays, and identifies areas for improvement. Agencies should have complementary plans and train together to ensure cooperation. Planning and training must take into consideration challenges identified in previous responses, which include self-dispatch of responding units causing congestion at the scene; overload of the hospitals in the immediate vicinity of the event; self-evacuation of patients from the scene to the nearest emergency department (ED) prior to EMS evaluation; and the least severe patients often arriving first in the ED (4).

Risk assessment of potential MCI scenarios in a service area is essential. It involves recognizing and characterizing likely sites of an MCI, such as industrial complexes, airports, residential areas (e.g., high-rise apartments, special-needs facilities), highways and railways, and unique facilities, such as nuclear power plants.

A mechanism for rapidly triaging victims of an MCI should be identified and rehearsed. The objective of patient triage is to do the greatest good for the greatest number of victims. Given that several triage criteria have been published and disasters often cross jurisdictional boundaries, the Model Uniform Core Criteria for Mass Casualty Triage (5) was developed to serve as a national guideline for mass casualty triage with the goal of facilitating interoperability and standardization. The criteria include four categories: (1) general considerations, (2) global sorting, (3) lifesaving interventions, and (4) individual assessment of triage category. The SALT (Sort-Assess-Lifesaving Interventions-Triage/Treat) triage system is freely available and meets the Core Criteria (Fig. 376.1). Patients are ultimately assigned to severity categories with the goal of identifying those who require treatment and transport to a medical treatment facility most urgently. Patients are assigned to one of five categories: immediate (red), delayed (yellow), minimal (green), expectant (gray), or dead (black). *Immediate* patients are critically wounded with obvious life-threatening injuries and will require immediate

care. *Delayed* patients have a serious injury but will likely not deteriorate with a slight delay in care. *Minimal* patients do not have life-threatening injury and will likely do well even if care is withheld several hours or days. *Expectant* (gray) and *dead* (black) victims have injuries consistent with little or no chance for survival or have already expired. It is important to note that patients may be triaged several times on their way to definitive care to account for changes in their condition.

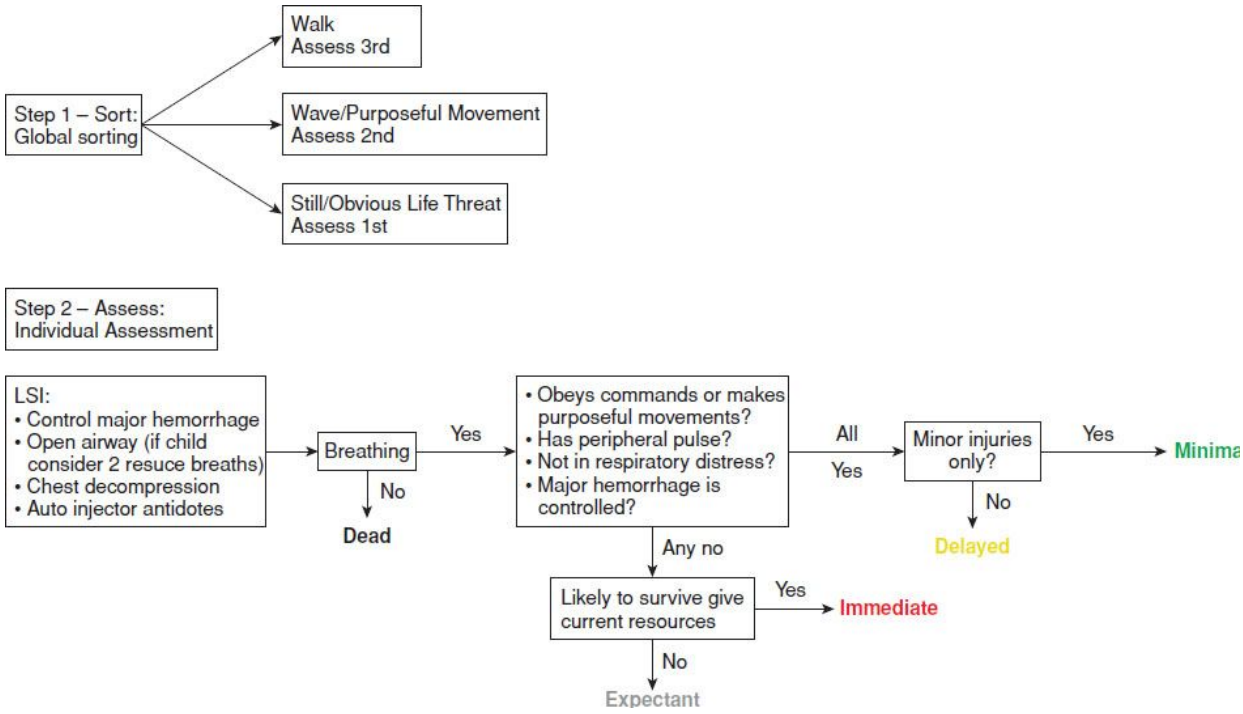

FIGURE 376.1 SALT mass casualty triage (in the public domain).

A communication plan is essential. Often, however, it is the part of the response that fails most rapidly in an MCI. Overloaded radio channels, cell channels, and phone lines can be expected. Loss of radio towers and telephone wires may occur. The plan should identify ways to minimize the effect of these occurrences.

Mutual aid agreements with EMS, police, and fire services and medical treatment facilities in contiguous service areas should be in place. The ability to assemble out-of-hospital and hospital assets beyond the affected area is often essential for a timely response to an

MCI. The plan should identify the resources, personnel, transport, equipment, and facilities that can be called upon.

A clearly defined incident command structure should also be in place. In some states, the highest-ranking fire officer serves as overall "incident commander," with police, EMS, and other agencies functioning as subcommands under incident command rules. All involved must use common nomenclature, practice, and communications protocols. There should be clear direction regarding what freedom of operation prehospital providers might have without resorting to frequent online medical direction. Freedom of operation can be accomplished by having the medical director or designee assume medical command at the scene or via radio.

Special planning is required for HAZMAT situations, terrorist activities, weapons of mass destruction, and mass gatherings. Finally, a debriefing plan is necessary to allow for psychological recovery of involved personnel and for the planning to manage future MCIs.

Mass gathering medicine, defined as organized emergency care for mass gathering events, has evolved and become more sophisticated in the last 30 years. The concentration of many people in a small geographic space can pose significant challenges to proper prehospital management of patients. Recognition of a medical emergency may be difficult, and access to the patient may be hindered, delaying care. An MCI might quickly develop, and on-site resources can quickly be overwhelmed. Agreement with the event organizer about what medical resources are required to provide adequate emergency services may be difficult. Demands for medical care are often not defined by crowd size alone. Exposure to adverse weather conditions, spectator use of alcohol, inadequate intake of water, consumption of contaminated food, and violent spectator behavior can all increase the likelihood of injury and requirement for medical attention. Rock concerts (0.96 to 17 injuries per 1,000 fans) have, for example, had a higher incidence or injury than major sporting events (0.3 to 1.6 injuries per 1,000 fans) (6). The threat of terrorism has also influenced the development of mass gathering medicine. On a national level, an event may be deemed a national security special event because it is high profile and identified as a

possible target of terrorism. In addition to enhanced security measures coordinated by the US Secret Service, medical assets, in the form of disaster medical assistance teams may be deployed to assist local responders in the event of an MCI. The Olympics, major political conventions, and the World Economic Forum are examples of such events.

FINANCING EMS SYSTEMS

The expense of an EMS system is a function of personnel, administration, maintenance, training, equipment, and facilities. Other variables include the level of service provided, response-time requirements, how the cost will be apportioned among patient revenues, tax revenues, and other subsidies, the insurance coverage of the population served, and the cost of medical oversight.

Funding of EMS systems varies greatly from system to system but can be divided into four major categories: taxes, fee-for-service billing, subscription program revenues, and special service contracts. Local and state tax subsidies can entirely fund an EMS system in which care is provided as a public service. Most often, this funding comes from general tax revenues and must compete with other public programs for scarce tax dollars.

In some states, the law allows citizens to approve a dedicated tax levy for specific purposes, and voters direct funding for EMS services. Because EMS has a very positive public image, EMS systems tend to enjoy a greater degree of financial support under such a system. In other systems, tax subsidies may simply offset costs that cannot be covered by revenues from EMS billing. Subsidies are often required in small communities that lack economies of scale, yet operate a full-service EMS system, and in urban and rural settings. It may flow through the budget of a government agency, in the case of third service or FD, or it may be a contractual agreement between a private ambulance provider and a local government. With private contracts, most cities and towns have enjoyed almost a decade of subsidy-free EMS services, as providers have received sufficient revenue from Medicare and Medicaid reimbursement. Diminishing reimbursement from these sources has significantly reduced the

ability of private ambulances to continue subsidy-free 911 contracts. Systems serving communities with a large number of uninsured indigent patients are particularly in need of funding sources to offset costs that cannot be covered by revenues.

In a service that generates its revenue from a fee-for-service plan, income is derived from emergency and nonemergency patient transports, interfacility transfers, and special-event coverage. To balance the budget, these systems must have adequate economies of scale, a population base that has the means to pay, efficient management, and effective billing. Among the billed entities are Medicare, Medicaid, private insurance companies, and individual patients.

Subscription programs are marketed to the populace by a vendor who essentially enrolls people as an "insurance policy" in case they need ambulance services. This type of system also provides service to unenrolled members but at a charge significantly greater than the enrollment fee. Some arrangements also allow the company to bill third-party payers. Special-events coverage, interfacility transport, air transport, and other contracts can provide added revenue.

EMS FOR CHILDREN

Perhaps no group of patients inspires more angst among EMS providers (and emergency medicine personnel) than ill and injured children. Although they make up only a very small percentage of EMS patient interactions, they are among the most difficult to manage. Children younger than the age of 18 make up approximately 13% of all EMS transports (3). Half of these calls are for a traumatic condition, with falls and vehicular trauma being the leading causes of injury. Respiratory difficulty, seizures, ingestions, drowning and near-drowning, fever, and altered mental status are common chief complaints. Sick children generate tremendous feelings in the medical professionals who treat them. Being able to simultaneously deal with the needs of the critically ill or injured child and the provider's own emotions (especially if they have children of their own) is a serious challenge to the provider's professionalism. Almost all EMS personnel can relate to a

particularly ill or injured child who affected them on a visceral level during their careers. Finally, children are different from adults. Their anatomy, physiology, and responses to interventions differ from those of adults. Thus, when dealing with sick children, EMS providers are treating a group they rarely see, who will affect them emotionally, and are different from the vast majority of patients they encounter on a daily basis.

Emergency medical services for children (EMSC) is a federal, state, and local effort to ensure that all children have the same access to high-quality EMS care as do adults. Starting in the 1980s, with federal legislation providing for grant programs based in the US Department of Health and Human Services, EMSC has funded databases, provided grants to the states to study and address the issues experienced by ill or injured children, and convened expert panels to enhance the care delivered to children in the out-of-hospital setting.

A key portion of the EMSC initiative is improved education of EMS providers on the special needs and requirements of ill and injured children. Traditionally, EMS providers had little to no experience or training in treating children. EMTs and paramedics would typically receive 1% to 2% of their total training time on the unique aspects of treating pediatric patients. This has been changing. Paramedic training now includes the Pediatric Advanced Life Support course and the new Pediatric Education for Prehospital Providers course. In addition, many state EMS protocols have specific pediatric protocols, written by emergency physicians and pediatric emergency medicine specialists to guide prehospital providers in treating children. Innovative programs, such as having paramedics spend time in pediatricians' offices, are increasing the comfort levels of both the prehospital providers and the pediatric community. Physicians who provide both online and off-line medical direction are assisting in these developments and are now active participants in furthering the care of pediatric patients.

Special Challenges in Treating Pediatric Patients

Prehospital personnel are faced with a unique set of demands and must use a different set of knowledge and skills when dealing with pediatric patients. As examples, children have a relatively larger occiput than adults, requiring that their torsos be elevated to the level of the occiput to achieve an anatomically neutral position during spinal immobilization. Airway anatomy is different and physiologically, children have higher metabolic rates, requiring higher oxygen demand per unit body mass. The EMT or paramedic with little pediatric experience may fail to accommodate these differences with subsequent clinical deterioration of the child.

Peer-reviewed literature has challenged the "basic" tenets of treating the injured or ill child. One study questions the benefits of prehospital intubation over noninvasive airway management (7). No difference was demonstrated in the outcome of children managed with an endotracheal tube versus conventional bag-valve-mask ventilation. The study, however, was criticized for having an extremely low rate of success for paramedic field intubations in children and frequent complications of airway management, such as unrecognized esophageal intubations. Medical directors evaluating this study may conclude it better to noninvasively manage pediatric airways. Conversely, EMS medical directors may opt for more robust training and oversight of their system's pediatric intubation program. A recent review of a statewide EMS database revealed >67% ALS providers performed two or fewer endotracheal intubations per year, and >39% did not perform any (8). Another study evaluated pediatric medication dosing errors in children treated by EMS. During the study period 4% of the children were administered drugs and had a documented weight. Weight-based medication dosing errors occurred in 35% of drug administrations (9). Paramedic encounters with pediatric patients are infrequent. Alone they are unlikely to ensure clinical acumen and skill proficiency. Robust EMS educational initiatives are needed to address the maintenance of pediatric skills in prehospital providers.

EMS AND TRAUMA

The “modern era” of EMS in this country was ushered in as a response to traumatic injury and death on America’s highways. Trauma was the catalyst for the drafting of the white paper (“Accidental Death and Disability: The Neglected Disease of Modern Society”) that prompted improvement of essential prehospital infrastructure, training of personnel, and establishment of practice guidelines. In the 50 years since the drafting of the white paper, three basic tenets of trauma patient management in the prehospital setting have clearly evolved. They include (a) rapid response to the patient, (b) effective management of ventilation, oxygenation, perfusion, and immobilization, and (c) rapid transport to the most appropriate facility.

Rapid response to the patient is determined by multiple factors including recognition of the event, access to the 911 system, the efficiency of the communications center, and the proximity of units available to respond to the scene.

Effective management of ventilation, oxygenation, and perfusion is determined by the quality of the education provided for the responding EMS personnel and the quality of medical oversight enjoyed by the service. Quality adjuncts to the core curriculum of training exist in programs such as Prehospital Trauma Life Support and Basic Trauma Life Support. These programs champion principles of prehospital trauma care, such as scene safety, rapid primary survey, airway control, adequate oxygen delivery and ventilation, control of hemorrhage, management of shock, immobilization, and transport.

Rapid transport of the patient to an appropriate facility is determined by EMS education and medical oversight but can also be facilitated by regional trauma systems. EMS education and oversight are critical for limiting the scene time, focusing on those interventions that are thought to be life saving in the first few minutes of the EMS response and not wasting precious time on interventions that could be performed en route to or in the hospital. The goal is to preserve as much as possible the “golden hour” after the injury until arrival at the appropriate medical treatment facility. Regional trauma systems facilitate this tenet of prehospital care by

identifying the appropriate trauma centers in a region and establishing guidelines for patient transport to these facilities. Guidelines are published for field triage of trauma patients (Fig. 376.2) (10). Air medical transport systems also play a role in regional trauma systems and assist in ensuring the rapid transport of injured patients to appropriate medical facilities. Guidelines for the use of air transport are promulgated by the National Association of EMS Physicians and the Air Medical Physicians Association (11).

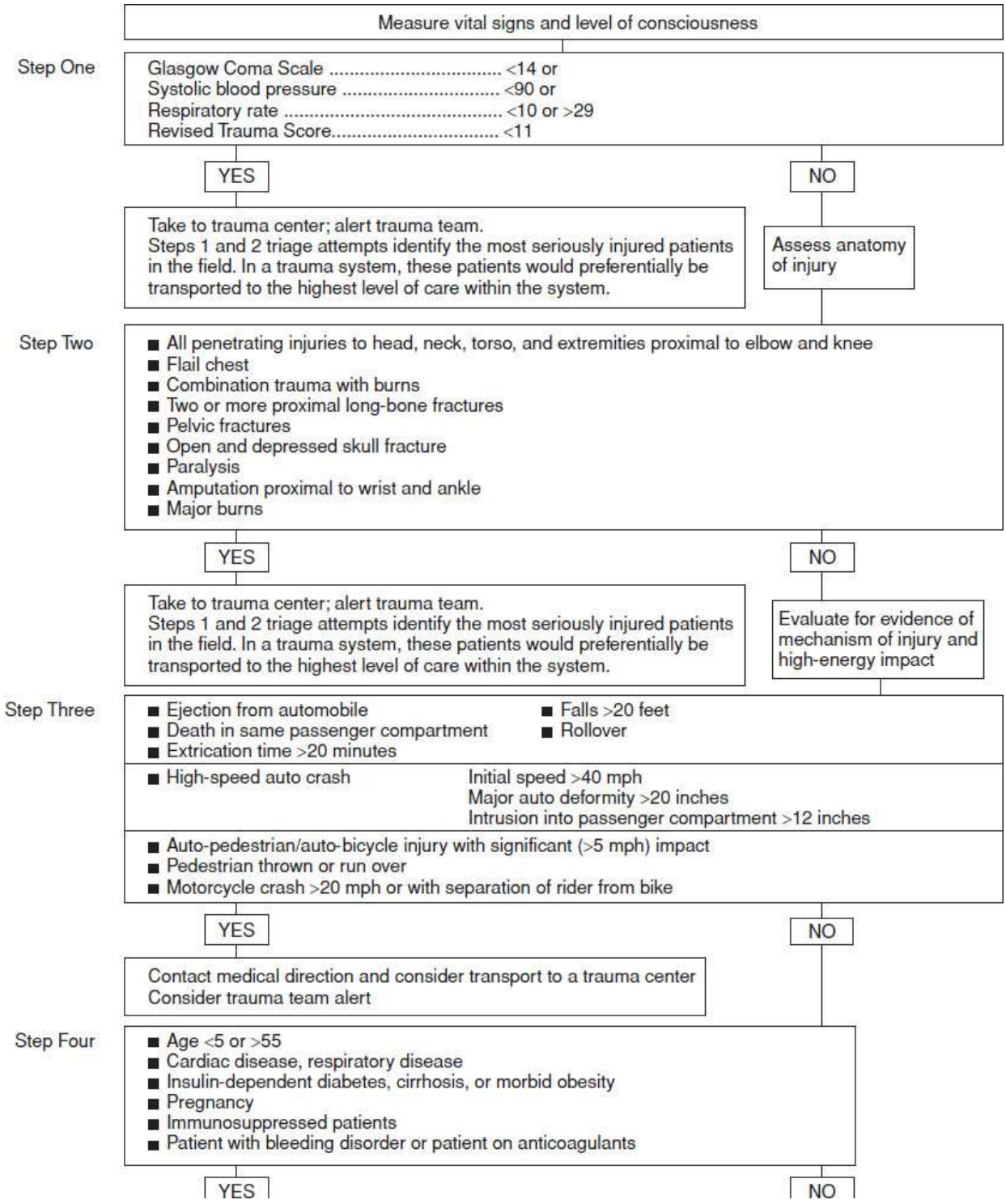

FIGURE 376.2 2011 Guidelines for field triage of injured patients (in the public domain and available at http://www.cdc.gov/fieldtriage/pdf/decisionscheme_poster_a.pdf).

The NHTSA and many other stakeholders in the management of trauma patients have drafted the Trauma System Agenda for the Future. Prehospital care is identified as a fundamental component of the trauma care system, along with injury prevention, acute care hospitals, and posthospital care. Challenges to quality prehospital care of trauma patients include isolation of EMS from the injury prevention and acute care hospital components of care, inadequacies of the national 911 system, inequities in distribution of EMS resources, prolonged transport times from rural communities, over- and undertriage of patients to trauma centers, and ED overcrowding and diversion. Visions for the future include (a) better integration of EMS into injury prevention initiatives and improved dialogue with treatment facilities, (b) standardized protocols and triage, (c) strategic placement of transport vehicles to improve access in rural, underserved communities, and (d) improved communications, including automated collision notification, universal 911 coverage, and enhanced communication with prehospital providers facilitating more accurate triage and delivery of care.

There is a need for prospective randomized controlled clinical trials to resolve the many controversies regarding medical interventions in the prehospital care of the trauma patient. Research can challenge the very basic tenets of patient management in the out-of-hospital setting.

Because of the risk of aspiration and increased mortality associated with hypoxemia in patients with traumatic brain injury (TBI), endotracheal intubation has become a goal of prehospital management. It was then somewhat surprising when, in a recent study, paramedic rapid-sequence intubation protocols, which have been shown to increase the intubation success rate, were associated with an increase in mortality in head-injured patients (12). Another study showed that when compared with ED endotracheal intubation, prehospital intubation of TBI patients was associated with nearly a fourfold increase in mortality (13). These studies and others have led to a careful examination of inadvertent hyperventilation and the increased mortality associated with severe hypocarbia in TBI patients intubated in the field (14). Research of clinical care provided in the

prehospital environment is critical for evaluation of interventions and their contribution to patient outcome.

Management of casualties on the battlefield is informing the control of external hemorrhage. Demonstrated efficacy of the prehospital application of tourniquets with minimal associated complications, when ischemic times are limited, has led to adoption of their use in the civilian environment for control of rapid extremity exsanguination. The use of hemostatic agents in the prehospital setting is also being adopted (15).

Longboards used for spinal immobilization are increasingly recognized as contributors to pain, patient agitation, and respiratory compromise. More judicious backboard use and setting appropriate alternatives are being encouraged (16).

RESEARCH AND INITIATIVES FOR THE FUTURE

Proper prehospital provision of care requires research that explores both system design and clinical interventions. Much of the delivery of prehospital care is not supported by research that demonstrates improved patient outcome. The NHTSA and its partners address the science of prehospital care in its National EMS Research Agenda. It identifies five major impediments to the performance of high-quality research: (a) a paucity of highly skilled researchers, (b) inadequate funding, (c) failure of EMS professionals to acknowledge the importance of EMS research and its transition into practice, (d) lack of data integration that promotes study of patient outcomes, and (e) difficulty in obtaining informed consent in the prehospital environment. The Agenda offers a strategy to overcome these obstacles.

Despite these obstacles to evidence-based care, several good studies have been published that better inform the design of EMS systems and delivery of out-of-hospital care.

The Ontario Prehospital Advanced Life Support (OPALS) Study is a large prehospital study that involved more than 25,000 CA patients with the intention of evaluating the incremental benefit of rapid defibrillation and prehospital ALS measures for CA survival (17). Phase I of this trial reported the baseline survival status after

introduction of an automatic external defibrillation (AED) program in an area in which no AED or ALS services were present (18). Improved survival from CA was associated with younger age and a witnessed event. The authors identified three other areas that are amenable to EMS system optimization: (a) survival may be improved by minimizing EMS response intervals; (b) survival is improved threefold if CPR is initiated by a bystander; and (c) survival doubled if initiated by fire or police first responders. Phase II of the trial verified that procedures that reduced the time to defibrillation significantly improved the survival to hospital discharge rate. An improvement from 72% to 93% for calls responded to within 8 minutes or less by the AED crew resulted in a 33% relative increase in the survival rate (19). Phase III of this study evaluated introduction of ALS interventions (endotracheal intubation, intravenous drug therapy) for the management of out-of-hospital CA in a previously optimized rapid defibrillation program (20). This trial did not identify any incremental mortality benefit associated with ALS interventions in this setting, though intermediate survival outcomes, such as return of spontaneous circulation and admission to hospital, did improve. It did also confirm the association of early access, early CPR, and early defibrillation with improved mortality. The OPALS study also evaluated a specific regimen of ALS interventions for the management of acute respiratory distress (congestive heart failure, pneumonia, chronic obstructive pulmonary disease, and asthma). The study showed a significant decrease in mortality from 14.3% to 12.4% when ALS interventions were introduced (21).

The study of out-of-hospital CA survival is one important benchmark for the evaluation of EMS system effectiveness. The Cardiac Arrest Registry to Enhance Survival (CARES) collects standardized, confidential, out-of-hospital CA survival data and shares it with the local EMS providers and communities, giving them the opportunity to evaluate, benchmark, and improve their survival rate from sudden cardiac death (22).

EMS faces significant challenges. A dated but still accurate assessment of state systems found a lack of (a) comprehensive EMS

legislation and statewide EMS plans, (b) enhanced communication systems, (c) consistent quality-assurance programs for training courses and instructors, (d) enabling legislation for trauma system development, (e) consistent and adequate funding sources, (f) priority for public information and education programs, and (g) effective data collection and evaluation systems (23). The EMS Agenda for the Future is a blueprint with recommendations for improvement of 14 EMS attributes: (a) integration of prehospital care with public health, injury prevention, and acute care, (b) EMS research, (c) legislation and regulation that will fund essential federal and state initiatives, (d) system finance to ensure proper EMS infrastructure development, (e) human resources to provide a viable career path for prehospital care providers, (f) medical direction with appropriate credentials and sufficient resources, (g) education systems for the development of quality prehospital providers, (h) public education to better inform the community on EMS utilization, (i) injury prevention, (j) public access, (k) EMS communications, (l) prehospital clinical care, (m) information systems, and (n) evaluation of service regarding medical outcomes and cost effectiveness (24). Through its unique position in the community as a link to healthcare access, the "scope of service" of EMS systems may expand to encompass injury prevention and preventive medicine initiatives, complementing and enhancing roles currently served separately and independently by other agencies.

Common Pitfalls

- Introduction of prehospital medical interventions without adequate investigation regarding improvement in patient outcome.
- Failure to insist on engaged medical direction in the delivery of prehospital medical care.
- Failure to have a well-understood, rehearsed, and commonly recognized plan for responding to an MCI.
- Failure to provide an effective plan for communication during an MCI.

- Failure to adequately plan for HAZMAT situations, terrorist activities, and mass gatherings.
- Failure to educate EMS providers on the special needs and management of ill and injured children.

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CHAPTER 377

Air Medical Services

Theodore R. Delbridge

Air medical services provide transportation by rotor or fixed-wing aircraft while delivering sophisticated medical care. Optimally, they are well integrated with regional emergency medical services (EMS) and the entire emergency healthcare system. Emergency physicians should be aware of local air medical service resources, potential advantages and disadvantages of their utilization, flight physiology that may affect patients, and limitations of caring for patients in an aircraft.

HISTORICAL PERSPECTIVE

Currently, there are more than 260 air medical services deploying more than 900 helicopters throughout the United States. From 2003 to 2012, the number of helicopters being used as air ambulances increased each year (1). More than 100 services utilize fixed-wing aircraft for longer-distance transports. Approximately 30% of helicopter medical missions involve response directly to an injury or illness scene. The remainder of air medical cases involves the spectrum of seriously ill and injured patients requiring transfer from one medical facility to another.

The genesis of air medical transport can be linked to military conflict. During the Korean Conflict, mortality among wounded US soldiers was less than during World War II. At least part of that reduction was attributed to faster access to surgical care as a result of helicopter use. Helicopters were tools to overcome rough terrain and poor roads that ground vehicles would have to use. However,

no care was provided during transport, as patients were secured to litters outside the aircraft cockpit. By the Vietnam War, both helicopters and medical care had become more sophisticated. Wounded soldiers evacuated from the field were now transferred inside a helicopter, and emergency medical care commenced or was continued in flight. Air evacuation of wounded soldiers contributed to lowering the mortality rate to less than 1 per 100 casualties. The average time to reach definitive surgical care decreased from 6 to 12 hours during World War II, to 2 to 4 hours during the Korean Conflict, to 35 minutes during the Vietnam War. Currently, well-coordinated rotor and fixed-wing transport systems can get wounded soldiers to specialized definitive surgical care on a different continent within 12 to 18 hours of sustaining a serious injury.

During 1966 and 1967, army helicopters evacuated 40 civilian patients in Alabama and Texas. Between 1967 and 1970, government-funded projects verified the utility of helicopters for civilian air medical missions. They confirmed that helicopters could evacuate rural patients, make safe landings in metropolitan areas, and save valuable time. The Military Assistance to Safety and Traffic program, initiated in 1970, resulted in average time savings of 53 minutes, when compared to ground ambulances (2).

In 1970, the Maryland State Police also established its medevac program as part of a statewide EMS system. Placing helicopter bases throughout the state resulted in shorter response times to scenes and referring hospitals. The first civilian hospital-based medical helicopter program began operation at St. Anthony Hospital Systems in Denver, CO in October 1972.

Many of the same issues that affected earlier air medical programs are still germane. These include maintenance of complex and expensive communications systems. Such systems must provide reliable means of receiving requests for service from various sorts of callers, dispatching helicopters, following the progress of ongoing flights, transmitting and receiving clinical information, and facilitating online medical direction. Advances in technology have improved the reliability of effective communications across large

areas. At the same time expectations have expanded regarding the types and amount of data that are conveyed, including aircraft systems, crew, and patient clinical information.

Preparation and monitoring of the air medical crew is an obvious concern. As the sophistication of medical care has increased, so has the complexity of patients being transported. Thus, air medical crews must be more familiar than ever with an always expanding potential of therapies and interventions that they might be called on to initiate or continue as part of safely moving a critically ill patient to definitive care. Monitoring performance is a clear priority and often a challenge as a result of the relative isolation in which care is delivered. Finally, air medical services have struggled and will continue to struggle with fiscal reality. The balance between the desire to provide service and the associated costs and ability to generate revenue can be delicate. Part of the struggle entails concerns for appropriate utilization.

Nevertheless, the priorities that initially stimulated development of air medical services still remain. Mortality from trauma is higher in rural areas where transit times to trauma centers are typically longer. Approximately 28% of the US population is within an hour of a level I or II trauma center only if there is a helicopter available in their region (3). A disproportionate number of motor vehicle–related deaths occur on rural roads and highways, emphasizing the need for an EMS transportation system that is capable of expeditiously moving patients to regional trauma centers. Furthermore, regionalization of systems to care for patients with stroke, acute myocardial infarction, and serious pediatric problems has relied on air transport to appropriately distribute patients to designated centers for the care they need (4,5).

ADVANTAGES OF AIR MEDICAL SERVICES

Air medical services offer two principal advantages over ground ambulances: speed and the ability to overcome geography. When used appropriately, these advantages can result in significant savings of time to reach a trauma center or other tertiary care

facility. In the case of trauma patients, there is an understanding that the sooner the patient arrives at the trauma center, the lower the morbidity and mortality. Reducing the time to receive definitive therapeutic interventions is also important for other conditions, including stroke and acute myocardial infarction. For critically ill patients being moved between hospitals, the speed of a helicopter or a fixed-wing aircraft may result in less time outside the more controlled environment of an emergency department (ED) or intensive care unit (ICU). This can be an important consideration when precipitous deterioration is potential or when complicated therapies are difficult to maintain in transit.

To fully benefit from the potential time savings of air medical transport, it is necessary to consider all of the related events that consume time. An aircraft might provide the fastest means to get a patient to his or her destination hospital, but a number of things must occur before the patient is actually on the way. Once dispatched, helicopter liftoff typically takes several minutes, and there is no established standard. Part of that time is consumed by the pilot who must make an assessment of all the factors, such as weather, that might affect the safety of the proposed mission. For the majority of air medical services the pilot's judgment then requires validation by an aviation dispatcher at an operations center in a different location. Response time to the scene must be considered, and landing might take an additional 3 to 5 minutes. Generally, the more familiar the helicopter crew is with the landing zone and the better prepared it is, the shorter the landing time will be. Established helipads provide for the fastest and safest approaches and landings. In many cases, as a result of the difficulties in caring for patients in an aircraft, additional patient preparation must occur before initiating transport.

When considering potential time savings of air medical transport, one must weigh the total interval from the time of the request for a helicopter or fixed-wing aircraft to patient arrival at the receiving facility. It is this time that should be compared to ground ambulance transportation. In general, to optimize time-saving effects of air

medical services, they should be requested as soon as there is sufficient information to indicate their need.

Medical helicopters often are based at or near the hospital to which patients will be transported. In those cases, the response time to an injury scene or to a referring hospital is the same as the transport time. However, when air medical resources are dispersed, so that helicopter bases are remote from the receiving hospital, response times to the referring scene or hospital may be shorter, and the time savings of air medical service utilization may be enhanced. Medical helicopters typically offer little advantage in urban areas or when transport distances are short. When the transport distance is longer than 25 miles and the medical helicopter is readily available, time savings are more likely. Time savings may result for shorter transport distances if the helicopter is dispatched before the patient is ready to go, such as in cases of prolonged extrication at crash sites or when stabilizing measures are ongoing in an ED. In these circumstances, the response time of the helicopter becomes negligible.

Two pitfalls of air medical service utilization are common. The first is not summoning the service immediately when the potential need is identified. Ideally, the patient would be ready for transport and the air medical service would be ready to receive the patient at the same time. Delays in requesting or dispatching a medical helicopter can result in a patient who is then waiting for the helicopter to arrive. The second is not accounting for all the time-consuming steps required to get a medical helicopter or fixed-wing aircraft to the patient. It is not unheard of that two patients are transported from the same motor vehicle crash. One goes by ground and the other by helicopter, and the one by ground arrives at the trauma center first. While the helicopter traveled faster, all the other required steps actually made it a slower means of achieving the primary objective.

There are cases when speed is not the primary factor in choosing to utilize an air medical service. An additional potential benefit is the availability of higher levels of care during transport. Air medical service crew configurations typically consist of two clinicians

including paramedics, nurses, respiratory therapists, and physicians. The crew configuration is the result of local preference and, in some cases, state regulations. In some systems, the crew may be modified for special clinical circumstances. The result is often an air medical crew that is able to manage ongoing or potential problems better than available ground ambulance resources. Thus, the clinical expertise of the transport team and its ability to move a patient safely in an environment that is less controlled than an ED or ICU may be the major indications for air medical service utilization.

DISADVANTAGES OF AIR MEDICAL SERVICES

The three principal disadvantages associated with air medical services are complex logistics, safety, and cost. These disadvantages are appropriate to consider each time an air medical mission is contemplated.

Logistically, getting a helicopter or fixed-wing aircraft to a scene or referring hospital can be complicated. After realizing the need for an air medical service, the first step is notifying a communications center. Calls may arrive at the center from many sources including hospitals, medical control facilities, EMS agencies, law enforcement agencies, fire departments, and other communications centers. The goal then becomes to determine the location, identify the closest available helicopter, and assess whether the mission can be completed safely.

The communications center must coordinate closely with the pilot, who should remain unaware of the clinical situation to avoid biased decision making. The pilot must assess suitability of the weather and the aircraft for the proposed mission. In addition to the air medical service's communications center, separate operations centers may monitor pilot decisions. These operations centers are specific to the aviation contractors who provide pilots, mechanics, and other resources to air medical services. For each proposed mission they verify weather conditions, the mechanical readiness of the aircraft, and the qualifications of the pilot, helping to ensure that pilots are making good preflight decisions.

The incident location must be translated into information that can be used for navigation, such as latitude and longitude that can be programmed into a global positioning system (GPS). Throughout the mission, the communications center should be in continual contact with the helicopter to track its progress, convey vital patient information to the medical crew, facilitate updates to the air medical crew from ground-based medical providers (and vice versa), and implement contingency plans when necessary. Contingency plans may be necessary in cases of mechanical failure, change in weather, or change in patient condition. While en route, the helicopter crew should be able to communicate with the ground team to receive updated patient-related information when appropriate and ensure adequate preparation for a safe landing zone.

Requesting a medical helicopter to transport a patient significantly increases the workload for on-scene EMS and public safety workers and for hospital personnel when the response is to a hospital. Resources at the scene or referring hospital must be sufficient to coordinate the helicopter's arrival without distracting medical personnel from delivering care.

Safety issues should always be at the forefront. Although many safety-motivated procedural improvements have been made over the past three decades, medical helicopter operations remain inherently more dangerous than other routine helicopter operations. The safety record of air medical services has fluctuated. From 2001 to 2010 there were 132 medical helicopter accidents, defined as events resulting in aircraft damage or injury. Of these, 34% resulted in at least one fatality (6). Year-to-year, medical helicopters consistently have higher rates of fatal crashes per 100,000 flight hours than other categories of aviation (7). Crashes that occurred in darkness and poor weather conditions were more likely to result in a fatality (8). However, not all crashes involved patient care missions, as some occurred during maintenance flights and other operations. Among 131 crash-related fatalities between 1998 and 2008, 16 were patients being transported (7). This represents an estimated risk of 0.76 per 100,000 air medical transports (7). How this compares to

ground ambulances and their potential for crashes given similar distances traveled remains unclear.

Nevertheless, each tragic event serves as a reminder that air medical service utilization is not without risk. Safety risks should be considered carefully and weighed against perceived benefits. Strict adherence to safety standards is mandatory for both personnel on the ground and those in the helicopter.

The costs associated with air medical services are considerable. Medical helicopter bases may require $1.5 to $3 million per year to maintain, depending on the helicopter model, personnel qualifications, and abilities to achieve economies of scale. It is predominantly these fixed costs that determine the expense of providing air medical services. The incremental costs for a specific mission (the additional costs for providing service to one more patient) are approximately $1,000 to $1,500 depending on the aircraft model and distance traveled. Most of that relates to fuel consumption and aircraft maintenance. In Maryland, where most air medical services are provided by the state police, the cost of completing one mission has been estimated to be $5,000 (9).

Although the cost of providing air medical services may be significant, these costs are not necessarily unreasonable when compared to other alternatives. Air medical services, as a system, may cost less than providing similar care for interfacility transportation through a network of ground ambulances. Cost differences relate directly to helicopters' capacities to effectively serve larger geographic areas by virtue of speed and abilities to eliminate geographic barriers. The cost-effectiveness of air medical services has previously been determined to be $1,400 to $9,677 per year of life saved. For trauma patients, in particular, the estimate is $2,227 to $3,292 per year of life saved (10). A cost-effectiveness model based on more than 200,000 trauma patients indicated that helicopter transport must provide a 15% relative risk reduction of mortality, or 1.3 patients per 100, to cost less than $100,000 per quality-adjusted life year gained (11). Such a cost is consistent with those for other societal healthcare priorities.

AVIATION ISSUES

Because air medical services are a tool for providing clinical care, it is helpful for physicians to understand some of the inherent aviation issues. The most relevant factors are the limitations of the aircraft and the limitations of the pilot. Weather is a consideration for both.

Medical helicopters are either single- or twin-engine turbine powered aircrafts. Twin-engine outnumber single-engine aircrafts for air medical use. They are generally felt to be safer by virtue of mechanical redundancy. However, it is not clear that the number of engines greatly affects the safety profiles of air medical services. Helicopter crashes with mechanical causes rarely have to do with engine failure. Helicopters generally travel between 100 and 160 miles/hr, with useful loads of 1,500 to 3,000 lb. The concept of *useful load* is important; it includes all the medical equipment and helicopter crew. The useful load can also be affected by weather conditions, the amount of fuel on board the helicopter, and the mean sea level altitude of the helipad from which the helicopter will be departing. All of this determines the weight of the patient who can be transported and the equipment, personnel, or family that may accompany him or her. Patients may be heavier if the helicopter crew is lighter, there is less equipment, there is less fuel on board, the weather is cooler and less humid, and the helipad or landing zone is closer to sea level.

Medical helicopters may not operate in icing conditions; this can be catastrophic if not avoided. Thus, operations in some forms of precipitation are not possible. Flight through clouds might not be possible depending on the air temperature.

Most air medical services operate under visual flight rules (VFRs), limiting the required equipment on board, the helicopter, and pilot qualifications. VFRs require visibility to be 1 mile during the daytime and 2 miles at nighttime and a cloud ceiling (distance from the ground to the base of clouds) to be 500 ft or higher. Local conditions, including topography, may necessitate the visibility and ceiling to be greater.

Some air medical programs are capable of operating under instrument flight rules (IFRs). As the term implies, the pilot flies the aircraft by reference to onboard instruments instead of outside visual clues. The general limitation of IFR operations is the necessity to fly from one airport to another one at which there is a bona fide instrument approach developed to facilitate landing in marginal or poor weather conditions. Thus, patients must be first moved to, and then from, an airport to travel via helicopter. This is obviously time-consuming, eliminating some of the benefit of air medical service. GPS technology enables development of instrument approaches to locations other than airports, including hospital helipads. Although these are not widespread, a few air medical services have developed GPS approaches to serve places they often are requested to respond to in suboptimal weather conditions.

The pilot is the lynch pin of air medical service operations, as he or she is ultimately responsible for the safety of the crew and aircraft. Potential for pilot fatigue should be monitored, as it may adversely affect performance. Pilots' decisions regarding aviation issues must be made in the absence of knowledge of clinical circumstances, which may be compelling and inappropriately bias the process. Pilots must maintain the authority and responsibility to make safe decisions and should not attempt to complete a transport mission in unsafe conditions.

One of the factors thought to make air medical service operations more dangerous is the need to land helicopters at makeshift landing zones. Ground personnel usually have variable experience in setting up landing zones and conveying information about hazards to the helicopter pilot. Pilots may be unfamiliar with the area and surrounding hazards and may be distracted by adjacent activity and lights. One solution is to develop predesignated landing zones that EMS and public safety agencies preferentially use. The air medical service can then have pre-existing knowledge about potential hazards, and the landing zones can be set up systematically when needed. Another advantage is pilots' familiarity, and established locations are easier to navigate to and identify.

In some regions, fixed-wing aircraft may be valuable components of air medical services. They are usually twin-engine propeller or jet engine aircraft, capable of cruise flight between 200 and 400 miles/hr. Their useful loads are generally thousands of pounds, and their range is much longer than helicopters. Another advantage is their ability to fly in more adverse weather conditions than helicopters can. Fixed-wing aircraft fly from airport to airport, necessitating ground transport legs on each end of the patient flight. Thus, a fixed-wing aircraft is used to save time when the transport distance is usually 150 miles or longer. Fixed-wing aircraft often cruise between 14,000 and 30,000 plus feet above the ground. Their cabins are typically pressurized to the equivalent of 4,000 to 8,000 ft above mean sea level.

MEDICAL ISSUES

Medical issues relate to the interplay between patients' clinical conditions and physiologic effects of flight and the capacity to initiate or continue care during air medical transport. When emergency care practitioners appreciate these issues, they are better able to select appropriate patients for air medical transport and prepare them for that event.

Flight physiology is a discipline unto its own. Two concepts are particularly germane to ill or injured patients. First, as altitude increases, atmospheric pressure decreases and gases expand. The result is that gas-filled spaces expand. For seriously ill or injured patients, critical spaces might include pneumothoraces and the gastrointestinal tract. Additional air-filled spaces that the air medical crew must be cognizant of include patients' middle ears, endotracheal tube cuffs, air splints, and intravenous fluid bags. Second, as atmospheric pressure decreases, the partial pressure of oxygen decreases. The proportion of oxygen in the air remains constant (approximately 21%). However, because the total atmospheric pressure is less at higher altitudes, so is the pressure of oxygen within the mixture of gases that comprise air. Because the solubility of a gas (i.e., oxygen) within a liquid (i.e., blood) is

proportional to the partial pressure of the gas in contact with the liquid (i.e., within the lung alveoli), a patient's ability to remain well-oxygenated decreases at higher altitudes.

Most air medical transports via helicopter are conducted within 2,500 ft of the ground. Thus, the physiologic effects of flight are limited. However, by merely ascending 2,000 ft above the ground, patients' oxygen requirements are increased by approximately 8%, and air-filled spaces will increase in volume by approximately 8%. Previous guidance suggested that a patient with a known pneumothorax should receive a thoracostomy tube prior to air medical transport. However, one model of pneumothorax found 1.5% increase for every 500 ft ascended (12). Thus, knowledge of local air medical services and their practices can help a referring physician consider the risks and benefits of placing a chest tube in the context of the clinical situation and physiologic changes that might occur in flight. A stable patient with a modest pneumothorax who is going to be taken to 1,500 ft above the ground might be considered for close observation during transport. A different patient with a larger pneumothorax or who is going to be taken to 5,000 ft above the ground should perhaps receive a chest tube before transport. The objective is to diminish the potential for precipitous deterioration as a result of pneumothorax expansion from the primary injury in conjunction with altitude changes.

Additionally, seriously ill and injured patients should receive supplemental oxygen during flight. It is important to understand that if there is difficulty in achieving adequate oxygenation on the ground, the problem will only worsen during air transport. There must always be the capacity to increase the supply of oxygen to patients during air transport beyond what they were receiving on the ground.

When patients are transported in helicopters operating in IFR conditions or in a fixed-wing aircraft, even more attention must be paid to the physiologic effects of flight. Helicopters operating in IFR conditions are often 5,000 or more feet above the ground and, as noted, fixed-wing aircraft cabin pressures are usually equivalent to 5,000 to 8,000 ft above mean sea level. Thus, the potential for air-

filled spaces to expand and patients' oxygen requirements to increase are significantly greater than during low-altitude helicopter operations. One specific group of patients for whom this is a concern are those with dysbarism related to scuba diving. Decreases in the atmospheric pressure to which they are exposed, whether via commercial air travel or air medical transport, can cause precipitous deterioration.

Other important factors include effects of vibration and decreased temperature and humidity as altitude increases. Air medical crews must be cognizant of patients' exposure to ambient air. Ill patients who might lack intact thermoregulation may be susceptible to rapidly changing air temperature as altitude changes. The adiabatic lapse rate results in approximately 2°C temperature decrease for every 1,000 ft ascended. Crews must also be aware of the need to monitor possible and insensible fluid loss, particularly among patients receiving nonhumidified oxygen. Finally, aircraft vibration and noise are thought to create a potential for autonomic instability in critically ill patients.

The capacity to monitor patients' conditions and initiate and continue care during air medical transport should be a constant concern. It is partly the difficulty in monitoring patients that prompts pretransport placement of thoracostomy tubes for patients with pneumothoraces. In helicopters and many fixed-wing aircraft, breath sounds can be difficult to hear, blood pressures can be difficult to auscultate, weak pulses can be difficult to palpate, and patients can be difficult to communicate with. Cardiac monitors, pulse oximeters, noninvasive blood pressure monitors, and capnographers facilitate patient monitoring, but none are entirely foolproof. Air medical crews must continuously assess the quality of data before interpreting and relying on it.

The ability to continue ongoing care is usually a function of its complexity and the qualifications of air medical crews. The most common emergency medicine–related examples relate to airway adjuncts and ventilation. It is important to be familiar with the types of airway adjuncts that an air medical crew is trained to use. For example, the crew might lack working knowledge of laryngeal

mask airways (LMAs) and would not be prepared to manage a patient with an LMA in the event it becomes dislodged. They might not be prepared to continue transtracheal jet ventilation. They might also be limited in their abilities to deliver specific modes of ventilation via mechanical ventilator or continuous positive airway pressure support to a spontaneously breathing patient. In such cases, air medical transport might be inappropriate, or modifications to ongoing care or support might be indicated. Another frequently encountered scenario involves ongoing medication infusions that require more intravenous pumps than the aircraft carries. Subsequently, decisions must be made about which medications to continue during transport and which to either hold or infuse without the regulation of a pump.

The ability to initiate new care is obviously limited by the available equipment and supplies within the helicopter or fixed-wing aircraft. The close quarters of an aircraft, limited access to the patient, and sometimes cumbersome access to available supplies can make initiating new therapy more difficult in the air than on the ground. Initiating intravenous access and administering intravenous medications are not too difficult. However, providing new airway support, although possible in most cases, is a task best completed on the ground. Conditions in a helicopter for tracheal intubation are far from ideal. Adult patients are not easily repositioned, and their heads often rest between the caregiver's legs. Thus, in cases in which a patient's airway stability is in question, the airway should be definitively secured before the patient is loaded into a helicopter, the procedure location of last resort.

Combative or uncooperative patients present a special dilemma. The cause of their agitation can be multifactorial, but the ability to address it while airborne is quite limited. Additionally, in such a condition, these patients present a significant risk to themselves and the helicopter crew while airborne. Thus, agitation must be dealt with prior to air medical transport. The risk of oversedation may be a concern due to difficulties in addressing airway instability should it subsequently occur. Therefore, many agitated patients are best

dealt with by sedation, neuromuscular blockade, and tracheal intubation.

A typical dilemma for an emergency care provider who is preparing a patient for air medical transport is how to determine the appropriate amount of preparation. Some clinical situations are best addressed prior to transport. However, not every eventuality can be predicted, nor is it feasible to spend an inordinate amount of time trying. Presumably, air medical transport has been chosen in most cases because of its speed, and there is some urgency in moving a patient from one location to another. It is reasonable to consider the likelihood of potentially serious complications of transport and do what can be done quickly to attenuate that likelihood. Beyond that, excessive efforts to "stabilize" patients before transport, particularly trauma patients, may do more harm than good by delaying arrival at definitive care. There are times when additional stabilizing interventions are preferred prior to transport. For example, some neonatal or pediatric teams bring their expertise to the patient rather than moving the patient to their expertise. They may be able to provide additional care that improves the safety of transport without delaying the care the patient is being transferred to receive. As each case is a unique event, it must be considered in its own context. However, it is always prudent to think about the amount of patient preparation for transport that is necessary and appropriate.

ADMINISTRATIVE ISSUES

The organizational structures of air medical services vary considerably. In the United States, they may be part of public safety agencies, military services in some cases, hospital-based programs, or independent nonprofit or profit-seeking organizations. Likewise, funding sources for these entities vary. Public safety agencies, for example, receive some or all of their support from taxes or licensing fees. Hospital-based programs attempt to recover costs through revenues from patients and their insurance carriers. However, the hospital may provide a substantial subsidy to support the program. Although the air medical program itself might not be profitable, the

patients it brings to its affiliated hospitals may generate significant income for them. Differences in funding sources result in variation in billing procedures and amounts. Third-party payers ultimately decide what appropriate compensation they are willing to provide for air medical services.

Selection of aircraft has multiple implications for air medical services. Helicopters routinely adapted for medical transport have varying characteristics. They differ in terms of size, performance, and operating costs. These result in variation regarding the types of patients and the associated equipment that can be transported. Aircraft size obviously affects interior design. With space at a premium, it is vital to consider equipment and supply needs and their optimal organization to facilitate patient monitoring and treatment. Interior layout among various aircraft even affects abilities to perform cardiopulmonary resuscitation. Ideally, from a physician's perspective, every aircraft would have an abundance of equipment and supplies, with redundancy, to enable optimal reaction to every eventuality and have enough interior room to maneuver about the patient. However, then the aircraft would have to be so large with performance characteristics that it would, for most services, make it prohibitively expensive to operate. Thus, the balance among aircraft performance, size, and cost to operate is important.

As the missions of many air medical services are diverse, so too may be medical direction. Medical directors have evolved from several disciplines, although emergency physicians make up the majority. Mission profiles of air medical services vary considerably. Those that include neonatal patients, complex pediatric medical cases, cardiac surgery patients with invasive assist devices, and other complicated or special populations often necessitate the appropriate inclusion of multiple physician advisors in the medical direction process. They bring added expertise and support for the service, helping to ensure the delivery of optimal care. Similar to the medical direction of a local EMS system, an air medical service medical director should have working relationships with regional

emergency clinicians to ensure excellent communication that facilitates continuous efforts to improve care and service.

Paramedics, nurses, respiratory therapists, and physicians serving as medical crew members typically deliver care using extensive protocols and standing orders. However, the communications system must function effectively so that field personnel can request and receive prompt and qualified online medical direction when indicated by clinical circumstances.

In most cases, the medical crew is composed of a flight nurse accompanied by another flight nurse, paramedic, or respiratory therapist. Part of their sophistication results from intense orientation and continuing education and from their continual exposure to critically ill and injured patients. Several states allow for medications and procedures by flight nurses and paramedics that are not available to ground-based paramedics (13).

Several hospital-based air medical services have, at one point or another, included a flight physician as part of the crew. Less than 10% still do. Earlier findings suggested that nurse–physician teams reduced mortality from trauma to better than what was predicted, and achieved outcomes that were better than nurse–nurse teams. However, these results have not been reproduced (14). As systems mature, it is possible that nurses and paramedics gain valuable experience to the point that adding a physician provides little significant value. Physicians' technical skills rarely augment the proficiency of nonphysician flight teams (15). Although physician judgment has been shown to make important contributions to treatment (15), it is possible that improved protocols and standing orders and communications systems that enable reliable online medical direction have negated some of that benefit.

Air medical services are often called to special situations where added expertise is valuable. Among these are transports involving neonatal or special pediatric populations. Working knowledge and technical competence with the specific needs of such patients is helpful in effecting safe transport to tertiary care centers. Neonatal and pediatric transport teams, supplementing or supplanting the routine air medical crew, often bring expertise in dealing with small

patients, including IV access, appropriate medications and doses, ventilatory support, and other special equipment.

Ensuring the quality of air medical services is a significant challenge with several facets. There are customer service dimensions involving interfaces between the air medical service and calls for help, EMS and public safety personnel, and hospital personnel. There are aviation-related dimensions focused on aircraft maintenance, pilot proficiency, and safety initiatives. And there are patient care dimensions focused on processes of care and outcomes.

Improving air medical service quality is a multidisciplined effort. Audits of certain types of cases and events may identify specific issues. Reviewing medical crew documentation provides only a limited perspective. However, involving the assessments of many of the people who participated in a case, both before and after the transport, helps to complete an appreciation of the entire event and identify areas for improvement in multiple dimensions. For this reason, many air medical services provide follow-up about patients to referral sources. Additionally, they implement systems or streamline processes that facilitate feedback to the air medical service when either positive or negative events occur and for receiving hospitals to provide outcomes' information that may be used to help assess utilization appropriateness.

To enhance safety and quality some air medical services have deployed crew voice recorders and video monitors in aircraft. While the practice might seem intrusive, the recordings have been used to clarify events, review unusual occurrences, and make improvements in aviation procedures, crew resource management, and clinical processes.

UTILIZATION REVIEW

An important aspect of quality improvement activity is utilization review. This should be a community effort to improve appropriate utilization of air medical services. Those who call on air medical services should review cases to determine their appropriateness and provide guidance to their staffs. Air medical services should review

their cases to provide guidance and feedback to referring agencies and hospitals.

Ideally, assessment of whether utilization of air medical services was warranted is based on some knowledge of the patients for whom it provided a difference. Unfortunately, this is not always entirely clear, although intuitively it makes sense in some clinical conditions. The most significant evaluations have been performed regarding trauma patients; however, these studies often suffer from limited sample sizes, selection biases, and confounding factors.

Previous investigations found reduced mortality among trauma patients when they were transported by a hospital-based helicopter as opposed to advanced life support ambulance. Among 150 trauma patients transported by helicopter and 150 by ground, mortality was 52% less than predicted in the air group, although it was higher than predicted in the ground group (16). The groups were not homogeneous, however. The ground-transported group was urban, and the helicopter-transported group was rural. A physician in the helicopter meant that initial patient-to-physician contact was sooner for the helicopter-transported group even though their arrival at the trauma center was later.

Among 1,273 patients transported directly from the scene by seven different air medical services, mortality was 21% lower than expected (17). Patients who were more seriously injured, with predicted survival less than 75%, benefited the most. The sicker the patient is, to a point, the more opportunity there is to benefit from an intervention. However, the factors that reduce mortality remain unclear. Although air medical services seem to provide a survival advantage for many trauma patients, the greatest advantage seems to be for the most seriously injured and those who are transported directly from the scene to a trauma center. Air medical response to patients with moderate to severe traumatic brain injury and subsequent transport directly to a trauma center is associated with improved odds of better outcomes (18). Further, among traumatic brain injury patients who underwent endotracheal intubation in the field, the odds ratio of mortality or poor neurologic outcome was

significantly higher if transported to the trauma center by ground ambulance as opposed to EMS helicopter (19).

Other studies have documented limited benefit when helicopter and ground-transported trauma patients were compared. When 15,938 helicopter-transported patients were compared with 6,473 ground-transported patients, there was no effect on estimated odds of survival (20). Another investigation yielded similar results after comparing 1,346 helicopter and 17,144 ambulance-transported trauma patients (21). There was a tendency toward improved survival among patients with higher injury scores, but most of the study population had relatively minor injuries.

Finally, an evaluation of the American College of Surgeons' National Trauma Data Bank examined a cohort of more than 200,000 patients taken to level I or II trauma centers by either medical helicopter or ground ambulance. Helicopter transport was found to have an absolute risk of mortality reduction of 1.5% (22). If true, then the number needed to treat, transport by helicopter instead of ground, to save one additional life is 65.

One reasonable conclusion to draw from the available literature is that air medical transport may positively affect outcomes among a subset of trauma patients: those who are more severely injured. Such patients are likely to have lower prehospital trauma scores and lower Glasgow Coma Scale scores. Thus, indicators of severe injury at the scene or community hospital ED may be reasonable indications for utilization of air medical services to transport a patient to a trauma center. An approach to achieving improved cost effectiveness is to utilize air medical services appropriately for patients at higher risk of death or poor outcomes, and to minimize their utilization for patients for whom they are not likely to make a difference (11). Ideally, each air medical service would strive to stay busy transporting patients for whom it might make a difference in outcomes.

The Association of Air Medical Services and the National Association of EMS Physicians have published criteria for appropriate use of air medical services (23). For trauma patients, consideration might be given to evidence of injury by virtue of

objective scoring systems, anatomic injury, or physiologic derangement; difficulty in accessing the patient by ground; serious mechanism of injury; and a significant increase in transport time. Many EMS systems have adapted these or similar criteria to guide decisions of whether to send or not send an air medical service to a scene.

Certain patients, by virtue of the extent of their injuries, are not appropriate for air medical transport. For example, patients who suffer blunt trauma cardiac arrest at the scene will not survive. Transport by helicopter will not change the outcome but exposes several people to the risk of flying and working around an operating helicopter (24).

For nontrauma patients, there is an even greater paucity of information regarding appropriate utilization of air medical services. Locally adapted guidelines might include cardiac patients requiring transport to receive emergency invasive reperfusion therapy, stroke patients being transported to receive emergency reperfusion therapy, neurosurgical patients who are to undergo emergency evaluation for potential craniotomy, high-risk obstetric patients with imminent complications, and tenuous pediatric and neonatal cases. In all such cases, there should be two overriding tenets: (a) The patient requires an emergency evaluation or therapy for a potentially life-threatening problem, and air medical transport saves significant time, or (b) the patient has a life-threatening condition such that ongoing care outside of an ICU is dangerous, and air medical transport significantly reduces the amount of time the patient will spend outside a controlled setting. Regional systems to care for acute myocardial infarction and stroke patients often rely on air medical services to get patients to the site for definitive evaluation and therapy within a defined window of opportunity (4,5). Though it may be possible to demonstrate the overall positive effects of such regional approaches to care, it is more difficult to single out the effects, if any, of air medical services' role. One simplistic view would be to determine what was possible only because the patient arrived to definitive care within a specific therapeutic window. For example, when air medical transport is the

only option for getting a stroke patient to time-sensitive reperfusion therapy within a defined window of opportunity, that might be appropriate utilization.

One approach to retrospectively assessing utilization appropriateness is to determine what critical interventions occurred during transport. The Therapeutic Intervention Scoring System serves this purpose. Previous estimates are that approximately 42% of air medical transports are indicated by virtue of the intensity of care required during transport or on the basis of objective scoring systems (25).

Continued evaluation by all stakeholders of air medical service utilization helps to ensure the appropriate allocation of resources. Just as some overtriage to trauma centers is expected (less injured patients being taken to trauma centers instead of other hospitals) to capture all the patients who might benefit, some overtriage to air medical transport should also be expected. However, to optimize cost effectiveness, it is necessary to keep air medical services busy transporting critically ill and injured patients who might benefit from them rather than keeping them busy transporting patients for whom there would be no benefit gleaned.

Consensus-created guidelines for utilizing air medical services are not equivalent to proof of effectiveness. However, such a proof does not exist for the many patient types routinely transported by helicopter or fixed-wing aircraft. Thus, such guidelines, when developed locally, represent one important basis for evaluating air medical service utilization.

Common Pitfalls

- Delaying helicopter transport by performing excessive efforts to stabilize the patient.
- Requesting air medical transport when it offers no advantage of time savings or safety for the patient.
- Delaying the request for medical helicopter transportation when it is appropriate.

- Failing to secure the airway prior to transport in patients in whom airway stability is in question or in combative patients.
- Failing to consider tube thoracostomy in patients with pneumothorax prior to transport in a helicopter.

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CHAPTER 378 Disaster Planning and Management

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In the past quarter century, disasters worldwide have claimed more than 3.4 million lives (1). As the world population increases and population density rises, a single catastrophic event may affect more victims simultaneously. Further, both the use of hazardous materials and population in hazardous environments (flood plains, earthquake zones, etc.) are rising. Disaster planning and response must include not only the ability to care for casualties but the ability to function in environments rendered dangerous or even actively hostile. The mission of the disaster responder is not only to render aid but also to restore society's homeostasis (2–7).

A "disaster" may be defined as a destructive event that disrupts the normal functioning of a community; it may be natural (e.g., Hurricanes Sandy or Katrina), technologic (e.g., chemical spill), or even deliberate (e.g., the 2013 Boston Marathon bombing, the September 11, 2001 terror attacks, the Madrid and London mass-transit bombings). Combinations of events can worsen the impact of each, such as the 2011 Fukushima nuclear plant disaster after an earthquake and tsunami in the area.

A medical disaster occurs when an event results in casualties that overwhelm the healthcare resources of the community involved (8). Many disasters, such as a jumbo jet crash without survivors, may not in this sense represent a medical disaster, although many slow-evolving events, such as pandemic influenza, may very well represent medical disasters. Response to a disaster may involve all

aspects and needs of a community, including restoring food, water, power, communication, and transportation networks. The role of the emergency physician in a response may not be narrowly limited to emergency medical care, as broader public health knowledge and organizational skills may be necessary, requiring emergency physicians to step outside their usual role of individual patient care and take more of a systems-management approach (9). In the largest-scale events, refugees and displaced populations can be both the result and the cause of disasters (10).

As noted, disasters are classified by origin. *Natural* disasters include earthquakes, floods, volcanic eruptions, hurricanes, tornadoes, winter storms, and other geologic and meteorologic phenomena; in this era of electronics, one may add the effects of solar storms disrupting pager and phone systems. *Human-caused* or *technologic* disasters include explosions, chemical spills, radiation leaks, biochemical terrorism, transportation accidents, civil disturbances, and armed conflicts. *Complex humanitarian* emergencies generally include features of both natural and technologic disasters, such as population displacement that results from a combination of drought, famine, and political upheaval.

In a model that is perhaps more useful for the planner, disasters also may be categorized by onset and impact. For example, earthquakes and tornadoes have a rapid onset, with a sudden impact on the community. In contrast, droughts and famines have a more gradual onset and generally have a prolonged impact. Numerous factors may modify the impact of a disaster on a community, including the nature of the event, time of day or year, health and age characteristics of the population affected, and the availability of resources. Planning for a sudden event should focus on responding with resources on hand, as opposed to the mobilization of resources that can occur in a slower-paced impact (11).

The impact of a disaster also depends on the location where it occurs. For example, an earthquake occurring in a sparsely populated area obviously injures fewer people. In contrast, a similar quake, even one of lesser magnitude, could produce extensive losses of life and property if it occurred in a densely populated region with

poor construction or limited medical resources. Additionally, many may be left homeless or without essential services. Even in the acute medical response to an event, a small community hospital could be easily overwhelmed by numbers and types of casualties that might be handled routinely by a large university hospital or metropolitan medical center (12). Hospitals can be resources in a response but also may be severely affected by the impact of a disaster, and the first priority of a hospital or other essential service must be to preserve its function so that it can play its assigned or necessary role in mitigating the disaster (5).

In the United States, although health care is generally provided by private-sector institutions, governments at all levels have both the responsibility and some capability of supporting disaster medical care. Town or municipal governments often regulate mass-casualty distribution and may coordinate the roles of local hospitals. State governments often serve as providers of funding and equipment, in a support role to local or county agencies, and provide a conduit to request federal aid. The federal government's main role is to provide funding for response, but there are also directly deployable federal assets (people, mobile hospitals, vehicles) available from the military, the Veterans Administration, and the National Disaster Medical System (NDMS). The NDMS has more than 30 specialty teams throughout the country that can deploy to provide field-hospital capability, including advanced specialty care (burns and pediatrics). These teams can be deployed within 6 to 24 hours of request by a state government. The NDMS also provides or coordinates patient evacuation and mass-fatality management (12,13).

DISASTER PLANNING

Disaster planning must address numerous types of events, ranging in scale from small mass-casualty incidents (MCIs), such as motor vehicle collisions with multiple victims, to extensive flooding or earthquake damage, to civil wars. The planning continuum includes advance preparations and provision for supplies, staff, and training

and actual event management and recovery efforts. Those people and organizations responsible for disaster plans must conduct extensive risk analyses, from the sanitation needs of crowds at mass gatherings to evacuation procedures for buildings and geographic areas to the threat posed by terrorist or military action that may be directed at an institution or its personnel (5,6,12,14).

Risk analysis is an essential feature of disaster planning in which a comprehensive inventory is created for all existing and potential hazards that are sufficiently likely to be a threat. Hazards may include such items as chemicals used by local industry, transportation elements such as airports and railroad stations, or collections of large groups of people in areas with limited access, such as high-rise office buildings, nursing homes, or sports stadiums. Environmental and meteorologic hazards must also be considered, such as the presence of fault lines and seismic zones and the seasonal risks posed by tornadoes, hurricanes, and snowstorms. Certain types of disasters can even be considered as "planned events" such as mass gatherings for sports or performance events or political conventions. These events require planning of the same type, although perhaps varying in detail, as do all other disaster responses (15).

Risk analysis should attempt to identify any groups of people at particular risk of injury or death or loss of property from each hazard and groups with particular needs such as children, the elderly, or the disabled. The estimated risk and patient load may vary by time of day, season, or location within a community. Properly conducted risk analysis necessitates the cooperation of corporate, governmental, and community groups to produce a comprehensive listing of potential hazards (1,12,16). It may be possible to reduce the relative risk posed by some hazards. For example, relocating a chemical depot further away from a school would reduce the risk that children would be exposed to hazardous materials.

The other essential step to take in planning is resource identification. Resources include both human and logistic elements, such as organizations with specialized personnel and equipment

(17,18). Disaster preparedness should include assembling lists of medical and paramedical groups, public works and other civic departments, and volunteer agencies, along with phone numbers and key contact personnel for each. Hospital departments should have readily available a complete record of all personnel, including home addresses and telephone numbers, accessible 24 hours a day. Local, state, or federal teams of responders may be available, and a planner must know how this aid can be activated or requested. In the realm of terrorism with weapons of mass destruction, highly trained and extensively equipped specialty teams may be an absolute need for effective disaster mitigation.

Effective disaster planning must occur at all levels, from local institutions to municipal, state, and federal governments, including private, volunteer, and international agencies (19). All groups should understand their own capabilities and limitations and those of the organizations with which interactions are anticipated or intended. The use of a hierarchical management system, such as the Incident Command System (ICS), to coordinate the information and resource management is essential for any large-scale disaster. The ICS is a command system for large-scale firefighting developed by the federal government, which has now been adopted under the name National Incident Management System as the standard system for all US public safety response agencies. Hospitals may choose to use a variant of the Hospital Emergency Incident Command System (a California-developed adaptation of ICS for hospitals) to function within the same structure as all other responding agencies (12). Disaster plans should be both structured and flexible, with provisions made for plan activation and decision making by field-level managers, if indicated.

Once a plan has been devised or a strategy outlined, it must be used and tested. Staff must be trained to carry out their roles in the plan. In general, the best plans assign to each person a role as close as possible to his or her everyday job: “Do what you always do, but faster.” A recurring problem in disaster response is “failure of communications,” but this often actually represents failure of coordination; the message may get through, but the person getting it

does not know what to do about it. True communication failures also may result from several conditions, including loss of infrastructure damaged by the disaster itself, and lack of operator familiarity, excessive demands, inadequate supplies, and lack of integration with other communications providers and technologies. Back-up communications systems, such as wireless, hardwire, and cellular telephones, may reduce the impact of disrupted standard communications. However, frequently, even advanced technology has been ineffectual or overloaded during disasters, pointing out the need for personnel to be well trained in their roles so they can function with minimal outside direction.

An essential step in planning and preparedness is the evaluation of the response, both to real events and after drills and exercises. Exercises to test plans are usually “tabletop” drills in which the responders gather around a tabletop and discuss their theoretical actions. More complex drills may involve activation of communications systems or transport of supplies or staff to different location. The most complex and helpful “functional exercises” may take the form of full-scale multijurisdictional exercises, using moulaged victims and requiring vast resources of supplies and personnel. A plan also may be assessed by computer simulations or seminar sessions focusing on key personnel or limited aspects of the disaster response, but generally this will be of minimal assistance in testing a plan’s real value.

The specific goal of any drill should be clearly understood in advance. If drills are to be used as training sessions and evaluations of preparations and response plans, personnel are more likely to make the correct or most appropriate response choices during the drill if they are prepared. Consequently, they will be more likely to take appropriate actions when faced with an unexpected disaster situation in the future. The more realistic the exercise, the more likely it is that useful information about the strengths and weaknesses of both the disaster plan and the responders will be acquired. The factor common to all disasters is a local shortage of available resources; without experiencing at least some of the stress which accompanies that situation, it is unlikely that the disaster

plan and response will be taxed at a level that realistically simulates the circumstances of an actual disaster.

Essential features of all effective disaster drills are the inclusion of all parties likely to be involved in the disaster response and a joint critique, with a formal debriefing of all participants after the exercise. This review should consider comments from all individuals, groups, or agencies involved in the drill. It is helpful, and essentially mandatory, to designate observers in advance to assess specific aspects of the plan, such as effectiveness of a phone tree or accuracy of medication dispensing. The observations and comments should result in modifications of the disaster plan, if necessary (20). A drill that produces no changes in plans or goals likely did not sufficiently stress the system. Any alterations in disaster plans or response procedures must be communicated to all groups involved or affected. Periodic evaluations of disaster plans are essential to ensure that personnel have adequate familiarity with their roles in disaster situations and to provide for changes in regional emergency response operations, hospital renovations and closings, and other variables. Hospitals have a requirement to conduct at least two disaster-plan exercises per year to maintain compliance with the standards of the Joint Commission on Accreditation of Healthcare Organizations (12,21).

Mass gatherings provide a unique form of “planned disaster.” In general, they will occur in a defined location such as a sports stadium, concert hall, waterfront, or field. Planning should include basic sanitation needs, hydration and environmental protection (against sun, heat, or cold exposure), and both routine medical care (acetaminophen and abrasion care) and full emergency care (cardiac resuscitation). Additionally, planning must address the medical response to a mass-casualty event at the scene, such as might be caused by a vehicle accident or terrorist attack. Staffing for a mass gathering is generally composed of a mix of provider types and levels (first aid, emergency medical service [EMS], nurses, physicians, security, fire, and rescue), a mix of venues (first aid stations, medical tents, ambulances), a mix of roles (on-scene care, evacuation, command and control), and a mix of jurisdictions

(private providers, public safety, city authorities, venue staff, state or federal authorities). This complexity makes preplanning critical for success. In terms of types of patient encounters to be anticipated, the best guide is prior experience at the same event, if available (such as recurring races, sporting events, or concerts). Some data are available in the literature, but the numbers are highly variable. In general, patient volume will be higher in outdoor environments, with younger average crowd age (confounded by event type) and with the increased use of alcohol or other substances in the environment (15,22). It may be appropriate to plan for care of victims of terrorism or other causes of mass casualties at an event.

DISASTER MANAGEMENT

The philosophy of disaster management may be summed up in the phrase, "The needs of the many outweigh the needs of the few." Resources may be so limited that stringent rationing of care or supplies is vital to the survival of the maximum number of people. Austere conditions may be alien to responders accustomed to ample quantities of medical supplies, equipment, personnel, and time, but they are commonly encountered with many large-scale disasters. In this setting, difficult triage decisions must be made to ensure that all resources are used in the most efficient and pragmatic manner (5,22).

The goal of disaster management is to provide the most appropriate intervention and assistance based on the most accurate information available in a timely manner. Disaster response includes several phases (Table 378.1) but must begin with recognition that disaster conditions exist. Some disasters, such as hurricanes, may be preceded by a period of time, called the *preimpact phase,* during which advance information may be gathered about the potential effects of the disaster. The data acquired during the preimpact phase may allow prepositioning of personnel and resources in a strategic location. As a result of a lack of verifiable data, it may be necessary, at times, to begin a response or asset deployment without full

intelligence, with efforts made to tailor and modify the response as updated information becomes available (23).

TABLE 378.1
Components of a Disaster Response

Activation
Notification and initial response
Scene assessment
Response
Organization of command
Search and rescue
Victim triage, stabilization, and transport
Mitigation
Definitive management of scene hazards and victims
Recovery
Scene withdrawal
Return to normal operations
Debriefing
Updating and improving plans and planning
Drills and exercises

The EMS and hospital responders must be aware that triage in a disaster is devoted to providing the greatest good for the greatest number, rather than maximal effort for each patient. Often, patients in cardiac arrest who would normally have received a great deal of care are instead triaged as “expectant” (not resuscitated) so that the personnel and supplies saved may be used to help numerous other salvageable patients. The presence of toxic substances or radioactive materials may also change triage priorities (e.g., severely injured and heavily irradiated patients may be unsalvageable in a disaster setting). There are numerous methods for rapid triage that have been devised, such as the “START” (Simple Triage and Rapid Transport) system, and planners and responders should be familiar with the system in use in their area or institution (12).

Inevitably, in the event of a disaster that produces significant morbidity and mortality, including psychological threats and fears

resulting from terrorist actions, the physician on duty in the emergency department will be one of the first people called on to assume a leadership role. The existence of a hospital disaster plan provides a valuable resource but, ideally, the emergency physician should already be well versed in the administrative and logistical aspects of the plan and the purely medical functions. The response will evolve more smoothly if the emergency physician understands both the hospital plan and resources, capabilities, and disaster plans of the first responders and EMS system in the region. The physician may be required to coordinate or facilitate the hospital response and to provide direction for numerous aspects of the regional response and may be looked to as a resource for hospital administrators who want to know "What should I do?" The physician may also be consulted regarding the need for the deployment of agencies and resources from outside the affected region and will need to know where to direct these inquiries, because they are unlikely to have the knowledge to appropriately answer them. Additionally, emergency department staff should expect to be bombarded with requests for information on all aspects of the disaster and response —from family members, media, and government representatives and from the public at large—and be prepared to refer or respond to such questions. Early in a disaster, the emergency physician and staff will likely be expected to disseminate information about the disaster event, demonstrate expertise and leadership in the response and management efforts, and even make the initial determination that disaster conditions exist. Hospital administrators, social services, and public relations personnel will need to assume their proper roles to allow the ED to continue to provide medical care and should be notified as soon as a disaster is recognized.

In the case of damaged or destroyed healthcare facilities or after a large-scale disaster, the physician may also be called on to provide medical care in unconventional settings. In the situation in which field medical care stations must be established, coordinating responses with other agencies is essential. It is important to remember, during the early stage of the disaster, that information available from those at the disaster area (data regarding death,

injury, or damage) may not be accurate. Problems with communications are frequently the source of delays and misapplications of disaster resources. The ability of those in a region devastated by a disaster to survey the population and infrastructure may be severely curtailed by damage, such that even initial calls for help may be impossible. It is essential, therefore, that external resources of personnel and equipment be available and accessible if anticipation of potential need for them arises (5,22). Conversely, as a result of disruption of communications and transportation, it is possible for the effects of the disaster to be overestimated. To minimize damage and disruption, expedient decisions must be made, with future consequences of such actions considered as well. Short-term benefits and costs must be weighed against their long-term counterparts. Disasters are costly events, but judicious initial expenditures may result in substantial savings, in both monetary and humanitarian terms, over the long haul. Conversely, excessive spending by individuals, agencies, or organizations may result in prolonged or delayed recovery from the disaster and may restrict the capability to prepare or respond when the next disaster strikes.

In the case of a disaster that causes substantial destruction of infrastructure, the response may be prolonged, requiring that long-term healthcare and support services be established. Issues such as nutrition evaluation and ongoing disease surveillance may require the expertise of numerous other healthcare providers and agencies. Additionally, mental health issues must also be considered for the victims and the responders during both the emergency phase and the recovery. Posttraumatic stress disorder, major depression, generalized anxiety disorder, and substance abuse are frequently reported among disaster survivors who have experienced traumatic bereavement or severe disruption of their lives. Early and voluntary access to mental health workers for evaluation and intervention may reduce the incidence and severity of such reactions (2,24).

Common Pitfalls

- Failure to prepare for a disaster by identifying potential hazards in the local environment and hazards that may be brought in, whether by nature or human action.
- Failure to develop appropriate multiagency and multijurisdictional contingency plans.
- Failure to properly exercise and update disaster plans.
- Failure to appreciate that disrupted communication and transportation systems frequently cause problems in assessing and responding to disasters and that redundancy of equipment, training in its use, and flexibility of use of communication and transportation resources are desirable.
- Failure to consider the needs of the elderly, children, and other special populations and to include such things as appropriate medical supplies, diapers, formula, medications, interpreters, and special transportation requirements in disaster planning and response.
- Failure to appreciate that disaster responders may become casualties themselves, that they may suffer psychological effects during and after the event, and that personal planning and institutional support are crucial to minimize the impact of disruptions in the personal or professional lives of disaster responders.

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PART 2 • PATIENT SAFETY, ETHICAL, LEGAL, AND REGULATORY ISSUES

CHAPTER 379
Errors and Patient Safety

Robin R. Hemphill

Patient safety may be defined as those events that should never happen to patients as they interact with the health system. Put more eloquently, patient safety is a dynamic nonevent. Despite increased attention, patients continue to be harmed by the very system that intends to heal them. The emergency department (ED) setting is a particularly challenging arena and is prone to errors for a variety of reasons (Table 379.1).

TABLE 379.1
ED Conditions Conducive to Errors

1. Limited information creating diagnostic uncertainty
2. Cognitive overload
3. Low rate of serious conditions hidden within high rates of less serious disease (low signal to noise ratio)
4. Requirement for rapid decision making
5. No prior relationships with patients
6. Difficulty with continuity of care
7. Overcrowding
8. Limited feedback
9. Shift work contributing to fatigue
10. Understaffing
11. Multiple interruptions
12. Variation of team members
13. Excessive noise
14. Multiple transitions of care

Opportunity to improve may come from those industries that are recognized as High Reliability Organizations (HROs). These organizations are ones that are at high risk for hazard, yet have

lower rates of accidents and adverse events than one would expect given the complexity of their operations. Examples include the airline industry, aircraft carriers, and nuclear and chemical plants. Weick and Sutcliff (1) have studied such organizations and find that all have five things in common: preoccupation with failure, reluctance to simplify, sensitivity to operations, commitment to resilience, and deference to expertise.

While the healthcare system is not identical to any of the industries mentioned, a framework can be developed to help operationalize these concepts (Fig. 379.1). A successful journey to high reliability must balance across all of the elements in this diagram.

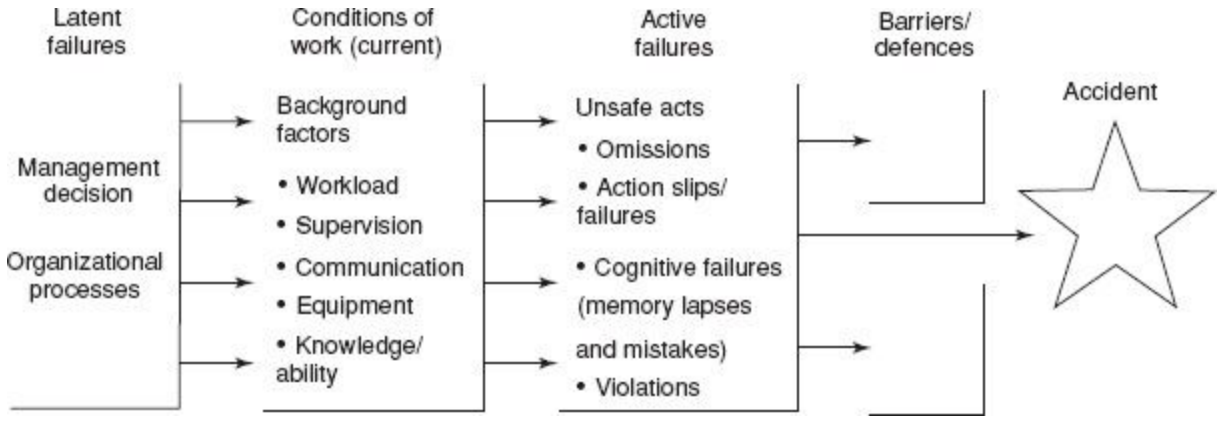

FIGURE 379.1 Anatomy of a complex accident. (Reproduced with permission from Vincent C, Taylor-Adams S, Stanhope N. Framework for analysing risk and safety in clinical medicine. *BMJ*. 1998;316(7138):1154–1157.)

FRAMEWORK FOR HIGH RELIABILITY IN HEALTH CARE

Culture of Safety

Put simply, a safe culture is one in which those in charge are willing to hear bad news and act appropriately. Developing such a culture is a central element of efforts to improve both the safety and the quality of care provided to patients (2).

Just Culture

A Just Culture is one in which the line between acceptable and unacceptable behavior is clearly stated. It recognizes that individuals make mistakes and acknowledges that even the most committed professionals will develop unhealthy norms (short cuts, rule violations, etc.), but has no tolerance for behaviors that are repeatedly or purposefully harmful (3).

When an error or adverse event occurs, rather than asking “who is at fault,” a Just Culture asks “why did this happen.” Human error can be viewed in one of two ways: (1) It is the fault of the people working in the system (violations of procedure or policy, loss of situational awareness, careless or poorly trained individuals) or (2) it is a symptom of a system that has latent vulnerabilities dispersed throughout it. Latent failures are faults created by policies, directives, or decisions that have been made remote from immediate patient care settings. These latent failures typically occur at higher levels in the organization and they may be difficult to see until such time that they combine with other active failures and triggering factors that together combine to overwhelm barriers put in place to protect patients. This results in a near miss or actual harm. Examples of latent failures specific to the ED setting include hospital policies that impact patient flow in the ED, high patient volume resulting in cognitive overload, multiple interruptions, limited patient information, inadequate staffing, frequent overtime or long shifts, complex medical equipment, limited standardization of medical equipment, and challenging computer interfaces, among others.

If the assumption is made that individuals do not come to work with the intent to cause harm, then it is important to move beyond blaming the individual and instead look for the system vulnerabilities (latent errors) that have contributed to the adverse event. HROs do not look for the first or most simple answer found when considering adverse events; they dig below the obvious to find and correct the latent problems within the system that if uncorrected will likely cause another similar adverse event in the future. If the individual involved is blamed and punished for the error, it is unlikely that underlying contributing factors will be

found. Furthermore, others who witness the punitive action will be unlikely to disclose their own errors or near misses. Opportunities will be lost to focus on and understand failures and near misses and we will continue to blame people who find themselves at the end of a series of events (environmental and design, and occasionally policy) that make it very easy to do the wrong thing.

It is important to note that a Just Culture does expect accountability for acts that are indeed blameworthy. Individuals who purposely violate policies intended to protect patients should be counseled and disciplined appropriately. Furthermore, accountability in a Just Culture expects managers and supervisors to address problem employees before they make an error that harms a patient, rather than waiting to act until a problem employee makes an error that might have been prevented.

It is questionable whether we can fully understand the intention of an individual when an adverse event has occurred. When reviewing an error that has harmed a patient, it is almost impossible to avoid “hindsight bias” (i.e., once the outcome is known, overestimating the clarity of events to those involved at the time) and some events can be seen to rise to the level of a willful disregard for patient safety. But such confident leaps should be approached cautiously. Iatrogenic harm is not necessarily caused by the random collision of independent failures, human errors, and intentional behaviors. Rather, it often results from a systematic migration of organizational behavior caused by the stress of operating in an underresourced and demanding environment where cutting corners to improve efficiency is not only valued, but openly celebrated. The more success that is attained at this limit of safe operating capacity, the more accepted (and even expected) it will become until a tragedy occurs. This is called the normalization of deviance, and is difficult to appreciate as it is happening. Only in hindsight is it clear that limits were being pushed well beyond what was safe. At that point there is often a single individual who appears to be at fault.

Engaged Leadership

Leadership is the driving force behind a safety culture and senior leaders have the responsibility as well as the authority to make safety a priority. It is critical for leadership to make safety part of the daily discussion and a center point of major meetings and strategy sessions (4). Frontline staff will believe that safety is important to the organization's senior leadership if those leaders visit the departments where the work occurs (leadership walk or sit rounds) and engage directly with the staff about what they see and what their concerns are. This allows for a cyclical flow of information (5) from staff to leaders and back. Leadership in the ED should also show support for directives and policies that enhance safety (time outs, checklists, follow-through on actions after root cause analyses (RCAs), daily safety huddles, etc.). It is also important for leadership to support the transparent reporting of adverse events to affected patients and families. Finally, leadership will determine the response to adverse events and should establish nonpunitive reporting systems, as well as help providers recover from the emotional distress they may feel after being involved in an event that harmed a patient.

High Functioning Clinical Teams

Medical training is competitive and not necessarily conducive to the development of team behaviors. The assumption that individuals will by themselves emerge from their training environment with team skills is not justified. Developing truly high functioning teams takes training and practice.

Health care is provided by teams of individuals with specialized knowledge, skills, and roles but who should share a common goal in patient care. They are dependent upon one another and their actions need to be coordinated to achieve the desired goal. Members of the team must have a shared mental model that allows each person to maintain situational awareness, the continuous perception of the team in relation to its dynamic environment, and the perceived ability to make adjustments. It includes being aware of critical

information, comprehending the meaning of this information, and planning for future possibilities (6).

Much of the recent work in improving team performance in the medical environment has been based upon the aviation model of Crew Resource Management (CRM). Multidisciplinary training in CRM teaches behaviors to help manage human error. This includes team practice behaviors to avoid error (marking a site, conducting a briefing, checklists), team practice behaviors to trap error (closed loop communication such as read-backs, redundant double-checks, and timeouts as a final check that ensure that the message transmitted is the message heard and acted upon), and team practice behaviors to mitigate the consequences if an error affects the patient (immediate reporting of errors which act to reduce the impact of an error). Achieving such levels of performance requires individuals to learn both leadership and follower behaviors, including an understanding of how leadership styles can impact team performance as well as skills to bring critical information to the attention of team members. In the operating room, these behaviors along with a checklist-guided team briefing that precedes every operation have been a cornerstone of improved outcomes. Critical information is shared, reviewed, and confirmed by the team. Any concerns or questions can be addressed prior to the start of the case. Potential complications can be reviewed and anticipated. In the operating room these briefings have resulted in improved perceptions of teamwork, prophylactic administration of antibiotics, and deep venous thrombosis treatment (7), as well as decreased operative mortality (8). While much of the work thus far has been in the surgical literature, success has been noted in a variety of clinical settings. These techniques may also be applied to the ED setting (9,10). For example, in cases of care delivered to a critically ill patient, the provider can discuss what the diagnosis is thought to be, the treatment options chosen, and a brief review of what the team should see if the patient responds, as well as what might occur if the early diagnosis is incorrect.

Understanding Complexity and Improving the Environment of Care

Health care is complex. This means that it consists of interdependent and diverse components that adapt to changes in the environment and is distinct from complicated systems that are not able to adapt to change. For example, one's car is complex and has many interdependent parts, but if it runs out of gas, it cannot adapt in some way to keep running. The ED on the other hand has many interdependent parts, but if it is poorly staffed, it does not shut down, it adapts. This means that even the best of intended changes can ripple through the system and manifest in unexpected, and occasionally harmful, ways. If one understands that the components of the healthcare system will interact with and adapt to changes and barriers, it should be clear that a culture that values the reporting of errors, concerns, risks, or near misses is imperative to prevent or mitigate harms that may emerge in this system. The only way to identify these harms, however, is for the organization to be willing to discuss and face its problems. This is why the Just Culture is so critical if we are to improve patient safety. If individuals are punished for errors, the problem may appear to have been solved, but organizational failures almost never have a single cause. Unless the latent errors that contributed to the problem are uncovered, adverse events will likely recur. When near misses or error occur, these incidents should be understood to present opportunities to learn from the event. Tools such as RCA may be used to more fully understand and identify the system vulnerabilities that may have contributed to an adverse event or near miss. The RCA process helps identify root and contributory factors that led to the event and then recommends strategies to reduce future similar events. Other tools, such as healthcare failure and effect analysis (HFMEA), offer opportunities to assess for system vulnerabilities before a close call or adverse event occurs. This tool allows a team to map out a high-risk process and assess its vulnerabilities so that mitigation steps can be built into the system. Each of these tools offers the possibility of recognizing contributors of harm and responsing with efforts to

improve the environment of care. In the case of RCA, the lessons learned are retrospective but can still be very helpful. Over time these reporting systems can help identify problems at the macro system level and so large-scale improvements can be considered. Such improvements should be informed by the use of human factor techniques when possible, so that the system is designed taking into account an understanding of the causes of human error and an emphasis on making it easier to do the right thing. For example, a common error in anesthesia practice was to accidentally attach the tubing designed to deliver oxygen to the patient to the wall valve that delivered only air. When the valve was redesigned to make it difficult to attach oxygen tubing to the air valve, the problem was largely eliminated. While such redesigns of systems present distinct challenges and are not always possible, this type of solution should be the goal. Interventions such as training programs and letters of reprimand will not improve safety comparably over the long term.

CHALLENGES TO MEASURING SAFETY

The Centers of Medicare and Medicaid Services has defined "never events" and it is fair to classify these as breakdowns in safety. At a single institution such cases are thankfully rare. Thus, it can be challenging to answer the simple question as to how safe an individual ED is. A recent framework to help measure safety has been suggested and consists of five broad classes (11):

- Past harm: This considers whether patients have been safe in the past and might include mortality statistics, use of a global trigger tool (12), incident reports, RCA collections, and other sources indicative of past harm.
- Reliability: This asks whether clinical systems, processes, and behaviors are reliable. Examples include compliance with hand washing, medication error rates, or percentage of patients who are appropriately consented prior to a procedure.
- Sensitivity to operations: This attempts to determine how safe care is today and relies on individuals and teams maintaining awareness. Strategies to achieve this include safety walk rounds

(13), the designation of patient safety officers, and operational meetings, among others.
- Anticipation and preparedness: This attempts to determine whether care will be safe in the future. Examples include surgical checklists which force a period of reflection in which problems associated with the procedure can be reviewed, HFMEAs, and a focus on creating a culture of safety.
- Integration and learning: The focus here is on responding and improving. Examples of this might be the review of common contributors to errors found through RCAs used to improve processes or tools to reduce recurrence of similar errors.

Approaches to Improving Patient Safety

- Make a discussion of safety and quality of a part of every ED staff meeting.
- Commit to a Just Culture where adverse events and near misses are freely discussed without punishment and accountability processes are clearly defined.
- Engage in team training to enhance communication and to increase team situational awareness.
- Focus on improving the environment of care using human factors approaches to make it easier to do the right thing.
- Complexity is the enemy of safety—focus on ways to minimize unneeded hand-offs and process steps (e.g., transcribing physician orders into a computer increases the risk of error more than having the physician enter orders directly).
- Reduce reliance on memory—use checklists, algorithms, and clinical pathways, and allow easy access to current references.
- Standardize processes when appropriate.
- Focus on developing measures to determine how safe the care in the ED is.
- Review recent literature on safety strategies that are ready for adoption now and tailor those that are appropriate to the ED setting (14).

- Be familiar with The Joint Commission National Patient Safety Goals for 2013 and develop strategies to address those relevant to the ED (see Table 379.2) (15).

TABLE 379.2
2013 Joint Commission Patient Safety Goals Relevant to EM

Description
Identifying Patients Correctly: Use at least two ways to identify patients
Improve Staff Communication: Get important test results to the right staff person on time
Use Medications Safely: Before a procedure, label medicines that are not labeled
Use Medications Safely: Take extra care with patients who take medicines to thin their blood
Use Medications Safely: Record and pass along correct information about a patient's medicines
Prevent Infection: Use the hand cleaning guidelines from the Centers for Disease Control and Prevention or the World Health Organization
Prevent Infection: Use proven guidelines to prevent infections that are difficult to treat
Prevent Infection: Use proven guidelines to prevent infection of the blood from central lines
Prevent Infection: Use proven guidelines to prevent infections of the urinary tract that are caused by catheters
Identify Patient Safety Risks: Use proven guidelines to prevent infections of the urinary tract that are caused by catheters

Common Pitfalls

- Failure of leadership—failure to commit to development of culture and team development. Safety is not a person, it is an ongoing value that infuses all aspect of clinical practice.
- Resistance to standardization.
- Burying patient safety in the system—bad news needs to get to the top.
- Failure to understand that safety and efficiency are in tension—in our efforts to push the system to be more efficient we can begin to compromise safety. Many things seen as duplicative and wasteful are redundancies built into the system to maintain safety.
- Settling for easy answers rather than understanding.

- Overreliance on technology. Advances in technology have enhanced safety in many areas, but technology may add layers of complexity that increase the risk of errors.
- Failure to engage the patient. Patients and their families can be effective in identifying errors. They should be informed about the expected course of their ED visit and encouraged to ask questions and speak up when they perceive that something is not consistent with the plan that was discussed.

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CHAPTER 380 Quality Improvement

Robin R. Hemphill

In contrast to "patient safety," which is concerned with those events that should never happen to patients as they interact with the healthcare system, quality improvement may be defined by concern about all the things that *should* happen to patients to increase the likelihood of desired health outcomes and to meet their expectations. This goal is challenging to achieve because it is so broad. In *Crossing the Quality Chasm,* the Institute of Medicine (IOM) has offered a blueprint that identifies and classifies the elements of quality through six desired characteristics of quality care (1):

1. Safe: Care should be free from preventable harms (see Chapter 379).
2. Effective: Evidence should be applied to the delivery of care.
3. Efficient: Resource use should be assessed in achieving desired results and waste should be removed.
4. Timely: Waits and delays should be understood and minimized.
5. Patient centered: The health system should focus around the goals and needs of the patient and respect the decisions and preferences of the patient.
6. Equitable: Disparities in care should be removed.

To achieve these, administrative leaders require a set of skills that focus on patients, the use of data, and the engagement of the healthcare workforce.

QUALITY IMPROVEMENT PROCESSES

Industry has developed a variety of systems to guide quality improvement efforts, many of which can be applied in the

emergency eepartment (ED) setting. The goal is to develop a system that consistently delivers the correct care to a patient at the best price in a manner that meets the patient's expectations. A guiding principle is that one must understand the goal to be achieved before determining how to accomplish it. Specific methodologies for improving quality are summarized in Table 380.1. Each follows a procedure of repeated testing and intervention.

TABLE 380.1
Comparison of Improvement Process Methods

	PDSA	Lean	Six Sigma
Process Steps	Plan, Do, Study, Act	Eliminate nonvalue steps, Value stream mapping Kaizen (continuous improvement)	Define, Measures, Analyze, Improve, Control (DMAIC)
Improvement Targets	Small tests of change to identify optimal process improvement opportunity	Eliminate waste, improve system flow	Eliminate variation and defects
Strengths	Useful when time and resources are limited and desire to test a theory prior to wide spread implementation	Useful when a clear process can be defined and appears to have nonvalue activities embedded in process	Useful when process variation should be minimized and the activity is high volume
Weaknesses	Changes done in isolation may cause unintended consequences downstream of the changes	Some steps seen as waste may be redundancies put in place to maintain safety	Reduction in resilience may occur if appropriate variation is minimized

IMPROVEMENT PROCESS METHODS

Plan, Do, Study, Act (PDSA) Cycle

This is a method of trial and error carried out over a series of small cycles (2). Small tests of change are attempted before proceeding with broader implementation.

- Plan: In this phase it is helpful to consider three questions (3):
  1. What are we trying to accomplish?
  2. How will we know change is an improvement?
  3. What changes might allow the desired changes to be achieved?
- Do: Carry out the plan on a small scale, identifying problems, and make other observations. Data analysis begins here.
- Study: Assess the effects of the initial change and compare them to those which were aimed for. Summarize the lessons learned and identify any further changes that appear to be needed.
- Act: Decide whether the cycle should be repeated with modifications or whether the initial goals have been achieved.

Note any remaining gaps in desired performance and determine whether additional PDSA cycles should be undertaken.

Lean Methodology

Lean thinking focuses on improving flow and reducing cost by removing activities or processes that use resources but create no value. This is referred to generically as "waste." This includes waste of over- and underproduction, waste of inventory (e.g., unused medications which may expire), waste of rework (e.g., redo of x-rays when poorly done), waste of motion (e.g., repeatedly checking to see if a patient has returned to a room after testing), waste of waiting (e.g., both providers and patients waiting on laboratory tests prior to disposition), waste of processing (e.g., decreasing steps of ED triage process), waste of transporting (e.g., excessive distance from the ED to the cath lab). Lean processes also focus on improving the delivery of services or products by aligning the best steps in the best sequence. Simplification of processes can result in less variation and more consistent output.

Six Sigma Methodology

Six sigma refers to a control process in which 99.99966% of outcomes are within the desired range of acceptability. Opportunities for improvement or for correction of problems are identified through a series of steps (DMAIC): Define the problem and the improvement objective, Measure each of the process steps, Analyze the collected data to provide insight into the process, Improve the process by developing solutions and changes, and Control the process if it is performing at the desired level, while continuing to monitor for unexpected events. This methodology is based on the idea that reduction of variation leads to both consistent output and improved efficiency.

QUALITY MEASUREMENT

Measures of performance are critical to the ability to improve. Appropriate quality measures are essential to improving care in the

ED setting and increasingly there is an expectation that performance data will be made available to the public. Emergency medicine providers currently have a variety of externally imposed quality measures (some of dubious value) (4,5), and there is a need to develop measures that better reflect the quality of care that emergency physicians wish to provide. The Centers for Medicare and Medicaid now require reporting of a variety of performance measures. Examples relevant to emergency medicine providers are listed in Table 380.2.

TABLE 380.2
2013 PQRS Measures Relevant to Emergency Medicine

Description
• Aspirin at Arrival for Acute Myocardial Infarction (AMI)
• Stroke and Stroke Rehabilitation: DVT Prophylaxis for Ischemic Stroke or ICH
• Stroke and Stroke Rehabilitation: Screening for Dysphagia
• 12 Lead ECG Performed for Non-Traumatic Chest Pain if >40 years old
• 12 Lead ECG Performed for Syncope if >60 years old
• Community-Acquired Pneumonia (CAP): Vital Signs
• Community-Acquired Pneumonia (CAP): Empiric Antibiotic
• Prevention of Catheter-Related Bloodstream Infections (CRBSI: Central Venous Catheter Insertion Protocol)
• Acute Otitis Externa: Topical Therapy
• Acute Otitis Externa: Systemic Antimicrobial Therapy- Avoidance of Inappropriate Use
• Stroke and Stroke Rehabilitation: Thrombolytic Therapy
• Heart Failure Left Ventricular Function Testing
• Anticoagulation for Acute Pulmonary Embolism
• Ultrasound Determination of Pregnancy Location for Pregnant Abdominal Pain
• Rh Immunoglobulin for Rh-Negative Pregnant Women at Risk for Fetal Blood Exposure
• Prevention Care and Screening: Screening for High Blood Pressure

When determining what to measure it is important to take into account how such measures will be used. Measures developed to help *understand* performance may later become measures used to *enforce* performance. This shift in use is unhealthy since it may induce providers to resist the development of other measures in the future.

Desirable characteristics of quality measures are listed in Table 380.3 (6).

TABLE 380.3
Desirable Characteristics of Quality Measures

Characteristic	Description
Relevance	The measure should be important and valuable to all involved stakeholders—providers, patients, payers (e.g., diagnostic accuracy would be relevant to all stakeholders)
Evidence-Based	The measure should link structure and/or processes to the desired outcome. When scientific evidence is avail-able it should be used to guide the quality measures being developed (e.g., delivery of certain treatments for specific diagnosis)
Reproducible	Once developed the quality measure should produce the same results when repeated over time (e.g., the time that an antibiotic is administered in the ED)
Valid	The quality measure should be associated with what it claims to be measuring (e.g., a computer-generated time stamp indicating when a patient is seen by an ED provider should accurately represent when the patient was actually seen by the provider, not necessarily when the provider signed up for the patient)
Feasible	The measures should be practical to collect (e.g., rates of diagnostic error is a relevant and important quality measure, but can be very difficult to determine)

APPROACHES TO IMPROVING QUALITY

- Meaningful engagement of physician leaders is critical if long-term gains are to be made in both quality and safety. Leaders give legitimacy to improvement efforts, tie them to strategic priorities, and can direct needed resources. Change will not be achieved by the efforts of only a few committed individuals on the front line. Quality and safety should be a part of every staff meeting.
- Emergency physicians should take part in the development of quality measures relevant to emergency practice. Performance data should be transparent and accessible. Decreasing practice variation may provide opportunities to improve patient care. Processes should be standardized when appropriate. This includes the use of clinical pathways.
- Initial ED improvement efforts should focus, whenever possible, on areas where there is widespread support for change.
- Patients and families may give physicians critical insight into ways they may improve the delivery of care in the ED.

- Develop strategies to understand and limit procedures and tests that are overused in the ED (7).
- A particular focus should be on improving transitions of care. This includes handoffs between emergency physicians during turnover, handoffs when admitting patients to inpatient settings, and the patient discharge process. Quality and safety are compromised by the limits of human cognition, particularly in the ED setting. A deeper understanding of how decisions are made may provide opportunities to recognize the limits of clinical judgment and to take this into account when designing ED protocols and procedures (8).

Common Pitfalls

- Failure of leadership. Just as leadership can support quality management, it can also obstruct it. The ED leader must constantly demonstrate visible support for the quality effort.
- Prioritizing physician autonomy over appropriate standardization of care.
- Using quality improvement measures as performance measures.
- Failure to develop meaningful performance measurements. Often things are measured because they are easy to measure, not because they matter.
- Failure to sustain gains made during improvement projects. It is important to cement gains that have been made before moving from one project to the next. Cooperation will wane if the work put into quality efforts does not result in long-term improvement.

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CHAPTER 381 Legal and Ethical Issues

Dave W. Lu and James G. Adams

Ethical and legal issues are present in every doctor–patient encounter. They become more poignant in the emergency setting where decisions often need to be made in a time-sensitive manner and without all the necessary information available. The potential for retrospective scrutiny of actions performed in emergency settings can make decisions surrounding complex legal and ethical issues particularly challenging and stressful for providers. Emergency physicians nonetheless can successfully manage the most common legal and ethical dilemmas that arise in their practice with a thorough understanding of core legal and ethical principles. Legal and ethical conflict in emergency medicine usually involves issues regarding consent and refusal of care, dilemmas near the end of life, questions of decisional capacity, use of patient restraints, and patient confidentiality. This chapter presents specific situations in the emergency department (ED) in which legal and ethical questions are most likely to arise and offers frameworks to assist in decision-making.

CONSENT ISSUES

Autonomy is a core principle of medical ethics, and it is widely accepted that adults with intact decisional capacity have the right to accept or refuse recommended medical care. There are three types of consent important in emergency medicine: informed consent, general consent, and emergency exception to consent.

Informed consent by a voluntary patient with decision-making capacity gives a healthcare provider permission to proceed with a proposed treatment. The ethical requirement for *informed* medical decision-making is to ensure that patients are provided a fair and reasonable explanation of their medical condition and the risks and benefits of all treatment options, including the option of having no treatment (1). Although informed consent is often equated with a signed consent form, it is important to recognize that truly informed consent is not merely a signature on paper but the actual process of effective communication that results in patient understanding. Elements of informed consent include a discussion of: (a) the nature of the recommended treatment; (b) the risks associated with the treatment; (c) the risks associated with not having the treatment; (d) any available alternative treatments (including no treatment); and (e) the risks associated with the alternative treatments. A patient can give informed consent only if he has the sufficient and appropriate decision-making capacity to comprehend the nature of the illness and the risk–benefit analysis of the treatment plan (1).

General consent is the type of consent obtained in routine practice when a patient presents to the ED for care. In the case of a patient who willingly requests medical treatment, it is implied that he will consent to medical staff taking vital signs, performing basic diagnostic tests, and initiating noninvasive or minimally invasive treatment. These characteristics of general consent make it *not* equivalent to informed consent, since little—if any—discussion about the nature of the patient's illness or anticipated diagnostic and treatment plan occurs. Although the scope of general consent is broad and allows providers to perform a wide variety of actions on the patient's behalf, it is inadequate for procedures or tests that may be associated with a substantial risk of harm or injury.

When patients are unable to provide consent due to critical illness or the loss of their decision-making capacity, it is widely accepted that physicians can still treat patients under an emergency exception to consent. The emergency exception is narrowly structured and requires specific conditions to be met (2):

1. The patient must be unconscious or without capacity to make a decision, and no legally authorized representative who can act on behalf of the patient is available.
2. The patient must be in an emergency medical situation, such that delay of appropriate treatment to obtain consent would subject the patient to the risk of serious injury or death.
3. Under the same circumstances, a reasonable person would consent to the treatment.

Although these conditions permit an emergency exception to consent, consent is not completely waived. If the physician clearly knows that the patient would not have consented to the proposed life-saving treatment, such a treatment should not be administered. For example, patients near the end of life carry formal documentation that explicitly delineates their refusal of cardiopulmonary resuscitation, even if such a refusal results in their deaths. In such instances, unless there is evidence indicating the patient would have revoked their refusal or doubt regarding the validity of the signed documentation, the emergency physician should not initiate unwanted care.

Emergency consent is also only applicable until the patient recovers the capacity to make informed decisions or when a legally authorized representative becomes available. Physicians should take care to document in the medical record evidence supporting their clinical determination of an emergency medical situation necessitating an emergency exception to consent. Physicians also need to diligently note their determination of the patient's decision-making capacity, or lack thereof, when invoking the emergency exception. In situations where there is doubt as to whether the emergency exception applies, it is usually best to err on the side of treatment and to obtain the patient's or legally authorized representative's consent as early and reasonable as possible.

Refusal of Care

Conflict may arise when the patient refuses care or particular elements of treatment. Patients can and do refuse care, even when

that care is essential to preserve their life or health. In these not uncommon situations, providing unwanted treatment over the objection of a patient with sufficient decision-making capacity may render the physician liable for battery (3). Conversely, an impulsive or incompletely informed refusal leading to lack of treatment leaves the physician liable for negligence. Resolving this paradox in an emergency setting requires ethical skill.

A valid refusal requires sufficient decisional capacity on the part of the patient. A patient has decisional capacity when he is able to understand his medical condition, the treatment suggested, and the risks and benefits of each course of action (1). The patient must also be able to demonstrate that his decision derives from reasoning that is in keeping with his general goals and values. The criteria for refusal of care are consequently stricter than those for consent. Whereas general consent can be implied by a patient who arrives voluntarily to the ED, refusal of care *cannot* similarly be implied because the medical knowledge involved in an informed refusal is initially held only by the physician and not the patient. Therefore, whenever a patient refuses care, it is strongly recommended that the patient's decisional capacity be noted in the medical record, with special attention to the information that was specifically communicated and understood by the patient.

A great challenge for emergency physicians is to expertly assess decisional capacity to understand when a refusal is informed and when it is an impulsive gesture of a person who lacks decisional capacity due to severe psychiatric disease, intoxication, or overwhelming medical illness (4). For example, medical conditions such as hypoglycemia, encephalopathy, and hypoxemia can make patients impulsive, restless, angry, and antagonistic such that there may be confusion regarding their ability to reason. However, the mere presence of an intoxicant or medical illness—even a life-threatening one—does not necessarily imply that the patient lacks sufficient decisional capacity. The complexity of the information and decision, as well as the impact of the medical condition on the person's ability to process that information, should factor in assessing a patient's decisional capacity (1). The challenge then is to

ensure that the patient understands the risks and benefits of his options and can subsequently make a reasoned decision, even if it seems unreasonable to the healthcare provider. Patient refusal of care may apply to a specific test or treatment (e.g., a rectal examination or lumbar puncture), to any further care (e.g., a patient asking to leave during care or refusing admission to the hospital), or to a portion of the physician's plan of therapy (e.g., follow-up appointments, prescribed medications, or use of helmets). The critical and necessary skill of the emergency physician is to be able to differentiate refusal of care from a patient with decisional capacity from that of a patient who lacks such capacity as a result of serious illness or intoxication. It is not the responsibility of patients to prove they have decisional capacity; it is the responsibility of the physician to identify any impairment of such capacity.

When there is doubt regarding a patient's decisional capacity, medical care should always proceed to restore his capacity. In the meantime, protecting the patient from a dangerous decision is justifiable when sufficient uncertainty exists about whether the refusal represents a reasoned, durable decision. When treatment is delivered over a patient's expressed objection, the substantial impairment of the patient's decisional capacity should be clearly documented.

Patients who leave against medical advice should still be provided discharge instructions, follow-up information, and any medications that may help address the complaint or diagnosis. In addition, the discharge of patients from the ED against medical advice, even if amicable and mutually acceptable, should include a formal process (e.g., signing a leaving against medical advice form) in which the patient is made to understand the reasonable consequences of refusing to follow the discharge instructions. This information and its understanding by the patient should be fully documented (1).

CONSENT IN SPECIAL PATIENT POPULATIONS

Minors

There are special operational and ethical challenges associated with the care of minors. With rare exception, parents or legal guardians *must* consent for the care of a minor (5). The primary question that ED providers have regarding patients who are minors is when they can deliver care without parental consent or before parental consent. Should a teenager with a dislocated shoulder be made to wait until his parents arrive? Should a child with a laceration be put on hold? Should the ED physician respect the wishes of an adolescent who requests that his parents not be told of his visit? The answer to each question is predicated on a multitude of factors, including the maturity of the minor, the immediacy of harm from delay, the risk of the intervention, the type of illness, and whether the minor is emancipated.

There are several important exceptions to the requirement for prospective parental consent in the treatment of minors. First and foremost, in the presence of imminent harm wherein a delay of treatment poses a danger to the life or health of the minor, essential treatment should be provided. This provision is federally mandated under the Emergency Medical Treatment and Active Labor Act (EMTALA), which requires healthcare providers to provide stabilizing treatment to anyone who presents to an ED for medical care (6). Emergency physicians should be mindful that only care needed to preserve life and health should be administered and that simultaneous attempts at parental contact and consent remain necessary for continued care, even if the care is obviously needed.

If attempts to reach the minor's parents or appropriate surrogate are unsuccessful, the physician or social worker should notify state child protective services or the department of family services, who stand in the position of *parens patriae,* until the child can be released to the care of parents or surrogate caregivers.

Parental consent is also not required if the minor is legally emancipated. *Emancipated minors* have a different legal status than that of other minors, as defined by specific state law. In general, minors are considered emancipated and capable of making their own medical decisions when any one of the following conditions is met (7):

- Marital status: The minor is married, divorced, separated, or widowed.
- The nature of the minor's physical condition: The patient believes that she is pregnant or that he or she may be suffering from or have come into contact with any disease defined as a danger to public health (e.g., a sexually transmitted infection). Each state has differing requirements and age thresholds for these cases and ED providers should become familiar with the laws in their jurisdiction.
- Legal or financial status: The patient is either living on his own or is financially independent.
- The minor is a member of the armed forces.
- The minor is a parent.

In contrast to the emancipated minor, a special category of minor who may be able to offer *limited* consent for his own care is the *mature minor*. The mature minor (usually 14 years and older) is emotionally and intellectually sophisticated enough to be able to appreciate the nature of the illness along with the risks and benefits of proposed treatment (7). A mature minor's opinions and preferences should be taken into account when making treatment decisions (5). In some cases, a minor originally and incorrectly determined to be emancipated may meet standards for mature minor status. Because the mature minor may not be able to provide complete consent, including both the parents and mature minor in medical decisions is optimal.

In rare circumstances, a parent may refuse emergency treatment of a minor, even if such a refusal may cause severe injury or risk of death (5). In these cases all efforts must be made to ensure that communication between the providers and parent has been clear and adequate. This may require the involvement of social workers, chaplains, other family members, or other physicians to explore the parent's reasons for refusing treatment. When there is substantial risk to the minor in situations of parental refusal of consent, the minor should be taken into protective custody so that treatment can be given. For example, courts have held that physicians may administer life-saving blood products to a young child over the

objections of his or her Jehovah's Witness parents (3,8). The situation becomes more complicated when deciding if a mature minor's consent or refusal of essential care should be honored over a parent's objection. Courts have allowed mature minors to refuse life-saving treatment such as blood transfusions and chemotherapy over the objections of parents (8). Such cases often require emergency judicial intervention to clarify the physician's responsibility to the minor patient.

Psychiatric Patients

Patients with psychiatric disease who possess adequate decision-making capacity may refuse or consent to treatment just like any other patient. However, suicidal or homicidal patients who meet their state's statutory criteria for civil psychiatric commitment may not refuse treatment or leave the hospital against medical advice (9). Under the common law of all 50 states, emergency medical treatment of a suicidal patient may proceed against the patient's wishes for as long as it takes to stabilize the patient medically. This is in contrast to an initial limit of 72 to 96 hours (depending on the state) mental health providers have to evaluate and treat nonconsenting suicidal or homicidal patients (9). In cases wherein patients with psychiatric disease have been declared mentally incompetent by a court and placed under a conservatorship or guardianship, only the court-appointed conservator or guardian, and *not* the patient, can legally consent or refuse treatment. As noted above, in situations when the conservator or guardian is unavailable, emergency medical care for the patient should not be delayed.

Prisoners and Detainees

Patients who present under police custody can consent to or refuse medical care similar to any other nondetained patient. When a prisoner or detainee refuses treatment, the physician should follow the usual guidelines pertaining to the management of treatment refusals that apply to all patients, including an evaluation of the individual's decision-making capacity. Although patients in police

custody have the right to refuse medical treatment, they have no legal right to choose where they are incarcerated. A prisoner or detainee who has refused treatment but who is suffering from a potentially significant medical condition may still be admitted to a hospital's jail ward against his wishes at the request of law enforcement authorities.

Prisoners and detainees have a legal right to medical care under federal law, and the failure of authorities to provide such care may be regarded by the courts as a violation of the prisoners' civil rights (10). It is in this context that police and prison officials bring prisoners and detainees to the ED for treatment and "medical clearance" evaluations. Emergency physicians should remember that many prisoners and detainees suffer from poorly controlled or untreated conditions, including polysubstance abuse, that are associated with a variety of health risks that may go undetected in a detention facility staffed by personnel who lack medical training. Depending on the clinical circumstances, it may be wise to consider hospital admission if there is a concern that a prisoner or detainee may require a level of treatment or monitoring that is otherwise unavailable in jail or prison.

Intoxicated Patients

Emergency physicians are often confronted with patients under the influence of alcohol or drugs who refuse medical care. Physicians can make a determination of a patient's sobriety or intoxication based on clinical examination alone, and a blood alcohol level is not required. Although an intoxicated patient does not completely lack decision-making capacity, the threshold to override the patient's refusal is lower. An intoxicated patient cannot refuse emergency medical treatment or sign out against medical advice without exhibiting the ability to fully comprehend the risks associated with refusing treatment (10). In such cases the emergency physician would be prudent to carefully document his reasons for overriding the intoxicated patient's wishes.

Restraints

Violent or combative patients who present an immediate risk to themselves or others in the ED may require the use of physical or chemical restraints. Courts have generally deferred to the professional judgment of a physician to determine when restraints are necessary (11). Physicians, however, must adhere to federal regulations governing the use of restraints and document the clinical need for restraints. Federal regulations require that orders for restraints: (a) cannot be written as a standing or on an as-needed basis; (b) be implemented in the least restrictive manner; (c) are in accordance with safe and appropriate restraining techniques; and (d) end at the earliest possible time (12). Restraints should only be used to ensure the safety of patients and providers, and never punitively when a patient is disruptive or noncompliant. Providers must understand that the inappropriate use of restraints—both *actual* (wrist and ankle straps or administration of medication) or *apparent* (verbal threats, presence of guards, being placed in a locked examination room)—can represent false imprisonment and subject the provider to liability. Providers should therefore pay special attention to documenting in the medical record reasons for the use of restraints. Finally, as restrained patients are unable to care for themselves and may continue to be agitated, care should be taken by staff to monitor them for safety. Most centers remove physical restraints and transition to chemical restraints in the form of sedative medications as early as possible.

END OF LIFE ISSUES

"Do Not Resuscitate" Orders, Advance Directives, and Living Wills

Death and dying are deeply personal and emotional matters, and many patients near the end of life may wish to forgo extraordinary life-sustaining measures. By enacting a "do not resuscitate" (DNR) order, advance directive, or living will, patients allow their wishes to be known when they are unable to communicate them.

Unfortunately, there exists much confusion about DNR orders, advance directives, and living wills.

Advance directives and living wills are broad documents that outline the general end-of-life wishes of the patient. These documents can be established by patients and do not always contain specific provisions about withholding cardiopulmonary resuscitation. As a result, unless a living will or advance directive contains DNR clauses, they may not be helpful in the emergency setting. DNR orders, in contrast, specifically address a patient's wishes with regard to cardiopulmonary resuscitation and it is an order written by a physician. Many states employ specific and standardized forms that must be used to establish a valid DNR order. Hospitals are also required to have mechanisms in place for patients to express therapy-limiting decisions and to ensure that this information is available to healthcare providers (13).

When a DNR order, advance directive, or living will accompanies a patient without decisional capacity to the hospital, in theory, no proxy decision maker may be necessary since the document was designed to speak for the patient. In cases when there is no uncertainty regarding the patient's medical condition and wishes, the DNR order, advance directive, or living will should rightfully be honored. Problems can arise when uncertainty exists. When the designated surrogate decision maker, for example, disagrees with a plan to limit treatment, most emergency physicians would properly deliver care until the incongruity can be sorted out. Similarly, a patient who resides in one state and has a specific, valid advance directive may find himself in need of emergency medical care while vacationing in a neighboring state, in which his advance directive may not be legally recognized. While some emergency physicians would consider the intent of the legally invalid advance directive and limit care in accordance with the document, others may feel compelled to render care until this legal dilemma can be formally resolved. The problem of rapidly determining the validity of a variety of legal documents regarding end-of-life preferences in an emergency setting will not be resolved until an easily interpretable,

portable, and widely available form (paper or electronic) that is recognizable across all healthcare settings becomes available (14).

Another problem of DNR orders, advance directives, and living wills is their applicability in unforeseen circumstances. For example, a cancer patient who with his oncologist enacts a DNR order to forgo cardiopulmonary resuscitation and intubation in anticipation of his advancing disease, poses significant ethical and legal problems when he unexpectedly presents to the emergency room in respiratory distress due to anaphylaxis from an accidental food allergy. While the patient's DNR order specifically indicates his desire to not be intubated, it was created under the rubric of his underlying cancer and unlikely accounted for a scenario such as anaphylaxis from a food allergy. The proper question from an ethical view is whether there is clear, sufficient, and valid evidence of what the patient would want for this specific circumstance. If there is doubt, resuscitative attempts should proceed. Emergency physicians can take comfort in knowing that there is no legal or ethical distinction between withdrawing unwanted care and not initiating care (15). Undesired interventions can be withdrawn once the proper information becomes available regarding the patient's end-of-life wishes. As additional information is gained about the medical condition and the patient's enduring wishes, goals, and values, ongoing treatment can then be modified. Relevant information must be incorporated into the decision-making process and shared with the patient and family to achieve the best possible resolution.

Surrogate Decision Makers

The Uniform Health-Care Decisions Act permits an individual to appoint a legally authorized surrogate for healthcare decisions (13). The surrogate may then authorize medical treatment and provide information regarding patient wishes if the patient loses decisional capacity. As is often the case in the ED, the surrogate may not be available when the patient requires emergent medical treatment. Relying on available family members who are not the legally

authorized decision maker may be problematic, as these family members and the legally authorized surrogate may disagree about treatment decisions. The emergency physician should inquire whether the patient has a legally designated decision maker, clarify roles and relationships of those expressing opinions, and document the input received. If the official surrogate is unavailable or if the emergency physician identifies uncertainty because of sudden or unusual medical circumstances, it is appropriate to deliver care so that decision-making can be later clarified. Alternatively, if an authorized surrogate requests that treatment be withdrawn, this desire can be honored when there is no uncertainty or conflict, and when the decision would be concordant with the patient's understood wishes. It is important to note that in the absence of any established designated surrogate, the following persons, in decreasing order of priority, may lawfully consent to treatment on the patient's behalf: the patient's spouse; adult child; parent; brother or sister; or relative by blood or marriage.

COMMUNICATION, PRIVACY, AND CONFIDENTIALITY

Patient privacy—the physical and psychological condition of appropriate separation from others—is deserved by patients, is a challenge for caregivers, and is sometimes impossible in a busy, crowded ED (16). The ED is a unique environment in that there are no limits on the number of patients requiring immediate medical attention. Care is routinely provided in hallways when critical medical tasks take priority over important privacy needs. Privacy must also be sacrificed for patient safety. A highly private environment, for example, does not allow for visual monitoring by nurses and doctors and may impair medical care. Though it may be easy for many providers to forgo privacy for the sake of providing timely treatment to critically ill patients, the better position may be to attempt to maintain the value of privacy despite the ED's challenging conditions. In the clinical environment, this may require softer voices on the part of caregivers when discussing patients during shift transitions. Physicians can also be mindful of keeping

curtains fully drawn during physical examinations. Though these issues may seem trivial when lives are at stake, they are meaningful ways to respect patients and demonstrate high ideals of the profession.

Just as providers should aim for as much patient privacy as possible in the emergency care setting, patient confidentiality must also be ensured. Patient information should not be seen by anyone other than those individuals with a duty to care for the patient. The Health Insurance Portability and Accountability Act (HIPAA) provides specific instructions regulating and protecting the confidentiality of a patient's medical information, and must be followed by all who might encounter such information, including doctors, nurses, secretaries, clerks, pharmacists, allied providers, insurance agencies, health plans, and businesses with transactional relationships with healthcare systems (17). The increased rigor applied to the sharing of patient information can sometimes result in higher costs and burdens on healthcare providers in their ability to use and share full medical information when treating patients in a timely and efficient manner. Nevertheless, it remains prudent to remind all who work in the ED that they have knowledge of the patient's condition only because of their privileged position as a healthcare worker and that information should be shared only for the medical treatment of the patient.

The confidentiality of information provided by minors during their care in the ED is a common area of concern (5). Although it is widely known that adolescent patients are more candid when they are assured confidentiality, ED providers need to exercise caution in overpromising confidentiality when HIPAA allows parents of minors to access medical records. Still, ED providers should be aware that HIPAA does permit a licensed healthcare professional to deny parental access to medical records under certain circumstances, such as when the provider believes that the access requested is reasonably likely to endanger the life or physical safety of the patient or another person (18).

TRUTH TELLING AND RELATIONSHIP BUILDING

Though it may initially seem simplistic to discuss how to tell patients the truth, in practice, truth telling is not always so easy in an emergency setting. The emergency physician and the patient often do not have a pre-existing relationship, do not know each other well, and may not share a mutual trust. In the busy ED, it is difficult to spend sufficient time with patients and families such that a productive therapeutic relationship can be established. It therefore becomes crucial that emergency physicians are mindful of the first impressions they make with patients and their families. The truthful and trusting relationship begins with proper eye contact, prudent physical contact such as a handshake, attentive body language, and active listening. Elements of this relationship must be established quickly in the ED. Although a busy physician may feel there is little time to establish this connection, these elements make up the essential core around which a satisfactory relationship is established.

These aspects of truth telling and relationship building are important under all circumstances but more so when upsetting results of diagnostic tests need to be communicated or when bad news must be delivered. Perhaps more important, the trusting alliance may need to be established at the same time that information regarding medical errors are disclosed. Many professional societies, patient safety experts, and standard practice guidelines recommend disclosure (19). There are many reasons favoring the disclosure of harmful errors to patients. Disclosure supports truth telling, patient autonomy and informed decision-making, and is consistent with patients' preferences (20). Patients want to know about errors even when the harm is minor, and expect a full explanation and an apology (20). Patients also seek acknowledgement of the pain and suffering that was caused by the error, along with reassurance that recurrences will be prevented. In addition, disclosure can facilitate the principle of justice, as patients cannot seek compensation for medical injuries they did not know were caused by a medical error. Finally, disclosing errors to patients

promotes patient safety, as it enables the critical appraisal of the conditions leading to errors and the development of interventions to prevent recurrences.

The patient and family must sense honesty in the language, openness in the posture, and integrity in the practice. Patients can often tolerate mistakes, but they will not tolerate physicians who do not care. To complicate matters, many patients at the outset are suspicious, untrusting, demanding, or even violent during their ED visit, making the act of error disclosure even more risky. Information regarding errors must be explained to the patient in the proper context, even though the physician's natural instinct may be to cover up mistakes. This is a precarious maneuver both professionally and legally, especially if the patient or family later discovers the error. Conversely, if the patient is unable or unwilling to engage in a conversation, attempts to divulge a medical error should be noted on the record, and plans for later communication should be made.

Historically, physicians were advised not to disclose errors to patients by risk managers and lawyers who worried that offering an apology or an admission of fault would precipitate malpractice suits. Recent research suggests this assumption may be unfounded (19). Many patients who file medical malpractice claims do so because they believe that disclosure was absent or inadequate and see legal action as their only option for finding out what happened. In addition, healthcare organizations that have adopted robust disclosure programs are reporting favorable outcomes (21). The University of Michigan, which couples disclosure with offers of financial compensation for harmful errors, reported significant reductions in the number of claims filed, litigation costs, and time to resolution (21). In addition, 35 states and the District of Columbia have adopted laws making medical apology inadmissible as a statement of fault, with some states even requiring the disclosure of serious unanticipated outcomes to patients (22). These developments have led many risk managers and malpractice insurers to strongly advocate for disclosure.

When disclosing a harmful medical error to a patient and his or her family, the provider should focus the conversation around the needs of the patient (19,20). The provider needs to present information in a fashion that the patient and family can comprehend. Patients should be told the facts surrounding the event, what steps have been taken to address any medical repercussions, and plans to prevent recurrences. It is also important to explain to the patient and family that they will not incur additional financial costs due to the medical error. Finally, the provider should apologize and express regret for the error. It takes expertise to know how to disclose errors and communicate properly, and emergency physicians should aim to master these special and important skills.

USE OF THE NEWLY DEAD FOR EDUCATION

Emergency physicians must develop and maintain expertise in a wide array of procedural skills, some of which are rarely performed. Many training programs in the past taught procedures on patients who were pronounced dead in the ED (23). The tactile accuracy, accessible teaching opportunity, and situational realism enabled the development of expertise for young physicians who would soon have full responsibility to perform the life-saving skill on future patients. Because it was believed that there was a broad societal obligation to support the training of physicians that could not be easily obtained in another way, the teaching of procedures performed on the newly deceased was conducted. This practice, however, was fraught with ethical controversy and complications mainly because the teaching was often performed without the awareness or permission of the family. Some of the debate surrounding procedural teaching on the recently deceased focused on the type of procedure being taught. Needle insertion, incision, and physical inspection were considered variably acceptable, based primarily on the degree of invasiveness. Endotracheal intubation, for example, might be considered relatively more acceptable, because it was not disfiguring, whereas cricothyrotomy might be

deemed unacceptable. Although there may be some merit to such distinctions, the delineation has not been fully satisfactory.

The answer to this dilemma is rooted in the core ethical obligation of the profession. Physicians must maintain the trust of the individual and the public. The transformation of a person from a patient to a teaching tool seems contrary to the requirement to maintain trust. Therefore, family permission is always encouraged before teaching invasive procedures (23).

PROFESSIONAL LIABILITY

Despite the best intentions of healthcare providers and institutions, adverse events and medical errors occur relatively frequently. Approximately 400,000 adverse drug events and 100,000 patient deaths are estimated to occur annually in American hospitals and clinics, figures that may be conservative given the prevalence of underreporting (24). The ED is one of the most error-prone settings in healthcare (25). The ED practice environment is often chaotic, unpredictable, and potentially hazardous. Emergency physicians make critical medical decisions with incomplete information and under time pressure, and confront a wide range of undifferentiated medical problems. For these reasons, emergency physicians should have at least a basic understanding of professional liability.

Elements of Professional Liability

In a professional liability action against an emergency physician, the plaintiff must prove that (1) the emergency physician owed the patient a duty of reasonable care; (2) the physician breached that duty; (3) there is a causal connection between the physician's conduct and the resulting injury to the plaintiff; and (4) there is an actual injury to the patient (26).

The first two elements of duty and breach of that duty constitute negligence. Legally, negligence is defined as the "failure to use such care as a reasonably prudent and careful person would use under similar circumstances; it is the doing of some act which a person of ordinary prudence would not have done under similar

circumstances or failure to do what a person of ordinary prudence would have done under similar circumstances" (27). Negligence consists of a breach of the duty to adhere to a concept known as the "standard of care." The traditional measure of the standard of care for physicians requires that a physician exercise the "average degree of skill, care, and diligence exercised by members of the same profession, practicing in the same or similar locality in light of the present state of medical and surgical science" (28). It is important to note that the "locality" rule has since expanded into a national standard as a result of advances in modern medical education and training, medical journals that reach a national audience, and continuing medical education courses at the national level.

The courts depend on expert medical testimony to assist in determining whether a physician's conduct was negligent and whether the alleged negligent conduct was the proximate cause of the patient's injury. For the court to find a causal connection, the patient's injury must be a foreseeable consequence of the physician's conduct. If the patient's injury is not causally related to the physician's alleged negligent conduct, there is no professional liability. Unlike the causation element in a product liability case, in which it is usually clear that a particular product caused a particular injury, the causation element of a professional liability action in medical cases is extremely complex and strenuously contested because bad outcomes frequently accompany serious disease processes in the absence of negligence.

Failure to Diagnose

Most professional liability actions against emergency physicians arise under allegations of a failure to diagnose a serious emergency medical condition in a timely manner. Four important factors have been identified as being responsible for breakdowns in the diagnostic process: (1) failure to order an appropriate diagnostic test; (2) failure to create a proper follow-up plan; (3) failure to obtain an adequate history or to perform an adequate physical examination; and (4) incorrect interpretation of a diagnostic test

(29). Emergency physicians are the most frequently involved clinicians (52%) in diagnostic errors, followed by primary care physicians (28%), surgeons (20%), radiologists (16%), and nurses (10%). Residents are involved in 56% of cases (25). These data highlight the high stakes and complicated nature of emergency medicine of which even seasoned emergency physicians should always be mindful.

Hindsight Bias in Professional Liability Actions

In making allegations of professional negligence, plaintiffs' attorneys are aided by a phenomenon, first described by cognitive psychologists, known as hindsight bias. Hindsight bias describes how knowledge of a particular adverse outcome may bias an observer's perspective of a complex series of events such that a person who has knowledge of the adverse event cannot maintain an unbiased view of the reasons for the adverse event. Hindsight bias creates a "knew it all along" effect in which observers of past events exaggerate what other people should have been able to anticipate prospectively (30). However elusive the patient's diagnosis on initial presentation, the diagnosis appears deceptively and obviously simple to those with knowledge of the adverse event acquired in hindsight. Jurors are prohibited from using knowledge based on hindsight in their deliberations and are so instructed in their jury instructions. Unfortunately, as a result of the hindsight bias effect inherent in cases of delayed diagnoses, anyone with knowledge of the adverse outcome will know exactly what definitive diagnostic test or treatment the emergency physician could have ordered, and improperly impute that knowledge should have been apparent to the physician. It is a small step for jurors armed with hindsight to proceed to the erroneous conclusion that a physician's failure to order a particular test or treatment course constituted negligence and hold the physician liable to the patient.

Common Pitfalls

- Failure to assess and document the decisional capacity of patients who refuse care.
- When encountering an advance directive or living will, failure to ask, “does this represent clear, consistent, and valid evidence of what the patient would want for this specific circumstance?” If there is an affirmative response, the directive should be honored.
- Failure to document the provision of an explanation of medical risks to patients leaving against medical advice, as well as failure to give them discharge instructions, medications, and follow-up information as appropriate.
- Failure to document patient’s expressed wishes on the medical record.
- Failure to document justification for the use of physical or chemical restraints.

ACKNOWLEDGMENT

The authors thank and recognize Howard A. Peth, Jr. for his prior contribution to and the integration of parts of Chapter 383: Legal Issues from the 5th edition into this current edition.

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CHAPTER 382

Regulatory Issues

Larry D. Weiss and Jorge A. Martinez

Ever increasingly, state and federal regulations control the practice of medicine in the United States. Each state has agencies which conduct activities such as licensure, provider and institutional compliance, and disciplinary actions. In addition, Congress and federal agencies including the Drug Enforcement Agency, the Center for Medicare and Medicaid Services, and the Federal Trade Commission regulate, administer, and monitor the practice of medicine throughout the United States and oversee reimbursement for healthcare services.

THE AFFORDABLE CARE ACT

The Patient Protection and Affordable Care Act (ACA), which became effective in 2010, represents an effort by Congress and the Obama administration to significantly reform the health insurance industry in the United States (1). Congress intended these reforms to (1) provide near universal health insurance coverage, (2) improve the quality of care, and (3) lower the cost of care. Unlike many European countries which have a centrally controlled single payor system, the ACA provided a complex system of controls to reform the myriad payor systems existing in the United States. Thus, the ACA reforms payor systems in the United States while preserving the basic underlying insurance systems.

The ACA intervenes in more than 25 significant ways to improve the availability of private health insurance. It dramatically expands the government funded Medicaid insurance system for poor

patients. For the first time, Medicaid will provide coverage for all poor patients with a household income of less than 133% of the federal poverty level. Even though the US Supreme Court mostly upheld the constitutionality of the ACA in a June 2012 decision, it declared that Congress could not coerce state governments to expand Medicaid in their respective states (2). Therefore, states may independently decide whether to participate in Medicaid expansion. Many commentators predict up to 20 states may elect not to initially participate when Medicaid expands on January 1, 2014.

To capture patients who earn more than 133% of the federal poverty level, but still may lack the funds to purchase traditional health insurance products, the ACA provides for the creation of state heath benefit exchanges whereby patients may select lower cost "qualified health plans" which must include a list of "essential health benefits." Finally, the ACA provides for near universal health insurance coverage by requiring an individual "mandate" to purchase insurance by January 1, 2014. Failure to purchase insurance will result in a fine, payable on a sliding scale according to income. Those who would have to spend more than 8% of their adjusted gross income on health insurance would not have to pay a fine.

The ACA hopes to improve the quality of care and lower the cost of care primarily through the operation of Accountable Care Organizations (ACOs). A description of the functioning of ACOs lies beyond the scope of this chapter. It suffices to say that ACOs will establish quality and cost goals. If the ACO meets these goals, providers will receive cash payments through "gainsharing" rewards from the Medicare and Medicaid programs. If they fail to meet these goals, then providers must pay a penalty.

A large title of the ACA deals with workforce issues, and will have a largely negative impact on emergency medicine. This section of the ACA provides funds for the training of physician extenders and primary care physicians. However, the ACA defines primary care as general internal medicine, family practice, and general pediatrics. The ACA provides for an immediate redistribution of residency slots toward the three primary care specialties. Initially, these

redistributed slots will come from two sources, (1) slots that were unfilled for 3 years, and (2) slots from closed hospitals. Thereafter, Medicare graduate medical education funds will provide for new primary care residency programs and the expansion of existing primary care residencies.

After the ACA went into effect in 2010, the various federal departments and agencies began writing regulations required by the ACA. Most of these regulations will come from the Center for Medicare and Medicaid Services (CMS). These regulations will deal with payment, quality control, ACOs, tax issues, medical education and training, and a host of other related issues. On the one hand, the ACA banned the use of "prior authorization" requirements by insurance companies for emergency department (ED) visits, and banned the use of higher copayments for ED visits, but on the other hand, a recent CMS Regulation allows insurance companies to choose a low level of reimbursement for emergency medicine providers (3). Emergency medicine advocates have an opportunity to influence the regulatory process, and a number of emergency medicine societies banded together to form lobbying groups (4).

Another area of potential difficulty in the regulatory process concerns the regulation of ACOs. In most communities, an ACO will include at least one hospital and many physicians and other providers. When the ACO contracts with insurance companies, it will have to negotiate price. This will create antitrust risk for physicians and other providers, as competitors may not discuss price, and definitely may not enter into agreements on price. Government expects all physicians in a market area to act as competitors. Two exceptions exist to this general rule, (1) physicians who practice in a group and use the same taxpayer identification number, and (2) employees. Even if an ACO includes only one emergency physician group, government investigators could consider these emergency physicians as competitors of other physicians in the ACO, such as primary care physicians, anesthesiologists, or any other physician who performs a service similar to any ED service.

Therefore if these physicians bargain for price with an insurance company, a government inspector could decide that these physicians engaged in price fixing, usually a criminal violation of the Sherman Antitrust Act. To avoid such potential liability, the ACO would have to evolve into a truly integrated delivery system, or the physicians would have to become employees of the hospital. Of these two options, becoming an employee would be the only sure way to avoid antitrust liability. For these reasons, unless physicians receive some regulatory antitrust relief, the development of ACOs may lead many physicians to become employees. In emergency medicine, this could threaten the viability of independent democratic groups. It could also threaten the viability of large contract management groups.

Advocacy efforts on behalf of emergency medicine should focus on influencing the regulatory process in the following areas: modification of regulations controlling payment for emergency services, antitrust relief to facilitate the development of ACOs, and modification of workforce policies that will restrict future training positions in emergency medicine. The ACA will create profound and long-lasting changes in the practice of medicine. Many of these changes will have a negative impact on emergency medicine, but many of these changes may be mitigated through appropriate advocacy during the regulatory process.

THE EMERGENCY MEDICAL TREATMENT AND ACTIVE LABOR ACT

Congress enacted the Emergency Medical Treatment and Active Labor Act (EMTALA) in 1986 to prevent financial discrimination in hospital EDs. Congress was concerned about economic dumping of uninsured patients from hospital EDs. The purpose of the Act was to prevent discrimination in the evaluation and treatment of ED patients in any form. The crux of the statute is to ensure similar and nondiscriminatory evaluation and treatment of all individuals who present to an ED, whether insured or not.

Under EMTALA, if an individual comes to an ED and a request is made on their behalf for examination or treatment, then they must

receive (1) an appropriate medical screening examination (AMSE), (2) stabilization of their emergency medical condition, and (3) appropriate transfer when indicated (5). EMTALA does not define what constitutes an “appropriate medical screening examination,” but does declare that the examination must include ancillary services routinely available to determine whether an emergency medical condition exists (6). Federal courts concluded that an AMSE requires hospitals and physicians to provide an examination comparable to similarly situated patients (7).

EMTALA provides that any individual found to have an emergency medical condition (EMC), including active labor, must be stabilized before they may be transferred. Stabilization means “to assure, within reasonable medical probability, that no material deterioration of the condition is likely to result from or occur during the transfer” (8). EMTALA defines transfer as “the movement (including the discharge) of an individual outside a hospital’s facilities at the direction of any person employed by (or affiliated or associated, directly or indirectly, with) the hospital . . . It does not include such movement of an individual who has been declared dead or leaves the facility without the permission of any such person (9). EMTALA allows a physician to transfer an unstable patient to another hospital, if the medical benefits of the transfer outweigh the risks (10). Additionally, a competent patient or surrogate decision maker may also request a transfer. In either situation the transferring hospital must provide all treatment within its capabilities; must obtain the consent of the patient or surrogate for transfer; must contact the receiving hospital and secure approval for the transfer; must document that the receiving hospital accepted the patient; must send all relevant medical records, and must assure that the patient is transferred by qualified personnel with adequate equipment to complete the transfer (11).

Hospitals may not delay AMSEs to inquire about payment for services or insurance coverage (12). Furthermore, hospitals with specialized capabilities, or regional referral hospitals in rural areas, may not refuse appropriate transfers, if they have available beds and staffing (13). EMTALA obligations end once a patient with an EMC

is admitted in good faith to a hospital as an inpatient (14). Plaintiffs may only file suit against a hospital, for an alleged EMTALA violation, not the physician (15). Hospitals and physicians may be fined up to $50,000 per occurrence and be excluded from Medicare for flagrant or repeated violations. Hospitals have the right to sue physicians in indemnification to recover the cost of the fines.

CMS wrote a series of regulations that interpret the EMTALA statute and guide its implementation. An individual has "come to the ED" when he arrives on hospital property (16). Hospital property is defined as (1) the area immediately adjacent to the main building, and (2) other areas owned and operated by the hospital within a 250-yard radius of the main building (16). An off-campus facility qualifies as a dedicated ED if (1) it has an ED license, (2) it holds itself out to the public as providing emergency care, or (3) during the preceding year, one-third of outpatient visits were for emergency medical conditions (16). EMTALA does not apply to inpatients, unless the hospital admits the patient in bad faith to avoid providing stabilizing treatment. Nor does it apply to scheduled outpatient visits in a hospital clinic (16). Finally, hospitals must maintain an on-call list of physicians on its medical staff based on the needs of its patients, resources available, and availability of on-call physicians. They must have written policies and procedures to respond to situations where a particular specialty is not available or the on-call physician cannot respond because of circumstances beyond the physician's control. They must also provide that emergency services are available to meet the needs of patients if the hospital elects to permit on-call physicians to schedule elective surgery or cover concurrent on-call duties (16).

HIPAA AND HITECH

Access to a patient's health information (HI) is essential to provide appropriate and comprehensive medical care. During treatment, a patient's HI is exposed to numerous healthcare providers, support personnel, and payers. A major concern is that persons not involved in a patient's medical care may gain unauthorized access or

exposure to HI inadvertently or intentionally and divulge it to third parties.

In response Congress enacted the Health Insurance Portability and Accountability Act (HIPAA) in 1996. The intent of the Act was to guarantee that individuals retain access and control of their HI and to ensure that healthcare providers treat HI in a confidential manner. HIPAA applies to all HI, whether communicated, stored, or transmitted in oral, written, or electronic form. This includes oral conversations, telephone calls, faxes, letters, e-mails, text messaging, computer drives, and data centers.

The principal part of HIPAA affecting the ED is the *Administrative Simplification* section, 45 CFR Parts 160, 162, 164 (1996). It contains privacy and security regulations which (1) describes how an individual's HI may be used and disclosed, (2) incorporates privacy and security standards to safeguard the integrity, confidentiality, and availability of HI, and (3) provides specific patient rights concerning their HI; and creates national standards for electronic healthcare transactions, including data and transaction formats and specific code sets for diagnosis, procedures, and medications. The law compels privacy and security measures to prevent unauthorized disclosure, access, alteration, destruction, or release of HI. It also establishes unique identifiers for providers and third-party payers, and details sanctions for violations.

A covered entity (CE) under HIPAA may use protected health information (PHI) for treatment, payment, and healthcare operations (17). CEs are not required to obtain an individual's authorization to use PHI. HIPAA requires a CE to obtain an individual's written authorization before it may disclose PHI outside of the CE (18). Exceptions allowing PHI to be disclosed without prior authorization involve public health matters.

On February 13, 2009, Congress passed the Health Information Technology for Economic and Clinical Health Act (HITECH). Through HITECH Congress instituted incentives for the meaningful use of electronic health records (EHRs). It also expanded HIPAA's privacy and security provisions directly to business associates, revised civil monetary penalties for violations, and mandated

accountings for disclosures made for payment, treatment, or healthcare operations via an EHR.

Civil penalties are tiered based on severity of the violations. The minimum fine is $100; the maximum fine is $50,000 per individual violation. Maximum civil penalties for multiple violations range from $25,000 to $1.5 million per year (19). Moreover, criminal sanctions may be imposed against CEs and persons within the CE. If the PHI is obtained or disclosed without authorization, the fine is $50,000 and/or incarceration for up to 1 year.

Common Pitfalls

- The Affordable Care Act and its Regulations contains many pitfalls for the specialty of emergency medicine including limitations on reimbursement for emergency services, antitrust risks for physicians in ACOs, and future financial limitations on emergency medicine training programs.
- Failure to provide an AMSE for every individual who seeks care in an ED.
- Failure to provide stabilizing treatment to the maximum capability of the hospital before transferring patients.
- Failure to obtain proper authorization prior to the release of protected health information.
- Failure to establish administrative, physical, and technical safeguards to protect the privacy and integrity of health information.

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2. *NFIB v. Sebelius,* 567 U.S. __ (2012).
3. 45 CFR §147.138(b)(3).
4. *See, e.g.:* www.acep.org/emactionfund.
5. 42 USC §1395 dd.
6. 42 USC §1395 dd (a).

7. *Summers v. Baptist Medical Center, Arkadelphia,* 69 F.3 d 902 (8th Cir 1995), rev on reh 91 F.3 d 1132(1996).
8. 42 USC §1395 dd (b).
9. 42 USC §1395 dd (e)(4).
10. 42 USC §1395 dd (c).
11. 42 USC §1395 dd (c)(2).
12. 42 USC §1395 dd (h).
13. 42 USC §1395 dd (g).
14. *Harry v. Marchant,* 291 F.3 d 767 (11th Cir. 2002).
15. *Baber v. Hospital Corporation of America,* 977 F.2 d 872 (4th Cir. 1992).
16. 42 CFR §489.24.
17. 45 CFR §164.502.
18. 45 CFR §164.508.
19. 42 USC §1320 d-5.

CHAPTER 383

Interpersonal Violence

Abigail Hankin-Wei and Debra Houry

The term *interpersonal violence* implies violence between two people with some relationship (partner, family, acquaintance, gang-related, patient, etc.). This chapter focuses specifically on intimate partner violence (IPV) and provider exposure to violence in the emergency department (ED) setting. Specific information on sexual assault (Chapter 135); trauma in older adults (Chapter 53); and pediatric physical and sexual abuse and neglect (Chapter 290) can be found elsewhere in this textbook.

Also known as *domestic violence, spousal abuse,* or *battering,* IPV can present in the form of physical, sexual, or psychological abuse, or a combination of multiple forms of abuse—perpetrated against a former or current partner. A recent population-based study reported that 29% of women have experienced physical, sexual, or psychological IPV in their lifetime (1). IPV results in nearly 2 million injuries and 1,300 deaths nationwide every year (1).

The incidence of IPV victimization within the past 12 months among female ED patients has been reported to range from 11% to 20% (2–4). Many victims of IPV seek medical care for their injuries in EDs (2,5,6), while others present to EDs for treatment of complaints related to IPV, such as depression, posttraumatic stress disorder, substance abuse or complications of pregnancy secondary to abuse (7,8). In many cases, the ED is the primary access to health care for these patients. The lifetime prevalence of IPV exposure in ED patients has been estimated to be as high as 50% (9). In a recent report, the Institute of Medicine issued a recommendation that screening and counseling for IPV for all women, as part of standard

preventative services, noting that such screening should be done in a "culturally sensitive and supportive manner" (10).

Violence within the ED is a problem that is underreported. The ED lends itself to promotion of a violent environment as a result of the volume of sick patients, long wait times, availability of drugs, 24-hour accessibility, and potentially violent psychiatric patients awaiting medical clearance. In one survey of emergency physicians in Michigan, 74.9% of those surveyed reported a verbal threat in the prior 12 months, while 28.1% reported that they had been physically assaulted in the workplace in the same interval. Among physicians, female gender and fewer years in practice were significantly associated with risk of assault (11).

Multiple studies have shown that, while workplace violence is common, victims often suffer in silence, with severe consequences for their mental health. Gates et al. (12) reported that 65% of assaulted ED workers did not report the assault to hospital authorities. Kowalenko et al. (6) reported that 81% of emergency physicians were occasionally fearful of workplace violence and 9% were frequently fearful. In one study, 42% of emergency physicians sought various forms of protection including obtaining a weapon to protect their personal safety (11).

The American College of Emergency Physicians (ACEP) developed a policy statement on protection from physical violence in the ED (5). ACEP stated that hospitals must ensure the provision of adequate security personnel, coordination of hospital security with local law enforcement agencies, the development of written protocols for violent situations in the ED, and education of staff on violent situations.

CLINICAL PRESENTATION

Intimate Partner Violence

IPV risk crosses all societal categories. However, studies have shown that risk of IPV victimization increases among patients with poor mental health (including depression and increased suicide risk), poor physical health and concurrent medical comorbidities, low

income and low level of educational attainment, as well as race/ethnicity (although differences in ethnicity disappear when socioeconomic status is controlled for) (7,13,14).

IPV victims may present to the ED for treatment of an injury from IPV, evaluation of a chief complaint exacerbated by their situation (headache, anxiety, chronic pain), evaluation of nonspecific general medical complaints such as mental illness, substance use, or poorly controlled comorbid conditions, or a history of IPV that is elucidated via standard screening. Common presentations of battered women are listed in Table 383.1.

TABLE 383.1
Common Presentations of Women Experiencing Intimate Partner Violence

Trauma to the face, neck, or throat
Trauma to the chest, breast, abdomen, or genitals
Bilateral or "pattern" injuries
Sexual assault
Chronic pain
Multiple injuries in various stages of healing
Extent or type of injury inconsistent with patient's explanation
Repeated use of the ED
Psychological or emotional complaints
Evidence of alcohol or drug abuse
Suicidal ideation or behavior

Violence in the ED

Patient-based factors that predict agitation and risk for violent behavior include substance abuse and intoxication, explosive or unpredictable anger, intimidating behavior, hostile and threatening verbal behavior, a history of self-harm, and resistance to medical care (15). At a facility level, interventions that reduce risk of violence in the ED include the use of metal detectors, security staff presence in the ED, and structural changes including panic buttons,

improved lighting and visibility, and surveillance camera monitoring of the entire department (16).

DIFFERENTIAL DIAGNOSIS

IPV should be considered in the differential diagnosis of every ED patient, particularly in patients with nonspecific symptoms, or complaints associated with substance abuse or mental health. Patients with recurrent visits to the ED for vague, somatic complaints should be asked about IPV, as this may be the underlying etiology. Patients with traumatic injuries should be questioned specifically about how the injury occurred, especially if the physical examination findings are inconsistent with the stated mechanism. Without asking specifically about IPV, the diagnosis of abuse may not be made in these cases (17). It is important to ask about and identify IPV, as women who disclose IPV are at risk for incurring future injury (3).

With respect to the violent patient in the ED, it is important that clinicians evaluate for medical causes of the patient's agitation after securing patient and staff safety. Metabolic abnormalities, infection, and trauma are life-threatening causes of altered mental status and agitation that must be ruled out. Table 383.2 lists key diagnoses to be considered.

TABLE 383.2
Organic Causes of Violent Behavior

Drug intoxication: PCP, LSD, cocaine, barbiturates, amphetamines, and alcohol
Trauma: closed-head injury, subdural hematoma, tension pneumothorax
Infection: AIDS, encephalitis, meningitis
Metabolic: hypoglycemia, thyroid storm, renal or liver failure, adrenal crisis, ketoacidosis, hypoxia, hypothermia, hyperthermia, and vitamin deficiency
Neurologic: tumors, epilepsy, cerebrovascular accidents, infections
Iatrogenic: medication-induced delirium

ED EVALUATION

Intimate Partner Violence

Studies have reported that patients will not disclose IPV unless prompted by a health provider (17). Thus, ED patients should be routinely screened for IPV. This can be done as part of the nurse's triage intake or during the physician's history and physical examination. Questioning should always be carried out in private and with a nonjudgmental manner.

Physicians have several specific areas of responsibility in the evaluation and management of patients who are experiencing IPV: to screen for IPV; to provide medical treatment; to document findings and utterances; to facilitate appropriate referrals and follow-up; and to ensure the patient's safety.

Patients thought to have injuries resulting from IPV should be interviewed in a quiet, secure area of the ED without their partner, family, or friends present. Patients should be asked in private whether they want their companion to accompany them into the treatment area, to minimize the chances that they will feel coerced into silence by an abusive companion. If there is a concern for the patient's safety or a companion refuses to leave the patient in private, hospital security or police should be involved. A history of previous trauma, chronic complaints, psychological symptoms, or other red flags for IPV (inconsistent story, injury not consistent with chief complaint, multiple injuries in various stages of healing, partner who will not leave the patient's side) should be sought when obtaining the history. If there is a language barrier, an interpreter should be provided. It is inappropriate to use a family member as an interpreter when IPV is suspected.

Multiple approaches to universal, standard screening for IPV are available, and can be implemented via face-to-face screening, paper screening, or computerized screenings. The Partner Violence Screen is one option, which has been previously validated in healthcare settings (18). It is a simple, three-question screen for IPV that is easy and quick to administer. The screen is as follows:

1. Have you been hit, kicked, punched, or otherwise hurt by someone in the past year? If so, by whom?
2. Do you feel safe in your current relationship?

3. Is there a partner from a previous relationship who is making you feel unsafe now?

If a patient discloses IPV, the physician's first task is to assess the patient's safety. It is important to determine whether the patient has a safe place to stay and has a safety plan if she chooses to return home. Regardless of the severity of the presenting complaint or injury, the best indicator of danger is the patient's own assessment. The frequency and severity of previous attacks, as well as verbal threats of violence are also good guides to current risk. Presence of a weapon in the home, prior battering episodes, and partner substance use may increase risk of harm. Additionally, IPV victims are most likely to be killed when they are in the act of leaving or immediately after they have left their abuser. Enlisting the services of a social worker can help bring victims into contact with resources such as shelters, social services, legal assistance, support groups, and other referrals that may benefit the patient.

Providers should also document the ED visit thoroughly. A review of IPV patient ED charts found that site of assault was not documented in 88% of charts, force/object use was not documented in 13% of charts, and police involvement was documented in only 54% of cases in a state that mandates reporting of IPV (12). It is also important to document the patient's exact words, affect, and emotions, as factors can determine whether the patient's statement will be admissible as evidence in court. Additionally, photographs or body maps should be used to document injuries. An accurate and thoroughly documented medical record can be an asset to an IPV victim's case.

Violence in the ED

Many violent encounters in the ED can be prevented if a situation is recognized and controlled before an incident occurs. It is important to take steps to avoid confrontation, as patients often act out of a sense of fear or danger. Healthcare providers should never respond to patients' threats with threats of their own. All assaults against medical personnel should be reported to law enforcement agencies.

The patient should be approached from the side and should be watched for possible missiles or weapons. A nonoffensive posture, with hands out front but not raised, should be employed. The care provider should be cognizant of the patient's personal space and stay approximately two arm lengths away. It is important to acknowledge the patient's needs and ask him or her to discuss the problem. The patient should be informed in a low voice that help is available and that support will be provided but that the patient must take control of his or her own behavior. Expectations should be defined, and the consequences of aggressive behavior need to be clear. Frequently, talking to the patient and making offers of food and drinks may be calm and defuse the situation.

When possible, the patient should be interviewed alone and in private, but the provider should keep the door ajar and maintain space between the patient and the door should an escape be necessary. Some patients may not respond to these measures, and here a "show of force" may be needed. Before interviewing the patient, assemble a group of security personnel who will remain within calling distance. Frequently, this show of force may be sufficient to help disorganized patients gain control of their thoughts and behavior and back down.

The history may be difficult to obtain, and other sources, such as family members, friends, and medical records, should be used. A physical examination should be performed to exclude an organic cause of the patient's behavior (see Table 383.2). Blood tests, including toxicology screen and a blood sugar, should be obtained.

ED MANAGEMENT

Interpersonal Violence

If the police are not already involved, the physician can offer to call them or help the victim to do so. The patient should be told that battering is a crime and that he or she does not deserve to be treated in this manner. If a sexual assault occurred, state law often requires providers to report all rapes and sexual assaults. Cases involving the abuse or neglect of elders, minors, and certain persons

with disabilities must also be reported to the appropriate government agencies.

Some states may also require reporting of injuries from IPV. It is important to be familiar with the state laws that apply to reporting IPV, because these laws vary considerably.

If the patient chooses not to talk with police or social workers, it is important for the provider to be empathic and not to criticize the patient. Offer the patient information and contact numbers, which she may use later. Ensure that the patient is safe to go home and that he or she has a safety plan such as preparing an escape route should the situation at home escalate.

Violence in the ED

If a patient is or becomes combative or poses a danger to themselves or others, physical restraints may be needed. Explain clearly to the patient what is about to happen and why. Assemble a team, preferably with five members, four to restrain the limbs and one to act as team leader. Soft restraints should be used to secure each limb to the stretcher. After the patient is restrained, he or she should be searched for weapons or objects that could inflict harm and then moved to a quiet area. Zun (19) reported that the most common complications of physical restraints were vomiting, injuring self, and increasing the patient's agitation.

Pharmacologic intervention may be required if the patient remains agitated and uncooperative. Twenty-eight percent of patients in one study who were already physically restrained required chemical restraints (19). Frequently used agents include haloperidol (2 to 10 mg intramuscularly or intravenously in the young and 0.5 to 2.0 mg in the elderly) or benzodiazepines (e.g., diazepam 5 to 10 mg, or lorazepam 2 to 4 mg, intravenously or orally). Geodon (10 mg intramuscularly every 2 hours or 20 mg intramuscularly every 4 hours) has also been approved by the US Food and Drug Administration (FDA) for active psychosis. One randomized trial reported that haloperidol produced a faster onset of sedation and more clinical improvement over the first 2 hours

than did lorazepam, although there were no differences in the need for additional intervention or physical restraints between these medications (20). The reason for physical or chemical restraint use, as well as specific alternative measures implemented to avoid restraints and to ensure the patient's comfort and safety in restraints should be clearly documented in the medical record (19).

CRITICAL INTERVENTIONS

- Identify victims of violence.
- Develop a safety plan and involve authorities and local agencies with victims.
- Intervene early with potentially violent patients prior to escalation.

DISPOSITION

Victims of IPV should be asked where they will go if they leave the ED and who is waiting for them outside. If necessary, they can leave through a less-visible exit. All patients at risk for IPV should be given a list of emergency numbers and community resources. The option of overnight hospitalization should be discussed with the victim if he or she does not have a safe place to go upon discharge.

The discharge plan should include specific considerations for the patient's need including a safe place to stay and resources for daily living, including as money, personal documents, car keys, and clothing for herself and her children. IPV victims should be informed of local programs for battered women that provide free, confidential social and legal services as well as housing, child care, and practical support.

Physicians should discuss protection against sexually transmitted diseases and pregnancy, especially for those patients who have been raped or who have experienced coercive sexual activity as part of the violence.

For patients with violent behavior in the ED, some may be discharged after a period of observation in the ED (e.g., those with alcohol- or drug-induced violent behavior). Some may require

admission because of an underlying medical condition. Other patients may require further evaluation by mental health services and admission to psychiatric facilities. Patients without medical or psychiatric conditions requiring admission and who are under arrest may be discharged to the custody of law enforcement authorities after a medical evaluation.

Common Pitfalls

- Failure to make the diagnosis of IPV (especially in patients who may not disclose abuse, including elderly patients, patients with a language barrier, or patients who present to the ED with the perpetrator).
- Asking about IPV in the presence of a partner or family members.
- Failure to provide appropriate referrals and follow-up for victims of IPV.
- Failure to recognize the patient who is starting to escalate and who could have been calmed before the situation gets out of control.
- Attributing violent behavior to drug or alcohol intoxication without looking for an organic cause.

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